

Treatment for Hepatitis C Virus Infection in Adults

Appendixes

Appendix A. Exact Search Strategy

The following databases have been searched for relevant information:

Database Searches: Hepatitis C: Treatment

Name	Date Limits	Platform Provider
Medline	2002 to February Week 3 2011	OvidSP
Embase	2002-2011	Embase (Elsevier)
Cochrane Library: CDSR, DARE, CCRCT	2002-2011	Cochrane Library
Clinical Trials.gov	2002-2011	
Drugs@FDA	2002-2011	
Health Canada Drug Products Database	2002-2011	
European Public Assessment Reports (European Medicine Agency)	2002-2011	
Scopus	2002-2011	Scopus
PsycINFO	2002 to February Week 4 2011	OvidSP

Hand Search of Journals & Supplements - Topic-Specific Search Terms

Concept	Controlled Vocabulary	Keywords
Hepatitis C	Hepatitis C/ Hepatitis C,` Chronic/ Hepacivirus/ OR	hcv.mp hepacivirus\$.mp
Treatment	Antiviral agents/ Interferons/ Interferon-alpha/ Interferon Alfa-2a/ Interferon Alpha-2b/ Exp Polyethylene Glycols/ Ribavirin/ Exp Protease Inhibitors/	Interferon\$ interferon alpha-2a interferon alpha-2b IFNalpha2a IFNalpha2b interferon alpha 2a interferon alpha 2b pegasys Peg-intron peginterferon alpha-2a peginterferon alpha-2b peginterferon alpha 2a peginterferon alpha 2b pegylated interferon\$ IFN\$ PEG IFN\$ Ribavirin

		RBV protease inhibitor\$ polymerase inhibit\$ HCV protease\$ Telaprevir boceprevir
Harms - treatment	AE.fs MO.fs PO.fs TO.fs CT.fs AE=adverse effects CT=contraindications MO=mortality PO=poisoning TO=toxicity	Unsafe Safety harm\$ complication\$ poison\$ risk\$ side-effect\$ side effect\$ (undesirable ADJ1 effect\$) (treatment ADJ1 emergent) tolerab\$ toxic\$ adrs (adverse ADJ2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)) (undesirable ADJ1 effect\$) (treatment ADJ1 emergent) tolerab\$ toxic\$ adrs (adverse ADJ2 (effect or effects or reaction or reactions or event or events or outcome or outcomes))

Ovid MEDLINE (R) and Ovid OLDMED (R) 1947 to February Week 3 2011

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations February 28, 2011

Date Searched: 2/28/2011

1	Hepatitis C/ or Hepatitis C, Chronic/ or Hepacivirus/ or Hepatitis C.mp. or hepacivirus\$.mp. or HCV.mp.	58837
2	Antiviral agents/ or Interferons/ or Interferon-alpha/ or Interferon Alfa-2a/ or Interferon Alpha-2b/ or Interferon\$.mp. or interferon alpha-2a.mp. or interferon alpha-2b.mp. or IFNalpha2a.mp. or IFNalpha2b.mp. or	379770

	interferon alpha 2a.mp. or interferon alpha 2b.mp. or exp Polyethylene Glycols/ or pegasys.mp. or Peg-intron.mp. or peginterferon alpha-2a.mp. or peginterferon alpha-2b.mp. or peginterferon alpha 2a.mp. or peginterferon alpha 2b.mp. or pegylated interferon\$.mp. or IFN\$.mp. or PEG IFN\$.mp. or Ribavirin/ or ribavirin.mp. or RBV.mp. or exp Protease Inhibitors/ or protease inhibitor\$.mp. or polymerase inhibit\$.mp. or HCV protease\$.mp. or telaprevir.mp. or boceprevir.mp.	
3	1 and 2	17643
4	(randomized controlled trial or controlled clinical trial or meta analysis or review).pt. or clinical trials as topic/ or cohort studies/ or randomized.ab. or randomly.ab. or placebo.ab. or (systematic adj1 review).ti,ab.	2497187
5	3 and 4	5889
6	limit 5 to (yr="2002 -Current" and ("adult (19 to 44 years)" or "middle age (45 to 64 years)" or "all aged (65 and over)"))	1380
7	(unsafe or safety or harm\$ or complication\$ or poison\$ or risk\$).mp. or AE.fs. or MO.fs. or PO.fs. or TO.fs. or CT.fs. or side-effect\$.mp. or (undesirable adj1 effect\$).mp. or (treatment adj1 emergent).mp. or tolerab\$.mp. or toxic\$.mp. or adrs.mp. or (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).mp.	3889277
8	1 and 2 and 7	7391
9	4 and 8	3164
10	limit 9 to (yr="2002 -Current" and ("adult (19 to 44 years)" or "middle age (45 to 64 years)" or "all aged (65 and over)"))	883
11	Counseling/ or Sex Counseling/ or Health Education/ or Patient Education as Topic/ or Psychotherapy/ or Behavior Therapy/ or Cognitive Therapy/ or Immunization/ or Immunotherapy/ or Psychotherapy, Brief/ or Socioenvironmental Therapy/	268554
12	1 and 11	660

Medline Update Search

Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) 1946 to November Week 3 2011,

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations December 15, 2011

Date Searched: 12/16/2011

1	Hepatitis C/ or Hepatitis C, Chronic/ or Hepacivirus/ or Hepatitis C.mp. or hepacivirus\$.mp. or HCV.mp.	58901
2	Antiviral agents/ or Interferons/ or Interferon-alpha/ or Interferon Alfa-2a/ or Interferon Alpha-2b/ or Interferon\$.mp. or interferon alpha-2a.mp. or interferon alpha-2b.mp. or IFNalpha2a.mp. or IFNalpha2b.mp. or interferon alpha 2a.mp. or interferon alpha 2b.mp. or exp Polyethylene Glycols/ or pegasys.mp. or Peg-intron.mp. or peginterferon alpha-2a.mp. or peginterferon alpha-2b.mp. or peginterferon alpha 2a.mp. or peginterferon alpha 2b.mp. or pegylated interferon\$.mp. or IFN\$.mp. or PEG IFN\$.mp. or Ribavirin/ or ribavirin.mp. or RBV.mp. or exp Protease Inhibitors/ or protease inhibitor\$.mp. or polymerase inhibit\$.mp. or HCV protease\$.mp. or telaprevir.mp. or boceprevir.mp.	379981
3	1 and 2	17670
4	(randomized controlled trial or controlled clinical trial or meta analysis or review).pt. or clinical trials as topic/ or cohort studies/ or randomized.ab. or randomly.ab. or placebo.ab. or (systematic adj1 review).ti,ab.	2498350
5	3 and 4	5896
6	limit 5 to (yr="2002 -Current" and ("adult (19 to 44 years)" or "middle age (45 to 64 years)" or "all aged (65 and over)"))	1382
7	(unsafe or safety or harm\$ or complication\$ or poison\$ or risk\$).mp. or AE.fs. or MO.fs. or PO.fs. or TO.fs. or CT.fs. or side-effect\$.mp. or (undesirable adj1 effect\$).mp. or (treatment adj1 emergent).mp. or tolerab\$.mp. or toxic\$.mp. or adrs.mp. or (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).mp.	3892024
8	1 and 2 and 7	7401
9	4 and 8	3168

10	limit 9 to (yr="2002 -Current" and ("adult (19 to 44 years)" or "middle age (45 to 64 years)" or "all aged (65 and over)"))	885
11	Counseling/ or Sex Counseling/ or Health Education/ or Patient Education as Topic/ or Psychotherapy/ or Behavior Therapy/ or Cognitive Therapy/ or Immunization/ or Immunotherapy/ or Psychotherapy, Brief/ or Socioenvironmental Therapy/	268601
12	1 and 11	662
13	6 and (201102* or 201103* or 201104* or 201105* or 201106* or 201107* or 201108* or 201109* or 201110* or 201111* or 201112*).ed.	132
14	10 and (201102* or 201103* or 201104* or 201105* or 201106* or 201107* or 201108* or 201109* or 201110* or 201111* or 201112*).ed.	90
15	12 and (201102* or 201103* or 201104* or 201105* or 201106* or 201107* or 201108* or 201109* or 201110* or 201111* or 201112*).ed.	33

Appendix B. Hepatitis C Treatment: Inclusion Criteria by Key Question

	Inclusion Criteria
Populations	<p>Asymptomatic adults with chronic hepatitis C virus infection who have not received antiviral drug treatment previously</p> <p>Subgroups include: HCV genotype, race, sex, stage of disease, viral load, weight, and others (e.g. genetic markers)</p> <ul style="list-style-type: none"> • Excluded: Pregnant women, HIV co-infected, transplant recipients, patients with renal failure
Interventions	<p>KQ 1a and b:</p> <p>1a. What is the comparative effectiveness of antiviral treatment in improving health outcomes in patients with HCV infection?</p> <p>1b. How does the comparative effectiveness of antiviral treatment for health outcomes vary according to patient subgroup characteristics, including but not limited to HCV genotype, race, sex, disease severity or genetic markers?</p> <p>KQ 2a and b:</p> <p>2. What is the comparative effectiveness of antiviral treatments in improving intermediate outcomes, such as the rate of viremia, aminotransaminase levels, and histologic changes?</p> <p>2a. How does the comparative effectiveness of antiviral treatment for intermediate outcomes vary according to patient subgroup characteristics, including but not limited to HCV genotype, race, sex, disease severity or genetic markers?</p> <p>KQ 3a and b:</p> <p>3a. What are the comparative harms (including intolerance to treatment) associated with antiviral treatment?</p> <p>3b. Do these harms differ according to patient subgroup characteristics, including HCV genotype, race, sex, disease severity or genetic markers?</p> <p>KQ 4:</p> <p>Have improvements in intermediate outcomes (viremia, liver function tests, histologic changes) been shown to reduce the risk or rates of health outcomes from HCV infection?</p>

	Inclusion Criteria
Comparisons	<p>KQ 1a and b: 1a. What is the comparative effectiveness of antiviral treatment in improving health outcomes in patients with HCV infection? 1b. How does the comparative effectiveness of antiviral treatment for health outcomes vary according to patient subgroup characteristics, including but not limited to HCV genotype, race, sex, disease severity or genetic markers?</p> <p>KQ 2a and b: 2a. What is the comparative effectiveness of antiviral treatments in improving intermediate outcomes, such as the rate of viremia, aminotransaminase levels, and histologic changes? 2b. How does the comparative effectiveness of antiviral treatment for intermediate outcomes vary according to patient subgroup characteristics, including but not limited to HCV genotype, race, sex, disease severity or genetic markers?</p> <p>KQ 3a and b: 3. What are the comparative harms (including intolerance to treatment) associated with antiviral treatment? 3a. Do these harms differ according to patient subgroup characteristics, including HCV genotype, race, sex, disease severity or genetic markers?</p> <p>KQ 4: Have improvements in intermediate outcomes (viremia, liver function tests, histologic changes) been shown to reduce the risk or rates of health outcomes from HCV infection?</p>
Outcomes	<p>Clinical outcomes</p> <ul style="list-style-type: none"> • Mortality (all-cause or hepatic) • Cirrhosis • Hepatic decompensation • Hepatocellular carcinoma • Need for liver transplantation • Quality of life • Harms from antiviral treatments (including withdrawals due to adverse events, neutropenia, anemia, psychological adverse events, flu-like symptoms, rash) <p>Intermediate outcomes</p> <ul style="list-style-type: none"> • Sustained virological response • Improvement in liver histology
Settings	All settings (including primary care and specialty settings) and locales, though focus on studies conducted in the U.S. and other developed countries.
Study designs	<p>KQ 3a and b: 3a. What are the comparative harms (including intolerance to treatment) associated with antiviral treatment? 3b. Do these harms differ according to patient subgroup characteristics, including HCV genotype, race, sex, disease severity or genetic markers?</p> <p>KQ 4: Have improvements in intermediate outcomes (viremia, liver function tests, histologic changes) been shown to reduce the risk or rates of health outcomes from HCV infection?</p>

Appendix C. Included Studies List

Key Question 1: Not Applicable

Key Questions 2 and 3:

Abergel A, Hezode C, Leroy V, et al. Peginterferon alpha-2b plus ribavirin for treatment of chronic hepatitis C with severe fibrosis: a multicentre randomized controlled trial comparing two doses of peginterferon alpha-2b. *Journal of Viral Hepatitis*. 2006 Dec;13(12):811-20. PMID: 17109680

Andriulli A, Cursaro C, Cozzolongo R, et al. Early discontinuation of ribavirin in HCV-2 and HCV-3 patients responding to Peg-interferon alpha-2a and ribavirin. *Journal of Viral Hepatitis*. 2009 Jan;16(1):28-35. PMID: 18761603

Ascione A, De Luca M, Tartaglione MT, et al. Peginterferon alfa-2a plus ribavirin is more effective than peginterferon alfa-2b plus ribavirin for treating chronic hepatitis C virus infection. *Gastroenterology*. 2010 Jan;138(1):116-22. PMID: 19852964

Berg T, von Wagner M, Nasser S, et al. Extended treatment duration for hepatitis C virus type 1: comparing 48 versus 72 weeks of peginterferon-alfa-2a plus ribavirin. *Gastroenterology*. 2006 Apr;130(4):1086-97. PMID: 16618403

Berg T, Weich V, Teuber G, et al. Individualized treatment strategy according to early viral kinetics in hepatitis C virus type 1-infected patients. *Hepatology*. 2009 Aug;50(2):369-77. PMID: 19575366

Brady DE, Torres DM, An JW, et al. Induction pegylated interferon alfa-2b in combination with ribavirin in patients with genotypes 1 and 4 chronic hepatitis C: a prospective, randomized, multicenter, open-label study. *Clinical Gastroenterology & Hepatology*. 2010 Jan;8(1):66-71.e1. PMID: 19747986

Brandao C, Barone A, Carrilho F, et al. The results of a randomized trial looking at 24 weeks vs 48 weeks of treatment with peginterferon alpha-2a (40 kDa) and ribavirin combination therapy in patients with chronic hepatitis C genotype 1. *Journal of Viral Hepatitis*. 2006 Aug;13(8):552-9. PMID: 16901286

Bronowicki J-P, Ouzan D, Asselah T, et al. Effect of ribavirin in genotype 1 patients with hepatitis C responding to pegylated interferon alfa-2a plus ribavirin. *Gastroenterology*. 2006 Oct;131(4):1040-8. PMID: 17030174

Buti M, Lurie Y, Zakharova NG, et al. Randomized trial of peginterferon alfa-2b and ribavirin for 48 or 72 weeks in patients with hepatitis C virus genotype 1 and slow virologic response. *Hepatology*. 2010 Oct;52(4):1201-7. PMID: 20683847

Dalgard O, Bjoro K, Ring-Larsen H, et al. Pegylated interferon alfa and ribavirin for 14 versus 24 weeks in patients with hepatitis C virus genotype 2 or 3 and rapid virological response. *Hepatology*. 2008 Jan;47(1):35-42. PMID: 17975791

Escudero A, Rodriguez F, Serra MA, et al. Pegylated alpha-interferon-2a plus ribavirin compared with pegylated alpha-interferon-2b plus ribavirin for initial treatment of chronic hepatitis C virus: prospective, non-randomized study. *Journal of Gastroenterology & Hepatology*. 2008 Jun;23(6):861-6. PMID: 18422960

Ferenci P, Laferl H, Scherzer T-M, et al. Peginterferon alfa-2a/ribavirin for 48 or 72 weeks in hepatitis C genotypes 1 and 4 patients with slow virologic response.[Reprint in *Korean J Hepatol*. 2010 Jun;16(2):201-5; PMID: 20606507]. *Gastroenterology*. 2010 Feb;138(2):503-12. PMID: 19909752

Fried MW, Jensen DM, Rodriguez-Torres M, et al. Improved outcomes in patients with hepatitis C with difficult-to-treat characteristics: randomized study of higher doses of peginterferon alpha-2a and ribavirin. *Hepatology*. 2008 Oct;48(4):1033-43. PMID: 18697207

Hadziyannis SJ, Sette H, Jr., Morgan TR, et al. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. *Annals of Internal Medicine*. 2004 Mar 2;140(5):346-55. PMID: 14996676

Helbling B, Jochum W, Stamenic I, et al. HCV-related advanced fibrosis/cirrhosis: randomized controlled trial of pegylated interferon alpha-2a and ribavirin. *Journal of Viral Hepatitis*. 2006 Nov;13(11):762-9. PMID: 17052276

Hezode C, Forestier N, Dusheiko G, et al. Telaprevir and peginterferon with or without ribavirin for chronic HCV infection. *New England Journal of Medicine*. 2009 Apr 30;360(18):1839-50. PMID: 19403903

Ide T, Hino T, Ogata K, et al. A randomized study of extended treatment with peginterferon alpha-2b plus ribavirin based on time to HCV RNA negative-status in patients with genotype 1b chronic hepatitis C. *American Journal of Gastroenterology*. 2009 Jan;104(1):70-5. PMID: 19098852

Jacobson (a) IM, Brown RS, Jr., Freilich B, et al. Peginterferon alfa-2b and weight-based or flat-dose ribavirin in chronic hepatitis C patients: a randomized trial. *Hepatology*. 2007 Oct;46(4):971-81. PMID: 17894303

Jacobson (b) IM, Brown RS, Jr., McCone J, et al. Impact of weight-based ribavirin with peginterferon alfa-2b in African Americans with hepatitis C virus genotype 1. *Hepatology*. 2007 Oct;46(4):982-90. PMID: 17894323

Jacobson IM, McHutchison JG, Dusheiko G, et al. Telaprevir for Previously Untreated Chronic Hepatitis C Virus Infection. *New England Journal of Medicine*. 2011;364(25):2405-16. PMID: 21696307

Kamal SM, Ahmed A, Mahmoud S, et al. Enhanced efficacy of pegylated interferon alpha-2a over pegylated interferon and ribavirin in chronic hepatitis C genotype 4A randomized trial and quality of life analysis. *Liver Int*. 2011;31(3):401-11. PMID: 21281434

Kamal SM, El Tawil AA, Nakano T, et al. Peginterferon {alpha}-2b and ribavirin therapy in chronic hepatitis C genotype 4: impact of treatment duration and viral kinetics on sustained virological response. *Gut*. 2005 Jun;54(6):858-66. PMID: 15888797

Kawaoka T, Kawakami Y, Tsuji K, et al. Dose comparison study of pegylated interferon-alpha-2b plus ribavirin in naive Japanese patients with hepatitis C virus genotype 2: a randomized clinical trial. *Journal of Gastroenterology & Hepatology*. 2009 Mar;24(3):366-71. PMID: 19032459

Khan AQ AA, Shahbuddin S, Iqbal Q. Abstract # S1231: Peginterferon Alfa 2a / Ribavirin versus Peginterferon Alfa 2b / Ribavirin combination therapy in Chronic Hepatitis C Genotype 3. *Gastroenterology*. 2007;132(4):A200. PMID: n/a

Krawitt EL, Gordon SR, Grace ND, et al. A study of low dose peginterferon alpha-2b with ribavirin for the initial treatment of chronic hepatitis C. *American Journal of Gastroenterology*. 2006 Jun;101(6):1268-73. PMID: 16771948

Kwo PY, Lawitz EJ, McCone J, et al. Efficacy of boceprevir, an NS3 protease inhibitor, in combination with peginterferon alfa-2b and ribavirin in treatment-naive patients with genotype 1 hepatitis C infection (SPRINT-1): an open-label, randomised, multicentre phase 2 trial.[Erratum appears in *Lancet*. 2010 Oct 9;376(9748):1224 Note: SPRINT-1 investigators [added]; multiple investigator names added]. *Lancet*. 2010 Aug 28;376(9742):705-16. PMID: 20692693

Lagging M, Langeland N, Pedersen C, et al. Randomized comparison of 12 or 24 weeks of peginterferon alpha-2a and ribavirin in chronic hepatitis C virus genotype 2/3 infection. *Hepatology*. 2008 Jun;47(6):1837-45. PMID: 18454508

Lam KD, Trinh HN, Do ST, et al. Randomized controlled trial of pegylated interferon-alfa 2a and ribavirin in treatment-naive chronic hepatitis C genotype 6. *Hepatology*. 2010 Nov;52(5):1573-80. PMID: 21038410

Liu C-H, Liu C-J, Lin C-L, et al. Pegylated interferon-alpha-2a plus ribavirin for treatment-naive Asian patients with hepatitis C virus genotype 1 infection: a multicenter, randomized controlled trial. *Clinical Infectious Diseases*. 2008 Nov 15;47(10):1260-9. PMID: 18834319

Magni C NF, Argentero B, Giorgi R, Mainini A, Pastecchia C, Ricci E, Schiavini M, Terzi R, Vivrito MC, Resta M. Abstract #883: Antiviral activity and tolerability between pegylated interferon alpha 2a and

alpha 2b in naive patients with chronic hepatitis C: Results of a prospective monocentric randomized trial. *Hepatology*. 2009;50(S4):720A. PMID: n/a

Mangia A, Santoro R, Minerva N, et al. Peginterferon alfa-2b and ribavirin for 12 vs. 24 weeks in HCV genotype 2 or 3. *New England Journal of Medicine*. 2005 Jun 23;352(25):2609-17. PMID: 15972867

Manns MP, McHutchison JG, Gordon SC, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet*. 2001;358(9286):958-65. PMID: 11583749

Marcellin P, Forns X, Goeser T, et al. Telaprevir is effective given every 8 or 12 hours with ribavirin and peginterferon alfa-2a or -2b to patients with chronic hepatitis C. *Gastroenterology*. 2011 Feb;140(2):459-68.e1; quiz e14. PMID: 21034744

McHutchison JG, Everson GT, Gordon SC, et al. Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection.[Erratum appears in *N Engl J Med*. 2009 Oct 8;361(15):1516]. *New England Journal of Medicine*. 2009 Apr 30;360(18):1827-38. PMID: 19403902

McHutchison JG, Lawitz EJ, Shiffman ML, et al. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection.[Erratum appears in *N Engl J Med*. 2009 Sep 3;361(10):1027]. *New England Journal of Medicine*. 2009 Aug 6;361(6):580-93. PMID: 19625712

Mecenate F, Pellicelli AM, Barbaro G, et al. Short versus standard treatment with pegylated interferon alfa-2A plus ribavirin in patients with hepatitis C virus genotype 2 or 3: the cleo trial. *BMC Gastroenterology*. 2010;10:21. PMID: 20170514

Meyer-Wyss B, Rich P, Egger H, et al. Comparison of two PEG-interferon alpha-2b doses (1.0 or 1.5 microg/kg) combined with ribavirin in interferon-naive patients with chronic hepatitis C and up to moderate fibrosis. *Journal of Viral Hepatitis*. 2006 Jul;13(7):457-65. PMID: 16792539

Mimidis K, Papadopoulos VP, Elefsiniotis I, et al. Hepatitis C virus survival curve analysis in naive patients treated with peginterferon alpha-2b plus ribavirin. A randomized controlled trial for induction with high doses of peginterferon and predictability of sustained viral response from early virologic data. *Journal of Gastrointestinal & Liver Diseases*. 2006 Sep;15(3):213-9. PMID: 17013444

Pearlman BL, Ehleben C, Saifee S. Treatment extension to 72 weeks of peginterferon and ribavirin in hepatitis c genotype 1-infected slow responders. *Hepatology*. 2007 Dec;46(6):1688-94. PMID: 18046717

Poodad F, McCone J, Jr., Bacon BR, et al. Boceprevir for untreated chronic HCV genotype 1 infection. *New England Journal of Medicine*. 2011 Mar 31;364(13):1195-206. PMID: 21449783

Reddy KR, Shiffman ML, Rodriguez-Torres M, et al. Induction pegylated interferon alfa-2a and high dose ribavirin do not increase SVR in heavy patients with HCV genotype 1 and high viral loads. *Gastroenterology*. 2010 Dec;139(6):1972-83. PMID: 20816836

Roberts SK, Weltman MD, Crawford DHG, et al. Impact of high-dose peginterferon alfa-2A on virological response rates in patients with hepatitis C genotype 1: a randomized controlled trial. *Hepatology*. 2009 Oct;50(4):1045-55. PMID: 19676125

Rumi MG, Aghemo A, Prati GM, et al. Randomized study of peginterferon-alpha2a plus ribavirin vs peginterferon-alpha2b plus ribavirin in chronic hepatitis C. *Gastroenterology*. 2010 Jan;138(1):108-15. PMID: 19766645

Sanchez-Tapias JM, Diago M, Escartin P, et al. Peginterferon-alfa2a plus ribavirin for 48 versus 72 weeks in patients with detectable hepatitis C virus RNA at week 4 of treatment.[Erratum appears in *Gastroenterology*. 2006 Oct;131(4):1363]. *Gastroenterology*. 2006 Aug;131(2):451-60. PMID: 16890599

Sherman KE, Flamm SL, Afdhal NH, et al. Response-guided telaprevir combination treatment for hepatitis C virus infection. *N Engl J Med*. 2011;365(11):1014-24. PMID: 21916639

Shiffman ML, Suter F, Bacon BR, et al. Peginterferon alfa-2a and ribavirin for 16 or 24 weeks in HCV genotype 2 or 3. *New England Journal of Medicine*. 2007 Jul 12;357(2):124-34. PMID: 17625124

Sood A, Midha V, Hissar S, et al. Comparison of low-dose pegylated interferon versus standard high-dose pegylated interferon in combination with ribavirin in patients with chronic hepatitis C with genotype 3: an Indian experience. *Journal of Gastroenterology & Hepatology*. 2008 Feb;23(2):203-7. PMID: 17645472

von Wagner M, Huber M, Berg T, et al. Peginterferon-alpha-2a (40KD) and ribavirin for 16 or 24 weeks in patients with genotype 2 or 3 chronic hepatitis C. *Gastroenterology*. 2005 Aug;129(2):522-7. PMID: 16083709

Yenice N, Mehtap O, Gumrah M, et al. The efficacy of pegylated interferon alpha 2a or 2b plus ribavirin in chronic hepatitis C patients. *Turkish Journal of Gastroenterology*. 2006 Jun;17(2):94-8. PMID: 16830289

Yu M-L, Dai C-Y, Huang J-F, et al. Rapid virological response and treatment duration for chronic hepatitis C genotype 1 patients: a randomized trial. *Hepatology*. 2008 Jun;47(6):1884-93. PMID: 18508296

Yu M-L, Dai C-Y, Huang J-F, et al. A randomised study of peginterferon and ribavirin for 16 versus 24 weeks in patients with genotype 2 chronic hepatitis C. *Gut*. 2007 Apr;56(4):553-9. PMID: 16956917

Yu M-L, Dai C-Y, Lin Z-Y, et al. A randomized trial of 24- vs. 48-week courses of PEG interferon alpha-2b plus ribavirin for genotype-1b-infected chronic hepatitis C patients: a pilot study in Taiwan. *Liver International*. 2006 Feb;26(1):73-81. PMID: 16420512

Zeuzem S, Diago M, Gane E, et al. Peginterferon alfa-2a (40 kilodaltons) and ribavirin in patients with chronic hepatitis C and normal aminotransferase levels. *Gastroenterology*. 2004 Dec;127(6):1724-32. PMID: 15578510

Key Question 4:

Arase Y, Ikeda K, Suzuki F, et al. Long-term outcome after interferon therapy in elderly patients with chronic hepatitis C. *Intervirology*. 2007;50(1):16-23. PMID: 17164553

Arora S, O'Brien C, Zeuzem S, et al. Treatment of chronic hepatitis C patients with persistently normal alanine aminotransferase levels with the combination of peginterferon alpha-2a (40 kDa) plus ribavirin: impact on health-related quality of life. *Journal of Gastroenterology & Hepatology*. 2006 Feb;21(2):406-12. PMID: 16509866

Backus LI, Boothroyd DB, Phillips BR, et al. A sustained virologic response reduces risk of all-cause mortality in patients with hepatitis C. *Clinical Gastroenterology & Hepatology*. 2011;9:509-16. PMID: 21397729

Bernstein D, Kleinman L, Barker CM, et al. Relationship of health-related quality of life to treatment adherence and sustained response in chronic hepatitis C patients. *Hepatology*. 2002 Mar;35(3):704-8. PMID: 11870387

Bini EJ, Mehandru S. Sustained virological response rates and health-related quality of life after interferon and ribavirin therapy in patients with chronic hepatitis C virus infection and persistently normal alanine aminotransferase levels. *Aliment Pharmacol Ther*. 2006;23(6):777-85. PMID: 16556180

Bonkovsky HL, Woolley JM. Reduction of health-related quality of life in chronic hepatitis C and improvement with interferon therapy. The Consensus Interferon Study Group. *Hepatology*. 1999;29(1):264-70. PMID: 9862876

Bruno S, Stroffolini T, Colombo M, et al. Sustained virological response to interferon-alpha is associated with improved outcome in HCV-related cirrhosis: a retrospective study. *Hepatology*. 2007 Mar;45(3):579-87. PMID: 17326216

Cardoso A-C, Moucari R, Figueiredo-Mendes C, et al. Impact of peginterferon and ribavirin therapy on hepatocellular carcinoma: incidence and survival in hepatitis C patients with advanced fibrosis. *Journal of Hepatology*. 2010 May;52(5):652-7. PMID: 20346533

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Appendix D. Excluded Studies List

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Everhart, et al. Weight-related effects on disease progression in the hepatitis C antiviral long-term treatment against cirrhosis trial. *Gastroenterology*. 2009 Aug;137(2):549-57. PMID: 19445938. **Exclusion Reason -Not Relevant**

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Fontana, et al. Cognitive function does not worsen during long-term low-dose peginterferon therapy in patients with chronic hepatitis C. *American Journal of Gastroenterology*. 2010 Jul;105(7):1551-60. PMID: 20104219. **Exclusion Reason** -Not Relevant

Fontana, et al. Cognitive function does not worsen during pegylated interferon and ribavirin retreatment of chronic hepatitis C. *Hepatology*. 2007 May;45(5):1154-63. PMID: 17465000. **Exclusion Reason** -Not Relevant

Fontana, et al. Factors that determine the development and progression of gastroesophageal varices in patients with chronic hepatitis C. *Gastroenterology*. 2010 Jun;138(7):2321-31. PMID: 20211180. **Exclusion Reason** -Not Relevant

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Foster, et al. Telaprevir Alone or With Peginterferon and Ribavirin Reduces HCV RNA in Patients With Chronic Genotype 2 but Not Genotype 3 Infections. *Gastroenterology*. 2011;141(3):881-889.e1. PMID: 21699786. **Exclusion Reason** -wrong outcomes

Fuster, et al. Results of a study of prolonging treatment with pegylated interferon-alpha2a plus ribavirin in HIV/HCV-coinfected patients with no early virological response.[Erratum appears in *Antivir Ther*. 2006;11(5):667]. *Antiviral Therapy*. 2006;11(4):473-82. PMID: 16856621. **Exclusion Reason** -Not Relevant

Gane, et al. Oral combination therapy with a nucleoside polymerase inhibitor (RG7128) and danoprevir for chronic hepatitis C genotype 1 infection (INFORM-1): a randomised, double-blind, placebo-controlled, dose-escalation trial. *Lancet*. 2010 Oct 30;376(9751):1467-75. PMID: 20951424. **Exclusion Reason** -Not Relevant

Garg, et al. Effect of Telaprevir on the Pharmacokinetics of Midazolam and Digoxin. *The Journal of Clinical Pharmacology*. 2011 December 12, 2011 PMID: 22162542. **Exclusion Reason** -wrong study design

Garg, et al. Effect of telaprevir on the pharmacokinetics of cyclosporine and tacrolimus. *Hepatology*. 2011;54(1):20-27. PMID: 21618566. **Exclusion Reason** -wrong study design

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Geitmann, et al. Mechanistic and kinetic characterization of hepatitis C virus NS3 protein interactions with NS4A and protease inhibitors. *Journal of Molecular Recognition*. 2011;24(1):60-70. PMID: 21194118. **Exclusion Reason** -not relevant

Gheorghe, et al. Efficacy, tolerability and predictive factors for early and sustained virologic response in patients treated with weight-based dosing regimen of PegIFN alpha-2b ribavirin in real-life healthcare setting. *Journal of Gastrointestinal & Liver Diseases*. 2007 Mar;16(1):23-9. PMID: 17410285. **Exclusion Reason** -Not Relevant

Giannini, et al. Long-term follow up of chronic hepatitis C patients after α -interferon treatment: A functional study. *Journal of Gastroenterology and Hepatology*. 2001;16(4):399-405. PMID: 11354278. **Exclusion Reason** -Wrong Drug

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Goodman, et al. Fibrosis progression in chronic hepatitis C: morphometric image analysis in the HALT-C trial. *Hepatology*. 2009 Dec;50(6):1738-49. PMID: 19824074. **Exclusion Reason** -Not Relevant

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Grebely, et al. Directly observed therapy for the treatment of hepatitis C virus infection in current and former injection drug users. *Journal of Gastroenterology & Hepatology*. 2007 Sep;22(9):1519-25. PMID: 17645460. **Exclusion Reason** -Not Relevant

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Han, et al. Interferon beta 1a versus interferon beta 1a plus ribavirin for the treatment of chronic hepatitis C in Chinese patients: a randomized, placebo-controlled trial. *Digestive Diseases & Sciences*. 2008 Aug;53(8):2238-45. PMID: 18080763. **Exclusion Reason** -Not Relevant

Harrington, et al. Clinical relevance of detectable but not quantifiable hepatitis C virus RNA during boceprevir or telaprevir treatment. *Hepatology*. 2011:n/a-n/a. PMID: 22095516. **Exclusion Reason** - wrong outcomes

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Hinrichsen, et al. Short-term antiviral efficacy of BILN 2061, a hepatitis C virus serine protease inhibitor, in hepatitis C genotype 1 patients. *Gastroenterology*. 2004 Nov;127(5):1347-55. PMID: 15521004. **Exclusion Reason** -Not Relevant

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Iacobellis, et al. Peginterferon alfa-2b and ribavirin in patients with hepatitis C virus and decompensated cirrhosis: a controlled study. *Journal of Hepatology*. 2007 Feb;46(2):206-12. PMID: 17125876. **Exclusion Reason** -Not Relevant

Ikeda, et al. A Long-Term Glycyrrhizin Injection Therapy Reduces Hepatocellular Carcinogenesis Rate in Patients with Interferon-Resistant Active Chronic Hepatitis C: A Cohort Study of 1249 Patients. *Digestive Diseases and Sciences*. 2006;51(3):603-609. PMID: 16614974. **Exclusion Reason** -Wrong Drug

Imai, et al. Interferon therapy for aged patients with chronic hepatitis C: improved survival in patients exhibiting a biochemical response. *Journal of Gastroenterology*. 2004 Nov;39(11):1069-77. PMID: 15580400. **Exclusion Reason** -Not Relevant

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Zeuzem, et al. International, multicenter, randomized, controlled study comparing dynamically individualized versus standard treatment in patients with chronic hepatitis C. *Journal of Hepatology*. 2005 Aug;43(2):250-7. PMID: 16082736. **Exclusion Reason** -Not Relevant

Zeuzem, et al. Albinterferon Alfa-2b was not inferior to pegylated interferon- in a randomized trial of patients with chronic hepatitis C virus genotype 1. *Gastroenterology*. 2010 Oct;139(4):1257-66. PMID: 20600013. **Exclusion Reason** -Not Relevant

Zeuzem, et al. Albinterferon alfa-2b dosed every two or four weeks in interferon-naive patients with genotype 1 chronic hepatitis C. *Hepatology*. 2008 Aug;48(2):407-17. PMID: 18666223. **Exclusion Reason** -Not Relevant

Zhao, et al. Peginterferon vs. interferon in the treatment of different HCV genotype infections in HIV patients. *European Journal of Clinical Microbiology & Infectious Diseases*. 2008 Dec;27(12):1183-92. PMID: 18560911. **Exclusion Reason** -wrong population

Zhao, et al. Treatment with peginterferon versus interferon in Chinese patients with chronic hepatitis C. *European Journal of Clinical Microbiology & Infectious Diseases*. 2011 Jan;30(1):51-7. PMID: 20827497. **Exclusion Reason** -Not Relevant

Zhao, et al. Treatment with peginterferon plus ribavirin vs. interferon plus ribavirin for 48 weeks in Chinese patients with chronic hepatitis C. *International Journal of Clinical Practice*. 2009 Sep;63(9):1334-9. PMID: 19691617. **Exclusion Reason** -Not Relevant

Appendix E. Quality Assessment Methods

Individual studies were rated as “good,” “fair” or “poor” as defined below¹:

For Controlled Trials:

Each criterion was give an assessment of yes, no, or unclear.

1. Was the assignment to the treatment groups really random?
 - Adequate approaches to sequence generation:
 - Computer-generated random numbers
 - Random numbers tables
 - Inferior approaches to sequence generation:
 - Use of alternation, case record numbers, birth dates or week days
 - Randomization reported, but method not stated
 - Not clear or not reported
 - Not randomized
2. Was the treatment allocation concealed?
 - Adequate approaches to concealment of randomization:
 - Centralized or pharmacy-controlled randomization (randomization performed without knowledge of patient characteristics).
 - Serially-numbered identical containers
 - On-site computer based system with a randomization sequence that is not readable until allocation
 - Sealed opaque envelopes
 - Inferior approaches to concealment of randomization:
 - Use of alternation, case record numbers, birth dates or week days
 - Open random numbers lists
 - Serially numbered non- opaque envelopes
 - Not clear or not reported
3. Were the groups similar at baseline in terms of prognostic factors?
4. Were the eligibility criteria specified?
5. Were outcome assessors and/or data analysts blinded to the treatment allocation?
6. Was the care provider blinded?
7. Was the patient kept unaware of the treatment received?
8. Did the article include an intention-to-treat analysis, or provide the data needed to calculate it (i.e., number assigned to each group, number of subjects who finished in each group, and their results)?
9. Did the study maintain comparable groups?
10. Did the article report attrition, crossovers, adherence, and contamination?
11. Is there important differential loss to followup or overall high loss to followup?

For Cohort Studies:

Each criterion was give an assessment of yes, no, or unclear.

1. Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?
2. Were the groups comparable at baseline on key prognostic factors (e.g., by restriction or matching)?
3. Did the study use accurate methods for ascertaining exposures, potential confounders, and outcomes?
4. Were outcome assessors and/or data analysts blinded to treatment?
5. Did the article report attrition?
6. Did the study perform appropriate statistical analyses on potential confounders?
7. Is there important differential loss to followup or overall high loss to followup?
8. Were outcomes pre-specified and defined, and ascertained using accurate methods?

Appendix F. Sustained Virologic Response and Quality of Life

Author, Year Country Quality	Comparison Definition of Sustained Virologic Response	Population Characteristics	Treatments	Results (by clinical outcome)
Arora (2006) ¹ Australia, Europe, New Zealand, North America, and South America Quality: Poor	SVR vs. no SVR SVR=No detectable HCV RNA at end of followup (72 weeks)	Not reported by SVR status Mean age: 43 years Female: 60% Race: Non-white: 14% Advanced fibrosis: 10% Genotype 1: 68% Viral load: 1.1-1.2 x 10 ⁶ copies/ml IVDU: 30% HIV positive: excluded	Pegylated interferon alfa- 2a (24 or 48 weeks)	SVR vs. no SVR, mean difference in change from baseline SF-36 physical function: +4.7 (p<0.05) SF-36 role limitations- physical: +13 (p<0.05) SF-36 bodily pain: +11 (p<0.0001) SF-36 general health: +10 (p<0.0001) SF-36 vitality: +9.3 (p<0.0001) SF-36 social function: +5.1 (p>0.05) SF-36 role limitations- emotional: +7.3 (p>0.05) SF-36 mental health: +3.1 (p>0.05) SF-36 physical component summary: +4.9 (p<0.0001) SF-36 mental component summary: +2.0 (p>0.05) Fatigue Severity Scale, total score: -4.4 (p<0.01) Fatigue Severity Scale, VAS: -10 (p<0.01)

Author, Year Country Quality	Comparison Definition of Sustained Virologic Response	Population Characteristics	Treatments	Results (by clinical outcome)
Bernstein (2002) ² Australia, North America, Europe, Taiwan, New Zealand Quality: Poor	SVR vs. no SVR SVR=No detectable HCV RNA 24 weeks after completion of antiviral therapy	Not reported by SVR status Mean age <=40 years: 41% Female: 32% Race: Non-white: 14% Cirrhosis: 32% Genotype, viral load, HIV infection, IV drug use not reported	Pegylated interferon alfa- 2a or interferon alfa- 2a	SVR vs. no SVR, mean difference in change from baseline SF-36 physical function: +4.6 (p<0.001) SF-36 role limitations- physical: +9.8 (p<0.001) SF-36 bodily pain: +2.9 (p<0.01) SF-36 general health: +9.1 (p<0.001) SF-36 vitality: +9.6 (p<0.001) SF-36 social function: +6.2 (p<0.001) SF-36 role limitations- emotional: +8.4 (p<0.01) SF-36 mental health: +4.6 (p<0.001) SF-36 physical component summary: +2.8 (p<0.001) SF-36 mental component summary: +3.0 (p<0.001) Fatigue Severity Scale, total score: -0.5 (p<0.001) Fatigue Severity Scale, VAS: -11.5 (p<0.001)

Author, Year Country Quality	Comparison Definition of Sustained Virologic Response	Population Characteristics	Treatments	Results (by clinical outcome)
Bini(2006) ³ USA Quality: Poor	SVR vs. no SVR SVR=No detectable HCV RNA 24 weeks after completion of antiviral therapy	Normal ALT and elevated ALT groups, respectively (not reported by SVR status) Mean age: 50 and 49 years Female: 11% and 8% Race: Non-white: 59% and 66% Normal ALT and elevated ALT groups, respectively (not reported by SVR status) Cirrhosis: 11% and 11% Genotype 1: 78% and 78% Viral load >2 x 10 ⁶ copies/ml: 44% and 44% IVDU: 67% and 65% HIV positive: excluded	Interferon alfa- 2b + ribavirin	SVR vs. no SVR, mean difference in change from baseline (normal ALT and elevated ALT subgroups, respectively; p values not reported) SF-36 physical function: +18 and +15 SF-36 role limitations- physical: +22 and +27 SF-36 bodily pain: +3.4 and +9.3 SF-36 general health: +3.0 and +9.9 SF-36 vitality: +12 and +12 SF-36 social function: +9.5 and +11 SF-36 role limitations- emotional: +20 and +18 SF-36 mental health: +14 and +18 SF-36 physical component summary: +3.8 and +7.1 SF-36 mental component summary: +6.0 and +2.1 Positive well being: +14 and -3.1 Sleep somnolence: +11 and +5.4 Health distress: +9.3 and +11 Hepatitis-specific health distress: +5.4 and +2.6 Hepatitis-specific limitations: +13 and +3.8
Bonkovsky (1999) ⁴ USA and Canada Quality: Poor	SVR vs. no SVR SVR=No detectable HCV RNA 24 weeks after completion of antiviral therapy	Not reported by SVR status Mean age: 43 years Female: 27% Race: Non-white: 23% Cirrhosis: 16% Genotype 1: 68% Viral load: Not reported IVDU: 41% HIV positive: excluded	Consensus interferon or interferon alfa- 2b	SVR vs. no SVR, mean difference in change from baseline (values estimated from graph) SF-36 physical function: +6.0 (p<0.05) SF-36 role limitations- physical: +22 (p<0.01) SF-36 bodily pain: -0.5 (p>0.05) SF-36 general health: +7.5 (p<0.01) SF-36 vitality: +9.5 (p<0.05) SF-36 social function: +10 (p<0.05) SF-36 role limitations- emotional: +11 (p>0.05) SF-36 mental health: +4.0 (p>0.05)

Author, Year Country Quality	Comparison Definition of Sustained Virologic Response	Population Characteristics	Treatments	Results (by clinical outcome)
Hassanein (2004) ⁵ Australia, North America, Europe, Taiwan, Brazil, Mexico Quality: Poor	SVR vs. no SVR SVR=No detectable HCV RNA 24 weeks after completion of antiviral therapy	Not reported by SVR status Mean age: 43 years Female: 29% Race: Non-white: 16% Cirrhosis: 13% Genotype 1: 63% Viral load: 5.9 to 6.0 x 10 ⁶ copies/ml IVDU: Not reported HIV positive: excluded	Pegylated interferon alfa- 2a, pegylated interferon alf- 2a +ribavirin, or interferon alfa-2b + ribavirin	SVR vs. no SVR, mean difference in change from baseline SF-36 physical function: +5.5 (p<0.01) SF-36 role limitations- physical: +5.7 (p<0.05) SF-36 bodily pain: +4.1 (p<0.05) SF-36 general health: +8.6 (p<0.01) SF-36 vitality: +6.3 (p >0.05) SF-36 social function: +5.8 (p<0.01) SF-36 role limitations- emotional: +9.3 (p<0.01) SF-36 mental health: +5.0 (p<0.01) SF-36 physical component summary: +2.2 (p<0.01) SF-36 mental component summary: +2.6 (p<0.01) Total fatigue: +3.3 (p<0.01) Fatigue severity: +7.4 (p<0.01)
McHutchison (2001) ⁶ USA Quality: Poor	SVR vs. relapse vs. non-responder SVR=No detectable HCV RNA 24 weeks after completion of antiviral therapy Relapse: Not defined	Mean age: 43 vs. 44 years Female: 42% vs. 32% Race: Non-white: 8% vs. 12% Cirrhosis: Not reported Genotype 1: 43% vs. 81% Viral load >2 million copies/ml: 58% vs. 74% IVDU: Not reported HIV positive: excluded	Interferon alfa- 2a for 24 or 48 weeks, with or without ribavirin	SVR and relapse, mean difference in change from baseline vs. non-responder (p not reported, values estimated from graph) SF-36 physical function: +2.4 and +0.8 SF-36 role limitations- physical: +5.2 and +3.2 SF-36 bodily pain: +1.6 and +1.7 SF-36 general health: +5.2 and +1.5 SF-36 vitality: +4.7 and +2.0 SF-36 social function: +3.1 and +0.4 SF-36 role limitations- emotional: +3.0 and +1.2 SF-36 mental health: +2.0 and 0.0 Sleep somnolence: +3.4 and +2.3 Health distress: +5.4 and +1.2 Hepatitis-related health distress: +5.7 and +1.1 Hepatitis-related limitations: +4.6 and +2.1

Author, Year Country Quality	Comparison Definition of Sustained Virologic Response	Population Characteristics	Treatments	Results (by clinical outcome)
Rasenack (2003) ⁸ Germany, Canada, New Zealand, Spain Quality: Poor	SVR vs. no SVR SVR=No detectable HCV RNA 24 weeks after completion of antiviral therapy	Not reported by SVR status Mean age: 41 years Female: 33% Race: Non-white: 15% Bridging fibrosis/cirrhosis: 13% Injection drug use: 37% Viral load: 7.4 to 8.2 x 10 ⁶ copies/ml HIV positive: Not reported Genotype: Not reported	Pegylated interferon alfa- 2a or interferon alfa- 2a	SVR vs. no SVR, mean difference in change from baseline SF-36 physical function: +5.0 (p=0.001) SF-36 role limitations- physical: +14 (p<0.001) SF-36 bodily pain: +5.2 (p=0.014) SF-36 general health: 12 (p<0.001) SF-36 vitality: +9.4 (p<0.001) SF-36 social function: +5.8 (p=0.005) SF-36 role limitations- emotional: +8.4 (p=0.02) SF-36 mental health: +5.3 (p=0.001) SF-36 physical component summary: +3.2 (p<0.001) SF-36 mental component summary: +2.9 (p=0.005) Fatigue Severity Scale, total score: -0.5 (p=0.001) Fatigue Severity Scale, VAS: -8.4 (p<0.001)
Ware (1999) ⁹ Australia, North America, and Europe Quality: Poor	SVR vs. no SVR SVR=No detectable HCV RNA 24 weeks after completion of antiviral therapy Overall response vs. no overall response Overall response=SVR + Knodell histology activity index inflammation score improved by 2 U or more	Not reported by response status Mean age: 43 years Female: 35% Race: Non-white: 6.4% Bridging fibrosis/cirrhosis: 18% Injection drug use: 40% Viral load: 4.8 to 5.2 x 10 ⁶ copies/ml HIV positive: Excluded Genotype 1: 56%	Interferon alfa- 2b or interferon alfa- 2b + ribavirin	SVR vs. no SVR and overall response vs. no overall response, mean difference in change from baseline (p values not reported) SF-36 physical function: +2.6 and +3.5 SF-36 role limitations- physical: +1.5 and +3.1 SF-36 bodily pain: +0.45 and +1.6 SF-36 general health: +3.3 and +3.5 SF-36 vitality: +2.2 and +2.8 SF-36 social function: +3.4 and +4.3 SF-36 role limitations- emotional: -0.02 and +1.1 SF-36 mental health: +1.3 and +0.62 Sleep: +0.02 and +1.2 Health distress: +7.6 and +6.2 Chronic hepatitis C health distress: +11.5 and +11.3 Chronic hepatitis C limitations: +5.3 and +7.5

Abbreviations: ALT, alanine aminotransferase; HCV, hepatitis C virus; SVR, sustained virologic response.

Appendix F References

1. Arora S, O'Brien C, Zeuzem S, et al. Treatment of chronic hepatitis C patients with persistently normal alanine aminotransferase levels with the combination of peginterferon alpha-2a (40 kDa) plus ribavirin: impact on health-related quality of life. *Journal of Gastroenterology & Hepatology*. 2006 Feb;21(2):406-12. PMID: 16509866.
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Appendix G. Overall Strength of Evidence

Key Question	Number of studies	Quality (Good, Fair, Poor)	Consistency (Consistent or Inconsistent)	Directness (Direct or indirect)	Precision (Precise or imprecise)	Number of subjects	Strength of Evidence
1a. What is the comparative effectiveness of antiviral treatment in improving health outcomes in patients with HCV infection?							
Long-term clinical outcomes	0 randomized trials	No evidence	No evidence	No evidence	No evidence	No evidence	Insufficient
Short-term clinical outcomes	3 randomized trials (mortality) 2 randomized trials (quality of life)	Fair	Consistent	Direct	Imprecise		Insufficient
1b. How does the comparative effectiveness of antiviral treatment for health outcomes vary according to patient subgroup characteristics, including but not limited to HCV genotype, race, sex, disease severity or genetic markers?							
Any clinical outcome	0 randomized trials	No evidence	No evidence	No evidence	No evidence	No evidence	Insufficient
2a. What is the comparative effectiveness of antiviral treatments in improving intermediate outcomes, such as the rate of viremia, aminotransaminase levels, and histologic changes?							
Dual therapy with pegylated interferon plus ribavirin	9 randomized trials	Fair	Consistent	Direct	Precise		Moderate

Key Question	Number of studies	Quality (Good, Fair, Poor)	Consistency (Consistent or Inconsistent)	Directness (Direct or indirect)	Precision (Precise or imprecise)	Number of subjects	Strength of Evidence
Duration effects (genotype 2 or 3)	10 randomized trials	Fair	Consistent	Direct	Precise		Moderate
Dose effects (genotype 2 or 3), pegylated interferon	5 randomized trials	Fair	Consistent	Direct	Precise		Moderate
Dose effects (genotype 2 or 3), ribavirin	4 randomized trials	Fair	Some inconsistency	Direct	Some imprecision		Moderate
Triple therapy with boceprevir	2 randomized trials	Fair	Consistent	Direct	Some imprecision		Moderate
Triple therapy with telaprevir	5 randomized trials	Fair	Consistent	Direct	Some imprecision		Moderate
2b. How does the comparative effectiveness of antiviral treatment for intermediate outcomes vary according to patient subgroup characteristics, including but not limited to HCV genotype, race, sex, disease severity or genetic markers?							
Dual therapy with pegylated interferon plus ribavirin	5 randomized trials	Fair	Consistent	Direct	Precise		Moderate
Triple therapy with boceprevir	2 randomized trials	Fair	Consistent	Direct	Some imprecision		Moderate
Triple therapy with telaprevir	1 randomized trial	Fair	One study	Direct	Imprecise		Low
3a. What are the comparative harms (including intolerance to treatment) associated with antiviral treatment?							
Dual therapy with pegylated interferon plus ribavirin	6 randomized trials	Fair	Consistent	Direct	Precise		Moderate
Triple therapy with boceprevir	2 randomized trials	Fair	Consistent	Direct	Some imprecision		Moderate
Triple therapy with telaprevir	5 randomized trials	Fair	Consistent	Direct	Some imprecision		Moderate

Key Question	Number of studies	Quality (Good, Fair, Poor)	Consistency (Consistent or Inconsistent)	Directness (Direct or indirect)	Precision (Precise or imprecise)	Number of subjects	Strength of Evidence
3b. Do these harms differ according to patient subgroup characteristics, including HCV genotype, race, sex, disease severity or genetic markers?							
Dual therapy with pegylated interferon plus ribavirin	3 randomized trials	Fair	Consistent	Indirect (no study stratified harms by patient subgroups)	Some imprecision		Insufficient
Protease inhibitors	0 randomized trials	No evidence	No evidence	No evidence	No evidence	No evidence	Insufficient
4. Have improvements in intermediate outcomes (viremia, liver function tests, histologic changes) been shown to reduce the risk or rates of health outcomes from HCV infection?							
Mortality and long-term hepatic complications	8 cohort studies	Fair	Consistent	Direct	Precise		Moderate
Short-term quality of life	9 cohort studies	Poor	Consistent	Direct	Precise		Low

Appendix H. Evidence Tables and Quality Ratings

Key Questions 2a - 3b

Evidence Table 1. Pegylated Interferon alpha 2a compared with alpha 2b (head-to-head)

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race
<p>Ascione, 2010¹ Liver Unit of Cardarelli Hospital - Napoli, Italy</p> <p>Pegylated Interferon alfa-2a plus Ribavirin is more effective than Pegylated Interferon alfa-2b plus Ribavirin for treating chronic HCV Infection</p> <p>Overall Quality: Fair</p>	<p>A: Pegylated interferon alpha- 2a 180 µg/week for 24 or 48 weeks (genotype 2/3 and 1/4 respectively)</p> <p>B: Genotype 2/3: Pegylated interferon alpha- 2b 1.5 µg/kg/week for 24 or 48 weeks (genotype 2/3 and 1/4 respectively)</p>	<p>A: 800-1200 mg daily for 24 or 48 weeks (genotype 2/3 and 1/4 respectively)</p> <p>B: 800-1200 mg daily for 24 or 48 weeks (genotype 2/3 and 1/4 respectively)</p>	None	<p>Detectable serum HCV RNA level ALT level 1.5x the upper limit of normal for 6 months Liver biopsy within 12 months of starting treatment graded according to Scheuer's criteria (2002) Negative pregnancy test result/using Contraceptive methods during therapy and for 6 months after the end of treatment No alcohol use 6 months pre- enrollment Cirrhosis on basis of clinical/lab testing liver-spleen ultrasonography Upper gastrointestinal endoscopy for patients who did not have a biopsy</p>	<p>Hemoglobin level <120 g/L Neutrophil count <1.5x10⁹/L or a platelet count <70x10⁹/L Abnormal serum creatinine level; Hepatitis B surface antigen positive HIV+ Any other cause of liver disease History of liver decompensation Clinically relevant depression or any other Psychiatric disease Cancer Severe cardiac/pulmonary/renal disease Uncontrolled diabetes or severe hypertension with vascular complications including Retinopathy</p>	408/322/320/320	<p>A vs. B Age (mean): 51 vs. 49 years Female: 49% vs. 61% Race: Not reported</p> <p>Cirrhosis: 21% vs. 16%⁴ (overall) Minimal or no fibrosis: Not reported Elevated transaminases: 100% (mean ALT 2.4 vs. 2.4 upper limit of normal)</p>

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race
Bruno, 2004 ² Italy Viral dynamics and pharmacokinetics of Pegylated interferon alpha-2a and Pegylated interferon alpha-2b in naïve patients with chronic hepatitis C; a randomized, controlled study Overall Quality: Poor	A. Pegylated interferon alpha-2a 180 mcg/week for 12 weeks B. Pegylated interferon alpha-2b 1.0 mcg/week for 12 weeks	A. 1000-1200mg mg/day depending of body weight for 12 weeks (≤ 75 kg / >75 kg) B. 1000-1200mg mg/day depending of body weight for 12 weeks (<75 kg / >75 kg)	None	Treatment-naïve HCV-RNA ≥ 2000 / mL ALT $>$ upper limit of normal within 6 months of study Liver biopsy consistent with chronic hepatitis	Neutrophils <1500 /mL3 Platelet count $< 90K$ mL3 Hemoglobin <12 g/dL in women and <13 g/dL in men Creatinine level >1.5 times upper limit of normal Co infection with HIV Decompensated liver disease Poorly controlled psychiatric disease Alcohol or drug abuse within year Substantial coexisting medical conditions	NR/NR/22/22	A vs. B Age mean: 47 vs. 40 Female: 30% vs. 25% Non-White: 10% vs. 0%
DiBisceglie, 2007 ³ United States Early virologic response after Pegylated interferon alpha-2a plus ribavirin or Pegylated interferon alpha-2b plus ribavirin treatment in patients with chronic hepatitis C Overall Quality: Fair	A. Pegylated interferon alpha-2a 180 mcg weekly for 12 weeks B. Pegylated interferon alpha-2b 1.5 mcg/kg weekly for 12 weeks	A. 1000-1200mg mg/day depending of body weight for 12 weeks (≤ 75 kg / >75 kg) B. 1000-1200mg mg/day depending of body weight for 12 weeks (<75 kg / >75 kg)	None	Treatment-naïve patients Chronic HCV genotype 1 infection Age 18 years or older HCV RNA $>800K$ IU/mL	HBV HIV co infection History of other chronic liver disease Decompensated liver disease or Child-Pugh score >6 Alcohol or drug abuse within year Pregnant or breastfeeding women and male partners Neutrophils <1500 /mL3 Platelet count $<90K$ /mL3 Hemoglobin <12 g/dL in women and <13 g/dL in men Creatinine >1.5 times upper limit of normal History of server psychiatric, immunologically mediated, cardiac, or chronic pulmonary disease	NR/NR/385/380	A vs. B Age mean: 47 vs. 48 Female: 36% vs. 29% Non-White: 31% vs. 28%

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race
Escudero, 2008 ⁴ Valencia, Spain (outpatient clinic - Service of Hepatology of University Hospital Clinic) Pegylated alpha- interferon-2a plus ribavirin compared with pegylated alpha- interferon-2b plus ribavirin for initial treatment of chronic HCV: prospective, non-randomized study Overall Quality: Poor	A: Pegylated interferon alpha- 2a 180 µg/week for 24 or 48 weeks (genotype 2/3 and 1/4 respectively) B: Genotype 2/3: Pegylated interferon alpha- 2b 1.5 µg/kg/week for 24 or 48 weeks (genotype 2/3 and 1/4 respectively)	A: 800-1200 mg daily for 24 or 48 weeks (genotype 2/3 and 1/4 respectively) B: 800-1200 mg daily for 24 or 48 weeks (genotype 2/3 and 1/4 respectively)	None	Treatment naïve patients 18 years and older Sero-positive Genotype-RNA Evidence of Genotype 1,2,3 or 4 infection Serum Genotype RNA concentration > 30 IU/mL ALT above upper limit of normal Diagnostic liver biopsy done within 6 months prior to enrollment	HIV infection, Hepatitis B infection Autoimmune disease Autoimmune hepatitis, decompensated Liver disease hematological conditions Decompensated diabetes Thyroid disease (poorly controlled) History of Severe Psychiatric Disease, Alcohol or Drug dependence within 1 year prior to entry into study Subjects recruited in actual conditions of daily practice in outpatient clinic	NR/NR/183/183	A vs. B Age: mean (SD): 44.4(9.34) vs. 43.6(9.62) years Male - 64/91(70%) vs. 56/92 (61%) Race: N/R

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race
Kamal, 2011 ³ Egypt Enhanced efficacy of pegylated interferon alpha-2a over pegylated interferon and ribavirin in chronic hepatitis C genotype 4A randomized trial and quality of life analysis Overall Quality: Fair	A. Pegylated interferon alfa- 2a 180 mcg/week for 48 weeks B. Pegylated interferon alfa- 2b 1.5 mcg/kg/week for 48 weeks	A. Ribavirin 1000-1200 mg daily (<75 kg / >75 kg) for 48 weeks B. Ribavirin 1000-1200 mg daily(<75 kg / >75 kg) for 48 weeks	None	Treatment naïve Age 18-60 years HCV genotype 4 ALT at least twice the upper limit of normal during the 6 months prior Detectable anti-HCV antibodies Detectable HCV RNA Histologic evidence of chronic hepatitis C in liver biopsy within preceding year	Evidence of other liver disease Co-infection with HIV, hepatitis A, B, or schistosomiasis Leucocytes <3000/mm ³ Neutrophils <1500/mm ³ Hemoglobin <12 g/dl for women or <13 g/dl for men Thrombocytopenia <90K/mm ³ Creatinine >1.5x upper limit of normal Organ transplantation Cancer Severe cardiac or pulmonary disease Unstable thyroid dysfunction Severe depression or psychiatric disorder Active substance abuse Pregnancy Breast feeding BMI>30Kg/m ² Known sensitivity to drugs tested Determined by investigators to be unreliable or non-compliant	226/217/217/217	A vs. B Age: 42 vs. 41 Female: 46% vs. 56% Race: NR (Egyptian centers)

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race
<p>Khan, 2007⁶ Pakistan</p> <p>Pegylated interferon alfa-2a ribavirin vs. Pegylated interferon alfa-2b/ribavirin combination therapy in chronic hepatitis C genotype 3</p> <p>Overall Quality: Not Assessed</p>	<p>A: Pegylated interferon alfa-2a 180 mcg/week for 24 weeks B: Pegylated interferon alfa-2b 1.0 mcg/week for 24 weeks</p>	<p>A: 800 mg/day for 24 weeks B: 800 mg/day for 24 weeks</p>	None	NR	NR	NR/NR/NR/66	NR
<p>Magni, 2009⁷</p> <p>Antiviral activity and tolerability between pegylated interferon alfa-2a and alfa-2b in naïve patients with chronic hepatitis C: results of a prospective monocentric randomized trial</p> <p>Overall Quality: Not Assessed</p>	<p>A: Pegylated interferon alfa-2a 180 mcg/week for 24-48 weeks based on genotype B: Pegylated interferon alfa-2b 1.0 mcg/week for 24-48 weeks based on genotype</p>	<p>A: 10.5 mg/kg for 24-48 weeks based on genotype B: 10.5 mg/kg for 24-48 weeks based on genotype</p>	None	NR	NR	NR/NR/NR/218	NR

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race
McHutchison, 2008 ⁸ US Individualized Dosing Efficacy vs. Flat Dosing to Assess Optimal Pegylated Interferon Therapy (IDEAL) Overall Quality: Fair	A. Pegylated interferon alfa- 2b 1.0 mcg/kg/week for 48 weeks. B. Pegylated interferon alfa- 2b 1.5 cg/kg/week for 48 weeks. C. Pegylated interferon alfa- 2a 180 mcg/week for 48 weeks. Discontinued if HCV RNA detectable and not decreased by 2 log IU from baseline at 12 weeks or HCV RNA detectable at 24 weeks	A. Weight- based 800-1400 mg daily for 48 weeks B. Weight- based 800-1400 mg daily for 48 weeks C. 1000 mg (<75 kg) - 1200 mg (≥75 kg) daily for 48 weeks Weight-based dosing ≤ 65 kg: 800 mg daily 66 - 85kg: 1000 mg daily 86-105kg: 1200 mg daily 106 -125kg: 1400 mg daily Discontinued if HCV RNA detectable and not decreased by 2 log IU from baseline at 12 weeks or HCV RNA detectable at 24 weeks	None	Treatment-naïve Ages 18 years or older Chronic HCV genotype 1 infection Detectable HCV RNA level Neutrophil count ≥ 1500 /mm ³ Platelets ≥ 80,000 /mm ³ Hemoglobin ≥ 12 g/dL for women or 13 g/dL for men	HIV HBV Other liver disease Poorly controlled diabetes Weight >125 kg Severe depression Severe psychiatric disorder Active substance abuse	4469/3431/3083/3070	A vs. B vs. C Age mean: 48 vs. 48 vs. 48 Female: 40% vs. 40% vs. 41% Non-White: 29% vs. 28% vs. 29%

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race
Rumi, 2010 ⁹ University of Milan, Italy Clinical Advances in Liver, Pancreas, and Biliary Tract (MIST Study) - Randomized Study of Pegylated interferon-alpha-2a Plus Ribavirin vs. Pegylated interferon- alpha-2b plus Ribavirin in Chronic Hepatitis C Overall Quality: Fair	Genotype 1/4: A. Pegylated interferon alfa- 2a 180 mcg/week for 48 weeks B. Pegylated interferon alfa- 2b 1.5 mcg/kg/week for 48 weeks Genotype 2/3: A. Pegylated interferon alfa- 2a 180 mcg/week for 24 weeks B. Pegylated interferon alfa- 2b 1.5 mcg/kg/week for 24 weeks	Genotype 1/4: A. 1000-1200 mg/day for 48 weeks B. 800-1200 mg/day for 48 weeks Genotype 2/3: A. 800 mg/day for 24 weeks B. 800-1200 mg/day for 24 weeks	None	Treatment naïve patients 18-70 years old with serum HCV-RNA Higher than normal ALT activity, and Diagnostic Liver Biopsy done within 24 months prior to enrollment	Persistently normal ALT Hemoglobin \leq 12g/dL in women and \leq 13g/dL in men White Blood Cell count \leq 2.5x10 ³ /mm ³ Neutrophil \leq 1.5x10 ³ /mm ³ Platelet count \leq 75x10 ³ /mm ³ Serum creatinine level >1.5x upper limit of normal Liver disease (any other) HIV co infection Autoimmune diseases Contraindications to Interferon and Ribavirin	473/447/447/431	A vs. B Age: Mean (SD): 51.6(12.0) vs. 52.8(12.0) years Male - 128/212 (60.4%) vs. 120/219 (54.8%) Race: N/R
Silva, 2006 ¹⁰ Argentina, Mexico, Germany A randomized trial to compare the pharmacokinetics, pharmacodynamic, and antiviral effects of pegylated interferon alfa-2b and Pegylated interferon alfa-2b in patients with chronic hepatitis C Overall Quality: Poor	A. Pegylated interferon alfa- 2a 180 mcg/week for 8 weeks B. Pegylated interferon alfa- 2b 1.5 mcg/kg/week for 8 weeks After study patients were offered full course of weight-based pegylated interferon alfa- 2b and ribavirin	A. 13 mcg/kg in divided dose (BID) after 4th week B. 13 mcg/kg in divided dose (BID) after 4th week	None	Treatment-naïve patients Genotype 1a or 1b Ages 18-65 years HCV-RNA $>6 \times 10^5$ IU/mL ALT/AST \leq 10x the upper limit of normal Normal hemoglobin White-blood cells \geq cells/mcg L, Neutrophils \geq 1500 /mcg L Platelets \geq 100K/mcg L	Liver disease of other cause HIV Hemoglobinopathy Hemophilia Severe psychiatric disease Poorly controlled diabetes mellitus Significant ischemic heart disease Chronic obstructive pulmonary disease Active immune disease	NR/NR/32/32	A vs. B Age mean: 46 vs. 48 Female: 50% vs. 44% Non-White: 11% vs. 22%

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race
Yenice, 2006 ¹¹ Okmeydani Research & Training Hospital (Istanbul, Turkey) The efficacy of pegylated interferon alpha 2a or 2b plus ribavirin in chronic hepatitis C patients Overall Quality: Poor	A: Pegylated interferon alpha- 2a 180µg/week for 48 weeks B: Pegylated- interferon alpha- 2b 1.5µg/kg for 48 weeks	A: 800-1200 mg daily for 48 weeks B: 800-1200 mg daily for 48 weeks	None	Anti HCV+, normal and/or elevated serum transaminase levels HCV+ RNA At least stage 1 fibrosis according to Knodell Scoring System on liver biopsy Hemoglobin 12 g/dl for women and 13 g/dl for men Leukocyte 3x10 ³ /mm ³ Neutrophils 1.5x10 ³ /mm ³ Platelets 100x10 ³ /mm ³ Normal range: bilirubin, albumin, and creatinine No positive test results for hepatitis B, hepatitis D, or human immunodeficiency virus antibodies or antigens.	Abdominal ascites History of bleeding from esophageal varicosities Hepatocellular carcinoma (HCC) or other malignant disorders Use of antidepressants or tranquilizing agents for more than 3 months History of depression, psychosis or suicide attempt Significant cardiac or pulmonary problems Hepatitis B or D Human Immunodeficiency Virus or antibodies (HIV)	NR/80/80/74	A vs. B Age - Mean: 48.2 vs. 50.8 Male - 24/37(65%) vs. 27/37(73%) Race: N/R

Author, Year Country Study Name Quality	Genotype Severity of Liver Disease Proportion Treatment-Naïve	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
<p>Ascione, 2010¹ Liver Unit of Cardarelli Hospital – Napoli, Italy</p> <p>Pegylated Interferon alfa-2a plus Ribavirin is more effective than Pegylated Interferon alfa-2b plus Ribavirin for treating chronic HCV Infection</p> <p>Overall Quality: Fair</p>	<p>A vs. B Genotype 1/4 - 93/160(58%) vs. 93/160(58%) Genotype 2/3 - 67/160(42%) vs. 67/160(42%)</p> <p>Severity by liver biopsygraded via "simple system" (Scheuer et al 2002): Chronic Hepatitis: 127/160(79.4%) vs. 134/160(83.7%) Cirrhosis (with biopsy): 33/160(20.6%) vs. 26/160(16.3%) Cirrhosis (without biopsy): 12/160(7.5%) vs. 7/160(4.4%)</p> <p>100% treatment naïve</p>	<p>Followup at 3 and 6 months post- treatment (12 and 24 weeks)</p>	<p>A vs. B ETR: 134/160(83.8%) vs. 103/160(64.4%), p=<.0001</p> <p>SVR: 110/160(68.8%) vs. 87/160(54.4%), p=.008</p>	<p>NR</p>	<p>A vs. B Genotype 1/4 - 51/93(54.8%) vs. 37/93(39.8%), p=.04 Genotype 2/3 - 59/67(88.1%) vs. 50/67(74.6%), p=.046 Genotype 2 - 45/49(91.8%) vs. 38/50(76.0%), p=.062 Genotype 3 - 14/18(77.8%) vs. 12/17(70.6%), p=.92</p> <p>Chronic hepatitis - 96/127(75.6%) vs. 75/134(55.9%), p=.005 Cirrhosis - 14/33(42.4%) vs. 12/26(46.1%), p=.774</p> <p>SVR by baseline Genotype RNA level in serum, no./total (%): <500,000 IU/mL - 52/76(68.4%) vs. 44/67(65.7%), p=.727 >500,000 IU/mL - 58/84(69.0%) vs. 43/93(46.2%), p=.002</p>	<p>NR</p>	<p>A vs. B Overall Withdrawals: 4/160(3%) vs. 22/160(14%) Withdrawals due to adverse events; 4/160 (3%) vs. 17/160 (11%) Deaths: none Severe Adverse Events: none</p> <p>Fatigue - 93/160(58%) vs. 86/160(54%) Arthralgia - 48/160(30%) vs. 66/160(41%) Irritability - 53/160(33%) vs. 49/160(31%) Decreased appetite - 30/160(19%) vs. 34/160(21%) Fever - 30/160(19%) vs. 75/160(47%) Pruritus - 27/160(17%) vs. 24/160(15%) Headache - 25/160(16%) vs. 28/160(18%) Cough - 20/160(13%) vs. 20/160(13%) Myalgia - 23/160(14%) vs. 30/160(19%) Dermatitis - 19/160(12%) vs. 9/160(6%) Nausea - 14/160(9%) vs. 15/160(9%) Dyspnea - 13/160(8%) vs. 19/160(12%)</p>	<p>Cardarelli Hospital, Napoli, Italy</p>

Author, Year Country Study Name Quality	Genotype Severity of Liver Disease Proportion Treatment-Naïve	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Ascione, 2010 ¹ Liver Unit of Cardarelli Hospital - Napoli, Italy Continued							Thyroid - 12/160(8%) vs. 9/160(6%) Insomnia - 11/160(7%) vs. 17/160(11%) Alopecia - 9/160(6%) vs. 22/160(14%) Depression - 11/160(7%) vs. 9/160(6%) Dose modification due to: Anemia - 30/160(19%) vs. 30/160(19%) Neutropenia - 4/160(3%) vs. 4/160(3%) Thrombocytopenia - 7/160(4%) vs. 6/160(4%)	
Bruno, 2004 ² Italy Viral dynamics and pharmacokinetics of Pegylated interferon alpha-2a and Pegylated interferon alpha-2b in naïve patients with chronic hepatitis C; a randomized, controlled study Overall Quality: Poor	A vs. B Genotype 1: 70% vs. 50% Treatment-naïve: all Cirrhosis/transition to cirrhosis: 20% vs. 16% HCV-RNA mean (log): 5.8 vs. 5.6	12 weeks	NA	NA	NA	NA	NR	Hoffman- LaRoche

Author, Year Country Study Name Quality	Genotype Severity of Liver Disease Proportion Treatment-Naïve	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
DiBisceglie, 2007 ³ United States Early virologic response after Pegylated interferon alpha-2a plus ribavirin or Pegylated interferon alpha-2b plus ribavirin treatment in patients with chronic hepatitis C Overall Quality: Fair	A vs. B Genotype 1: all Treatment-naïve: all Cirrhotic: 14.8% vs. 15.2% HCV RNA mean (log): 6.5 vs. 6.5	12 weeks	NA	NA	NA	NA	A vs. B Overall withdrawals: 18/189 (10%) vs. 27/191 (14%); p=NS Withdrawals for adverse events: 2/189 (1%) vs. 11/191 (6%); p=NS Serious adverse events: NR Deaths: NR Fatigue: 132/187 (71%) vs. 137/190 (72%); p=NS Headache: 105/187 (56%) vs. 112/190 (59%); p=NS Nausea: 77/187 (41%) vs. 85/190 (45%); p=NS Chills: 46/187 (25%) vs. 79/190 (42%); p<0.001 Irritability: 58/187 (31%) vs. 57/190 (30%); p=NS Fever: 38/187 (20%) vs. 62/190 (33%); p=NS Depression: 46/187 (25%) vs. 46/190 (24%); p=NS Arthralgia: 45/187 (24%) vs. 44/190 (23%); p=NS Dizziness: 39/187 (21%) vs. 48/190 (25%); p=NS Influenza-like illness: 34/187 (18%) vs. 44/190 (23%); p=NS Diarrhea: 33/187 (18%) vs. 39/190 (21%); p=NS Decreased appetite: 28/187 (15%) vs. 40/190 (21%); p=NS	Roche

Author, Year Country Study Name Quality	Genotype Severity of Liver Disease Proportion Treatment-Naïve	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
DiBisceglie, 2007 United States Continued							Rash: 27/187 (14%) vs. 39/190 (21%); p=NS Myalgia: 31/187 (17%) vs. 34/190 (18%); p=NS Vomiting: 26/187 (14%) vs. 38/190 (20%); p=NS Injection-site erythema: 25/187 (13%) vs. 38/190 (20%); p=NS Anemia: 20/187 (11%) vs. 22/190 (12%); p=NS Dysgeusia: 17/187 (9%) vs. 21/190 (11%); p=NS	

Author, Year Country Study Name Quality	Genotype Severity of Liver Disease Proportion Treatment-Naïve	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Escudero, 2008 ⁴ Valencia, Spain (outpatient clinic - Service of Hepatology of University Hospital Clinic) Pegylated alpha- interferon-2a plus ribavirin compared with pegylated alpha- interferon-2b plus ribavirin for initial treatment of chronic HCV: prospective, non-randomized study Overall Quality: Poor	A vs. B Genotype 1- 59/91(65%) vs. 58/92(64%) Genotype 2- 5/91(6%) vs. 4/92(4%) Genotype 3- 13/91(14%) vs. 23/92(25%) Genotype 4- 12/91(13%) vs. 6/92(7%) Genotype 5- 2/91(2%) vs. 1/92(1%) Scale by Batts & Ludwig, 1995: Grade - mean (SD): 2.1(.81) vs. 2.1(.91) Stage - mean (SD): 2.1(.98) vs. 2.0(1.07) Steatosis - 30/91(34%) vs. 43/92(46.7%) HCVRNA mean(log IU/mL): 5.9 vs. 5.8 100% Treatment- naïve	Followup at 24 weeks post- treatment	A vs. B ETR: N/R SVR: 60/91(65.9%) vs. 57/92(62%)	NR	A vs. B Variables significantly associated with response to antiviral therapy: Genotype (odds ratio [OR] = 0.076, 95% confidence interval [CI] 0.029 – 0.198, P = 0.000) Presence of steatosis in the liver biopsy (OR = 2.799, 95% CI 1.362–5.755, p=.005). Genotype 1: steatosis was the only variable significantly associated with response to antiviral treatment: (OR = 2.450, 95% CI 1.126–5.332, p=.024) SVR: Genotype 1 - 30/59 (50.8%) vs. 27/58(46.6%) Genotype 2/3 - 17/18 (95%) vs. 24/27(89.3%) Genotype 4 - 11/12 (91.7%) vs. 5/6(83.3%)	NR	A vs. B Overall withdrawals - 22/91(24%) vs. 28/92(30%) Deaths - N/R Dermatological symptoms: 5/183(3%) Severe neutropenia (<0.5 x 10 ⁹ cells/L): 3/183(2%) Depression-related events: 2/183(1%) Anemia (hemoglobin, <10.0 g/dL): 2/183(1%) Thrombocytopenia (<50 x 10 ⁹ cells/L): 2/183(2%) Hypothyroidism: 2/183(1%) Tachyarrhythmia: 1/183(0.5%) Poor tolerability with various adverse events: 5/183(3%) Dose modifications because of neutropenia: 8/91(8%) vs. 7/92(8%)	Internal funding

Author, Year Country Study Name Quality	Genotype Severity of Liver Disease Proportion Treatment-Naïve	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Kamal, 2011 ⁵ Egypt Enhanced efficacy of pegylated interferon alpha-2a over pegylated interferon and ribavirin in chronic hepatitis C genotype 4A randomized trial and quality of life analysis Overall Quality: Fair	A vs. B Genotype 1: 0% Genotype 4: 100% Grade 3 Steatosis: 38% vs. 37%	24 weeks after treatment completion	A vs. B SVR: 77/109 (70.6%) vs. 59/108 (54.6%); p=0.0172 SF-6D (During Treatment): 0.735 vs. 0.730; p=0.8067 SF-6D (after treatment): 0.769 vs. 0.737; =0.04 Chronic Liver Disease Health Survey Questionnaire (CLDQ) (during treatment): 5.3 vs. 5.0; p=0.16 CLDQ (after treatment): 5.9 vs. 5.5; p=0.02	NR	NR	NR	A vs. B Overall withdrawals: 2/109 (2%) vs. 1/108 (1%); p=ns Withdrawals for adverse events: 1/109 (1%) vs. 1/108 (1%); p=ns Mild adverse events: 54/109 (50%) vs. 40/108 (37%); p=ns Moderate adverse events; 18/109 (17%) vs. 12/108 (11%); p=ns Severe adverse events; 4/109 (4%) vs. 3/108 (3%); p=ns	Ain Shams University
Khan, 2007 ⁶ Pakistan Pegylated interferon alfa-2a ribavirin vs. Pegylated interferon alfa-2b/ribavirin combination therapy in chronic hepatitis C genotype 3 Overall Quality: Not Assessed	Genotype 1: 0% Genotype 4: 100%	24 weeks after end of treatment	A vs. B SVR: 26/33 (79%) vs. 27/33 (82%); p=ns	NR	NR	NR	A vs. B Overall withdrawals: 1/33 (3%) vs. 1/33 (3%)	NR

Author, Year Country Study Name Quality	Genotype Severity of Liver Disease Proportion Treatment-Naïve	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Magni, 2009 ⁷ Antiviral activity and tolerability between pegylated interferon alfa-2a and alfa-2b in naïve patients with chronic hepatitis C: results of a prospective monocentric randomized trial Overall Quality: Not Assessed	A vs. B Genotype 1/4: 61% vs. 51% Genotype 2/3: 39% vs. 49%	24 weeks after end of treatment	A vs. B SVR: 68/100 (68%) vs. 79/118 (67%); p=ns	NR	A vs. B Genotype 1/4: 36/58 (62%) vs. 34/55 (62%); p=ns Genotype 2/3: 32/37 (87%) vs. 45/52 (87%); p=ns	NR	A vs. B Withdrawals due to adverse events: 5% vs. 6.8%; p=NS	NR

Author, Year Country Study Name Quality	Genotype Severity of Liver Disease Proportion Treatment-Naïve	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
McHutchison, 2008 ⁸ US Individualized Dosing Efficacy vs. Flat Dosing to Assess Optimal Pegylated Interferon Therapy (IDEAL) Overall Quality: Fair	A vs. B vs. C Genotype 1: all Metavir fibrosis score 3 or 4: 11% vs. 11% vs. 11% HCV-RNA _≥ 600K: 82% vs. 82% vs. 82% Treatment-naïve: all	24 weeks after treatment completion	A vs. B vs. C ETR: 500/1016 (49%) vs. 542/1016 (53%) vs. 667/1035 (64%); (p=0.04 for A vs. B, p<0.001 for B vs. C) SVR: 386/1016 (38%) vs. 406/1019 (40%) vs. 423/1035 (41%); (p=0.20 for A vs. B, p=0.57 for B vs. C)	A vs. B vs. C (p-values from interaction models given) Black: 31/187 (17%) vs. 42/183 (23%) vs. 52/200 (26%); White: 316/362 (36%) vs. 319/732 (44%) vs. 324/733 (44%); (p=0.18 for A vs. B, p=0.62 for B vs. C) Female: 147/409 (36%) vs. 180/406 (44%) vs. 177/422 (42%) Male: 239/607 (39%) vs. 226/613 (37%) vs. 246/613 (40%); (p=0.01 for A vs. B, p=0.20 for B vs. C)	A vs. B vs. C Metavir fibrosis score F3 or F4: 32/107 (30%) vs. 23/111 (21%) vs. 26/110 (24%) Metavir fibrosis score F0-F2: 335/864 (39%) vs. 366/869 (42%) vs. 376/862 (44%); (p=0.06 for A vs. B, p=0.75 for B vs. C) Baseline HCV RNA >600K IU/mL: 277/830 (33%) vs. 295/836 (35%) vs. 303/852 (36%) Baseline HCV RNA<600K IU/mL: 109/186 (59%) vs. 111/183 (61%) vs. 120/183 (66%); (p=0.99 for A vs. B, p=0.41 for B vs. C) Weight <75 kg: 211/555 (38%) vs. 219/564 (39%) vs. 264/605 (44%) Weight >75 kg: 175/461 (38%) vs. 187/455 (41%) vs. 159/430 (37%); (weight in kg as continuous variable p=0.94 for A vs. B; p=0.39 for B vs. C)	NR	A vs. B vs. C Overall withdrawals: 523/1016 (52%) vs. 479/1019 (47%) vs. 414/1035 (40%); (p=0.04 for A vs. B, p=0.001 for B vs. C, p<0.001 for A vs. C) Withdrawals for adverse events: 98/1016 (10%) vs. 129/1019 (13%) vs. 135/1035 (13%); (p=0.03 for A vs. B, p=0.80 for B vs. C, p<0.001 for A vs. C) Deaths: 1/1016 (<1%) vs. 5/1019 (<1%) vs. 6/1035 (<1%); (p=NS) Serious adverse event: 94/1016 (9%) vs. 88/1019 (9%) vs. 121/1035 (12%); (p=0.63 for A vs. B, p=0.02 for B vs. C, p=0.07 for A vs. C) Fatigue: 676/1016 (67%) vs. 672/1016 (66%) vs. 656/1035 (63%); (p=NS) Headache: 486/1016 (48%) vs. 508/1019 (50%) vs. 438/1035 (42%); (p=0.36 for A vs. B, p=0.001 for B vs. C, p=0.01 for A vs. C) Nausea: 377/1016 (37%) vs. 433/1019 (43%) vs. 377/1035 (36%); (p=0.01 for A vs. B, p=0.005 for B vs. C, p=0.75 for A vs. C)	Schering- Plough

Author, Year Country Study Name Quality	Genotype Severity of Liver Disease Proportion Treatment-Naïve	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
McHutchison, 2008 ⁸ US Continued				Age ≤40: 72/154 (47%) vs. 74/140 (53%) vs. 91/163 (56%) Age >40: 314/862 (36%) vs. 332/879 (38%) vs. 332/872 (38%); (p=0.46 for A vs. B, p=0.67 for B vs. C)			Pyrexia: 311/1016 (33%) vs. 356/1019 (35%) vs. 237/1035 (23%); (p=0.26 for A vs. B, p<0.001 for B vs. C, p<0.001 for A vs. C) Myalgia: 270/1016 (27%) vs. 274/1019 (27%) vs. 233/1035 (23%); (p=0.87 for A vs. B, p=0.02 for B vs. C, p=0.03 for A vs. C) Depression: 197/1016 (19%) vs. 260/1019 (26%) vs. 217/1035 (21%); (p=0.001 for A vs. B, p=0.02 for B vs. C, p=0.37 for A vs. C) Neutropenia: 188/1016 (19%) vs. 263/1019 (26%) vs. 326/1035 (32%); (p<0.001 for A vs. B, p=0.004 for B vs. C, p<0.001 for A vs. C) Anemia: 293/1016 (29%) vs. 345/1016 (34%) vs. 348/1035 (34%); (p=0.02 for A vs. B, p=0.91 for B vs. C, p=0.02 for A vs. C) Neutrophils <750/mm ³ : 147/1008 (15%) vs. 222/1000 (22%) vs. 279/1034 (27%); (p<0.001 for A vs. B, p=0.01 for B vs. C, p<0.001 for A vs. C) Hemoglobin <10 g/dl: 255/1008 (25%) vs. 307/1000 (31%) vs. 306/1034 (30%); (p=0.007 for A vs. B, p=0.59 for B vs. C, p=0.03 for A vs. C)	

Author, Year Country Study Name Quality	Genotype Severity of Liver Disease Proportion Treatment-Naïve	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Rumi, 2010 ⁹ University of Milan, Italy Clinical Advances in Liver, Pancreas, and Biliary Tract (MIST Study) - Randomized Study of Pegylated interferon-alpha-2a Plus Ribavirin vs. Pegylated interferon- alpha-2b plus Ribavirin in Chronic Hepatitis C Overall Quality: Fair	A vs. B Genotype 1- 91/212 (42.9%) vs. 87/219 (39.7%) Genotype 2- 69/212 (32.5%) vs. 74/219 (33.8%) Genotype 3- 34/212 (16.0%) vs. 32/219 (14.6%) Genotype 4- 18/212 (08.5%) vs. 26/219 (11.9%) Ishak score of S5, 6: Overall: 81/212(38%) vs. 39/219(18%) HCV-RNA >600K IU/L: 53% vs. 55% 100% Treatment- naïve	Followup at 24 weeks post- treatment	A vs. B ETR: 166/212 (78%) vs. 146/219 (67%), p=.009 SVR: 140/212 (66%) vs. 119/219 (54%), p=.02	NR	A vs. B ETR: Genotype 1: 59/91 (65%) vs. 38/87 (44%), p=.007 Genotype 2: 66/69 (96%) vs. 69/74 (93%), p=.09 Genotype 3: 32/34 (94%) vs. 29/32 (91%), p=.09 Genotype 4: N/R ("sound comparison of treatment efficacy compromised by small sample size") SVR: Genotype 1: 44/91 (48%) vs. 28/87 (32%), p=.04 Genotype 2: 66/69 (96%) vs. 61/74 (82%), p=.01 Genotype 3: 22/34 (65%) vs. 22/32 (69%), p=.09 Genotype 4: N/R ("sound comparison of treatment efficacy compromised by small sample size")	NR	A vs. B Discontinuation due to adverse events: 16/212(8%) vs. 17/219(8%) Overall Withdrawals (including loss to followup and "other"): 46/212(22%) vs. 73/219(33%) Deaths: N/R Serious Adverse Events: 2/212 (1%) vs. 2/219(1%) Adverse Events: Grade 2 anemia: 35/212(16%) vs. 50/219(23%) Grade 3 anemia: 2/212(1%) vs. 2/219(1%) Grade 3 neutropenia: 46/212(22%) vs. 34/219(16%) Grades 2 or 3/thrombocytopenia: 5/212 (2%) vs. 3/219(1%) Treated with GCSF: 21/212(10%) vs. 15/219(7%) Treated with erythropoietin: 30/212(14%) vs. 27/219(12%) Depression: 19/212(9%) vs. 15/219 (7%)	Schering- Plough (now Merck), Roche, Novartis, Vertex

Author, Year Country Study Name Quality	Genotype Severity of Liver Disease Proportion Treatment-Naïve	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Rumi, 2008 ⁸ University of Milan, Italy Continued							Influenza-like syndrome: 134/212(63%) vs. 136/219(62%) Gastrointestinal symptoms: 8/212(4%) vs. 12/219(5%) Psychiatric symptoms: 79/212(37%) vs. 70/219(32%) Coughing and dyspnea: 22/212(10%) vs. 25/219(11%) Dermatologic symptoms: 99/212(47%) vs. 91/219(42%)	

Author, Year Country Study Name Quality	Genotype Severity of Liver Disease Proportion Treatment-Naïve	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Silva, 2006 ¹⁰ Argentina, Mexico, Germany A randomized trial to compare the pharmacokinetics, pharmacodynamic, and antiviral effects of pegylated interferon alfa-2b and Pegylated interferon alfa-2b in patients with chronic hepatitis C Overall Quality: Poor	A vs. B genotype 1: all Treatment-naïve: all Fibrosis stage: NR HCV-RNA mean (x10 ⁶ IU/mL): 1.8 vs. 1.8	8 weeks	NA	NA	NA	NA	A vs. B Overall withdrawals: NR Withdrawals for adverse events: 2/18 (11.1%) vs. 4/18 (22.2%); p=NS Serious adverse events: NR Deaths: NR Fatigue: 4/18 (22%) vs. 6/18 (33%); p=NS Fever: 1/18 (6%) vs. 10/18 (56%); p=0.001 Headache: 16/18 (89%) vs. 16/18 (89%); p=NS Influenza-like symptoms: 3/18 (17%) vs. 5/18 (28%); p=NS Anemia: 9/18 (50%) vs. 10/18 (56%); p=NS Hematocrit decrease: 9/18 (50%) vs. 5/18 (28%); p=NS Hemoglobin decrease: 12/18 (67%) vs. 6/18 (33%); p=0.05 Leukopenia: 14/18 (78%) vs. 9/18 (50%); p=NS Neutropenia: 12/18 (67%) vs. 10/18 (56%); p=NS Myalgia: 7/18 (39%) vs. 11/18 (61%); p=NS Platelet count decrease: 5/18 (28%) vs. 5/18 (28%); p=NS Thrombocytopenia: 5/18 (28%) vs. 3/18 (17%); p=NS	Schering Plough

Author, Year Country Study Name Quality	Genotype Severity of Liver Disease Proportion Treatment-Naïve	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Yenice, 2006 ¹¹ Okmeydani Research & Training Hospital (Istanbul, Turkey) The efficacy of pegylated interferon alpha 2a or 2b plus ribavirin in chronic hepatitis C patients Overall Quality: Poor	A vs. B Genotype 1 - 100% of subjects including 3 subtypes: Genotype 1a: 7/37 (18.9%) vs. 2/37(5.5%) Genotype 1b: 28/37(75.6%) vs. 35/37(94.6%) Genotype 1c: 2/37(5.5%) vs. 0/37(0%) 100% of subjects included had at least Stage 1 fibrosis (Knodell scale) 100% Treatment naïve	Followup at 24 weeks post- treatment Most patients refused a followup biopsy at the end of treatment; therefore, histological improvement was not assessed in this study due to the low number of followup biopsies.	A vs. B ETR: 28/37(75.7%) vs. 27/37(73%), p=.79 SVR: 18/37(48.6%) vs. 13/37(35.1%), p=.239	NR	NR	NR	A vs. B Discontinuation: 3/37(8%) vs. 3/37(8%) Overall Withdrawals: 3/37(8%) vs. 3/37(8%) Deaths: NR Serious Adverse Events: NR	Okmeydani Research and Training Hospital

Evidence Table 2. Quality rating: Pegylated Interferon alpha 2a vs. alpha 2b (head-to-head)

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition and withdrawals reported?	Loss to followup: differential/high?	Intention-to-treat analysis	Quality	Funding
Ascione, 2010 ¹	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Fair	Carderelli Hospital, Napoli, Italy
Escudero, 2008 ⁴	No	No	Yes	Yes	No	No	No	No	Unclear	Yes	Poor	Hoffman-LaRoche
Kamal, 2011 ⁵	Yes	Yes	Yes	Yes	No - open label	No - open label	No - open label	Yes	No	Yes	Fair	NR
McHutchison 2008 ⁸	Yes	Yes	Unclear	Unclear	Unclear	Yes	Unclear	Yes	Fair	Yes	Fair	Vertex Pharmaceuticals
Rumi, 2010 ⁹	Yes	Unclear	Yes	Yes	No	No	No	Yes	Unclear	Yes	Fair	Roche
Yenice, 2006 ¹¹	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Yes	No	No	Poor	Okmeydani Research and Training Hospital

Evidence Table 3. Protease inhibitors plus pegylated interferon and ribavirin

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment- Naïve
Hezode, 2009 ¹² Europe Protease Inhibition for Viral Evaluation 2 (PROVE2) Overall Quality: Fair	A. Pegylated interferon alfa-2a 180 mcg weekly for 24 weeks B. Pegylated interferon alfa-2a 180 mcg weekly for 12 weeks C. Pegylated interferon alfa-2a 180 mcg weekly for 12 weeks D. Pegylated interferon alfa-2a 180 mcg weekly for 48 weeks	A. Ribavirin1000- 1200 mg daily for 24 weeks B. Ribavirin1000- 1200 mg daily for 12 weeks C. Placebo D. Ribavirin1000- 1200 mg daily for 48 weeks 1000 mg daily for patients <75 kg 1200 mg daily for patients ≥ 75 kg	A. Telaprevir 750 mg tid for 12 weeks B. Telaprevir 750 mg tid for 12 weeks C. Telaprevir 750 mg tid for 12 weeks D. placebo On day 1, patients received telaprevir 1250 mg	Treatment naïve patients ages 18- 65 years Genotype 1 with detectable HCV RNA	histologic evidence of cirrhosis within 2 years of enrollment	388/334/334/323	A vs. B vs. C vs. D Age median: 46 vs. 44 vs. 45 vs. 45 Female: 33% vs. 40% vs. 45% vs. 44% Non-White: 7% vs. 7% vs. 1% vs. 7%	A vs. B vs. C vs. D Genotype 1: all Cirrhosis: 0% vs. 0% vs. 1% vs. 0% Minimal or no Fibrosis: 43% vs. 37% vs. 40% vs. 34% Treatment- naïve: all

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment- Naïve
Jacobson, 2011 ¹³ International Telaprevir for previously untreated chronic hepatitis C virus infection North America, Europe Overall Quality: Good	A. Pegylated interferon alfa-2a 180 mcg/week for 24 or 48 weeks (Response guided: if HCV RNA undetectable at weeks 4 and 12 then 24 total weeks, 48 weeks otherwise) B. Pegylated interferon alfa-2a 180 mcg/week for 24 or 48 weeks (Response guided: if HCV RNA undetectable at weeks 4 and 12 then 24 total weeks, 48 weeks otherwise) C. Pegylated interferon alfa-2a 180 mcg/week for 48 weeks	A. 1000-1200 mg/day for 24 or 48 weeks (Response guided: if HCV RNA undetectable at weeks 4 and 12 then 24 total weeks, 48 weeks otherwise) B. 1000-1200 mg/day for 24 or 48 weeks (Response guided: if HCV RNA undetectable at weeks 4 and 12 then 24 total weeks, 48 weeks otherwise) C. 1000-1200 mg/day for 48 weeks	A. Telaprevir 750 mg tid for 12 weeks B. Telaprevir 750 mg tid for 8 weeks C. Placebo for 12 weeks	Treatment naïve Ages 18-70 years of age HCV genotype 1 infection HCV virus confirmed with liver biopsy in the previous year Neutrophil count \geq 1500 /mm ³ Platelets \geq 90,000 / mm ³ Hemoglobin \geq 12 g/dL in women and \geq 13 g/dL in men	Decompensated liver disease Hepatocellular carcinoma HBV HIV	NR/NR/1095/1088	A vs. B vs. C Age median: 49 vs. 49 vs. 49 Female: 41% vs. 42% vs. 42% Non-White: 10% vs. 13% vs. 12%	A vs. B vs. C Genotype 1: all Proportion treatment- naïve: all Cirrhosis: 6% overall Minimal or no fibrosis: 28% Elevated transaminases: NR HCV RNA \geq 800,000: 77% vs. 77% vs. 77%

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment- Naïve
<p>Kwo, 2010¹⁴ US, Canada, Europe</p> <p>Efficacy of boceprevir, an Ns3 protease inhibitor, in combination with Pegylated interferon alfa- 2b and ribavirin in treatment- naïve patients with genotype 1 hepatitis C infection (SPRINT-1): an open-label, randomized, multicentre phase 2 trial</p> <p>Overall Quality: Fair</p>	<p>A. Pegylated interferon alfa-2b 1.5 mcg/kg weekly for 48 weeks B. Pegylated interferon alfa-2b 1.5 mcg/kg weekly for 28 weeks C. Pegylated interferon alfa-2b 1.5 mcg/kg weekly for 48 weeks D. Pegylated interferon alfa-2b 1.5 mcg/kg weekly for 28 weeks E. Pegylated interferon alfa-2b 1.5 mcg/kg weekly for 48 weeks</p>	<p>A. 800-1400 mg daily for 48 weeks B. 800-1400 mg daily for 28 weeks C. 800-1400 mg daily for 48 weeks D. 800-1400 mg daily for 28 weeks E. 800-1400 mg daily for 48 weeks</p> <p>≤ 65 kg: 400 mg bid 66-80 kg: 400 mg every morning, 600 mg every evening 81-105 kg: 600 mg bid >105 kg: 600 mg every morning, 800 mg every evening</p>	<p>A. Boceprevir 800 mg tid for 48 weeks B. Boceprevir 800 mg tid for 28 weeks C. Boceprevir 800 mg tid for weeks 5 through 48 (44 weeks total) D. Boceprevir 800 mg tid for weeks 5 through weeks 28 (24 weeks total) E. Placebo</p>	<p>Treatment naïve patients with genotype 1 Ages 18-60 years Liver biopsy consistent with chronic HCV infection within 5 years of enrollment Hemoglobin ≥ 130 g/L in men ≥ 120 g/L in women Neutrophils ≥ 1500/mm³ Platelets ≥ 100K/ mm³ Normal bilirubin, albumin, and creatinine</p>	<p>History of decompensated cirrhosis HIV infection Previous organ transplantation Other causes of liver disease Pre-existing psychiatric disease Seizure disorder Cardiovascular disease Hemoglobinopathies Hemophilia Poorly controlled diabetes Autoimmune disease</p>	765/642/520/520	<p>A vs. B vs. C vs. D vs. E Age: mean 47 vs. 46 vs. 48 vs. 48 vs. 48 Female: 39% vs. 41% vs. 44% vs. 50% vs. 33% Non-White: 16% vs. 20% vs. 17% vs. 20%</p>	<p>A vs. B vs. C vs. D vs. E Genotype 1: 100% Cirrhosis: 9% vs. 7% vs. 6% vs. 7% vs. 8% Minimal or no fibrosis: NR Elevated transaminases: NR Treatment- naïve: 100% HCV-RNA ≥600K IU/mL: 91% vs. 92% vs. 90% vs. 87% vs. 90%</p>

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment- Naïve
<p>Kwo, 2010¹⁴ US, Canada, Europe</p> <p>Efficacy of boceprevir, an Ns3 protease inhibitor, in combination with Pegylated interferon alfa- 2b and ribavirin in treatment- naïve patients with genotype 1 hepatitis C infection (SPRINT-1): an open-label, randomized, multicentre phase 2 trial</p> <p>Overall Quality: Fair</p>	<p>A. Pegylated interferon alfa-2b 1.5 mcg/kg weekly for 48 weeks B. Pegylated interferon alfa-2b 1.5 mcg/kg weekly for 48 weeks</p>	<p>A. 400-1000 mg daily for 48 weeks B. 800-1400 mg daily for 48 weeks</p>	<p>A. Boceprevir 800 mg tid for 48 weeks B. Boceprevir 800 mg tid for 48 weeks</p>	<p>Treatment naïve patients with genotype 1 Ages 18-60 years Liver biopsy consistent with chronic HCV infection within 5 years of enrollment Hemoglobin \geq 130 g/L in men \geq B4 120 g/L in women Neutrophils \geq 1500/mm³ Platelets \geq 100K/ mL Normal bilirubin, albumin, and creatinine</p>	<p>History of decompensated cirrhosis HIV infection Previous organ transplantation Other causes of liver disease Pre-existing psychiatric disease Seizure disorder Cardiovascular disease Hemoglobinopathies Hemophilia Poorly controlled diabetes Autoimmune disease</p>	765/642/75/75	<p>A vs. B Age: mean 49 vs. 50 Female: 31% vs. 44% Non-White: 27% vs. 25%</p>	<p>A vs. B Genotype 1: 100% Cirrhosis: 7% vs. 0% Treatment- naïve: 100% HCV-RNA \geq600K IU/mL: 83% vs. 81%</p>

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment- Naïve
<p>Marcellin, 2011¹⁵ Europe</p> <p>Telaprevir is effective given every 8 or 12 Hours with ribavirin and Pegylated interferon alfa-2a or 2b to patients with chronic hepatitis C</p> <p>Overall Quality: Fair</p>	<p>A. Pegylated interferon alfa-2a 180 mcg/week for 24 or 48 weeks</p> <p>B. Pegylated interferon alfa-2b 1.5 mcg/kg/week for 24 or 48 weeks</p> <p>C. Pegylated interferon alfa-2a 180 mcg/week for 24 or 48 weeks</p> <p>D. Pegylated interferon alfa-2b 1.5 mcg/kg/week for 24 or 48 weeks</p> <p>Response guided: 24 weeks total if HCV RNA undetectable from weeks 4 through 20, 48 weeks total otherwise</p>	<p>A. 1000-1200 mg/day for 24 or 48 weeks</p> <p>B. 800-1200 mg/day for 24 or 48 weeks</p> <p>C. 1000-1200 mg/day for 24 or 48 weeks</p> <p>D. 800-1200 mg/day for 24 or 48 weeks</p> <p>Response guided: 24 weeks total if HCV RNA undetectable from weeks 4 through 20, 48 weeks total otherwise</p>	<p>A. Telaprevir 750 mg tid for 12 weeks</p> <p>B. Telaprevir 750 mg tid for 12 weeks</p> <p>C. Telaprevir 1125 mg bid for 12 weeks</p> <p>D. Telaprevir 1125 mg bid for 12 weeks</p>	<p>Treatment-naïve</p> <p>Ages 18-65 years</p> <p>Chronic HCV genotype 1 infection</p> <p>HCV RNA >10,000 IU/mL</p> <p>Neutrophil count \geq 1500 mm³</p> <p>Platelets \geq 100,000 mm³</p> <p>Liver fibrosis status documented within 18 months</p>	<p>Contraindication to pegylated interferon or ribavirin</p> <p>History of drug use</p> <p>Documented cirrhosis</p> <p>Hepatitis B</p> <p>Hepatocellular cancer</p> <p>HIV</p> <p>History or suspicion of alcohol abuse</p>	176/170/166/161	<p>A vs. B vs. C vs. D</p> <p>Age median: 47 vs. 46 vs. 40 vs. 49</p> <p>Female: 50% vs. 52% vs. 48% vs. 51</p> <p>Non-White: 10% vs. 10% vs. 10% vs. 8%</p>	<p>A vs. B vs. C vs. D</p> <p>Genotype 1: all</p> <p>Cirrhosis: 2.5% vs. 2.4% vs. 0 vs. 5.1%</p> <p>Minimal or no fibrosis: 39% overall</p> <p>Elevated transaminases: NR</p> <p>Proportion treatment-naïve: all</p> <p>HCV-RNA \geq 800K IU/mL: 75% vs. 81% vs. 83% vs. 87%</p>

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment- Naïve
McHutchison, 2009 ¹⁶ US Protease Inhibition for Viral Evaluation 1 (PROVE1)	A. Peg interferon alfa-2a 180 mcg weekly for 24 weeks B. Pegylated interferon alfa-2a 180 mcg weekly for 48 weeks C. Pegylated interferon alfa-2a 180 mcg weekly for 12 weeks D. Pegylated interferon alfa-2a 180 mcg weekly for 48 weeks	A. Ribavirin 1000- 1200 mg daily for 24 weeks B. Ribavirin 800- 1400 mg daily for 48 weeks C. Ribavirin 800- 1400 mg daily for 12 weeks D. Ribavirin 1000- 1200 mg daily for 48 weeks 1000 mg daily for patients <75 kg 1200 mg daily for patients ≥ 75 kg	A. Telaprevir 750 mg tid for 12 weeks B. Telaprevir 750 mg tid for 12 weeks C. Telaprevir 750 mg tid for 12 weeks D. Placebo On day 1, patients received telaprevir 1250 mg	Treatment naïve patients ages 18- 65 years, neutrophils ≥ 1500 / mm ³ , platelets ≥ 90K / mm ³ , normal hemoglobin	decompensated liver disease, hepatocellular carcinoma, cirrhosis (liver biopsy within 2 years)	329/ 263/ 263/ 250	Age: median 49 vs. 50 vs. 49 vs. 49 Female: 32% vs. 39% vs. 29% vs. 43% non-White: 24% vs. 24% vs. 24% vs. 21%	Genotype 1: all Portal or Bridging fibrosis: 70% vs. 57% vs. 76% vs. 75% Treatment- naïve: all

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment- Naïve
Poordad , 2011 ¹⁷ USA and Europe Serine Protease Inhibitor Therapy 2 (SPRINT-2) Overall Quality: Fair	A: Pegylated interferon alfa-2b 1.5 µg/kg/week for 48 weeks B: Pegylated interferon alfa-2b 1.5 µg/kg 1x/week for 48 weeks -if HCV RNA undetectable from week 8 through 24 treatment completed -if HCV RNA detectable at any point from week 8 through 23 Pegylated interferon continued through week 48 C: Pegylated interferon alfa-2b 1.5 µg/kg 1x/week for 48 weeks	A: 600-1400 mg (weight-based) daily for 48 weeks B: 600-1400 mg (weight-based) daily for 48 weeks -if HCV RNA undetectable from week 8 through 24 treatment completed -if HCV RNA detectable at any point from week 8 through 23 ribavirin continued through week 48 C: 600-1400 mg (weight-based) daily for 48 weeks * <51 kg: 600mg/day 51-65 kg: 800mg/day 66 - 75 kg: 1000mg/day 76 - 105 kg: 1200mg/day >105 kg: 1400mg/day	A: Boceprevir 800 mg by mouth tid from weeks 5 to 28 (24 weeks total) B: Boceprevir 800 mg by mouth tid from weeks 5 to 48 (44 weeks total) C: Placebo	No previous treatment for HCV infection Age 18 years or older Weight 40 to 125 kg Chronic infection with HCV genotype 1 Plasma HCV RNA level \geq 10,000 IU/mL	Liver disease of other cause Decompensated cirrhosis Renal insufficiency HIV or hepatitis B infection Pregnancy or current breast-feeding Active cancer	1472/NR/1099/1097	A vs. B vs. C Age: Mean 49 vs. 50 vs. 49 years Female: 40% vs. 38% vs. 43% Non-White: 19% vs. 17% vs. 18%	A vs. B vs. C Genotype 1: 100% Cirrhosis (METAVIR fibrosis score 3 or 4): 11% vs. 9% vs. 7% Treatment- naïve: All

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment- Naïve
Sherman, 2011 ¹⁸ Europe and US Response- Guided Telaprevir Combination Treatment for Hepatitis C Virus Infection Overall Quality: Fair	A. Pegylated interferon alfa-2a 180 mcg weekly for 24 weeks B. Pegylated interferon alfa-2a 180 mcg weekly for 48 weeks C. Pegylated interferon alfa-2a 180 mcg weekly for 48 weeks (not randomized)	A. Ribavirin 1000-1200 mg daily for 24 weeks B. Ribavirin 1000-1200 mg daily for 48 weeks C. Ribavirin 1000-1200 mg daily for 48 weeks (not randomized)	A. Telaprevir 750 mg tid for 12 weeks B. Telaprevir 750 mg tid for 12 weeks C. Telaprevir 750 mg for 12 weeks	Treatment-naïve Ages between 18 and 70 years Chronic HCV genotype 1 infection Detectable HCV RNA Diagnosis for at least 6 months before screening Neutrophils \geq 1500/mm ³ Hemoglobin \geq 12 g/dL for women and \geq 13 g/dL for men Platelets \geq 90K/mm ³ Liver biopsy in past year	HIV HBV Hepatic decompensation Clinically significant liver disease of other etiology Active cancer in previous 5 years (except basal-cell carcinoma)	NR/544/322/322 Subjects treated for 20 weeks prior to randomization. Only subjects who completed 20 weeks and had an early rapid virologic response were randomized.	A vs. B Age median: 51 vs. 50 Female: 36% vs. 39% Non-White: 17% vs. 18%	A vs. B Genotype 1: all Treatment- naïve: all Cirrhosis: 11% vs. 8% Minimal or no fibrosis: 27% HCV RNA \geq 800K IU/ml: 77% vs. 79%

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Hezode, 2009 ¹² Europe Protease Inhibition for Viral Evaluation 2 (PROVE2) Overall Quality: Fair	Up to 48 weeks following treatment completion	A vs. B vs. C vs. D ETR: 57/81 (70%) vs. 66/82 (80%) vs. 48/78 (62%) vs. 45/82 (55%); (A,B,C vs. D p<0.05) SVR: 56/81 (69%) vs. 49/82 (60%) vs. 28/78 (36%) vs. 38/82 (46%); (A vs. D p<0.01; B, C vs. D p=NS)	Not reported multivariate predictors of SVR presented in supplementary table (variables included treatment arm HCV geno-subtype, baseline HCV RNA, age): Baseline HCV RNA <800KIU/ml adjusted odds ratio 4.69 (95% 2.22-9.88) Age ≤45 years adjusted odds ratio 1.59 (0.99- 2.57)	NR	NR	A vs. B vs. C vs. D Overall withdrawals: 20/81 (25%) vs. 10/82 (12%) vs. 8/78 (10%) vs. 32/82 (39%); (p=0.05 for A vs. D, p<0.01 for B, C vs. D) Withdrawals due to adverse events: 11/81 (14%) vs. 9/82 (11%) vs. 7/78 (9%) vs. 6/82 (7%); (p=NS for A, B, C vs. D) Serious adverse event: 13/81 (16%) vs. 17/82 (21%) vs. 10/78 (13%) vs 13/82 (16%); (p=NS for A, B, C vs. D) Asthenia: 37/81 (46%) vs. 43/82 (52%) vs. 30/78 (38%) vs. 26/82 (32%); (p<0.05 A, B vs. D, p=0.37 for C vs. D) Influenza-like illness: 32/81 (40%) vs. 32/82 (39%) vs. 28/78 (36%) vs. 43/82 (52%); (p=NS for A, B vs. D, p=0.04 for C vs. D) Fatigue: 21/81 (26%) vs. 23/82 (28%) vs. 26/78 (33%) vs. 30/82 (37%); (p=NS for A, B, C vs. D) Pyrexia: 14/81 (17%) vs. 15/82 (18%) vs. 15/78 (19%) vs. 19/82 (23%); (p=NS for A, B, C vs. D) Pruritus: 41/81 (51%) vs. 52/82 (63%) vs. 46/78 (59%) vs. 29/82 (35%); (p<0.05 for A, B, C vs. D) Any rash: 40/81 (49%) vs. 36/82 (44%) vs. 37/78 (47%) vs. 29/82 (35%); (p=NS for A, B, C vs. D) Nausea: 39/81 (48%) vs. 39/82 (48%) vs. 24/78 (31%) vs. 33/82 (40%); (p=NS for A, B, C vs. D) Headache: 36/81 (44%) vs. 32/82 (39%) vs. 37/78 (47%) vs. 37/82 (45%); (p=NS for A, B, C vs. D) Depression: 16/81 (20%) vs. 18/82 (22%) vs. 17/78 (22%) vs. 19/82 (23%); (p=NS for A, B, C vs. D) Myalgia: 11/81 (14%) vs. 12/82 (15%) vs. 12/78 (15%) vs. 17/82 (21%); (p=NS for A, B, C vs. D) Arthralgia: 8/81 (10%) vs. 8/82 (10%) vs. 20/78 (26%) vs. 14/82 (17%); (p=NS for A, B, C vs. D) Anemia: 22/81 (27%) vs. 15/82 (18%) vs. 7/78 (9%) vs. 14/82 (17%); (p=NS for A, B, C vs. D)	Vertex Pharmace uticals

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Jacobson, 2011 ¹³ International Telaprevir for previously untreated chronic hepatitis C virus infection North America, Europe Overall Quality: Good	Up to week 72	A vs. B vs. C ETR: 314/363 (87%) vs. 295/364 (81%) vs. 229/361 (63%); p<0.001 for A or B vs. C SVR: 271/363 (75%) vs. 250/364 (69%) vs. 158/361 (44%); p<0.001 for A or B vs. C	A vs. B vs. C Male: 159/214 (74%) vs. 147/211 (70%) vs. 94/211 (45%); A or B vs. C p<0.001 Female: 112/149 (75%) vs. 103/153 (67%) vs. 64/150 (43%); A or B vs. C p<0.001 Age <45 years: 118/142 (83%) vs. 102/139 (73%) vs. 74/143 (52%); A or B vs. C p<0.001 Age >45 to <65 years: 150/214 (70%) vs. 145/222 (65%) vs. 82/216 (38%); A or B vs. C p<0.001 White: 244/325 (75%) vs. 220/315 (70%) vs. 147/318 (46%); A or B vs. C p<0.001 Black: 16/26 (62%) vs. 23/40 (58%) vs. 7/28 (25%); A vs. C p=0.05; B vs. C p=0.04 BMI <25: 129/155 (83%) vs. 104/145 (72%) vs. 57/130 (44%); A or B vs. C p<0.001	A vs. B vs. C HCV genotype 1a: 138/210 (66%) vs. 152/213 (71%) vs. 85/208 (41%); A or B vs. C p<0.001 HCV genotype 1b: 111/151 (74%) vs. 118/149 (79%) vs. 73/151 (48%); A or B vs. C p<0.001 Baseline HCVRNA <800K IU/ml: 67/85 (79%) vs. 64/82 (78%) vs. 57/82 (70%); A vs. C p=0.16; B vs. C p=0.19 Baseline HCVRNA >800K IU/ml: 183/279 (66%) vs. 207/281 (74%) vs. 101/279 (36%); A or B vs. C p<0.001 No or minimal fibrosis: 101/128 (79%) vs. 109/134 (81%) vs. 67/147 (46%); A or B vs. C p<0.001	NR	A vs. B vs. C Overall withdrawals: 95/363 (26%) vs. 104/364 (29%) vs. 159/361 (44%); A or B vs. C p<0.001 Withdrawals for adverse events: 36/363 (10%) vs. 37/364 (10%) vs. 26/361 (7%); p=NS Serious adverse events: 33/363 (9%) vs. 31/364 (9%) vs. 24/361 (7%); p=NS Deaths: 0 vs. 0 vs. 1 (<1%); p=NS Fatigue: 207/363 (57%) vs. 211/364 (58%) vs. 206/361 (57%); p=NS Influenza-like illness 102/363 (28%) vs. 105/364 (29%) vs. 101/361 (28%); p=NS Pyrexia: 95/363 (26%) vs. 108/364 (30%) vs. 87/361 (24%); p=NS Pruritus: 181/363 (50%) vs. 165/364 (45%) vs. 131/361 (36%); p=NS Rash: 133/363 (37%) vs. 129/364 (35%) vs. 88/361 (24%); A or B vs. C p<0.01 Anemia: 135/363 (37%) vs. 141/364 (39%) vs. 70/361 (19%); A or B vs. C p<0.001 Neutropenia: 51/363 (14%) vs. 62/364 (17%) vs. 68/361 (19%); p=NS Depression: 66/363 (18%) vs. 61/364 (17%) vs. 79/361 (22%); p=NS Myalgia: 54/363 (15%) vs. 76/364 (21%) vs. 77/361 (21%); p=NS Arthralgia: 49/363 (13%) vs. 56/364 (15%) vs. 68/361 (19%); p=NS	Vertex, Tibotec

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Jacobson, 2011 ¹³ International Continued			BMI >25 and <30: 87/129 (67%) vs. 92/131 (70%) vs. 65/144 (45%); A or B vs. C p<0.001 BMI >30: 55/77 (71%) vs. 53/86 (62%) vs. 36/87 (41%); A vs. C p<0.001, B vs. C p=0.02	Portal fibrosis: 104/151 (69%) vs. 117/156 (75%) vs. 67/141 (48%); A or B vs. C p<0.001 Bridging fibrosis: 34/59 (58%) vs. 32/52 (62%) vs. 17/52 (33%); A vs. C p=0.02, B vs. C p=0.01 Cirrhosis: 11/26 (42%) vs. 13/21 (62%) vs. 7/21 (33%); A vs. C p=0.04; B vs. C p=0.15			

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Kwo, 2010 ¹⁴ US, Canada, Europe Efficacy of boceprevir, an Ns3 protease inhibitor, in combination with Pegylated interferon alfa- 2b and ribavirin in treatment- naïve patients with genotype 1 hepatitis C infection (SPRINT-1): an open-label, randomized, multicentre phase 2 trial Overall Quality: Fair	24 weeks after end of treatment	A vs. B vs. C vs. D vs. E ETR: 76/103 (74%) vs. 84/107 (79%) vs. 81/103 (79%) vs. 79/103 (77%) vs. 53/104 (51%) (A, B, C, D vs. E p<0.01) SVR: 69/103 (67%) vs. 58/107 (54%) vs. 77/103 (75%) vs. 58/103 (56%) vs. 39/104 (38%); (A, B, C, D vs. E p<0.01)	A vs. B vs. C vs. D vs. E Black: 4/14 (29%) vs. 7/18 (39%) vs. 8/15 (53%) vs. 6/15 (40%) vs. 2/16 (13%); (A, B, D vs. E p=NS, C vs. E p<0.05) Non-black 65/89 (73%) vs. 51/89 (57%) vs. 69/88 (78%) vs. 52/88 (59%) vs. 37/88 (42%) (A, B, C, D vs. E p<0.05) Male: 40/63 (64%) vs. 33/63 (52%) vs. 41/58 (71%) vs. 33/51 (65%) 28/70 (40%); (A, C, D vs. E p<0.01; B vs. E p=0.15) Female: 29/40 (73%) vs. 25/44 (59%) vs. 36/45 (80%) vs. 25/52 (48%) vs. 11/34 (32%) (A, B, C vs. E p<0.05, D vs. E p=0.15)	A vs. B vs. C vs. D vs. E Cirrhosis: 7/9 (78%) vs. 4/7 (57%) vs. 3/6 (50%) vs. 4/7 (57%) vs. 2/8 (25%) (A vs. E p=0.04; B, C, D vs. E p=NS) non-Cirrhosis: 62/97 (66%) vs. 54/100 (54%) vs. 74/97 (76%) vs. 54/96 (56%) vs. 37/96 (39%) (A, B, C, D vs. E p<0.05) Baseline HCV-RNA >600K IU/mL: 63/97 (67%) vs. 52/99 (53%) vs. 67/92 (73%) vs. 48/89 (54%) vs. 30/93 (32%) (A, B, C, D vs. E p<0.01) Baseline HCV-RNA< 600K IU/mL: 6/9 (67%) vs. 6/8 (75%) vs. 10/11 (91%) vs. 10/14 (71%) vs. 9/11 (89%) (A, B, C, D vs. E p=NS) HCV genotype 1a: 32/55 (58%) vs. 34/67 (51%) vs. 43/60 (72%) vs. 27/53 (51%) vs. 16/53 (30%) (A, B, C, D vs. E p<0.05) HCV genotype 1b: 30/36 (83%) vs. 21/30 (70%) vs. 29/35 (83%) vs. 22/37 (60%) vs. 17/42 (41%) (A, B, C vs. E p<0.05, D vs. E p=0.09)	NR	A vs. B vs. C vs. D vs. E Overall Withdrawals: 40/103 (39%) vs. 30/107 (28%) vs. 27/103 (26%) vs. 27/103 (26%) vs. 16/104 (15%); (A, B vs. E p<0.05; C, D vs. E p=0.055) Withdrawals due to adverse events: 20/103 (19%) vs. 12/107 (11%) vs. 9/103 (9%) vs. 15/103 (15%) vs. 8/104 (8%); (A vs. E p=0.01, B vs. E p=0.38, C vs. E p= 0.78, Dives E p=0.12) Influenza-like illness: 19/103 (18%) vs. 24/107 (22%) vs. 15/103 (15%) vs. 21/103 (20%) vs. 25/104 (24%); p=NS for all comparisons Fatigue: 51/103 (50%) vs. 65/107 (61%) vs. 73/103 vs. 70/103 (68%) vs. 57/104 (55%); (A vs. E p = 0.45; B vs. E p=0.38, C vs. E p=0.02, D vs. E p=0.05) Headache: 44/103 (43%) vs. 52/107 (49%) vs. 54/103 (52%) vs. 41/103 (40%) vs. 45/104 (43%); (A, B, C, D vs. E p=NS) Nausea: 56/103 (54%) vs. 41/107 (38%) vs. 48/103 (47%) vs. 42/103 (41%) vs. 45/104 (43%); (A, B, C, D vs. E p=NS) Pyrexia: 41/103 (40%) vs. 28/107 (26%) vs. 35/103 (34%) vs. 27/103 (26%) vs. 35/104 (34%); (A, B, C, D vs. E p=NS) Chills: 33/103 (32%) vs. 31/107 (29%) vs. 35/103 (34%) vs. 31/103 (30%) vs. 35/104 (34%); (A, B, C, D vs. E p=NS) Dysgeusia: 33/103 (32%) vs. 23/107 (21%) vs. 28/103 (27%) vs. 27/103 (26%) vs. 9/104 (9%); (A, B, C, D vs. E p<0.01) Influenza-like illness: 19/103 (18%) vs. 24/107 (22%) vs. 15/103 (15%) vs. 21/103 (20%) vs. 25/104 (24%); (A, B, C, D vs. E p=NS) Arthralgia: 21/103 (20%) vs. 14/107 (13%) vs. 19/103 (18%) vs. 22/103 (21%) vs. 21/104 (20%); (A, B, C, D vs. E p=NS)	Merck

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Kwo, 2010 ¹⁴ US, Canada, Europe Continued						Neutrophils <750: 38/103 (37%) vs. 36/107 (34%) vs. 37/103 (36%) vs. 21/103 (20%) vs. 18/104 (17%); (A, B, C vs. E p<0.01, D vs. E p=0.52) Hemoglobin <100 g/L: 48/103 (47%) vs. 57/107 (53%) vs. 48/103 (47%) vs. 51/103 (50%) vs. 25/104 (24%); (A, B, C, D vs. E p<0.01) Platelets <50K/ mm ³ : 1/103 (1%) vs. 4/107 (4%) vs. 4/103 (4%) vs. 2/103 (2%) vs. 0/104 (0%); (A, B, C, D vs. E p=NS)	
Kwo, 2010 ¹⁴ US, Canada, Europe Efficacy of boceprevir, an Ns3 protease inhibitor, in combination with Pegylated interferon alfa-2b and ribavirin in treatment-naïve patients with genotype 1 hepatitis C infection (SPRINT-1): an open-label, randomized, multicentre phase 2 trial Overall Quality: Fair	25 weeks after end of treatment	A vs. B ETR: 28/59 (48%) vs. 9/16 (56%) (p=NS) SVR: 21/59 (36%) vs. 8/16 (50%) (p=NS)	NR	NR	NR	A vs. B Overall withdrawals: 31/59 (53%) vs. 8/16 (50%) p=NS Withdrawals due to adverse events: 7/59 (12%) vs. 4/16 (25%) p=NS Fatigue: 40/59 (68%) vs. 11/16 (69%) p=NS Headache: 29/59 (49%) vs. 13/16 (81%) p<0.05 Nausea: 35/59 (59%) vs. 10/16 (63%) p=NS Pyrexia: 26/59 (44%) vs. 7/16 (44%) p=NS Chills: 26/59 (44%) vs. 5/16 (31%) p=NS Dysgeusia: 18/59 (31%) vs. 7/16 (44%) p=NS Influenza-like illness: 11/59 (19%) vs. 6/16 (38%) p=NS Arthralgia: 11/59 (19%) vs. 5/16 (31%) p=NS Neutrophils <750/mL: 12/59 (20%) vs. 2/16 (14%) p=NS Hemoglobin <100 g/L: 12/59 (20%) vs. 9/16 (56%) p<0.01 Platelets <50K/mL: 1/59 (2%) vs. 0/16 (0%) p=NS	Merck

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Marcellin, 2011 ¹⁵ Europe Telaprevir is effective given every 8 or 12 Hours with ribavirin and Pegylated interferon alfa- 2a or 2b to patients with chronic hepatitis C Overall Quality: Fair	24 weeks after end of treatment	A vs. B vs. C vs. D ETR: 37/40 (93%) vs. 37/42 (88%) vs. 37/40 (93%) vs. 34/39 (87%); Pooled A+B (TID telaprevir) vs. C+D (BID telaprevir) p=NS Pooled A+C (alpha-2a) vs. B + D (alpha-2b) p=NS SVR: 34/40 (85%) vs. 34/42 (81%) vs. 33/40 (83%) vs. 32/39 (82%) Pooled A+B (TID telaprevir) vs. C+D (BID telaprevir) p=NS Pooled A+C (alpha-2a) vs. B + D (alpha-2b) p=NS	NR	NR	NR	A vs. B vs. C vs. D vs. E Overall withdrawals: 10/40 (25%) vs. 8/42 (19%) vs. 11/40 (28%) vs. 17/39 (44%); Withdrawals due to adverse events: 3/40 (7.5%) vs. 2/42 (5%) vs. 4/40 (10%) vs. 4/39 (10%) Nausea: 18/40 (45%) vs. 14/42 (33%) vs. 16/40 (40%) vs. 23/39 (59%) Fatigue: 15/40 (38%) vs. 15/42 (36%) vs. 16/40 (40%) vs. 15/39 (39%) Influenza-like illness: 16/40 (40%) vs. 19/42 (45%) vs. 11/40 (28%) vs. 20/39 (51%) Pyrexia: 9/40 (23%) vs. 15/42 (36%) vs. 9/40 (23%) vs. 12/39 (31%) Depression: 7/40 (18%) vs. 9/42 (21%) vs. 4/40 (10%) vs. 9/39 (23%) Pruritus: 19/40 (48%) vs. 23/42 (55%) vs. 20/40 (50%) vs. 25/39 (64%) Rash: 29/40 (73%) vs. 23/42 (55%) vs. 20/40 (50%) vs. 25/39 (64%) Anemia: 18/40 (45%) vs. 14/42 (33%) vs. 18/40 (45%) vs. 20/39 (51%) Leukopenia: 9/40 (23%) vs. 9/42 (21%) vs. 9/40 (23%) vs. 10/39 (26%) Pooled A+C (alpha-2a) vs. B + D (alpha-2b) - all comparisons p=NS Pooled A+B (TID telaprevir) vs. C+D (BID telaprevir) - all comparisons p=NS	Janssen, Vertex Pharmace uticals

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
McHutchison, 2009 ¹⁶ US Protease Inhibition for Viral Evaluation 1 (PROVE1)	Up to 24 weeks following treatment completion	A vs. B vs. C vs. D ETR: 45/79 (57%) vs. 51/79 (65%) vs. 12/17 (71%) vs. 35/75 (47%) (A, C vs. D p=NS, B vs. D p=0.03) SVR: 48/79 (61%) vs. 53/79 (67%) vs. 6/17 (35%) vs. 31/75 (41%); (A vs. D p=0.02, B vs. D p=0.002, C vs. D p=NS)	NR	NR	NR	A vs. B vs. C vs. D Overall withdrawals: 26/79 (33%) vs. 25/79 (32%) vs. 4/17 (24%) vs. 17/75 (23%) Withdrawals due to adverse events (telaprevir regimens A+B+C vs. D): 37/175 (21%) vs. 8/75 (11%) Fatigue: 70% vs. 73% vs. 82% vs. 76% Nausea: 56% vs. 48% vs. 65% vs. 29% Influenza-like illness: 49% vs. 40% vs. 24% vs. 23% Pruritus: 48% vs. 40% vs. 24% vs. 23% Headache: 47% vs. 43% vs. 53% vs. 60% Rash: 60% vs. 61% vs. 53% vs. 41% Vomiting: 24% vs. 20% vs. 18% vs. 12% Arthralgia: 17% vs. 22% vs. 24% vs. 21% Myalgia: 11% vs. 19% vs. 18% vs. 24% Chills: 10% vs. 23% vs. 18% vs. 19% Anemia: 37% vs. 29% vs. 35% vs. 27% Neutropenia: 14% vs. 24% vs. 0% vs. 24%	Vertex Pharmace uticals

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Poordad, 2011 ¹⁷ USA and Europe Serine Protease Inhibitor Therapy 2 (SPRINT-2) Overall Quality: Fair	72 weeks (24 weeks after treatment end)	A vs. B vs. C ETR: 277/366 (76%) vs. 261/368 (71%) vs. 191/363 (53%) (p<0.001 for A or B vs. C) SVR: 242/366 (66%) vs. 233/368 (63%) vs. 137/363 (38%) (p<0.001 for A or B vs. C)	A vs. B vs. C Black: 29/55 (53%) vs. 22/52 (42%) vs. 12/52 (23%) (p=0.004 for A vs. C, p=0.04 for B vs. C) Non-black: 197/313 (63%) vs. 192/314 (61%) vs. 102/308 (33%) (p<0.001 for A or B vs. C) Male: 145/221 (66%) vs. 149/229 (65%) vs. 72/206 (35%) (p<0.001 for A or B vs. C) Female: 97/145 (67%) vs. 84/139 (60%) vs. 65/157 (41%) (p<0.001 for A or B vs. C) Age <=40 years: 41/59 (69%) vs. 37/51 (73%) vs. 35/67 (52%) (p<0.001 for A or B vs. C) Age >40 years: 201/307 (65%) vs. 196/317 (62%) vs. 102/296 (34%) (p<0.001 for A or B vs. C) Weight <75 kg: 83/131 (63%) vs. 82/131 (63%) vs. 67/146 (46%) (p<0.001 for A or B vs. C) Weight >=75 kg): 159/235 (68%) vs. 151/237 (64%) vs. 70/217 (32%) (p<0.001 for A or B vs. C)	A vs. B vs. C METAVIR score 0, 1, or 2: 211/313 (67%) vs. 213/319 (67%) vs. 123/328 (38%) (p<0.001 for A or B vs. C) METAVIR score 3 or 4: 22/42 (52%) vs. 14/34 (41%) vs. 9/24 (38%) (p=0.31 for A vs. C and p=1.0 for B vs. C) Low viral load (<=800,000 IU/mL): 45/53 (85%) vs. 41/54 (76%) vs. 35/55 (64%) High viral load: 197/313 (63%) vs. 192/314 (61%) vs. 102/308 (33%) (p<0.001 for A or B vs. C) Genotype 1a: 118/187 (63%) vs. 106/179 (59%) vs. 62/177 (35%) (p<0.001 for A or B vs. C) Genotype 1b: 93/133 (70%) vs. 89/134 (66%) vs. 51/128 (40%) (p<0.001 for A or B vs. C) Cirrhosis: 10/24 (42%) vs. 5/16 (31%) vs. 6/13 (46%); p=ns for A or B vs. C Non-cirrhosis: 223/331 (67%) vs. 222/337 (66%) vs. 126/339 (37%); (p<0.001 for A or B vs. C)	NR	A vs. B vs. C Overall withdrawals: 152/367 (41%) vs. 139/368 (38%) vs. 205/364 (56%) (p<0.001 for A or B vs. C) Withdrawals due to adverse events: 60/366 (16%) vs. 45/368 (12%) vs. 57/363 (16%) (p>0.05) Deaths: 1/366 (<1%) vs. 1/368 (<1%) vs. 4/363 (1%) (p>0.05) Serious adverse event: 45/366 (12%) vs. 42/368 (11%) vs. 31/363 (9%) (p>0.05) Fatigue: 209/366 (57%) vs. 196/368 (53%) vs. 217/363 (60%) (p>0.05) Headache: 167/366 (46%) vs. 168/368 (46%) vs. 153/363 (42%) (p>0.05) Nausea: 159/366 (43%) vs. 175/368 (48%) vs. 153/363 (42%) (p>0.05) Pyrexia: 118/366 (32%) vs. 123/368 (33%) vs. 121/363 (33%) (p>0.05) Chills: 121/366 (33%) vs. 134/368 (36%) vs. 102/363 (28%) (p=0.15 for A vs. C, p=0.02 for B vs. C) Dysgeusia: 156/366 (43%) vs. 137/368 (37%) vs. 64/363 (18%) (p<0.001 for A or B vs. C) Neutrophil count <750 per mm ³ : 119/366 (32%) vs. 108/368 (29%) vs. 66/363 (18%) (p<0.001 for A or B vs. C) Neutrophil count <500 per mm ³ : 29/366 (8%) vs. 21/368 (6%) vs. 16/363 (4%) (p>0.05) Use of granulocyte stimulating agent: 31/366 (8%) vs. 43/368 (12%) vs. 21/363 (6%) (p=0.20 for A vs. C, p=0.006 for B vs. C) Platelet count <50,000 per mm ³ : 14/366 (4%) vs. 12/368 (3%) vs. 5/363 (1%) (p=0.99 for A or B vs. C) Hemoglobin <8.0 g/dl: 13/366 (4%) vs. 9/368 (2%) vs. 6/363 (2%) (p>0.05) Red-cell transfusion: 9/366 (2%) vs. 11/368 (3%) vs. 2/363 (1%) (p=0.06 vs. A vs. C and p=0.02 for B vs. C) Erythropoietin use: 159/366 (43%) vs. 159/368 (43%) vs. 87/363 (24%) (p<0.001 for A or B vs. C)	Schering- Plough (now Merck)

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Sherman, 2011 ¹⁸ Europe and US Response- Guided Telaprevir Combination Treatment for Hepatitis C Virus Infection Overall Quality: Fair	72 weeks	A vs. B vs. C ETR: 159/162 (98%) vs. 154/160 (96%) vs. 97/118 (82%); As B p=NS SVR: 149/162 (92%) vs. 140/160 (88%) vs. 76/118 (64%); A non-inferior to B	A vs. B Black: 15/17 (88%) vs. 15/17 (88%) White: 126/135 (93%) vs. 114/131 (87%) Asian/other: 8/10 (80%) vs. 11/12 (92%) BMI \geq 30: 55/61 (90%) vs. 43/49 (88%) BMI \geq 25 to <30: 51/56 (91%) vs. 46/51 (90%) BMI <25: 42/44 (95%) vs. 51/60 (85%)	A vs. B HCV genotype 1a: 103/115 (90%) vs. 10/117 (88%) HCV genotype 1b: 45/46 (98%) vs. 37/43 (86%) Bridging fibrosis or cirrhosis: 31/38 (82%) vs. 29/33 (88%) no Bridging fibrosis or cirrhosis: 118/124 (95%) vs. 111/127 (87%)	NR	A vs. B vs. C Overall withdrawals (after randomization): 1/162 (1%) vs. 41/160 (26%) vs. 39/118 (33%) Withdrawals for adverse events: 1/162 (1%) vs. 20/160 (13%) vs. 12/118 (10%) Serious adverse events: 4/162 (2) vs. 16/160 (10%) vs. 7/118 (6%) Deaths: NR Fatigue: 110/162 (68%) vs. 111/160 (69%) vs. 81/118 (69%) Nausea: 71/162 (44%) vs. 76/160 (48%) vs. 61/118 (52%) Diarrhea: 48/162 (30%) vs. 54/160 (34%) vs. 38/118 (32%) Pruritus: 95/162 (59%) vs. 83/160 (52%) vs. 55/118 (47%) Rash: 60/162 (37%) vs. 62/160 (39%) vs. 47/118 (40%) Headache: 61/162 (38%) vs. 57/160 (36%) vs. 51/118 (43%) Insomnia: 50/162 (31%) vs. 62/160 (39%) vs. 44/118 (37%) Anemia: 68/162 (42%) vs. 66/160 (41%) vs. 38/118 (32%)	Vertex, Tibotec

Evidence Table 4. Quality rating: Protease Inhibitors plus pegylated interferon and ribavirin

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition and withdrawals reported?	Loss to followup: differential/high?	Intention-to-treat analysis	Quality	Funding
Hezode 2009 ¹²	Unclear	Yes	Yes	Yes	Unclear	Unclear	Unclear	Yes	Unclear	Yes	Fair	Vertex Pharmaceuticals
Jacobson 2011 ¹³	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good	Vertex, Tibotec
Kwo 2010 ¹⁴	Yes	Yes	Yes	Yes	No	No	No	Yes	No	Yes	Fair	Merck
Marcellin 2011 ¹⁵	Unclear	Unclear	Yes	Yes	No	No	No	Yes	No	No	Fair	Janssen, Vertex Pharmaceuticals
McHutchison 2009 ¹⁶	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Yes	Unclear	Yes	Fair	Vertex Pharmaceuticals
Poordad 2011 ¹⁷	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Fair	Schering-Plough (now Merck)
Sherman 2011 ¹⁸ ILLUMINATE Study	Unclear	Yes	Yes	Yes	No	No	No	No	No	Yes	Fair	Vertex

Evidence Table 5. Duration in trials of pegylated interferon plus ribavirin

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Andriulli , 2009 ¹⁹ Italy Early discontinuation of ribavirin in HCV-2 and HCV-3 patients responding to Peg-interferon alpha-2a and ribavirin Overall Quality: Fair	A: Pegylated interferon alpha-2a 180 mcg / week for 12 weeks B: Pegylated interferon alpha-2a 180 mcg / week for 12 weeks	A: 1000-1200 mg/day depending of body weight for 6 weeks B: 1000-1200 mg/day depending of body weight for 12 weeks Patients with rapid virologic response (undetectable HCV-RNA) at week 4 were randomized to A or B above	None	Treatment-naïve Ages 18-70 years Detectable HCV-RNA levels Infection with genotype 2 or 3 Abnormal ALT	Neutrophils <3000 Platelets <80K Hemoglobin <12 g/dL for females and <13 g/dL for males HIV co-infection Alcohol intake >30 g daily Drug abuse Chronic disease Psychiatric disorders Autoimmune diseases Pregnancy or lactation	NR/NR/149 /120	(A vs. B): Age mean: 53 vs. 53 Female: 41% vs. 51% non- white: NR	(A vs. B): Genotype 1: none Treatment-naïve: all Fibrosis stage 3 or platelets <140K: 14% vs. 10% HCV-RNA >600K: 64% vs. 52% Cirrhosis: NR
Berg, 2006 ²⁰ Germany Extended treatment duration for hepatitis C virus type 1: Comparing 48 vs. 72 weeks of pegylated interferon alfa- 2a plus ribavirin Overall Quality: Fair	A: Pegylated interferon alfa-2a 180 mcg/week for 48 weeks B: Pegylated interferon alfa-2a 180 mcg/week for 72 weeks	A: 400 mg twice daily for 48 weeks B: 400 mg twice daily for 72 weeks	None	Treatment naïve Ages 18-70 years of age HCV genotype 1 infection HCV RNA >1000 IU/mL Increased ALT at screening Liver biopsy within the preceding 18 months showing chronic hepatitis Neutrophils > 1500 Platelets > 90K Hemoglobin > 12g/dL for women and > 13 g/dL for men Creatinine <1.5 mg/dL	HCV genotype other than type 1 Decompensated liver disease Liver disease of other etiology HBV or HIV co-infection Autoimmune disorder Clinically significant cardiovascular disease Organ grafts Systemic infections Clinically significant bleeding disorders Malignant neoplasm Concomitant immunosuppressive medication use Alcohol or drug abuse in the past year	467/459/45 5/455	(A vs. B): Age mean: 43 vs. 43 Female: 44% vs. 46% non- White: 3% vs. 5%	(A vs. B): Genotype 1: all Treatment-naïve: all Fibrosis stage 3-4: 7% vs. 9% HCV RNA (log IU/mL) mean: 5.8 vs. 5.8

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Berg T, 2009 ²¹ Germany Individualized treatment strategy according to early viral kinetics in hepatitis C virus type 1- infected patients Quality: Poor	A: Pegylated interferon alfa-2b 1.5 mcg/kg for a duration determined by the time required to achieve HCV-RNA negativity at weeks 3,4,5,6,7, or 8 (times a factor of 6) B: Pegylated interferon alfa-2b 1.5 mcg/kg for 48 weeks	A: 800-1400 mg daily for a duration determined by the time required to achieve HCV-RNA negativity at weeks 3,4,5,6,7, or 8 (times a factor of 6) B: 800-1400 mg daily for 48 weeks	None	Treatment-naïve Ages 18-70 years HCV genotype 1 infection Positive test for anti-HCV antibodies HCV-RNA >1000 IU/mL Increased ALT Liver biopsy within 24 months of enrollment confirming chronic hepatitis Neutrophils > 1500 Platelets >80K Hemoglobin >12 g/dL for females and >13 g/dL for males Creatinine <1.5 mg/dL	HCV genotype other than type 1 Decompensated liver disease HBV or HIV co-infection Liver disease of other causes Autoimmune disorder Concomitant immunosuppressive medication use Clinically significant bleeding disorders Clinically significant cardiac abnormalities Organ grafts Systemic infection Preexisting severe psychiatric condition Neoplastic disease Excessive alcohol intake Drug abuse in the past year Unwillingness to use contraception	438/433/433/3/433	(A vs. B): Age mean: 43 vs. 43 Female: 46% vs. 43% Non-White: NR	(A vs. B): Genotype 1: all Treatment-naïve: all Fibrosis stage 3-4: 15% vs. 13% HCV-RNA mean: 5.7 vs. 5.7
Brandao, 2006 ²² Brazil The results of a randomized trial looking at 24 weeks vs. 48 weeks of treatment with pegylated interferon alfa-2a and ribavirin combination therapy in patients with chronic hepatitis C genotype 1 Overall Quality: Fair	A: Pegylated interferon alfa-2a 180 mcg/week for 24 weeks B: Pegylated interferon alfa-2a 180 mcg/week for 48 weeks	A: 400 mg twice daily for 24 weeks B: 400 mg twice daily for 48 weeks	None	Treatment naïve Aged >18 years HCV RNA >1000 IU/mL ALT above upper limit of normal on two occasions within the last 6 months Liver biopsy in the last 18 month consistent with chronic hepatitis C	Treatment with systemic antivirals, antineoplastics, immunomodulators, or any other investigational drugs with perceived effect against HCV	NR/NR/63/63	(A vs. B): Age mean: 41 vs. 41 Female: 41% vs. 39% Non-white: 19% vs. 16%	(A vs. B): Genotype 1: all HCV RNA >800,000 IU/mL: 72% v 61% Bridging fibrosis: 16% vs. 6%

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Buti, 2010 ²³ International Randomized trial of pegylated interferon alfa- 2b and ribavirin for 48 or 72 weeks in patients with hepatitis C virus genotype 1 and slow virologic response Overall Quality: Fair	All patients were treated for 12 weeks. Patients with a 2 log drop in HCV RNA and undetectable HCV RNA at week 12 were continued until week 48 (group C). Subjects with a 2 log drop in HCV RNA at week 12 and detectable HCV RNA at 12 weeks were continued for another 12 weeks. Subjects with undetectable HCV RNA at week 24 (slow responders) were randomized to groups A or B A: Pegylated interferon alfa-2b 1.5 mcg/kg/week for 48 weeks B: Pegylated interferon alfa-2b 1.5 mcg/kg/week for 72 weeks Non-randomized C: Pegylated interferon alfa-2b 1.5 mcg/kg/week for 48 weeks	All patients were treated for 12 weeks. Patients with a 2 log drop in HCV RNA and undetectable HCV RNA at week 12 were continued until week 48 (group C). Subjects with a 2 log drop in HCV RNA at week 12 and detectable HCV RNA at 12 weeks were continued for another 12 weeks. Subjects with undetectable HCV RNA at week 24 (slow responders) were randomized to groups A or B A: 800-1400 mg/day based on body weight for 48 weeks B: 800-1400 mg/day based on body weight for 72 weeks Nonrandomized C: 800-1400 mg/day based on body weight for 48 weeks	None	Treatment naïve Aged 18-70 years Compensated HCV with confirmed diagnosis of hepatitis by ALT and liver biopsy	Weight >125 kg HIV HBV Liver disease of other etiologies	NR/1427/1 59/159	(A vs. B): Age mean: 45 vs. 47 Female: 40% vs. 37% Non- white: 0% vs. 4.1%	(A vs. B): Genotype 1: all HCV RNA>800,000: 87 vs. 93%

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Dalgard, 2008 ²⁴ Denmark, Sweden, Norway Pegylated interferon alpha and ribavirin for 12 vs. 24 weeks in patients with hepatitis C virus genotype 2 or 3 and rapid virological response Overall Quality: Fair	All patients were treated for 4 weeks. Subjects with rapid virologic response after 4 weeks were randomized to A. or B. Subjects without rapid virologic response were allocated to group C. A: Pegylated interferon alfa-2b 1.5 mcg/kg/week for 14 weeks B: Pegylated interferon alfa-2b 1.5 mcg/kg/week for 24 weeks C: Pegylated interferon alfa-2b 1.5 mcg/kg/week for 24 weeks	All patients were treated for 4 weeks. Subjects with rapid virologic response after 4 weeks were randomized to A or B. Subjects without rapid virologic response were allocated to group C. A: 800-1400 mg/day based on body weight for 14 weeks B: 800-1400 mg/day based on body weight for 24 weeks C: 800-1400 mg/day based on body weight for 24 weeks	None	Treatment naïve HCV RNA positive HCV genotype 2 or 3 Elevated ALT at least once during the prior 6 months	Injection drug use or alcohol abuse in the prior 6 months Poorly controlled psychiatric illnesses Decompensated cirrhosis HBV positive HIV positive Liver disease of other etiologies	NR/428/29 8/298	(A vs. B vs. C) Age median: 38 vs. 38 vs. 43 Female: 36% vs. 35% vs. 41% Non- white: NR	(A vs. B vs. C) Genotype 2/3: all Proportion treatment-naïve: all Fibrosis: NR HCV RNA >400,000: 64% vs. 58% vs. 75% Cirrhosis: NR

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<p>Ferenci, 2010²⁵ Austria</p> <p>Pegylated interferon alfa-2a and ribavirin for 24 weeks in hepatitis C type 1 and 4 patients with rapid virologic response</p> <p>Overall Quality: Poor</p>	<p>All patients were treated for 4 weeks. Subjects with rapid virologic response (HCV-RNA <50 IU/mL) were treated with 24 weeks. Subjects without rapid virologic response continued to week 12 and were re-evaluated. Subjects with early virologic response (HCV RNA <600 IU/mL or a 2 log decrease in serum HCV RNA) were randomized to complete either 48 weeks or 72 weeks of treatment.</p> <p>A: Pegylated interferon alfa-2a 180 mcg/week for 48 weeks B: Pegylated interferon alfa-2a 180 mcg/week for 72 weeks</p>	<p>A: 1000-1200 mg/day depending of body weight for 48 weeks B: 1000-1200 mg/day depending of body weight for 72 weeks</p>	None	<p>Treatment-naïve Ages 18-65 years Chronic HCV genotype 1 or 4 infection Positive HCV antibody test Quantifiable HCV RNA Elevated ALT Histologic findings consistent with chronic hepatitis C on liver biopsy within the previous 6 months Neutrophils >3000 Platelets >100K Hemoglobin > 12 g/dL in women and > 13 g/dL in men Serum creatinine <1.5 times the upper limit of normal Thyroid-stimulating hormone within normal limits</p>	<p>Chronic liver disease of other etiology Evidence of decompensation Co-infection with HBV or HIV Systematic immunomodulatory or antineoplastic therapy within previous 6 months Diabetes mellitus treated with insulin Severe psychiatric disorders History of immunologically mediated disease Other severe chronic or uncontrolled disease</p>	NR/551/289/289	<p>(A vs. B): Age mean: 45 vs. 44 Female 36% vs. 35% non-White: NR</p>	<p>(A vs. B): Genotype 1: 91% vs. 89% Treatment-naïve: all HCV-RNA level >800K IU: 38% vs. 44% Fibrosis stage 3-4: 20% vs. 19%</p>

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Hadziyannis, 2004 ²⁶ Europe, North & South America, Australia, New Zealand, and Taiwan (99 centers world-wide) Peginterferon- α 2a and Ribavirin Combination Therapy in Chronic Hepatitis C Overall Quality: Fair	A: Pegylated interferon alpha-2a 180 μ g/week for 24 weeks B: Pegylated interferon alpha-2a 180 μ g/week for 24 weeks C: Pegylated interferon alpha-2a 180 μ g/week for 48 weeks D: Pegylated interferon alpha-2a 180 μ g/week for 48 weeks	A: ("Low dose -24" or "24-LD") Ribavirin 800 mg/day for 24 weeks B: ("Standard dose-24" or "24-SD") Ribavirin 1000 mg/day for 24 weeks, (Body weight <75kg) or Ribavirin 1200 mg/day for 24 weeks, (Body weight >75kg) C: ("Low dose-48" or "48-LD") Ribavirin 800 mg/day for 48 weeks D: ("Standard dose-48" or "48-SD") Ribavirin 1000 mg/day for 48 weeks, (Body weight <75kg) or Ribavirin 1200 mg/day for 48 weeks, (Body weight >75kg)	None	Treatment naive adults with serum hepatitis C virus (Genotype) RNA concentration greater than 2000 copies/mL Elevated serum alanine aminotransferase(ALT) level documented on 2 or more occasions 14 days or more apart within the previous 6 months Compensated liver disease and a liver biopsyspecimen consistent with chronic hepatitis C obtained in the previous 15 months Patients with compensated cirrhosis or transition to cirrhosis (Child–Pugh class A) Negative pregnancy test result 24 hours before the first dose of study medications	Neutropenia (neutrophil count <1.5 x10 ⁹ cells/L) Thrombocytopenia (platelet count <90x10 ⁹ cells/L) Anemia (hemoglobin level <120 g/L in women and <130 g/L in men) - or a medical condition that would be clinically significantly worsened by anemia Serum creatinine level more than 1.5 times the upper limit of normal Co-infection with hepatitis A or B virus or HIV History of bleeding from esophageal varices or other conditions consistent with Decompensated liver disease Organ transplant Severe or poorly controlled psychiatric disease (especially depression) malignant neoplastic disease Severe cardiac or chronic pulmonary disease Immunologically mediated disease (except controlled thyroid disease) Seizure disorder Severe retinopathy Alcohol or drug dependence within 1 year of study entry Clinically significant co morbid medical conditions Pregnancy or unwillingness to practice contraception	1736/1373/ 1311/1284	(A vs. B vs. C vs. D): Age (mean): 41 vs. 42 vs. 43 years Female: 32% vs. 34% vs. 27% vs. 34% Race: White - 88% vs. 91% vs. 87% vs. 90% Non-White - 12% vs. 9% vs. 13% vs. 10%	(A vs. B vs. C vs. D) Genotype, n (%): Genotype 1 - 101/207(49%) vs. 118/280(42%) vs. 250/361(69%) vs. 271/436(62%) Genotype 2 - 39/207(19%) vs. 53/280(19%) vs. 46/361(13%) vs. 66/436(15%) Genotype 3 - 57/207(28%) vs. 91/280(33%) vs. 53/361(15%) vs. 87/436(20%) Other - 106/207(51%) vs. 162/280(58%) vs. 111/361(31%) vs. 165/436(38%) Histologic diagnosis using Ishak scores: Non-cirrhotic - 163/207(79%) vs. 209/280(75%) vs. 270/361(75%) vs. 321/436(74%) Cirrhosis - 10/207(5%) vs. 20/280(7%) vs. 25/361(7%) vs. 35/436(8%)

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Hadziyannis, 2004 ²⁶ Europe, North & South America, Australia, New Zealand, and Taiwan (99 centers world- wide)					Severe psychiatric disease was defined as treatment with an antidepressant medication or major tranquilizer for major depression or psychosis - for 3+ months /or period of disability due to psychiatric disease History of a suicide attempt/hospitalization			Bridging fibrosis - 34/207(16%) vs. 51/280(18%) vs. 66/361(18%) vs. 80/436(18%) 100% Treatment naïve
Continued								

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Ide, 2009 Japan ²⁷ A Randomized Study of Extended Treatment with Pegylated interferon alpha-2b Plus Ribavirin Based on Time to HCV RNA Negative- status in Patients with Genotype 1b Chronic Hepatitis C Overall Quality: Fair	A: (Standard group - received a 48-week course of treatment) Pegylated interferon α-2b - 1.5 µg/kg/week for 48 weeks B: (Extended group – treatment course performed for 44 weeks after HCV RNA first became negative) Pegylated interferon α-2b - 1.5 µg/kg/week for 48-68 weeks	A: (Standard group - received a 48-week course of treatment) Ribavirin by body weight: < 60 kg - 600 mg/day for 48 weeks 60-80 kg - 800 mg/day for 48 weeks > 80 kg - 1000 mg/day for 48 weeks B: (Extended group – treatment course performed for 44 weeks after HCV RNA first became negative) Ribavirin by body weight: < 60 kg - 600 mg/day for 48-68 weeks 60-80 kg - 800 mg/day for 48-68 weeks > 80 kg - 1000 mg/day for 48-68 weeks	None	Male and female patients aged 20–75 years Compensated chronic HCV genotype 1b infection Positive for HCV RNA by a quantitative reverse-transcription PCR with a concentration >100K IU / ml At least one elevated serum alanine aminotransferase level at the time of screening or entry into the trial	Patients with an HCV genotype other than 1b infection Hepatitis B surface antigen Autoimmune hepatitis Primary biliary cirrhosis Sclerosing cholangitis Decompensated cirrhosis (Child – Pugh class B or C) Evidence of hepatocellular carcinoma Patients with platelet counts of < 8 x 10 ⁴ /mm ³ , leukocyte counts of 2,500/ml or less, or hemoglobin levels of < 12 g/dl	NR/NR/113 /113	(A vs. B): Age (Mean): 55.3 vs. 54.6 years Female: 53.6% vs. 47.4% Non- white: NR	(A vs. B): Genotype 1b: 100% Fibrosis Stage (Desmet et al 1994): 1/2 - 67.8% vs. 52.6% 3/4 - 19.6% vs. 19.3% Treatment naïve: NR

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Kamal, 2005 ²⁸ Egypt Pegylated interferon alpha-2b and ribavirin therapy in chronic hepatitis C genotype 4: impact of treatment duration and viral kinetics on sustained virological response Overall Quality: Fair	A: Pegylated interferon alfa-2b 1.5 µg/kg for 24 weeks B: Pegylated interferon alfa-2b 1.5 µg/kg for 36 weeks C: Pegylated interferon alfa-2b 1.5 µg/kg for 48 weeks	A: Ribavirin 10.6 mg/kg/day for 24 weeks B: Ribavirin 10.6 mg/kg/day for 36 weeks C: Ribavirin 10.6 mg/kg/day for 48 weeks	None	Documented chronic hepatitis C according to the following criteria: elevated serum alanine aminotransferase (ALT) above the upper limit of normal (40 U/l) on two occasions during the preceding six months Anti-HCV positive antibody status assessed by second generation enzyme linked immunosorbent assay Positive polymerase chain reaction for HCV RNA Genotype 4 Chronic hepatitis C in liver biopsy performed within the preceding year with no signs of cirrhosis or bridging fibrosis on pretreatment liver biopsy	Previous IFN-a therapy Other liver diseases such as hepatitis A, hepatitis B, schistosomiasis, autoimmune hepatitis, alcoholic liver disease, drug induced hepatitis, or decompensated liver disease Co infection with schistosomiasis or human immunodeficiency virus Neutropenia (1,500/mm ³) Thrombocytopenia (90,000/mm ³) Creatinine concentration >1.5 x the upper limit of normal Serum a fetoprotein concentration >25 ng/ml Organ transplant Neoplastic disease Severe cardiac or pulmonary disease Unstable thyroid dysfunction Psychiatric disorder Current pregnancy or breast feeding Therapy with immunomodulatory agents within the last six months	335/287/27 9/271	(A vs. B vs. C): Age (Mean):4 2 vs. 44 vs. 41 Female:4 8% vs. 47% vs. 48% Non- white: NR	(A vs. B vs. C): Genotype 4: 100% (Ishak et al 1995) Inflammation grade (mean): 8.2 vs. 7.6 vs. 9.1 Fibrosis stage (mean): 1.8 vs. 2.3 vs. 2.1 HCV RNA mean: 2.8 vs. 2.7 vs. 2.8 Treatment naïve: 100%

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Lagging, 2008 ²⁹ Denmark & Finland Randomized Comparison of 12 or 24 Weeks of Pegylated interferon alpha-2a and Ribavirin in Chronic Hepatitis C Virus Genotype 2/3 Infection Overall Quality: Fair	A: Pegylated interferon alfa-2a 180 µg/week for 12 weeks B: Pegylated interferon alfa-2a 180 µg/week for 24 weeks	A: Ribavirin 800 mg/day (2 equal doses) for 12 weeks B: Ribavirin 800 mg/day (2 equal doses) for 24 weeks	None	Adults age 18 years and older Compensated liver disease Treatment-naïve for hepatitis C Seronegative for hepatitis B surface antigen and for antibodies to human immunodeficiency virus Positive test for anti- HCV antibody Infection with HCV genotypes 2 and/or 3 but not genotypes 1, 4, 5, or 6 HCV-RNA 600 IU/mL within 6 months of treatment initiation Liver biopsy consistent with chronic hepatitis C within 24 months of entry	NR	392/382/38 2/382	(A vs. B): Age (Mean): 42 vs. 42 years Female: 37% vs. 44% Non- white: NR	(A vs. B): Genotype 2: 28% vs. 26% Genotype 3: 71% vs. 74% Bridging fibrosis (Ishak stage 3-4): 39% vs. 40% Cirrhosis (Ishak stage 5-6): 13% vs. 13% Steatosis present (grade 1-3): 64% vs., 69% Moderate or severe steatosis (grade 2- 3): 29% vs. 27% Treatment naïve : 100%

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Lam, 2010 ³⁰ California & Texas, USA (limited to Southeast Asian populations) Randomized Control Trial of Pegylated Interferon-Alfa 2a and Ribavirin in Treatment- naïve Chronic Hepatitis C Genotype 6 Overall Quality: Fair	A: Pegylated interferon alfa-2a 180 µg/week for 24weeks B: Pegylated interferon alfa-2a 180 µg/week for 48 weeks	A: Ribavirin 800- 1200 mg/day for 24 weeks B: Ribavirin 800- 1200 mg/day for 48 weeks	None	Treatment-naïve patients with CHC between 18 and 70 years of age Southeast Asian ethnicities Positive anti-HCV and positive HCV RNA polymerase chain reaction (PCR) Presence of HCV genotype 6 or its subtypes Stage 1 or more fibrosis by the METAVIR scoring system Evidence of chronic hepatitis on liver histology Compensated liver disease Absence of hepatocellular carcinoma by imaging studies Presence of alpha- fetoprotein (AFP)	Pregnancy Suspected hypersensitivity to IFN or PEG IFN, or RBV Receiving treatment with any other systemic antiviral, antineoplastic, or immunomodulating treatment less than 6 months prior to first dose of study drug Any types of liver diseases other than CHC, anemia, or having decompensated cirrhosis (Child- Pugh score >6, coagulopathy, hyperbilirubinemia, hepatic encephalopathy, hypoalbuminemia, ascites, bleeding from esophageal varices). Co infection with hepatitis B virus or human immunodeficiency virus Organ transplant history Pre-existing medical conditions that could interfere with subjects' participation in protocol including severe psychiatric illness or poorly controlled cardiac, pulmonary, or diabetic disease	75/68/60/ 60	(A vs. B): Age (Mean): 50 vs. 53 years Female: 42% vs. 54% Non- white: 100%	(A vs. B): Genotype 6: 100% ALT (Mean): 84.6 vs. 64.6 U/L, p=0.14 HCV RNA (Mean): 6.24 vs. 6.28 log IU/mL, p=0.14 Low (< 800,000 IU/mL) 26% vs. 36%, p=0.39 High (> 800,000 IU/mL) 74% vs. 64% Liver histology (METAVIR scoring) Stage (Mean) - 2.14 vs. 2.09, p=0.81 Grade (Mean) - 2.15 vs. 2.21, p=0.77 Sever fibrosis or cirrhosis: 26% vs. 27% Treatment naïve – 100%

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Liu, 2008 ³¹ Taiwan Pegylated Interferon- alpha-2a plus Ribavirin for Treatment- Naïve Asian Patients with Hepatitis C Virus Genotype 1 Infection: A Multicenter Randomized Controlled Trial Overall Quality: Fair	A: Pegylated interferon alfa-2a 180 µg/week for 24 weeks B: Pegylated interferon alfa-2a 180 µg/week for 48 weeks	A: (24-week group) Ribavirin by body weight: < 75 kg - 1000 mg/day for 24 weeks > 75 kg - 1200 mg/day for 24 weeks B: (48-week group) Ribavirin by body weight: < 75 kg - 1000 mg/day for 48 weeks > 75 kg - 1200 mg/day for 48 weeks	None	Treatment-naïve patients with chronic hepatitis C Aged >18 years Presence of anti-HCV antibody Detectable serum HCV RNA level determined by real-time RT-PCR analysis for 16 months HCV-1 infection confirmed by a reverse hybridization assay Serum alanine aminotransferase (ALT) level > upper limit of normal Liver histologic characteristics consistent with chronic viral hepatitis within the previous 3 months	Anemia (hemoglobin level,<13 g/dL for men and <12 g/dL for women) Neutropenia (neutrophil count, <1500 cells/mm ³) Thrombocytopenia (platelet count, <70,000 cells/mm ³) Mixed infection with HCV-1 and another genotype of HCV Co infection with hepatitis B virus or HIV Chronic alcohol abuse (daily alcohol consumption, 120 g/day) Decompensated cirrhosis (Child- Pugh class B or C) Serum creatinine level 11.5x the upper limit of normal Autoimmune liver disease Neoplastic disease Organ transplantation or immunosuppressive therapy Evidence of drug abuse Pregnancy Poorly controlled autoimmune disease Cardiopulmonary disease Neuropsychiatric disorders Diabetes mellitus with retinopathy Unwillingness to receive contraception during the study period	768/326/30 8/308	(A vs. B): Age (Mean): 54 vs. 53 years Female: 42.9% vs. 43.5% Non- white: NR	(A vs. B): Genotype 1a: 2.6% vs. 1.9% Genotype 1b: 92.9% vs. 94.2% Genotype 1a & 1b: 4.5% vs. 3.9% Fibrosis (Ishak 1995)- > 3 : 78.6% vs. 76.0% 6: 22.7% vs. 20.1% Steatosis - present: 44.2% vs. 41.6% absent: 55.8% vs. 58.4% Treatment naïve: 100%

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Mangia, 2005 ³² Italy Pegylated interferon alfa- 2b and Ribavirin for 12 vs. 24 Weeks in HCV Genotype 2 or 3 Overall Quality: Fair	A: Pegylated interferon alfa-2b 1.0 µg/kg/week for 24 weeks (control standard duration group) B: Pegylated interferon alfa-2b 1.0 µg/kg/week for 12 or 24 weeks depending on if HCV RNA at week 4 (variable duration group)	A: (control standard duration group) Ribavirin by body weight: < 75 kg - 1000 mg/day for 24 weeks > 75 kg - 1200 mg/day for 24 weeks B: (variable duration group) Ribavirin by body weight: < 75 kg - 1000 mg/day for 48 weeks > 75 kg - 1200 mg/day for 48 weeks	None	18 to 70 years of age Presence of antibodies to HCV Infection with genotype 2 or 3 Abnormal alanine aminotransferase levels Treatment naïve	Leukocyte count < 3000/cubic millimeter Platelet count < 80,000/cubic millimeter Hemoglobin level <12 g/deciliter for women and <13 g/deciliter for men Infection with the human Immunodeficiency virus (HIV) Alcohol intake > 20 g daily Presence of drug abuse Presence of Chronic disease Presence of Psychiatric disease Presence of Autoimmune disease Presence of Pregnancy and lactation	NR/NR/283 /283	(A vs. B): Age (Mean): 49.7 vs. 46.6 years Female: 44% vs. 44% Non- white: NR	(A vs. B): Genotype 2: 76% vs. 75% Genotype 3: 24% vs. 25% HCV-RNA (>800,00 IU/mL): 66% vs. 64% Liver fibrosis (Scheuer 1991): stage > 3 - 23% vs. 16% Steatosis: (moderate/severe) - 36% vs. 31% Treatment naïve: 100%

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Mecenate, 2010 ³³ Italy Short vs. standard treatment with pegylated interferon alfa- 2A plus ribavirin in patients with hepatitis C virus genotype 2 or 3: the CLEO trial Overall Quality: Fair	Patients with negative HCV RNA at week 4 randomized to either 12 or 24 weeks of treatment A1: Pegylated interferon alpha-2a 180 µg/week for 12 weeks A2: Pegylated interferon alpha-2a 180 µg/week for 24 weeks B: Pegylated interferon alpha-2a 180 µg/week for 24 weeks (nonrandomized arm of patient without rapid virologic response)	Patients with negative HCV RNA at week 4 randomized to either 12 or 24 weeks A1: Ribavirin 800- 1200 mg daily for 12 weeks A2: Ribavirin 800- 1200 mg daily for 24 weeks B: Ribavirin 800- 1200 mg daily for 24 weeks (non- randomized arm of patient without rapid virologic response)	None	HCV-RNA positive HCV genotype 2 or 3 Elevated alanine aminotransferase (>40 U/L) at least 8 months prior to study entry Histologically proven chronic HCV hepatitis	History of injected drugs or alcohol abuse (>40 g ethanol/day) within the 6 months prior to study entry Poorly controlled psychiatric illness Decompensated cirrhosis Positive for human immunodeficiency antibody virus (HIV) or positive for hepatitis B surface antigen (HBV) Pregnancy Lactation Impaired renal function Other concurrent medical conditions of the liver different from HCV infection	NR/210/14 3/143	(All groups - not broken down by arm) Age (Mean): 43 years Female: 19% Non- white: NR	(All groups - not broken down by arm) Genotype 2: 55% Genotype 3: 45% Cirrhosis (Ishak stage 5-6): 10% Bridging fibrosis (Ishak stage 3-4): 19% Treatment naïve: NR

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Pearlman, 2007 ³⁴ Atlanta, GA - USA Treatment Extension of 72 Weeks of Pegylated interferon and Ribavirin in Hepatitis C Genotype 1- Infected Slow Responders Overall Quality: Fair	A: (Standard) Pegylated interferon α-2b - 1.5 µg/kg/week for 48 weeks B: (Extended) Pegylated interferon α-2b - 1.5 µg/kg/week for 72 weeks	A: (Standard) Ribavirin by body weight: < 64 kg - 800 mg/day for 48 weeks 65 - 84 kg - 1000 mg/day for 48 weeks 85 - 104 kg - 1200 mg/day for 48 weeks >105 kg - 1400 mg/day for 48 weeks B: (Extended) Ribavirin by body weight: < 64 kg - 800 mg/day for 72 weeks 65 - 84 kg - 1000 mg/day for 72 weeks 85 - 104 kg - 1200 mg/day for 72 weeks >105 kg - 1400 mg/day for 72 weeks	None	Chronic HCV genotype 1–infected patients Baseline elevated serum alanine aminotransferase levels Detectable serum HCV-RNA via nucleic acid testing Treatment-naïve Age >18 years Liver biopsy in the past 2 years consistent with chronic hepatitis	HCV/human immunodeficiency virus co infection HCV genotype other than 1 Decompensated cirrhosis Other causes of liver disease, including co infection with hepatitis B Creatinine clearance <50 mL/minute (modification of diet in renal disease equation) Platelet count <80x10 ⁹ /L Neutrophil count <1.5x10 ⁹ /L Hemoglobin concentration 13 g/dL and 12 g/dL in men and women Co-existing uncontrolled psychiatric or cardiopulmonary disorders Hemoglobinopathy Sarcoidosis Malignant neoplasm Receipt of immunosuppressive or immunomodulatory therapy in the previous 6 months Pregnancy Men whose partners were pregnant or unwilling to use contraception during the study period Patients were also excluded if they imbibed significant amounts of alcohol (30 g/day) Active substance abusers in the past 6 months	NR/112/10 1/101	(A vs. B): Age (Mean): 56 vs. 54 years Female: 33% vs. 35% Non- white: 47% vs. 48%	(A vs. B): Genotype 1 : 100% Fibrosis (METAVIR) F3/F4 - 27% vs. 25%, p=.86 Treatment-naïve: 100%

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Sanchez-Tapias, 2006 ³⁵ Spain Peginterferon- Alfa2a Plus Ribavirin for 48 Vs. 72 weeks in Patients with Detectable Hepatitis C Virus RNA at Week 4 of Treatment Overall Quality: Fair	Patients with positive HCV RNA at week 4 randomized to 48 or 72 weeks A: (Total treatment duration, 48 weeks) Pegylated interferon- alfa-2a 180 µg/week for 48 weeks B: (Total treatment duration, 72 weeks) Pegylated interferon- alfa-2a 180 µg/week for 72 weeks Arms C and D not randomized (24 or 48 by genotype) C: (Total treatment duration, 24 weeks: RVR at week 4 and HCV-RNA levels <800,000 IU/mL) Pegylated interferon- alfa-2a 180 µg/week for 24 weeks D: (Total treatment duration, 48 weeks: Genotype 1/4, RVR at week 4 and HCV- RNA levels >800,000 IU/mL) Pegylated interferon-alfa-2a 180 µg/week for 48 weeks	Patients with positive HCV RNA at week 4 randomized to 48 or 72 weeks A: (Total treatment duration, 48 weeks) Ribavirin 800 mg/day for 48 weeks B: (Total treatment duration, 72 weeks) Ribavirin 800 mg/day for 72 weeks Arms C and D not randomized (24 or 48 by genotype) C: (Total treatment duration, 24 weeks: RVR at week 4 and HCV- RNA levels <800,000 IU/mL) Ribavirin 800 mg/day for 24 weeks D: (Total treatment duration, 48 weeks: Genotype 1/4, RVR at week 4 and HCV-RNA levels >800,000 IU/mL) Ribavirin 800 mg/day for 48 weeks	None	Treatment-naïve patients with CHC consecutively referred to 28 specialist hepatology centers in Spain Older than 18 years Persistent increase of serum alanine transaminase levels during the past 6 months Positive anti-HCV antibody test Serum HCV-RNA concentration greater than 600 IU/mL Histologic evidence of chronic hepatitis in a liver biopsyspecimen obtained within the preceding 24 months Written informed consent to participate in the study All participants had to use 2 forms of effective contraception during treatment and throughout the 24- week followup phase of the study	Decompensated liver disease Co-existing serious medical or psychiatric illness Liver disease other than that caused by HCV infection Neutrophil count less than 1.5 x10 ⁹ /L Platelet count less than 90x10 ⁹ /L Hemoglobin concentration less than 12 g/dL in women or less than 13 g/dL in men Serum creatinine level greater than 1.5 times the upper limit of the normal range Presence of co-infection with hepatitis A virus Hepatitis B virus or human immunodeficiency virus (HIV) Patients who received any systemic antiviral, antineoplastic, or immunomodulatory therapy within 6 months before the study Pregnant and breast-feeding women and male partners of pregnant women	NR/NR/522 /522 Randomize d population: 326/326	(A vs. B vs. C vs. D): Age (Mean): 42.8 vs. 43.2 vs. 39.3 vs. 42.4 years Female: 21% vs. 27% vs. 30% vs. 44% Non- white: NR	(A vs. B vs. C vs. D): Genotype 1: 90.3% vs. 88.2% vs. 30.4% vs. 97% Genotype 2: .6% vs. .6% vs. 12.2% vs. 0% Genotype 3: 4% vs. 5% vs. 50.7% vs. 0% Genotype 4: 5% vs. 5% vs. 6.8% vs. 3% Other (not- typeable): 0% vs. 1.2% vs. 0% vs. 0% HCV-RNA>800,00 IU/mL (Mean): 963 vs. 1110 vs. 648 vs. 1612 Treatment naïve: 100%

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Shiffman, 2007 ³⁶ 132 centers worldwide Pegylated interferon alfa- 2a and Ribavirin for 16 or 24 Weeks in HCV Genotype 2 or 3 Overall Quality: Good	A: Pegylated interferon alfa-2a 180 µg/week for 16 weeks B: Pegylated interferon alfa-2a 180 µg/week for 24 weeks	A: Ribavirin 800 mg/day for 16 weeks B: Ribavirin 800 mg/day for 24 weeks	None	Eligible patients were those who were 18 years of age or older Infected with HCV genotype 2 or 3 Had a quantifiable serum HCV RNA level (>600 IU per milliliter) Elevated serum alanine transaminase level Findings on liver biopsy consistent with chronic HCV infection	Other liver diseases Human immunodeficiency virus (HIV) Hepatocellular carcinoma Severe depression or another severe psychiatric disease Clinically significant cardiovascular or renal disease Uncontrolled seizure disorder Severe retinopathy Previously received interferon or ribavirin (not treatment naïve) Patients with cirrhosis had to have a Child–Pugh score of less than 7 to be eligible	1810/1469/ 1469/1465	(A vs. B): Age (Mean): 46 vs. 45.6 years Female: 39% vs. 37% Non- white: 13% vs. 13%	(A vs. B): Genotype 2: 50.8% vs. 48.7% Genotype 3: 49.2% vs. 51.3% Steatosis (% of hepatocytes): none - 20% vs. 21% >0-5% - 26% vs. 25% 6-33% - 12% vs. 12% 34-66% - 7% vs. 7% >66% - 2% vs. <1% unknown - 33% vs. 34% Treatment naïve: 100%

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Von Wagner, 2005 ³⁷ Germany Peginterferon- alpha-2a (40KD) and Ribavirin for 16 or 24 Weeks in Patients with Genotype 2 or 3 Chronic Hepatitis C Overall Quality: Fair	Patients with negative HCV RNA at week 4 randomized to either 16 or 24 weeks of treatment A: Pegylated interferon alfa-2a 180 µg/week for 16 weeks B: Pegylated interferon alfa-2a 180 µg/week for 24 weeks C: Pegylated interferon alfa-2a 180 µg/week for 24 weeks (non randomized patients who did not achieve RVR)	A: Ribavirin by body weight: < 65 kg - 800 mg/day for 16 weeks 65 - 85 kg - 1000 mg/day for 16 weeks > 85 kg - 1200 mg/day for 16 weeks B: Ribavirin by body weight: < 65 kg - 800 mg/day for 24 weeks 65 - 85 kg - 1000 mg/day for 24 weeks > 85 kg - 1200 mg/day for 24 weeks C: (Non- randomized): Ribavirin by body weight: < 65 kg - 800 mg/day for 24 weeks 65 - 85 kg - 1000 mg/day for 24 weeks > 85 kg - 1200 mg/day for 24 weeks	None	Male and female patients above 18 years of age with compensated chronic HCV infection not previously treated with interferon and/or ribavirin Tested positive for anti-HCV antibody and for HCV RNA (600 IU/mL by quantitative reverse transcription- polymerase chain reaction) Had a liver biopsy specimen taken within 18 months prior to the screening visit showing chronic hepatitis Had at least 1 serum alanine aminotransferase (ALT) level elevated at screening or entry into the trial Entry neutrophil and platelet counts at least 1500/L and 90,000/L, respectively Hemoglobin values at entry visit at least 12 g/dL for females and at least 13 g/dL for males	Any other cause of liver disease or other relevant disorders including human immunodeficiency or hepatitis B virus co infection Clinically significant hematologic, hepatic, metabolic, renal, rheumatologic, neurologic, or psychiatric disease Clinically significant cardiac or cardiovascular abnormalities; Organ grafts Systemic infection Clinically significant bleeding disorders Evidence of malignant neoplastic disease Concomitant immunosuppressive medication Excessive daily intake of alcohol or drug abuse within the past year Pregnancy and lactation, and male partners of pregnant women	NR/153/15 3/153	(A vs. B vs. C): Age (Mean): 38 vs. 39 vs. 42 years Female: 26% vs. 42% vs. 64% Non- white: MR	(A vs. B vs. C): Genotype 2: 27% vs. 27% vs. 9% Genotype 3: 72% vs. 73% vs. 91% Fibrosis (Mean Ishak score): A (interface hepatitis) - 1 vs. 1.1 vs. 1.4 B (confluent necrosis) - 0.3 vs. 0.4 vs. 0.4 C (focal inflammation) - 1.4 vs. 1.4 vs. 1.4 D (portal inflammation) - 1.6 vs. 1.7 vs. 1.8 A-D (total inflammation) - 4.3 vs. 4.6 vs. 5.0 F (fibrosis) - 1.6 vs. 1.6 vs. 2.4 Cirrhosis: NR Treatment naive: 100%

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Yu, 2006 ³⁸ Taiwan A randomized trial of 24- vs. 48-week courses of PEG interferon alpha-2b plus ribavirin for genotype-1b- infected chronic hepatitis C patients: a pilot study in Taiwan Overall Quality: Fair	A: Pegylated interferon alpha-2b by body weight: < 60 kg - 80 µg/week for 24 weeks > 60 kg - 100 µg/week for 24 weeks B: Pegylated interferon alpha-2b by body weight: < 60 kg - 80 µg/week for 48 weeks > 60 kg - 100 µg/week for 48 weeks	A: Ribavirin by body weight: < 75 kg - 1000 mg/day for 24 weeks > 75 kg - 1200 mg/day for 24 weeks B: Ribavirin by body weight: < 75 kg - 1000 mg/day for 48 weeks > 75 kg - 1200 mg/day for 48 weeks	None	Eligible subjects were previously untreated Taiwanese chronic hepatitis C patients 18 to 65 years old, who: (1) Were seropositive for HCV antibodies and HCV RNA by polymerase chain reaction (PCR); (2) Had undergone a liver biopsy within 1 year before entry that was consistent with chronic hepatitis; (3) Had displayed elevated serum alanine transaminase (ALT), defined as >1.5 times the upper limit of the normal range for at least two measurements within 6 months preceding the trial entry; (4) Possessed an HCV genotype 1b infection Neutrophil count greater than 1500/mm ³	Patients with HCV genotype other than 1b infection Hepatitis B surface antigen Human immunodeficiency virus infection Autoimmune hepatitis Primary biliary cirrhosis Sclerosing cholangitis Wilson's disease a1-antitrypsin deficiency Decompensated cirrhosis (Child- Pugh class B or C) Overt hepatic failure History of alcohol abuse Psychiatric condition Previous liver transplantation or with evidence of hepatocellular carcinoma	NR/NR/60/ 60	(A vs. B): Age (Mean): 45.4 vs. 45.1 years Female: 38% vs. 27% Non- white: NR	(A vs. B): Genotype 1b: 100% Fibrosis Score (Knodell, 1981): Score 0–2 - 71.1% vs. 73.3% Score 3–4 - 28.9% vs. 26.7% Treatment naïve: 100%

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Yu, 2006 ³⁸ Taiwan Continued				Platelet count greater than 1x10 ⁵ /mm ³ Hemoglobin level greater than 13 g/dl for males and 12 g/dl for females Serum creatinine level less than 1.5 mg/dl No pregnancy or lactation and the use of a reliable method of contraception				
Yu, 2007 ³⁹ Taiwan A randomized study of pegylated interferon and ribavirin for 16 vs. 24 weeks in patients with genotype 2 chronic hepatitis C Overall Quality: Fair	A: Pegylated interferon alfa-2a 180 µg/week for 24 weeks B: Pegylated interferon alfa-2a 180 µg/week for 16 weeks	A: Ribavirin by body weight: < 75 kg - 1000 mg/day for 24 weeks > 75 kg - 1200 mg/day for 24 weeks B: Ribavirin by body weight: < 75 kg - 1000 mg/day for 16 weeks > 75 kg - 1200 mg/day for 16 weeks	None	Eligible patients were previously untreated Taiwanese patients with CHC, aged 18–65 years, who: (1) Were seropositive for HCV antibodies (2) Had undergone a liver biopsy within 1 year before entry, the result of which was consistent with chronic hepatitis (3) Displayed an increased serum alanine transaminase level, defined as >1.5 times the upper limit of the normal range for at least two measurements within 6 months preceding the trial entry (4) Had HCV2 infection	Patients with an HCV genotype infection other than type 2 infection Hepatitis B surface antigen HIV infection Autoimmune hepatitis Primary biliary cirrhosis Sclerosing cholangitis Wilson's disease α1-antitrypsin deficiency Decompensated cirrhosis (Child–Pugh class B or C) Overt hepatic failure Current alcohol misuse or history of alcohol misuse (>20 g/day) Psychiatric condition Previous liver transplantation Evidence of hepatocellular carcinoma were excluded from the study	326/152/150/150	(A vs. B): Age (Mean): 49.4 vs. 50.2 years Female: 40% vs. 34% Non-white: NR	(A vs. B): Genotype 2 - 100% Fibrosis (Knodell) F 0–2 - 80% vs. 78% F 3–4 - 20% vs. 22% Steatosis None (0) - 67% vs. 68% Mild (1) - 28% vs. 26% Moderate to severe (2–3) - 5% vs. 6% Treatment naïve: NR

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Yu, 2007 ³⁹ Taiwan Continued				Neutrophil count >1500/mm ³ Platelet count >9x10 ⁴ /mm ³ Hemoglobin concentration >12 g/dl for men, and 11 g/dl for women Serum creatinine concentration < 1.5 mg/dl No pregnancy or lactation Use of a reliable method of contraception for women				

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Yu, 2008 ⁴⁰ Taiwan Rapid Virological Response and Treatment Duration for Chronic Hepatitis C Genotype 1 Patients: A Randomized Trial Overall Quality: Fair	A: Pegylated interferon alfa-2a 180 µg/week for 24 weeks B: Pegylated interferon alfa-2a 180 µg/week for 48 weeks	A: Ribavirin by body weight: < 75 kg - 1000 mg/day for 24 weeks > 75 kg - 1200 mg/day for 24 weeks B: Ribavirin by body weight: < 75 kg - 1000 mg/day for 48 weeks > 75 kg - 1200 mg/day for 48 weeks	None	Eligible patients were previously untreated Taiwanese patients with CHC, aged 18–65 years, who: (1) Were seropositive for HCV antibodies (2) Had undergone a liver biopsy within 1 year before entry, the result of which was consistent with chronic hepatitis (3) Displayed an increased serum alanine transaminase level, defined as >1.5 times the upper limit of the normal range for at least two measurements within 6 months preceding the trial entry (4) Had HCV2 infection Neutrophil count >1500/mm ³ Platelet count >9x10 ⁴ /mm ³ Hemoglobin concentration >12 g/dl for men, and 11 g/dl for women Serum creatinine concentration < 1.5 mg/dl	Patients with an HCV genotype infection other than type 1 infection Hepatitis B surface antigen HIV infection Autoimmune hepatitis Primary biliary cirrhosis Sclerosing cholangitis Wilson's disease a1-antitrypsin deficiency Decompensated cirrhosis (Child– Pugh class B or C) Overt hepatic failure Current alcohol misuse or history of alcohol misuse (>20 g/day) Psychiatric condition Previous liver transplantation Evidence of hepatocellular carcinoma were excluded from the study	NR/NR/200 /200	(A vs. B): Age (Mean): 49.7 vs. 49.1 years Female: 43% vs. 42% Non- white: NR	(A vs. B): Genotype 1 - 100% Fibrosis (Knodell) F 0–2 - 75% vs. 81% F 3–4 - 25% vs. 19% Treatment naïve: NR

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Yu, 2008 ⁴⁰ Taiwan Continued				No pregnancy or lactation Use of a reliable method of contraception for women				

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Zeuzem, 2004 ⁴¹ Australia, Europe, New Zealand, North & South America Pegylated interferon alfa-2a (40 Kilodaltons) and Ribavirin in Patients with Chronic Hepatitis C and Normal Aminotransferase Levels Overall Quality: Fair	A: Pegylated interferon alfa-2a 180 µg/week for 24 weeks B: Pegylated interferon alfa-2a 180 µg/week for 48 weeks C: No treatment	A: Ribavirin 800 mg/day (2 equal doses) for 24 weeks B: Ribavirin 800 mg/day (2 equal doses) for 48 weeks C: No treatment	None	Treatment-naïve patients aged 18 years or older with a positive antibody to hepatitis C virus (HCV) antibody test Detectable HCV RNA in serum Biopsy findings consistent with a diagnosis of chronic hepatitis C Persistently normal ALT levels (equal to or below the upper limit) of normal (ULN) documented on at least 3 occasions, a minimum of 4 weeks apart, with at least one value obtained during the 42-day screening period and at least one value obtained 6-18 months before screening.	No histologic evidence of liver disease One or more elevated ALT values (i.e., greater than the ULN) within the previous 18 months Patients with transition to cirrhosis or cirrhosis on liver biopsy History of bleeding from esophageal varices Other conditions consistent with decompensated liver disease were excluded to avoid the possibility of including individuals whose ALT levels had returned to the normal range as a consequence of advanced liver disease Neutropenia (absolute neutrophil count 1500 cells/mm ³) Thrombocytopenia (90,000 platelets/mm ³) Anemia (hemoglobin concentration 12 g/dL in women and 13 g/dL in men) or a medical condition that would be significantly worsened by anemia Serologic evidence of infection with human immunodeficiency virus or hepatitis A or B virus, and serum creatinine level 1.5 times the ULN Organ transplant recipients Individuals with severe cardiac disease History of severe psychiatric disease (especially depression) Evidence of drug abuse (including excessive alcohol consumption) within the preceding year	NR/NR/514/491	A vs. B vs. C: Age (Mean): 44 vs. 44 vs. 41 years Female: 58% vs. 61% vs. 62% Non-white race: 14% vs. 14% vs. 17%	(A vs. B vs. C): Genotype 1: 68% vs. 67% vs. 68% Genotype 1a: 36% vs. 42% vs. 38% Genotype 1b: 31% vs. 25% vs. 30% Genotype (other type 1): 1% vs. 0% vs. 0% Genotype 2: 18% vs. 20% vs. 19% Genotype 3: 9% vs. 9% vs. 9% Genotype 4: 4% vs. 4% vs. 3% Genotype 5: 1% vs. 0% vs. 0% Genotype 6: 1% vs. 1% vs. 1% Cirrhosis: 0% vs. 1% vs. 0% Fibrosis (Ishak): 0-1: 66% vs. 69% vs. 77% 2: 21% vs. 20% vs. 14% 3-4: 12% vs. 9% vs. 7% >4: 0% vs. 1% vs. 0% Treatment naïve: 100%

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Zeuzem , 2004 ⁴¹ Australia, Europe, New Zealand, North & South America Continued					Other serious systemic disease Pregnant or lactating women and male partners of pregnant women. All fertile men and women who participated in the trial were required to use two forms of effective contraception during treatment and for 6 months after the end of treatment			

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Andriulli, 2008 ¹⁹ Italy Early discontinuation of ribavirin in HCV-2 and HCV-3 patients responding to Peg-interferon alpha-2a and ribavirin Overall Quality: Fair	Followup visits at 24 weeks after completion of treatment	(A vs. B): SVR: 32 /59 (54%) vs. 50 / 61 (82%); p<0.001	NR (only one arm reported)	(A vs. B): Baseline HCV RNA<300K: 12/14 (86%) vs. 17/21 (81%); p=NS Baseline HCVRNA 300K-700K: 7/10 (70%) vs. 10/14 (71%); p=NS Baseline HCVRNA >700K: 13/35 (37%) vs. 23/26 (88%); p<0.001	NR	(A vs. B): Overall withdrawals: NR Withdrawals for adverse events: 5/120 (4%) vs. 2/24(8%); p=0.33 Serious adverse events: NR Deaths: NR Interferon-related adverse events: 66% vs. 63% Neutrophils <1000 at 12 weeks: 17% vs. 16%	Investigator funded
Berg T, 2006 ²⁰ Germany Extended treatment duration for hepatitis C virus type 1: Comparing 48 vs. 72 weeks of pegylated interferon alfa-2a plus ribavirin Overall Quality: Fair	Followup visits at 24 weeks after completion of treatment	(A vs. B): SVR: 121/230 (53%) vs. 121/225 (54%); p=0.8	(A vs. B): White: 115/222 (52%) vs. 115/213 (54%); p=NS non-White: 6/8 (75%) vs. 6/12 (50%); p=NS Male: 73/128 (57%) vs. 66/122 (54%); p=NS Female: 48/102 (47%) vs. 55/103 (53%); p=NS	(A vs. B): Genotype 1b: 75/155 (48%) vs. 66/132 (50%); p=NS Genotype 1a: 38/60 (63%) vs. 40/67 (60%); p=NS Genotype 1a/1b: 4/6 (67%) vs. 13/18 (72%); p=NS Fibrosis Stage 0-2: 117/214 (55%) vs. 116/205 (57%); p=NS Fibrosis Stage 3-4: 4/16 (25%) vs. 5/20 (25%); p=NS	NR	(A vs. B): Overall withdrawals: 55/230 (24%) vs. 92/225 (41%); p<0.001 Withdrawals due to adverse events: 21/230 (9%) vs. 26/225 (12%); p=NS Serious adverse events: 15.6% vs. 11.1%; p=NS Deaths: NR	Roche

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Berg, 2009 ²¹ Germany Individualized treatment strategy according to early viral kinetics in hepatitis C virus type 1-infected patients Quality: Poor	Followup visits at 24 weeks after completion of treatment	(A vs. B): SVR: 72/208 (35%) vs. 108/225 (48%); p=0.005	NR	NR	NR	(A vs. B): Overall withdrawals: 63/208 (30.3%) vs. 71/225 (31.6%); p=ns Withdrawals for adverse events: 4 / 208 (1.9%) vs. 7/226 (3.1%); p=ns Serious adverse events: 5/208 (2.6%) vs. 14/225 (6.2%); p=ns Deaths: NR Other adverse events not reported	Schering- Plough

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Brandao, 2006 ²² Brazil The results of a randomized trial looking at 24 weeks vs. 48 weeks of treatment with pegylated interferon alfa-2a and ribavirin combination therapy in patients with chronic hepatitis C genotype 1 Overall Quality: Fair	Followup visits at 24 weeks after completion of treatment	(A vs. B): SVR: 6/32 (19%) vs. 15/31 (48%)	NR	(A vs. B): Baseline HCVRNA <800K IU/mL: 3/9 (33%) vs. 7/12 (58%); p=NS Baseline HCVRNA >800K IU/mL: 3/23 (13%) vs. 8/19 (43%); p=NS Bridging fibrosis: 0/5 (0%) vs. 1/2 (50%); p=0.04 non-bridging fibrosis: 6/27 (22%) vs. 14/29 (48%); p=0.04	NR	(A vs. B): Overall withdrawals: 2/32 (6%) vs. 0/31 (0%); p=ns Withdrawals for adverse events: 2/32 (6.3 %) vs. 0/31 (0%); p=NS Serious adverse events: 3/32 (9.4%) vs. 1/31 (3.2%); p=NS Deaths: NR Headache: 14/32 (44%) vs. 16/31 (52%); p=NS Pyrexia: 13/32 (41%) vs. 16/31 (52%); p=NS Influenza-like illness 8/32 (25%) vs. 10/31 (32%); p=NS Neutropenia: 8/32 (25%) vs. 14/31 (45%); p=NS Myalgia: 7/32 (22%) vs. 14/31 (45%); p=0.05 Fatigue: 10/32 (31%) vs. 11/31 (36%); p=NS Asthenia: 7/32 (22%) vs. 13/31 (42%); p=NS Pruritus: 9/32 (28%) vs. 6/31 (19%); p=NS Irritability: 8/32 (25%) vs. 7/31 (23%); p=NS Thrombocytopenia: 3/32 (9%) vs. 7/31 (23%); p=NS Leukopenia: 4/32 (13%) vs. 6/31 (19%); p=NS Nausea: 6/32 (19%) vs. 9/31 (29%); p=NS Alopecia: 7/32 (22%) vs. 9/31 (29%); p=NS Diarrhea: 9/32 (28%) vs. 8/31 (26%); p=NS Arthralgia: 7/32 (22%) vs. 5/31 (16%); p=NS Depression: 5/32 (16%) vs. 5/31 (16%); p=NS Rigors: 3/32 (9%) vs. 6/31 (19%); p=NS Cough: 4/32 (13%) vs. 7/31 (23%); p=NS	Roche

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Buti, 2010 ²³ International Randomized trial of pegylated interferon alfa-2b and ribavirin for 48 or 72 weeks in patients with hepatitis C virus genotype 1 and slow virologic response International Overall Quality: Fair	Followup visits at 24 weeks after completion of treatment	(A vs. B): SVR: 37/86 (43%) vs. 35/73 (47.9%); p=NS	NR	NR	NR	(A vs. B vs. C [only A and B randomized]): Overall withdrawals: 8/86 (9.3%) vs. 17/73 (23.3%) vs. 100/816 (12.3%); A vs. B p=NS Withdrawals for adverse events: 3/86 (3.5%) vs. 6/73 (8.2%) vs. 39/816 (5.0%); A vs. B p=NS Serious adverse events: 6/86 (7.0%) vs. 6/73 (8.2%) vs. 57/816 (7.0%); A vs. B p=NS Influenza-like illness: 36/86 (41.9%) vs. 34/73 (46.6%) vs. 347/816 (42.5%); A vs. B p=NS Fatigue: 24/86 (27.9%) vs. 18/73 (24.7%) vs. 202/816 (24.8%); A vs. B p=NS Myalgia: 22/86 (25.6%) vs. 12/73 (16.4%) vs. 162/816 (19.9%); A vs. B p=NS Pyrexia: 21/86 (24.4%) vs. 18/73 (24.7%) vs. 245/816 (30%); A vs. B p=NS Pruritus: 20/86 (23.3%) vs. 12/73 (16.4%) vs. 176/816 (21.6%); A vs. B p=NS Neutropenia: 18/86 (20.9%) vs. 16/73 (21.9%) vs. 175/816 (21.4%); A vs. B p=NS Nausea: 18/86 (20.9%) vs. 15/73 (20.5%) vs. 159/816 (19.5%); A vs. B p=NS	Schering- Plough (now Merck)

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Dalgard, 2008 ²⁴ Denmark, Sweden, Norway Pegylated interferon alpha and ribavirin for 12 vs. 24 weeks in patients with hepatitis C virus genotype 2 or 3 and rapid virological response Overall Quality: Fair	Up to 24 weeks after treatment completion (week 48)	(A vs. B vs. C): ETR: 136/148 (91.9%) vs. 144/150 (96.0%) vs. NR; A vs. B p=NS SVR: 120/148 (81.1%) vs. 136/150 (90.7%) vs. 69/126 (58.5%); A vs. B p=NS	(A vs. B): Female: 47/52 (90%) vs. 49/53 (93%); p=NS Male: 73/87 (84%) vs. 87/93 (93%); p=NS Age < 40: 79/89 (89%) vs. 88/90 (98%); p=NS Age >40: 41/50 (82%) vs. 48/56 (86%); p=NS	(A vs. B): HCV RNA >400K IU/ml: 77/88 (87%) vs. 75/85 (88%); p=NS HCV RNA <400K IU/ml: 35/42 (83%) vs. 55/55 (100%); p=NS Genotype 3: 93/110 (84%) vs. 106/115 (92%); p=NS Genotype 2: 27/29 (93%) vs. 30/31 (97%); p=NS	NR	(A vs. B): Treatment discontinuations (<80% of prescribed injections): 9/148 (6%) vs. 32/150 (21%); p=0.02 Hemoglobin <10g/dL: 9/148 (6.1%) vs. 13/150 (8.7%); p=0.39 Neutrophils <700/mm ³ : 9/148 (6.1%) vs. 15/149 (10.1%); p=0.31 Depression: 29/110 (26.4%) vs. 37/124 (29.8%); p=0.56	Schering- Plough (now Merck)

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Ferenci, 2010 ²⁵ Austria Pegylated interferon alfa-2a and ribavirin for 24 weeks in hepatitis C type 1 and 4 patients with rapid virologic response Overall Quality: Poor	Followup visits at 24 weeks after completion of treatment	(A vs. B): SVR: 71 / 139 (51.1%) vs. 88 / 150 (58.7%); p=NS	NR	(A vs. B): Genotype 1: 65/127 (51.2%) vs. 81/134 (60.4%); p=NS Genotype 4: 6/12 (50.0%) vs. 7/16 (43.8%); p=NS Baseline HCV-RNA >400K IU/mL: 51/105 (48.6%) vs. 64/113 (56.6%); p=NS Baseline HCV- RNA<400K IU/mL: 20/34 (58.8%) vs. 24/37 (64.9%); p=NS Fibrosis F3-4: 18/32 (56.3) vs. 19/34 (55.9%); p=NS Fibrosis F0-2: 53/107 (49.5%) vs. 69/116 (59.5%); p=NS	NR	(A vs. B): Overall withdrawals: 26/139 (18.7%) vs. 48 / 150 (32.0%); p<0.01 Withdrawals for adverse events: 7/139 (5.07%) vs. 8/150 (5.3%); p=ns Serious adverse events: 38 / 139 (27.3%) vs. 51 / 150 (34.0%); p=ns Deaths: NR Serious hematologic adverse event: 1 /139 (0.007%) vs. 2 / 150 (1.3%); p=ns Serious gastrointestinal adverse event: 5/139 (3.6%) vs. 2/150 (1.3%); p=ns Serious infectious adverse event: 2/139 (1.4%) vs. 8/150 (5.3%); p=ns Serious pulmonary adverse event; 3/139 (2.2%) vs. 5/150 (3.3%); p=ns Serious neuropsychiatric adverse event: 5/139(3.6%) vs. 4/150 (2.7%); p=ns Serious cardiovascular adverse event: 3/139 (2.2%) vs. 3/ 150 (2.0%); p=ns Serious skin adverse event: 1/139 (0.007%) vs. 1/150 (1.3%); p=ns	Roche

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Ide, 2009 ²⁷ Japan A Randomized Study of Extended Treatment with Pegylated interferon alpha- 2b Plus Ribavirin Based on Time to HCV RNA Negative-status in Patients with Genotype 1b Chronic Hepatitis C Overall Quality: Fair	Followup visits at 24 weeks after completion of treatment	(A vs. B): SVR: 20/56(36%) vs. 30/57(53%), p=0.07	NR	NR	NR	(A vs. B): Overall withdrawals: 11/56 (20%) vs. 9/57 (16%); p=ns Withdrawal due to adverse event: 7/56 (13%) vs. 6/57 (11%); p=ns	Internal Funding

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Kamal, 2005 ²⁸ Egypt Pegylated interferon alpha- 2b and ribavirin therapy in chronic hepatitis C genotype 4: impact of treatment duration and viral kinetics on sustained virological response Overall Quality: Fair	Followup visits at 48 weeks after completion of treatment	(A vs. B vs. C): ETR: 45/95(48%) vs. 65/96(68%) vs. 67/96(70%), p=0.04 (A and B); p=0.02 (A and C), p=0.4(B and C) SVR: 28/95 (29%) vs. 63/96 (66%) vs. 66/96 (69%), p=0.001 (A and B); p=0.001(A and C); p=0.5(B and C)	NR	NR	(A vs. B vs. C): All patients underwent liver biopsy before and after treatment. Pair wise comparison of histological grading and staging scores for the initial and followup biopsies showed no deterioration or progression of fibrosis in any patient and improvement (>2 point necro- inflammatory score improvement) was detected in 155 patients (54%):	(A vs. B vs. C): Deaths: NR Life-threatening Adverse Events: NR Severe Adverse Events: NR Overall Treatment Withdrawals: 3/95 (3%) vs. 5/96 (5%) vs. 5/96 (5%) Withdrawals due to Adverse Events: 1(2%) vs. 2(2%) vs. 4(4%) Neutropenia (<500/mm ³) 1/95 (1%) vs. 1/96 (1%) vs. 3/96 (3%) Fatigue- 56/95(60%) vs. 59/96(64%) vs. 62/96(66%) Influenza-like illness- 53 (57%) vs. 58/96(63%) vs. 59/96(63%) Headache- 49/95(53%) vs. 52/96(57%) vs. 58/96(62%) Myalgia- 48/95(52%) vs. 52/96(57%) vs. 58/96(62%) Pyrexia- 41/95(44%) vs. 50/96(54%) vs. 53/96(62%) Insomnia- 31/95(33%) vs. 35/96(38%) vs. 46/96(49%) Injection site erythema - 28/95(30%) vs. 34/96(37%) vs. 39/96(42%) Irritability- 26/95(28%) vs. 33/96(36%) vs. 30/96(32%) Back pain- 23/95(25%) vs. 25/96(27%) vs. 29/96(31%) Rigors- 16/95(17%) vs. 17/96(18%) vs. 21/96(22%) Sore throat- 13/95(14%) vs. 16/96(17%) vs. 20/96(21%) Cough- 12/95(13%) vs. 15/96(16%) vs. 20/96(21%) Pruritus- 10/95(11%) vs. 15/96(16%) vs. 18/96(19%) Anorexia- 9/95(10%) vs. 14/96(15%) vs. 18/96(19%)	Fulbright Foundation Grants(NIAID (R2) AI054887) & the Alexander von Humboldt Foundation (Germany)

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Kamal, 2005 ²⁸ Egypt Continued					Histological response was more likely in those who received longer treatment schedules as Histological improvement was detected in: (>2 point necro-inflammatory score improvement): 12/95(12.6%) vs. 67/96(69.8%) vs. 71/96 (73.9%)	Arthralgia- 8/95(9%) vs. 12/96(13%) vs. 17/96(18%) Dyspnea- 8/95(9%) vs. 11/96(12%) vs. 15/96(16%) Rash- 7/95(8%) vs. 10/96(11%) vs. 12/96(13%) Depression- 3/95(3%) vs. 3/96(3%) vs. 9/96(9%) Dry mouth- 5/95(5%) vs. 7/96(8%) vs. 8/96(9%) Alopecia- 4/95(4%) vs. 6/96(7%) vs. 7/96(7%) Nausea- 4/95(4%) vs. 4/96(4%) vs. 7/96(7%) Dizziness- 3/95(3%) vs. 5/96(5%) vs. 6/96(6%) Abdominal pain- 3/95(3%) vs. 5/96(5%) vs. 7/96(7%) Dry skin- 2/95(2%) vs. 6/96(7%) vs. 7/96(7%) Diarrhea- 2/95(2%) vs. 6/96(7%) vs. 8/96(9%) Vomiting- 1/95(2%) vs. 3/96(3%) vs. 5/96(5%)	

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Lagging, 2008 ²⁹ Denmark & Finland Randomized Comparison of 12 or 24 Weeks of Pegylated interferon alpha- 2a and Ribavirin in Chronic Hepatitis C Virus Genotype 2/3 Infection Overall Quality: Fair	Followup visits at 24 weeks after completion of treatment	(A vs. B): SVR: 114/194 (59%) vs. 147/188 (78%); p<0.0001	(A vs. B): Age <40: 61/76 (80%) vs. 63/76 (83%);p=NS Age >40: 53/118 (45%) vs. 84/112 (84%); p<0.0001	(A vs. B): No significant fibrosis - 59/85(69%) vs. 69/83(84%); p=0.022 Bridging fibrosis - 36/70(51%) vs. 53/70(76%); p=0.0051 Cirrhosis - 19/23(84%) vs. 13/23(57%); p=NS Genotype 2: 31/55 (56%) vs. 40/49 (82%); p=0.0057 Genotype 3: 79/137 (58%) vs. 108/139 (78%); p=0.0015	NR	(A vs. B): Deaths: NR Life-threatening Adverse Events: NR Severe Adverse Events: NR Withdrawals: 12/194 (6%) vs. 46/188 (24%); p<0.001 Withdrawals due to adverse events: 2/194(1%) vs. 20/188 (11%); P=0.0001	Swedish Society of Medicine, Swedish Medical Council, Swedish Society of Microbiology, Avtal om lakarutbildn- ing och forskning (ALF) Funds, and Roche affiliates (Nordic region)

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Lam, 2010 ³⁰ California & Texas, USA (limited to Southeast Asian populations) Randomized Control Trial of Pegylated Interferon-Alfa 2a and Ribavirin in Treatment-naïve Chronic Hepatitis C Genotype 6 Overall Quality: Fair	Followup visits at 4, 8 and 24 weeks after completion of treatment	(A vs. B): ETR: 24/27(89%) vs. 31/33(94%) ,p=0.48 SVR: 19/27(70%) vs. 26/33(79%),p=0.45	NR	NR	NR	(A vs. B): Withdrawals: 6/27 (22%) vs. 6/33 (18%); p=ns Withdrawals due to adverse events: 4/27 (15%) vs. 2/33 (6%); p=ns Serious Adverse Events: 15/27 (4%) vs. 6/33(2%); p=0.003 Adverse events: Myalgia - 21/27(81%) vs. 23/33(70%), p=0.29 Anorexia - 19/27(71%) vs. 21/33(67%), p=0.72 Headache - 18/27(67%) vs. 16/33(55%), p=0.34 Nausea - 18/27(67%) vs. 15/33(42%), p=0.06 Fever - 16/27(59%) vs. 17/33(52%), p=0.55 Vomiting - 11/27(37%) vs. 6/33(18%), p=0.10 Rash - 19/27(70%) vs. 24/33(76%), p=0.64 Alopecia - 14/27(56%) vs. 21/33(61%), p=0.69 Injection site irritation - 13/27(44%) vs. 17/33(51%), p=0.59 Insomnia - 15/27(59%) vs. 16/33(48%), p=0.41 Depressed mood - 12/27(40%) vs. 9/33(24%), p=0.17 Shortness of breath - 13/27(48%) vs. 20/33(61%), p=0.34 Chestpain - 10/27(33%) vs. 11/33(33%), p=0.99 Hematologic Anemia (Hb < 11 g/dL) - 12/27(44%) vs. 18/33(72%), p=0.03 Neutropenia (ANC < 750 cells/IL) - 6/27(19%) vs. 6/33(23%), p=0.66 Thrombocytopenia (platelet < 50 cells/IL) - (4%) vs. (0%), p= 0.26	Investigator initiated research grant from Roche Laboratories, LLC to Pacific Health Foundation

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Liu, 2008 ³¹ Taiwan Pegylated Interferon-alpha- 2a plus Ribavirin for Treatment- Naïve Asian Patients with Hepatitis C Virus Genotype 1 Infection: A Multicenter Randomized Controlled Trial Overall Quality: Fair	Followup visits at 24 weeks after completion of treatment	(A vs. B): SVR: 49/87(56%) vs. 89/117(76%), P<.001	NR	NR	Histological Response: 42/71(59%) vs. 76/97(78%), p=.001 ALT normalization: 38/75(51%) vs. 77/107(72%), p<.001	(A vs. B): Overall withdrawals: 7/154 (5%) vs. 4/154 (3%); p=ns Withdrawal due to adverse events: 6/154(4%) vs. 4/154 (3%) p=ns Dose reduction due to Adverse Events: 69/154(45%) 82/154(53%) p=ns Deaths: 0/154(0%) vs. 1/154(<1%); p=ns Serious Adverse Event: 4/154(2%) vs. 11/154(7%); p=ns Adverse Events: Fever - 35/154(23%) vs. 33/154(21%); p=ns Rigor - 19/154 (12%) vs. 13/154(8%); p=ns Fatigue - 88/154 (57%) vs. 100/154(65%); p=ns Headache - 28/154 (18%) vs. 35/154(23%); p=ns Myalgia - 40/154(26%) vs. 36/154(23%); p=ns Arthralgia - 8/154(5%) vs. 13/154(8%); p=ns Insomnia - 61/154(40%) vs. 69/154(45%); p=ns Irritability - 19/154(12%) vs. 22/154(14%); p=ns Depression - 36/154(23%) vs. 26/154(17%); p=ns Anorexia - 63/154(41%) vs. 80/154(52%); p=ns Constipation - 10/154(6%) vs. 15/154(10%); p=ns Diarrhea - 14/154(9%) vs. 18/154(12%); p=ns Body weight loss - 29/154(19%) vs. 46/154(30%); p=0.02 Hair loss/alopecia - 24/154(16%) vs. 36/154(23%); p=ns	National Taiwan University Hospital, National Science Council, and Department of Health, Executive Yuan, Taiwan

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Liu, 2008 ³¹ Taiwan Continued						Aphthous ulcer - 22/154(14%) vs. 34/154(22%); p=ns Cough - 28/154(18%) vs. 32/154(21%); p=ns Nasal congestion - 13/154(8%) vs. 17/154(11%); p=ns Tinnitus - 13/154(8%) vs. 20/154(13%); p=ns Dermatitis - 44/154(29%) vs. 48/154(31%); p=ns Injection reaction - 22/154(14%) vs. 29/154(19%); p=ns Anemia - 60/154(39%) vs. 68/154(44%); p=ns Neutropenia - 34/154(22%) vs. 42/154(27%); p=ns Thrombocytopenia - 25/154(16%) vs. 23/154(15%); p=ns	
Mangia, 2005 ³² Italy Pegylated interferon alfa-2b and Ribavirin for 12 vs. 24 Weeks in HCV Genotype 2 or 3 Overall Quality: Fair	Followup visits at 24 weeks after completion of treatment	(A vs. B): SVR: 53/70(76%) vs. 164/213(77%)	NR	(A vs. B): SVR: Genotype 2: 40/53 (75%) vs. 131/160 (82%); p=ns Genotype 3: 13/17 (76%) vs. 33/53 (62%); p=ns	NR	(A vs. B): Withdrawals: 4/70 (6%) vs. 5/213 (2.3%); p=ns Withdrawals due to adverse events: NR Deaths: NR Serious adverse events: NR	Italian branch of Schering- Plough

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Mecenate, 2010 ³³ Italy Short vs. standard treatment with pegylated interferon alfa-2A plus ribavirin in patients with hepatitis C virus genotype 2 or 3: the Cleo trial Overall Quality: Fair	Followup visits at 24 weeks after completion of treatment	(A1 vs. A2): SVR: 60/72(83%) vs. 53/71(75%) p=ns	NR	(A1 vs. A2): SVR: Genotype 2: 32/60(53%) vs. 31/53(50%); p=ns Genotype 3: 28/60(47%) vs. 22/53(42%); p=ns	NR	(A1 vs. A2): Withdrawals: 0/72 (0%) vs. 5/71 (7%) Discontinuation due to Adverse Events - 0/72(0%) vs. 5/71(7%) Deaths: NR Life-threatening Adverse Events: NR Serious Adverse Events: NR Adverse events: Anemia: 5/72(7%) vs. 6/71(8%); p=ns Neutropenia: 2/72(3%) vs. 1/71(1%); p=ns Depression: 2/72(3%) vs. 2/71(3%); p=ns Cutaneous rash: 0/72(0%) vs. 0/71(0%); p=ns Alopecia: 0/72(0%) vs. 1/71(1%); p=ns Fatigue: 2/72(3%) vs. 4/71(5%); p=ns	NR
Pearlman, 2007 ³⁴ Atlanta, GA - USA Treatment Extension of 72 Weeks of Pegylated interferon and Ribavirin in Hepatitis C Genotype 1- Infected Slow Responders Overall Quality: Fair	Followup visits at 24 weeks after completion of treatment	(A vs. B): SVR: 9/49 (18%) vs. 20/52 (38%), p=.03	(A vs. B): SVR: African Americans: 12% vs. 21%, p=.02	NR	NR	(A vs. B): Overall withdrawals: 7/49(14%) vs. 8/52(15%); p=ns Withdrawals due to adverse events: 6/49(12%) vs. 5/52(10%); p=ns Deaths: NR Life-threatening Adverse Events: NR Serious Adverse Events: NR Dose Reduction due to Adverse Event: (Week 1 -19) - 14/49(29%) vs. 15/52(29%); p=ns (Week 24-48) - 4/49(8%) vs. 2/52(4%); p=ns Discontinuation due to Adverse Event: (Week 24-48) - 7/49(14%) vs. 8/52(15%); p=ns	NR

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Sanchez-Tapias, 2006 ³⁵ Spain Peginterferon- Alfa2a Plus Ribavirin for 48 Vs. 72 weeks in Patients with Detectable Hepatitis C Virus RNA at Week 4 of Treatment Overall Quality: Fair	Followup visits at 24 weeks after completion of treatment	(A vs. B): SVR: 53/165(32%) vs. 72/161(45%)	NR	NR	NR	(A vs. B): Deaths: NR Serious Adverse Events: 4.8% vs. 8%; p=ns Treatment discontinuation - 29/165(18%) vs. 58/161(36%); p<0.001 Discontinuation due to Adverse event - 14/165(8%) vs. 19/161 (12%); p=ns Dose reduction - 74/165(45%) vs. 96/161 (59%); p=ns Adverse Events: Asthenia - 98/165(59%) vs. 95/161 (59%); p=ns Headache - 50/165(30%) vs. 53/161 (33%); p=ns Fever - 45/165(27%) vs. 45/161 (28%); p=ns Neutropenia - 40/165(24%) vs. 41/161 (25%); p=ns Influenza-like symptoms - 39/165(24%) vs. 28/148 (17%); p=ns Pruritus - 34/165(21%) vs. 41/161 (25%); p=ns Insomnia - 29/165(18%) vs. 41/161 (25%); p=ns Anorexia - 34/165(21%) vs. 23/161 (14%); p=ns Irritability - 28/165(17%) vs. 35/161 (22%); p=ns Anemia - 30/165(18%) vs. 34/161 (21%); p=ns Depression - 19/165(12%) vs. 31/161 (19%); p=ns Myalgia - 23/165(14%) vs. 22/161 (14%); p=ns Alopecia - 22/165(13%) vs. 27/161 (17%); p=ns	NR

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Sanchez-Tapias, 2006 ³⁵ Spain Continued						Leukopenia - 18/165(11%) vs. 18/161 (11%); p=ns Injection site reaction - 12/165(7%) vs. 19/161 (12%); p=ns	
Shiffman, 2007 ³⁶ 132 centers worldwide Pegylated interferon alfa-2a and Ribavirin for 16 or 24 Weeks in HCV Genotype 2 or 3 Overall Quality: Good	Followup visits at 24 weeks after completion of treatment	(A vs. B): ETR: 651/732(89%) vs. 599/731(82%) SVR: 455/732(62%) vs. 515/731(70%); p<0.001	NR	(A vs. B): (p-value for interaction) Genotype 2: 232/358(62%) vs. 268/356(75%); p=0.06 Genotype 3: 221/358(62%) vs. 244/369(66%); HCV RNA >800: 280/506 (55%) vs. 344/501 (67%); p=0.26 HCV RNA 400-800: 43/65 (66%) vs. 59/80 (74%) HCV RNA<400: 132/161 (82%) vs. 122/150 (81%) Cirrhosis or bridging fibrosis: 88/185 (48%) vs. 95/165 (58%); p=0.82 No Cirrhosis or bridging fibrosis: 367/547 (67%) vs. 420/566 (74%)	NR	(A vs. B): Deaths: NR Life-threatening Adverse Events: NR Serious Adverse Events: 5% vs. 6% Withdrawals: 41/736(5%) vs. 91/731(12%); p<0.0001 Withdrawal due to Adverse Events: 30/736(4%) vs. 25/731(5%); p=ns Neutropenia (Grade 4): 13/733 (2%) vs. 20/732 (3%); p=ns Anemia (<8.5 g/dL): 4/733 (<1%) vs. 4/732 (<1%); p=ns	Roche

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
<p>Von Wagner, 2005³⁷ Germany</p> <p>Peginterferon-alpha-2a (40KD) and Ribavirin for 16 or 24 Weeks in Patients with Genotype 2 or 3 Chronic Hepatitis C</p> <p>Overall Quality: Fair</p>	<p>Followup visits at 4, 12 and 24 weeks after completion of treatment</p>	<p>(A vs. B):</p> <p>SVR: 58/71(82%) vs. 57/71(80%); p=ns</p>	<p>NR</p>	<p>(A vs. B):</p> <p>SVR: Genotype 2:18/19 (95%) vs. 18/19 (95%); p=ns Genotype 3: 39/51 (76%) vs. 39/52 (75%); p=ns</p> <p>HCV RNA <800: 33/35 (94%) vs. 27/31 (87%); p=ns HCV RNA>800: 24/35 (69%) vs. 30/40 (75%); p=ns</p>	<p>NR</p>	<p>(A vs. B):</p> <p>Withdrawals: 1/71 (1.4%) vs. 6/71 (8.5%) Withdrawal due to Adverse Events: NR Deaths: NR Life-threatening Adverse Events: NR Severe Adverse Events: NR Withdrawals: NR</p> <p>Adverse events: Flu-like symptoms: 37/71(52.1%) vs. 33/71 (46.5%); p=ns Fatigue: 26/71(36.6%) vs. 30/71 (42.3%); p=ns Pruritus: 19/71(26.8%) vs. 24/71 (33.8%); p=ns Headache: 18/71(25.4%) vs. 22/71 (31.0%); p=ns Anorexia: 16/71(22.5%) vs. 19/71 (26.8%); p=ns Alopecia: 15/71(21.1%) vs. 18/71 (25.4%); p=ns Asthenia: 12/71(16.9%) vs. 18/71(25.4%); p=ns Pain: 9/71(12.7%) vs. 16/71(22.5%); p=ns Dyspnea: 10/71(14.1%) vs. 16/71(22.5%); p=ns Sleeping disturbance: 9/71(12.7%) vs. 16 (22.5%); p=ns Pyrexia: 10/71(14.1%) vs. 13/71(18.3%); p=ns Dry skin: 13/71(18.3%) vs. 9/71(12.7%); p=ns Aggressivity: 8/71(11.3%) vs. 12/71(16.9%); p=ns Depression: 8/71(11.3%) vs. 10/71 (14.1%); p=ns Chills: 10/71(14.1%) vs. 8/71(11.3%); p=ns Nausea: 5/71(7.0%) vs. 11/71(15.5%); p=ns Dry Mouth: 4/71(5.6%) vs. 8/71(11.3%); p=ns</p>	<p>Hoffman-La Roche (Grenzach, Germany) & the German Hepatitis Network of Competence (Hep-Net)</p>

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Yu, 2006 ³⁸ Taiwan A randomized trial of 24- vs. 48-week courses of PEG interferon alpha-2b plus ribavirin for genotype-1b-infected chronic hepatitis C patients: a pilot study in Taiwan Overall Quality: Fair	Followup visits at 24 weeks after completion of treatment	(A vs. B): SVR: 22/45(48.9%) vs. 12/15(80%)	(A vs. B): SVR: Male: 14/28 (50%) vs. 8/11 (72%); p=ns Female: 8/17 (47%) vs. 4/4 (100%); p=ns	(A vs. B): SVR: Fibrosis score 0-2: 18/32(56.3%) vs. 8/11(72.7%), p=ns Fibrosis score 3-4: 4/13(30.8%) vs. 4/4(100%), p=.029 Baseline HCV-RNA <400,000 IU/mL: 14/22(63.6%) vs. 4/5(80%), p=ns Baseline HCV-RNA >400,000 IU/mL: 8/23(34.8%) vs. 8/10(80%), p=.026	NR	(A vs. B): Deaths: NR Life-threatening Adverse Events: NR Severe Adverse Events: NR Withdrawals: 1/45 (2%) vs. 3/15 (20%); p=0.02 Withdrawal due to Adverse Events:1/45 (2%) vs. 2/15 (13%); p=ns Dose reduction due to Adverse Events: 19/45 (42.2%) vs. 7/15 (46.7%); p=ns Adverse Events: Fever - 31/45 (68.9%) vs. 10/15 (66.7%); p=ns Chills - 10/45 (22.2%) vs. 4/15 (26.7%); p=ns Myalgia - 26/45 (57.7%) vs. 6/15 (40.0%); p=ns Headache - 32/45 (71.1%) vs. 9/15 (60.0%); p=ns Asthenia - 29/45 (64.4%) vs. 8/15 (53.3%); p=ns Anorexia - 14/45 (31.1%) vs. 3/15 (20.0%); p=ns Nausea - 16/45 (35.6%) vs. 6/15 (40.0%); p=ns Diarrhea - 3/45 (6.7%) vs. 3/15 (20.0%); p=ns Anxiety/depression - 19/45 (42.2%) vs. 8/15 (53.3%); p=ns Insomnia - 26/45 (57.7%) vs. 10/15 (66.6%); p=ns Hair loss - 24/45 (53.3%) vs. 10/15 (66.6%); p=ns Skin rash - 30/45 (66.7%) vs. 9/15 (60.0%); p=ns Injection site erythema - 16/45 (35.5%) vs. 6/15 (40.0%); p=ns	Taiwan Liver Research Foundation

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Yu, 2006 ³⁸ Taiwan Continued						Body weight loss - 8/45 (17.7%) vs. 2/15 (13.3%); p=ns Anemia (hemoglobin \leq 10 g/dl) - 20/45 (44.4%) vs. 8/15 (53.3%); p=ns Leukopenia White cell count $<$ 3000/mm ³ - 34/45 (75.5%) vs. 11/15 (73.3%); p=ns White cell count $<$ 1500/mm ³ - 1/45 (2.2%) vs. 2/15 (13.3%); p=ns Thrombocytopenia ($<$ 100 K/mm ³) - 20/45 (44.4%) vs. 4/15 (26.6%); p=ns Abnormal thyroid function tests - 4/45 (8.8%) vs. 1/15 (6.6%); p=ns	

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Yu, 2007 ³⁹ Taiwan A randomized study of pegylated interferon and ribavirin for 16 vs. 24 weeks in patients with genotype 2 chronic hepatitis C Overall Quality: Fair	Followup visits at 24 weeks after completion of treatment	(A vs. B): 95/100 (95%) vs. 47/50 (94%); p=ns	(A vs. B): Age: <50 years - 46/46(100%) vs. 19/19(100%);p=NS >50 years - 49/54(91%) vs. 28/31(90%); p=NS Female: 38/42(91%) vs. 16/18(89%); p=NS Male: 57/58 (98%) vs. 31/32 (97%): p=NS BMI <25: 49/53 (93%) vs. 25/27 (93%); p=NS BMI>25: 46/47 (98%) vs. 22/23 (96%); p=NS	(A vs. B): Fibrosis F0-2: 76/80 (95%) vs. 34/39 (95%); p=NS Fibrosis F3-4: 19/20 (95%) vs. 10/11 (91%); p=NS HCVRNA <800K: 81/85 (95%) vs. 39/41 (95%); p=NS HCVRNA>800K: 14/15 (93%) vs. 8/9 (89%); p=NS	NR	(A vs. B): Deaths: NR Life-threatening Adverse Events: NR Severe Adverse Events: NR Withdrawals: 1/100(1%) vs. 0/50(0%); p=1 Withdrawal due to Adverse Events: 1/100(1%) vs. 0/50(0%); p=1 Dose reduction due to Adverse Events - 54/100(54%) vs. 26/50 (52%), p=0.817 Adverse Events: Fever: 55/100 (55%) vs. 29/50 (58%), p=0.727 Chills: 28/100 (28%) vs. 12/50 (24%), p=0.602 Headache: 39/100 (39%) vs. 21 /50 (42%), p=0.724 Anorexia: 46/100 (46%) vs. 20/50 (40%), p=0.601 Nausea: 15/100 (15%) vs. 3/50 (6%), p=0.181 Diarrhea: 9/100 (9%) vs. 5/50 (10%), p=1 Anxiety: 7/100 (7%) vs. 4/50 (8%), p=1 Depression: 10/100 (10%) vs. 3/50 (6%), p=0.545 Insomnia: 57/100 (57%) vs. 23/50 (46%), p=0.227 Hair loss: 49/100 (49%) vs. 10/50 (20%), p=0.001* Skin rash: 54/100 (54%) vs. 22/50 (44%), p= 0.248 Leukopenia(white cell count,1500/mm3): 2/100 (2%) vs. 1/50 (2%), p=1 Anemia (hemoglobin level<10g/dl): 53/100(53%) vs. 27/50 (54%), p=0.908 Thrombocytopenia(<50,000/mm3: 1/100 (1%) vs. 0/50 (0%), p=1 Abnormal thyroid function tests: 13/100 (13%) vs. 4/50 (8%), p=0.362	Taiwan Liver Research Foundation

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Yu, 2008 ⁴⁰ Taiwan Rapid Virological Response and Treatment Duration for Chronic Hepatitis C Genotype 1 Patients: A Randomized Trial Overall Quality: Fair	Followup visits at 24 weeks after completion of treatment	(A vs. B): SVR: 59/100(59%) vs. 79/100(79%)	(A vs. B): SVR: Male: 34/57 (60%) vs. 46/58 (79%); p=ns Female: NR	(A vs. B): SVR: Fibrosis score F0- 2: 48/75 (64%) vs. 62/84 (77%); p=ns Fibrosis score F3- 4: 11/25 (44%) vs. 17/19 (89%); p=0.002 HCV RNA <400K: 34/45 (76%) vs. 36/44 (82%); p=ns HCV RNA>400K: 25/55 (45%) vs. 43/56 (77%); p<0.001	NR	(A vs. B): Withdrawals: 3/100(3%) vs. 10/100(10%), p=.045 Withdrawal due to Adverse Events: 3/100 (3%) vs. 9/100 (9%); p=ns Deaths: NR Life-threatening Adverse Events: NR Serious Adverse Events: 1/100 (1%) vs. 1/100 (1%); p=ns Dose reduction due to adverse events: 54/100(54.0%) vs. 65/100(65.0%), p=.113 Influenza-like symptoms (fever, chills, headache): 76/100(76%) vs. 74/100(74%), p=.744 Anorexia and/or nausea - 50 (50%) vs. 53 (53%), p=.671 Diarrhea - 18 (18%) vs. 26 (26%), p=.172 Anxiety - 31 (32%) vs. 36/100(36%), p=.454 Depression - 24 (24%) vs. 34/100(34%), p=.119 Insomnia - 59 (59%) vs. 65/100(65%), p=.382 Hair loss – 66/100(66%) vs. 72/100(72%), p=.359 Skin rash – 54/100(54%) vs. 66/100(66%), p=.083 Leukopenia (white cell count < 1500 mm ⁻³) – 5/100(5%) vs. 8/100(8%), p=.39 Anemia (hemoglobin < 10 g/dl) – 39/100(39%) vs. 48/100(48%), p=.199 Thrombocytopenia (< 50,000 mm ⁻³) – 2/100(2%) vs. 6/100(6%), p=.279 Abnormal thyroid function tests – 13/100(13%) vs. 15/100(15%), p=.684	Taiwan Liver Research Foundation

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Zeuzem, 2004 ⁴¹ Australia, Europe, New Zealand, North & South America Pegylated interferon alfa-2a (40 Kilodaltons) and Ribavirin in Patients with Chronic Hepatitis C and Normal Aminotransferase Levels Overall Quality: Fair	Followup visits at 24 weeks after completion of treatment	(A vs. B): ETR: NR SVR: 63/212(30%) vs. 109/210(52%); p<0.001	NR	(A vs. B): ETR: NR SVR: Genotype 1 - 19/144(13%) vs. 57/141(40%); p<0.001 Genotypes 2/3 - 42/58(72%) vs. 46/59(78%); p=ns Genotypes 4 - 1/8(13%) vs. 5/9(56%); p=ns HCV RNA <800 IU/mL: 39/123 (32%) vs. 72/127 (57%); p<0.001 HCV RNA >800 IU/mL: 24/87(28%) vs. 36/82(44%); p=0.03	NR	(A vs. B): Withdrawals: 20/212 (9%) vs. 58/210 (28%); p<0.001 Withdrawals due to adverse events: 15/212 (7%) vs. 38/210 (18%); p<0.001 Severe adverse events 56/212 (26%) vs. 70/210 (33%); p=ns Life-threatening adverse events - 3/212 (1%) vs. 8/210 (4%) Serious adverse events - 18/212 (8%) vs. 34/210 (16%); p=0.02 Deaths - 0/212(0%) vs. 0/210(0%); p=ns Dose reduction due to adverse events - 65/212(32%) vs. 102/210(49%); p<0.001 Adverse Events: Headache - 93/212 (44%) vs. 117/210 (56%); p=0.02 Fatigue - 109/212 (51%) vs. 107/210 (51%); p=ns Myalgia - 81/212 (38%) vs. 93/210 (44%); p=ns Pyrexia - 64/212 (30%) vs. 90/210 (43%); p<0.01 Insomnia - 74/212 (35%) vs. 76/210 (36%); p=ns Nausea - 68/212 (32%) vs. 84/210 (40%); p=ns Arthralgia - 68/212 (32%) vs. 62/210 (30%); p=ns Depression - 55/212 (26%) vs. 57/210 (27%); p=ns Irritability - 58/212 (27%) vs. 55/210 (26%); p=ns Rigors - 50/212 (24%) vs. 53/210 (25%); p=ns Alopecia - 43/212 (20%) vs. 59/210 (28%); p=ns Asthenia - 47/212 (22%) vs. 48/210 (23%); p=ns	Roche (Basel, Switzerland)

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Zeuzem, 2004 ⁴¹ Australia, Europe, New Zealand, North & South America Continued						Diarrhea - 40/212 (19%) vs. 55/210 (26%); p=ns Pruritus - 34/212 (16%) vs. 42/210 (20%); p=0.03 Hemoglobin <10.0 to >8.5 g/dL - 10/212 (5%) vs. 24/210 (11%); p=0.01 Hemoglobin <8.5 g/dL - 3/212 (1%) vs. 1/210 (1%); p=ns Neutrophils <0.5 x10 ⁹ /L - 10/212 (5%) vs. 10/210 (5%); p=ns Platelets <50 x10 ⁹ /L - 3/212 (1%) vs. 4/210 (2%); p=ns Hypothyroidism - 0/212 (0%) vs. 5/210 (2%); p=ns Hyperthyroidism - 1/212 (1%) vs. 3/210 (1%); p=ns	

Evidence Table 6. Quality rating: Duration in trials of pegylated interferon plus ribavirin

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition and withdrawals reported?	Loss to followup: differential/high?	Intention-to-treat analysis	Quality	Funding
Andriulli, 2009 ¹⁹	Unclear	Yes	Unclear	Yes	No, open label	No, open label	No, open label	Yes	No	Yes	Fair	Investigator funded
Berg, 2006 ²⁰	Unclear	Unclear	Yes	Yes	No, open label	No, open label	No, open label	yes	No	Yes	Fair	Roche
Berg, 2009 ²¹	Unclear	Unclear	Unclear	Yes	No, open label	No, open label	No, open label	Yes	Yes	Yes	Poor	Schering-Plough
Brandao, 2006 ²²	Yes	Unclear	Yes	Yes	No, open label	No, open label	No, open label	Yes	No	Yes	Fair	Roche
Bronowicki, 2006 ⁴²	Yes	Unclear	Unclear	Yes	No, open label	No, open label	No, open label	Yes	NO	Yes	Fair	Roche
Buti, 2010 ²³	Yes	Unclear	Yes	Yes	No, open label	No, open label	No, open label	Yes	No	Yes	Fair	Schering-Plough (now Merck)
Dalgard, 2008 ²⁴	Unclear	Unclear	Yes	Yes	No, open label	No, open label	No, open label	Yes	No	Yes	Fair	Schering-Plough (now Merck)
Ferenci, 2010 ²⁵	Unclear	unclear	Unclear	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes	Poor	Roche
Ide, 2009 ²⁷	Unclear	Yes	Unclear	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes	Fair	Internal Funding
Kamal, 2005 ²⁸	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Yes	No	Yes	Fair	Fulbright Foundation Grants(NIAID (R2) AI054887) & the Alexander von Humboldt Foundation (Germany)

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition and withdrawals reported?	Loss to followup: differential/high?	Intention-to-treat analysis	Quality	Funding
Lagging, 2008 ²⁹	Unclear	Unclear	Yes	Yes	No, open label	No, open label	No, open label	Yes	No	Yes	Fair	Swedish Society of Medicine, Swedish Medical Council, Swedish Society of Microbiology, Avtal om lakarutbildning och forskning (ALF) Funds, and Roche affiliates (Nordic region)
Lam, 2010 ³⁰	Unclear	Yes	Yes	Yes	No, open label	No, open label	No, open label	No	No	Yes	Fair	investigator initiated research grant from Roche Laboratories, LLC to Pacific Health Foundation
Liu, 2008 ³¹	Unclear	Unclear	Yes	Yes	No, open label	No, open label	No, open label	Yes	No	Yes	Fair	National Taiwan University Hospital, National Science Council, and Department of Health, Executive Yuan, Taiwan
Mangia, 2005 ³²	Unclear	Unclear	Yes	Yes	No, open label	No, open label	No, open label	No	No	Yes	Fair	Italian branch of Schering-Plough

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition and withdrawals reported?	Loss to followup: differential/high?	Intention-to-treat analysis	Quality	Funding
Mecenate, 2010 ³³	Unclear	Unclear	Unclear	Yes	No, open label	No, open label	No, open label	Yes	No	Yes	Fair	NR
Pearlman, 2007 ³⁴	Unclear	Unclear	Yes	Yes	No, not described	No, not described	No, not described	Yes	No	Yes	Fair	NR
Sanchez-Tapias, 2006 ³⁵	Yes	Yes	Unclear	Yes	No, open label	No, open label	No, open label	Yes	No	Yes	Fair	NR
Shiffman, 2007 ³⁶	Unclear	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Good	Roche
Von Wagner, 2005 ³⁷	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	Unclear	Yes	No	Yes	Fair	Hoffman-La Roche (Grenzach, Germany) & the German Hepatitis Network of Competence (Hep-Net)
Yu, 2006 ³⁸	Yes	Unclear	Unclear	Yes	No, open label	No, open label	No, open label	Yes	No	Yes	Fair	Taiwan Liver Research Foundation
Yu, 2007 ³⁹	Yes	Unclear	Unclear	Yes	No, open label	No, open label	No, open label	Yes	No	Yes	Fair	Taiwan Liver Research Foundation
Yu, 2008 ⁴⁰	Yes	Yes	Unclear	Yes	No - open label	No - open label	No - open label	Yes	No	Yes	Fair	Taiwan Liver Research Foundation
Zeuzem, 2004 ⁴¹	Unclear	Unclear	Yes	Yes	No, open label	No, open label	No, open label	Yes	Yes	Yes	Fair	Roche (Basel, Switzerland)

Evidence Table 7. Dose comparison in trials of pegylated interferon plus ribavirin

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Abergel, 2006 ⁴³ France Pegylated interferon alpha-2b plus ribavirin for treatment of chronic hepatitis C with severe fibrosis: a multicenter randomized controlled trial comparing two doses of Pegylated interferon alpha-2b Overall Quality: Fair	A: (standard- dose) Pegylated interferon alpha-2b 1.5 µg/kg 1x/week/48 weeks B: (low- dose) Pegylated interferon alpha-2b 0.75 µg/kg 1x/week/48 weeks	A: Ribavirin 800 mg/day/48week s B: Ribavirin 800 mg/day/48 weeks	None	Age between 18 and 75 years No previous treatment with IFN and/or ribavirin Alanine aminotransferase (ALT) > upper limit of normal (ULN) at least once during the last 12 months Positive serum HCV- RNA using qualitative polymerase chain reaction (PCR) and severe fibrosis on liver biopsy defined by a METAVIR fibrosis stage of F3 or F4 at histological examination of the liver	Recent history of alcohol abuse or IV drug addiction Hemoglobin <12 g/dL in women and <13 g/dL in men Platelets <75 000/L Neutrophils <1500/L Decompensated cirrhosis (ascites, variceal hemorrhage encephalopathy) Albumin <30 g/L Prothrombin <60% Bilirubin >34 µmol/L HCC Chronic hepatitis B infection HIV infection	NR/210/ 210/203	A vs. B Age(Mean): 49.3 vs. 51.1 years Female: 36% vs. 32% Race: NR	A vs. B Genotype 1 - 50/101(49.5%) vs. 54/102(52.9%) Genotype 2 - 11/101(10.9%) vs. 9/102(8.8%) Genotype 3 - 30/101(29.7%) vs. 28/102(27.5%) Genotype 4 - 5/101(5%) vs. 4/102(3.9%) Genotype 5 - 5/101(5%) vs. 7/102(6.9%) Fibrosis stage: F3 - 55/101(54.4%) vs. 44/102(43.1%) F4 - 46/101(45.6%) vs. 58/102(56.9%) Cirrhosis: 46% vs. 57% 100% Treatment naïve

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Brady, 2010 ⁴⁴ United States Induction pegylated interferon alfa- 2b combination with ribavirin in patients with genotype 1 and 4 chronic hepatitis C: a prospective, randomized, multicenter, open-label study Overall Quality: Fair	A. Pegylated interferon alfa-2b 3.0 mcg/kg/week for 12 weeks followed by 1.5 mcg/kg/week for 36 weeks B. Pegylated interferon alfa-2b 1.5 mcg/kg/week for 48 weeks	A. 800-1400 mg/day for 48 weeks B. 800-1400 mg/day for 48 weeks	NA	Treatment-naïve patients Genotype 1 or 4 Positive HCV antibodies and detectable HCV RNA Liver biopsy consistent with viral hepatitis within the past 48 months Cirrhosis no worse than Child-Pugh Class A Hemoglobin \geq 12 g/dL in females and 13 g/dL in males White blood cells \geq 3000 Neutrophil \geq 1500 Platelet \geq 65K Direct bilirubin within 20% of upper limits of normal Creatinine within 20% of upper limits of normal Albumin within normal limits	Non-genotype 1 or 4 HCV infection Decompensated liver disease Evidence of co-existing liver disease Co-infection with HIV or HBV Hemochromatosis Alpha-1 antitrypsin deficiency Wilson disease Autoimmune hepatitis Alcoholic liver disease Hepatocellular carcinoma Pregnancy Psychiatric conditions Significant cardiovascular dysfunction within the past 1 year Poorly controlled diabetes mellitus Chronic pulmonary disease Clinically significant retinal abnormalities Immunologically mediated diseases Any medical condition requiring systemic steroids Active clinical gout Substance abuse in the past 6 months	NR/NR/ 623/610	A vs. B Age mean: 45 vs. 45 Female: 50% vs. 50% non- White: 32% vs. 28%	A vs. B genotype 1: 99% vs. 99% Treatment-naïve: all Fibrosis stage 3 or 4: 26% vs. 23% HCV- RNA \geq 800K: 71% vs. 62%

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Bronowicki, 2006 ⁴² France Effect of ribavirin in genotype 1 patients with hepatitis C responding to pegylated interferon alfa- 2a plus ribavirin Overall Quality: Fair	A. Pegylated interferon alfa-2a 180 mcg/week for 48 weeks B. Pegylated interferon alfa-2a 180 mcg/week for 48 weeks	All patients treated for 24 weeks of ribavirin 400 mg twice daily. At week 24 patients with indictable HCV RNA were randomized at week 26 to 22 more weeks (48 weeks total) of: A. 400 mg twice daily B. Placebo	NA	Treatment naïve Aged ≥ 18 years HCV genotype 1 infection HCV RNA >600 IU/mL Increased ALT levels documented 2 times in last 6 months Liver biopsy consistent with chronic hepatitis C obtained within 18 months before therapy	chronic liver disease of other etiology Evidence of decompensation Co-infection with HBV or HIV Neutrophils $<1500/\text{mm}^3$ platelets $<90,000/\text{mm}^3$ Hemoglobin level less than 12 g/dL (women) or less than 13 g/dL (men) Risk factor for anemia Serum creatinine >1.5 times upper limit of number Severe psychiatric disease Significant co-morbid medical conditions	NR/516/ 349/349	A vs. B Age mean: 44.2 vs. 45.4 Female: 43% vs. 43% Non- White: NR	A vs. B Genotype 1: all HCV RNA $>800,000$: 62% vs. 71% Fibrosis score F3 or F4: 27% vs. 28%

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
<p>Ferenci, 2008⁴⁵ Austria</p> <p>A Randomized, Prospective Trial of Ribavirin 400 mg/Day Vs. 800 mg/Day in Combination with Pegylated interferon Alfa- 2a in Hepatitis C Virus Genotypes 2 and 3</p> <p>Overall Quality: Fair</p>	<p>A: Pegylated interferon alpha-2a 180 µg/week/24 weeks B: Pegylated interferon alpha-2a 180 µg/week/24 weeks</p>	<p>A: Ribavirin 800 mg/day/24 weeks B: Ribavirin 400 mg/day/24 weeks</p>	None	<p>Treatment-naïve adult Aged 18 to 65 years Chronic hepatitis C HCV genotype 2 or 3 infection Quantifiable HCV RNA in serum and elevated serum ALT activity (1.5 times the upper limit of normal [ULN] in the previous 6 months and during screening) Hemoglobin value 12 g/dL (women) or 13 g/dL (men) Leukocyte count 3000/L Platelet count 100,000/L Serum creatinine level 1.5 times the ULN. Women of childbearing potential were required to have a negative pregnancy test within 24 hours of the first dose All fertile male and female participants were required to use two forms of effective contraception during treatment and for 6 months after the end of treatment</p>	<p>Pregnant or breast-feeding women and male partners of pregnant women Received prior treatment with interferon or ribavirin at any time Co infected with hepatitis B virus or human immunodeficiency virus Decompensated liver disease or chronic liver disease attributable to another cause Coronary heart disease Diabetes mellitus requiring insulin therapy Autoimmune disorders Any other unstable chronic medical condition Severe psychiatric disease, especially depression History of active alcohol or drug addiction within the previous 6 months</p> <p>*Patients on opiate substitution therapy were eligible if they were treated by the drug treatment centre in the Department of Psychiatry, Medical University of Vienna</p>	291/282/ 250/250	<p>A vs. B Age (Mean): 37 vs. 36 years Female: 40% vs. 38% Race: NR</p>	<p>A vs. B Genotype 2 – 18/141(13%) vs. 19/141(14%) Genotype 3 - 123/141(87%) vs. 122/141(86%) Severity of liver disease- HCV RNA < 800,000 IU/mL - 5.9 vs. 5.7 Cirrhosis: NR Minimal or no fibrosis: NR 100% Treatment naïve</p>

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Fried., 2008 ⁴⁶ USA Improved Outcomes in Patients with Hepatitis C with Difficult-to- Treat Characteristics: Randomized Study of Higher Doses of Pegylated interferon α -2a and Ribavirin Overall Quality: Fair	A: Pegylated interferon alfa-2a 180 μ g/week/48 weeks B: Pegylated interferon alfa-2a 180 μ g/week/48 weeks C: Pegylated interferon alfa-2a 270 μ g/week/48 weeks D: Pegylated interferon alfa-2a 270 μ g/week/48 weeks	A: Ribavirin 1200 mg/day/48 weeks B: Ribavirin 1600 mg/day/48 weeks C: Ribavirin 1200 mg/day/48 weeks D: Ribavirin 1600 mg/day/48 weeks	None	Treatment-naïve Age 18 years or older Weighing 85 kg Chronic hepatitis C infection with genotype 1 Baseline HCVRNA level 800,000 IU/mL determined by quantitative polymerase chain reaction (PCR) assay Positive anti- HCV antibody test Elevated serum alanine aminotransferase level within the previous 6 months Compensated liver disease Liver biopsy specimen consistent with chronic hepatitis C obtained within the previous 24 months	Infection with an HCV genotype other than 1 Previous treatment with interferon-based therapy, ribavirin, or any investigational drug for chronic hepatitis C History or other evidence of liver disease not associated with chronic hepatitis C Neutrophil count 1.5×10^9 cells/L Platelet count 90 109 cells/L Hemoglobin level 12 g/dL in women and 13 g/dL in men Increased risk of anemia or for whom anemia would be medically problematic Serum creatinine level more than 1.5 times the upper limit of normal Co infection with hepatitis B virus or human immunodeficiency virus Other serious chronic disease History of severe psychiatric disease (a history of a suicide attempt, hospitalization or period of disability due to psychiatric disease, and/or a Beck Depression Inventory score 20) Evidence of alcohol or drug abuse within 1 year of study entry	301/193/ 188/187	A vs. B vs. C vs. D Age (Mean): 47.1 vs. 49.6 vs. 47.1 vs. 48.5 years Female: 20% vs. 13% vs. 26% vs. 21% Race: White - 70% vs. 62% vs. 74% vs. 68% Non- White- 30% vs. 38% vs. 26% vs. 32%	A vs. B vs. C vs. D Genotype 1 – 100% Histologic diagnosis: Non-cirrhotic -83% vs. 81% vs. 83% vs. 81% Cirrhosis - 17% vs. 19% vs. 17% vs. 19% HCV RNA (IU/mLx106): 4.9 vs. 6.2 vs. 5.5 vs. 5.2 100% Treatment naïve

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Helbling, 2006 ⁴⁷ Switzerland HCV-related advanced fibrosis/cirrhosis: randomized controlled trial of pegylated interferon α -2a and ribavirin Overall Quality: Fair	A: Pegylated interferon α -2a 180 μ g/week/48 weeks B: Pegylated interferon α -2a 180 μ g/week/48 weeks	A: (standard dose) Ribavirin <75 kg - 1000 mg/day/48 weeks >75 kg - 1200 mg/day in 2 divided doses/48 weeks B: (low dose) Ribavirin <75 kg - 600 mg/day/48 weeks >75 kg - 800 mg/day in 2 divided doses/48 weeks	None	Age 18–70 years Biopsy proved (within \leq 12 months) chronic hepatitis C with advanced fibrosis/cirrhosis (Ishak stage F4–F6 <7 Child–Pugh points No previous antiviral treatment Elevated alanine aminotransferase (ALT; on \geq 2 occasions within >6 months) Serum HCV RNA positive Hemoglobin \geq 11 g/dL Neutrophil count >1500/L Platelet count \geq 75 000/L Serum creatinine \leq 1.5 times upper limit of normal Normal fasting glucose (or \leq 8 μ mol/L provided HbA1c \leq 8.5%) Hbs-antigen negative antinuclear antibodies \leq 1:160 Normal thyroid stimulating hormone Normal alpha- fetoprotein Focal lesions ruled out by ultrasound (within 1 month of study entry)	Concomitant liver disease Ongoing substance abuse including alcohol (\geq 80 g/day) Hepatocellular carcinoma Clinically relevant disorders of other organs/systems Pregnancy or lactation Refusal to practice effective contraception during treatment/followup Immunomodulatory treatment within 6 months or treatment with any investigational drug within 30 days of study entry	NR/126/ 126/124	A vs. B Age - Median: 47 vs. 47 years Female: 30% vs. 40% Race: NR	A vs. B Genotype 1 – 30/64(47%) vs. 25/60(42%) Genotype 2 – 11/64(17%) vs. 7/60(12%) Genotype 3 - 18/64(28%) vs. 24/60(40%) Genotype 4 - 4/64(6%) vs. 3/60(4%) Histologic stage (Ishak , 1995): 3 - 3/64(5%) vs. 4/60(7%) 4 - 26/64(41%) vs. 18/60(30%) 5 - 19/64(30%) vs. 21/60(35%) 6 - 14/64(22%) vs. 13/60(22%) Cirrhosis: 57% vs. 52% Minimal or no fibrosis: 6% vs. 2% 100% Treatment naïve

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
<p>Jacobson, 2007⁴⁸ USA (236 practice sites nation-wide)</p> <p>Pegylated interferon alfa-2b and Weight-Based or Flat-Dose Ribavirin in Chronic Hepatitis C Patients: A Randomized Trial</p> <p>Jacobson, 2007⁴⁹ (African-American subgroup) USA (236 practice sites nation-wide)</p> <p>Impact of Weight-based Ribavirin with Pegylated interferon alfa-2b in African-Americans with Hepatitis C Virus Genotype 1</p> <p>Overall Quality: Fair</p>	<p>A: Pegylated interferon alfa-2b 1.5 µg/kg 1x/week/24 - 48 weeks depending on genotype</p> <p>B: Pegylated interferon alfa-2b 1.5 µg/kg 1x/week/24 - 48 weeks depending on genotype</p>	<p>A: Ribavirin 800 mg/day 24- 48 weeks depending on genotype</p> <p>B: Ribavirin 800-1400 mg/day for 24- 48 weeks depending on genotype</p> <p><65kg - Ribavirin 800 mg/week/48 weeks</p> <p>65-85 kg - Ribavirin 1000 mg/week/48 weeks</p> <p>>85-105 kg - Ribavirin 1200 mg/week/48 weeks</p> <p>>105 kg but <125 kg - Ribavirin 1400 mg/week/48 weeks</p>	None	<p>Treatment-naïve chronic hepatitis C patients</p> <p>18 to 70 years old</p> <p>Body weight less than 125 kg</p> <p>Treatment-naïve adult patients with HCV RNA levels detectable by (PCR)/branched DNA assay</p> <p>Compensated liver disease</p> <p>Liver biopsy showing HCV infection within 36 months prior to screening</p> <p>Elevated ALT at least once during the 6 months prior to screening</p> <p>Alpha-fetoprotein level of ≤100 ng/mL in the year preceding entry</p>	<p>Positive test result for hepatitis B surface antigen or human immunodeficiency virus (HIV)</p>	<p>Paper 1: NR/NR/ 5519/4913</p> <p>Paper 2: 4913/387/ 387/387 (sub-population from Jacobson, 2007a)</p>	<p>A vs. B</p> <p>Age - Mean: - 45.8 vs. 45.8 years</p> <p>Female - 37.7% vs. 36.2%</p> <p>Race: White - 80.7% vs. 78.8% Non-White - 19.3% vs. 21.2%</p> <p>Paper 2: Race: 100% Non-White (African-American)</p>	<p>A vs. B</p> <p>Genotype 1 - 1512/2469 (61.2%) vs. 1506/2444 (61.6%)</p> <p>Genotype 2 - 499/2469 (20.2%) vs. 525/2444 (21.5%)</p> <p>Genotype 3 - 421/2469 (17.1%) vs. 386/2444 (15.8%)</p> <p>Genotype 4/5/6 - 33/2469 (1.3%) vs. 23/2444 (0.9%)</p> <p>Genotype viral load >600,000 IU/mL - 1232/2469 (49.9%) vs. 1125/2444 (46.0%)</p> <p>METAVIR stage: F0–F2 - 1729/2469 (70.0%) vs. 1709/2444 (69.9%)</p> <p>F3 - 486/2469 (19.7%) vs. 489/2444 (20.0%)</p> <p>F4 - 254/2469 (10.3%) vs. 246/2444 (10.1%)</p> <p>ALT abnormal: 2119/2469 (85.8%) vs. 2105/2444 (86.1%)</p> <p>HCV viral load (> 600,000 IU/mL): 1232/2469(49.9%) vs. 1125/2444(46%)</p> <p>100% Treatment naïve</p> <p>Paper 2: (African-Americans)</p> <p>Genotype 1: 100%</p> <p>HCV viral load > 600,000 IU/mL - 119/202(59%) vs. 116/185(63%)</p> <p>METAVIR stage F3-F4 (%) - 60/202(30%) vs. 58/185(31%)</p> <p>Cirrhosis: 10% vs. 10%</p> <p>Minimal or no fibrosis: NR</p> <p>100% Treatment naïve</p>

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
<p>Kawaoka, 2009⁵⁰ Japan</p> <p>Dose comparison study of pegylated interferon-α-2b plus ribavirin in naïve Japanese patients with hepatitis C virus genotype 2: A randomized clinical trial</p> <p>Overall Quality: Fair</p>	<p>A: Pegylated interferon alpha-2a 1.0 μg/kg/week/24 weeks</p> <p>B: Pegylated interferon alpha-2a 1.5 μg/kg/week/24 weeks</p>	<p>A: Ribavirin 60 kg - 600 mg/week/24 weeks</p> <p>>60 kg \leq80 kg - 800 mg/week/24 weeks</p> <p>>80 kg - 1000 mg/week/24 weeks</p> <p>B: Ribavirin 60 kg - 600 mg/week/24 weeks</p> <p>>60 kg <80 kg - 800 mg/week/24 weeks</p> <p>>80 kg - 1000 mg/week/24 weeks</p>	None	<p>Patients with chronic hepatitis C</p> <p>Age >20 years</p> <p>Treatment naïve</p> <p>Genotype 2</p>	<p>Patients treated with Shosaiko-to, a Japanese herbal medicine considered to improve liver function</p> <p>Patients with autoimmune hepatitis</p> <p>Patients with a history of hypersensitivity to Pegylated Interferon-alpha-2a or other interferons</p> <p>History of hypersensitivity to biological products, such as vaccines</p> <p>Decompensated liver cirrhosis (LC)</p> <p>Hepatocellular carcinoma (HCC) or malignant tumors in other tissues</p> <p>History of severe psychosis, such as being severely depressed and/or suicidal</p> <p>Women who were pregnant or lactating or who were suspected of being pregnant</p> <p>Patients judged by the investigator not to be appropriate for inclusion</p>	NR/55/53/53	<p>A vs. B</p> <p>Age - Median: 57 vs. 55 years</p> <p>Female: 65% vs. 44%</p> <p>Race: NR (study conducted in Japan)</p>	<p>A vs. B</p> <p>Genotype 2a: 13/26(50%) vs. 13/27(48%)</p> <p>Genotype 2b: 13/26(50%) vs. 14/27(52%)</p> <p>Histological stage (Desmet, 1994):</p> <p>F0 - 1/26(4%) vs. 0/27(0%)</p> <p>F1 - 14/26(51%) vs. 13/27(48%)</p> <p>F2 - 8/26(31%) vs. 9/27(33%)</p> <p>F3 - 3/26(12%) vs. 5/27(19%)</p> <p>Cirrhosis: None</p> <p>Minimal or no fibrosis: 55% vs. 48%</p> <p>100% Treatment naïve</p>

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Krawitt, 2006 ⁵¹ USA (New York/New England) A Study of Low Dose Pegylated interferon Alpha-2b with Ribavirin for the Initial Treatment of Chronic Hepatitis C Overall Quality: Fair	A: (low dose) Pegylated interferon alpha-2b 50 µg/week/24 weeks (treatment continued for additional 24 weeks if HCV RNA undetectable by PCR at week 24) B: (standard dose) pegylated interferon alpha-2b <75 kg - 100 µg/week/24 weeks ≥75kg - 150 µg/week/24 weeks (treatment continued for additional 24 weeks if HCV RNA undetectable by PCR at week 24)	A: Ribavirin 1000 mg/day/24 weeks (treatment continued for additional 24 weeks if HCV RNA undetectable by PCR at week 24) B: Ribavirin 1000 mg/day/24 weeks (treatment continued for additional 24 weeks if HCV RNA undetectable by PCR at week 24)	None	Age ≥ 18 years older Detectable serum hepatitis C virus (HCV) RNA Treatment naive Liver biopsy consistent with the diagnosis of chronic hepatitis C, performed not longer than 5 yr prior to entry, with histological interpretation performed by pathologists at the study site locations Chronic hepatitis alone (F0) Chronic hepatitis with fibrosis, including bridging fibrosis (F1–F3) Chronic hepatitis with cirrhosis (F4)	Positive serum hepatitis B surface antigen Any chronic liver disease other than chronic hepatitis C Hemoglobinopathies Evidence of hepatic decompensation(ascites, encephalopathy, gastrointestinal bleeding secondary to portal hypertension) Other conditions that could interfere with participation in the protocol - (i.e. coronary artery disease, uncontrolled hypertension, clinically significant retinal abnormalities, pregnancy, nursing, severe preexisting psychiatric disorders Active substance dependency within 6 months of screening for entry into the study Methadone maintenance (unless a program of continual testing was in use) History of organ transplantation Participation in any other clinical trial or use of another investigational drug within 30 days of entry	NR/NR/ 314/301	A vs. B Age: > 50 years - 18% vs. 19% Female - 38% vs. 36% Race: Non-White - 4.6% vs. 3.1%	A vs. B Genotype 1 - 109/152(71.7%) vs. 119/162(73.5%) Genotype 2/3 - 43/152(28.3%) vs. 43/162(26.5%) Histology Fibrosis - 80/152(52.6%) vs. 92/162(56.8%) Cirrhosis - 26/152(17.1%) vs. 17/162(10.5%) Baseline HCV RNA: ≤ 2 x 10 ⁶ copies/ml - 67/152(44.1%) vs. 86/162(40.7%) > 2 x 10 ⁶ copies/ml - 85/152(55.9%) vs. 96/162(59.3%) 100% Treatment naive

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Manns, 2001 ⁵² US & UK Peginterferon alfa-2b plus ribavirin compared with interferon alfa- 2b plus ribavirin for initial treatment of chronic hepatitis C: a randomized trial Overall Quality: Fair	A: Pegylated interferon alfa-2b 1.5 g/kg/4 weeks followed by Pegylated interferon 0.5 g/kg/week/4 4 weeks B: interferon alfa-2b 3 million units/3x week/48 weeks	A: (weight- based) Ribavirin 1000–1200 mg/day/48 weeks 75 kg > 1000 mg 75 kg < 1200 mg B: (weight- based) Ribavirin 1000–1200 mg/day/48 weeks 75 kg > 1000 mg 75 kg < 1200 mg	NA	Eligible patients were previously untreated adults who had HCV RNA detectable in serum by PCR, who had undergone a liver biopsy within 1 year before entry that was consistent with chronic hepatitis, and who had high serum values of alanine aminotransferase (above the upper limit of normal >43 IU/L for men, >34 IU/L for women) with minimum hematological and biochemical values of: hemoglobin 120 g/L for women and 130 g/L for men; white-blood-cell count 3 109/L; neutrophil count 1.5 109/L; platelet count 100 109/L; and bilirubin, albumin, and creatinine within normal limits.	Patients were excluded if they had decompensated cirrhosis, serum-fetoprotein concentration of more than 50 g/L, HIV infection, previous organ transplantation, other causes of liver disease, pre-existing psychiatric disease, seizure disorders, cardiovascular disease, hemoglobinopathies, hemophilia, poorly controlled diabetes, or autoimmune type disease, or if they were unable to use contraception.	NR/2316/1 530/1530	A vs. B: Age (Mean): 44 vs. 43 years Female: 168/514(3 3%) vs. 169/505(3 3%) Race: NR	A vs. B Genotype 1: 68% vs. 68% Genotype 2/3: 30% vs. 29% Genotype 4, 5, or 6: 2% vs. 3% Histology Mean (SD) baseline Knodell inflammatory score: 7.9 (2.3) vs. 7.8 (2.5) Bridging fibrosis/cirrhosis: 146/491 (30%) vs. 132/468 (28%) Treatment naive : 100%

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Meyer-Wyss, 2006 ⁵³ Switzerland Comparison of two PEG- interferon alpha-2b doses (1.0 or 1.5µg/kg) combined with ribavirin in interferon- naïve patients with chronic hepatitis C and up to moderate fibrosis Overall Quality: Poor	A: Pegylated- interferon alpha-2b 1.0 µg/kg/week/ 24-48 depending on genotype B: Pegylated- interferon alpha-2b 1.5 µg/kg/week/ 24-48 depending on genotype	A: Ribavirin 800mg/day/24- 48 depending on genotype B: Ribavirin 800mg/day/24- 48 depending on genotype	None	Treatment-naïve patients Aged 18–65 years Biopsy-proven chronic hepatitis C within ≤12 months Up to moderate fibrosis (METAVIR score ≤F2) with elevated alanine aminotransferase levels (ALT; on at least two occasions, at least 6 months apart) HCV-RNA positive serum	Subjects participating in any study within 30 days prior to entry into the trial Pregnant or nursing women Positive human immunodeficiency virus (HIV) status Liver disease other than chronic hepatitis C Elevated levels of fasting blood glucose Abnormal values of thyroid stimulating hormone Hemophilia or Hemoglobinopathy Any known pre-existing medical condition that could interfere with the patient's participation and completion of the study including: History of severe psychiatric disorders Central nervous system trauma/active seizure disorders Significant cardiovascular Pulmonary, or retinal disorders Clinically manifested gout Substance abuse Chronic systemic administration of steroids/other immunosuppressants Immunologically mediated disease.	NR/NR/ 227/219	A vs. B Age - Median: 39 vs. 42 years Female: 43% vs. 28% Race: NR	A vs. B Genotype 1 - 49/113(43%) vs. 64/106(60%) Genotype 2 - 14/113(12%) vs. 10/106(9%) Genotype 3 - 41/113(36%) vs. 26/106(9%) Genotype 4 - 9/113(8%) vs. 6/106(6%) Histological stage (METAVIR score): 0 - 21/113(19%) vs. 13/106(12%) 1 - 44/113(39%) vs. 39/106(37%) 2 - 48/113(42%) vs. 54/106(51%) Cirrhosis: None Minimal of no fibrosis: NR 100% Treatment naïve

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Mimidis, 2006 ⁵⁴ Greece Hepatitis C virus survival curve analysis in naïve patients treated with Pegylated interferon alpha-2b plus ribavirin. A randomized controlled trial for induction with high doses of Pegylated interferon and predictability of sustained viral response from early virologic data Overall Quality: Poor	A. Pegylated interferon alfa-2b 3.0 mcg/kg weekly for 12 weeks followed by 1.5 mcg/kg weekly for 36 weeks B. Pegylated interferon alfa-2b 1.5 mcg/kg weekly for 48 weeks	A. 800-1200 mg daily (11 mg/kg) B. 800-1200 mg daily (11 mg/kg)	NA	Treatment-naïve HCV RNA detected in serum Liver biopsy consistent with chronic hepatitis within 6 months before enrollment Elevated ALT at entry and at least once in 6 months before screening	HBV HIV co-infection Hemochromatosis Alpha-1 anti-trypsin deficiency Wilson's disease Autoimmune hepatitis Alcohol drug or obesity induced liver disease Substance abuse Any known pre-existing condition that could interfere with patient's participation Creatinine >1.5 mg/dL ³ Neutrophils <1000/mL ³ Platelets <50K/mL ³ Hemoglobin <11 g/dL	NR/NR/ 188/120	A vs. B Age mean: NR Sex: 36% vs. 38% non- White: NR	A vs. B genotype 1/4: 46% vs. 52% Treatment-naïve: all Fibrosis: NR Cirrhosis: NR HCV RNA _≥ 800k IU/mL: NR

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Reddy, 2010 ⁵⁵ International, 14 countries Induction pegylated interferon alfa- 2a and high dose ribavirin do not increase SVR in heavy patients with HCV genotype 1 and high viral loads Overall Quality: Fair	A. Pegylated interferon alpha-2a 360 mcg weekly for 12 weeks then 180 mcg weekly for 36 weeks B. Pegylated interferon alpha-2a 360 mcg/weekly for 12 weeks then 180 mcg weekly for 36 weeks C. Pegylated interferon alpha-2a 180 mcg weekly for 48 weeks D. Pegylated interferon alpha-2a 180 mcg weekly for 48 weeks	A. 1400 - 1600 mg/day for 48 weeks depending on weight B. 1200 mg/day for 48 weeks C. 1400 - 1600 mg/day for 48 weeks depending on weight D. 1200 mg/day for 48 weeks	NA	Treatment-naïve Aged 18 years or older Weight \geq 85 kg HCV genotype 1 infection HCV RNA \geq 400k IU/mL Liver biopsy in past 24 months consistent with chronic hepatitis C	co-infection with HBV, HAV, or HIV Chronic liver disease of other origin Current or past history of chronic systemic disease including severe psychiatric disease Increased baseline risk of anemia Neutrophils $<$ 1500/mL ³ Platelets $<$ 90K/mL ³ Hemoglobin $<$ 12 g/dL in men or $<$ 13 g/dL in women Creatinine $>$ 1.5 times upper limit of normal Pregnant or breastfeeding women and male partners	NR/NR/ 1175/1145	A vs. B vs. C vs. D Age mean: 46 vs. 46 vs. 45 vs. 46 Female: 19% vs. 24% vs. 22% vs. 19% non- White: 14% vs. 13% vs. 19% vs. 13%	A vs. B vs. C vs. D genotype 1: all Treatment-naïve: all Bridging fibrosis/cirrhosis: 12% vs. 8% vs. 10% vs. 12% HCV RNA \geq 800k IU/mL: 86% vs. 83% vs. 84% vs. 82%

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Roberts, 2009 ⁵⁶ Australia Impact of high- dose Pegylated interferon alfa- 2a on virologic response rates in patients with hepatitis C genotype 1: a randomized controlled trial Overall Quality: Fair	A. Pegylated interferon alfa-2a 360 mcg weekly for 12 weeks followed by 180 mcg for 36 weeks (48 weeks total) B. Pegylated interferon alfa-2a 180 mcg weekly for 48 weeks	A. 1000-1200 mg/day for 48 weeks B. 1000-1200 mg/day for 48 weeks	NA	Treatment naïve Ages 18 -75 years HCV genotype 1 infection HCV RNA >600 IU/mL Elevated ALT Compensated liver disease (Child-Pugh score <7) Histologic findings consistent with chronic hepatitis on liver biopsy within last 36 months *Protocol modified during study to remove ALT, pretreatment biopsy, and compensated cirrhosis inclusion/exclusion requirements	HBV HIV co-infection History of decompensated liver disease Evidence of hepatocellular carcinoma Liver disease of other origin Therapy with systemic antiviral, antineoplastic, or immunomodulatory agents within 6 months Pregnancy or breast feeding and male partner of women Neutrophils <1500/mL ³ Hemoglobin <12 g/dL in women and <13 g/dL in men Creatinine >1.5 times the upper limit of normal Active severe psychiatric disease Any severe chronic or uncontrolled disease Current or recent drug or alcohol abuse Cirrhosis	NR/NR/ 896/871	A vs. B Age mean: 44 vs. 43 Female: 31% vs. 35% non- White: 18% vs. 17%	A vs. B genotype 1: all Treatment-naïve: all Fibrosis stage 3 or 4: 14% vs. 16% HCV RNA \geq 800K: 70% vs. 67%

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Sood, 2008 ⁵⁷ India Comparison of low-dose pegylated interferon vs. standard high- dose pegylated interferon in combination with ribavirin in patients with chronic hepatitis C with genotype 3: An Indian Experience Overall Quality: Fair	A: Pegylated- interferon alpha-2b 1.0 µg/kg/week/ 24 weeks B: Pegylated- interferon alpha-2B 1.5 µg/kg/week/ 24 weeks	A: Ribavirin 10- 12 mg.kg/day/24 weeks B: Ribavirin 10- 12 mg.kg/day/24 weeks	None	Aged between 16– 70-years-old HCV-RNA positive with genotype 3 Treatment naïve ALT >1.2 x Upper limit of Normal (ULN) at screening and for at least the previous 6 months Liver biopsy–proven chronic HCV within 6 months prior to inclusion	Chronic HCV patients with genotypes other than Genotype 3 Total leukocyte count < 3000 per cubic millimeter Platelet count < 70 000 per cubic millimeter, Hemoglobin level lower than 10 g per deciliter co infection with hepatitis B virus or human immunodeficiency virus, Alcohol intake exceeding 20 g/day Presence of drug abuse, psychiatric illness, or thyroid dysfunction Pregnancy and lactation Decompensated liver disease Evidence of liver disease due to other etiology such as autoimmune or drug-induced hepatitis Serious concurrent medical illnesses (such as malignancy, severe cardiopulmonary disease, or uncontrolled diabetes mellitus) Inability to give an informed written consent	NR/103/ 103/103	A vs. B Age - Mean: 43 vs. 37 years Female: 12% vs. 22% Race: NR	A vs. B Genotype 3: 100% (Knodell) HAI score - Mean (SD): 7.2 (3.15) vs. 4.68(2.12) Fibrosis score - Mean(SD): 2.34(1.27) vs. 1.64(1.29) Cirrhosis: NR 100% Treatment naïve

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Abergel, 2006 ⁴³ France Pegylated interferon alpha- 2b plus ribavirin for treatment of chronic hepatitis C with severe fibrosis: a multicenter randomized controlled trial comparing two doses of Pegylated interferon alpha- 2b Overall Quality: Fair	Followup visits at 24 weeks after completion of treatment	A vs. B ETR: 59/101(62.8%) vs. 57/102(59.4%) SVR: 50/101(49.5%) vs. 38/102(37.2%)	A vs. B ETR: NR SVR: BMI <27 kg/m ² - 35/70 (50.0%) vs. 26/70 (37.1%); p=ns BMI ≥27 kg/m ² - 10/31 (32.3%) vs. 12/32 (37.5%); p=ns gamma glutamyl transpeptidase (GGT) used as a marker for steatosis: GGT <1.6 ULN - 29/48 (60.4%) vs. 23/48 (47.9%); p=ns GGT ≥1.6 ULN - 13/50 (26.0%) vs. 13/51 (25.5%); p=ns	A vs. B ETR: NR SVR: Genotypes 1, 4, 5, - 15/60(25.0%) vs. 11/65 (16.9%); p=ns Genotype 1 - 12/50 (24.0%) vs. 09/54 (16.7%); p=ns Genotypes 2, 3 - 30/41 (73.2%) vs. 27/37 (73.0%); p=ns Viremia <800.000 IU/mL - 25/55 (45.5%) vs. 20/47 (42.5%); p=ns Viremia ≥800 000 IU/mL - 20/44 (45.5%) vs. 17/53 (32.1%); p=ns Cirrhosis (F4) - 18/46 (39.1%) vs. 20/58 (34.5%); p=ns Severe fibrosis(F3) - 27/55 (49.1%) vs. 18/44 (40.1%); p=ns	None	A vs. B Discontinuation - 30/101(31 %) vs. 28/102(27 %) Discontinuation or treatment reduction – 53/101(54%) vs. 37/102(36 %), p <0.03 Treatment reduction - 36/101(37%) vs. 13/102(12%), p <0.0002 Overall withdrawals - NR Deaths - NR Severe Adverse Events: Adverse event - 8/101(9%) vs. 4/102(3%) Cytopenia -7/101(7%) vs. 1/102(1%) Others - 7/101(8%) vs. 3/102(2 %) Adverse events Adverse event - 15/101(16%) vs. 4/102(3%), p <0.01 Cytopenia - 20/101(21 %) vs. 9/102(8%), <0.03 Anemia - 9/101(10%) vs. 5/102(4 %) Neutropenia - 10/101(11 %) vs. 4/102(3%) Thrombopenia - 3/101(3 %) vs. 0/102(0%) Others - 2/101(1%) vs. 0/102(1%) Hemoglobin < 10g/dL - 27/101(27 %) vs. 16/102(15%), p=0.054 Neutrophils < 750/μL - 21/101(21%) vs. 8/102(7%), p <0.01 Platelets < 50 000/ μL - 7/101(7%) vs. 7/102(6 %) Depression - 13/101(12%) vs. 15/102(14%) Suicide - 2/101(1%) vs. 0/102(0%) Hypothyroidism (treated) - 9/101(10%) vs. 1/102(.5%)	Schering- Plough, France and Delegation Regionale a la Recherche Clinique, Clermont- Ferrand, France

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Brady, 2010 ⁴⁴ United States Induction pegylated interferon alfa- 2b combination with ribavirin in patients with genotype 1 and 4 chronic hepatitis C: a prospective, randomized, multicenter, open-label study Overall Quality: Fair	24 weeks following treatment completion	A vs. B ETR: 126/299 (42.1%) vs. 121/311 (38.9%); p= SVR: 96/299 (32.1%) vs. 92/311 (29.6%); p=0.434	A vs. B Black: 13/36 (36.1%) vs. 12/37 (32.4%); p=0.9 Hispanic: 29.9% vs. 22.5%; p=0.292 (absolute numbers NR) Weight <85 kg: 26% vs. 31% (p=NS); (absolute numbers NR) Weight ≥85 kg: 38% vs. 28% (p=0.08); (absolute numbers NR)	NR	NR	A vs. B Overall withdrawals: 146/299 (48.8%) vs. 133/311 (42.7%); p=0.2 Withdrawals for adverse events: NR Serious adverse events: NR Deaths: NR Neutropenia <500: 10/299 (3.4%) vs. 5/311 (1.6%); p=0.261 Anemia hemoglobin <10: 50/299 (16.7%) vs. 50/311 (16.1%); p=0.916 Thrombocytopenia platelets <50: 3/299 (1.0%) vs. 4/311 (1.3%); p=1.0 Pyrexia: 68/299 (22.7%) vs. 80/311 (25.7); p=0.445 Myalgia: 114/299 (38.1%) vs. 108/311 (34.7%); p=0.430 Rash: 34/299 (11.4%) vs. 58/311 (18.6%); p=0.016 Fatigue: 131/299 (43.8%) vs. 156/311 (50.2%); p=0.136 Headache: 30/299 (10.0%) vs. 47/311 (15.1%); p=0.077 Insomnia: 47/299 (15.7%) vs. 51/311 (16.4%); p=0.906 Depression: 55/299 (18.4%) vs. 70/311 (22.5%); p=0.247 Nausea: 37/299 (12.4%) vs. 40/311 (12.9%); p=0.953	Schering Plough

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Bronowicki, 2006 ⁴² France Effect of ribavirin in genotype 1 patients with hepatitis C responding to pegylated interferon alfa- 2a plus ribavirin Overall Quality: Fair	24 weeks following treatment completion	A vs. B SVR: 93/176 (52.8%) vs. 118/173 (68.2%); p=0.004 Hepatitis Quality of Life Questionnaire: Scores for all domains not significantly different between two treatment regimens at any point in time	NR	NR	NR	A vs. B Overall withdrawals: NR Withdrawals for adverse events: 3/173 (1.7%) vs. 4/176 (2.3%); p=NS Serious adverse events: 13/173 (7.5%) vs. 12/176 (6.8%); p=NS Deaths: 1/173 (0.5%) vs. 0/176 (0%); p=NS Asthenia: 19/173 (10.6%) vs. 13/176 (7.3%); p=NS Headache: 7/173 (3.9%) vs. 6/176 (3.4%); p=NS Depression: 13/173 (7.5%) vs. 16/176 (9.1%); p=NS Myalgia: 6/173 (3.4%) vs. 6/176 (3.4%); p=NS Leukopenia: 5/173 (2.8%) vs. 5/176 (2.8%); p=NS	Roche
Ferenci, 2008 ⁴⁵ Austria A Randomized, Prospective Trial of Ribavirin 400 mg/Day Vs. 800 mg/Day in Combination with Pegylated interferon Alfa- 2a in Hepatitis C Virus Genotypes 2 and 3 Overall Quality: Fair	Followup visits at 24 weeks after completion of treatment	A vs. B ETR: NR SVR: 97/141 (68.8%) vs. 90/141 (63.8%)	NR	A vs. B SVR: Genotype 2 - 14/18 (77.8%) vs. 12/16 (63.2%); p=ns Genotype 3 - 83/122 (67.5%) vs. 78/122 (63.9%); p=ns	NR	A vs. B Overall withdrawals: 13/141 (9%) vs. 22/141 (16%) p=ns Withdrawals due to adverse events: NR Deaths: NR Severe Adverse Events: NR Adverse events: Pruritus: 48/141 (34%) vs. 50/141 (35%); p=ns Psychiatric events (mostly depression): 49/141 (35%) vs. 56/141 (40%); p=ns Hemoglobin <8.5 g/dL: 2/141 (1.4%) vs. 1/141 (0.7%); p=ns Neutrophils <1000/mm ³ : 73/141 (52%) vs. 71/141 (50%); p=ns Platelets <50K/mm ³ : 6/141 (4%) vs. 6/141 (4%); p=ns	Roche, Austria

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Fried, 2008 ⁴⁶ USA Improved Outcomes in Patients with Hepatitis C with Difficult-to-Treat Characteristics: Randomized Study of Higher Doses of Pegylated interferon α -2a and Ribavirin Overall Quality: Fair	Followup visits at 24 weeks after completion of treatment	A vs. B vs. C vs. D ETR: 21/46(45.7%) vs. 27/47(57.4%) vs. 26/47(55.3%) vs. 26/47(55.3%) SVR: 13/46(28.3%) vs. 15/47(31.9%) vs. 17/47(36.2%) vs. 22/47(46.8%)	NR	NR	NR	A vs. B vs. C vs. D Overall withdrawals: 13/46(28%) vs. 9/47(19%) vs. 15/47(32%) vs. 17/47(36%) Withdrawals for adverse events: 5/46(11%) vs. 1/47(2%) vs. 7/47(15%) vs. 9/47(19%) Deaths: NR Serious Adverse Events: 4/46(9%) vs. 6/47(13%) vs. 6/47(13%) vs. 5/47(11%) Adverse events: (significant p-values noted for A vs. B, A vs. C, or C vs. D) Fatigue - 36/46(78%) vs. 32/47(68%) vs. 35/47(74%) vs. 34/47(72%) Headache - 24/46(52%) vs. 18/47(38%) vs. 22/47(47%) vs. 21/47(45%) Insomnia - 18/46(39%) vs. 20/47(43%) vs. 22/47(47%) vs. 24/47(51%) Nausea - 18/46(39%) vs. 20/47(43%) vs. 18/47(38%) vs. 18/47(38%) Chills - 15/46(33%) vs. 14/47(30%) vs. 19/47(40%) vs. 17/47(36%) Myalgia - 14/46(30%) vs. 16/47(34%) vs. 19/47(40%) vs. 16/47(34%) Depression - 14/46 (30%) vs. 20/47(43%) vs. 12/47(26%) vs. 16/47(34%) Arthralgia - 13/46(28%) vs. 16/47(34%) vs. 16/47(34%) vs. 15/47(32%) Irritability - 14/46(30%) vs. 14/47(30%) vs. 12/47(26%) vs. 16/47(34%) Pyrexia - 12/46(26%) vs. 14/47(30%) vs. 16/47(34%) vs. 14/47(30%) Rash - 12/46(26%) vs. 11/47(23%) vs. 15/47(32%) vs. 12/47(26%) Diarrhea - 12/46(26%) vs. 9/47(19%) vs. 11/47(23%) vs. 10/47(21%) Cough - 9/46(20%) vs. 12/47(26%) vs. 12/47(26%) vs. 8/47(17%) Dyspnea - 9/46(20%) vs. 12/47(26%) vs. 8/47(17%) vs. 12/47(26%) Dizziness - 12/46(26%) vs. 9/47(19%) vs. 7/47(15%) vs. 9/47(19%) Back pain - 1/46(2%) vs. 11/47(23%) vs. 4/47(9%) vs. 3/47(6%); (B vs. D p=0.02) Injection site erythema - 10/46(22%) vs. 9/47(19%) vs. 6/47(13%) vs. 5/47(11%)	Hoffman La Roche

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Helbling, 2006 ⁴⁷ Switzerland HCV-related advanced fibrosis/cirrhosis: randomized controlled trial of pegylated interferon α -2a and ribavirin Overall Quality: Fair	Followup visits at 24 weeks post- treatment	A vs. B ETR: NR SVR: 33/64(52%) vs. 23/60(38%), p=0.153	NR	A vs. B ETR: NR SVR: Fibrosis (Ishak, 2005): F4 - 15/26(58%) vs. 6/18(33%) F5-6 - 14/33(42%) vs. 14/34(41%) Genotype 1/4 - 20/63(32%) vs. 19/59(32%) Genotype 2/3 - 45/63(72%) vs. 26/59(45%)	NR	A vs. B Discontinuation: 15/64 (23%) vs. 16/60 (27%); p=ns Discontinuation (due to AE): 6/64(9%) vs. 9/60(15%); p=ns Overall withdrawals: 18/64(28%) vs. 23/60(38%); p=ns Deaths: 0/64(0%) vs. 2/60(3%); p=ns Severe Adverse Events: 9/64(14%) vs. 11/60(18%); p=ns Adverse events: Psychiatric - 1/64(2%) vs. 4/60(7%); p=ns Neurologic - 3/64 (5%) vs. 1/60(2%); p=ns Infectious - 1/64(2%) vs. 2/60(3%); p=ns Neoplastic - 2/64 (3%) vs. 1/60(2%); p=ns Skin - 0/64(0%) vs. 1/60(2%); p=ns Endocrine and Metabolism - 0/64(0%) vs. 1/60(2%); p=ns Eye - 1/64(2%) vs. 0/60(0%); p=ns Gastrointestinal - 0/64(0%) vs. 1/60(2%); p=ns Cardiovascular - 1/64(2%) vs. 0/60(0%); p=ns	NR

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<p>Jacobson, 2007⁴⁸ USA (236 practice sites nation-wide)</p> <p>Pegylated interferon alfa-2b and Weight-Based or Flat-Dose Ribavirin in Chronic Hepatitis C Patients: A Randomized Trial</p> <p>Jacobson, 2007⁴⁹ (African-American subgroup) USA (236 practice sites nation-wide)</p> <p>Impact of Weight-based Ribavirin with Pegylated interferon alfa-2b in African-Americans with Hepatitis C Virus Genotype 1</p> <p>Overall Quality: Fair</p>	<p>Followup visits at 24 weeks after completion of treatment</p>	<p>A vs. B ETR: 1193/2102(56.8%) vs. 1255/2121(59.2%), p= 0.082</p> <p>SVR: 852/2102(40.5%) vs. 938/2121(44.2%), p=0.010</p>	<p>A vs. B 65-85 kg: 43.8% vs. 45.2% 85-105 kg: 38.8% vs. 42% >105 kg: 33.5% vs. 47.3%</p> <p>African-Americans Genotype 1: 19/188(10.1%) vs. 36/174(20.7%), p=0.006</p>	<p>A vs. B Genotype1: 337/1305 (29%) vs. 447/1313 (34%); p=0.005 Genotype 2/3: 462/777 (60%) vs. 479/775 (62%); p=0.252</p> <p>Genotype 1 High Viral Load - 199/744(26.7%) vs. 246/789(31.2%), p=0.056 Genotype 1 Low Viral Load - 149/427(34.9%) vs. 151/381(39.6%); p=0.164</p>	<p>NR</p>	<p>A vs. B Discontinuation: 354/2444(14.5%) vs. 369/2469(14.9%); p=ns Overall withdrawals: 913/2444(37.3%) vs. 895/2469(36.2%); p=ns Death: 5/2444(<1%) vs. 9/2469(<1%); p=ns Serious Adverse Event: 279/2444(11.4%) vs. 287/2469(11.6%); p=ns</p> <p>Adverse events: Cardiovascular – 136/2444(5.6%) vs.162/2469(6.6%); p=ns Psychiatric - 1685/2444(68.9%) vs. 1667/2469(67.5%); p=ns Anemia - 473/2444(19.4%) vs. 721/2469(29.2%); p<0.001</p> <p>Paper 2 (African Americans): Discontinuation: 85/202(42%) vs. 68/165(41%); p=ns Overall withdrawals: 35/202(17%) vs. 30/165(18%); p=ns Deaths: NR Severe Adverse Events: NR Adverse events: Nadir hemoglobin- <10 g/dL - 30/202(15%) vs. 37/185(20%); p=ns <8.5 g/dL - 2/202(1%) vs. 8/185(4%); p=0.04 RBV dose-reduction - 53/202(26%) vs. 69/185(37%);p=0.02 Nadir Absolute Neutrophil Count- <750 cells/mm³ - 56/202(28%) vs. 44/185(24%); p=ns <500 cells/mm³ - 10/202(5%) vs. 15/185(8%); p=ns Nadir platelets: <100 x 10³ cells/mm³ - 30/202(15%) vs. 21/185(11%); p=ns <50 x 10³ cells/mm³ - 2/202(1%) vs. 2/185(1%); p=ns</p>	<p>Schering-Plough Corp., Kenilworth, NJ</p>

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Kawaoka, 2009 ⁵⁰ Japan Dose comparison study of pegylated interferon- α -2b plus ribavirin in naïve Japanese patients with hepatitis C virus genotype 2: A randomized clinical trial Overall Quality: Fair	24 weeks following treatment completion	A vs. B ETR: 23/26(88.5%) vs. 25/27(92.6%), p=0.13 SVR: 10/26(38.5%) vs. 20/27(74.1%), p=0.013	NR	NR	NR	A vs. B Overall withdrawals/drop-out: 2/26(7.2%) vs. 2/27(7.6%); p=NS Discontinuation (pre-mature withdrawal of treatment due to AE): 3/26(11.5%) vs. 2/27(7.4%); p=NS Depression - 1/26(3.8%) vs. 0/27(0%); p=NS Fatigue - 1/26(3.8%) vs. 1/27(4%); p=NS Excitability - 0/26(0%) vs. 1/27(4%); p=NS Deaths: NR Severe Adverse Events: NR Adverse events (leading to dose-reduction): Thrombocytopenia - 1/26(4%) vs. 0/27(0%); p=NS Fatigue - 1/26(4%) vs. 3/27(11%); p=NS Neutropenia - 0/26(0%) vs. 1/27(4%); p=NS Anemia - 15/26 (57.7%) vs. 10/27 (37%); p=NS Reduced Ribavirin - 21/26 (80.7%) vs. 22/27(81.5%); p=NS	NR

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Krawitt, 2006 ⁵¹ USA (New York/New England) A Study of Low Dose Pegylated interferon Alpha- 2b with Ribavirin for the Initial Treatment of Chronic Hepatitis C Overall Quality: Fair	Followup visits at 24 weeks Post- treatment	A vs. B ETR: NR SVR: 50/152(33%) vs. 73/162(45%), p=0.02	A vs. B ETR: NR SVR: Age: ≤ 40 years - 13/33(39%) vs. 18/38(47%), p= 0.63 > 40 - ≥ 50 years - 28/91(31%) vs. 40/93(43%), p= 0.09 > 50 years - 9/28 (32%) vs. 15/31 (48%), p= 0.29 Male: 29/94 (31%) vs. 44/110 (40%); p=0.14 Female - 21/58(36%) vs. 29/52(56%), p=0.06 Race: Caucasian - 50/145 (34%) vs. 70/157 (45%), p= 0.08 African-American - 0/6 (0%) vs. 3/4 (75%), p= 0.03 Hispanic/Other - 0/1 (0%) vs. 0/1 (0%), p= 1.00 Weight: < 75 kg - 20/50 (40%) vs. 24/42 (57%), p= 0.14 ≥ 75 kg - 30/102 (29%) vs. 49/120 (41%), p= 0.09	A vs. B ETR: NR SVR: HCV Genotype: Genotype 1 - 26/109 (24%) vs. 45/119 (38%), p= 0.03 Genotype 2/3 - 24/43 (56%) vs. 28/43 (65%), p= 0.51 Baseline HCVRNA: ≤ 2×10 ⁶ copies/ml - 19/67 (28%) vs. 37/66 (56%), p= 0.002 > 2×10 ⁶ copies/ml - 31/85 (36%) vs. 36/96 (38%), p= 1.00 Histology: No fibrosis or cirrhosis: 17/46 (37%) vs. 29/53 (55%); p=0.11 Fibrosis - 27/80 (34%) vs. 39/92 (42%), p= 0.27 Cirrhosis - 6/26 (23%) vs. 5/17 (29%), p= 0.73	NR	A vs. B Total Discontinuation: 9/147(6%) vs. 28/154(18%); p=0.0015 Discontinuation due to AE: 5/147(3%) vs. 14/154(9%); p=0.04 Overall withdrawals: NR Deaths: NR Severe Adverse Events: NR	Integrated Therapeutics Group (Schering- Plough)

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Manns, 2001 ⁵² US & UK Peginterferon alfa-2b plus ribavirin compared with interferon alfa- 2b plus ribavirin for initial treatment of chronic hepatitis C: a randomized trial Overall Quality: Fair	24 weeks following treatment completion	SVR: 333/511(65%) vs. 289/514(56%) vs. 271/505(54%), p<0.001 (A vs. B), p=0.41 (A vs. C)	NR	A vs. B vs. C: SVR: Genotype 1: 42% (145/348) vs. 34% (118/349) vs. 33% (114/343), p=0.02 (A vs. B), p=0.94(A vs C) Genotype 2/3: 82% (121/147) vs. 80% (122/153) vs. 79% (115/146), p=0.46(A vs. B), p=0.89 (A vs. C) Genotype 4/5/6: 50% (8/16) vs. 33% (4/12) vs. 38% (6/16), p=0.72 (A vs B), p>0.99 (A vs. C) SVR by baseline HCV: >2 10 ⁶ /mL: 42% (149/351) vs. 42% (144/345) vs. 42% (145/344) 2 10 ⁶ /mL: 78% (125/160) vs. 59% (100/169) vs. 56% (90/161) SVR by degree of fibrosis: No/minimal fibrosis - 57% (189/333) vs. 51% (175/345) vs. 49% (164/336) Bridging fibrosis/cirrhosis - 44% (60/136) vs. 43% (63/146) vs. 41% (54/132)	NR	A vs B vs. C: Overall withdrawals: NR Withdrawals for adverse events: 42/511 vs. 36/514 vs. 34/505 Serious adverse events: NR Deaths: NR Adverse Events: Anemia: 9/511 vs. 12/514 vs. 13/505 Neutropenia: 18/511 vs. 10/514 vs. 8/505 Asthenia 18/511 vs. 16/514 vs. 18/505 Fatigue 64/511 vs. 62/514 vs. 60/505 Fever 46/511 vs. 44/514 vs. 33/505 Headache 62/511 vs. 58/514 vs. 58/505 Rigors 48/511 vs. 45/514 vs. 41/505 Weight decrease 29/511 vs. 17/514 vs. 20/505 Dizziness 21/511 vs. 21/514 vs. 17/505 Arthralgia 34/511 vs. 34/514 vs. 28/505 Musculoskeletal pain 21/511 vs. 17/514 vs. 19/505 Myalgia 56/511 vs. 48/514 vs. 50/505 Anorexia 32/511 vs. 29/514 vs. 27/505 Diarrhea 22/511 vs. 16/514 vs. 17/505 Nausea 43/511 vs. 36/514 vs. 33/505 Vomiting 14/511 vs. 14/514 vs. 12/505 Concentration impairment 17/511 vs. 16/514 vs. 21/505 Depression 31/511 vs. 29/514 vs. 34/505 Insomnia 40/511 vs. 40/514 vs. 41/505 Irritability 35/511 vs. 34/514 vs. 34/505 Coughing 17/511 vs. 15/514 vs. 13/505 Dyspnea 26/511 vs. 23/514 vs. 24/505 Alopecia 36/511 vs. 29/514 vs. 32/505 Pruritus 29/511 vs. 26/514 vs. 28/505 Rash 24/511 vs. 22/514 vs. 23/505 Dry skin 24/511 vs. 18/514 vs. 23/505 Injection-site inflammation 25/511 vs. 27/514 vs. 18/505 Injection-site reaction 58/511 vs. 59/514 vs. 36/505	Schering Plough Research Institute, Kenilworth, NJ, and clinical research centre grants from Massachusetts General Hospital (MO1- RR01066), Scripps Clinic (MO1- RR00833), and University of Florida (5MO1- RR00082).

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Meyer-Wyss , 2006 ⁵³ Switzerland Comparison of two PEG- interferon alpha- 2b doses (1.0 or 1.5µg/kg) combined with ribavirin in interferon-naïve patients with chronic hepatitis C and up to moderate fibrosis Overall Quality: Poor	Followup visits at 4 and 24 weeks post- treatment	A vs. B ETR: NR SVR: 61/113(53%) vs. 56/106(53%), p= ns	NR	A vs. B ETR: 17/39(49%) vs. 23/49(47%) SVR: Genotype 1/4: 22/58 (38%) vs. 27/70 (39%), p= ns Genotypes 2/3: 39/55 (71%) vs. 29 /36 (81%), p = ns >800K IU/mL: 28/48 (58%) vs. 40/69 (43%); p=ns <800 IU/mL: 34/65 (52%) vs. 40/69 (58%); p=ns	NR	A vs. B Discontinuation: 14/115(12%) vs. 28/112(25%); p=0.01 Deaths: 0/115(0%) vs. 1/112(0%); p=ns Life-threatening Adverse Events: 4/115(3%) vs. 9/112(9%); p=ns Severe Adverse Events: 62/115(54%) vs. 59/112(53%) ; p=ns Withdrawals due to AE: 22/115 (19%) vs. 34/112 (30%); p=0.05 Adverse events (only body systems listed with at least 10% of patients reporting): Thrombocytopenia: 1/115(1%) vs. 1/112(1%); p=ns Leukopenia: 9/115(8%) vs. 5/112(4%); p=ns Neutropenia: 20/115(17%) vs. 18/112(16%); p=ns Hemolytic anemia: 3/115(3%) vs. 3/112(3%); p=ns Blood and lymphatic system disorders - 44/115(38.3%)vs. 41/112 (36.6%); p=ns General disorders and administration site conditions - 112/115(97.4%) vs. 108/112(96.4%); p=ns Gastrointestinal disorders - 81/115(70.4%)vs. 84/112(75.0%); p=ns Metabolism and nutrition disorders - 16/115(13.9%) vs. 29/112(25.9%); p=0.02 Musculoskeletal and connective tissue disorders - 27/115(23.5%) vs. 33/112(29.5%); p=ns Nervous system disorders - 70/115(60.9%) vs. 80/112(71.4%); p=ns Psychiatric disorders - 71/115(61.7%) vs. 76/112(67.9%); p=ns Respiratory, thoracic and mediastinal disorders 18/115(15.7%) vs. 24/112(21.4%); p=ns Skin and subcutaneous disorders - 83/115(72.2%) vs. 76/112(67.9%); p=ns	EssexChemie AG, Lucerne

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Mimidis, 2006 ³⁴ Greece Hepatitis C virus survival curve analysis in naïve patients treated with Pegylated interferon alpha-2b plus ribavirin. A randomized controlled trial for induction with high doses of Pegylated interferon and predictability of sustained viral response from early virologic data Overall Quality: Poor	Week 72	A vs. B ETR: NR SVR: 38/89 (42.7%) vs. 47/87 (54%)	NR	A vs. B Genotype 1: 9/35 (25.7%) vs. 18/40 (45%); p=NS Genotype 2/3: 23/48 (47.9%) vs. 25/42 (59.5%); p=NS Genotype 4: 6/6 (100%) vs. 4/5 (80%); p=NS	NA	NR	NR

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Reddy, 2010 ³⁵ International, 14 countries Induction pegylated interferon alfa- 2a and high dose ribavirin do not increase SVR in heavy patients with HCV genotype 1 and high viral loads Overall Quality: Fair	Week 72	A vs. B vs. C vs. D ETR: NR SVR: 156/383 (40.7%) vs. 166/382 (43.5%) vs. 81/189 (42.9%) vs. 72/191 (37.7%); (p=NS for all comparisons)	A vs. B vs. C vs. D (counts not reported) Weight <95 kg: 44% vs. 46% vs. 44% vs. 49% Weight ≥95 kg: 38% vs. 41% vs. 41% vs. 29%	A vs. B vs. C vs. D (counts not reported) Steatosis score <5%: 42% vs. 48% vs. 48% vs. 47% Steatosis score ≥5%: 36% vs. 30% vs. 32% vs. 13%	NA	A vs. B vs. C vs. D Overall withdrawals: 117/383 (31%) vs. 109/382 (29%) vs. 53/189 (28%) vs. 54/191 (28%); A vs. C p=NS; B vs. D p=NS Withdrawals for adverse events: 47/383 (12%) vs. 40/382 (10%) vs. 17/189 (9%) vs. 22/191 (12%); A vs. C p=NS; B vs. D p=NS Serious adverse events: 39/383 (10%) vs. 36/382 (9%) vs. 20/189 (11%) vs. 22/191 (12%); A vs. C p=NS; B vs. D p=NS Deaths: 2/383 (<1%) vs. 2/382 (<1%) vs. 3/189 (1%) vs. 1/191 (<1%); A vs. C p=NS; B vs. D p=NS Pyrexia: 205/383 (54%) vs. 176/382 (46%) vs. 78/189 (41%) vs. 83/191 (43%); A vs. C p=NS; B vs. D p=NS Fatigue: 182/383 (48%) vs. 185/382 (48%) vs. 102/189 (54%) vs. 66/191 (35%); A vs. C p=NS; B vs. D p=NS Headache: 168/383 (44%) vs. 152/382 (40%) vs. 76/189 (76%) vs. 75/191 (39%); A vs. C p=0.006; B vs. D p=0.002 Chills: 132/383 (34%) vs. 122/382 (32%) vs. 55/189 (29%) vs. 42/191 (22%); A vs. C p=NS; B vs. D p=0.001 Myalgia: 113/383 (30%) vs. 98/382 (26%) vs. 45/189 (24%) vs. 46/191 (24%); A vs. C p=NS; B vs. D p=NS Arthralgia: 89/383 (23%) vs. 88/382 (23%) vs. 49/189 (26%) vs. 50/191 (26%); A vs. C p=NS; B vs. D p=NS Depression: 58/383 (15%) vs. 72/382 (19%) vs. 36/189 (19%) vs. 32/191 (17%); A vs. C p=NS; B vs. D p=NS Hemoglobin <8.5 g/dL: 22/383 (6%) vs. 9/382 (2%) vs. 12/189 (6%) vs. 6/191 (3%); A vs. C p=NS; B vs. D p=NS	Roche

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Reddy, 2010 ³⁵ International, 14 countries Continued						Neutrophils <500/mL3: 26/383 (7%) vs. 25/382 (7%) vs. 10/189 (5%) vs. 9/191 (5%); A vs. C p=NS; B vs. D p=NS Platelets <20K/mL3: 3/383 (1%) vs. 0/382 (0%) vs. 0/189 (0%) vs. 3/191 (2%); A vs. C p=NS; B vs. D p=NS	
Roberts, 2009 ³⁶ Australia Impact of high-dose Pegylated interferon alfa-2a on virologic response rates in patients with hepatitis C genotype 1: a randomized controlled trial Overall Quality: Fair	24 weeks after end of treatment (week 72)	A vs. B ETR: 70% vs. 66%; p=0.18 SVR: (230/433) 53% vs. (219/438) 50%; p=0.29	A vs. B White: 183/355 (52%) vs. 167/365 (46%); p=NS Asian: 40/61 (66%) vs. 40/55 (73%); p=NS Other: 7/17 (41%) vs. 12/18 (67%); p=NS Male: 149/298 (50%) vs. 134/285 (47%); p=NS Female: 81/135 (60%) vs. 85/153 (56%); p=NS <40 years: 104/146 (71%) vs. 97/141 (69%); p=NS >40 years: 126/287 (44%) vs. 122/297 (41%); p=NS Weight <85 kg: 167/294 (57%) vs. 156/297 (53%); p=NS Weight >85 kg: 63/139 (45%) vs. 63/141 (45%); p=NS	A vs. B HCV RNA <800K: 81/125 (65%) vs. 84/138 (61%); p=NS HCV RNA ≥800K: 147/302 (49%) vs. 132/293 (45%); p=NS Fibrosis METAVIR stage 3 or 4: 17/60 (28%) vs. 16/67 (24%); p=NS Fibrosis METAVIR stage 0,1, or 2: 148/256 (58%) vs. 134/242 (55%); p=NS	NR	A vs. B Overall withdrawals: 113/433 (26%) vs. 136/438 (31%); p=ns Withdrawals due to adverse events: 44/433 (10%) vs. 36/438 (8%); p=ns Deaths: NR Serious adverse events: 46/433 (11%) vs. 45/438 (10%); p=ns Headache: 227/433 (52%) vs. 208/438 (47%); p=ns Influenza like illness: 180/443 (42%) vs. 183/438 (42%); p=ns Nausea: 179/433 (41%) vs. 169/438 (39%); p=ns Fatigue: 159/433 (37%) vs. 174/438 (40%); p=ns Myalgia: 114/433 (26%) vs. 97/438 (22%); p=ns Rash: 110/433 (25%) vs. 116/438 (26%); p=ns Depression: 84/433 (19%) vs. 85/438 (19%); p=ns Arthralgia: 82/433 (19%) vs. 76/438 (17%); p=ns Pyrexia: 66/433 (15%) vs. 47/438 (11%); p=ns Chills: 64/433 (15%) vs. 34/438 (8%); p<0.001 Neutropenia: 76/433 (21%) vs. 55/438 (13%); p=0.05 Thrombocytopenia: 17 (4%) vs. 6 (1%); p=0.02 Anemia: 5 (1%) vs. 3 (1%); p=ns	Roche

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Sood, 2008 ⁵⁷ India Comparison of low-dose pegylated interferon vs. standard high- dose pegylated interferon in combination with ribavirin in patients with chronic hepatitis C with genotype 3: An Indian Experience Overall Quality: Fair	Followup visits at 24 weeks post- treatment	A vs. B ETR: 72/76(94.7%) vs. 24/27(88.9%), p=0.375 SVR: 60/76(78.9%) vs. 25/27(92.6%), p=0.145	NR	NR	NR	A vs. B Overall withdrawals: 1/76 (1.3%) vs. 2/27 (7.4%); p=ns Withdrawals (due to AE): 0/76 vs. 1/27 (4%); p=ns Deaths: NR Severe Adverse Events: NR Adverse events: Influenza-like symptoms - 20/27(74.0 %%) vs. 44/76(57.9%); p=ns Malaise or fatigue -10/27(37.0%) vs. 22/76(29.0%); p=ns Nausea or vomiting - 5/27(18.5%) vs. 11/76(14.5%) p=ns Headache - . 4/27 (14.8%) vs. 8/76(10.5%); p=ns Abdominal discomfort - 4/27(14.8%) vs. 8/76 (10.5%); p=ns Diarrhea - . 4/27(14.8%) vs. 9 /76(11.8%); p=ns Grade III or IV laboratory abnormalities Neutrophils - 3/27(11.1%) vs. 1/76(1.3%); p=0.02 Platelets - 4/27(14.8%) vs. 2/76(2.6%); p=0.02	NR

Evidence Table 8. Quality rating: Dose comparison in trials of pegylated interferon plus ribavirin

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition and withdrawals reported?	Loss to followup: differential/high?	Intention-to-treat analysis	Quality	Funding
Abergel, 2006 ⁴³	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	Unclear	No	Unclear	Yes	Fair	NR
Brady, 2010 ⁴⁴	Yes	Unclear	Yes	Yes	No, open label	No, open label	No, open label	Yes	Yes	Yes	Fair	Schering Plough
Fried, 2008 ⁴⁶	Unclear	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Fair	NR
Hadziyannis, 2004 ²⁶	Yes	Yes	No	Yes	Yes	Unclear	Unclear	Yes	Unclear	Yes	Fair	Roche, Basel, Switzerland
Helbling, 2006 ⁴⁷	Yes	Yes	Yes	Yes	No, open label	No, open label	No, open label	Yes	No	Yes	Fair	NR
Jacobson, 2007a ⁴⁸	Yes	Yes	Yes	Yes	No, open label	No, open label	No, open label	Yes	Yes	Yes	Fair	Schering-Plough Corp. , Kenilworth, NJ
Jacobson, 2007b ⁴⁹	Yes	Yes	Yes	Yes	No, open label	No, open label	No, open label	Yes	Yes	Yes	Fair	Schering-Plough Corp. , Kenilworth, NJ
Kawaoka, 2009 ⁵⁰	Unclear	Unclear	Unclear	Yes	No, open label	No, open label	No, open label	Yes	No	Yes	Fair	NR
Krawitt, 2006 ⁵¹	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Fair	Integrated Therapeutics Group (Schering-Plough)
McHutchison, 2009 ⁵⁸	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Yes	Unclear	Yes	Fair	Schering-Plough
Meyer-Wyss, 2006 ⁵³	Unclear	Yes	No	Yes	No, open label	No, open label	No, open label	Yes	Yes	Yes	Poor	Essex Chemie AG, Lucerne

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition and withdrawals reported?	Loss to followup: differential/high?	Intention-to-treat analysis	Quality	Funding
Mimidis, 2006 ⁵⁴	Unclear	Unclear	Unclear	Yes	No (not described)	No (not described)	No (not described)	No	No	No	Poor	NR
Reddy, 2010 ⁵⁵	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Fair	Roche
Roberts, 2009 ⁵⁶	Unclear	Unclear	Yes	Yes	No, open label	No, open label	No, open label	Yes	Yes	Yes	Fair	NR
Sood, 2008 ⁵⁷	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	Unclear	Yes	No	Yes	Fair	NR

Key Question 4

Evidence Table 9. Sustained virologic response and clinical outcomes

Author, Year Country Quality	Study Type Duration of Followup	Comparison Definition of Sustained Virological Response	Inclusion Criteria	Exclusion Criteria	Number analyzed Number meeting inclusion criteria excluded due to missing data or lost to followup	Population Characteristics
Arase, 2007 ⁵⁹ Japan Overall Quality: Fair	Retrospective cohort study Duration of followup: Mean 7.4 years	SVR vs. no SVR SVR=Undetectable HCV RNA 6 months after completion of long-term IFN therapy	>=60 years of age; ALT elevation greater than double upper limits within 6 months (ALT normal range 12-50IU/l); no corticosteroid immunosuppressive agents or antiviral agents used in last 6 months; no hepatitis B surface antigens, antinuclear antibodies, or antimitochondrial antibodies detectable in serum; leukocytes >3000/mm ³ , platelet count >80,000/mm ³ , and bilirubin <2.0 mg/ml; IFN therapy >4 weeks	History of alcohol abuse or advanced liver cirrhosis, encephalopathy, bleeding esophageal varices, or ascites	Number analyzed: 500 Excluded due to missing data or lost to followup: Unclear	SVR (n=140) vs. no SVR (n=360) Mean age (years): 63 vs. 64 (p=0.07) Female: 41% vs. 53% (p=0.01) Race: Not reported Genotype 1b: 34% vs. 71% (p<0.0001) Viral load (kIU/ml): 172 vs. 661 (p<0.0001) Cirrhosis (Knodell F4): 9% vs. 16% (p=0.009)

Author, Year Country Quality	Study Type Duration of Followup	Comparison Definition of Sustained Virological Response	Inclusion Criteria	Exclusion Criteria	Number analyzed Number meeting inclusion criteria excluded due to missing data or lost to followup	Population Characteristics
Backus, 2011 ⁶⁰ USA Overall Quality: Fair	Retrospective cohort study Duration of followup: Median 3.8 years	SVR vs. no SVR SVR=Undetectable HCV RNA 6 months after completion of antiviral therapy	HCV genotype 1, 2, or 3; started pegylated interferon + ribavirin between January 2001 and June 2007; stopped treatment by June 2008; HCV RNA test after end of treatment	HIV infection, hepatocellular cancer prior to treatment	Number analyzed: 16,864 Excluded due to missing data or lost to followup: 5365	SVR vs. no SVR (genotypes 1 [n=12,166], 2 [n=2904], and 3 [n=1794],) Mean age (years): 51 vs. 52, 53 vs. 53. and 51 vs. 51 Female: 5% vs. 4%, 4% vs. 3%, and 4% vs. 3% Non-white: 40% vs. 51%, 33% vs. 31%, and 30% vs. 29% Genotype: Results stratified by genotype Viral load >=500,000 IU/mL: 70% vs. 82%, 78% vs. 83%, and 64% vs. 68% Cirrhosis: 9% vs. 15%, 7% vs. 12%, and 12% vs. 20%
Bruno, 2007 ⁶¹ Italy Overall Quality: Fair	Retrospective cohort study Duration of followup: Mean 8 years	SVR vs. no SVR SVR=Undetectable HCV RNA 6 months after completion of antiviral therapy	Anti-HCV and HCV-RNA positive and diagnosis of complete cirrhosis by histological criteria (Ishak score of 6 or Knodell score of 4); liver biopsy within 18 months of start of IFN treatment	Over 70 years of age; lack of histological diagnosis of cirrhosis, gastroesophageal varices; previous episodes of decompensation or bleeding; Child class B or C, concurrent Hepatocellular carcinoma or extra hepatic tumors; subjects co-infected with hepatitis B or HIV	Number analyzed: 883 Excluded due to missing data or lost to followup: Unclear	SVR (n=124) vs. no SVR (n=759) Mean age (years): 53 vs. 44 (p=0.004) Female: 27% vs. 38% (p<0.001) Non-White: 0 (0%) vs. 0 (0%) Race: Not reported Genotypes 1 and 4: 37% vs. 63% (p<0.001) Viral load: Not reported Cirrhosis: All (inclusion criterion)

Author, Year Country Quality	Study Type Duration of Followup	Comparison Definition of Sustained Virological Response	Inclusion Criteria	Exclusion Criteria	Number analyzed Number meeting inclusion criteria excluded due to missing data or lost to followup	Population Characteristics
Cardoso, 2010 ⁶² France Overall Quality: Fair	Retrospective cohort study (of patients originally enrolled in clinical trials) Duration of followup: Median 3.5 years	SVR vs. no SVR SVR=Undetectable HCV RNA 6 months after completion of antiviral therapy	Anti-HCV and HCV RNA positive, documented chronic hepatitis C, biopsy- proven bridging fibrosis or cirrhosis, treated with interferon-based therapy in clinical trials between 1987 and 2007	HBV, hepatitis D virus, or HIV infection co-infection; history of hepatic decompensation	Number analyzed: 307 Excluded due to missing data or lost to followup: Unclear	SVR (n=103) vs. no-SVR (n=204) Mean age (years): 55 vs. 55 (p=0.93) Female: 30% vs. 34% (p=0.51) Race: Not reported Genotype 1: 36% vs. 72% (p<0.001) Viral load (log ₁₀ I/ml): 5.5 vs. 5.7 (p=0.08) Cirrhosis (METAVIR F4): 53% vs. 61% (p=0.19)
Coverdale, 2004 ⁶³ Australia Overall Quality: Poor	Prospective cohort study (some patients originally enrolled in randomized trials) Duration of followup: Median 9 years	SVR vs. response relapse vs. non- response SVR=Undetectable HCV RNA on at least 2 occasions at least 2 years after completion of therapy	Virologically and histologically proven chronic hepatitis C	Clinical or imaging evidence of liver-related complications	Number analyzed: 343 Excluded due to missing data or lost to followup: Unclear	Demographics for all treated patients (not reported by SVR status) Median age (years): 37 Female: 33% Race: Not reported Genotype 1: 38% Viral load: Not reported Median fibrosis score (Scheuer): 2

Author, Year Country Quality	Study Type Duration of Followup	Comparison Definition of Sustained Virological Response	Inclusion Criteria	Exclusion Criteria	Number analyzed Number meeting inclusion criteria excluded due to missing data or lost to followup	Population Characteristics
El Braks, 2007 ⁶⁴ France Overall Quality: Poor	Retrospective cohort study Duration of followup: Mean 7.7 years	SVR vs. no SVR SVR=Undetectable HCV RNA 6 months after completion of antiviral therapy	HCV-related cirrhosis defined by association of positive serum HCV antibodies and RNA, with typical liver histology; absence of complication before or at inclusion; daily alcohol consumption <50 g; at least 3 month course of antiviral treatment using standard or pegylated interferon with or without ribavirin, according to therapeutic advance over time and initial guidelines; a regular followup >=30 months after the starting of first treatment; residence in France allowing regular followup	HBV or HIV co-infection; contraindication to antiviral treatment, particularly platelet and polymorphonuclear counts >=80,000/mm ³ and 1500/mm ³ , respectively; Hepatocellular carcinoma or suspicious findings such as liver nodule or serum level of alpha- fetoprotein above 50 ng/mL	Number analyzed: 113 Excluded due to missing data or lost to followup: Unclear	SVR (n=37) vs. no SVR (n=76) Mean age (years): 51 vs. 56 (p=0.02) Female: 16% vs. 50% (p=0.0005) Race: Not reported HCV genotype 1: 36% vs. 73% (p=0.0001) Viral load: Not reported Cirrhosis: All (inclusion criterion)

Author, Year Country Quality	Study Type Duration of Followup	Comparison Definition of Sustained Virological Response	Inclusion Criteria	Exclusion Criteria	Number analyzed Number meeting inclusion criteria excluded due to missing data or lost to followup	Population Characteristics
Fernandez- Rodriguez, 2010 ⁶⁵ Spain Overall Quality: Poor	Retrospective cohort study Duration of followup: Median 35 months	SVR vs. no SVR SVR=Undetectable HCV RNA 6 months after completion of antiviral therapy	HCV-associated cirrhosis	Child-Pugh-Turcotte's score (CPT) >6; HIV or HBV co infection; alcohol intake >40 g per day in males or >20 g per day in females; present or past psychosis or severe depression; neutropenia <1500 per ml and/or thrombocytopenia <100,000 platelets per ml; organ transplantation; severe heart disease; uncontrolled seizures; uncontrolled diabetes; autoimmune disorders; end-stage renal failure; anemia; hemoglobinopathies; severe heart disease; pregnancy; no reliable method of contraception; uncontrolled arterial hypertension; age older than 70 years	Number analyzed: 509 Excluded due to missing data or lost to followup: 59	SVR (n=174) vs. no SVR (n=394) Mean age (years): 51 vs. 52 (p=0.31) Female: 69% vs. 73%, p=0.37 Genotype 1: 24% vs. 55% (p=0.001) Race: Not reported Viral load (10 ⁶ IU/ml): 1.7 vs. 3.1 (p=0.001) Cirrhosis: All (inclusion criterion)
Hasegawa, 2007 ⁶⁶ Japan Overall Quality: Fair	Retrospective cohort study Duration of followup: Median 4.6 years	SVR vs. no SVR SVR=Sustained undetectable HCV RNA after completion of antiviral therapy (duration of undetectability not specified)	HCV-associated cirrhosis	HBV co-infection	Number analyzed: 105 Excluded due to missing data or lost to followup: Unclear	SVR (n=48) vs. no SVR (n=58) Age >56 years: 60% vs. 55% (p>0.05) Male: 65% vs. 66% (p>0.05) Race: Not reported Genotype 1b: 19% vs. 21% (p>0.05) Viral load >=100 KIU/ml or >=1 mq/mL: 25% vs. 62% (p<0.001) Cirrhosis: All (inclusion criterion)

Author, Year Country Quality	Study Type Duration of Followup	Comparison Definition of Sustained Virological Response	Inclusion Criteria	Exclusion Criteria	Number analyzed Number meeting inclusion criteria excluded due to missing data or lost to followup	Population Characteristics
Hung, 2006 ⁶⁷ Taiwan Overall Quality: Fair	Cohort study (unclear if retrospective or prospective) Duration of followup: Median 37 months	SVR vs. no SVR SVR=Undetectable HCV RNA 6 months after completion of antiviral therapy	Anti-HCV positive; elevated ALT values for at least 6 months; Child-Pugh score A	HIV or HBV co-infection; alcoholism; autoimmune hepatitis; major contraindications to IFN or ribavirin therapy; severe thrombocytopenia or a history of hepatic encephalopathy, bleeding esophageal varices and ascites	Number analyzed: 132 Excluded due to missing data or lost to followup: Unclear	SVR (n=73) vs. no SVR (n=59) Mean age (years): 55 vs. 58 (p=0.07) Female: 43% vs. 54% (p=0.12) Race: Not reported Genotype 1b: 27% vs. 78% (p<0.001) Viral load $\geq 2 \times 10^6$ copies/ml: 21% vs. 51% (p<0.001) Cirrhosis: 100% (inclusion criterion)
Imazeki, 2003 ⁶⁸ Japan Overall Quality: Fair	Retrospective cohort study Duration of followup: Mean 8.2 years	SVR vs. no SVR SVR=Undetectable HCV RNA 6 months after completion of antiviral therapy	HCV RNA positive who underwent liver biopsy	Hepatocellular carcinoma detected within six months of liver biopsy	Number analyzed: 459 Excluded due to missing data or lost to followup: 9	Demographics for all treated patients (not reported by SVR status) Mean age (years): 49 Female: 36% Race: Not reported Genotype 1: 74% Viral load: Not reported Cirrhosis (Desmet F4): 13%
Izumi, 2005 ⁶⁹ Japan Overall Quality: Fair	Cohort study, appears retrospective Duration of followup: Not reported	SVR vs. no SVR SVR=Undetectable HCV RNA 6 months after completion of antiviral therapy	Chronic HCV infection, underwent antiviral therapy	Not reported	Number analyzed: 495 Excluded due to missing data or lost to followup: Unclear	Demographics for patients treated with interferon monotherapy and interferon plus ribavirin combination therapy, respectively (not reported by SVR status) Mean age (years): 52 and 58 Female: 43% and 44% Race: Not reported Genotype 1b: 71% and 80% Median viral load (kIU/ml): 470 and 680 Cirrhosis: 35% and 2%

Author, Year Country Quality	Study Type Duration of Followup	Comparison Definition of Sustained Virological Response	Inclusion Criteria	Exclusion Criteria	Number analyzed Number meeting inclusion criteria excluded due to missing data or lost to followup	Population Characteristics
Kasahara, 2004 ⁷⁰ Japan Overall Quality: Poor	Retrospective cohort Duration of followup: Mean 6 years	SVR vs. no SVR SVR=Undetectable HCV RNA 6 months after completion of antiviral therapy	Histological diagnosis of chronic hepatitis or cirrhosis	History of clinical signs at entry into the study of complications of cirrhosis, i.e. ascites, jaundice, encephalopathy, or variceal bleeding; evidence of Hepatocellular carcinoma at entry as assessed by ultrasonography and/or computed tomography; HBV co-infection; co- existing liver diseases such as autoimmune hepatitis or primary biliary cirrhosis; excessive alcohol consumption (>80 g/day); HIV co-infection	Number analyzed: 2698 Excluded due to missing data or lost to followup: Unclear	SVR (n=738) vs. no-SVR (n=1930) Median age (years): 51 vs. 54 (p=0.12) Female: 31% vs. 37% (p=0.32) Race: Not reported Genotype 1: Not reported Viral load: Not reported Cirrhosis (Desmet F4): 3.0% vs. 5.4% (p=0.34)
Morgan, 2010 ⁷¹ USA Overall Quality: Fair	Prospective cohort study of patient enrolled in a randomized trial Duration of followup: Median 79 to 86 months	SVR vs. no SVR SVR=Undetectable HCV RNA 6 months after completion of antiviral therapy	Advanced hepatic fibrosis (Ishak fibrosis score 3) according to liver biopsy performed within 12 months; lack of SVR to previous treatment for at least 24 weeks with standard interferon with or without ribavirin; no history of hepatic decompensation or Hepatocellular carcinoma	Not reported	Number analyzed: 526 Excluded due to missing data or lost to followup: 30 of 180 patients with SVR, not reported for breakthrough/relapse and non-responder groups	SVR (n=140) vs. breakthrough/relapse (n=77) vs. no SVR (n=309) Mean age (years): 49 vs. 49 vs. 50 (p=0.23) Female: 24% vs. 26% vs. 30% (p=0.30) Non-white: 20% vs. 20% vs. 32% (p=0.001) Genotype 1: 72% vs. 86% vs. 94% (p<0.0001) Viral load: Not reported Cirrhosis (Ishak 5 or 6): 21% vs. 31% vs. 43% (p<0.0001)

Author, Year Country Quality	Study Type Duration of Followup	Comparison Definition of Sustained Virological Response	Inclusion Criteria	Exclusion Criteria	Number analyzed Number meeting inclusion criteria excluded due to missing data or lost to followup	Population Characteristics
Shiratori, 2005 ⁷² Japan Overall Quality: Poor	Prospective cohort study of patients enrolled in randomized trials Duration of followup: Median 6.8 years	SVR vs. no SVR SVR=Undetectable HCV RNA 6 months after completion of antiviral therapy	HCV positive, elevated ALT levels for more than 6 months, abnormal histologic findings on liver biopsy specimens, indicating fibrotic state F4, platelet count greater than 3×10^9 cells/L and Child-Pugh A classification	HBV infection, autoimmune hepatitis, primary biliary cirrhosis, drug-induced liver disease, hepatocellular carcinoma on imaging prior to enrollment	Number analyzed: 271 Excluded due to missing data or lost to followup: 30 at 3 years, 86 at 7 years	For all treated patients (not reported by SVR status) Mean age (years): 57 Female: 62% Race: Not reported Genotype 1: 75% Viral load (\log_{10} copies/ml): 5.8 Cirrhosis: 100% (inclusion criterion)
Veldt, 2004 ⁷³ Europe Overall Quality: Fair	Retrospective cohort study (meta-analysis)	SVR vs. biochemical responders SVR=no detectable HCV-RNA at the end of treatment and after 6 months followup	Chronic hepatitis C patients with response to interferon monotherapy; HCV-RNA data available at the end of treatment and after 6 months of followup		NR screened/NR eligible/343/343	SVR (n=286) vs. biochemical responders (n=50) Mean age: 41 (17-72) vs. 45 (23-72), p=0.04 Male: 59% vs. 52%, p=0.35
Veldt, 2007 ⁷⁴ Europe and Canada Overall Quality: Poor	Retrospective cohort Duration of followup: Median 2.1 years	SVR vs. no SVR SVR=Undetectable HCV RNA 6 months after completion of antiviral therapy	Biopsy-proven advanced fibrosis or cirrhosis (Ishak score, 4 to 6) treated with interferon-based regimen	HIV or HBV co-infection; decompensated liver disease	Number analyzed: 479 Excluded due to missing data or lost to followup: Unclear	SVR (n=142) vs. no-SVR (n=337) Mean age (years): 48 vs. 49 (p=0.45) Female: 27% vs. 32% (p=0.23) Race: Not reported Genotype 1: 39% vs. 67% (p<0.001) Viral load ($\times 10^5$ IU/mL): 8.5 vs. 8.0 (p=0.75) Cirrhosis (Ishak 5 or 6): 71% vs. 77% (p=0.45)
Yoshida, 2002 ⁷⁵ Japan Overall Quality: Poor	Retrospective cohort Duration of followup: Mean 5.4 years	SVR vs. no SVR SVR=Undetectable HCV RNA 6 months after completion of antiviral therapy	HCV antibody positive; received liver biopsy	HBV co-infection, alcoholic liver disease, autoimmune hepatitis, or primary biliary cirrhosis.	Number analyzed: 2889 Excluded due to missing data or lost to followup: Unclear	SVR (817) vs. non-SVR (1613) Mean age (years): 48 vs. 51 Female: 30% vs. 40% Race: Not reported Genotype: Not reported Viral load: Not reported Cirrhosis (Desmet F4): 6.5% vs. 11%

Author, Year Country Quality	Study Type Duration of Followup	Comparison Definition of Sustained Virological Response	Inclusion Criteria	Exclusion Criteria	Number analyzed Number meeting inclusion criteria excluded due to missing data or lost to followup	Population Characteristics
Yu, 2006 ⁷⁶ Taiwan Overall Quality: Poor	Retrospective cohort Duration of followup: Mean 5.2 years	SVR vs. no SVR SVR=Undetectable HCV RNA 6 months after completion of antiviral therapy	Seropositive for anti-HCV antibody and HCV RNA and biopsy-proven chronic hepatitis with or without cirrhosis	Concurrent HBV infection, HIV infection, autoimmune hepatitis, heavy ETOH use (>80g/day), or evidence of Hepatocellular carcinoma	Number analyzed: 1057 Excluded due to missing data or lost to followup: Unclear	For all treated patients (not reported by SVR status) Mean age (years): 47 Female: 40% Race: Not reported Genotype 1: 46% Viral load: Not reported Cirrhosis (criteria not reported): 16%

Author, Year Country Quality	Treatments	Variables Assessed as Univariate Predictors	Variables Included in Multivariate Models	Results	Funding Source
Arase, 2007 ⁵⁹ Japan Overall Quality: Fair	Interferon alpha-2a or - Interferon alpha-2b monotherapy: 94% Interferon plus ribavirin combination therapy: 6%	Age, sex, liver fibrosis, liver activity, viral load, genotype, AST, ALT	Hepatocellular cancer: Sex, liver fibrosis All-cause and liver-related mortality: Sex, liver fibrosis	SVR vs. no SVR Hepatocellular cancer: Adjusted HR 0.19 (0.08- 0.45) All-cause mortality: Adjusted HR 0.39 (0.16- 0.93) Liver-related mortality: Adjusted HR 0.13 (0.03- 0.59)	Okinaka Memorial Institute for Medical Research and Japanese Ministry of Health, Labor and Welfare
Backus, 2011 ⁶⁰ USA Overall Quality: Fair	Pegylated interferon (alfa- 2aa or 2b) plus ribavirin	Age, sex, albumin, AST, AST/ALT ratio, creatinine clearance, platelets, sodium, cirrhosis, Chronic obstructive pulmonary disease (COPD), diabetes, HTN, tobacco use, treatment duration <60% recommended, bilirubin, body mass index, HBV co- infection, viral load, hemoglobin, CAD, cancer, congestive heart failure, cerebrovascular disease, schizophrenia, recent alcohol abuse, anxiety disorder, depression, hard drug use, post-traumatic stress disorder (PTSD), socioeconomic status instability, multiple treatment course, erythropoiesis stimulating agent use, granulocyte colony stimulating factor use, year of treatment start	Age, sex, albumin, AST, AST/ALT ratio, creatinine clearance, platelets, sodium, cirrhosis, Chronic obstructive pulmonary disease (COPD), diabetes, HTN, tobacco use, treatment duration <60% recommended, bilirubin, body mass index, HBV co- infection, viral load, hemoglobin, coronary artery disease, cancer, congestive heart failure, cerebrovascular disease, schizophrenia, recent alcohol abuse, anxiety disorder, depression, hard drug use, post-traumatic stress disorder (PTSD), socioeconomic status instability, multiple treatment course, erythropoiesis stimulating agent use, granulocyte colony stimulating factor use, year of treatment start	SVR vs. no SVR (genotypes 1, 2, and 3, respectively) All-cause mortality: Adjusted HR 0.71 (0.60- 0.86), 0.62 (0.44-0.87), and 0.51 (0.35-0.75)	US Department of Veterans Affairs, Veterans Health Administration, Office of Public Health and Environmental Hazards

Author, Year Country Quality	Treatments	Variables Assessed as Univariate Predictors	Variables Included in Multivariate Models	Results	Funding Source
Bruno, 2007 ⁶¹ Italy Overall Quality: Fair	Interferon monotherapy	Age, sex, platelet count, genotype	Hepatocellular carcinoma: Age, sex, platelet count Liver-related mortality: Age, platelet count	SVR vs. no SVR Ascites, encephalopathy, or gastrointestinal bleeding: Not calculated, 0 events/1061 person-years vs. 107 events/5703 person-years (1.88 events/100 person-years) Hepatocellular carcinoma: Adjusted HR 0.39 (0.17- 0.88) Liver-related mortality: 0.14 (0.04-0.59)	Associazione per la Ricerca sulle Malattie Epatiche (ARME), Bologna, Italy
Cardoso, 2010 ⁶² France Overall Quality: Fair	Pegylated interferon and ribavirin: 252 (82%) Pegylated interferon monotherapy: 22 (7%) Conventional interferon with or without ribavirin: 33 (11%)	Age, sex, BMI, alcohol consumption, diabetes, ALT, bilirubin, albumin, platelets, genotype, viral load, inflammation, fibrosis and steatosis scores	Hepatocellular carcinoma: Age, bilirubin, albumin, platelet count Ascites/variceal bleeding and liver-related mortality: Bilirubin, albumin, platelets	SVR vs. no SVR Hepatocellular carcinoma: Adjusted HR 0.33 (0.23- 0.89) Ascites or variceal bleeding: Adjusted HR 0.21 (0.05-0.92) Liver-related mortality: Adjusted HR 0.27 (0.08- 0.95)	Schering Plough

Author, Year Country Quality	Treatments	Variables Assessed as Univariate Predictors	Variables Included in Multivariate Models	Results	Funding Source
Coverdale, 2004 ⁶³ Australia Overall Quality: Poor	Interferon alpha-2a or Interferon alpha-2b	Statistically significant predictors of outcomes in univariate analyses were age, duration, place of birth, mode of transmission, genotype, fibrosis score, albumin, bilirubin, prothrombin time. Other tested variables not reported.	Age, duration, place of birth, mode of transmission, genotype, fibrosis score, albumin, bilirubin, prothrombin time	SVR vs. response-relapse vs. non-response Liver-related complications (hepatic decompensation, complications of portal hypertension, hepatocellular carcinoma, liver transplantation, and liver-related mortality) at 10 years: Not statistically significant in multivariate analysis, adjusted HR not reported (p=0.06) Hepatocellular carcinoma at 10 years: Not statistically significant in multivariate analysis, adjusted HR and p value not reported Liver transplant or liver-related death at 10 years: Not statistically significant in multivariate analysis, adjusted HR not reported (p=0.20)	National Institutes of Health
El Braks, 2007 ⁶⁴ France Overall Quality: Poor	Interferon monotherapy: 35/113 (31%) Interferon + ribavirin: 40/113 (35%) Pegylated interferon + ribavirin: 38/113 (34%)	Age, sex, genotype, duration of treatment	Duration of treatment	SVR (n=37) vs. no SVR (n=76) Clinical events (hepatocellular cancer, ascites, hepatic encephalopathy, or death): Adjusted HR 0.14 (0.04-0.45)	Not reported

Author, Year Country Quality	Treatments	Variables Assessed as Univariate Predictors	Variables Included in Multivariate Models	Results	Funding Source
Fernandez-Rodriguez, 2010 ⁶⁵ Spain Overall Quality: Poor	Pegylated interferon-2a or 2b	Statistically significant predictors of outcomes in univariate analyses were age, albumin, esophageal varices, ultrasonographic signs of portal hypertension, platelet count, bilirubin, prothrombin activity. Other tested variables not reported.	Age, albumin, esophageal varices, ultrasonographic signs of portal hypertension, platelet count, bilirubin, prothrombin activity	SVR vs. no SVR Combined clinical endpoint (hepatic decompensation, upper gastrointestinal bleeding secondary to rupture of esophageal or gastric varices, hepatocellular carcinoma, liver transplantation, and liver-related or liver-unrelated mortality): Adjusted HR 0.38 (0.18-0.76)	Study conducted on behalf of the Group for the Assessment of Prevention of Cirrhosis Complications and Virological Response (APREVIR). No additional funding sources.
Hasegawa, 2007 ⁶⁶ Japan Overall Quality: Fair	Natural or recombinant Interferon alpha: 67% Natural Interferon-beta: 31% Both: 1.6%	Age, sex, BMI, albumin, cholinesterase, platelet count, alpha-fetoprotein, indocyanine green retention rate at 15 minutes, fasting blood glucose, AST, ALT, viral load, genotype, use of combination therapy, total dose of interferon, daily dose of interferon, use of induction therapy, type of interferon	Choline esterase, alpha-fetoprotein, viral load, daily dose of interferon, duration of interferon, use of induction therapy	SVR vs. no SVR Hepatocellular carcinoma: Adjusted HR 0.18 (0.04-0.81)	Not reported
Hung, 2006 ⁶⁷ Taiwan Overall Quality: Fair	Interferon-2b plus ribavirin	Age, sex, body weight, viral load, platelet count, ALT, Histological Activity Index score, genotype	Age, sex, body weight, viral load, platelet count, ALT, Histological Activity Index score, genotype	SVR vs. no SVR Hepatocellular carcinoma: Adjusted HR 0.28 (0.09-0.92)	Chang Gung Memorial Hospital and Department of Health of Taiwan
Imazeki, 2003 ⁶⁸ Japan Overall Quality: Fair	Interferon-2a: 84% Interferon-2b: 12% Both: 4%	Age, sex, fibrosis stage, AST, ALT, albumin, platelet count, viral load, genotype, alcohol consumption, duration of disease, BMI, co morbidities, diabetes mellitus, hypertension, fatty liver, cardiopulmonary disease	Age, sex, fibrosis stage, AST, ALT, albumin, platelet count, alcohol consumption, duration of disease	SVR vs. untreated and no SVR vs. untreated Liver-related mortality: Adjusted HR 0.06 (0.007-0.43) and 0.55 (0.27-1.1) All-cause mortality: Adjusted HR 0.030 (0.003-0.27) and 0.26 (0.11-0.61)	Not reported
Izumi, 2005 ⁶⁹ Japan Overall Quality: Fair	Interferon monotherapy: 69% Interferon-2b plus ribavirin combination therapy: 34%	Not reported	Unclear; age, sex, and fibrosis stage reported as statistically significant predictors of outcomes in multivariate model	SVR vs. no SVR Hepatocellular carcinoma: Adjusted HR 0.36 (0.04-0.83)	Japanese Ministry of Health Labor and Welfare

Author, Year Country Quality	Treatments	Variables Assessed as Univariate Predictors	Variables Included in Multivariate Models	Results	Funding Source
Kasahara, 2004 ⁷⁰ Japan Overall Quality: Poor	Interferon	Univariate analyses not performed	Age, sex, fibrosis score, time at liver biopsy	SVR vs. no SVR Liver-related mortality: Adjusted HR 0.04 (0.005-0.30) All-cause mortality: Adjusted HR 0.14 (0.06-0.35)	Not reported
Morgan, 2010 ⁷¹ USA Overall Quality: Fair	Pegylated interferon-2a-180 µg/week + ribavirin 1000-12000 mg/day for 24 weeks	Not reported	Age, race, platelet count, AST/ALT ratio, albumin, alkaline phosphatase, alpha-fetoprotein	SVR vs. no SVR All-cause mortality or liver transplantation: Adjusted HR 0.17 (0.06-0.46) Any liver-related outcome (decompensated liver disease [ascites, variceal bleeding, hepatic encephalopathy, spontaneous bacterial peritonitis], hepatocellular carcinoma, liver transplantation, liver-related mortality): Adjusted HR 0.15 (0.06-0.38) Decompensated liver disease: Adjusted HR 0.13 (0.03-0.53) Hepatocellular carcinoma: Adjusted HR 0.19 (0.04-0.80) Liver-related mortality or liver transplantation: Adjusted HR 0.12 (0.03-0.48)	National Institute of Diabetes and Digestive and Kidney Diseases, National Institute of Allergy and Infectious Diseases, the National Cancer Institute, the National Institutes of Health, and Hoffmann-La Roche, Inc
Shiratori, 2005 ⁷² Japan Overall Quality: Poor	Interferon α-2a: 58% Natural interferon α: 42%	Univariate analyses not performed	Age	SVR vs. untreated patients and no SVR vs. untreated patients Hepatocellular carcinoma: Adjusted HR 0.31 (0.16-0.61) and 0.77 (0.51-1.2) All-cause mortality: Adjusted HR 0.05 (0.006-0.34) and 0.71 (0.43-1.2)	None declared

Author, Year Country Quality	Treatments	Variables Assessed as Univariate Predictors	Variables Included in Multivariate Models	Results	Funding Source
Veldt, 2004 ⁷³ Europe Overall Quality: Fair	Interferon monotherapy		Age, gender, fibrosis stage pretreatment, activity score pretreatment, SVR vs. biochemical response to therapy	<p>Standard mortality ratios SVR vs. biochemical responders 1.4 (0.3-2.5) vs. 5.6 (0.0-12.6)</p> <p>*No statistically significant difference in mortality between sustained virological responders and general population, matched for age and sex</p> <p>Change in fibrosis SVR vs. biochemical responders 2 points progression: 3% vs. 7% 1 point progression: 3% vs. 13% No change: 65% vs. 80% 1 point regression: 21% vs. 0% 2 points regression: 8% vs. 0%</p> <p>Multiple regression analysis of risk factors for fibrosis progression Biochemical response vs. SVR: HR 0.31 (0.3-1.49), p<0.01 (age, fibrosis stage pretreatment, activity score pretreatment also significant)</p>	Grant from the European Union (Biomed grant No BMMI-CT 92-0755, Eurohep), by an unrestricted grant from Schering-Plough International, Kenilworth, USA, and by the Foundation for Liver Research (SLO) Rotterdam

Author, Year Country Quality	Treatments	Variables Assessed as Univariate Predictors	Variables Included in Multivariate Models	Results	Funding Source
Veldt, 2007 ⁷⁴ Europe and Canada Overall Quality: Poor	Interferon monotherapy: 27% Interferon and ribavirin: 27% Pegylated interferon monotherapy: 2.1% Pegylated interferon and ribavirin: 43%	Univariate analyses not performed	All outcomes: Age, sex, previous non-response, bilirubin level, albumin level, platelet count, treatment center, treatment period Hepatocellular carcinoma: Also adjusted for anti-hepatitis B core antigen positivity	SVR vs. no SVR Any event (death, liver failure, and hepatocellular cancer): Adjusted HR 0.20 (0.07-0.58) All-cause mortality: Adjusted HR 0.31 (0.07-1.4) Liver-related mortality: Adjusted HR 0.19 (0.02-1.4) Hepatocellular carcinoma: Adjusted HR 0.46 (0.12-1.70)	Netherlands Organisation for Health Research and Development
Yoshida, 2002 ⁷⁵ Japan Overall Quality: Poor	Interferon-alpha: 84% Interferon-beta: 14% Both: 2%	Univariate analyses not performed	Age, sex	SVR vs. untreated and no SVR vs. untreated Liver-related mortality: Adjusted HR 0.050 (0.01-0.22) and 0.39 (0.22-0.68) All-cause mortality: Adjusted HR 0.15 (0.06-0.34) and 0.47 (0.29-0.76)	Ministry of Health, Labour, and Welfare of Japan and Ministry of Education, Culture, Sports, Science, and Technology of Japan
Yu, 2006 ⁷⁶ Taiwan Overall Quality: Poor	Interferon monotherapy: 28% Interferon plus ribavirin combination therapy: 72%	Univariate analyses not reported	Age, sex, ALT, genotype, interferon monotherapy or interferon plus ribavirin combination therapy	SVR vs. untreated and no SVR vs. untreated Hepatocellular carcinoma: Adjusted HR 0.25 (0.13-0.46) and 0.99 (0.64-1.5) All-cause mortality: Adjusted HR 0.37 (0.14-0.99) and 1.3 (0.56-3.1)	Department of Health, Taiwan and Taiwan Liver Research Foundation

Evidence Table 10. Quality rating: Sustained virologic response and clinical outcomes

Author, Year	(1) Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	(2) Were the groups comparable at baseline on key prognostic factors (e.g., by restriction or matching)?	(3) Did the study use accurate methods for ascertaining exposures, potential confounders, and outcomes?	(4) Were outcome assessors and/or data analysts blinded to treatment?	(5) Did the article the number of patients who met inclusion criteria excluded due to missing data or loss to followup?	(6) Did the study perform appropriate statistical analyses on potential confounders (should evaluate at least age, sex, genotype, fibrosis stage, viral load)?	(7) Is there important (overall or differential) exclusion of patients due to missing data or loss to followup?	(8) Were outcomes pre-specified and defined, and ascertained using accurate methods?	Overall Quality (good, fair, poor)
Arase, 2007 ⁵⁹	Yes	No	Yes	Unclear	No	Yes	Unclear	Yes	Fair
Backus, 2011 ⁶⁰	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Fair
Bruno, 2007 ⁶¹	Yes	No	Yes	Unclear	No	No	Unclear	Yes	Fair
Cardoso, 2010 ⁶²	Yes	No	Yes	Unclear	No	Yes	Unclear	Yes	Fair
Coverdale, 2004 ⁶³	Unclear	No	Unclear	No	No	Unclear	Unclear	Yes	Poor
El Braks, 2007 ⁶⁴	Yes	No	Yes	Unclear	No	No	Unclear	Yes	Poor
Fernandez-Rodriguez, 2010 ⁶⁵	Unclear	No	Yes	No	Yes	Unclear	No	Yes	Poor
Hasegawa, 2007 ⁶⁶	Unclear	Unclear	Yes	Unclear	No	Yes	Unclear	Yes	Fair
Hung, 2006 ⁶⁷	Yes	No	Yes	Unclear	No	Yes	Unclear	Yes	Fair
Imazeki, 2003 ⁶⁸	Yes	No	Yes	Unclear	Yes	Yes	No	Yes	Fair
Izumi, 2005 ⁶⁹	Yes	Unclear	Yes	Unclear	No	Unclear	Unclear	Yes	Fair
Kasahara, 2004 ⁷⁰	No	Yes	Yes	Unclear	No	No	Unclear	Yes	Poor
Morgan, 2010 ⁷¹	Yes	No	Yes	Unclear	No	Unclear	Unclear	Yes	Fair
Shiratori, 2005 ⁷²	Unclear	Yes	Yes	Unclear	Yes	No	Yes	Yes	Poor
Veldt, 2004 ⁷³	Yes	No	Yes	No	Yes	Yes	No	Yes	Fair
Veldt, 2007 ⁷⁴	Yes	No	Yes	No	No	No	Unclear	Yes	Poor
Yoshida, 2002 ⁷⁵	Yes	No	Yes	No	No	No	Unclear	Yes	Poor
Yu, 2006 ⁷⁶	Yes	No	Yes	No	No	No	Unclear	Yes	Poor

Evidence Table 11. Sustained virologic response and quality of life

Author, Year Country Quality	Study Type	Comparison	Duration of Followup	Inclusion Criteria	Exclusion Criteria	Number Screened/ Eligible/ Enrolled/ Analyzed
Arora, 2006 ⁷⁷ Australia, Europe, New Zealand, North America, and South America Overall Quality: Poor	Cohort study (patients enrolled in an randomized trial)	SVR vs. no SVR SVR=No detectable HCV RNA at end of followup (72 weeks)	72 weeks	No prior treatment for chronic hepatitis C infection, positive HCV RNA, normal ALT	Cirrhosis, other chronic liver disease, HIV infection, other serious chronic illness, pregnancy	Number screened: Not reported Number eligible: Not reported Number enrolled: 440 (randomized to an antiviral treatment arm) Number analyzed: Unclear
Bernstein, 2002 ⁷⁸ Australia, North America, Europe, Taiwan, New Zealand Overall Quality: Poor	Cohort study (patients originally enrolled in 3 randomized trials)	SVR vs. no SVR SVR=No detectable HCV RNA 24 weeks after completion of antiviral therapy	72 weeks	Not previously treated with interferon-based therapies, positive HCV antibody, elevated serum ALT level, positive HCV RNA	Other chronic liver disease, significant co morbid conditions, pregnancy, evidence of substance abuse within 1 year	Number screened: Not reported Number eligible: Not reported Number enrolled: 1441 Number analyzed: 983 (275 SVR, 708 no SVR)

Author, Year Country Quality	Study Type	Comparison	Duration of Followup	Inclusion Criteria	Exclusion Criteria	Number Screened/ Eligible/ Enrolled/ Analyzed
Bini, 2006 ⁷⁹ USA Overall Quality: Poor	Prospective cohort study	SVR vs. no SVR SVR=No detectable HCV RNA 24 weeks after completion of antiviral therapy	48 or 72 weeks (24 weeks after end of treatment)	No prior treatment for chronic hepatitis C infection, positive HCV antibody, positive HCV RNA, liver biopsy consistent with chronic HCV infection Each patient with normal ALT matched with 2 patients with elevated ALT on genotype, HCV viral load, and presence of cirrhosis	HBV infection, HIV infection, neutropenia, anemia, thrombocytopenia, renal insufficiency, AFP >50 ng/ml, decompensated cirrhosis, prior organ transplantation, cancer, severe co morbid condition, poorly controlled diabetes or thyroid disease, autoimmune disease, seizure disorder, concurrent immunosuppressive therapy, more than 10 g alcohol/day or illicit drugs within 6 months	Number screened: Not reported Number eligible: Not reported Number enrolled: 138 (46 normal ALT, 92 elevated ALT) Number analyzed: 138
Bonkovsky, 1999 ⁸⁰ USA and Canada Overall Quality: Poor`	Cohort study (patients enrolled in a randomized trial)	SVR vs. no SVR SVR=No detectable HCV RNA 24 weeks after completion of antiviral therapy	72 weeks	Positive HCV antibody, positive HCV RNA, ALT >1.5 times upper limit of normal, liver biopsy confirming diagnoses of chronic hepatitis	Malignancy, depressive illness, HIV infection, decompensated liver disease, previous use of interferon, previous use of chemotherapeutic of other agents, thyroid abnormality	Number screened: Not reported Number eligible: Not reported Number enrolled: 704 Number analyzed: 437 (41 SVR, 396 no SVR)

Author, Year Country Quality	Study Type	Comparison	Duration of Followup	Inclusion Criteria	Exclusion Criteria	Number Screened/ Eligible/ Enrolled/ Analyzed
Hassanein, 2004 ⁸¹ Australia, North America, Europe, Taiwan, Brazil, Mexico Overall Quality: Poor	Cohort study (patients enrolled in a randomized trial)	SVR vs. no SVR SVR=No detectable HCV RNA 24 weeks after completion of antiviral therapy	72 weeks	No prior interferon, HCV RNA >=2000 copies/ml, ALT >upper limit of normal, liver biopsy consistent with chronic hepatitis C	Neutrophils <1500 per cubic millimeter, platelets <90,000 per cubic millimeter, hemoglobin <12 g/dl in women or <13 g/dl in men, HIV infection, decompensated liver disease, serum creatinine >1.5 times upper limit of normal, poorly controlled psychiatric disease, alcohol or drug dependence within one year before study entry, substantial coexisting medical conditions	Number screened: 1459 Number eligible: Not reported Number enrolled: 1149 Number analyzed: 649
McHutchison, 2001 ⁸² USA Overall Quality: Poor	Cohort study (patients enrolled in a randomized trial)	SVR vs. relapse vs. non- responder SVR=No detectable HCV RNA 24 weeks after completion of antiviral therapy Relapse: Not defined	72 weeks	Positive HCV RNA, liver biopsy consistent with chronic hepatitis, elevated serum ALT	Decompensated cirrhosis, AFP >50 ng/ml, anemia (hemoglobin <12 g/dl in women and <13 g/dl in men), HIV infection, psychiatric conditions, seizure disorders, cardiovascular disease, hemophilia, poorly controlled diabetes mellitus, autoimmune diseases, s/p organ transplantation, unable to practice contraception	Number screened: 1337 Number eligible: 933 Number enrolled: 933 Number analyzed: 824 (195 SVR, 150 relapse, 478 non- responder)
Neary, 1999 ⁸³ USA, Europe, Australia Overall Quality: Poor	Cohort study (patients enrolled in a randomized trial)	SVR vs. no SVR and overall response vs. no overall response SVR=No detectable HCV RNA 24 weeks after completion of antiviral therapy Overall response=SVR plus >=2-point improvement in Knodell HAI score	72 weeks (24 weeks after end of treatment)	Chronic HCV infection, previously treated with one or two courses of interferon alpha with relapse on most recent course, liver biopsy showing chronic hepatitis after relapse	Women not using effective birth control, decompensated cirrhosis, anemia (hemoglobin <12 g/dl in women and <13 g/dl in men), white blood cell count <3000 per cubic mm, neutrophil count <1500 per cubic mm, platelet count less than 100,000 per cubic mm, HIV infection, prior organ transplantation, severe psychiatric conditions, seizure disorder, cardiovascular disease, renal insufficiency, hemoglobinopathy, hemophilia, poorly controlled diabetes mellitus, immunologically mediated diseases	Number screened: 495 Number eligible: Unclear Number enrolled: 349 Number analyzed: Unclear (257 with "complete data")

Author, Year Country Quality	Study Type	Comparison	Duration of Followup	Inclusion Criteria	Exclusion Criteria	Number Screened/ Eligible/ Enrolled/ Analyzed
Rasenack, 2003 ⁸⁴ Germany, Canada, New Zealand, Spain Overall Quality: Poor	Cohort study (patients enrolled in a randomized trial)	SVR vs. no SVR SVR=No detectable HCV RNA 24 weeks after completion of antiviral therapy	72 weeks (24 weeks after end of treatment)	Positive HCV antibody, positive HCV RNA, persistently elevated ALT, liver biopsies consistent with chronic hepatitis C	Prior interferon therapy, other disease of the liver or other major diseases, pregnant, substance abuse within the last year	Number screened: Not reported Number eligible: Not reported Number enrolled: 531 Number analyzed: Unclear
Ware, 1999 ⁸⁵ Australia, North America, and Europe Overall Quality: Poor	Cohort study (patients enrolled in a randomized trial)	SVR vs. no SVR SVR=No detectable HCV RNA 24 weeks after completion of antiviral therapy Overall response vs. no overall response Overall response=SVR + Knodell histology activity index inflammation score improved by 2 U or more	72 weeks (24 weeks after end of treatment)	Chronic HCV infection, relapsed after response to interferon treatment,	Decompensated cirrhosis, hemoglobin <12 g/dl in women and <13 g/dl in men, WBC <3000 per cubic millimeter, neutrophil count <1500 per cubic millimeter, platelet count <100,000 per cubic millimeter, HIV infection, prior organ transplantation, severe psychiatric conditions, seizure disorder, cardiovascular disease, renal insufficiency, hemoglobinopathy, hemophilia, poorly controlled diabetes mellitus, immunologically mediated diseases	Number screened: 495 Number eligible: 349 Number enrolled: 349 Number analyzed: 250 (66 SVR and 184 no SVR)

Author, Year Country Quality	Demographic characteristics of study population (age, race, mean viral load)	Genotype HCV viral load HIV infection IV drug use	Treatments	Confounders assessed in analysis	Results (by clinical outcome)	Funding source
Arora, 2006 ⁷⁷ Australia, Europe, New Zealand, North America, and South America Overall Quality: Poor	Not reported by SVR status Mean age: 43 years Female: 60% Non-white: 14%	Not reported by SVR status Advanced fibrosis: 10% Genotype 1: 68% Viral load: 1.1-1.2 x 10 ⁶ copies/ml IVDU: 30% HIV positive: excluded	Pegylated interferon alfa-2a (24 or 48 weeks)	Genotype, country, treatment, fibrosis stage, baseline score	SVR vs. no SVR, mean difference in change from baseline SF-36 physical function: +4.7 (p<0.05) SF-36 role limitations-physical: +13 (p<0.05) SF-36 bodily pain: +11 (p<0.0001) SF-36 general health: +10 (p<0.0001) SF-36 vitality: +9.3 (p<0.0001) SF-36 social function: +5.1 (p>0.05) SF-36 role limitations -emotional: +7.3 (p>0.05) SF-36 mental health: +3.1 (p>0.05) SF-36 physical components summary: +4.9 (p<0.0001) SF-36 mental component summary: +2.0 (p>0.05) Fatigue Severity Scale, total score: -4.4 (p<0.01) Fatigue Severity Scale, VAS: -10 (p<0.01)	Roche Pharmaceuticals
Bernstein, 2002 ⁷⁸ Australia, North America, Europe, Taiwan, New Zealand Overall Quality: Poor	Not reported by SVR status Mean age <=40 years: 41% Female: 32% Non-white: 14%	Not reported by SVR status Cirrhosis: 32% Genotype, viral load, HIV infection, IV drug use not reported	Pegylated interferon alfa-2a or interferon alfa- 2a	None	SVR vs. no SVR, mean difference in change from baseline SF-36 physical function: +4.6 (p<0.001) SF-36 role limitations-physical: +9.8 (p<0.001) SF-36 bodily pain: +2.9 (p<0.01) SF-36 general health: +9.1 (p<0.001) SF-36 vitality: +9.6 (p<0.001) SF-36 social function: +6.2 (p<0.001) SF-36 role limitations -emotional: +8.4 (p<0.01) SF-36 mental health: +4.6 (p<0.001) SF-36 physical components summary: +2.8 (p<0.001) SF-36 mental component summary: +3.0 (p<0.001) Fatigue Severity Scale, total score: -0.5 (p<0.001) Fatigue Severity Scale, VAS: -11.5 (p<0.001)	F. Hoffman-La Roche

Author, Year Country Quality	Demographic characteristics of study population (age, race, mean viral load)	Genotype HCV viral load HIV infection IV drug use	Treatments	Confounders assessed in analysis	Results (by clinical outcome)	Funding source
Bini, 2006 ⁷⁹ USA Overall Quality: Poor	Normal ALT and elevated ALT groups, respectively (not reported by SVR status) Mean age: 50 and 49 years Female: 11% and 8% Non-white: 59% and 66%	Normal ALT and elevated ALT groups, respectively (not reported by SVR status) Cirrhosis: 11% and 11% Genotype 1: 78% and 78% Viral load >2 x 10 ⁶ copies/ml: 44% and 44% IVDU: 67% and 65% HIV positive: excluded	Interferon alfa-2b + ribavirin	None	SVR vs. no SVR, mean difference in change from baseline (normal ALT and elevated ALT subgroups, respectively; p values not reported) SF-36 physical function: +18 and +15 SF-36 role limitations-physical: +22 and +27 SF-36 bodily pain: +3.4 and +9.3 SF-36 general health: +3.0 and +9.9 SF-36 vitality: +12 and +12 SF-36 social function: +9.5 and +11 SF-36 role limitations-emotional: +20 and +18 SF-36 mental health: +14 and +18 SF-36 physical component summary: +3.8 and +7.1 SF-36 mental component summary: +6.0 and +2.1 Positive well being: +14 and -3.1 Sleep somnolence: +11 and +5.4 Health distress: +9.3 and +11 Hepatitis-specific health distress: +5.4 and +2.6 Hepatitis-specific limitations: +13 and +3.8	No external funding
Bonkovsky, 1999 ⁸⁰ USA and Canada Overall Quality: Poor	Not reported by SVR status Mean age: 43 years Female: 27% Non-white: 23%	Not reported by SVR status Cirrhosis: 16% Genotype 1: 68% Viral load: Not reported IVDU: 41% HIV positive: excluded	Consensus interferon or interferon alfa-2b	None	SVR vs. no SVR, mean difference in change from baseline (values estimated from graph) SF-36 physical function: +6.0 (p<0.05) SF-36 role limitations-physical: +22 (p<0.01) SF-36 bodily pain: -0.5 (p>0.05) SF-36 general health: +7.5 (p<0.01) SF-36 vitality: +9.5 (p<0.05) SF-36 social function: +10 (p<0.05) SF-36 role limitations-emotional: +11 (p>0.05) SF-36 mental health: +4.0 (p>0.05)	Amgen Inc.; United States Public Health Service

Author, Year Country Quality	Demographic characteristics of study population (age, race, mean viral load)	Genotype HCV viral load HIV infection IV drug use	Treatments	Confounders assessed in analysis	Results (by clinical outcome)	Funding source
Hassanein, 2004 ⁸¹ Australia, North America, Europe, Taiwan, Brazil, Mexico Overall Quality: Poor	Not reported by SVR status Mean age: 43 years Female: 29% Non-white: 16%	Not reported by SVR status Cirrhosis: 13% Genotype 1: 63% Viral load: 5.9 to 6.0 x 10 ⁶ copies/ml IVDU: Not reported HIV positive: excluded	Pegylated interferon alfa-2a, pegylated interferon alf-2a +ribavirin, or interferon alfa-2b + ribavirin	None	SVR vs. no SVR, mean difference in change from baseline SF-36 physical function: +5.5 (p<0.01) SF-36 role limitations-physical: +5.7 (p<0.05) SF-36 bodily pain: +4.1 (p<0.05) SF-36 general health: +8.6 (p<0.01) SF-36 vitality: +6.3 (p >0.05) SF-36 social function: +5.8 (p<0.01) SF-36 role limitations-emotional: +9.3 (p<0.01) SF-36 mental health: +5.0 (p<0.01) SF-36 physical component summary: +2.2 (p<0.01) SF-36 mental component summary: +2.6 (p<0.01) Total fatigue: +3.3 (p<0.01) Fatigue severity: +7.4 (p<0.01)	Roche Pharmaceuticals
McHutchison, 2001 ⁸² USA Overall Quality: Poor	Mean age: 43 vs. 44 years Female: 42% vs. 32% Non-white: 8% vs. 12%	Cirrhosis: Not reported Genotype 1: 43% vs. 81% Viral load >2 million copies/ml: 58% vs. 74% IVDU: Not reported HIV positive: excluded	Interferon alfa-2a for 24 or 48 weeks, with or without ribavirin	None	SVR and relapse, mean difference in change from baseline vs. non-responder (p not reported, values estimated from graph) SF-36 physical function: +2.4 and +0.8 SF-36 role limitations-physical: +5.2 and +3.2 SF-36 bodily pain: +1.6 and +1.7 SF-36 general health: +5.2 and +1.5 SF-36 vitality: +4.7 and +2.0 SF-36 social function: +3.1 and +0.4 SF-36 role limitations-emotional: +3.0 and +1.2 SF-36 mental health: +2.0 and 0.0 Sleep somnolence: +3.4 and +2.3 Health distress: +5.4 and +1.2 Hepatitis-related health distress: +5.7 and +1.1 Hepatitis-related limitations: +4.6 and +2.1	Schering-Plough and Scripps Clinic

Author, Year Country Quality	Demographic characteristics of study population (age, race, mean viral load)	Genotype HCV viral load HIV infection IV drug use	Treatments	Confounders assessed in analysis	Results (by clinical outcome)	Funding source
Neary, 1999 ⁸³ USA, Europe, Australia Overall Quality: Poor	Not reported by SVR or overall response status Mean age: 43 years Female: 35% Non-white: 6.4%	Not reported by SVR or overall response status Bridging fibrosis or cirrhosis: 17% Genotype 1: 56% Viral load >2 million copies/ml: 75% IVDU: 40% HIV positive: excluded	Interferon alfa-2b with or without ribavirin	None	SVR and relapse. mean difference in change from baseline vs. non-responder (estimated from graph) (p values not reported) SF-36 physical function: +8.0 and +3.8 SF-36 role limitations-physical: +7.6 and +4.9 SF-36 bodily pain: +2.4 and +2.7 SF-36 general health: +9.4 and +5.6 SF-36 vitality: +7.8 and +5.6 SF-36 social function: +9.4 and +4.1 SF-36 role limitations-emotional: +6.0 and +12 SF-36 mental health: +2.8 and +1.8 Sleep somnolence: +2.1 and +3.8 Health distress: +8.9 and +1.6 Hepatitis-related health distress: +11 and - 0.8 Hepatitis-related limitations: +6.7 and +2.6 Mental health-18: +3.4 and +2.3 Overall response vs. no response (estimated from graph) SF-36 physical function: +8.3 (p<0.05) SF-36 role limitations-physical: +10 (p>0.05) SF-36 bodily pain: +3.7 (p>0-.05) SF-36 general health: +6.9 (p<0.05) SF-36 vitality: +5.8 (p<0.05) SF-36 social function: +9.2 (p<0.05) SF-36 role limitations-emotional: +3.6 (p>0.05) SF-36 mental health: +1.3 (p>0.05) Sleep somnolence: +1.5 (p>0.05) Health distress: +6.4 (p<0.05) Hepatitis-related health distress: +12 (p<0.05) Hepatitis-related limitations: +7.8 (p<0.05) Mental health-18: +1.5 (p>0.05)	Schering-Plough

Author, Year Country Quality	Demographic characteristics of study population (age, race, mean viral load)	Genotype HCV viral load HIV infection IV drug use	Treatments	Confounders assessed in analysis	Results (by clinical outcome)	Funding source
Rasenack, 2003 ⁸⁴ Germany, Canada, New Zealand, Spain Overall Quality: Poor	Not reported by SVR status Mean age: 41 years Female: 33% Non-white: 15%	Not reported by SVR status Bridging fibrosis/cirrhosis: 13% Injection drug use: 37% Viral load: 7.4 to 8.2 x 10 ⁶ copies/ml HIV positive: Not reported Genotype: Not reported	Pegylated interferon alfa-2a or interferon alfa- 2a	None	SVR vs. no SVR, mean difference in change from baseline SF-36 physical function: +5.0 (p=0.001) SF-36 role limitations-physical: +14 (p<0.001) SF-36 bodily pain: +5.2 (p=0.014) SF-36 general health: 12 (p<0.001) SF-36 vitality: +9.4 (p<0.001) SF-36 social function: +5.8 (p=0.005) SF-36 role limitations-emotional: +8.4 (p=0.02) SF-36 mental health: +5.3 (p=0.001) SF-36 physical component summary: +3.2 (p<0.001) SF-36 mental component summary: +2.9 (p=0.005) Fatigue Severity Scale, total score: -0.5 (p=0.001) Fatigue Severity Scale, VAS: -8.4 (p<0.001)	F. Hoffman-La Roche
Ware, 1999 ⁸⁵ Australia, North America, and Europe Overall Quality: Poor	Not reported by response status Mean age: 43 years Female: 35% Non-white: 6.4%	Not reported by response status Bridging fibrosis/cirrhosis: 18% Injection drug use: 40% Viral load: 4.8 to 5.2 x 10 ⁶ copies/ml HIV positive: Excluded Genotype 1: 56%	Interferon alfa-2b or interferon alfa- 2b + ribavirin	None	SVR vs. no SVR and overall response vs. no overall response, mean difference in change from baseline (p values not reported) SF-36 physical function: +2.6 and +3.5 SF-36 role limitations-physical: +1.5 and +3.1 SF-36 bodily pain: +0.45 and +1.6 SF-36 general health: +3.3 and +3.5 SF-36 vitality: +2.2 and +2.8 SF-36 social function: +3.4 and +4.3 SF-36 role limitations-emotional: -0.02 and +1.1 SF-36 mental health: +1.3 and +0.62 Sleep: +0.02 and +1.2 Health distress: +7.6 and +6.2 Chronic hepatitis C health distress: +11.5 and +11.3 Chronic hepatitis C limitations: +5.3 and +7.5	Integrated Therapeutics Group, Inc (subsidiary of Schering- Plough)

Evidence Table 12. Quality rating: Sustained virologic response and quality of life

Author, Year	(1) Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	(2) Were the groups comparable at baseline on key prognostic factors (e.g., by restriction or matching)?	(3) Did the study use accurate methods for ascertaining exposures, potential confounders, and outcomes?	(4) Were outcome assessors and/or data analysts blinded to treatment?	(5) Did the article report attrition?	(6) Did the study perform appropriate statistical analyses on potential confounders (should adjust for at least age, sex, genotype, fibrosis stage)?	(7) Is there important differential loss to followup or overall high loss to followup?	(8) Were outcomes pre-specified and defined, and ascertained using accurate methods?	Overall Quality
Arora, 2006 ⁷⁷	Yes	Unclear	Yes	No (patients aware of SVR status)	No	Yes	Unclear	Yes	Poor
Bernstein 2002 ⁷⁸	Yes	Unclear	Yes	No (patients aware of SVR status)	No	No	Unclear	Yes	Poor
Bini 2006 ⁷⁹	Unclear	Unclear	Yes	No (patients aware of SVR status)	No	No	Unclear	Yes	Poor
Bonkovsky 1999 ⁸⁰	Yes	Unclear	Yes	Yes (blinded to virological status, though not histological status)	Yes	No	Yes (high)	Yes	Poor
Hassanein 2004 ⁸¹	Yes	Unclear	Yes	No (patients aware of SVR status)	Yes	No	Yes (high)	Yes	Poor
McHutchison 2001 ⁸²	Yes	No	Yes	Unclear	Yes	No	No	Yes	Poor
Neary 1999 ⁸³	Yes	Unclear	Yes	Unclear	Yes	No	Yes (high)	Yes	Poor
Rasenack 2003 ⁸⁴	Yes	Unclear	Yes	No (patient aware of SVR status)	Yes	No	Yes (high)	Yes	Poor
Ware 1999 ⁸⁵	Yes	Unclear	Yes	No (patient aware of SVR status)	Yes	No	Yes (high)	Yes	Poor

Evidence Table 13. Sustained virologic response and clinical outcomes study overview

Author, Year Country Quality	Study Type Sample Size Duration of Followup	Population Characteristics	Variables Assessed as Univariate Predictors	Variables Included in Multivariate Models	Results
Arase, 2007 ⁵⁹ Japan Overall Quality: Fair	Retrospective cohort study n=500 Mean 7.4 years	SVR (n=140) vs. no SVR (n=360) Mean age (years): 63 vs. 64 (p=0.07) Female: 41% vs. 53% (p=0.01) Race: Not reported Genotype 1b: 34% vs. 71% (p<0.0001) Viral load (kIU/ml): 172 vs. 661 (p<0.0001) Cirrhosis (Knodell F4): 9% vs. 16% (p=0.009)	Age, sex, liver fibrosis, liver activity, viral load, genotype, AST, ALT	Hepatocellular cancer: Sex, liver fibrosis All-cause and liver-related mortality: Sex, liver fibrosis	SVR vs. no SVR Hepatocellular cancer: Adjusted HR 0.19 (0.08-0.45) All-cause mortality: Adjusted HR 0.39 (0.16-0.93) Liver-related mortality: Adjusted HR 0.13 (0.03-0.59)
Backus, 2011 ⁶⁰ # USA Overall Quality: Fair	Retrospective cohort study n=16,864 Median 3.8 years	SVR vs. no SVR (genotype 1 [n=12,166], 2 [n=2904], and 3 [n=1794], respectively) Mean age (years): 51 vs. 52, 53 vs. 53. and 51 vs. 51 Female: 5% vs. 4%, 4% vs. 3%, and 4% vs. 3% Non-white: 40% vs. 51%, 33% vs. 31%, and 30% vs. 29% Genotype: Results stratified by genotype Viral load >=500,000 IU/mL: 70% vs. 82%, 78% vs. 83%, and 64% vs. 68% Cirrhosis: 9% vs. 15%, 7% vs. 12%, and 12% vs. 20%	Age, sex, albumin, AST, AST/ALT ratio, creatinine clearance, platelets, sodium, cirrhosis, COPD, diabetes, hypertension, tobacco use, treatment duration <60% recommended, bilirubin, body mass index, HBV co-infection, viral load, hemoglobin, CAD, cancer, congestive heart failure, cerebrovascular disease, schizophrenia, recent alcohol abuse, anxiety disorder, depression, hard drug use, PTSD, socioeconomic status instability, multiple treatment course, erythropoiesis stimulating agent use, granulocyte colony stimulating factor use, year of treatment start	Age, sex, albumin, AST, AST/ALT ratio, creatinine clearance, platelets, sodium, cirrhosis, COPD, diabetes, hypertension, tobacco use, treatment duration <60% recommended, bilirubin, body mass index, HBV co-infection, viral load, hemoglobin, CAD, cancer, congestive heart failure, cerebrovascular disease, schizophrenia, recent alcohol abuse, anxiety disorder, depression, hard drug use, PTSD, socioeconomic status instability, multiple treatment course, erythropoiesis stimulating agent use, granulocyte colony stimulating factor use, year of treatment start	SVR vs. no SVR (genotypes 1, 2, and 3, respectively) All-cause mortality: Adjusted HR 0.71 (0.60-0.86), 0.62 (0.44-0.87), and 0.51 (0.35-0.75)

Author, Year Country Quality	Study Type Sample Size Duration of Followup	Population Characteristics	Variables Assessed as Univariate Predictors	Variables Included in Multivariate Models	Results
Bruno, 2007 ⁶¹ Italy Overall Quality: Fair	Retrospective cohort study n=883 Mean 8 years	SVR (n=124) vs. no SVR (n=759) Mean age (years): 53 vs. 44 (p=0.004) Female: 27% vs. 38% (p<0.001) Non-White: 0 (0%) vs. 0 (0%) Race: Not reported Genotypes 1 and 4: 37% vs. 63% (p<0.001) Viral load: Not reported Cirrhosis: All (inclusion criterion)	Age, sex, platelet count, genotype	Hepatocellular carcinoma: Age, sex, platelet count Liver-related mortality: Age, platelet count	SVR vs. no SVR Ascites, encephalopathy, or gastrointestinal bleeding: Not calculated, 0 events/1061 person-years vs. 107 events/5703 person-years (1.88 events/100 person-years) Hepatocellular carcinoma: Adjusted HR 0.39 (0.17-0.88) Liver-related mortality: 0.14 (0.04-0.59)
Cardoso, 2010 ⁶² # France Overall Quality: Fair	Retrospective cohort study (of patients originally enrolled in clinical trials) n=307 Median 3.5 years	SVR (n=103) vs. no-SVR (n=204) Mean age (years): 55 vs. 55 (p=0.93) Female: 30% vs. 34% (p=0.51) Race: Not reported Genotype 1: 36% vs. 72% (p<0.001) Viral load (log ₁₀ I/ml): 5.5 vs. 5.7 (p=0.08) Cirrhosis (METAVIR F4): 53% vs. 61% (p=0.19)	Age, sex, BMI, alcohol consumption, diabetes, ALT, bilirubin, albumin, platelets, genotype, viral load, inflammation, fibrosis and steatosis scores	Hepatocellular carcinoma: Age, bilirubin, albumin, platelet count Ascites/variceal bleeding and liver- related mortality: Bilirubin, albumin, platelets	SVR vs. no SVR Hepatocellular carcinoma: Adjusted HR 0.33 (0.23-0.89) Ascites or variceal bleeding: Adjusted HR 0.21 (0.05-0.92) Liver-related mortality: Adjusted HR 0.27 (0.08-0.95)

Author, Year Country Quality	Study Type Sample Size Duration of Followup	Population Characteristics	Variables Assessed as Univariate Predictors	Variables Included in Multivariate Models	Results
Coverdale, 2004* Australia Overall Quality: Poor	Prospective cohort study (some patients originally enrolled in randomized trials) n=343 Median 9 years	Demographics for all treated patients (not reported by SVR status) Median age (years): 37 Female: 33% Race: Not reported Genotype 1: 38% Viral load: Not reported Median fibrosis score (Scheuer): 2	Statistically significant predictors of outcomes in univariate analyses were age, duration, place of birth, mode of transmission, genotype, fibrosis score, albumin, bilirubin, prothrombin time. Other tested variables not reported.	Age, duration, place of birth, mode of transmission, genotype, fibrosis score, albumin, bilirubin, prothrombin time	SVR vs. response-relapse vs. non- response Liver-related complications (hepatic decompensation, complications of portal hypertension, hepatocellular carcinoma, liver transplantation, and liver-related mortality) at 10 years: Not statistically significant in multivariate analysis, adjusted HR not reported (p=0.06) Hepatocellular carcinoma at 10 years: Not statistically significant in multivariate analysis, adjusted HR and p value not reported Liver transplant or liver-related death at 10 years: Not statistically significant in multivariate analysis, adjusted HR not reported (p=0.20)
El Braks, 2007 ⁶⁴ France Overall Quality: Fair	Retrospective cohort study n=113 Mean 7.7 years	SVR (n=37) vs. no SVR (n=76) Mean age (years): 51 vs. 56 (p=0.02) Female: 16% vs. 50% (p=0.0005) Race: Not reported HCV genotype 1: 36% vs. 73% (p=0.0001) Viral load: Not reported Cirrhosis: All (inclusion criterion)	Age, sex, genotype, duration of treatment	Duration of treatment	SVR (n=37) vs. no SVR (n=76) Clinical events (hepatocellular cancer, ascites, hepatic encephalopathy, or death): Adjusted HR 0.14 (0.04-0.45)

Author, Year Country Quality	Study Type Sample Size Duration of Followup	Population Characteristics	Variables Assessed as Univariate Predictors	Variables Included in Multivariate Models	Results
Fernandez-Rodriguez, 2010 ⁶⁵ # Spain Overall Quality: Poor	Retrospective cohort study n=509 Median 35 months	SVR (n=174) vs. no SVR (n=394) Mean age (years): 51 vs. 52 (p=0.31) Female: 69% vs. 73%, p=0.37 Genotype 1: 24% vs. 55% (p=0.001) Race: Not reported Viral load (10 ⁶ IU/ml): 1.7 vs. 3.1 (p=0.001) Cirrhosis: All (inclusion criterion)	Statistically significant predictors of outcomes in univariate analyses were age, albumin, esophageal varices, ultrasonographic signs of portal hypertension, platelet count, bilirubin, prothrombin activity. Other tested variables not reported.	Age, albumin, esophageal varices, ultrasonographic signs of portal hypertension, platelet count, bilirubin, prothrombin activity	SVR vs. no SVR Combined clinical endpoint (hepatic decompensation, upper gastrointestinal bleeding secondary to rupture of esophageal or gastric varices, hepatocellular carcinoma, liver transplantation, and liver-related or liver-unrelated mortality): Adjusted HR 0.38 (0.18-0.76)
Hasegawa, 2007 ⁶⁶ A Japan Overall Quality: Fair	Retrospective cohort study n=105 Median 4.6 years	SVR (n=48) vs. no SVR (n=58) Age >56 years: 60% vs. 55% (p>0.05) Male: 65% vs. 66% (p>0.05) Race: Not reported Genotype 1b: 19% vs. 21% (p>0.05) Viral load >=100 KIU/ml or >=1 Meq/mL: 25% vs. 62% (p<0.001) Cirrhosis: All (inclusion criterion)	Age, sex, BMI, albumin, cholinesterase, platelet count, alpha-fetoprotein, indocyanine green retention rate at 15 minutes, fasting blood glucose, AST, ALT, viral load, genotype, use of combination therapy, total dose of interferon, daily dose of interferon, use of induction therapy, type of interferon	Choline esterase, alpha-fetoprotein, viral load, daily dose of interferon, duration of interferon, use of induction therapy	SVR vs. no SVR Hepatocellular carcinoma: Adjusted HR 0.18 (0.04-0.81)
Hung, 2006 ⁶⁷ Taiwan Overall Quality: Fair	Cohort study (unclear if retrospective or prospective) n=132 Median 37 months	SVR (n=73) vs. no SVR (n=59) Mean age (years): 55 vs. 58 (p=0.07) Female: 43% vs. 54% (p=0.12) Race: Not reported Genotype 1b: 27% vs. 78% (p<0.001) Viral load >=2 x 10 ⁶ copies/ml: 21% vs. 51% (p<0.001) Cirrhosis: 100% (inclusion criterion)	Age, sex, body weight, viral load, platelet count, ALT, Histological Activity Index score, genotype	Age, sex, body weight, viral load, platelet count, ALT, Histological Activity Index score, genotype	SVR vs. no SVR Hepatocellular carcinoma: Adjusted HR 0.28 (0.09-0.92)

Author, Year Country Quality	Study Type Sample Size Duration of Followup	Population Characteristics	Variables Assessed as Univariate Predictors	Variables Included in Multivariate Models	Results
Imazeki, 2003 ⁶⁸ Japan Overall Quality: Fair	Retrospective cohort study n=459 Mean 8.2 years	Demographics for all treated patients (not reported by SVR status) Mean age (years): 49 Female: 36% Race: Not reported Genotype 1: 74% Viral load: Not reported Cirrhosis (Desmet F4): 13%	Age, sex, fibrosis stage, AST, ALT, albumin, platelet count, viral load, genotype, alcohol consumption, duration of disease, BMI, co morbidities, diabetes mellitus, hypertension, fatty liver, cardiopulmonary disease	Age, sex, fibrosis stage, AST, ALT, albumin, platelet count, alcohol consumption, duration of disease	SVR vs. untreated and no SVR vs. untreated Liver-related mortality: Adjusted HR 0.06 (0.007-0.43) and 0.55 (0.27-1.1) All-cause mortality: Adjusted HR 0.030 (0.003-0.27) and 0.26 (0.11-0.61)
Izumi, 2005 ⁶⁹ Japan Overall Quality: Fair	Cohort study, appears retrospective n=495 Duration of follow- up: Not reported	Demographics for patients treated with interferon monotherapy and interferon plus ribavirin combination therapy, respectively (not reported by SVR status) Mean age (years): 52 and 58 Female: 43% and 44% Race: Not reported Genotype 1b: 71% and 80% Median viral load (kIU/ml): 470 and 680 Cirrhosis: 35% and 2%	Not reported	Unclear; age, sex, and fibrosis stage reported as statistically significant predictors of outcomes in multivariate model	SVR vs. no SVR Hepatocellular carcinoma: Adjusted HR 0.36 (0.04-0.83)
Kasahara, 2004 ⁷⁰ Japan Overall Quality: Poor	Retrospective cohort n=2698 Mean 6 years	SVR (n=738) vs. no-SVR (n=1930) Median age (years): 51 vs. 54 (p=0.12) Female: 31% vs. 37% (p=0.32) Race: Not reported Genotype 1: Not reported Viral load: Not reported Cirrhosis (Desmet F4): 3.0% vs. 5.4% (p=0.34)	Univariate analyses not performed	Age, sex, fibrosis score, time at liver biopsy	SVR vs. no SVR Liver-related mortality: Adjusted HR 0.04 (0.005-0.30) All-cause mortality: Adjusted HR 0.14 (0.06-0.35)

Author, Year Country Quality	Study Type Sample Size Duration of Followup	Population Characteristics	Variables Assessed as Univariate Predictors	Variables Included in Multivariate Models	Results
Morgan, 2010 ⁷¹ # USA Overall Quality: Fair	Prospective cohort study of patient enrolled in a randomized trial n=526 Median 79 to 86 months	SVR (n=140) vs. breakthrough/relapse (n=77) vs. no SVR (n=309) Mean age (years): 49 vs. 49 vs. 50 (p=0.23) Female: 24% vs. 26% vs. 30% (p=0.30) Non-white: 20% vs. 20% vs. 32% (p=0.001) Genotype 1: 72% vs. 86% vs. 94% (p<0.0001) Viral load: Not reported Cirrhosis (Ishak 5 or 6): 21% vs. 31% vs. 43% (p<0.0001)	Not reported	Age, race, platelet count, AST/ALT ratio, albumin, alkaline phosphatase, alpha-fetoprotein	SVR vs. no SVR All-cause mortality or liver transplantation: Adjusted HR 0.17 (0.06-0.46) Any liver-related outcome (decompensated liver disease [ascites, variceal bleeding, hepatic encephalopathy, spontaneous bacterial peritonitis], hepatocellular carcinoma, liver transplantation, liver-related mortality): Adjusted HR 0.15 (0.06- 0.38) Decompensated liver disease: Adjusted HR 0.13 (0.03-0.53) Hepatocellular carcinoma: Adjusted HR 0.19 (0.04-0.80) Liver-related mortality or liver transplantation: Adjusted HR 0.12 (0.03-0.48)
Shiratori, 2005 ⁷² Japan Overall Quality: Poor	Prospective cohort study of patients enrolled in randomized trials n=271 Median 6.8 years	For all treated patients (not reported by SVR status) Mean age (years): 57 Female: 62% Race: Not reported Genotype 1: 75% Viral load (log ₁₀ copies/ml): 5.8 Cirrhosis: 100% (inclusion criterion)	Univariate analyses not performed	Age	SVR vs. untreated patients and no SVR vs. untreated patients Hepatocellular carcinoma: Adjusted HR 0.31 (0.16-0.61) and 0.77 (0.51-1.2) All-cause mortality: Adjusted HR 0.05 (0.006-0.34) and 0.71 (0.43-1.2)

Author, Year Country Quality	Study Type Sample Size Duration of Followup	Population Characteristics	Variables Assessed as Univariate Predictors	Variables Included in Multivariate Models	Results
Veldt, 2007 ⁷⁴ Europe and Canada Overall Quality: Fair	Retrospective cohort n=479 Median 2.1 years	SVR (n=142) vs. no-SVR (n=337) Mean age (years): 48 vs. 49 (p=0.45) Female: 27% vs. 32% (p=0.23) Race: Not reported Genotype 1: 39% vs. 67% (p<0.001) Viral load (x10 ⁵ IU/mL): 8.5 vs. 8.0 (p=0.75) Cirrhosis (Ishak 5 or 6): 71% vs. 77% (p=0.45)	Univariate analyses not performed	All outcomes: Age, sex, previous non-response, bilirubin level, albumin level, platelet count, treatment center, treatment period Hepatocellular carcinoma: Also adjusted for anti-hepatitis B core antigen positivity	SVR vs. no SVR Any event (death, liver failure, and hepatocellular cancer): Adjusted HR 0.20 (0.07-0.58) All-cause mortality: Adjusted HR 0.31 (0.07-1.4) Liver-related mortality: Adjusted HR 0.19 (0.02-1.4) Hepatocellular carcinoma: Adjusted HR 0.46 (0.12-1.70)
Yoshida, 2002 ⁷⁵ Japan Overall Quality: Poor	Retrospective cohort n=2889 Mean 5.4 years	SVR (817) vs. non-SVR (1613) Mean age (years): 48 vs. 51 Female: 30% vs. 40% Race: Not reported Genotype: Not reported Viral load: Not reported Cirrhosis (Desmet F4): 6.5% vs. 11%	Univariate analyses not performed	Age, sex	SVR vs. untreated and no SVR vs. untreated Liver-related mortality: Adjusted HR 0.050 (0.01-0.22) and 0.39 (0.22-0.68) All-cause mortality: Adjusted HR 0.15 (0.06-0.34) and 0.47 (0.29-0.76)
Yu, 2006 ³⁸ Taiwan Overall Quality: Poor	Retrospective cohort n=1057 Mean 5.2 years	For all treated patients (not reported by SVR status) Mean age (years): 47 Female: 40% Race: Not reported Genotype 1: 46% Viral load: Not reported Cirrhosis (criteria not reported): 16%	Univariate analyses not reported	Age, sex, ALT, genotype, interferon monotherapy or interferon plus ribavirin combination therapy	SVR vs. untreated and no SVR vs. untreated Hepatocellular carcinoma: Adjusted HR 0.25 (0.13-0.46) and 0.99 (0.64-1.5) All-cause mortality: Adjusted HR 0.37 (0.14-0.99) and 1.3 (0.56-3.1)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CAD, coronary artery disease; COPD, coronary obstructive pulmonary disease; HBV, hepatitis B virus; HR, hazard ratio; PTSD, posttraumatic stress disorder; SVR, sustained virologic response.

SVR defined in all studies as undetectable HCV RNA in serum 6 months after the end of antiviral therapy, except as noted.

* SVR defined as undetectable HCV RNA on at least 2 occasions at least 2 years after completion of antiviral therapy.

^ Duration of undetectability after completion of antiviral therapy to meet definition of SVR not reported.

Study primarily evaluated patients who received pegylated interferon plus ribavirin.

Evidence Table 14. Sustained virologic response and clinical outcomes summary results

Author, Year Country Quality	Study Type Number Analyzed Duration of Followup Proportion with Cirrhosis: SVR vs. no SVR	Hepatocellular Carcinoma: Adjusted Hazards Ratio (95% CI)	Liver-Related Mortality: Adjusted Hazard Ratio (95% CI)	All-Cause Mortality: Adjusted Hazard Ratio (95% CI)	Other Clinical Outcomes: Adjusted Hazard Ratio (95% CI)	Results Adjusted for at Least Age, Sex, Viral Load, Genotype, and Fibrosis Stage, or no Association Found in Univariate Analyses
<i>Studies of general populations of treated patients with HCV infection</i>						
Arase, 2007 ⁵⁹ Japan Overall Quality: Fair	Retrospective cohort n=500 Mean 7.4 years Cirrhosis: 9% vs. 16%	SVR vs. no SVR: 0.19 (0.08-0.45)	SVR vs. no SVR: 0.13 (0.03-0.59)	SVR vs. no SVR: 0.39 (0.16-0.93)	NR	Yes
Backus, 2011 ⁶⁰ # USA Overall Quality: Fair	Retrospective cohort n=16,864 Median 3.8 years Cirrhosis: 9-12% vs. 12- 20%	NR	NR	SVR vs. no SVR (genotypes 1, 2, and 3, respectively): 0.71 (0.60- 0.86), 0.62 (0.44-0.87), and 0.51 (0.35-0.75)	NR	Yes
Coverdale, 2004* Australia Overall Quality: Poor	Prospective cohort (some patients originally enrolled in randomized trials) n=343 Median 9 years Cirrhosis: Not reported, median fibrosis score F2 (Scheuer)	SVR vs. response- relapse vs. nonresponse Adjusted HR not reported (p>0.05)	SVR vs. response- relapse vs. nonresponse Liver transplant or liver-related death: Adjusted HR not reported (p=0.20)	NR	SVR vs. response- relapse vs. nonresponse Liver-related complications:** Adjusted HR not reported (p=0.06)	Unclear
Imazeki, 2003 ⁶⁸ Japan Overall Quality: Fair	Retrospective cohort n=459 Mean 8.2 years Cirrhosis: 13% overall	NR	SVR vs. untreated: 0.06 (0.007-0.43) No SVR vs. untreated: 0.55 (0.27-1.1) SVR vs. no SVR: 0.11 (0.01-0.96)	SVR vs. untreated: 0.03 (0.003-0.27) No SVR vs. untreated: 0.26 (0.11-0.61) SVR vs. no SVR: 0.12 (0.01-1.3)	NR	Yes
Izumi, 2005 ⁶⁹ Japan Overall Quality: Fair	Cohort study, appears retrospective n=495 Duration of followup: Not reported Cirrhosis: 5.1% overall	SVR vs. no SVR: 0.36 (0.04-0.83)	NR	NR	NR	Unclear
Kasahara, 2004 ⁷⁰ Japan Overall Quality: Poor	Retrospective cohort n=2698 Mean 6 years Cirrhosis: 3.0% vs. 5.4%	NR	SVR vs. no SVR: 0.04 (0.005-0.30)	SVR vs. no SVR: 0.14 (0.06-0.35)	NR	No

Author, Year Country Quality	Study Type Number Analyzed Duration of Followup Proportion with Cirrhosis: SVR vs. no SVR	Hepatocellular Carcinoma: Adjusted Hazards Ratio (95% CI)	Liver-Related Mortality: Adjusted Hazard Ratio (95% CI)	All-Cause Mortality: Adjusted Hazard Ratio (95% CI)	Other Clinical Outcomes: Adjusted Hazard Ratio (95% CI)	Results Adjusted for at Least Age, Sex, Viral Load, Genotype, and Fibrosis Stage, or no Association Found in Univariate Analyses
Yoshida, 2002 ⁷⁵ Japan Overall Quality: Poor	Retrospective cohort n=2889 Mean 5.4 years Cirrhosis: 6.5% vs. 11%	NR	SVR vs. untreated: 0.05 (0.01-0.22) No SVR vs. untreated: 0.39 (0.22-0.68) SVR vs. no SVR: 0.13 (0.02-0.66)	SVR vs. untreated: 0.15 (0.06-0.34) No SVR vs. untreated: 0.47 (0.29-0.76) SVR vs. no SVR: 0.32 (0.12-0.86)	NR	No
Yu, 2006 ³⁸ Taiwan Overall Quality: Poor	Retrospective cohort n=1057 Mean 5.2 years Cirrhosis: 16% overall	SVR vs. untreated: 0.25 (0.13-0.46) No SVR vs. untreated: 0.99 (0.64-1.5) SVR vs. no SVR: 0.25 (0.13-0.54)	NR	SVR vs. untreated: 0.37 (0.14-0.99) No SVR vs. untreated: 1.3 (0.56-3.1) SVR vs. no SVR: 0.28 (0.08-1.0)	NR	No
<i>Studies of populations with advanced fibrosis and cirrhosis</i>						
Bruno, 2007 ⁶¹ Italy Overall Quality: Fair	Retrospective cohort study n=883 Mean 8 years Cirrhosis: All	SVR vs. no SVR: 0.39 (0.17-0.88)	SVR vs. no SVR: 0.14 (0.04-0.59)	NR	SVR vs. no SVR Ascites, encephalopathy, or gastrointestinal bleeding: Not calculated, 0 events/1061 person-years vs. 107 events/5703 person-years (1.88 events/100 person- years)	No
Cardoso, 2010 ⁶² France Overall Quality: Fair	Retrospective cohort study (of patients originally enrolled in clinical trials) n=307 Median 3.5 years Cirrhosis: 53% vs. 61%	SVR vs. no SVR: 0.33 (0.23-0.89)	SVR vs. no SVR: 0.27 (0.08-0.95)	NR	SVR vs. no SVR Ascites or variceal bleeding: 0.21 (0.05-0.92)	Yes

Author, Year Country Quality	Study Type Number Analyzed Duration of Followup Proportion with Cirrhosis: SVR vs. no SVR	Hepatocellular Carcinoma: Adjusted Hazards Ratio (95% CI)	Liver-Related Mortality: Adjusted Hazard Ratio (95% CI)	All-Cause Mortality: Adjusted Hazard Ratio (95% CI)	Other Clinical Outcomes: Adjusted Hazard Ratio (95% CI)	Results Adjusted for at Least Age, Sex, Viral Load, Genotype, and Fibrosis Stage, or no Association Found in Univariate Analyses
El Braks, 2007 ⁶⁴ France Overall Quality: Poor	Retrospective cohort study n=113 Mean 7.7 years Cirrhosis: All	NR	NR	NR	SVR vs. no SVR Clinical events (hepatocellular cancer, ascites, hepatic encephalopathy, or death): 0.14 (0.04- 0.45)	No
Fernandez-Rodriguez, 2010 ⁶⁵ # Spain Overall Quality: Poor	Retrospective cohort study n=509 Median 35 months Cirrhosis: All	NR	NR	NR	SVR vs. no SVR Combined clinical endpoint:*** 0.38 (0.18-0.76)	Unclear
Hasegawa, 2007 ⁶⁶ ^ Japan Overall Quality: Fair	Retrospective cohort study n=105 Median 4.6 years Cirrhosis: All	SVR vs. no SVR: 0.18 (0.04-0.81)	NR	NR	NR	Yes
Hung, 2006 ⁶⁷ Taiwan Overall Quality: Fair	Cohort study (unclear if retrospective or prospective) n=132 Median 37 months Cirrhosis: All	SVR vs. no SVR: 0.28 (0.09-0.92)	NR	NR	NR	Yes
Morgan, 2010 ¹¹ # USA Overall Quality: Fair	Prospective cohort study of patient enrolled in a randomized trial n=526 Median 79 to 86 months Cirrhosis: 21% vs. 43%	SVR vs. no SVR: 0.19 (0.04-0.80)	SVR vs. no SVR Liver-related mortality or liver transplantation: 0.12 (0.03-0.48)	SVR vs. no SVR All-cause mortality or liver transplantation: 0.17 (0.06-0.46)	SVR vs. no SVR Any liver-related outcome: ^ 0.15 (0.06-0.38) Decompensated liver disease: 0.13 (0.03-0.53)	Unclear
Shiratori, 2005 ⁷² Japan Overall Quality: Poor	Prospective cohort study of patients enrolled in randomized trials n=271 Median 6.8 years Cirrhosis: All	SVR vs. untreated: 0.31 (0.16-0.61) No SVR vs. untreated: 0.77 (0.51-1.2) SVR vs. no SVR: 0.40 (0.18-0.89)	NR	SVR vs. untreated: 0.05 (0.006-0.34) No SVR vs. untreated: 0.71 (0.43-1.2) SVR vs. no SVR: 0.07	NR	No

Author, Year Country Quality	Study Type Number Analyzed Duration of Followup Proportion with Cirrhosis: SVR vs. no SVR	Hepatocellular Carcinoma: Adjusted Hazards Ratio (95% CI)	Liver-Related Mortality: Adjusted Hazard Ratio (95% CI)	All-Cause Mortality: Adjusted Hazard Ratio (95% CI)	Other Clinical Outcomes: Adjusted Hazard Ratio (95% CI)	Results Adjusted for at Least Age, Sex, Viral Load, Genotype, and Fibrosis Stage, or no Association Found in Univariate Analyses
Veldt, 2007 ⁷⁴ Europe and Canada Overall Quality: Fair	Retrospective cohort n=479 Median 2.1 years Cirrhosis: 71% vs. 77%	SVR vs. no SVR: 0.46 (0.12-1.7)	SVR vs. no SVR: 0.19 (0.02-1.4)	SVR vs. no SVR: 0.31 (0.07-1.4)	SVR vs. no SVR Any event (death, liver failure, and hepatocellular cancer): 0.20 (0.07- 0.58)	No

Abbreviations: HCV, hepatitis C virus; NR, not reported; SVR, sustained virologic response.

Note: SVR defined in all studies as undetectable HCV RNA in serum 6 months after the end of antiviral therapy, except as noted.

* SVR defined as undetectable HCV RNA on at least 2 occasions at least 2 years after completion of therapy.

^ Duration of undetectability to meet criteria for SVR not reported.

Study primarily evaluated patients who received pegylated interferon plus ribavirin.

** Hepatic decompensation, complications of portal hypertension, hepatocellular carcinoma, liver transplantation, and liver-related mortality.

*** Hepatic decompensation, upper gastrointestinal bleeding secondary to rupture of esophageal or gastric varices, hepatocellular carcinoma, liver transplantation, and liver-related or liver-unrelated mortality.

^^ Decompensated liver disease (ascites, variceal bleeding, hepatic encephalopathy, spontaneous bacterial peritonitis), hepatocellular carcinoma, liver transplantation, and liver-related mortality.

Evidence Table 15. Sustained virologic response and quality of life study overview

Author, Year Country Quality	Study Type Sample Size Duration of Followup	Population Characteristics	Treatments Prior Antiviral Treatment Status	Adjustment for Confounders
Arora, 2006 ⁷⁷ Australia, Europe, New Zealand, North America, and South America Overall Quality: Poor	Cohort study (patients enrolled in a randomized trial) Sample size unclear (440 enrolled in trial from which cohort taken) 72 weeks	Not reported by SVR status Mean age: 43 years Female: 60% Non-white: 14% Genotype 1: 68% Viral load: 1.1-1.2 x 10 ⁶ copies/ml Advanced fibrosis: 10%	Pegylated interferon alfa-2a (24 or 48 weeks) Antiviral-naïve	Genotype, country, treatment, fibrosis stage, baseline score
Bernstein, 2002 ⁷⁸ Australia, North America, Europe, Taiwan, New Zealand Overall Quality: Poor	Cohort study (patients originally enrolled in 3 randomized trials) n=983 72 weeks	Not reported by SVR status Mean age <=40 years: 41% Female: 32% Non-white: 14% Genotype: Not reported Viral load: Not reported Cirrhosis: 32%	Pegylated interferon alfa-2a or interferon alfa-2a Antiviral-naïve	None
Bini 2006 ⁷⁹ USA Overall Quality: Poor	Prospective cohort study n=138 48 or 72 weeks (24 weeks after end of treatment)	Normal ALT and elevated ALT groups, respectively (not reported by SVR status) Mean age: 50 and 49 years Female: 11% and 8% Non-white: 59% and 66% Genotype 1: 78% and 78% Viral load >2 x 10 ⁶ copies/ml: 44% and 44% Cirrhosis: 11% and 11%	Interferon alfa-2b + ribavirin Antiviral-naïve	None
Bonkovsky 1999 ⁸⁰ USA and Canada Overall Quality: Poor	Cohort study (patients enrolled in a randomized trial) n=437 72 weeks	Not reported by SVR status Mean age: 43 years Female: 27% Non-white: 23% Genotype 1: 68% Viral load: Not reported Cirrhosis: 16%	Consensus interferon or interferon alfa-2b Antiviral-naïve	None
Hassanein, 2004 ⁸¹ Australia, North America, Europe, Taiwan, Brazil, Mexico Overall Quality: Poor	Cohort study (patients enrolled in a randomized trial) n=649 72 weeks	Not reported by SVR status Mean age: 43 years Female: 29% Non-white: 16% Genotype 1: 63% Viral load: 5.9 to 6.0 x 10 ⁶ copies/ml Cirrhosis: 13%	Pegylated interferon alfa-2a, pegylated interferon alf-2a +ribavirin, or interferon alfa-2b + ribavirin Antiviral-naïve	None

Author, Year Country Quality	Study Type Sample Size Duration of Followup	Population Characteristics	Treatments Prior Antiviral Treatment Status	Adjustment for Confounders
McHutchison, 2001 ⁸² USA Overall Quality: Poor	Cohort study (patients enrolled in a randomized trial) n=824 72 weeks	Mean age: 43 vs. 44 years Female: 42% vs. 32% Non-white: 8% vs. 12% Genotype 1: 43% vs. 81% Viral load >2 million copies/ml: 58% vs. 74% Cirrhosis: Not reported	Interferon alfa-2a for 24 or 48 weeks, with or without ribavirin Antiviral naïve	None
Neary, 1999 ⁸³ USA, Europe, Australia Overall Quality: Poor	Cohort study (patients enrolled in a randomized trial) Sample size unclear (257 had "complete data") 72 weeks	Not reported by SVR or overall response status Mean age: 43 years Female: 35% Non-white: 6.4% Genotype 1: 56% Viral load >2 million copies/ml: 75% Bridging fibrosis or cirrhosis: 17%	Interferon alfa-2b with or without ribavirin Relapsers	None
Rasenack, 2003 ⁸⁴ Germany, Canada, New Zealand, Spain Overall Quality: Poor	Cohort study (patients enrolled in a randomized trial) n=531 72 weeks	Not reported by SVR status Mean age: 41 years Female: 33% Non-white: 15% Genotype: Not reported Viral load: 7.4 to 8.2 x 10 ⁶ copies/ml Bridging fibrosis or cirrhosis: 13%	Pegylated interferon alfa-2a or interferon alfa-2a Antiviral-naïve	None
Ware, 1999 ⁸⁵ Australia, North America, and Europe Overall Quality: Poor	Cohort study (patients enrolled in a randomized trial) n=250 72 weeks	Not reported by response status Mean age: 43 years Female: 35% Non-white: 6.4% Genotype 1: 56% Viral load: 4.8 to 5.2 x 10 ⁶ copies/ml Bridging fibrosis or cirrhosis: 18%	Interferon alfa-2b or interferon alfa-2b + ribavirin Relapsers	None

Abbreviations: ALT, alanine aminotransferase; SVR, sustained virologic response.

Evidence Table 16. Sustained virologic response and quality of life summary table scores

Author, Year Country	SF-36 Physical Function	SF-36 Role Limitations- Physical	SF-36 Bodily Pain	SF-36 General Health	SF-36 Vitality	SF-36 Social Function	SF-36 Role Limitations- Emotional	SF-36 Mental Health
Arora, 2006 ⁷⁷ Australia, Europe, New Zealand, North America, and South America	+4.7 (p<0.05)	+13 (p<0.05)	+11 (p<0.0001)	+10 (p<0.0001)	+9.3 (p<0.0001)	+5.1 (p>0.05)	+7.3 (p>0.05)	+3.1 (p>0.05)
Bernstein, 2002 ⁷⁸ Australia, North America, Europe, Taiwan, New Zealand	+4.6 (p<0.001)	+9.8 (p<0.001)	+2.9 (p<0.01)	+9.1 (p<0.001)	+9.1 (p<0.001)	+6.2 (p<0.001)	+8.4 (p<0.01)	+4.6 (p<0.001)
Bini 2006 ^{79*} USA	+18 and +15	+22 and +27	+3.4 and +9.3	+3.0 and +9.9	+12 and +12	+9.5 and +11	+20 and +18	+14 and +18
Bonkovsky 1999 ⁸⁰ USA and Canada	+6.0 (p<0.05)	+22 (p<0.01)	-0.5 (p>0.05)	+7.5 (p<0.01)	+9.5 (p<0.05)	+10 (p<0.05)	+11 (p>0.05)	+4.0 (p>0.05)
Hassanein, 2004 ⁸¹ Australia, North America, Europe, Taiwan, Brazil, Mexico	+5.5 (p<0.01)	+5.7 (p<0.05)	+4.1 (p<0.5)	+8.6 (p<0.01)	+6.3 (p>0.05)	+5.8 (p<0.01)	+9.3 (p<0.01)	+5.0 (p<0.01)
McHutchison, 2001 ^{82^} USA	+2.4	+5.2	+1.6	+5.2	+4.7	+3.1	+3.0	+2.0
Neary, 1999 ^{83^#} USA, Europe, Australia	+8.0	+7.6	+2.4	+9.4	+7.8	+9.4	+6.0	+2.8
Rasenack, 2003 ^{84**} Germany, Canada, New Zealand, Spain	+5.0 (p=0.001)	+14 (p<0.001)	+5.2 (p=0.014)	+12 (p<0.001)	+9.4 (p<0.001)	+5.8 (p=0.005)	+8.4 (p=0.02)	+5.3 (p=0.001)
Ware, 1999 ^{85^} Australia, North America, and Europe	+2.6	+1.5	+0.45	+3.3	+2.2	+3.4	-0.02	+1.3

Author, Year Country Study Name	SF-36 Physical Component Summary	SF-36 Mental Component Summary	Sleep Somnolence	Fatigue Severity Scale, Total Score	Fatigue Severity Scale, Visual Analogue Scale	Health Distress	Hepatitis- Specific Health Distress	Hepatitis- Specific Limitations
Arora, 2006 ⁷⁷ Australia, Europe, New Zealand, North America, and South America	+4.9 (p<0.0001)	+2.0 (p>0.05)	NR	+4.4 (p<0.01)	-10 (p<0.01)	NR	NR	NR
Bernstein, 2002 ⁷⁸ Australia, North America, Europe, Taiwan, New Zealand	+2.8 (p<0.001)	+3.0 (p>0.001)	NR	-0.5 (p<0.001)	-12 (p<0.001)	NR	NR	NR
Bini 2006 ^{79*} USA	+3.8 and +7.1	+6.0 and +2.1	+11 and +5.4	NR	NR	+9.3 and +11	+5.4 and +2.6	+13 and +3.8
Bonkovsky 1999 ⁸⁰ USA and Canada	NR	NR	NR	NR	NR	NR	NR	NR
Hassanein, 2004 ⁸¹ Australia, North America, Europe, Taiwan, Brazil, Mexico	+5.0 (p<0.01)	+2.6 (p<0.01)	NR	+3.3 (p<0.01)	+7.4 (p<0.01)	NR	NR	NR
McHutchison, 2001 ^{82^} USA	NR	NR	+3.4	NR	NR	+5.4	+5.7	+4.6
Neary, 1999 ^{83^#} USA, Europe, Australia	NR	NR	+2.1	NR	NR	+8.9	+11	+6.7
Rasenack, 2003 ^{84**} Germany, Canada, New Zealand, Spain	+3.2 (p<0.001)	+2.9 (p=0.005)	NR	-0.5 (p=0.001)	-8.4 (p<0.001)	NR	NR	NR
Ware, 1999 ^{85^} Australia, North America, and Europe	+0.02	None	NR	NR	NR	+7.6	+12	+5.3

Abbreviations: NR, not reported.

Note: Absence of p values indicates that they were not reported.

* Results reported for normal alanine transaminase and elevated alanine transaminase subgroups, respectively

^ Results for relapsers reported separately and excluded from table.

Same cohort as Ware, 1999.

** Cohort included in Bernstein, 2002.

Appendix H References

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