Therapeutic Class Overview
Pegylated Interferons

Therapeutic Class

- **Overview/Summary:** The pegylated interferon alfa products included in this review are Food and Drug Administration (FDA) approved for the treatment of chronic hepatitis B (only pegylated interferon alfa-2a [Pegasys®]) and C.[1,2] In addition, pegylated interferon alfa-2b (Sylatron®) is approved for the treatment of melanoma.[3] There are six genotypes of hepatitis C virus (HCV) (genotypes 1 to 6), with genotype 1 being the most common within the United States, followed by genotypes 2 and 3. Genotyping is helpful in the clinical management of patients with hepatitis C for predicting the likelihood of response to treatment and in determining the optimal duration of treatment.[4] Due to the slow evolution of chronic infection it is difficult to demonstrate if treatment prevents complications of liver disease; therefore, response to treatment is defined by surrogate virological parameters. Of most importance is sustained virologic response (SVR), which is defined as the absence of HCV ribonucleic acid 24 weeks following discontinuation of treatment.[4] Of note, SVR rates are lowest with genotype 1 as compared to the other identified genotypes.[4] Combination treatment with pegylated interferon alfa and ribavirin remains the standard of care for the treatment of chronic hepatitis C. Guidelines do not give preference to one specific pegylated interferon alfa or ribavirin product over another.[4-8] The nonstructural protein 3 protease inhibitors, boceprevir or telaprevir, are recommended for the treatment of chronic hepatitis C genotype 1 infection when used with standard of care. Again, guidelines do not give preference to one specific protease inhibitor over another.[5,6] For the treatment of chronic hepatitis B, all FDA approved antiviral agents are recommended as potential treatment options, with entecavir, pegylated interferon alfa and tenofovir being preferred over the others.[7,9] The pegylated interferon alfa products are available as once weekly subcutaneous injections and there are no generics available within the class.

Table 1. Current Medications Available in the Therapeutic Class[1-3]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Peginterferon alfa-2a (Pegasys®, Pegasys Convenience Pack®, Pegasys ProClick®, Pegasys ProClick® Convenience Pack)	Chronic hepatitis B virus infection (hepatitis B e antigen positive and hepatitis B e antigen negative) in adults who have compensated liver disease and evidence of viral replication and liver inflammation, chronic hepatitis C virus infection, alone or in combination with Copegus® (ribavirin), in patients 5 years of age and older who have compensated liver disease and have not been previously treated with interferon alfa*	Autoinjector (Pegasys ProClick®, Pegasys ProClick® Convenience Pack): 135 µg/0.5 mL 180 µg/0.5 mL Prefilled syringe (Pegasys Convenience Pack®): 180 µg/0.5 mL Vial for injection (Pegasys®): 180 µg/mL	-
Peginterferon alfa-2b (PegIntron®, PegIntron Redipen®, PegIntron Redipen Pak 4®, Sylatron®)	Adjuvant treatment of melanoma with microscopic or gross nodal involvement within 84 days of definitive surgical resection including complete lymphadenectomy (Sylatron®), chronic hepatitis C virus infection, in combination with Rebetol® (ribavirin), in patients at least three years of age with compensated liver disease† (PegIntron®, PegIntron Redipen®,	Prefilled syringe (PegIntron Redipen®, PegIntron Redipen Pak 4®): 50 µg/0.5 mL 80 µg/0.5 mL 120 µg/0.5 mL 150 µg/0.5 mL	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	PegIntron Redipen Pak 4®), chronic hepatitis C virus infection in patients at least 18 years of age with compensated liver disease previously untreated with interferon alpha‡ (PegIntron®, PegIntron Redipen®, PegIntron Redipen Pak 4®)	Vial for injection: 50 µg/0.5 mL (PegIntron®) 80 µg/0.5 mL PegIntron®) 120 µg/0.5 mL PegIntron®) 150 µg/0.5 mL PegIntron®) 296 µg/1.25 mL (Sylatron®) 444 µg/1.25 mL (Sylatron®) 888 µg/1.25 mL (Sylatron®)	

*Efficacy has been demonstrated in patients with compensated liver disease and histological evidence of cirrhosis (Child-Pugh class A) and in adult patients with clinically stable human immunodeficiency virus disease and CD4 count >100 cells/mm^3. Use as monotherapy is not recommended for the treatment of chronic infection unless a patient has a contraindication or significant intolerance to ribavirin. Combination therapy provides substantially better response rates than monotherapy. Safety and efficacy have not been demonstrated for treatment longer than 48 weeks or in liver or other transplant recipients. Safety and efficacy have not been established in liver or other organ transplant recipients.
†Based on achieving undetectable hepatitis C virus ribonucleic acid after treatment for 24 or 48 weeks and maintaining a sustained virologic response 24 weeks after the last dose. Patients with the following characteristics are less likely to benefit from retreatment after failing a course of therapy: previous nonresponse, previous pegylated interferon treatment, significant bridging fibrosis or cirrhosis and genotype 1 infection. No safety and efficacy data are available for treatment of longer than one year.
‡Combination therapy with Rebetol® is preferred over pegylated interferon alfa-2b monotherapy unless there are contraindications or significant intolerance to Rebetol®. Combination therapy provides substantially better response rates than monotherapy.

Evidence-based Medicine

- Recently published clinical trials evaluating the pegylated interferon alfa products for the treatment of chronic hepatitis B and C have not produced clinically different results compared to trials included in the previous therapeutic class review.[10-25]
- For the treatment of hepatitis C genotype 1 infection, the addition of a nonstructural protein 3 protease inhibitor to standard combination therapy with pegylated interferon alfa and ribavirin is associated with a significant increase in the sustained virologic response rate, with an increased incidence of adverse events, compared to combination therapy alone.[26-30]
- For the treatment of melanoma, the safety and efficacy of pegylated interferon alfa-2b (Sylatron®) were demonstrated in an open-label, randomized controlled trial of 1,256 patients with surgically resected stage III melanoma. After a median of 3.8 years, significantly fewer recurrences had occurred with pegylated interferon alfa-2b compared to observation alone (328 vs 368; hazard ratio, 0.82; 95% confidence interval, 0.71 to 0.96; *P*=0.01). There was no difference in overall survival between the two regimens (*P*=0.78).[31]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - Hepatitis C:
        - Pegylated interferon alfa and ribavirin are the recommended standard of care for the treatment of chronic hepatitis C.[4-8]
            - No one pegylated interferon alfa or ribavirin product is preferred or recommended over another.
            - Patients with genotype 2 or 3 infection may receive treatment for up to 24 weeks and patients with genotype 1 or 4 infection may receive treatment for up to 48 weeks.

        - Patients with chronic hepatitis C genotype 1 infection may also be treated with a nonstructural protein 3 protease inhibitor, along with standard of care.[5,6]
            - No one protease inhibitor is preferred or recommended over another.
    - Hepatitis B:
        - All Food and Drug Administration approved antiviral agents are recommended as potential options for the treatment of chronic hepatitis B.[7,9]
        - According to the American Association for the Study of Liver Diseases, entecavir, pegylated interferon alfa or tenofovir are preferred over other available agents.[9]
    - Melanoma:
        - The National Comprehensive Cancer Network recommends high dose interferon or pegylated interferon alfa-2b as adjuvant treatment options in patients with completely resected stage III disease with positive sentinel nodes or clinically positive nodes. Other options include a clinical trial (preferred) or observation.[32]
- Other Key Facts:
    - No generic agents are available within the class.

References

1. Pegasys® [package insert]. South San Francisco (CA): Genentech USA, Inc.; 2011 Oct.
2. PegIntron® [package insert]. Whitehouse Station (NJ): Merck & Co., Inc.; 2013 May.
3. Sylatron® [package insert]. Whitehouse Station (NJ): Merck & Co., Inc.; 2012 Dec.
4. Ghany MG, Strader DB, Thomas DL, Seeff LB; American Association for the Study of Liver Diseases (AASLD). Diagnosis, management, and treatment of hepatitis C: an update. Hepatology. 2009 Apr;49(4):1335-74.
5. No authors listed; European Association for the Study of the Liver (EASL). EASL clinical practice guidelines: management of hepatitis C virus infection. J Hepatol. 2011 Aug;55(2):245-64.
6. Ghany MG, Nelson DR, Strader DB, Thomas DL, Seeff LB. An update on treatment of genotype 1 chronic hepatitis C virus infection: 211 practice guideline by the American Association for the Study of Liver Diseases. Hepatology. 2011 Oct;54(4):1433-44.
7. Centers for Disease Control and Prevention. Hepatitis ABC Fact Sheet [guideline on the Internet]. Atlanta (GA): CDC 2012 Aug [cited 2013 Jul 17]. Available at: http://www.cdc.gov/hepatitis/HCV/ProfResourcesC.htm#section1.
8. Dienstag JL, McHutchison JG. American Gastroenterological Association Medical position statement on the management of hepatitis C. Gastroenterology. 2006;130(1):225-30.
9. Lok AS, McMahon BJ. Chronic hepatitis B. Hepatology. 2009 Sep;50(3):1-38.
10. Rodriquez-Torres M, Jeffers LJ, Sheikh M, Rossaro L, Ankoma-Sey V, Hamzeh FM, et al. Peginterferon alfa-2a and ribavirin in Latino and non-Latino whites with hepatitis C. N Engl J Med. 2009;360:257-67.
11. Balart LA, Lisker-Melman M, Hamzeh FM, Kwok A, Lentz E, et al. Peginterferon α-2a plus ribavirin in Latino and non-Latino whites with HCV genotype 1: histologic outcomes and tolerability from the LATINO Study. Am J Gastroenterol. 2010;105:2177-85.
12. Moghaddam A, Melum E, Reinton N, Ring-Larsen H, Verbaan H, Bjoro K, et al. IL28B genetic variation and treatment response in patients with hepatitis C virus genotype 3 infection. Hepatology. 2011;53:746-54.
13. Buti M, Lurie Y, Zakharova NG, Blokhina NP, Horban A, Teuber G, Sarrazine C, 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;52:1201-7.
14. Muir AJ, Hu KQ, Gordon SC, Koury K, Boparai N, Noviello S, et al. Hepatitis C treatment among racial and ethnic groups in the IDEAL trial. J Viral Hepat. 2011;18:e134-e43.
15. Zhao S, Liu E, Wei K, Wang Y, Li Y, Huang B, et al. Treatment with peginterferon vs interferon in Chinese patients with chronic hepatitis C. Eur J Clin Microbiol Infect Dis. 2011;30:51-7.
16. Husa P, Oltman M, Ivanovski L, Rehak V, Messinger D, Tietz A, et al. Efficacy and safety of peginterferon α-2a (40 kD) plus ribavirin among patients with chronic hepatitis C and earlier treatment failure to interferon and ribavirin: an open-label study in central and Eastern Europe. Eur J Gastroenterol Hepatol. 2011;23:375-81.
17. Ho SB, Aqel B, Dieperink E, Liu S, Tetrick L, Falck-Ytter Y, et al. U.S. multicenter pilot study of daily consensus interferon (CIFN) plus ribavirin for “difficult-to-treat” HCV genotype 1 patients. Dig Dis Sci. 2011;56:880-8.
18. Mangia A, Bandiera F, Montalto G, Mottola L, Piazzolla V, Minerva N, et al. Individualized treatment with combination of peg-interferon alpha 2b and ribavirin in patients infected with HCV genotype 3 (abstract). J Hepatol. 2010 Dec;53(6):1000-5.
19. Singal AK, Anand BS. Tailoring treatment duration to 12 to 16 weeks in hepatitis C genotype 2 or 3 with rapid virologic response. Systematic review and meta-analysis of randomized controlled trials. J Clin Gastroenterol. 2010;44:583-7.
20. Schwarz KB, Gonzalez-Peralta RP, Murray KF, Molleston JP, Haber BA, Jonas MM, et al. The combination of ribavirin and peginterferon is superior to peginterferon and placebo for children and adolescents with chronic hepatitis C. Gastroenterology. 2011;140:450-8.
21. Rodrigue JR, Balistreri W, Haber B, Jonas MM, Mohan P, Molleston JP, et al. Peginterferon with or without ribavirin has minimal effect on quality of life, behavioral/emotional, and cognitive outcomes in children. Hepatology. 2011;53:1468-75.
22. Peck-Radosavljevic M, Boletis J, Besisik F, Ferraz ML, Alric L, Samuel D, et al. Low-dose peginterferon alfa-2a is safe and produces a sustained virologic response in patients with chronic hepatitis C and end-stage renal disease (abstract). Clin Gastroenterol Hepatol. 2011 Mar;9(3):242-8.

23. Kamal SM, Ahmed A, Mahmoud S, Nabegh L, Gohary IE, Obadan I, et al. Enhanced efficacy of pegylated interferon alfa-2a over pegylated interferon and ribavirin in chronic hepatitis C genotype 4A randomized trial and quality of life analysis. Liver Int. 2011 Mar;31(3):401-11.
24. Singal AK, Jampana SC, Anand BS. Peginterferon alfa-2a is superior to peginterferon alfa-2b in the treatment of naïve patients with hepatitis C virus infection: meta-analysis of randomized controlled trials. Dig Dis Sci. 2011;56:2221-6.
25. Di Bisceglie AM, Stoddard AM, Dienstag JL, Shiffman ML, Seeff LB, Bonkovsky HL, et al. Excess mortality in patients with advanced chronic hepatitis C treated with long-term peginterferon. Hepatology. 2011;53:1100-8.
26. Poordad F, McCone J Jr, Bacon BR, Bruno S, Manns MP, Sulkowski MS, et al. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med. 2011 Mar 31;364:1195-206.
27. Sherman KE, Flamm SI, Afdhal NH, Nelson DR, Sulkowski MS, Everson GT, et al. Response-guided telaprevir combination treatment for hepatitis C virus infection. N Engl J Med. 2011;365:1014-24.
28. Jacobson IM, McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, Bzowej NH, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. N Engl J Med. 2011;364:2405-16.
29. Bacon BR, Gordon SC, Lawitz E, Marcellin P, Vierling JM, Zeuzem S, et al. Boceprevir for previously treated chronic HCV genotype 1 infection. N Engl J Med. 2011 Mar 31;364:1207-17.
30. Zeuzem S, Andreone P, Pol S, Lawitz E, Diago M, Roberts S, et al. Telaprevir for retreatment of HCV infection. N Engl J Med. 2011;364:2417-28.
31. Eggermont AMM, Suciu S, Santiami M, Testori A, Kruit WHJ, Marsden J, et al. Adjuvant therapy with pegylated interferon alfa-2b vs observation alone in resected stage III melanoma: final results of EORTC 18991, a randomized phase III trial. Lancet. 2008;372:117-26.
32. National Comprehensive Cancer Network (NCCN). Melanoma [guideline on the Internet]. Fort Washington (PA): NCCN. 2012. Version 2 [cited 2013 Jul 17]. Available from: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp.

Therapeutic Class Review
Pegylated Interferons

Overview/Summary

The hepatitis C virus (HCV) is an enveloped ribonucleic acid virus that is transmitted through exposure with infected blood. It causes chronic infection in 70 to 85% of infected persons and the Centers for Disease Control and Prevention (CDC) estimates 3.2 million persons are chronically infected. Chronic HCV infection can lead to the development of active liver disease, and accounts for up to 40% of all patients undergoing liver transplantation.[1,2] There are six genotypes of HCV (genotypes 1 to 6), with genotype 1 being the most common within the United States, followed by genotypes 2 and 3. Genotyping is helpful in the clinical management of patients with hepatitis C for predicting the likelihood of response to treatment and in determining the optimal duration of treatment.[3] Treatment goals for the management of chronic hepatitis C include preventing complications and death. Due to the slow evolution of chronic infection it is difficult to demonstrate if treatment prevents complications of liver disease; therefore, response to treatment is defined by surrogate virological parameters. Of most importance is sustained virologic response (SVR), which is defined as the absence of HCV ribonucleic acid 24 weeks following discontinuation of treatment.[3] Of note, SVR rates are lowest with genotype 1 as compared to the other identified genotypes.[4] Combination treatment with pegylated interferon and ribavirin remains the standard of care for the treatment of chronic hepatitis C.[3-7] Newer treatment strategies which aim to improve efficacy, ease of administration, tolerability and patient adherence, as well as shorten treatment duration are currently being developed and include the nonstructural protein 3 protease inhibitors boceprevir and telaprevir.[4] According to the American Association for the Study of Liver Diseases, the protease inhibitors are recommended, along with standard of care, in patients with genotype 1 chronic hepatitis C.[5] Overall, guidelines do not give preference to one specific pegylated interferon or ribavirin product over another.[3-7] Furthermore, no one protease inhibitor is preferred over another and current recommendations for their use are in line with Food and Drug Administration (FDA) approved indications and dosing.[4,5]

The hepatitis B virus (HBV) is a deoxyribonucleic acid (DNA) virus that is transmitted through contact with infectious blood, semen and other body fluids. According to the CDC there are an estimated 1.25 million persons chronically infected, which can lead to the development of hepatocellular carcinoma. The goal of treatment in chronic infection is prevention of clinical and histologic progression, which can be achieved with either eradication or suppression of HBV replication to below the threshold for liver injury. Patients with hepatitis B e antigen-reactive and -negative infection are candidates for treatment with antiviral therapy when HBV DNA levels are >2 x 10^4 IU/mL. Candidates also typically have elevated alanine transaminase levels and histologic evidence of liver injury. Treatment is deemed successful when chronic hepatitis B is converted to an inactive carrier state. Of note, antiviral therapy is not appropriate in inactive carriers. Available antiviral agents FDA approved for the treatment of chronic hepatitis B include interferon alfa, pegylated interferon alfa and the nucleoside (entecavir, lamivudine, telbivudine) and nucleotide (adefovir dipivoxil, tenofovir disoproxil fumarate) analogues.[1,6] Any of the FDA approved agents are recommended as a potential treatment option; however, the American Association for the Study of Liver Diseases prefers the use of entecavir, pegylated interferon alfa or lamivudine. Furthermore, similar to the treatment of chronic hepatitis C, the different pegylated interferon alfa products are not distinguished within treatment guidelines for the treatment of chronic hepatitis B.[6,8]

The pegylated interferon alfa products included in this review are FDA approved for the treatment of chronic hepatitis B and C. Specifically, pegylated interferon alfa-2a (Pegasys®, Pegasys Convenience Pack®, Pegasys ProClick®, Pegasys ProClick® Convenience Pack) is approved for the treatment of both chronic hepatitis B and C, while pegylated interferon alfa-2b (PegIntron®, PegIntron Redipen®, PegIntron Redipen Pak 4®) is approved for the treatment of chronic hepatitis C only. For the treatment of chronic hepatitis C, pegylated interferon alfa-2a can be used in patients at least five years of age compared to patients at least three years of age with pegylated interferon alfa-2b.[9,10] In addition, Sylatron® (pegylated interferon alfa-2b) was more recently FDA approved as adjuvant treatment of melanoma.[11] The pegylated interferon alfa products are available as once weekly subcutaneous injections and there are no generics available within the class.[9-11]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade Name)	Medication Class	Generic Availability
Peginterferon alfa-2a (Pegasys®, Pegasys Convenience Pack®, Pegasys ProClick®, Pegasys ProClick® Convenience Pack)	Pegylated interferons	-
Peginterferon alfa-2b (PegIntron®, PegIntron Redipen®, Sylatron®, PegIntron Redipen Pak 4®)	Pegylated interferons	-

Indications

Table 2. Food and Drug Administration Approved Indications[9-10]

Indication	Peginterferon alfa-2a	Peginterferon alfa-2b
Adjuvant treatment of melanoma with microscopic or gross nodal involvement within 84 days of definitive surgical resection including complete lymphadenectomy		✔ (Sylatron®)
Chronic hepatitis B virus infection (hepatitis B e antigen positive and hepatitis B e antigen negative) in adults who have compensated liver disease and evidence of viral replication and liver inflammation	✔	
Chronic hepatitis C virus infection, alone or in combination with Copegus® (ribavirin), in patients ≥5 years of age who have compensated liver disease and have not been previously treated with interferon alfa*	✔	
Chronic hepatitis C virus infection, in combination with Rebetol® (ribavirin), in patients ≥3 years of age with compensated liver disease†		✔ (PegIntron®, PegIntron Redipen®, PegIntron Redipen Pak 4®)
Chronic hepatitis C virus infection in patients ≥18 years of age with compensated liver disease previously untreated with interferon alfa‡		✔ (PegIntron®, PegIntron Redipen®, PegIntron Redipen Pak 4®)

*Efficacy has been demonstrated in patients with compensated liver disease and histological evidence of cirrhosis (Child-Pugh class A) and in adult patients with clinically stable human immunodeficiency virus disease and CD4 count >100 cells/mm^3. Use as monotherapy is not recommended for the treatment of chronic infection unless a patient has a contraindication or significant intolerance to ribavirin. Combination therapy provides substantially better response rates than monotherapy. Safety and efficacy have not been demonstrated for treatment longer than 48 weeks or in liver or other transplant recipients. Safety and efficacy have not been established in liver or other organ transplant recipients.
†Based on achieving undetectable hepatitis C virus ribonucleic acid after treatment for 24 or 48 weeks and maintaining a sustained virologic response 24 weeks after the last dose. Patients with the following characteristics are less likely to benefit from retreatment after failing a course of therapy: previous nonresponse, previous pegylated interferon treatment, significant bridging fibrosis or cirrhosis and genotype 1 infection. No safety and efficacy data are available for treatment of longer than one year.
‡Combination therapy with Rebetol® is preferred over pegylated interferon alfa-2b monotherapy unless there are contraindications or significant intolerance to Rebetol®. Combination therapy provides substantially better response rates than monotherapy.

Pegylated interferon alfa-2a has the potential to be used off-label in the treatment of hepatitis C in patients who did not respond to previous interferon alfa and ribavirin therapy. Pegylated interferon alfa-2b has the potential to be used off-label in the treatment of treatment-resistant condyloma acuminatum in patients infected with human immunodeficiency virus (HIV) and in patients co-infected with hepatitis C and HIV.[12]

Pharmacokinetics

Table 3. Pharmacokinetics[12]

Generic Name	Bioavailability (%)	Metabolism	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Peginterferon alfa-2a	>60	Hepatic (percent not reported)	Not reported	None	84 to 353
Peginterferon alfa-2b	Not reported	Hepatic (percent not reported)	30	None	22 to 60

Clinical Trials

Clinical trials demonstrating the safety and efficacy of the pegylated interferon alfa products for their Food and Drug Administration (FDA) approved indications are outlined in Table 4.[13-72]

Of the available pegylated interferon alfa products, only pegylated interferon 2a is FDA approved for the treatment of chronic hepatitis B. In Cooksley et al, when compared to patients receiving interferon alfa-2a, a significantly greater proportion of patients receiving varying doses of pegylated interferon alfa-2a achieved a combined response (hepatitis B e antigen loss, hepatitis B virus deoxyribonucleic acid suppression and alanine aminotransferase normalization) (24 vs 12%; *P*=0.036).[14] According to the American Association for the Study of Liver Diseases, the use of pegylated interferon alfa products is preferred over the use of nonpegylated interferon alfa, as well as other antiviral agents, for the treatment of chronic hepatitis B.[8]

The standard of care for the treatment of chronic hepatitis C has historically been pegylated interferon alfa and ribavirin, and several clinical trials demonstrate that a sustained virologic response (SVR), which is the goal of treatment, is consistently achieved with this combination.[15-34,47-52,55-72] Lower response rates were observed with pegylated interferon alfa monotherapy compared to combination therapy with ribavirin.[41] In addition, the pegylated interferon alfa products demonstrated "superior" efficacy compared to interferon products in achieving and SVR, as well as in normalization of liver function tests.[36-39,41,42] Of note, treatment guidelines do not prefer one specific pegylated interferon alfa product over another.[3-7] Few large, head-to-head clinical trials comparing pegylated interferon alfa-2a to pegylated interferon-2b have been conducted, but available data is in line with current treatment guidlines.[24-34] The IDEAL trial (N=3,070) demonstrated that after 48 weeks, comparable SVR rates between the two products were achieved (40.9 vs 39.8%; *P*=0.57), with higher end of treatment response (64.4 vs 53.2%; *P*<0.001) and relapse rates (31.5 vs 23.5%; *P* value not reported) associated with pegylated interferon alfa-2a.[32] Two open-label, randomized controlled trials demonstrated significantly higher SVR rates with pegylated interferon alfa-2a, and a meta analysis of nine randomized controlled trials conducted by Singal et al demonstrated similar results.[29,31,34]

Few clinical trials evaluating the safety and efficacy of pegylated interferon alfa products in patients who have previously failed therapy have been conducted; however, the limited available data demonstrates that patients can achieve a SVR with re-treatment.[47 to 54] Clinical trials investigating optimal treatment duration for chronic hepatitis C have also been conducted.[3-7,55-64] While select patients may benefit from a longer or shorter treatment duration, more clinical trials are needed and treatment guidelines should always be consulted.

In patients with genotype 1 hepatitis C, the addition of a nonstructural protein 3 C protease inhibitor to standard of care significantly increased the rate of SVR compared to pegylated interferon alfa and ribavirin alone. However, triple therapy is associated with a higher incidence of adverse events. The use of a protease inhibitor with pegylated interferon and ribavirin has been evaluated in both treatment naïve and experienced patients.[44-46,53,54]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Hepatitis B				
Caruntu et al[13] Peginterferon alfa-2a 180 µg weekly	MC, OL, PRO Patients 15 to 65 years of age who were HBsAg positive for 6 months or negative, HBeAg positive for ≥6 months, HBV DNA >500,000 copies/mL, ALT >1 to <10 times the upper limit of normal, no response/relapse after previous treatment with lamivudine or interferon alfa	N=43 48 weeks (plus 24 weeks of follow up)	Primary: HBeAg seroconversion rates, suppression of viral replication Secondary: Normalization of ALT, safety	Primary: At the end of treatment, 4.65% (n=2) of patients had achieved HBeAg seroconversion and at the end of the follow up period, the HBeAg seroconversion rate was 11.62% (n=5). At the end of treatment, 23.25% (n=10) of patients had HBV DNA levels <100,000 copies/mL and at the end of the follow up period, 16.30% (n=7) did. Patients whose HBV DNA levels were <100,000 copies/mL at the end of follow up experienced a four log decline in HBV DNA from baseline. Secondary: At the end of treatment, 20.90% of patients had normalized ALT levels (CI, 8.75 to 33.05; *P*<0.05). At the end of the follow up period, the percent of patients with normalized ALT levels was 37.20% (CI, 22.75 to 51.65; *P*<0.05). Average ALT decreased significantly between baseline and end of treatment (135.1 to 76.5 U/L; *P*=0.03) and between baseline and end of follow up (135.1 to 58.3 U/L; *P*=0.02). The dose of peginterferon alfa-2a was reduced in 20.90% of patients, primarily for neutropenia and thrombocytopenia. The rate of significant adverse events was 11.60%. One patient reported depression.
Cooksley et al[14] Peginterferon alfa-2a 90, 180 or 270 µg weekly for 24 weeks vs interferon alfa-2a 4.5 MIU 3 times weekly for 24 weeks	RCT Adult patients positive for HBeAg for >6 months	N=194 48 weeks	Primary: Loss of HBeAg after 48 weeks, suppression of HBV, ALT, combined response (HBeAg loss, HBV DNA suppression and ALT normalization)	Primary: After 48 weeks, HBeAg was cleared in 37% of patients receiving peginterferon 90 µg, 35% of patients receiving peginterferon 180 µg and 29% of patients receiving peginterferon 270 µg compared to 25% of patients receiving interferon. The difference between the four treatments was not significant (*P*=0.295). Suppression of HBV occurred in 43% of patients receiving peginterferon 90 µg, 39% of patients receiving peginterferon 180 µg and 27% of patients receiving peginterferon 270 µg compared to 25% of patients receiving interferon. The difference between the four treatments was not significant (*P*=0.096).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Secondary: Not reported	The proportion of patients who developed normalized ALT was 43, 35 and 31% with peginterferon 90, 180 and 270 µg compared to 26% with interferon. The difference between the four treatments was not significant (*P*=0.096). The combined response of all peginterferon alfa-2a doses was twice of that achieved with conventional interferon alfa-2a (24 vs 12%; *P*=0.036). All treatments were similar with respect to frequency and severity of adverse events. Secondary: Not reported
Hepatitis C				
Dinges et al[15] Peginterferon alfa-2a 180 µg weekly plus ribavirin 10 mg/kg/day	OL Patients 18 to 65 years of age who have undergone a liver transplant for end-stage liver disease due to HCV, with presence of HCV RNA in serum, recurrent hepatitis of the graft and who were diagnosed at histology no less than 6 months after liver transplant and within the 12 months before the trial	N=19 48 weeks (plus 24 weeks of follow up)	Primary: Virological response Secondary: Not reported	Primary: An early virologic response was observed in 11 patients at week 12 which corresponded to a 69% response rate. At the end of therapy, HCV RNA was undetectable in 71% (10/14) of patients who had completed treatment as per schedule. Additionally, at the end of the 24 week follow up period, nine patients still had undetectable HCV RNA. Based on an ITT analysis, nine out of the 19 patients reached SVR (47%). The rate of SVR was 100% (4/4) in patients infected with HCV genotypes 2 or 3 and was 33% (5/15) in patients infected with HCV genotypes 1 and 4 (*P*=0.03). In patients who had negative or at least a two log decrease in serum HCV RNA with respect to pretreatment levels after 12 weeks of therapy, SVR was achieved by 82% (9/11) compared to none of the five patients who failed to significantly respond to therapy within the same time period (*P*=0.005). Nine of the 14 (64.3%) patients treated for >80% of the duration achieved SVR compared to none of the patients who received therapy for <80% of the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				scheduled duration (*P*=0.02). Secondary: Not reported
Hakim et al[16] Peginterferon alfa-2a 135 µg weekly plus ribavirin 200 mg 3 times a week	PRO Patients ≥18 years of age with presence of HCV RNA, with no hemolysis at baseline based on serum haptoglobin and lactate dehydrogenase and end-stage renal disease defined by requiring dialysis	N=20 48 weeks	Primary: Adverse events, virologic response Secondary: Not reported	Primary: Malaise/fatigue was present in all patients to some degree and there were minimal arthralgias and myalgias reported. Additionally, there were no reports of depression or leukocytopenia. Anemia was the most serious side effect associated with treatment. Overall, out of the 15 patients who began treatment, 53.3% (n=8) had a significant drop in their HCV levels at some point during treatment. Secondary: Not reported
Makhzangy et al[17] Peginterferon alfa-2a 180 µg/kg weekly plus ribavirin ≥11 mg/kg/day	OL, PRO Interferon-naïve Egyptian patients 18 to 65 years of age with chronic hepatitis C genotype 4, with positive HCV antibodies, detectable HCV RNA, elevated aminotransferases in the preceding 6 months and a liver biopsy showing Metavir score of ≥A1 and >F or >A1 and ≥F1	N=95 24 weeks (treatment was continued for a total of 48 weeks in patients with a negative HCV RNA test result at 24 weeks) (plus 24 weeks of follow up)	Primary: SVR Secondary: End of treatment response, safety, liver biopsy	Primary: Fifty eight out of 95 patients (61.1%) achieved a SVR (95% CI, 50.5 to 70.9). Secondary: The proportion of patients with end of treatment response was 69.5% (66/95; 95% CI, 59.0 to 78.5). Fifty nine patients (62.1%) experienced adverse events that required a dose reduction, 15 patients for clinical adverse events, 31 patients for biological adverse events and 13 patients for both. The most common clinical side effects were fatigue, myalgia, anorexia, arthralgia and irritability. The liver biopsy that was conducted at 72 weeks on 54 patients demonstrated that the mean change in baseline Metavir fibrosis score was -0.33 for patients with SVR (n=39; *P*=0.01) and 0.33 for patients without SVR (n=15; *P*>0.05). The mean change in Metavir activity score was -0.74 (*P*<0.001) and 0.0 (*P*>0.05) for patients with SVR and without SVR.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Rodriguez-Torres et al[18] LATINO Study Peginterferon alfa-2a 180 µg weekly plus ribavirin 1,000 or 1,200 mg/day	MC, nonrandomized, OL, PRO Patients 18 to 65 years of age with chronic HCV genotype 1 infection with no history of treatment for HCV infection	N=569 48 weeks (plus 24 weeks follow up)	Primary: SVR Secondary: Virologic response during the treatment period, relapse	Primary: The SVR rate was significantly lower in Latino patients compared to non-Latino patients (34 vs 49%; absolute difference, -16 percentage points; 95% CI, -24 to -8; *P*<0.001). Secondary: The rate of virologic response was lower among Latino patients at every time point at which data were available (week 4; *P*=0.045, weeks 12, 24, 48 and 72; *P*<0.001). The rate of relapse among patients with a response after 48 weeks (end of treatment) was 36 vs 26% among Latino and non-Latino patients. In the ITT population, the proportion of patients who had a relapse was similar between the two populations (19 vs 17%; *P* values not reported).
Balart et al[19] Peginterferon alfa-2a 180 µg weekly plus ribavirin 1,000 or 1,200 mg/day	Post hoc analysis of LATINO Study[17] Patients 18 to 65 years of age with chronic HCV genotype 1 infection with no history of treatment for HCV infection	N=569 48 weeks (plus 24 weeks follow up)	Primary: Ishak activity scores, Ishak fibrosis scores, steatosis scale, NASH grade scale, relationship between baseline patient/histologic characteristics and SVR Secondary: Not reported	Primary: Both Latino and non-Latino patients experienced a decrease in mean Ishak activity scores from baseline to week 72; however, the magnitude of improvement was significantly greater among non-Latino patients (mean change from baseline, -2.1 vs -1.4; *P*<0.0001). A significantly greater proportion of non-Latino patients had an Ishak activity response (≥2 point decrease in scores) (58.7 vs 47.1%; *P*=0.03). Among Latino patients, significant predictors of change in the Ishak activity score were age (*P*=0.0023), BMI (*P*=0.068), baseline ALT quotient (*P*=0.031), baseline Ishak activity scores (*P*<0.0001) and baseline Ishak fibrosis scores (*P*=0.021). The only predictor for non-Latino patients was baseline Ishak activity scores (*P*<0.0001). Both patient populations had improved Ishak fibrosis scores (≥1 category decrease) at week 72; however, a higher proportion of non-Latino patients showed improvement (42.3 vs 24.8%). A similar proportion of Latino and non-Latino patients had worsening scores (22.3 vs 17.9%). Among Latino patients, the only predictor of higher fibrosis scores was increasing baseline Ishak fibrosis scores (OR, 5.66; 95% CI, 3.93 to 8.16; *P*<0.0001). Among non-Latinos, significant predictors were age >40 years (OR, 2.91; 95% CI, 1.19 to 7.07; *P*=0.019), BMI >30 kg/m^2 (OR, 1.96; 95% CI, 1.08 to 3.58;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				P=0.028) and increasing baseline Ishak fibrosis scores (OR, 3.82; 95% CI, 2.81 to 5.19; *P*<0.0001). Of those who achieved SVR, there was a significantly greater proportion of patients with an improved fibrosis score among non-Latino patients (54.8 vs 36.6%; *P*=0.014). After 72 weeks, the proportion of patients with improved steatosis scale scores were 32.3 and 31.8% among non-Latino and Latino patients. The corresponding proportions with worsened scores were 16.4 vs 20.4% (*P* values not reported). With regards to the NASH grade scale, after 72 weeks, the majority of Latino and non-Latino patients (≥68%) experienced no change in the sinusoidal fibrosis, Mallory bodies and hepatocyte ballooning scores. Among Latino patients baseline HCV RNA titers >400,000, an Ishak fibrosis score of 5 to 6 vs 0 to 2 and an Ishak fibrosis score of 3 to 4 vs 0 to 2 were associated with a significantly lower likelihood of achieving SVR. In non-Latino patients a baseline ALT quotient less than or equal to three times the upper limit of normal, Ishak fibrosis score of 3 to 4 vs 0 to 2 and steatosis scores ≤5% vs >5% were significantly predictive of SVR. Baseline HCV RNA titers >400,000 and an Ishak fibrosis score 5 to 6 vs 0 to 2 were associated with a significantly lower likelihood of achieving SVR among non-Latino patients. The majority of Latino and non-Latino patients completed treatment (72.1 and 76.6%). Almost all patients in both populations experienced at least one adverse event and nearly all were treatment-related. The most frequently occurring adverse events included fatigue, pyrexia, influenza-like illness, irritability, nausea, diarrhea, insomnia, depression, headache, dizziness, rash, alopecia, pruritus, myalgia, arthralgia, cough and anemia. Overall, adverse events were more frequent among non-Latino patients. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Lam et al[20] Peginterferon alfa-2a 180 µg weekly plus ribavirin 800 to 1,200 mg/day	MC, OL, RCT Patients 18 to 70 years of age with HCV genotype 6 infection	N=60 24 or 48 weeks (plus 24 weeks of follow up)	Primary: SVR Secondary: Virologic response, biochemical response, compliance, safety	Primary: The SVR rates with 24 (n=27) and 48 weeks (n=33) of treatment were 70 and 79% (*P*=0.45). Secondary: Rapid virologic response was a significant predictor of SVR with 48 weeks of treatment. Eighty two and 83% of patients with a rapid virologic response achieved SVR vs 33 and 29% of patients with 24 (*P*=0.07) and 48 weeks (*P*=0.02) of treatment. The proportions of patients randomized to 24 and 48 weeks of treatment who achieved early virologic response were 96 and 97% (*P*=0.90). The proportions of patients randomized to 24 and 48 weeks of treatment who achieved an end of therapy virologic response were 89 and 94% (*P*=0.48). Normalization of serum ALT levels six months after therapy was lower with 24 vs 48 weeks of treatment (78 vs 91%; difference, 13%; 95% CI, -32 to 5; *P*=0.16). The most common side effects were generalized flu like symptoms, cutaneous and psychiatric symptoms. Anemia was more frequent with 48 weeks of treatment (72 vs 44%; *P*=0.03).
Peck-Radosavljevic et al (abstract)[21] Peginterferon alfa-2a 90 µg weekly vs peginterferon alfa-2a 135 µg weekly	MC, OL, RCT Patients with chronic hepatitis C and end-stage renal disease	N=85 48 weeks (plus 24 weeks of follow up)	Primary: SVR, safety Secondary: Not reported	Primary: The rate of SVR was 34.9 and 39.5% with peginterferon 90 and 135 µg (OR, 1.22; 95% CI, 0.49 to 3.06; *P*=0.67). Among those with undetectable HCV RNA after 12 weeks, 87.5 and 60.9% achieved an SVR. Therapy was well tolerated and there were no safety concerns. The most commonly reported adverse events included conditions associated with end-stage renal disease (i.e., anemia and hypertension) and with interferon based treatment. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Kainuma et al[22] Peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 600 to 1,000 mg/day	MC Adult Japanese patients with HCV	N=1,251 24 (genotype 2) or 48 weeks (genotype 1) (plus 24 weeks of follow up)	Primary: SVR, end of treatment response, safety Secondary: Not reported	Primary: The rates of SVR with genotypes 1 (n=938) and 2 (n=313) were 40.7 and 79.6%, respectively. The SVR rate decreased significantly with age with each genotype, and was markedly reduced with genotype 1 (*P*<0.001). The SVR rate was significantly higher with patients with genotype 1 who were <65 years of age (47.3%; n=685) compared to those ≥65 years of age (22.9%; n=253) (*P*<0.001), and was significantly higher in patients with genotype 2 who were <65 years of age (82.9%; n=252) compared to those ≥65 years of age (65.6%; n=61) (*P*=0.004). Among patients with genotype 1, the rate of end of treatment response was significantly higher in patients <65 years of age (72.5%; n=685) compared to those ≥65 years of age (45.0%; n=253) (*P*<0.001). There was no difference between these two age groups among patients with genotype 2 (94.8 vs 90.1%; *P* value not reported). A total of 314 (25.1%) patients did not complete treatment due to an adverse event or for other reasons. The discontinuation rate was significantly higher among patients with genotype 1 compared to genotype 2 (29.1 vs 13.1%; *P*<0.001). The rates of discontinuation due to adverse events was significantly higher with genotype 1 (14.4 vs 7.3%; *P*<0.010). Rates of discontinuation due to lack of efficacy (5.9 vs 0.3%; *P*<0.001) or economic reasons (1.6 vs 0.0%; *P*=0.025) were also significantly higher among patients with genotype 1. Only among patients with genotype 1 was there a significant difference in the discontinuation rate among patients <65 years of age and those ≥65 years of age (24.4 vs 42.9%; *P*<0.001). Secondary: Not reported
Moghaddam et al[23] Peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 800 to 1,400 mg/day	RETRO (data from 2 clinical trials) Patients of Scandinavian origin with HCV genotype 3	N=281 24 weeks (patients who achieved a rapid virologic	Primary: Relationship between the IL28B genotype and viral response to	Primary: No difference in the rate of SVR was observed between patients with responder genotype CC compared to the CT/TT at the rs12979860 locus (OR, 1.5; 95% CI, 0.9 to 2.8) or if they had responder genotype TT compared to the TG/GG at the rs8099917 locus (OR, 1.1; 95% CI, 0.6 to 2.1). SVR rates were significantly lower in patients with CC at rs12979860 compared to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	and had been treated per protocol; a control population of healthy Norwegian patients was identified via the Norwegian Bone Marrow registry	response may have received only 14 weeks of treatment) (plus 24 weeks of follow up)	therapy Secondary: Relationship between the IL28B genotype and natural history of infection	TT (77 vs 96%; *P*=0.038). Patients with CC genotype of rs12979860 or TT genotype or rs8099971 were significantly more likely to achieve a rapid virologic response compared to those with CT/TT (84 vs 61%; OR, 3.3; 95% CI, 1.9 to 5.8; *P*=0.00034) or TG/GG (78 vs 56%; OR, 2.7; 95% CI, 1.6 to 4.7; *P*=0.00003), respectively. Secondary: It was determined that pretreatment viral load and ALT in patients infected with genotype 3 were higher in patients carrying the CC genotype of rs12979860 compared to patients carrying CT or TT. Patients carrying TT at rs8099917 had higher baseline viral load and higher rates of normalized ALT compared to patients carrying TG. Patients with the CC genotype at rs12979860 had significantly higher probability of having aspartate aminotransferase platelet ratio index >1.5 (OR, 2.0; 95% CI, 1.1 to 3.5), indicative of cirrhosis or bridging fibrosis. This association was not present with the TT genotype at rs8099917 (OR, 1.3; 95% CI, 0.7 to 2.5).
Ascione et al[24] Peginterferon alfa-2a 180 µg weekly vs peginterferon alfa-2b 1.5 µg/kg weekly All patients received ribavirin 1,000 to 1,200 mg/day.	OL, PRO, RCT Patients ≥18 years of age with chronic hepatitis C, interferon-naïve, detectable HCV RNA levels, ALT >1.5 times the upper limit of normal for ≥6 months, negative pregnancy test, using contraception and no alcohol use for 6 months	N=320 24 (genotypes 2 and 3) or 48 weeks (genotypes 1 and 4) (plus 24 weeks of follow up)	Primary: SVR Secondary: Adverse reactions	Primary: Overall, SVR rates were significantly higher with peginterferon alfa-2a compared to peginterferon alfa-2b (110/160 [68.8%] vs 87/160 [54.4%]; difference, 14.4%; 95% CI, 3.7 to 24.6; *P*=0.008). With genotypes 1 and 4, rates of SVR were 54.5 vs 39.8% with peginterferon alfa-2a and peginterferon alfa-2b (95% CI, 0.14 to 26.40; *P*=0.04). With genotypes 2 and 3, rates of SVR were 88.1 vs 74.6% with peginterferon alfa-2a and peginterferon alfa-2b (*P*=0.046). There was no difference in the rates of relapse between genotypes 2 and 3 (7.5 vs 10.4%; *P*=0.54). Secondary: Twenty-six patients discontinued therapy and were classified as non-responders: four patients receiving peginterferon alfa-2a and 22 patients receiving peginterferon alfa-2b (*P*=0.0005). No serious adverse events (e.g., death, any life-threatening event, event

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				requiring hospitalization) were reported with either treatment.
Berenguer et al[25] Peginterferon alfa-2b 1.5 µg/kg weekly vs peginterferon alfa-2a 180 µg weekly All patients received ribavirin.	OL Patients with chronic hepatitis C infection, HIV infection and interferon treatment-naïve	N=557 5 years (plus 24 weeks of follow up)	Primary: SVR Secondary: End of treatment response rate, non-sustained virologic response rate, safety	Primary: No differences in SVR between the two treatments were observed (31 vs 33%; OR, 1.09; 95% CI, 1.16 to 2.29; *P*<0.01). Additionally, there were no differences in SVR between treatments when patients were grouped according to HCV genotype. Secondary: End of treatment response was significantly lower with peginterferon alfa-2b (40 vs 52%; OR, 1.63; 95% CI, 1.16 to 2.29; *P*<0.01). A significantly smaller proportion of patients receiving peginterferon alfa-2b relapsed compared to peginterferon alfa-2a (21 vs 37%; *P*=0.011). There were no differences between treatments in terms of frequency of adverse events (22 vs 17%; *P*=0.16).
Di Bisceglie et al[26] Peginterferon alfa-2a 180 µg weekly vs peginterferon alfa-2b 1.5 µg/kg weekly All patients received ribavirin 1,000 to 1,200 mg/day	OL, RCT Adult treatment-naïve patients who were infected with HCV genotype 1 and had high viral loads (>800,000 IU/mL)	N=380 12 weeks	Primary: Change from baseline in HCV RNA, virologic response Secondary: Not reported	Primary: There was no between group difference in viral load reduction over time and no difference in the proportion of patients receiving peginterferon alfa-2a or peginterferon alfa-2b who achieved early virologic response (defined as ≥2-$\log_{10}$ reduction in HCV RNA concentration or undetectable HCV RNA at 12 weeks) (66 vs 63%; *P* value not reported). Serum levels of peginterferon were more frequently below the level of quantitation in patients receiving peginterferon alfa-2b (58 to 68%) then peginterferon alfa-2a (1 to 2%). Overall, there were no differences in adverse events between the two treatments. However, the relative frequency of chills, fever, influenza-like illness, decreased appetite, rash, vomiting and injection-site erythema was ≥25% higher with peginterferon alfa-2b, whereas the relative frequency of dyspnea was ≥25% higher with peginterferon alfa-2a. The frequency and pattern of dose reductions were comparable between the two treatments.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Patients receiving peginterferon alfa-2b had higher rates of discontinuation for safety reasons (6 vs 1%; *P* value not reported). Discontinuation rates for non-safety reasons were similar between the two treatments (8 vs 9%; *P* value not reported). Secondary: Not reported
Escudero et al[27] Peginterferon alfa-2a 180 µg weekly vs peginterferon alfa-2b 1.5 µg/kg weekly All patients received ribavirin 800 to 1,200 mg/day.	OL, PRO Patients ≥18 years of age with chronic hepatitis C, treatment-naïve, serum ALT greater than the upper limit of normal and liver biopsy confirming diagnosis	N=183 24 (genotypes 2 and 3) or 48 weeks (genotypes 1 and 4) (plus 24 weeks of follow up)	Primary: SVR Secondary: Rapid virologic response, early virologic response, end of treatment response, adverse events	Primary: There was no difference in SVR rates between the two treatments (65.9 vs 62.0%; *P*=0.64). As a subgroup, there was no difference between treatments in SVR rates with genotype 1 (50.8 vs 46.6%; *P*=0.713). As a subgroup, there was no difference between treatments in SVR rates with genotypes 2 or 3 (95.0 vs 89.3%; *P*=0.63). As a subgroup, there was no difference between treatments in SVR rates with genotype 4 (91.7 vs 83.3%; *P*=1.0). Secondary: The proportion of patients with rapid virologic response and early virologic response were similar between the two treatments (*P* values not reported). Twenty two patients receiving peginterferon alfa-2a discontinued treatment early; 12 patients due to serious treatment related adverse events and 28 patients receiving peginterferon alfa-2b discontinued treatment early; 10 patients due to treatment related adverse events.
Laguno et al[28] Peginterferon alfa-2b 80 to 150 µg weekly vs	MC, OL, PRO, RCT Treatment-naïve patients with chronic hepatitis C, positive HCV RNA in the	N=182 48 weeks (plus 24 weeks of follow up)	Primary: SVR Secondary: Rate of early virological	Primary: The global SVR rate was 44%, with no difference between treatments (42 vs 43%; *P*=0.654). Additionally, SVR rates were not different among the different genotypes. For HCV genotypes 1 or 4, SVR rates were 28 vs 32% (*P*=0.676). For HCV

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
peginterferon alfa-2a 180 µg weekly All patients received ribavirin 800 to 1,200 mg/day.	plasma, ALT levels >1.5-fold higher than the upper limit of normal and histological modifications in the liver biopsy; control of HIV infection with CD4 cell count >250 cells/mm^3 and HIV viral load <50,000 copies/mL, in response to a stable antiretroviral treatment or without antiretroviral treatment if not required		response; rapid virological response and relapse, sustained biochemical response, safety	genotypes 2 or 3, SVR rates were 62 vs 71%, respectively (*P*=0.6). Secondary: The global rate of early virological response was 75%, with no difference between treatments (69 vs 80%, respectively; *P*=0.133). No differences in the rates of early virological response were seen among the different HCV genotypes (HCV genotype 1 or 4, 57 vs 71%; *P*=0.181 and HCV genotype 2 or 3, 83 vs 96%; *P*=0.197). Rapid virological response was achieved in 35% of patients, with no differences in rapid virological response rates between treatments within the HCV genotypes 1 or 4 groups (21 vs 16%; *P*=0.587) or genotypes 2 or 3 groups (55 vs 78%; *P*=0.141). Eight percent of patients receiving peginterferon alfa-2b and six percent of patients receiving peginterferon alfa-2a, who had HCV RNA undetectable during therapy, relapsed (*P*=0.774). Among patients with SVR, 18% did not achieve normal values of ALT at the end of follow up. Side effect profiles were similar with both treatments; however, patients receiving peginterferon alfa-2a had a significantly higher incidence of leucopenia and thrombocytopenia (*P*=0.004 and *P*=0.0037). Eight and 13% of patients receiving peginterferon alfa-2b and peginterferon alfa-2a discontinued treatment because of an adverse event with psychiatric disorders, severe flu-like syndrome or general discomfort, thrombocytopenia or leucopenia, lactic acidosis, severe debut of psoriatic arthritis, severe weight loss with worsening lipoatrophy and decompensated cirrhosis being the main causes (*P*=0.467).
Rumi et al[29] Peginterferon alfa-2a 180 µg weekly	OL, RCT Patients 18 to 70 years of age with hepatitis C previously untreated	N=431 24 (genotypes 2 and 3)	Primary: SVR, safety Secondary: Not reported	Primary: Overall, SVR rates were significantly higher with peginterferon alfa-2a compared to peginterferon alfa-2b (66 vs 54%; OR, 1.71; 95% CI, 1.14 to 2.57; *P*=0.02). There were similar rates of post-treatment relapse between the two treatments (16 vs 18%; *P*=0.6).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs peginterferon alfa-2b 1.5 µg/mg weekly All patients received ribavirin.	with serum HCV RNA, higher than normal ALT activity and a diagnostic liver biopsy done in the previous 24 months	or 48 weeks (genotypes 1 and 4) (plus 24 weeks of follow up)		SVR rates achieved by patients receiving peginterferon alfa-2a were significantly higher compared to patients receiving peginterferon alfa-2b with genotype 1 (48 [95% CI, 38 to 59] vs 32% [95% CI, 23 to 43]; *P*=0.05) and 2 (96 [95% CI, 88 to 99] vs 82% [95% CI, 73 to 91]; *P*=0.03). Similar SVR rates were seen with both treatments with genotypes 3 (*P*=0.8) and 4 (*P*=0.5). Eighteen and 23 patients receiving peginterferon alfa-2a and alfa-2b discontinued treatment (8 vs 11%; OR, 0.85; 95% CI, 0.34 to 1.65; *P*=0.6). Secondary: Not reported
Brixner et al[30] Peginterferon alfa-2a vs peginterferon alfa-2b All patients received ribavirin.	RETRO Patients ≥18 years of age diagnosed with hepatitis C, treated with a peginterferon product and ribavirin with continuous health plan enrollment; more patients treated with peginterferon alfa-2a were age 40 years or older (*P*<0.0213)	N=3,566 (1,783 matched pairs) 6 to 36 months The follow-up period for patients treated with peginterferon alfa-2a was significantly shorter, by 76 days (*P*<0.0001) than that for peginterferon alfa-2b.	Primary: Treatment persistence, annualized health care costs, annualized hepatitis C-attributable costs Secondary: Not reported	Primary: The median time to discontinuation was 245 days (95% CI, 227 to 268) with peginterferon alfa-2a and 226 days (95% CI, 210 to 238) with peginterferon alfa-2b. The between group differences were not different (*P*=0.0721). With peginterferon alfa-2a, the proportions of patients on therapy at Weeks12, 24 and 48 were 94.60, 76.10 and 33.85%, respectively. With peginterferon alfa-2b, the proportions of patients on therapy at Weeks 12, 24 and 48 were 95.20, 73.60 and 29.40%, respectively. At Week 48, a significantly greater proportion of patients receiving peginterferon alfa-2a were persistent with treatment compared to patients receiving peginterferon alfa-2b (*P*=0.013). (Week 48 reporting only included patients who were followed for at least 48 weeks). Mean annualized health care costs for patients receiving peginterferon alfa-2a were significantly lower compared to peginterferon alfa-2b ($72,442±118,489 vs $85,801±153,755; *P*=0.006). Mean hepatitis C attributable health care costs for patients receiving peginterferon alfa-2a were significantly lower compared to peginterferon alfa-

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				2b ($48,935±87,220 vs $54,885±58,266; *P*=0.0167). After adjusting for propensity score, peginterferon alfa-2b remained more costly for both annualized total health care costs and HCV attributable health care costs (cost ratio, 1.156 and 1.121 respectively; *P*<0.0001 for both). Secondary: Not reported
Kamal et al[31] Peginterferon alfa-2a 180 µg weekly vs peginterferon alfa-2b 1.5 mg/kg weekly All patients received ribavirin.	MC, OL, PG, PRO, RCT Patients 18 to 60 years of age with proven chronic HCV genotype 4 infection with elevated ALT during the preceding 6 months	N=217 48 weeks (plus 24 weeks of follow up)	Primary: SVR Secondary: Biochemical response, histological response, HRQOL scores, safety	Primary: In the entire cohort, the SVR rate was 59.9%. The SVR rate was significantly higher with peginterferon alfa-2a compared to peginterferon alfa-2b (70.6 vs 54.6%; *P*=0.0172), although the rates of end of treatment response did not differ between the treatments (*P*=0.6772). The discrepancy between rates of SVR and end of treatment response was attributed to the significant difference in relapse rates (5.1 vs 15.7%; *P*=0.0019). Secondary: Time to ALT normalization was no different between the two treatments (14.23±6.07 vs 13.71±5.43 weeks; *P*=0.5098). There was no difference in the proportions of patients who had improvement in liver steatosis (47.61 vs 42.85%; *P*=1.0000), liver fibrosis scores (9.52 vs 4.76%; *P*=1.000) and liver grading scores (61.90 vs 42.85%; *P*=0.3543). During therapy, the enrolled patients, overall and by group, scored significantly lower than population norms in the SF-6D health preference values and nearly all SF-36v2 scores. Significant differences were observed between the two treatments in the physical functioning and vitality domain scores during therapy being lower in patients receiving peginterferon alfa-2a. After completion of therapy, significant differences in the SF-36v2 bodily pain (*P*=0.0189), vitality (*P*=0.0492), social functioning (*P*=0.0498), role emotional (*P*=0.0486) and physical component summary (*P*=0.0190) domain scores, and all CLDQ domains except abdominal symptoms (*P*=0.6139) were observed between the two treatments, being higher in those receiving peginterferon alfa-2a.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Both treatments were tolerated similarly. Overall, there were no differences between the two treatments either in incidence or severity of adverse events.
McHutchison et al[32] IDEAL Peginterferon alfa-2b 1.5 µg weekly plus ribavirin 800 to 1,400 mg/day (standard dose) vs peginterferon alfa-2b 1 µg weekly plus ribavirin 800 to 1,400 mg/day (low dose) vs peginterferon alfa-2a 180 µg weekly plus ribavirin 1,000 to 1,200 mg/day	MC, RCT Patients ≥18 years of age who had compensated liver disease due to chronic hepatitis C genotype 1 infection and a detectable plasma HCV RNA level and who had not been previously treated for hepatitis C infection	N=3,070 48 weeks (plus 24 weeks of follow up)	Primary: SVR, safety Secondary: Virologic response, relapse	Primary: Rates of SVR were similar among the three treatments with a rate of 39.8 (95% CI, 36.8 to 42.8), 38.0 (95% CI, 35.0 to 41.0) and 40.9% (95% CI, 37.9 to 43.9) with standard dose peginterferon alfa-2b, low dose peginterferon alfa-2b and peginterferon alfa-2a (*P*=0.20 for standard vs low dose peginterferon alfa-2b; *P*=0.57 for standard dose peginterferon alfa-2b vs peginterferon alfa-2a). Estimated differences in response rates were 1.8% (95% CI, -2.3 to 6.0) between standard and low dose peginterferon alfa-2b and -1.1% (95% CI, -5.3 to 3.0) between standard dose peginterferon alfa-2b and peginterferon alfa-2a. The two primary endpoints of "superiority" were not met. The types and frequencies of adverse events were similar among all three treatments, with the most common adverse events reported including influenza-like symptoms, depression, anemia and neutropenia. The proportions of patients with neutropenia who met the criterion for peginterferon dose reduction were 19.4, 12.5 and 21.1% with the three treatments. The proportions of patients meeting the hemoglobin criterion for a ribavirin dose reduction was higher with standard dose peginterferon alfa-2b and alfa-2a (28.2 and 25.8%) compared to the low dose peginterferon alfa-2b (23.2%). Most psychiatric adverse events were mild or moderate and were treatment-limiting. Twelve patients died during the trial; seven patients during the treatment phase and five patients during the follow up phase. Two of the deaths were considered to be possibly related to study medications. Secondary: Response rates at the end of the treatment phase were higher with peginterferon alfa-2a (64.4%) compared to either treatment regimen of peginterferon alfa-2b (standard dose, 53.2%; low dose, 49.2%; *P*=0.04 standard dose vs low dose peginterferon alfa-2b and *P*<0.001 standard dose peginterferon alfa-2b vs peginterferon alfa-2a). Virologic relapse was higher

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				with peginterferon alfa-2a group (31.5 vs 23.5 and 20.0%; *P* values not reported).
Muir et al[33] Peginterferon alfa-2b 1.5 µg weekly plus ribavirin 800 to 1,400 mg/day vs peginterferon alfa-2b 1 µg weekly plus ribavirin 800 to 1,400 mg/day vs peginterferon alfa-2a 180 µg weekly plus ribavirin 1,000 to 1,200 mg/day	Post hoc analysis of the IDEAL trial based on racial and ethnic groups[29] Patients ≥18 years of age who had compensated liver disease due to chronic hepatitis C genotype 1 infection and a detectable plasma HCV RNA level and who had not been previously treated for hepatitis C infection	N=3,070 48 weeks (plus 24 weeks of follow up)	Primary: SVR Secondary: Virologic response, relapse	Primary: Overall, SVR rates were highest among Asian American patients (59%), similar for white (44%) and Hispanic patients (38%) and lowest for African American patients (22%) (*P* values not reported). Similar trends in SVR rates were seen within the racial groups despite different treatment regimens. Secondary: End of treatment response rates were, respectively, 76, 61, 55 and 33% in Asian American, white, Hispanic and African American patients (*P* values not reported). Relapse rates were 20, 25 and 29% for Asian Americans, whites and for both African American and Hispanic patients (*P* values not reported).
Singal et al[34] Peginterferon alfa-2a vs peginterferon alfa-2b	MA, SR (9 RCTs) Treatment-naïve patients with chronic HCV infection	N=3,546 Duration varied	Primary: SVR, safety Secondary: Not reported	Primary: Pooled analysis demonstrated the odds of achieving an SVR was higher by 36% with peginterferon alfa-2a compared to peginterferon alfa-2b (53 vs 48%; OR, 1.36; 95% CI, 1.07 to 1.73). The odds of treatment discontinuation due to a serious adverse event were similar with the two treatments (11 vs 12%; OR, 0.66; 95% CI, 0.37 to 1.16). Secondary: Not reported
Bernstein et al[35] Interferon alfa-2a 6	MA (3 MC, OL, RCT) Adult patients with	N=1,441 72 weeks	Primary: Relationship between SVR	Primary: SVR was associated with marked improvements in quality of life and fatigue from baseline to end of follow up in all patients (all *P*<0.01).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
MIU 3 times weekly for 12 weeks, followed by 3 MIU 3 times weekly for 36 weeks or 3 MIU 3 times weekly for 48 weeks vs peginterferon alfa-2a 90, 135 or 180 µg weekly	hepatitis C not previously treated with interferon-based therapy		and SF-36 and fatigue severity scale, determine whether impairment of quality of life during treatment contributes to early treatment discontinuation, comparison of quality of life between treatments Secondary: Not reported	Baseline to 24 week changes in fatigue and SF-36 mental and physical summary scores significantly predicted treatment discontinuation (all *P*<0.05). During treatment, patients receiving peginterferon had significantly better scores on both the SF-36 (*P*<0.04) and fatigue severity scale (*P*<0.02). SVR was associated with improvements in quality of life in patients with hepatitis C. Secondary: Not reported
Carrat et al[36] Interferon alfa-2b 3 MIU 3 times weekly for 48 weeks vs peginterferon alfa-2b 1.5 µg/kg weekly for 48 weeks All patients received ribavirin 800 mg/day.	RCT Adult HIV infected patients with a confirmed diagnosis of hepatitis C not previously treated with interferon alfa	N=412 72 weeks	Primary: SVR at week 72 Secondary: Histological improvement as measured by Metavir score and Ishak grade	Primary: SVR rates were significantly higher with peginterferon compared to interferon (27 vs 20%; *P*=0.01). Secondary: Metavir scores decreased significantly with peginterferon (-0.19 vs 0.01; *P*=0.02). Mean changes in Ishak score were -0.57 and -0.26 with peginterferon and interferon (*P*=0.24). Doses of peginterferon were modified in 16% of patients due to clinical adverse events compared to seven percent of patients with interferon (*P*=0.004). Dose adjustments due to laboratory abnormalities occurred in 20% of patients receiving peginterferon and seven percent of patients with interferon (*P*=0.004). Treatment discontinuation due to an adverse event was comparable between the two treatments.
Chung et al[37] Interferon alfa-2a 6	RCT Adult HIV infected	N=133 48 weeks	Primary: Virologic response at 24	Primary: At 24 weeks, 44 and 15% of patients receiving peginterferon and interferon had a virologic response (*P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
MIU 3 times weekly for 12 weeks, followed by 3 MIU 3 times weekly for 36 weeks vs peginterferon alfa-2a 180 µg weekly for 48 weeks All patients received ribavirin.	patients with a confirmed diagnosis of hepatitis C not previously treated with interferon alfa	(plus 24 weeks of follow up)	weeks Secondary: SVR, virologic response at end of treatment, histologic response, changes in HIV control	Secondary: SVR 24 weeks after treatment was reported in 27 and 12% of patients receiving peginterferon and interferon (*P*<0.03). At the end of treatment, 41 and 12% of patients receiving peginterferon and interferon had a virologic response (*P*<0.001). In patients without a virologic response, histologic response was reported in 35 and 36% of patients receiving peginterferon and interferon (*P* value not reported). CD4 cell counts increased in 3.5 and 3.0% of patients receiving peginterferon and interferon (*P* value not reported). Rates of influenza-like symptoms, depression and decreases in hemoglobin occurred at comparable rates between the two treatments. Eight patients in each treatment group withdrew from the trial due to an adverse event or laboratory value abnormality.
Lindsay et al[38] Interferon alfa-2b 3 MIU 3 times weekly vs peginterferon alfa-2b 0.5, 1 or 1.5 µg/kg weekly	RCT Adult patients with hepatitis C and compensated liver disease not previously treated	N=1,219 48 weeks (plus 24 weeks of follow up)	Primary: SVR Secondary: Normalization of ALT, improvement of liver histology	Primary: For all three doses of peginterferon, SVR was significantly higher compared to interferon (*P*≤0.042). Secondary: At the end of therapy, normal ALT values were significantly higher with peginterferon 1 (31%; *P*=0.002) and 1.5 µg/kg (33%; *P*<0.001) compared to interferon (20%). There were no differences between peginterferon 0.5 µg/kg and interferon. All three doses of peginterferon decreased liver inflammation to a greater extent compared to interferon (*P* values not reported). The incidence and severity of adverse events were similar between the treatments. Peginterferon did demonstrate a higher incidence of injection site reactions (*P* values not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Zeuzem et al[39] Interferon alfa-2a 6 MIU 3 times weekly for 12 weeks, followed by 3 MIU 3 times weekly for 36 weeks vs peginterferon alfa-2a 180 µg weekly for 48 weeks	RCT Interferon-naïve adult patients with a confirmed diagnosis of hepatitis C	N=531 72 weeks	Primary: Virologic response at 72 weeks, ALT normalization at 72 weeks Secondary: Not reported	Primary: At 72 weeks, 39 and 19% of patients receiving peginterferon and interferon had a virologic response (*P*=0.001). At 72 weeks, sustained normalization of ALT occurred in 45 and 25% of patients receiving peginterferon and interferon (*P*=0.001). The frequency and severity of drug-related adverse events were comparable between the two treatments. Depression occurred in 16 and 23% of patients receiving peginterferon and interferon (*P* value not reported). Psychiatric disorders were reported in six patients receiving peginterferon and four patients receiving interferon (*P* value not reported). Secondary: Not reported
Rasenack et al[40] Interferon alfa-2a 6 MIU 3 times weekly for 12 weeks, followed by 3 MIU 3 times weekly for 36 weeks vs peginterferon alfa-2a 180 µg weekly for 48 weeks Patients originally participated in an efficacy study conducted by Zeuzem et al.[39]	RCT Interferon-naïve adult patients with a confirmed diagnosis of hepatitis C	N=531 48 weeks	Primary: Quality of life measured by SF-36, fatigue measured by the fatigue severity scale Secondary: Not reported	Primary: At weeks two and 12, a significantly higher quality of life score was observed with peginterferon compared to interferon (*P*<0.05). No significant difference was observed between treatments at 24 or 48 weeks. At weeks two, 12 and 24, significantly less disabling fatigue was observed with peginterferon compared to interferon (*P*<0.01). No significant difference was observed between treatments at 48 weeks. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Fried et al[41] Interferon alfa-2b 3 MIU 3 time a week plus ribavirin 1,000 to 1,200 mg/day vs peginterferon alfa-2a 180 µg weekly vs peginterferon alfa-2a 180 µg weekly plus ribavirin 1,000 to 1,200 mg/day	RCT Adult patients with a confirmed diagnosis of hepatitis C not previously treated with interferon alfa	N=1,121 48 weeks (plus 24 weeks of follow up)	Primary: SVR Secondary: Virologic response at end of therapy, virologic response for genotypes 1, 2 and 3	Primary: SVR rates were significantly higher with peginterferon plus ribavirin (56%) compared to interferon plus ribavirin (44%; *P*<0.001) and peginterferon (29%; *P*<0.001). Secondary: Virologic response rates at end of therapy were significantly higher with peginterferon plus ribavirin (69%) compared to interferon plus ribavirin (52%; *P*<0.001) and peginterferon (59%; *P*=0.01). SVR rates with genotype 1 were significantly higher with peginterferon plus ribavirin (46%) compared to interferon plus ribavirin (36%; *P*=0.01) and peginterferon (21%; *P*<0.001). SVR rates with genotypes 2 or 3 were significantly higher with peginterferon plus ribavirin (76%) compared to interferon plus ribavirin (61%; *P*=0.005) and peginterferon (45%; *P* value not reported). Withdrawals due to adverse events were comparable between the three treatments (*P* values not reported). The most common reason for discontinuation was a psychiatric disorder. Both peginterferon regimens had a lower incidence of influenza-like symptoms and depression compared to interferon (*P*<0.05).
Manns et al[42] Interferon alfa-2b 3 MIU 3 times a week plus ribavirin 1,000 to 1,200 mg/day vs peginterferon alfa-2a 1.5 µg/kg weekly plus ribavirin 800 mg/day	RCT Adult patients with a confirmed diagnosis of hepatitis C not previously treated	N=1,530 48 weeks (plus 24 weeks of follow up)	Primary: SVR Secondary: SVR with genotypes 1, 2 and 3	Primary: SVR rates were significantly higher with high dose peginterferon (54%) compared to low dose peginterferon (47%; *P*=0.01) and interferon (47%; *P*=0.01). Secondary: The SVR rate with genotype 1 was 42% with high dose peginterferon compared to 34% with low dose peginterferon (*P* value not reported) and 33% with interferon (*P*=0.02 vs high dose peginterferon). The SVR rates with genotypes 2 and 3 were approximately 80% with all treatments (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(high dose) vs peginterferon alfa-2a 1.5 µg/kg weekly for 4 weeks then 0.5 µg/kg weekly plus ribavirin 1,000 to 1,200 mg/day (low dose)				The side effect profiles were comparable among the treatments.
Zhao et al[43] Peginterferon (peginterferon alfa-2a, peginterferon alfa-2b) vs interferon (interferon alfa-2a, interferon alfa-2b, interferon alfa-1b) All patients received ribavirin.	MA (18 RCTs) Chinese patients with chronic hepatitis C infection	N=1,148 24 (genotypes 2 and 3) or 48 weeks (plus 24 weeks of follow up)	Primary: SVR, safety Secondary: Not reported	Primary: SVR rates were significantly higher with peginterferon compared to interferon (64 [n=659] vs 40% [n=489]; RR, 1.56; 95% CI, 1.28 to 1.91; *P*<0.01), but the difference between peginterferon alfa-2b and interferon alfa-2b was not significant. Patients had a greater likelihood of achieving SVR with peginterferon alfa-2a. Patients with genotype 1 had a greater likelihood of achieving an SVR (53 vs 28%; RR, 1.66; 95% CI, 0.46 to 5.94; *P*>0.05). Withdrawal rates were similar between patients receiving peginterferon and interferon. The differences in the overall adverse events or intercurrent illnesses reported in the included trials between patients receiving peginterferon or interferon were not significant. Secondary: Not reported
Poordad et al[44] SPRINT-2 Group 1 (control): Peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 600 to 1,400 mg/day for 44 weeks vs	PC, PG, RCT Patients ≥18 years of age with a history of no previous treatment for HCV infection, weight 40 to 125 kg, chronic infection with HCV genotype 1 and plasma HCV RNA level	N=1,097 (n=938 [nonblack], n=159 [black]) 48 weeks (plus 24 weeks of follow up)	Primary: SVR, safety Secondary: Not reported	Primary: Among nonblack patients, the rate of SVR was 40, 67 and 68% in Groups 1, 2 and 3 (*P*<0.001 vs Group 1 for both Group 2 and 3). The corresponding numbers in black patients were 23, 42 (*P*=0.04 vs Group 1) and 53% (*P*=0.004 vs Group 1). Subgroup analyses revealed that at four weeks, 23 and 38% of nonblack and black patients had a decrease of <1 $\log_{10}$ IU/mL in HCV RNA level from baseline, which was associated with lower rates of SVR and higher rates of boceprevir-resistance-associated variants compared to those achieving a decrease of ≥1 $\log_{10}$ IU/mL from baseline. However, regardless of the degree of reduction achieved at week four, patients

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Group 2 (response guided therapy): boceprevir 800 mg three times a day plus peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 600 to 1,400 mg/day for 24 weeks, followed by an additional 20 weeks of peginterferon alfa-2b plus ribavirin in detectable HCV RNA levels at any visit from week 8 to 24 vs Group 3 (fixed duration therapy): boceprevir 800 mg three times a day plus peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 600 to 1,400 mg/day for 44 weeks All patients entered a 4 week lead in period in which peginterferon alfa-2b and ribavirin were administered. The trial consisted of	≥10,000 IU/mL			receiving boceprevir achieved consistently higher rates of SVR compared to patients who received control overall. Adverse events occurred in more than 98% of all patients, with serious adverse events in 9, 11 and 12% of patients in Groups 1, 2 and 3, respectively. There were six deaths during the trial; four deaths in Group 1 and two deaths from boceprevir-containing regimens. Two suicides (one in Group 1 and one in Group 2) were determined to have possibly been related to treatment with peginterferon. Fatigue, headache and nausea were the most commonly reported adverse events. The incidence of dysgeusia was higher with boceprevir treatment. Anemia was reported in 29 and 49% of patients receiving control and boceprevir, respectively. Overall, 13 and 21% of control- and boceprevir-treated patients required dose reductions because of anemia and erythropoietin was administered in 24 and 43% of patients. Neutropenia and thrombocytopenia also occurred more frequently with boceprevir treatment. Secondary: Not reported Response rates at the end of therapy (undetectable HCV RNA level at the time that the study therapy was discontinued) were significantly higher with boceprevir-containing regimens compared to the control regimen. Among nonblack patients, viral breakthrough (undetectable HCV RNA level and subsequent occurrence of an HCV RNA level >1,000 IU/mL) occurred in one to two percent of all patients, regardless of treatment regimen. In addition, relapse rates (undetectable HCV RNA level at the end of treatment but a detectable HCV RNA level at some point during the follow up period) were lower with boceprevir compared to control. The numbers of events among black patients were too few to permit comparison between the treatment groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
two cohorts enrolling nonblacks and blacks separately. Treatment was considered complete in Group 2 if the HCV RNA level was undetectable from week 8 through week 24 (total duration, 28 weeks). In all 3 treatment groups, treatment was discontinued for all patients with a detectable HCV RNA level at week 24 based on futility rules; these patients then entered the follow up period.				
Sherman et al[45] ILLUMINATE Peginterferon alfa-2a 180 µg weekly plus ribavirin 1,000 to 1,200 mg/day plus telaprevir 750 mg three times a day for 12 weeks (T12PR12), followed by peginterferon alfa-2a	MC, NI, OL, RCT Patients 18 to 70 years of age with chronic hepatitis C genotype 1 infection for ≥6 months, no previous treatment and with no hepatitis B or HIV	N=540 24 or 48 weeks (plus 24 weeks of follow up)	Primary: SVR in T12PR24 compared to T12PR48 Secondary: Not reported	Primary: The absolute difference in SVR rate between T12PR24 vs T12PR48 was four percentage points (92 vs 88%; 95% CI, -2 to 11). The lower limit of this 95% CI (-2%) exclude the NI margin -10.5%. The SVR rate in patients who did not achieve an extended rapid virologic response therefore received a total of 48 weeks of treatment was 64% (76/118) Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
plus ribavirin for 12 or 36 weeks. Patients who achieved an extended rapid virologic response (undetectable HCV RNA levels at weeks 4 and 12) after 20 weeks were randomized to continue peginterferon alfa-2a plus ribavirin for an additional 4 (24 weeks total treatment; T12PR24) or 28 weeks (48 total weeks of treatment; T12PR48). Patients who did not achieve an extended rapid virologic response after 20 weeks received peginterferon alfa-2a plus ribavirin for an additional 28 weeks (48 total weeks of treatment).				
Jacobson et al[46] ADVANCE Telaprevir 750 mg three times a day plus	DB, PC, PG, RCT Patients 18 to 70 years of age with chronic HCV genotype 1	N=1,088 48 weeks (plus 24 weeks of follow up)	Primary: SVR Secondary: Proportion of	Primary: SVR rates were significantly higher with telaprevir-containing regimens compared to control (75, 69 and 44% with T12PR, T8PR and control (*P*<0.001 for T12PR and T8PR vs control).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
peginterferon alfa-2a 180 µg weekly and ribavirin 1,000 or 1,200 mg/day for 12 weeks, followed by an additional 12 or 36 weeks of peginterferon alfa-2a plus ribavirin based on HCV RNA levels weeks 4 and 12 (T12PR) vs telaprevir 750 mg three times a day plus peginterferon alfa-2a 180 µg weekly and ribavirin 1,000 or 1,200 mg/day for 8 weeks, followed by an additional 16 or 40 weeks of peginterferon alfa-2a plus ribavirin based on HCV RNA levels weeks 4 and 12 (T8PR) vs peginterferon alfa-2a 180 µg weekly plus ribavirin 1,000 or	infection with no previous treatment		patients with undetectable HCV RNA at week 72, four, 12 or both four and 12, at the end of treatment and 12 weeks after the last planned dose of treatment; safety	Secondary: Seventy three, 67 and 44% of patients receiving T12PR, T8PR and control had undetectable HCV RNA 72 weeks after starting treatment (*P*<0.001 for T12PR and T8PR vs control). Sixty eight, 66 and nine percent of patients, respectively, had undetectable HCV RNA at week four (rapid virologic response), and 58, 57 and eight percent of patients, respectively, had undetectable HCV RNA at weeks four and 12 (extended rapid virologic response) (*P* values not reported). Among patients with an extended rapid virologic response assigned to receive a total of 24 weeks of therapy, SVR rates were 89 and 83% with T12PR and T8PR (*P* value not reported). Among patients who had undetectable HCV RNA levels after the last dose of treatment, relapse rates were nine, nine and 28% with T12PR, T8PR and control (*P* values not reported). Subgroup analyses demonstrated that SVR rates were higher with telaprevir-containing regimens. Subgroup analyses included HCV genotype subtype (1a and 1b), African Americans, baseline HCV RNA levels (≥800,000 IU) and bridging fibrosis or cirrhosis. The incidence of gastrointestinal disorders, pruritis, rash and anemia was ≥10 percentage points higher with telaprevir-containing regimens. A total of 10, 10 and seven percent of patients receiving T12PR, T8PR and control discontinued all treatment at some time during the trial owing to adverse events (*P* values not reported); with seven, eight and four percent of these patients discontinuing during the telaprevir (or placebo) phase. Anemia and rash were the most frequently reported adverse events that lead to discontinuation. One case of Stevens-Johnson syndrome occurred approximately 11 weeks after the last dose of telaprevir had been administered.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
1,200 mg/day for 48 weeks (control) Patients in the T12PR and T8PR groups who met criteria for an extended rapid virologic response (undetectable HCV RNA at weeks 4 and 12) received 12 additional weeks of treatment with peginterferon alfa-2a plus ribavirin (24 total weeks of treatment). Patients who had detectable HCV RNA either at week 4 or 12 received an additional 36 weeks of peginterferon alfa-2a plus ribavirin (48 total week of treatment).				
Hepatitis C – Retreatment				
Di Bisceglie et al[47] Peginterferon alfa-2a 90 µg weekly (low dose) vs no treatment	Post hoc analysis of the MC, PRO, RCT HALT-C study Patients ≥18 years of age HCV RNA positive or serology positive for HCV antibody, bridging fibrosis or cirrhosis who	N=1,050 5.7 years (median)	Primary: Mortality rates Secondary: Not reported	Primary: A total of 122 (12%) deaths occurred among the 1,050 patients over a median period of 5.7 years (range, zero to eight). Seventy four (seven percent) patients underwent liver transplantation, 10 of whom subsequently died and were included in the total number of deaths. Fifty three (43%) deaths occurred during the randomized phase of the trial, defined as 3.8 years after randomization when patients were being treated

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Patients received peginterferon alfa-2a 180 µg weekly plus ribavirin 1,000 to 1,200 mg/day during a 24 week lead-in period. If after 20 weeks, virus was still present in the blood, patients were randomized to the above treatment regimens. Patients who cleared the virus by week 20 continued treatment for a full 48 weeks.	had been previously treated with interferon ≥12 weeks, with or without ribavirin, but still had persistent viremia			actively with peginterferon or followed on no therapy. The remaining 69 (57%) deaths occurred after the conclusion of the randomized phased when all patients were being followed but no treatment was offered. More deaths occurred in patients in the cirrhosis stratum (n=80) than in the fibrosis stratum (n=42; *P*<0.0001). Seven year cumulative mortality rates were more than two times higher in patients with cirrhosis (27 vs 11%), which was equivalent to average annual death rates of 3.9% with cirrhosis and 1.5% with fibrosis. Similarly, the distributions of the combined outcome of death or liver transplantation differed significantly in the two strata (*P*<0.0001), resulting in seven year cumulative rates of 36 and 16%. Of the 122 deaths, 76 (62%) and 46 (38%) were categorized as liver- and nonliver-related. The proportion of liver-related deaths was slightly higher among patients with cirrhosis compared to fibrosis (65 vs 57%; *P*=0.39). Overall, the death rate was higher in patients receiving treatment (cumulative seven year death rate, 20 vs 15%; *P*=0.049). The mortality rates began to separate after three years of treatment and continued to separate during the two to three years of follow up after treatment. The difference in mortality rates between patients in the treatment and control groups was significant in the cirrhosis stratum (*P*=0.01) only. Similar results were observed when liver transplantation and death were combined into one outcome (n=186; 18%). The rates of death or transplantation were slightly higher among treated patients vs control patients (seven year cumulative death rate, 25 vs 24%; *P*=0.45). When separated by fibrosis stratum the difference was significant (19 vs 12%; *P*=0.02). When causes of death were categorized by liver-relatedness, the excess mortality in the treatment groups fibrosis stratum was primarily from nonliver causes (seven year cumulative death rate, 8 vs 4%; *P*=0.03). Most deaths occurred well after peginterferon treatment was stopped, with only eight patients (11%) dying within two months of receiving treatment.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
Camma et al (abstract)[48] Peginterferon plus ribavirin	MA (14 trials) Patients with chronic hepatitis C who did not respond to standard or pegylated interferon plus ribavirin therapy	N=not reported Duration not specified	Primary: SVR Secondary: Not reported	Primary: Pooled estimate of the SVR rate was 16.3% (95% CI, 8.3 to 29.6). By meta-regression, higher SVR rates were observed in trials with a lower prevalence of subjects with HCV genotype 1 and overweight patients. The use of a 24 week retreatment stopping rule did not affect SVR rates. Secondary: Not reported
Rustgi et al[49] Peginterferon alfa-2a 180 µg weekly plus ribavirin 1,000 to 1,200 mg/day Treatment was discontinued in patients with detectable HCV RNA after 12 weeks of therapy.	MC, OL Patients ≥18 years of age with HCV genotype 1 who did not tolerate (e.g., depression, fatigue, flu-like symptoms, injection-site reactions) or achieve early virologic response with up to 12 weeks of therapy with peginterferon alfa-2b plus ribavirin	N=57 36 (non-tolerants) or 60 weeks (non-responders) (plus 24 weeks of follow up)	Primary: SVR, safety Secondary: Not reported	Primary: Among patients who did not previously tolerate peginterferon alfa-2b, 92% (23/25) were HCV RNA negative after 12 weeks of therapy and 56% (14/25) achieved SVR. Among previous nonresponders, 13% (4/32) achieved an early virologic response with peginterferon alfa-2a and three percent (1/32) achieved SVR. Secondary: Not reported
Husa et al[50] Peginterferon alfa-2a 180 µg weekly plus ribavirin 1,000 to 1,200 mg/day	MC, OL Treatment experienced patients ≥18 years of age with serologically and histologically proven chronic hepatitis C genotype 1	N=203 48 weeks (plus 24 weeks of follow up)	Primary: SVR Secondary: Safety	Primary: The SVR rate was 31% (n=63). SVR rates were higher (38.1%) among patients with earlier breakthrough or relapse to therapy, and lower (23.9%) among those with previous nonresponse. Higher SVR rates were observed in patients without cirrhosis, in those with a lower baseline viral load (≤800,000 IU/mL) and in those ≤40 years. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	and detectable HCV RNA			Overall, 49 (21.4%) patients prematurely withdrew from treatment, with a lack of efficacy being the most commonly cited reason (11.8%), and withdrawal due to an adverse event representing a smaller proportion of patients (5.4%). Of these patients, one, seven and three withdrew due to adverse events during weeks one to 12, 13 to 24 and 25 to 48, respectively. Thirteen (6.4%) patients reported at least one serious adverse event and of these, five were judged to be treatment-related. The most commonly reported adverse events of special interest included hematological disorders. No patient reported a psychiatric disorder, and only three patients reported a respiratory event or infection considered to be treatment-related. One patient with hepatic cirrhosis died during treatment due to cardiac failure.
Jensen et al[51] Peginterferon alfa-2a 360 µg weekly for 12 weeks, followed by peginterferon alfa-2a 180 µg weekly for 60 weeks (Group A) vs peginterferon alfa-2a 360 µg weekly for 12 weeks, followed by peginterferon alfa-2a 180 µg weekly for 36 weeks (Group B) vs peginterferon alfa-2a	OL, PG, RCT Patients ≥18 years of age with serologic evidence of chronic hepatitis C; quantifiable serum HCV RNA levels (>600 IU/mL) and histologic findings on a liver biopsy specimen consistent with the diagnosis of chronic hepatitis C; patients were required to have a prior non-response to ≥12 weeks of combination therapy with peginterferon-alfa 2b (≥1 µg/kg/week) plus ribavirin (≥800 mg/day) and have	N=950 (Total) N=318 (Group A) N=158 (Group B) N=158 (Group C) N=316 (Group D) 48 to 72 weeks (plus 24 weeks of follow up)	Primary: SVR rates in Group A compared to Group D Secondary: Not reported	Primary: SVR rates in Groups A (72 weeks of treatment) and D (48 weeks of treatment) were 16 and 9% (RR, 1.80; 95% CI, 1.17 to 2.77; *P*=0.006). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
180 µg weekly for 72 weeks (Group C) vs peginterferon alfa-2a 180 µg weekly for 48 weeks (Group D) All patients received ribavirin 1,000 to 1,200 mg/day.	detectable serum HCV RNA after baseline assessment; treatment must have been discontinued ≥12 weeks before enrollment			
Poynard et al[52] Peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 800 to 1,400 mg/day	OL, PRO Patients 18 to 65 years of age with chronic hepatitis C and significant hepatic fibrosis/cirrhosis who failed combination therapy with nonpegylated or peginterferon plus ribavirin therapy, with HCV RNA polymerase chain reaction positivity, hepatic fibrosis, compensated liver disease, hemoglobin ≥12 g/dL for women and ≥13 g/dL for men, absolute neutrophil count ≥1,500/mm^3, platelet count ≥80,000/mm^{3}and	N=2,312 Up to 48 weeks (plus 24 weeks of follow up)	Primary: Response to treatment Secondary: Not reported	Primary: Twenty two percent of patients attained SVR. Among patients who did not respond to previous treatment or who relapsed, patients previously treated with interferon plus ribavirin responded better than those previously treated with peginterferon plus ribavirin (18 vs 6% and 43 vs 33%, respectively; *P* values not reported). Relapsers responded better to retreatment than nonresponders, regardless of previous treatment (*P* value not reported). Response rates for patients previously treated with peginterferon alfa-2b were similar to those previously treated with peginterferon alfa-2a (17 and 18%; *P* value not reported). Patients with HCV genotypes 2 or 3 responded better than patients with HCV genotype 1 (59 and 55 vs 15%; *P* values not reported). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	body weight of 40 to 125 kg			
Bacon et al[53] RESPOND-2 Group 1 (control): Peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 600 to 1,400 mg/day for 44 weeks vs Group 2 (response guided therapy): boceprevir 800 mg three times a day plus peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 600 to 1,400 mg/day for 32 weeks, followed by an additional 12 weeks of peginterferon alfa-2b plus ribavirin in detectable HCV RNA levels at week 8 but undetectable at week 12 vs Group 3 (fixed duration therapy): boceprevir 800 mg	PC, PG, RCT Patients with chronic HCV genotype 1 infection who demonstrated responsiveness to interferon (minimum duration of therapy, 12 weeks)	N=403 48 weeks (plus 24 weeks of follow up)	Primary: SVR, safety Secondary: Proportion of patients with an early response in whom a SVR was achieved, proportion of patients with a relapse	Primary: Rates of SVR were significantly higher with boceprevir-containing regimens compared to control, with overall rates of SVR of 21, 59 and 66% in Groups 1, 2 and 3, respectively (P<0.001). The increase observed with Groups 2 and 3 was largely due to end of treatment rates of response being higher (70 and 77 vs 31%) and relapse rates being lower (15 and 12 vs 32%) compared to Group 1. The absolute difference between Groups 2 and 1 was 34.7 percentage points (95% CI, 25.7 to 49.1), and between Groups 3 and 1 it was 45.2 percentage points (95% CI, 33.7 to 56.8). There was no difference in SVR rates between Groups 2 and 3 (OR, 1.4; 95% CI, 0.9 to 2.2). Overall, the most common adverse events were flulike symptoms, while dysgeusia, rash and dry skin were more commonly reported with boceprevir-containing regimens. A greater proportion of patients receiving boceprevir reported serious adverse events, and there were more discontinuations and dose modifications due to adverse events with boceprevir. Anemia occurred more frequently with boceprevir (43 to 46 vs 20%), and erythropoietin was administered more frequently to patients receiving boceprevir. Secondary: The proportion of patients with an undetectable HCV RNA level at week eight in Groups 2 and 3 (46 and 52%) was approximately six times the proportion in Group 1 (9%). Early response was associated with a high rate of SVR in all three treatment groups (100, 86 and 88% in Groups 1, 2 and 3; P values not reported). The rates of SVR among patients with prior relapse (undetectable HCV RNA level at the end of prior therapy, without subsequent attainment of a SVR) were 29, 69 and 75% in Groups 1, 2 and 3; respectively (P values not reported). And the patients with prior nonresponse (a decrease in the HCV RNA level of ≥2 $\log_{10}$ IU/mL by week 12 of prior therapy but a detectable HCV RNA level throughout the course of prior therapy, without subsequent attainment of a SVR), the corresponding rates were 7, 40 and 52% (P values

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
three times a day plus peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 600 to 1,400 mg/day for 44 weeks All patients entered a 4 week lead in period in which peginterferon alfa-2b and ribavirin were administered. Treatment was considered complete in Group 2 if the HCV RNA level was undetectable at weeks 8 and 12 (total duration, 36 weeks). In addition, in all 3 treatment groups, treatment was discontinued for all patients with a detectable HCV RNA level at week 12 based on futility rules; these patients then entered the follow up period.				not reported). Virologic breakthrough (achievement of an undetectable HCV RNA level and subsequent occurrence of an HCV RNA level >1,000 IU/mL) and incomplete virologic response (an increase of 1 $\log_{10}$ IU/mL in the HCV RNA level from the nadir, with an HCV RNA level >1,000 IU/mL) were infrequent during the treatment period. Multivariable stepwise logistic-regression analysis served to identify five baseline factor that were significantly associated with achievement of a SVR: assignment to boceprevir (OR for Groups 2 and 3 vs Group 1, 7.3 and 10.7, respectively; *P*<0.001 for both), previous relapse (OR vs previous nonresponse, 3.1; *P*<0.001), low viral load at baseline (OR vs high load, 2.5; *P*=0.02) and absence of cirrhosis (OR vs presence, 2.1; *P*=0.04).
Zeuzem et al[54] REALIZE Telaprevir 750 mg	DB, PC, RCT Patients 18 to 70 years of age with chronic	N=662 48 weeks (plus 24 weeks	Primary: SVR Secondary:	Primary: Compared to control, SVR rates were significantly higher with telaprevir-containing regimens in patients who had a previous relapse (83, 88 and 24% with T12PR48, Lead-in T12PR48 and control), for those who did not have a

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
three times a day plus peginterferon alfa-2a 180 µg weekly plus ribavirin 1,000 to 1,200 mg/day for 12 weeks, followed by an additional 36 weeks of peginterferon alfa-2a plus ribavirin (T12PR48) vs peginterferon alfa-2a 180 µg weekly plus ribavirin 1,000 or 1,200 mg/day for 4 weeks, followed by telaprevir 750 mg three times a day plus peginterferon alfa-2a 180 µg weekly and ribavirin 1,000 to 1,200 mg/day for 12 weeks, followed by an additional 32 weeks of peginterferon alfa-2a plus ribavirin (Lead-in T12PR48) vs peginterferon alfa-2a 180 µg weekly and ribavirin 1,000 to	HCV genotype 1 infection, no SVR to 1 previous course of peginterferon alfa and ribavirin despite receiving at least 80% of the intended dose	of follow up)	Effect of lead-in treatment with peginterferon alfa-2a plus ribavirin on SVR, proportion of patients who had undetectable HCV RNA at four and eight weeks, relapse, change from baseline in $\log_{10}$ HCV RNA, safety	previous virologic response (41, 41 and 9%), including those who had a partial response (59, 54 and 15%) and those who had no response (29, 33 and 5%) (*P*<0.001 for all comparisons). SVR rates were similar with T12PR48 and Lead-in T12PR48 among patients who had a relapse or no response or a partial response to previous therapy (*P* values not reported). Secondary: Overall, SVR rates were 64, 66 and 17% with T12PR48, Lead-in T12PR48 and control. Differences was 47 percentage points between T12PR48 and control (95% CI, 37 to 57; *P*<0.001) and 50 percentage points between Lead-in T12PR48 and control (95% CI, 40 to 60; *P*<0.001). In patients with a previous relapse, the proportion of patients with an undetectable HCV RNA were 70 and 93, three and 89 and three and 10% with T12PR48, Lead-in T12PR48 and control (*P* values not reported). In patients with a previous partial response, the corresponding proportions were 65 and 82, zero and 65 and zero and zero percent (*P* values not reported). Relapse rates were lower with telaprevir-containing regimens among patients who had a previous relapse or no response or a partial response to previous therapy. Changes in $\log_{10}$ HCV RNA levels are provided in graphic form only. The most frequently reported adverse events (>25% of patients) with telaprevir were fatigue, pruritus, rash, nausea, influenza-like illness, anemia and diarrhea. Serious adverse events (12 vs 5%) and those leading to treatment discontinuation (13 vs 3%) were more frequent with telaprevir.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
1,200 mg/day for 48 weeks (control) Patients could have 1 of 3 previous responses to peginterferon alfa plus ribavirin therapy; no response (reduction <2 log_{10} in HCV RNA after 12 weeks of therapy), partial response (reduction ≥2 log_{10} in HCV RNA after 12 weeks of therapy but with detectable HCV RNA) or relapse (undetectable HCV RNA at the end of a previous course of therapy with HCV RNA positivity thereafter).				
Hepatitis C - Varying Treatment Duration				
Mecenate et al[55] Peginterferon alfa-2a 180 µg week plus ribavirin 800 to 1,200 mg/day If HCV RNA after 4 weeks of treatment was <50 IU/mL (rapid	OL Patients with HCV genotype 2 or 3 infection, ALT >40 IU/L and histologically proven chronic hepatitis C	N=210 12 to 24 weeks (plus 24 weeks of follow up) (72 patients achieved rapid virologic response and	Primary: SVR Secondary: Safety	Primary: SVR rates were the following: Group 1, 83% (60/72 patients); Group 2, 75% (53/71 patients) and Group 3, 49% (33/67 patients) (*P* values not reported). Secondary: From Group 2, five patients (7%) withdrew from the trial due to adverse events and seven patients (10%) from Group 3 withdrew due to adverse events. Significantly more patients in group 3 (seven patients) discontinued the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
virologic response), patients were randomized to 12 (Group 1) or 24 weeks of treatment (Group 2); those with HCV RNA ≥50 IU/mL after 4 weeks were treated for 24 weeks (Group 3).		received 12 weeks of treatment, 71 patients achieved rapid virologic response and received 24 weeks of treatment and 67 patients did not achieve rapid virologic response and received 24 weeks of treatment)		medication due to adverse events than Group 1 (zero patients; *P*<0.05).
Liu et al[56] Peginterferon alfa-2a 180 µg weekly for 24 weeks vs peginterferon alfa-2a 180 µg weekly for 48 weeks All patients received ribavirin 1,000 to 1,200 mg/day.	MC, OL, PG, RCT Patients >18 years of age who were treatment-naïve with a presence of anti-HCV antibodies, a detectable serum HCV RNA level for >6 months, HCV 1 infection, ALT level greater than the upper limit of normal and liver histologic characteristics consistent with chronic viral hepatitis within the previous 3 months	N=308 24 or 48 weeks (plus 24 weeks of follow up)	Primary: SVR Secondary: Histologic response rates, ALT normalization	Primary: Patients who received 48 weeks of treatment had a significantly higher SVR rate compared to those who received 24 weeks of treatment (76 vs 56%; *P*<0.001). Secondary: At the end of follow up, patients who received 48 weeks of treatment had a significantly higher histologic response rate (78 vs 59%; *P*=0.001) and ALT normalization rate (72 vs 51%; *P*<0.001) compared to those who received 24 weeks of treatment.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Shiffman et al[57] Peginterferon alfa-2a 180 µg weekly for 16 weeks vs peginterferon alfa-2a 180 µg weekly for 24 weeks All patients received ribavirin 800 mg/day.	MC, NI, RCT Patients ≥18 years of age diagnosed with HCV genotype 2 or 3 infection, HCV RNA level >600 IU/mL, elevated ALT and liver biopsy consistent with chronic HCV infection	N=1,465 16 or 24 weeks (plus 24 weeks of follow up)	Primary: SVR Secondary: Rapid virologic response, virologic relapse, safety	Primary: Based on per-protocol analysis, patients treated for 16 weeks had significantly lower SVR rates compared to patients treated for 24 weeks (65 vs 76%; OR, 0.59; 95% CI, 0.46 to 0.76; *P*<0.001). Based on ITT analysis patients treated for 16 weeks had significantly lower SVR rates compared to patients treated for 24 weeks (62 vs 70%; OR, 0.67; 95% CI, 0.54 to 0.84; *P*<0.001). Both per-protocol and ITT analyses failed to show NI of 16 weeks of treatment compared to 24 weeks of treatment (*P* value not reported). Secondary: Of patients treated for 16 weeks, 67% achieved rapid virologic response and of those treated for 24 weeks, 64% achieved rapid virologic response. Significantly more patients treated for 16 weeks experienced viral relapse (31%; 95% CI, 27 to 34) compared to patients treated for 24 weeks (18%; 95% CI, 15 to 21; *P*<0.001). The proportion of patients who required dose reduction of peginterferon and the proportion reporting adverse or serious adverse events were similar between the two treatments. Rates of withdrawal during the first 16 weeks of the trial were similar between the two treatments. More patients treated for 24 weeks compared to 16 weeks required dose reduction of ribavirin (23 vs 16%; *P*=0.01). Dose reduction rates of peginterferon alfa-2a were similar between the two groups. The most common reason for dose modification was neutropenia due to peginterferon alfa-2a and anemia due to ribavirin.
Dalgard et al[58] Peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 800 to 1,200	Pooled analysis of 1 RCT and 1 non-RCT Treatment-naïve patients with HCV	N=550 14 or 24 weeks (plus 24 weeks of follow up)	Primary: SVR Secondary: Not reported	Primary: Based on per protocol analysis, SVR rates were 91.0 (181/199) and 94.9% (93/98) with 14 and 24 weeks of treatment (one sided 90% CI, 1.0 to -8.8). Based on per protocol analysis and a NI margin of 10%, the authors concluded that 14 weeks of treatment was NI to 24 weeks of treatment.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mg/day	genotype 2 or 3 infection, elevated ALT levels and rapid virologic response			Based on ITT analysis, SVR rates were 88.0 (204/233) and 93.2% (136/146) with 14 and 24 weeks of treatment (90% CI, -0.3 to -10.1) Secondary: Not reported
Mangia et al (abstract)[59] Peginterferon alfa-2b plus ribavirin 1,000 to 1,200 mg/day for 24 weeks (standard) vs peginterferon alfa-2b plus ribavirin 1,000 to 1,200 mg/day for 12 or 36 weeks (variable) In the variable treatment arm, patients with or without viral clearance after 4 weeks were allocated to either 12 or 36 weeks duration.	RCT Patients with HCV genotype 3 infection	N=414 24 or 12 to 36 weeks (plus 24 weeks of follow up)	Primary: Efficacy Secondary: Not reported	Primary: After four weeks, 262 patients were undetectable, 136 patients were randomized to standard treatment and 126 patients were randomized to variable treatment (*P*=0.41). In patients with undetectable levels after four weeks, end of treatment response rates were 80.4 (95% CI, 85.4 to 95.3) and 97.6% (95% CI, 94.9 to 99.9), respectively (*P*=0.019). In patients who were still detectable after four weeks, the corresponding rates were 61.9 (95% CI, 50.6 to 73.2) and 75.3% (95% CI, 65.9 to 84.6; *P*=0.08). SVR rates were 71.4 (95% CI, 65.3 to 77.6) and 74.3% (95% CI, 58.4 to 80.3) with standard and variable treatment (*P* value not reported). Among patients who were undetectable after four weeks, SVR rates were 81.6 (95% CI, 75.1 to 88.1) and 82.5% (95% CI, 75.9 to 89.1), respectively (*P* value not reported). The corresponding rates among those with detectable levels after four weeks were 52.1 (95% CI, 40.4 to 63.7) and 61.7% (95% CI, 51.1 to 72.3), respectively (*P*=0.25). Secondary: Not reported
Buti et al[60] SUCCESS Peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 800 to 1,400 mg/day for 48 weeks	MC, OL, PRO, RCT Patients 18 to 70 years of age with compensated chronic hepatitis C infection who were considered	N=159 48 or 72 weeks (plus 24 weeks of follow up)	Primary: SVR, relapse rates Secondary: Safety	Primary: The SVR rate was 43 and 48% with 48 and 72 weeks of treatment among slow responders (*P*=0.644). Among slow responders with a less than two log decrease in HCV RNA after eight weeks, SVR rates were 39 and 19% among patients treated for 72 and 48 weeks (*P* value not reported). Relapse rates were similar with 48 and 72 weeks of treatment (47 vs 33%;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 800 to 1,400 mg/day for 72 weeks Patients with detectable HCV RNA at week 12 (slow responders) were randomized to continue treatment for a total of 48 or 72 weeks.	slow responders based on HCV RNA levels after 12 weeks of standard of care			*P*=0.169). Secondary: The safety profile was similar in both treatment regimens. Serious adverse events leading to discontinuation of treatment were observed in 3.5 and 8.2% of slow responders treated for 48 and 72 weeks.
Brady et al[61] Peginterferon alfa-2b 3 µg/kg weekly for 12 weeks, followed by peginterferon alfa-2b 1.5 µg/kg/ weekly for 36 weeks (induction group) vs peginterferon alfa-2b 1.5 µg/kg weekly for 48 weeks (standard of care group) All patients received ribavirin 13±2	MC, OL, PRO, RCT Treatment-naïve genotype 1 or 4 chronic hepatitis C patients, with positive HCV antibodies, detectable HCV RNA and histologic evidence of ongoing liver disease consistent with viral hepatitis	N=310 48 weeks (plus 24 weeks of follow up)	Primary: SVR Secondary: Early virologic response and subgroup SVR analyses for African American and Hispanic patients, high vs low baseline viral load, heavy (≥85 kg) vs light weight populations	Primary: Overall SVR was achieved in 96 (32%) and 92 (29%) of the patients in the induction and standard of care groups (*P* value not reported). Secondary: At week 12, virus negativity was seen in 184 (62%) and 179 (58%) of the patients in the induction and standard of care groups (*P* value not reported). African American patients comprised 12% of the study population, and overall SVR was similar in this patient population to the entire study population, with no difference in SVR between patients in the induction group (n=13, 35%) and standard of care group (n=12, 32%; *P*=0.9). Overall SVR for Hispanic patients (n=76) was 36.1% in the induction group and 28.9% in the standard of care group (*P*=0.292). Overall SVR was the same when comparing the induction and standard of care groups when compared at the following three levels of stratification: lower virus load vs higher viral load (≥400 K, 600 K or 800 K; *P* values not

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mg/kg/day.				reported). Heavy weight patients in the induction group showed a trend toward higher rates of end of treatment virus negativity (47 vs 36%) and SVR (38 vs 28%) compared to heavy weight patients in the standard of care group. There were no differences between light weight patients (*P* values not reported). Furthermore, induction therapy worked better in heavy vs light weight patients with SVR of 38 vs 26% (*P*=0.04).
Dalgard et al[62] Peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 800 to 1,400 mg/day for 14 weeks vs peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 800 to 1,400 mg/day for 24 weeks	OL, NI, RCT Treatment-naïve patients with HCV genotype 2 or 3 infection and elevated ALT levels; patients with rapid virologic response (HCV RNA <50 IU/mL after 4 weeks of treatment) were randomized to treatment duration of 14 or 24 weeks	N=298 14 or 24 weeks (plus 24 weeks of follow up)	Primary: SVR Secondary: Safety	Primary: SVR rates were 81.1 (120/148) and 90.7% (136/150) with 14 and 24 weeks of treatment (difference, 9.6%; 95% CI, 1.7 to 17.7). Secondary: Adverse events were reported more frequently with 24 weeks of treatment between 18 to 24 weeks compared to 14 weeks of treatment. There was no difference in the rates of anemia, neutropenia, thyroid disturbances and depression between the treatment regimens.
Nagaki et al[63] Peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 200 mg/day for 24 weeks (72 weeks total treatment) vs peginterferon alfa-2b 0.75 µg/kg weekly plus ribavirin 200	MC, OL, PG, RCT Patients >18 years of age with HCV genotype 1 infection who were late responders (HCV RNA positive after 8 weeks of treatment and negative during weeks 12 to 48 of treatment) and elevated ALT	N=34 48 to 96 weeks (plus 24 weeks of follow up)	Primary: SVR Secondary: Rates of discontinuation	Primary: Among late responders, the SVR rates were 58 (7/12), 89 (8/9) and 38% (5/13) after 72, 96 and 48 weeks of treatment. The SVR rate was significantly higher with 96 weeks compared to 72 weeks (*P*=0.034). Secondary: During weeks 49 to 96, one patient discontinued treatment.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mg/day for 48 weeks (96 weeks total treatment) vs no treatment extension (48 weeks total treatment) All patients received peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 600 to 1,000 mg/day for the first 48 weeks of treatment.				
Singal et al[64] Peginterferon plus ribavirin for 12 to 16 weeks (short term) vs peginterferon plus ribavirin for 24 weeks (standard)	MA, SR (6 trials) Patients with HCV genotype 2 or 3 infection who achieved a rapid virologic response with peginterferon plus ribavirin	N=2,434 Duration varied	Primary: End of treatment response, SVR, relapse Secondary: Not reported	Primary: The pooled data demonstrated no difference in end of treatment response rates between short term and standard therapy (92 vs 87%; OR, 1.45; 95% CI, 0.82 to 2.56; *P*=0.20). The pooled data demonstrated a significantly higher SVR rate with standard therapy compared to short term therapy (79 vs 70%; OR, 0.54; 95% CI, 0.35 to 0.85; *P*=0.008). The pooled data demonstrated a significantly higher relapse rate with short term therapy compared to standard therapy (23 vs 9%; OR, 3.12; 95% CI, 1.99 to 4.91; *P*<0.00001). Subgroup analysis based on genotype and initial viral load did not show any differences in the rates of end of treatment response, SVR and relapse. Twelve percent (140/1,189) of patients receiving 24 weeks of therapy discontinued treatment prematurely compared to five percent (63/1,245) of patients receiving short term therapy (*P*<0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
Hepatitis C - Pediatric Patients				
Sokal et al[65] Peginterferon alfa-2a 100 µg/m^2 weekly plus ribavirin 15 mg/kg/day	MC, OL, PRO Children 6 to 17 years of age who were treatment-naïve and with positive anti-HCV serum antibodies, detectable serum HCV RNA and not co-infected with hepatitis B or HIV	N=65 24 (genotypes 2 or 3) or 48 weeks (genotypes 1, 4, 5 or 6) (plus 24 weeks of follow up)	Primary: SVR Secondary: Early virologic response, end of treatment response, safety	Primary: SVR rates were significantly higher with genotypes 2 and 3 compared to genotypes 1, 4, 5 or 6 (16/18 [89%] vs 27/47 [57%] respectively; *P*<0.01). Secondary: Early virologic response was achieved in 94 (15/16) and 59% (27/46) of patients with genotypes 2 and 3 and genotypes 1, 4, 5, or 6. Ten patients, all with genotype 1, 4, 5, or 6 discontinued treatment early, and eight of the ten patients discontinued due to lack of virological response at week 24. Dose adjustments of peginterferon were required in 15 patients due to neutropenia and of ribavirin in three patients due to anemia. Patients reported fatigue (34.0%), fever and flu-like symptoms (54.0%), headache (45.0%), irritability-depression-change in mood (34.0%), vomiting (23.0%), abdominal pain (38.0%), loss of appetite (21.5%), dermatitis (29.0%) and thyroid disease (11.0%).
Schwarz et al[66] Peginterferon alfa-2a (each dose was calculated using body surface area and the following equation: [body surface area (m^2)/1.73(m^2)] x 180 µg weekly dose) plus ribavirin 15 mg/kg/day	MC, OL Children 2 to 8 years of age with evidence of hepatitis C, chronic liver disease without evidence of cirrhosis and not co-infected with hepatitis B or HIV	N=14 48 weeks (plus 24 weeks of follow up)	Primary: SVR Secondary: Safety	Primary: Six of fourteen patients (43%) achieved SVR. Eight patients had undetectable HCV RNA levels after 24 weeks of treatment and seven patients (50%) achieved end of treatment response. Secondary: No serious adverse events were reported. The most commonly reported adverse events attributed to treatment were: pyrexia (11/14, 70%), headache (6/14, 43%), fatigue (3/14, 21%), vomiting (3/14, 21%), nausea (2/14, 14%), injection-site reactions (2/14, 14%) and irritability (2/14, 14%). Five patients required dose reductions due to low neutrophil counts. Three patients withdrew from the trial early (after 24 to 47 weeks) due to adverse

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				events. Three others withdrew due to administrative reasons.
Baker et al[67] Peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 800 mg/day	Case series Children 11 to 19 years of age chronically infected with hepatitis C and not co-infected with either hepatitis B or HIV	N=10 24 (genotype 3, n=1) or 48 weeks (genotypes 1 and 4, n=9) (plus 24 weeks of follow up)	Primary: SVR, HCV RNA levels Secondary: Transaminase levels, safety	Primary: Three of the 10 patients achieved SVR, including the one patient with genotype 3. Nine of the 10 patients achieved undetectable HCV RNA levels at some time during treatment, with four of the nine patients achieving early response, between weeks four and eight of treatment. Secondary: Transaminase levels decreased in all patients who had elevated levels at treatment onset (n=8). Eight out of ten patients lost weight during treatment and four patients had dose reductions due to weight loss. No patients experienced white blood cell count reductions that required dose reductions or treatment discontinuation. Two patients were treated for depression; one of which was treated prior to the study.
Jara et al[68] Peginterferon-alfa-2b 1 µg/kg weekly plus ribavirin 15 mg/kg/day	OL Children 3 to 16 years of age with chronic hepatitis C, elevated ALT levels and not co-infected with hepatitis B or HIV	N=30 24 (genotypes 2 or 3) or 48 weeks (genotypes 1 or 4) (plus 24 weeks of follow up)	Primary: SVR Secondary: Safety	Primary: SVR was achieved in 15 of the 30 patients; 3/3 patients (100%) with genotypes 2 or 3 and 12/27 patients (44%) with genotypes 1 or 4. Secondary: Seven patients with genotype 1 or 4 discontinued treatment early due to adverse events (three patients) or lack of response (four patients). The adverse events that resulted in withdrawal were high fever in one patient and hyperthyroidism in two patients. The most commonly reported adverse events were flu-like symptoms, weight loss and mild anxiety/irritability. Nine patients experienced neutrophil counts <1,000 $X10^9$ cells/L; seven of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				these patients had permanent dose reductions of peginterferon, but four achieved SVR despite change in regimen. ALT levels significantly decreased from baseline to treatment (*P*<0.01).
Wirth et al[69] Peginterferon alfa-2b 1.5 µg/kg/ weekly plus ribavirin 15 mg/kg/day	OL Children 2 to 17 years of age with chronic hepatitis C	N=62 48 weeks (plus 24 weeks of follow up)	Primary: SVR Secondary: Adverse effects	Primary: Of the 46 patients with genotype 1, 47.8% (n=22) achieved SVR. All 13 patients with genotypes 2 or 3 achieved SVR, irrespective of duration of treatment (24 or 48 weeks; *P*=0.0003). One of the two patients with genotype 4 achieved SVR. Secondary: Flu-like symptoms were reported by 50/61 (82%) patients. Weight loss, <10% was reported by 12 patients and nine patients reported temporary mood swings or behavioral changes.
Wirth et al[70] Peginterferon alfa-2b 60 µg/m^2/week plus ribavirin 15 mg/kg/day	MC, OL Children 3 to 17 years of age with previously untreated chronic hepatitis C, absolute neutrophil count ≥1,500/m^3, platelets ≥100,000/mm^3, hemoglobin levels ≥11 g/dL for females and ≥12 g/dL for males and not co-infected with hepatitis B or HIV	N=107 24 (genotypes 2 or genotype 3 with a low viral load) or 48 weeks (genotypes 1, 4 or 3 with a high viral load) (plus 24 weeks of follow up)	Primary: SVR Secondary: Early virologic response, end of treatment response, relapse, ALT normalization	Primary: In total, 70/107 (67%) patients achieved SVR. Of those with genotype 1, 53% achieved SVR; of those with genotype 2, 93% achieved SVR; of those with genotype 3, 93% achieved SVR and of those with genotype 4, 80% achieved SVR. Secondary: Of patients with genotype1, 60% achieved early virologic response and end of treatment response. Of patients with genotypes 2 and 3, 87% achieved early virologic response and 93% achieved end of treatment response. Of patients with genotype 4, 80% achieved early virologic response and end of treatment response. Baseline ALT was not found to be a predictor of response. Normalization of ALT occurred in 34 of the 44 (77%) patients with elevated ALT at baseline. Only patients with genotype 1 experienced relapse, at a rate of 12% in those with genotype 1.
Rodrigue et al[71] Peginterferon alfa-2b	MC, PC, PRO, RCT Children 5 to 18 years	N=114 24 or 48 weeks	Primary: CHQ-Parent Form 50 scores,	Primary: With regards to the CHQ-Parent Form 50, there was a significant decrease (worsening) in bodily pain (82.9±18.5 vs 74.5±23.0; *P*<0.001) and general

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
plus ribavirin vs peginterferon alfa-2b	of age with documented HCV viremia on 2 tests ≥6 months apart and/or 1 positive test in a child with maternal-fetal transmission, chronic hepatitis consistent with HCV infection on liver biopsy within 36 months of screening and compensated liver disease	(plus 24 weeks of follow up)	CBCL scores, BRIEF scores Secondary: Not reported	health (66.6±15.3 vs 63.3±18.1; *P*=0.02) scores from baseline to 24 weeks. Eight (15%) patients receiving combination therapy and five (9%) patients receiving monotherapy had a clinically significant decline in physical quality of life between baseline and 24 weeks (data and *P* values not reported). Four (7%) patients receiving combination therapy and three (5%) patients receiving monotherapy had a clinically significant decline in psychosocial quality of life (data and *P* values not reported). Among the 41 patients who continued combination therapy for a total of 48 weeks, 34 (83%) experienced no clinically significant change in physical quality of life during treatment. Of the 26 patients who continued monotherapy for a total of 48 weeks, 21 (81%) did not have any clinically significant decline in physical quality of life. With regards to the CBCL, six (three receiving combination therapy and three receiving monotherapy) and three (all receiving combination therapy) patients had clinically significant worsening of internalizing and externalizing behaviors, respectively, between baseline and 24 weeks. Three (5%) and zero patients receiving combination and monotherapy experienced a clinically significant increase in depression symptoms from baseline to 24 weeks. One patient receiving combination therapy was withdrawn due to a suicidal gesture and subsequent hospitalization, and one patient receiving monotherapy was withdrawn due to an increase in aggressive behaviors. Of the patients continuing combination therapy for a total of 48 weeks, most experienced no clinically significant change in internalizing behaviors (95%), externalizing behaviors (95%) or total behavioral problems (93%). Of the patients who continued monotherapy for a total of 48 weeks, the majority had no significant clinical change in internalizing (77%), externalizing (92%) or total behavior problems (88%). With regards to the BRIEF, three patients receiving combination therapy had significant clinical deterioration in their Global Executive functioning from baseline to week 24. One patient who continued combination therapy for 48 weeks experienced a clinically significant decline in executive functioning. None of the patients who continued monotherapy for a total of 48 weeks had a clinically significant increase in executive functioning problems.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
Melanoma				
Eggermont et al[72] EORTC Peginterferon alfa-2b 6 µg/kg weekly for 8 weeks (induction), followed by 3 µg/kg weekly (maintenance) vs observation	MC, RCT Patients 18 to 70 years of age with histologically documented stage III melanoma with the primary cutaneous melanoma completely excised with adequate surgical margins and complete regional lymphadenectomy occurring ≤70 days before randomization	N=1,256 5 years	Primary: Recurrence free survival Secondary: Distant metastasis free survival, overall survival, safety	Primary: Recurrence free survival was longer with peginterferon alfa-2b (median time to event, 34.8 vs 25.6 months) and there was a significant difference between the two regimens in favor of active treatment (four year rate, 45.6 vs 38.9%; HR, 0.82; 95% CI, 0.71 to 0.96; *P*=0.01). Secondary: Distant metastasis free survival was longer with peginterferon alfa-2b (median time to event, 45.5 vs 36.0 months); however, there was no significant difference between the two regimens (four year rate, 48.2 vs 45.4%; HR, 0.88; 95% CI, 0.75 to 1.03; *P*=0.11). There was no difference in overall survival observed between the two regimens (four year rate, 56.8 vs 55.7%; HR, 0.98; 95% CI, 0.82 to 1.16; *P*=0.78). Overall, the most commonly recorded adverse events were fatigue (99 vs 79), liver function tests (94 vs 41%), pyrexia (75 vs 9%), headache (70 vs 19%), myalgia (67 vs 23%) and depression (59 vs 25%). Grade 3 and 4 events occurred in more patients receiving peginterferon alfa-2b. A total of 262 vs 263 patients died during the trial. The incidence of the most frequent cause of death, malignant disease, was similar between the two regimens (40 vs 39%).

Drug regimen abbreviations: MIU=million international units
Study abbreviations: CI=confidence interval, DB=double-blind, HR=hazard ratio, ITT=intention to treat analysis, MA=meta-analysis, MC=multicenter, NI=noninferiority, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, RR=rate ratio, SR=systematic review
Miscellaneous abbreviations: ALT=alanine aminotransferase, BMI=body mass index, BRIEF=Behavior Rating Inventory of Executive Function, CBCL=Child Behavior Check List, CHQ-Parent Form=Child Health Questionnaire-Parent Form, CLDQ=Chronic Liver Disease Questionnaire, DNA=deoxyribonucleic acid, HBeAg=hepatitis B e antigen, HBsAg=hepatitis B surface antigen, HBV=hepatitis B virus, HCV=hepatitis C virus, HIV=human immunodeficiency virus, HRQOL=health related quality of life, IU=international units, NASH=nonalcoholic steatohepatitis, RNA=ribonucleic acid, SF-36=Short-Form Health Survey, SVR=sustained virologic response

Special Populations

Table 5. Special Populations[9-11,73,74]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Peg-interferon alfa-2a	No dosage adjustment required in elderly patients. Safety and efficacy in children <5 years of age have not been established.	Renal dosage adjustment required; for patients receiving hemodialysis, a dose reduction to 135 µg/week is recommended.	Hepatic dosage adjustment is required for the treatment of hepatitis B; for patients with increased liver function tests >5 times the upper limit of normal while on treatment, a dose reduction to 135 µg/week should be considered; and for liver function tests >10 times the upper limit of normal; treatment discontinuation should be considered. Hepatic dosage adjustment is required for the treatment of hepatitis C; for patients with increased liver function tests while on treatment, a dose reduction to 135 µg/ week is recommended. Contraindicated in decompensated liver disease.	C*	Unknown; use with caution.
Peg-interferon alfa-2b	No dosage adjustment required in elderly patients. Safety and efficacy in children <3 years of age have not been established (PegIntron®, PegIntron Redipen®, PegIntron Redipen Pak 4®).	Renal dosage adjustment required; for creatinine clearances 30 to 50 mL/ minute, a 25% dose reduction is recommended, and for creatinine clearances 10 to 29 mL/ minute or	Contraindicated in decompensated liver disease.	C*	Unknown; use with caution.

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	Safety and efficacy in children have not been established (Sylatron®).	hemodialysis patients, a 50% dose reduction is recommended.			

*Ribavirin has a pregnancy category of X.

Adverse Drug Events

Adverse events outlined in Table 6 are reported from clinical trial data in which pegylated interferon alfa-2a and -2b were administered with or without ribavirin for the treatment of chronic hepatitis C, as well as chronic hepatitis B.[9,10] Table 7 outlines the adverse events reported in clinical trials in which pegylated interferon alfa-2b (Sylatron®) was evaluated in the treatment of melanoma.[11]

Table 6. Adverse Drug Events (%)[9,10]

Adverse Event	Peginterferon alfa-2a	Peginterferon alfa-2b
Central Nervous System		
Agitation	-	2 to 8
Anxiety	-	11
Anxiety/emotional liability/irritability	-	28 to 47
Concentration impairment	8 to 10	10 to 17
Depression	18 to 20	19 to 31
Dizziness	14 to 16	12 to 21
Headache	27 to 64	47 to 62
Insomnia	9 to 30	23 to 40
Irritability	14 to 24	14 to 25
Irritability/anxiety/nervousness	19 to 33	-
Memory impairment	5 to 6	-
Mood alteration	3 to 9	-
Nervousness	-	4 to 6
Endocrine Disorders		
Hypothyroidism	3 to 4	5
Flu-like Symptoms and Signs		
Asthenia	-	15
Asthenia/fatigue	56 to 65	52 to 66
Fatigue	20 to 25	30 to 68
Influenza-like illness	81 to 91	15 to 16
Pain	10 to 11	-
Pyrexia	37 to 54	22 to 80
Rigors	25 to 35	21 to 48
Gastrointestinal		
Abdominal pain	8 to 15	10 to 21
Abdominal pain, upper	-	12
Constipation	-	1 to 5
Diarrhea	11 to 16	15 to 22
Dry mouth	4 to 6	6 to 12
Dyspepsia	<1 to 6	6 to 9
Gastrointestinal disorder	44 to 56	-
Nausea/vomiting	24 to 25	-
Nausea	-	18 to 43

Adverse Event	Peginterferon alfa-2a	Peginterferon alfa-2b
Vomiting	-	7 to 27
Hematologic		
Alanine transaminase increase	11	-
Anemia	2 to 14	0 to 35
Leukopenia	-	<1 to 10
Lymphopenia	3 to 14	-
Neutropenia	20 to 40	6 to 33
Thrombocytopenia	5 to 13	7 to 5
Metabolic and Nutritional		
Anorexia	16 to 24	20 to 32
Decreased appetite	11 to 14	22
Weight decrease	4 to 16	10 to 29
Musculoskeletal, Connective Tissue and Bone		
Arthralgia	22 to 28	17 to 34
Back pain	5 to 9	-
Musculoskeletal pain	29 to 35	21 to 28
Myalgia	26 to 40	17 to 56
Respiratory		
Cough	<1 to 4	8 to 23
Dyspnea	4 to 13	4 to 26
Dyspnea, exertional	<1 to 4	-
Pharyngitis	-	10 to 12
Rhinitis	-	2 to 8
Sinusitis	-	6 to 7
Upper respiratory tract infection	60	-
Skin and Subcutaneous Tissue		
Alopecia	18 to 28	17 to 36
Dermatitis	8 to 16	-
Dry skin	4 to 10	11 to 24
Eczema	1 to 5	-
Pruritus	11 to 19	12 to 29
Rash	5 to 15	6 to 29
Skin disorder	47	-
Sweating increased	6	6 to 11
Other		
Chest pain	-	6 to 8
Conjunctivitis	-	4
Flushing	-	4 to 6
Hepatomegaly	-	4 to 6
Injection site reaction	22 to 45	29 to 75
Malaise	-	4 to 7
Menstrual disorder	-	4 to 7
Resistance mechanism disorders, fungal infection	-	<1 to 6
Resistance mechanism disorders, overall	10 to 12	-
Resistance mechanism disorders, viral	-	11 to 12
Taste perversion	-	<1 to 9
Unspecified pain	-	12 to 13
Upper right quadrant pain	-	8 to 12
Vision blurred	4 to 5	2 to 5

-Event not reported.

Table 7. Adverse Drug Events (%)[11]

Adverse Event	Peginterferon alfa-2b
Central Nervous System	
Depression	59
Dizziness	35
Dysgeusia	38
Headache	70
Olfactory nerve disorder	23
Paraesthesia	21
Gastrointestinal Disorders	
Diarrhea	37
Nausea	64
Vomiting	26
General Disorders and Administrative Site Conditions	
Chills	63
Fatigue	94
Injection site reaction	62
Pyrexia	75
Metabolic/laboratory	
Alanine/aspartate transaminase increased	77
Anemia	6
Blood alkaline phosphatase increased	23
Gamma glutamyl transferase increased	8
Proteinuria	7
Weight decreased	11
Metabolic and Nutrition Disorders	
Anorexia	69
Musculoskeletal and Connective Tissue Disorders	
Arthralgia	51
Myalgia	68
Respiratory	
Cough	5
Dyspnea	6
Skin and Subcutaneous Tissue Disorders	
Alopecia	34
Exfoliative rash	36

Contraindications

Table 8. Contraindications[9-11]

Contraindications	Peginterferon alfa-2a	Peginterferon alfa-2b
Autoimmune hepatitis	✔	✔
Decompensated liver disease in cirrhotic patients	✔	✔
Decompensated liver disease in neonates	✔	✔
Hypersensitivity	✔	✔
Infants co-infected with hepatitis C and human immunodeficiency virus	✔	✔

Black Box Warning for Pegasys® (peginterferon alfa-2a) and PegIntron® (peginterferon alfa-2b)[9,10]

WARNING
Alfa interferons, including peginterferon alfa-2a and alfa-2b, may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations. Therapy should be withdrawn in patients with persistently severe or worsening signs or symptoms of these conditions. In many, but not all cases, these disorders resolve after stopping peginterferon alfa-2a or alfa-2b therapy. Use with ribavirin: ribavirin may cause birth defects and/or death of the fetus. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Ribavirin causes hemolytic anemia. The anemia associated with ribavirin therapy may result in a worsening of cardiac disease.

Black Box Warning for Sylatron® (peginterferon alfa-2b)[11]

WARNING
The risk of serious depression, with suicidal ideation and completed suicides, and other serious neuropsychiatric disorders are increased with alpha interferons, including peginterferon alfa-2b. Permanently discontinue peginterferon alfa-2b in patients with persistently severe or worsening signs or symptoms of depression, psychosis or encephalopathy. These disorders may not resolve after stopping peginterferon alfa-2b.

The standard of care for the treatment of hepatitis C is pegylated interferon alfa and ribavirin.[3-7]

Black Box Warnings for Copegus® (ribavirin), Rebetol® (ribavirin) and Ribasphere®/Ribasphere® RibaPak® (ribavirin)[75-77]

WARNING
Ribavirin monotherapy is no effective for the treatment of chronic hepatitis C virus infection and should not be used along for this indication. The primary clinical toxicity of ribavirin is hemolytic anemia. The anemia associated with ribavirin therapy may result in worsening of cardiac disease and lead to fatal and nonfatal myocardial infarctions. Patients with a history of significant or unstable cardiac disease should not be treated with ribavirin. Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. In addition, ribavirin has a multiple dose half-life of 12 days, and it may persist in non-plasma compartments for as long as six months. Therefore, ribavirin is contraindicated in women who are pregnant and in the male partners of women who are pregnant. Extreme care must be taken to avoid pregnancy during therapy and for six months after completion of therapy in both female patients and in female partners of male patients who are taking ribavirin therapy. At least two reliable forms of effective contraception must be utilized during treatment and during the six month post treatment follow up period.

Warnings and Precautions

Table 9. Warnings and Precautions[9-11]

Warnings/Precautions	Peginterferon alfa-2a	Peginterferon alfa-2b
Anemia: monitoring recommended	✔	✔
Autoimmune disorder: may be precipitated or aggravated; monitoring recommended; discontinue use if condition worsens or persists	✔	✔
Cardiovascular disorders: have been reported	✔	✔
Cerebrovascular events: have been reported	✔	✔

Warnings/Precautions	Peginterferon alfa-2a	Peginterferon alfa-2b
Cirrhosis: increased risk of hepatic decompensation; monitoring recommended; permanently discontinue for severe hepatic injury or hepatic decompensation	✔	✔
Colitis; ulcerative or hemorrhagic/ischemic have been reported; discontinue if signs or symptoms develop	✔	✔
Concomitant HAART in HIV coinfected patients: increased risk of hepatic decompensation; monitoring recommended; may require discontinuation of therapy	✔	✔
HIV coinfected patients: increased risk of neutropenia or thrombocytopenia and may result in serious infections or bleeding	✔	✔
Hyperglycemia, hypoglycemia, or diabetes mellitus; new onset or exacerbation of preexisting condition, use not recommended in patients with uncontrolled disease	✔	✔
Hypersensitivity reactions: have been reported; discontinuation of therapy recommended	✔	✔
Hyperthyroidism or hypothyroidism: new onset or exacerbation of preexisting condition; use not recommended in patients with uncontrolled disease	✔	✔
Infections: may be precipitated or aggravated; monitoring recommended; discontinue use if condition worsens or persists	✔	✔
Myelosuppression: dose adjustments or discontinuation may be necessary	✔	✔
Neuropsychiatric reactions: may be precipitated or aggravated; monitoring recommended; if severe discontinue use	✔	✔
Ophthalmic disorders: may be induced or aggravated; baseline and routine eye examinations recommended	✔	✔
Pancreatitis; has been reported; suspend treatment if signs/symptoms suggestive of pancreatitis occur; discontinue treatment if confirmed	✔	✔
Pulmonary disorders: may be induced or aggravated; suspend treatment if pulmonary infiltrates or pulmonary function impairment occurs	✔	✔
Renal impairment: monitoring and dose adjustments are recommended; discontinue if severe lab abnormalities or adverse effects occur	✔	✔
Skin reactions: have been reported; discontinuation of therapy recommended	✔	✔

HAART=highly active antiretroviral therapy, HIV= human immunodeficiency virus

Drug Interactions

There are no significant drug interactions associated with the pegylated interferon products.[78]

Dosage and Administration

Table 10. Dosing and Administration[9-11]

Generic Name	Adult Dose	Pediatric Dose	Availability
Peginterferon alfa-2a	Chronic hepatitis B virus infection (hepatitis B e antigen positive and hepatitis B e antigen negative) in adults who have compensated liver disease and evidence of viral replication and liver inflammation: Autoinjector, prefilled syringe, vial for injection: 180 µg once weekly for 48 weeks Chronic hepatitis C virus infection, alone or in combination with Copegus® (ribavirin), in adults who have compensated liver disease and have not been previously treated with interferon alfa:* Autoinjector, prefilled syringe, vial for injection (monotherapy): 180 µg once weekly for 48 weeks Autoinjector, prefilled syringe, vial for injection (combination ribavirin therapy): 180 µg once weekly for 24 (genotypes 2 and 3) or 48 weeks (genotypes 1 and 4)	Chronic hepatitis C virus infection, alone or in combination with Copegus® (ribavirin), in patients five to 18 years of age who have compensated liver disease and have not been previously treated with interferon alfa: Autoinjector, prefilled syringe, vial for injection: 180 µg/1.73 m^2 x body surface area once weekly for 24 (genotypes 2 and 3) or 48 weeks (genotypes 1 and 4)	Autoinjector (Pegasys ProClick®, Pegasys ProClick® Convenience Pack): 135 µg/0.5 mL 180 µg/0.5 mL Prefilled syringe (Pegasys Convenience Pack®): 180 µg/0.5 mL Vial for injection (Pegasys®): 180 µg/mL
Peginterferon alfa-2b	Adjuvant treatment of melanoma with microscopic or gross nodal involvement within 84 days of definitive surgical resection including complete lymphadenectomy:† Vial for injection: initial, 6 µg/kg/week for eight doses; maintenance, 3 µg/kg/week for up to five years Chronic hepatitis C virus infection, in combination with Rebetol® (ribavirin), in adults with compensated liver disease:‡ Prefilled syringe, vial for injection: 1.5 µg/kg/week for 24 (treatment naïve patients with genotype 2 or 3 infection) or 48 weeks (treatment experienced patients and treatment naïve patients with genotype 1 infection) Chronic hepatitis C virus infection in patients ≥18 years of age with compensated liver disease previously untreated with interferon alpha:‡ Prefilled syringe, vial for injection: 1 µg/kg/week for 1 year	Chronic hepatitis C virus infection, in combination with Rebetol® (ribavirin), in patients ≥3 to 18 years of age with compensated liver disease: Prefilled syringe, vial for injection:‡ 60 µg/m^2/week for 24 (genotypes 2 or 3) or 48 weeks (genotype 1)	Prefilled syringe (PegIntron Redipen®, PegIntron Redipen Pak 4®): 50 µg/0.5 mL 80 µg/0.5 mL 120 µg/0.5 mL 150 µg/0.5 mL Vial for injection: 50 µg/0.5 mL (PegIntron®) 80 µg/0.5 mL PegIntron®) 120 µg/0.5 mL PegIntron®) 150 µg/0.5 mL PegIntron®) 296 µg/1.25 mL (Sylatron®) 444 µg/1.25 mL (Sylatron®) 888 µg/1.25 mL (Sylatron®)

*Patients co-infected with human immunodeficiency virus should receive treatment for a total of 48 weeks, regardless of genotype and the use of monotherapy or combination therapy with ribavirin.
† Sylatron®.
‡ PegIntron®, PegIntron Redipen®, PegIntron Redipen Pak 4®.

Clinical Guidelines

Table 11. Clinical Guidelines

Clinical Guideline	Recommendation(s)
American Association for the Study of Liver Diseases: **Chronic Hepatitis B: Update 2009 (2009)**[8]	Hepatitis B e antigen (HBeAg)-positive chronic hepatitis B • Patients with alanine aminotransferase (ALT) levels ≥2 times the upper normal limit or moderate/severe hepatitis on biopsy, and hepatitis B virus (HBV) deoxyribonucleic acid (DNA) >20,000 IU/mL should be considered for treatment. Prompt treatment is recommended in patients with icteric ALT flares, however; treatment should generally be delayed for three to six months to determine if spontaneous HBeAg seroconversion occurs. Therapy can be initiated with any of the Food and Drug Administration (FDA) approved agents, however; entecavir, pegylated interferon alfa or tenofovir are preferred. Children should be initiated with interferon alfa or lamivudine. • In patients with ALT levels <2 times the upper normal limit, treatment should not be considered. Consideration of a liver biopsy is appropriate in patients with fluctuating or minimally elevated ALT levels, especially in patients >40 years of age. If moderate or severe necroinflammation or significant fibrosis is observed in a liver biopsy, treatment may be initiated. • Treatment with nucleoside analogues should be continued until HBeAg seroconversion has been achieved and serum HBV DNA levels have become undetectable, and the patient has completed at least six months of additional treatment after appearance of anti-HBe. HBeAg-negative chronic hepatitis B • Patients with ALT levels ≥2 times the upper normal limit and HBV DNA >20,000 IU/mL should be considered for treatment. • Therapy can be initiated with any FDA approved agent, however; entecavir, pegylated interferon alfa or tenofovir are preferred in view of long term treatment. Failure to respond to interferon alfa therapy • Treatment with nucleoside analogues are a treatment option for patients who failed to respond to prior interferon alfa therapy (standard or pegylated). • Patients who develop breakthrough infections while receiving nucleoside analogue therapy should have compliance assessed, have a confirmatory test for antiviral-resistant mutations, and be considered for rescue therapy. Patients in whom there was no clear indication for treatment and who continue to have compensated liver disease, withdrawal of therapy may be considered but close monitoring is required with treatment reinitiation if severe hepatitis flares occur. • Treatment should be continued until the patient has achieved HBeAg clearance. Resistant HBV • In lamivudine- (or telbivudine-) resistant HBV, if adefovir is used, lamivudine (or telbivudine) should not be discontinued due to risk of hepatitis flares or the development of subsequent adefovir resistance during the transition period. If tenofovir is used, lamivudine (or telbivudine) should be continued to decrease the risk of subsequent antiviral resistance. If entecavir is used, lamivudine (or telbivudine) should be discontinued as the continued presence of lamivudine (or telbivudine) resistant mutations increases the

Clinical Guideline	Recommendation(s)
	risk of entecavir resistance. • In adefovir-resistant HBV, entecavir, lamivudine or telbivudine may be added in patients with no prior exposure to other nucleoside analogues. In patients with prior nucleoside analogues exposure, adefovir should be stopped and tenofovir plus lamivudine or emtricitabine may be used. In patients with prior lamivudine resistance, in whom lamivudine was stopped and the patient was switched to adefovir, adefovir may be stopped and tenofovir plus lamivudine, emtricitabine or entecavir may be used. The durability of response to this combination is unknown. • In entecavir-resistant HBV, adefovir or tenofovir can be used. <u>Cirrhosis</u> • In compensated cirrhosis, treatment with entecavir or tenofovir is preferred in view of the need for long-term therapy. Interferon alfa is not recommended due to risk of interferon alfa-related hepatitis flares. Treatment in these patients should be long-term. • In decompensated cirrhosis, treatment with lamivudine or telbivudine in combination with adefovir or tenofovir may be used as initial treatment. Interferon alfa (standard or pegylated) therapy is not recommended due to risk of interferon alfa-related hepatitis flares. Life-long treatment is recommended in patients with decompensated cirrhosis and recurrent hepatitis B post-liver transplantation. <u>Coinfection with hepatitis C virus (HCV)</u> • Insufficient information on the treatment of HBV and HCV coinfection exists and recommendations on treatment cannot be made at this time. <u>Coinfection with human immunodeficiency virus (HIV)</u> • Patients who are not on highly active antiretroviral therapy (HAART) and who are not anticipated to require HAART in the near future should be treated with adefovir or pegylated interferon alfa as these therapies do not target HIV. Telbivudine should not be used in this circumstance even though it does not target HIV. • Patients already on an effective HAART regimen that does not include a drug active against HBV may be treated with adefovir or pegylated interferon alfa. • In lamivudine resistance, tenofovir should be added. • When HAART is adjusted, drugs effective against HBV should not be discontinued without substituting with another agent with activity against HBV, unless HBeAg seroconversion has been achieved and completion of an adequate course of consolidation treatment has occurred. <u>Hepatitis B carriers requiring immunosuppressive or cytotoxic therapy</u> • Prophylactic treatment with antiviral therapy is recommend for patients who are HBV carriers and are starting cancer chemotherapy or at the start of a finite course of immunosuppressive therapy. • Baseline HBV DNA levels define treatment durations. o For HBV DNA levels <2,000 IU/mL, continue treatment until six months after the completion of chemotherapy or immunosuppressive therapy. o For HBV DNA levels >2,000 IU/mL, continue treatment until they reach endpoints as in immunocompetent patients. • Lamivudine or telbivudine can be used if duration of treatment is ≤12

Clinical Guideline	Recommendation(s)
	months and baseline serum HBV DNA is undetectable. o Entecavir or tenofovir is preferred if treatment duration is longer. • Interferon alfa should be avoided in this population.
American Association for the Study of Liver Diseases: **An Update on Treatment of Genotype 1 Chronic Hepatitis C Virus Infection (2011 [limited revision online in 2013])**[5]	• The optimal therapy for hepatitis C virus (HCV) genotype 1 is the use of boceprevir or telaprevir in combination with pegylated interferon alfa and ribavirin. • Boceprevir and telaprevir should not be used without pegylated interferon alfa and weight based ribavirin. <u>Treatment naïve patients</u> • The recommended dose of boceprevir is 800 mg three times daily (every seven to nine hours) with food plus pegylated interferon alfa and weight based ribavirin for 24 to 44 weeks, preceded by four weeks of lead in pegylated interferon alfa plus ribavirin alone. o Patients without cirrhosis treated with boceprevir, pegylated interferon alfa and ribavirin, whose HCV ribonucleic acid (RNA) levels at weeks eight and 24 is undetectable, may be considered for a shortened duration of treatment of 28 weeks in total (four weeks lead in of combination therapy only, followed by 24 weeks of triple therapy). o Triple therapy should be stopped if the HCV RNA level is >100 IU/mL at treatment week 12 or detectable at treatment week 24. • The recommended dose of telaprevir is 750 mg three times daily (every seven to nine hours) with food (not low fat) plus pegylated interferon alfa and weight based ribavirin for 12 weeks followed by an additional 12 to 36 weeks of pegylated interferon alfa plus ribavirin alone. o Patients without cirrhosis treated with telaprevir, pegylated interferon alfa and ribavirin, whose HCV RNA level at weeks four and 12 is undetectable should be considered for a shortened duration of therapy of 24 weeks. o Triple therapy should be stopped if the HCV RNA levels is >1,000 IU/mL at treatment weeks four or 12 and/or detectable at treatment week 24. • Patients with cirrhosis treated with either boceprevir or telaprevir in combination with pegylated interferon alfa and ribavirin should receive therapy for 48 weeks. <u>Treatment experienced patients</u> • Retreatment with boceprevir or telaprevir, in combination with pegylated interferon alfa and weight based ribavirin, can be recommended for patients who had virological relapse or were partial responders after a prior course of treatment with standard interferon alfa or pegylated interferon alfa and/or ribavirin. • Retreatment with telaprevir, in combination with pegylated interferon alfa and weight based ribavirin, may be considered for prior null responders to a course of standard interferon alfa or pegylated interferon alfa and/or weight based ribavirin. • Response guided therapy of treatment experienced patients using either a boceprevir- or telaprevir-based regimen can be considered for relapsers, may be considered for partial responders but cannot be recommended for null responders. • Patients re-treated with boceprevir plus pegylated interferon alfa and ribavirin who continue to have detectable HCV RNA >100 IU at week 12

Clinical Guideline	Recommendation(s)
	should be withdrawn from all therapy because of the high likelihood of developing antiviral resistance. • Patients re-treated with telaprevir plus pegylated interferon alfa and ribavirin who continue to have detectable HCV RNA >1,000 IU at weeks four or 12 should be withdrawn from all therapy because of the high likelihood of developing antiviral resistance. Adverse events • Patients who develop anemia on protease inhibitor-based therapy for chronic hepatitis C should be managed by reducing the ribavirin dose. • Patients on protease inhibitor-based therapy should undergo close monitoring of HCV RNA levels and the protease inhibitors should be discontinued if virological breakthrough (greater than one log increase in serum HCV RNA above nadir) is observed. • Patients who fail to have a virological response, who experience virological breakthrough or who relapse on one protease inhibitor should not be retreated with other protease inhibitors. Use and interpretation of HCV RNA results during triple therapy • An HCV assay with a lower limit of quantification of ≤25 IU/mL and a limit of HCV RNA detection of approximately 10 to 15 IU/mL should be used to monitor response to triple therapy. • Response-guided therapy should only be considered when no virus is detected by a sensitive assay four weeks after initiation of the HCV protease inhibitor. IL28B testing • IL28B genotype is a robust pretreatment predictor of sustained virologic response (SVR) to pegylated interferon alfa and ribavirin as well as to protease inhibitor triple therapy in patients with chronic HCV genotype 1. Testing may be considered when the patient or provider wish additional information on the probability of treatment response or on the probable treatment needed.
American Association for the Study of Liver Diseases: **Diagnosis, Management, and Treatment of Hepatitis C: An Update (2009)**[3]	• Treatment decisions should be individualized based on severity of liver disease, the potential for serious side effects, the likelihood of treatment response, the presence of comorbid conditions and the patient's readiness for treatment. • Optimal therapy for chronic HCV infection is pegylated interferon alfa in combination with ribavirin. • In genotypes 1 and 4, treatment with pegylated interferon alfa and ribavirin for 48 weeks is recommended. In patients who do not achieve an early virological response (early virologic response; ≥2 log reduction in HCV RNA at 12 weeks), treatment may be discontinued. Patients who do not achieve a complete early virologic response (undetectable HCV RNA at 12 weeks) should be re-tested at week 24, and if HCV RNA remains positive, treatment should be discontinued. Finally, for patients who have delayed virus clearance (HCV RNA test becomes negative between 12 and 24 weeks); consideration should be given to extending therapy to 72 weeks. • In genotypes 2 or 3, treatment with pegylated interferon alfa and ribavirin for 24 weeks is recommended. Patients who receive treatment for 24 weeks and who have a negative HCV RNA measurement, should be retested for HCV RNA 24 weeks later to evaluate for a SVR. Regardless of genotype, patients with HCV-related cirrhosis who achieve a SVR should

Clinical Guideline	Recommendation(s)
	be monitored at six to 12 month intervals for hepatocellular carcinoma development. • The same criteria for evaluating which patients should receive treatment can be used to determine which children, age two to 17 years of age, who are infected with HCV should receive treatment. • Children should be treated with the combination of pegylated interferon alfa 2b, 60 µg/m^2 weekly, and ribavirin 15 mg/kg daily for 48 weeks.
European Association for the Study of the Liver: **Management of Hepatitis C Virus Infection (2011)**[4]	Goals and endpoints of HCV therapy • The goal of therapy is to eradicate HCV infection. • The endpoint of therapy is SVR, and once obtained, SVR usually equates to cure of infection in more than 99% of patients. • Intermediate endpoints to assess the likelihood of an SVR are HCV RNA levels at four, 12 and 24 weeks of therapy. Treatment-naïve patients • SVR is achieved in 40 to 54% of patients infected with HCV genotype 1 treated with pegylated interferon alfa plus ribavirin at approved doses for 48 weeks. • SVR is achieved in 65 to 82% of patients infected with HCV genotypes 2 or 3 treated with pegylated interferon alfa plus ribavirin at approved doses for 24 weeks. • SVR rates are slightly higher in patients infected with HCV genotype 2 than those with genotype 3. • Strongest baseline predictors of SVR are: o HCV genotype. o Genetic polymorphisms located in chromosome 19 (IL28B), particularly in genotype 1 patients. o Stage of liver fibrosis. Relapsers • Patients relapsing after treatment with standard therapy regimens respond to retreatment with pegylated interferon alfa and ribavirin in 32 to 53% of cases. Nonresponders • In the most recent trials, retreatment of patients infected with HCV genotype 1 who failed previous standard therapy ranged from 4 to 14%. Contraindications to therapy • Patients with absolute contraindications to standard of care should not receive therapy. Indications for treatment • All treatment naïve patients with compensated disease due to HCV should be considered for therapy. • Treatment should be initiated promptly in patients with advanced fibrosis (METAVIR score F3 to F4), and strongly considered in patients with moderate fibrosis (F2). • In patients with less severe disease, indication for therapy is individual. First line treatment of chronic hepatitis C • The combination of pegylated interferon alfa plus ribavirin is the approved standard of care for chronic hepatitis. Two pegylated interferon alfa

Clinical Guideline	Recommendation(s)
	molecules, pegylated interferon-2α (180 µg once weekly) and pegylated interferon-α2b (1.5 µg/kg once weekly), can be used in combination with ribavirin. • Ribavirin should be administered as a weight based dose of 15 mg/kg/day for genotypes 1, 4, 5 and 6, and at a flat dose of 800 mg/day for genotypes 2 and 3. • Patients with genotypes 2 and 3 with baseline factors suggesting low responsiveness should receive weight-based ribavirin at a dose of 15 mg/kg/day. Treatment monitoring • Patients treated with pegylated interferon alfa and ribavirin should be seen at a minimum of weeks four and 12 after initiation of treatment, then at a minimum of every 12 weeks until the end of treatment for both efficacy and side effects, and 24 weeks after the end of therapy to assess the SVR. • A real time polymerase chain reaction-based assay, with a lower limit of detection of 10 to 20 IU/mL is the best tool for monitoring therapy. • A low vs high baseline HCV RNA level is useful to guide treatment decisions. The best discriminating HCV RNA level is comprised between 400,000 and 800,000 IU/mL. • During treatment, HCV RNA measurements should be performed at weeks four, 12 and 24 to help tailor treatment. • The end of treatment virological response and the SVR 24 weeks after the end of treatment must be assessed. • Treatment toxicities should be assessed at weeks two and four of therapy and at four through eight week intervals thereafter. Treatment dose reductions and stopping rules • The pegylated interferon alfa dose should be reduced if the absolute neutrophil count falls below 750/mm^3, or the platelet count falls below 50,000/mm^3. Pegylated interferon alfa should be stopped if the neutrophil count falls below 500/mm^3 or the platelet count falls below 25,000/mm^3 or if severe unmanageable depression develops. • If neutrophil or platelet counts go up, treatment can be restarted, but at a reduced pegylated interferon alfa dose. • If hemoglobin <10 g/dL occurs, the dose of ribavirin should be adjusted downward by 200 mg at a time, and ribavirin should be stopped if hemoglobin falls below 8.5 g/dL. • Treatment should be stopped in case of a severe hepatitis flare or severe sepsis. Virological response guided therapy • Treatment duration should be tailored to the treatment virological response at weeks four and 12, and eventually week 24. The likelihood of SVR is directly proportional to the time of HCV RNA disappearance. • Treatment for all HCV genotypes should be stopped at week 12 if the HCV RNA decrease is <2 $\log_{10}$ IU/mL and at week 24 if HCV RNA is still detectable (≥50 IU/mL). • In patients with a rapid virologic response and low baseline viral load (<400,000 to 800,000 IU/mL), treatment for 24 weeks (genotypes 1 and 4) or 12 to 16 weeks (genotypes 2 and 3) can be considered. If negative predictors of response (i.e., advanced fibrosis/cirrhosis, metabolic syndrome, insulin resistance, hepatic stenosis) are present, evidence for

Clinical Guideline	Recommendation(s)
	equal efficacy of shortened treatment is insufficient. • Patients who have an early virologic response (HCV RNA which is detectable at week four but undetectable at week 12) should be treated for 48 weeks regardless of the HCV genotype and baseline viral load. • Patients with genotype 1 and a delayed virologic response can be treated for 72 weeks. This may also apply to other genotypes. <u>Measures to improve treatment success rates</u> • Full adherence to both pegylated interferon alfa and ribavirin should be the aim in order to optimize SVR rates. • Body weight adversely influences the response to pegylated interferon alfa and ribavirin; therefore, a reduction of body weight in overweight patients prior to therapy may increase the likelihood of SVR. • Insulin resistance is associated with treatment failure; however, insulin sensitizers have no proven efficacy in improving SVR rates in these patients. • Counseling on abstaining from alcohol during antiviral therapy should be provided. • Recombinant erythropoietin can be administered when the hemoglobin level falls <10 g/dL in order to avoid ribavirin dose reduction or discontinuation. • There is no evidence that neutropenia is associated with more frequent infection episodes, or that the use of granulocyte colony stimulating factor reduces the rate of infections and/or improves SVR rates. • Patients with a history and/or signs of depression should be seen by a psychiatrist before therapy. Patients who develop depression during therapy should be treated with antidepressants. Preventative antidepressant therapy in selected patients may reduce the incidence of this condition during treatment, without any impact on SVR. <u>Post treatment follow up of patients who achieve an SVR</u> • Noncirrhotic patients with SVR should be retested for alanine transaminase and HCV RNA at 48 and 96 weeks post treatment, then discharged if alanine transaminase is normal and HCV RNA negative. • In addition to the above, cirrhotic patients with SVR should undergo surveillance for esophageal varices every one to two years and hepatocellular carcinoma every six months by means of ultrasonography and α-fetoprotein. <u>Retreatment of nonsustained virological responders to pegylated interferon alfa and ribavirin</u> • Patients infected with HCV genotype 1 who failed to eradicate HCV in prior therapy with pegylated interferon alfa and ribavirin should generally not be retreated with the same drug regimen. They may be considered for retreatment with the triple combination of pegylated interferon alfa, ribavirin and a protease inhibitor when available. • Nonsustained virological responders to a prior course of pegylated interferon alfa and ribavirin can be retreated with pegylated interferon alfa and ribavirin if they have urgent indication for therapy, and/or if there is evidence of inadequate exposure to either pegylated interferon alfa or ribavirin due to dose adjustments or poor compliance during the first course of treatment. • Patients infected with HCV genotypes other than 1 who failed on prior

Clinical Guideline	Recommendation(s)
	therapy with pegylated interferon alfa with or without ribavirin can be retreated with pegylated interferon alfa and ribavirin as no other options will be available soon. • Maintenance therapy with a low dose of pegylated interferon alfa is not recommended. Treatment of patients with severe liver disease • Patients with compensated cirrhosis should be treated, in the absence of contraindications, in order to prevent short to midterm complications. • Assiduous monitoring and management of side effects, especially those linked to portal hypertension and hypersplenism, is required. Growth factors are particularly useful in this group. • Patients with cirrhosis should undergo regular surveillance for hepatocellular carcinoma, irrespective of SVR. • In patients awaiting liver transplantation, antiviral therapy, when feasible, prevents graft reinfection if an SVR is achieved. • Antiviral therapy may be started at the time of enlistment or while awaiting liver transplantation, with the goal of achieving an SVR or HCV RNA clearance before transplantation. • Antiviral therapy is indicated in patients with conserved liver function in whom the indication for transplantation is hepatocellular carcinoma. • In patients with a Child-Pugh B cirrhosis, antiviral therapy is offered on an individual basis in experienced centers, preferentially in patients with predictors of good response. • Patients with Child-Pugh C cirrhosis should not be treated with the current antiviral regimen, due to a high risk of life-threatening complications. • Treatment can be started at low doses of pegylated interferon alfa and ribavirin, following a low accelerated dose regimen or at full doses. In the latter case, dose reductions and treatment interruptions are required in >50% of cases. • Patients with post-transplant recurrence of HCV infection should initiate therapy once chronic hepatitis is established and histologically proven. Significant fibrosis or portal hypertension one year after transplantation predicts rapid disease progression and graft loss and indicates urgent antiviral treatment. • There is no evidence of benefit from low dose pegylated interferon alfa maintenance therapy in patients who do not achieve an SVR. • Graft rejection is rare but may occur during pegylated interferon alfa treatment. A liver biopsy should be performed whenever liver tests worsen upon antiviral therapy to guide treatment decisions. Treatment of special groups • Indications for HCV treatment in patients with HIV coinfection are identical to those in patients with HCV monoinfection. The same pegylated interferon alfa regimen should be used in HIV coinfected patients, but the ribavirin dose should always be weight based. • Longer treatment duration (72 weeks for genotype 1 and 48 weeks for genotypes 2 and 3) may be needed in patients with HIV coinfection. • Patients coinfected with hepatitis B should be treated with pegylated interferon alfa and ribavirin, following the same rules as monoinfected patients. • If hepatitis B virus replicates at significant levels before, during or after HCV clearance, concurrent hepatitis B virus nucleoside/nucleotide analogue

Clinical Guideline	Recommendation(s)
	therapy is indicated. • Patients on hemodialysis can be safely treated with pegylated interferon alfa monotherapy; however, combination therapy with ribavirin can be considered in select patients. • Patients with HCV and end stage renal disease scheduled for kidney transplantation should undergo antiviral therapy prior to transplantation due to the increased risk of acute transplant rejection. • Regular alcohol consumption should be strongly discouraged. • Treatment of patients with active illicit drug abuse has to be individualized. • Patients with hemoglobinopathies can be treated with combination therapy but need careful monitoring. Follow up of untreated patients and of nonsustained responders • Untreated patients with chronic hepatitis C and nonsustained responders should be followed regularly. • Hepatocellular carcinoma screening must be continued indefinitely in patients with cirrhosis. Treatment of acute hepatitis C • Pegylated interferon alfa monotherapy for 24 weeks is recommended in patients with acute hepatitis C and obtains viral eradication in >90% of patients. • Patients failing to respond should be retreated according to the standard of care for chronic hepatitis C. Perspective of triple therapy with pegylated interferon alfa, ribavirin and protease inhibitors • New direct acting antiviral agents should be used only according to the package label. • Potential challenges should be considered when using HCV protease inhibitors in combination with pegylated interferon alfa and ribavirin and include: o Rapid emergence of drug resistance in particular in previous nonresponders, patients not fully adherent to therapy and patients not being able to tolerate optimal doses of pegylated interferon alfa and ribavirin treatment. o More strict and frequent monitoring of serum HCV RNA. o Lower response rates to triple therapy in patients with advanced liver fibrosis. o Adherence to recommended stopping rules for the antiviral agent and/or the entire treatment regimen. o Additional side effects associated with protease inhibitor treatment.
Centers for Disease Control and Prevention: **Hepatitis ABC Fact Sheet (2012)**[6]	Hepatitis B • Supportive treatment is the only recommended treatment for patients with acute disease. • Regular monitoring for signs of liver disease progression is required with chronic hepatitis B infections and some patients are treated with antiviral drugs. Hepatitis C • For acute hepatitis C, antivirals and supportive treatments are used. • Regular monitoring for signs of liver disease progression is required and some patients are treated with antiviral drugs.

Clinical Guideline	Recommendation(s)

American Gastroenterological Association: **Medical Position Statement on the Management of Hepatitis C (2006)**[7]	• The treatment of choice is pegylated interferon plus ribavirin.
	• Patients with genotypes 1 and 4 require 48 weeks of therapy with pegylated interferon and high daily doses of ribavirin (1,000 to 1,200 mg, depending on weight).
	• Patients with genotypes 2 and 3 can be treated for only 24 weeks with pegylated interferon and 800 mg of ribavirin daily, with the following exceptions:
	  ◦ A longer duration of therapy may be considered on an individual patient basis taking into account factors such as elevated viral level, cirrhosis, or delayed response to therapy.
	  ◦ Twelve weeks of therapy suffices in patients in whom HCV RNA levels are undetectable at week four.
	  ◦ Patients with genotype 3, with high levels of HCV RNA or advanced fibrosis on liver biopsy, may require treatment for 48 weeks.

National Comprehensive Cancer Network: **Melanoma (2012)**[79]	<u>Primary melanoma</u> • Although surgical excision remains the standard of care for in situ melanoma, it is sometimes not feasible due to comorbidity or cosmetically-sensitive tumor location. • Topical imiquimod has emerged as a treatment option, especially for lentigo maligna; however, long term comparative trials are needed. • Radiotherapy has also been used for lentigo maligna. • If positive margins remain after optimal surgery, topical imiquimod or radiotherapy may be considered in select patients. <u>Lymph node dissection</u> • If the sentinel node is negative, regional lymph node dissection is not indicated. • Patients with stage III disease based on a positive sentinel lymph node biopsy should be offered a complete lymph node dissection of the involved nodal basin, either as standard of care or in the context of a clinical trial evaluating alternative strategies. • Patients presenting with clinical stage III and clinically positive nodes, without radiologic evidence of distant metastases, should undergo wide excision of the primary site (if present) and complete lymph node dissection of the involved nodal basin. • In the setting of inguinal lymphadenopathy, a deep groin dissection is recommended if the positron emission tomography or pelvic computed tomography scan reveals iliac and/or obturator lymphadenopathy or if a positive Cloquet's lymph node is found intraoperatively. • Deep groin dissection also should be considered for clinically positive nodes or if more than three superficial nodes are involved. <u>Adjuvant treatment for melanoma</u> • Most patients with in situ or early stage melanoma will be cured by primary excision alone. • Adjuvant therapy is not recommended for patients with in situ or node negative primary melanoma. For patients with node negative early stage melanoma who are at risk for recurrence, adjuvant treatment options include a clinical trial or observation. • For patients with node negative stage IIB or IIC disease, adjuvant treatment options include clinical trial, observation or high dose interferon alfa. • For patients with stage III melanoma, adjuvant treatment options include

Clinical Guideline	Recommendation(s)
	clinical trial (preferred), observation or interferon alfa. • Pegylated interferon alfa is an alternative to high dose interferon in completely resected stage III disease with either positive sentinel nodes or clinically positive nodes, but not for stage III in-transit disease. • Treatment with adjuvant high dose or pegylated interferon alfa is a category 2B recommendation in all of the above cases due to low benefit to risk ratio. Decisions about the appropriateness of adjuvant interferon alfa-2b treatment for patients should be made on an individual basis, after discussion with the patient, including an explanation of the potential benefits and side effects of interferon therapy. • For all patients who have been rendered free of disease by surgery, following initial treatment for recurrent or metastatic disease (stage III in-transit metastases or stage IV), consideration of adjuvant treatment is appropriate. • There is no evidence in support of the use of adjuvant interferon alfa for completely resected stage IV disease. <u>Treatment of metastatic melanoma</u> • Stage III: in-transit metastases: o For patients with one or a small number of in-transit metastases, complete surgical excision with histologically negative margins is preferred, if feasible. o In the patient undergoing curative resection of a solitary in-transit metastasis, sentinel node biopsy can be considered because of the high probability of occult nodal involvement. o If the patient has a limited number of in-transit metastases, particularly dermal lesions, which are not amenable to complete surgical excision, intralesional local injections with bacillus Calmette-Guerin or interferon alfa or topical imiquimod can be considered. Laser ablation may be used in selected patients. o For patients with multiple, regional, in-transit metastases not suitable for local therapies, regional chemotherapy is an option. o Radiation therapy is included as a treatment option, recognizing its relative inefficiency in controlling regional disease and lack of effect on overall survival. o Other alternatives include systemic therapy (particularly after failure of local and/or regional therapy) or treatment in the context of a clinical trial. • Stage IV: distant metastatic disease: o Resection, if feasible, is recommended for limited metastatic disease. o In select patients with a solitary site of visceral metastatic melanoma, a short period of observation or systemic treatment followed by repeat scans may be appropriate to rule out the possibility that the visceral metastasis is the first of many metastatic sites and to better select patients for surgical intervention. Following observation, patients with resectable solitary sites of disease should be assessed for surgery. If resected, patients can be offered adjuvant treatment on clinical trial. o Adjuvant interferon alfa monotherapy is inappropriate for resected stage IV disease. o Limited metastatic disease can be treated with systemic therapy either in the context of a clinical trial (preferred) or as a standard of

Clinical Guideline	Recommendation(s)
	care. o Residual disease following incomplete resection for limited metastases is treated as described for disseminated disease. o Disseminated disease is treated based on the presence or absence of brain metastases. o Patients without brain metastases have the following options for systemic therapy: clinical trial (preferred); ipilimumab; dacarbazine, temozolomide or high dose interleukin-2; combination chemotherapy or biochemotherapy (dacarbazine or temozolomide-based including cisplatin and vinblastine, with or without interleukin-2, interferon alfa) or paclitaxel-based chemotherapy (single agent or in combination with cisplatin or carboplatin). o For patients with brain metastases, treatment of the central nervous system disease usually takes priority. Treatment is based on symptoms, number of lesions present and location of the lesions. In addition to systemic therapy, surgical resection and/or radiation may be considered for palliation or management of symptoms. o Best supportive care is an alternative for these patients. o In patients with both brain and extracranial metastases, appropriate therapy may be administered during or after treatment of the central nervous system with the exception of high dose interleukin-2.

Conclusions

Pegylated interferon alfa-2a (Pegasys®) is Food and Drug Administration (FDA) approved for the treatment of chronic hepatitis B and C, while pegylated interferon alfa-2b (PegIntron®) is approved for the treatment of chronic hepatitis C only. For the treatment of chronic hepatitis C, pegylated interferon alfa-2a can be use in patients at least five years of age compared to patients at least three years of age with pegylated interferon alfa-2b.[9,10] In addition, Sylatron® (pegylated interferon alfa-2b) was recently FDA approved as adjuvant treatment of melanoma.[11] The pegylated interferon alfa products are available as once-weekly subcutaneous injections and there are no generics available within the class.[9-11]

Combination treatment with pegylated interferon alfa and ribavirin remains the standard of care for the treatment of chronic hepatitis C.[3-7] The nonstructural protein 3 protease inhibitors, boceprevir and telaprevir, are recommended, along with standard of care, for the treatment of chronic hepatitis C genotype 1 infection.[4,5] Treatment guidelines do not give preference to one specific pegylated interferon alfa or ribavirin product over another.[3-7] Furthermore, no one protease inhibitor is preferred over another and current recommendations for their use are in line with FDA approved indications and dosing.[4,5]

Currently all FDA-approved antiviral agents are recommended as potential options for the treatment of chronic hepatitis B. Available agents include interferon products, pegylated interferon alfa products and nucleoside (entecavir, lamivudine, telbivudine) and nucleotide (adefovir dipivoxil, tenofovir disoproxil fumarate) analogues. While the American Association for the Study of Liver Diseases gives preference to entecavir, pegylated interferon alfa and tenofovir, the Centers for Disease Control and Prevention does not distinguish among the FDA-approved agents.[6,8]

The National Comprehensive Cancer Network recommends high dose interferon or pegylated interferon alfa-2b as adjuvant treatment options in patients with completely resected stage III disease with positive sentinel nodes or clinically positive nodes. Other options include a clinical trial (preferred) or observation.[79]

References

1. Dienstag JL. Chronic Viral Hepatitis. In: Mandell GL, Bennett JE, Dolin R, editors. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 7th ed [monograph on the Internet]. Orlando (FL): Churchill Livingstone; 2009 [cited 2013 Jul 17]. Available from: http://www.mdconsult.com/books/page.do?eid=4-u1.0-B978-0-443-06839-3..X0001-X&isbn=978-0-443-06839-3&uniqId=288453679-2#4-u1.0-B978-0-443-06839-3..X0001-X--TOP.
2. Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines. MMWR. 2010 Dec 17;59(No. RR-12):[1-110].
3. Ghany MG, Strader DB, Thomas DL, Seeff LB; American Association for the Study of Liver Diseases (AASLD). Diagnosis, management, and treatment of hepatitis C: an update. Hepatology. 2009 Apr;49(4):1335-74.
4. No authors listed; European Association for the Study of the Liver (EASL). EASL clinical practice guidelines: management of hepatitis C virus infection. J Hepatol. 2011 Aug;55(2):245-64.
5. Ghany MG, Nelson DR, Strader DB, Thomas DL, Seeff LB. An update on treatment of genotype 1 chronic hepatitis C virus infection: 211 practice guideline by the American Association for the Study of Liver Diseases. Hepatology. 2011 Oct;54(4):1433-44.
6. Centers for Disease Control and Prevention. Hepatitis ABC Fact Sheet [guideline on the Internet]. Atlanta (GA): CDC 2012 Aug [cited 2013 Jul 17]. Available at: http://www.cdc.gov/hepatitis/HCV/ProfResourcesC.htm#section1.
7. Dienstag JL, McHutchison JG. American Gastroenterological Association Medical position statement on the management of hepatitis C. Gastroenterology. 2006;130(1):225-30.
8. Lok AS, McMahon BJ. Chronic hepatitis B. Hepatology. 2009 Sep;50(3):1-38.
9. Pegasys® [package insert]. South San Francisco (CA): Genentech USA, Inc.; 2011 Oct.
10. PegIntron® [package insert]. Whitehouse Station (NJ): Merck & Co., Inc.; 2013 May.
11. Sylatron® [package insert]. Whitehouse Station (NJ): Merck & Co., Inc.; 2012 Dec.
12. Micromedex® Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Reuters (Healthcare) Inc.; Updated periodically [cited 2013 Jul 17]. Available from: http://www.thomsonhc.com/.
13. Caruntu FA, Streinu-Cercel A, Gheorghe LS, Grigorescur M, Sporea I, Stancui C, et al. Efficacy and safety of peginterferon alfa-2a (40KD) in HBeAg-positive chronic hepatitis B patients. J Gastrointestin Liver Dis. 2009;18(4):425-31.
14. Cooksley WG, Piratvisuth T, Lee SD, Mahachai V, Chao YC, Tanwandee T, et al. Peginterferon alfa-2a (40 kDa): an advance in the treatment of hepatitis B e antigen-positive chronic hepatitis B. J Viral Hepat. 2003 Jul;10(4):298-305.
15. Dinges S, Morard I, Heim M, Dufour JF, Mullhaupt B, Giostra E, et al. Pegylated interferon-alpha2a/ribavirin treatment of recurrent hepatitis C after liver transplantation. Transpl Infect Dis. 2009;11:33-9.
16. Hakim W, Sheikh S, Inayat I, Caldwell C, Smith D, Lorber M, et al. HCV Response in patients with end stage renal disease treated with combination pegylated interferon α-2a and ribavirin. J Clin Gastroenterol. 2009;43(5):477-81.
17. Makhzangy HE, Esmat G, Said M, Raziky ME, Shouman S, Refai R, et al. Response to pegylated interferon alfa-2a and ribavirin in chronic hepatitis C genotype 4. Journal of Medical Virology. 2009;81:1576-83.
18. Rodriquez-Torres M, Jeffers LJ, Sheikh M, Rossaro L, Ankoma-Sey V, Hamzeh FM, et al. Peginterferon alfa-2a and ribavirin in Latino and non-Latino whites with hepatitis C. N Engl J Med. 2009;360:257-67.
19. Balart LA, Lisker-Melman M, Hamzeh FM, Kwok A, Lentz E, et al. Peginterferon α-2a plus ribavirin in Latino and non-Latino whites with HCV genotype 1: histologic outcomes and tolerability from the LATINO Study. Am J Gastroenterol. 2010;105:2177-85.
20. Lam KD, Trinh HN, Do ST, Nguyen TT, Garcia RT, Nguyen T, et al. Randomized controlled trial of pegylated interferon-alfa 2a and ribavirin in treatment-naïve chronic hepatitis C genotype 6. Hepatology. 2010;52:1573-80.
21. Peck-Radosavljevic M, Boletis J, Besisik F, Ferraz ML, Alric L, Samuel D, et al. Low-dose peginterferon alfa-2a is safe and produces a sustained virologic response in patients with chronic hepatitis C and end-stage renal disease (abstract). Clin Gastroenterol Hepatol. 2011 Mar;9(3):242-8.

22. Kainuma M, Furusyo N, Kajiwara E, Takahasi K, Nomura H, Tanabe Y, et al. Pegylated interferon α-2b plus ribavirin for older patients with chronic hepatitis C. World J Gastroenterol. 2010 Sep 21;16(35):4400-9.
23. Moghaddam A, Melum E, Reinton N, Ring-Larsen H, Verbaan H, Bjoro K, et al. IL28B genetic variation and treatment response in patients with hepatitis C virus genotype 3 infection. Hepatology. 2011;53:746-54.
24. Ascione A, De Luca M, Tartaglione MT, Lampasi F, Di Constanzo GG, Lanz AG, 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;138:116-22.
25. Berenguer J, Garcia-Gonzalez J, Aldeguer-Lopez J, Von-Wichmann MA, Quereda C, Hernando A, et al. Pegylated interferon α-2a plus ribavirin pegylated interferon α2b plus ribavirin for the treatment of chronic hepatitis C in HIV-infected patients. Journal of Antimicrobial Chemotherapy. 2009;63:1256-63.
26. Di Bisceglie AM, Ghalib RH, Hamzeh FM, Rustgi VK. Early virologic response after peginterferon alfa-2a plus ribavirin or peginterferon alfa-2b plus ribavirin treatment in patients with chronic hepatitis C. J Viral Hepat. 2007;14(10):721-9.
27. Escudero A, Rodriguez F, Serra MA, del Olmo JA, Montes F, Rodrigo JM. Pegylated α-interferon-2a plus ribavirin compared to pegylated α-interferon-2b plus ribavirin for initial treatment of chronic hepatitis C virus: Prospective, non-randomized study. Journal of Gastroenterology and Hepatology. 2008;23:861-6.
28. Laguno M, Cifuentes C, Murillas J, Veloso S, Larrousse M, Payeras A, et al. Randomized trial comparing pegylated interferon α-2b vs pegylated interferon α-2a, both plus ribavirin, to treat chronic hepatitis C in human immunodeficiency virus patients. Hepatology. 2009;49(1):22-31.
29. Rumi M, Aghemo A, Prati GM, D'Ambrosio, Donato MF, Soffredini R, et al. Randomized study of peginterferon-α2a plus ribavirin vs peginterferon- α2b plus ribavirin in chronic hepatitis C. Gastroenterology. 2010;138(1):108-15.
30. Brixner DI, Ye X, Chu T, Blumentals WA, Hassanein TI. Treatment persistence in and cost of therapy for patients with chronic hepatitis C: peginterferon alfa-2a plus ribavirin vs peginterferon alfa-2b plus ribavirin. Am J Health-Syst Pharm. 2009;66:2171-8.
31. Kamal SM, Ahmed A, Mahmoud S, Nabegh L, Gohary IE, Obadan I, et al. Enhanced efficacy of pegylated interferon alfa-2a over pegylated interferon and ribavirin in chronic hepatitis C genotype 4A randomized trial and quality of life analysis. Liver Int. 2011 Mar;31(3):401-11.
32. McHutchison JG, Lawitz EJ, Shiffman ML, Muir AJ, Galler GW, McCone J, et al. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. N Engl J Med. 2009;361:580-93.
33. Muir AJ, Hu KQ, Gordon SC, Koury K, Boparai N, Noviello S, et al. Hepatitis C treatment among racial and ethnic groups in the IDEAL trial. J Viral Hepat. 2011;18:e134-e43.
34. Singal AK, Jampana SC, Anand BS. Peginterferon alfa-2a is superior to peginterferon alfa-2b in the treatment of naïve patients with hepatitis C virus infection: meta-analysis of randomized controlled trials. Dig Dis Sci. 2011;56:2221-6.
35. Bernstein D, Kleinman L, Barker CM, Revicki DA, Green J. 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.
36. Carrat F, Bani-Sadr F, Pol S, Rosenthal E, Lunel-Fabiani F, Benzekri A, et al. Pegylated interferon alfa-2b vs standard interferon alfa-2b, plus ribavirin, for chronic hepatitis C in HIV-infected patients: a randomized controlled trial. JAMA. 2004 Dec 15;292(23):2839-48.
37. Chung RT, Andersen J, Volberding P, Robbins GK, Liu T, Sherman KE, et al. Peginterferon alfa-2a plus ribavirin vs interferon alfa-2a plus ribavirin for chronic hepatitis C in HIV-coinfected persons. N Engl J Med. 2004 Jul 29;351(5):451-9.
38. Lindsay KL, Trepo C, Heintges T, Shiffman ML, Gordon SC, Hoefs JC, et al. A randomized, double-blind trial comparing pegylated interferon alfa-2b to interferon alfa-2b as initial treatment for chronic hepatitis C. Hepatology. 2001 Aug;34(2):395-403.
39. Zeuzem S, Feinman SV, Rasenack J, Heathcote EJ, Lai MY, Gane E, et al. Peginterferon alfa-2a in patients with chronic hepatitis C. N Engl J Med. 2000;343(23):1666-72.

40. Rasenack J, Zeuzem S, Feinman SV, Heathcote EJ, Manns M, Yoshida EM, et al. Peginterferon alfa-2a (40kD) [Pegasys] improves HR-QOL outcomes compared to unmodified interferon alfa-2a [Roferon-A]: in patients with chronic hepatitis C. Pharmacoeconomics. 2003;21(5):341-9.
41. Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Goncales FL Jr, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med. 2002 Sep 26;347(13):975-82.
42. Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, et al. Peginterferon alfa-2b plus ribavirin compared to interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomized trial. Lancet. 2001 Sep 22;358(9286):958-65.
43. Zhao S, Liu E, Wei K, Wang Y, Li Y, Huang B, et al. Treatment with peginterferon vs interferon in Chinese patients with chronic hepatitis C. Eur J Clin Microbiol Infect Dis. 2011;30:51-7.
44. Poordad F, McCone J Jr, Bacon BR, Bruno S, Manns MP, Sulkowski MS, et al. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med. 2011 Mar 31;364:1195-206.
45. Sherman KE, Flamm SI, Afdhal NH, Nelson DR, Sulkowski MS, Everson GT, et al. Response-guided telaprevir combination treatment for hepatitis C virus infection. N Engl J Med. 2011;365:1014-24.
46. Jacobson IM, McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, Bzowej NH, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. N Engl J Med. 2011;364:2405-16.
47. Di Bisceglie AM, Stoddard AM, Dienstag JL, Shiffman ML, Seeff LB, Bonkovsky HL, et al. Excess mortality in patients with advanced chronic hepatitis C treated with long-term peginterferon. Hepatology. 2011;53:1100-8.
48. Camma C, Cabibbo G, Bronte F, Enea M, Licata A, Attanasio M, et al. Retreatment with pegylated interferon plus ribavirin of chronic hepatitis C non-responders to interferon plus ribavirin: a meta-analysis [abstract]. J Hepatol. 2009;51(4):675-81.
49. Rustgi VK, Esposito S, Hamzeh FM, Shiffman ML. Peginterferon alfa-2a/ribavirin in hepatitis C virus patients nontolerant or nonresponsive to peginterferon alfa-2b/ribavirin. Aliment Pharmacol Ther. 2008 Mar 1;27(5):433-40.
50. Husa P, Oltman M, Ivanovski L, Rehak V, Messinger D, Tietz A, et al. Efficacy and safety of peginterferon α-2a (40 kD) plus ribavirin among patients with chronic hepatitis C and earlier treatment failure to interferon and ribavirin: an open-label study in central and Eastern Europe. Eur J Gastroenterol Hepatol. 2011;23:375-81.
51. Jensen DM, Marcellin P, Freilich B, Andreone P, Di Bisceglie A, Brandao-Mella CE, et al. Re-treatment of patients with chronic hepatitis C who do not respond to peginterferon- α-2b. Ann Intern Med. 2009;150:528-40.
52. Poynard T, Colombo M, Bruix J, Schiff E, Terg R, Flamm S, et al. Peginterferon alfa-2b and ribavirin: effective in patients with hepatitis C who failed interferon alfa/ribavirin therapy. Gastroenterology. 2009;136:1618-28.
53. Bacon BR, Gordon SC, Lawitz E, Marcellin P, Vierling JM, Zeuzem S, et al. Boceprevir for previously treated chronic HCV genotype 1 infection. N Engl J Med. 2011 Mar 31;364:1207-17.
54. Zeuzem S, Andreone P, Pol S, Lawitz E, Diago M, Roberts S, et al. Telaprevir for retreatment of HCV infection. N Engl J Med. 2011;364:2417-28.
55. Mecenate F, Pellicelli AM, Barbaro G, Romano M, Barlattani A, Mazzoni E, et al. Short vs 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;10:21-7.
56. Liu CH, Liu CJ, Lin CL, Liang CC, Hsu SJ, Yan SS, et al. Pegylated interferon-α-2a plus ribavirin for treatment-naïve Asian patients with hepatitis C virus genotype 1 infection: a multicenter, randomized controlled trial. CID. 2008;47:1260-9.
57. Shiffmann ML, Suter F, Bacon B, Nelson D, Harly H, Sola R, et al. Peginterferon alfa-2a and ribavirin for 16 or 24 weeks in HCV genotype 2 or 3. N Engl J Med. 2007;357:124-34.
58. Dalgard O, Bjoro K, Ring-Larsen H, Verbaan H. In patients with HCV genotype 2 or 3 infection and RVR 14 weeks treatment is noninferior to 24 weeks. Pooled analysis of two Scandinavian trials. Eur J Gastroenterol Hepatol. 2010 May;22(5):552-6.
59. Mangia A, Bandiera F, Montalto G, Mottola L, Piazzolla V, Minerva N, et al. Individualized treatment with combination of peg-interferon alpha 2b and ribavirin in patients infected with HCV genotype 3 (abstract). J Hepatol. 2010 Dec;53(6):1000-5.

60. Buti M, Lurie Y, Zakharova NG, Blokhina NP, Horban A, Teuber G, Sarrazine C, 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;52:1201-7.
61. Brady DE, Torres DM, An JW, Ward JA, Lawitz E, Harrison SA. Induction pegylated interferon alfa-2b in combination with ribavirin in patients with genotype 1 and 4 chronic hepatitis C: A prospective, randomized, multicenter, open-label study. Clinical Gastroenterology and Hepatology. 2010;8:66-71.
62. Dalgard O, Bjoro K, Ring-Larsen H, Bjornsson E, Holberg-Petersen M, Skovlund E, et al. Pegylated interferon alfa and ribavirin for 14 vs 24 weeks in patients with hepatitis C virus genotype 2 or 3 and rapid virological response. Hepatology. 2008;47:35-43.
63. Nagaki M, Shimizu M, Sugihara JI, Tomita E, Sano C, Naiki T, et al. Clinical trial: extended treatment duration of peginterferon alfa-2b plus ribavirin for 72 and 96 weeks in hepatitis C genotype 1-infected late responders. Aliment Pharmacol Ther. 2009 Aug 15;30(4):343-51.
64. Singal AK, Anand BS. Tailoring treatment duration to 12 to 16 weeks in hepatitis C genotype 2 or 3 with rapid virologic response. Systematic review and meta-analysis of randomized controlled trials. J Clin Gastroenterol. 2010;44:583-7.
65. Sokal EM, Bourgois A, Stephenne X, Silveira T, Porta G, Gardovska D, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection in children and adolescents. J Hepatol. 2010 Jun;52(6):827-31.
66. Schwarz KB, Mohan P, Narkewicz MR, Molleston JP, Nash, SR, Hu S, et al. Safety, efficacy and pharmacokinetics of peginterferon alfa2a (40kd) in children with chronic hepatitis C. J Pediatr Gastroenterol Nutr. 2006 Oct;43(4):499-505.
67. Baker RD, Dee D, Baker SS. Response to pegylated interferon alfa-2b and ribavirin in children with chronic hepatitis C. J Clin Gastroenterol. 2007;41:111-14.
68. Jara P, Hierro L, de la Vega A, Diaz C, Camarena C, Frauca E, et al. Efficacy and safety of peginterferon –alfa2b and ribavirin combination therapy in children with chronic hepatitis C infection. Pediatr Infect Dis J. 2008;27:142-8.
69. Wirth S, Pieper-Boustani H, Lang T, Ballauff A, Kullmer U, Gerner P, et al. Peginterferon alfa-2b plus ribavirin treatment in children and adolescents with chronic hepatitis C. Hepatology. 2005;41:1013-18.
70. Wirth S, Ribes-Koninckz C, Calzado MA, Bortolotti F, Zancan L, Jara P, et al. High sustained virologic response rates in children with chronic hepatitis C receiving peginterferon alfa-2b plus ribavirin. J Hepatol. 2010;52:501-7.
71. Rodrigue JR, Balistreri W, Haber B, Jonas MM, Mohan P, Molleston JP, et al. Peginterferon with or without ribavirin has minimal effect on quality of life, behavioral/emotional, and cognitive outcomes in children. Hepatology. 2011;53:1468-75.
72. Eggermont AMM, Suciu S, Santiami M, Testori A, Kruit WHJ, Marsden J, et al. Adjuvant therapy with pegylated interferon alfa-2b vs observation alone in resected stage III melanoma: final results of EORTC 18991, a randomized phase III trial. Lancet. 2008;372:117-26.
73. Pegylated interferon (peginterferon) alfa-2a: drug information. In: Basow DS (Ed). UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2013 [cited 2013 Jul 17]. Available from: http://www.utdol.com/utd/index.do.
74. Pegylated interferon (peginterferon) alfa-2a: drug information. In: Basow DS (Ed). UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2013 [cited 2013 Jul 17]. Available from: http://www.utdol.com/utd/index.do.
75. Copegus® [package insert]. South San Francisco (CA): Genentech, Inc.; 2011 Aug.
76. Rebetol® [package insert]. Kenilworth (NJ): Schering-Plough Corporation; 2010 Oct.
77. Ribasphere® [package insert]. Greenville (NC): DSM Pharmaceuticals, Inc.; 2011 Jun.
78. Drug Facts and Comparisons 4.0 [database on the Internet]. St. Louis: Wolters Kluwer Health, Inc.; 2013 [cited 2013 Jul 17]. Available from: http://online.factsandcomparisons.com.
79. National Comprehensive Cancer Network (NCCN). Melanoma [guideline on the Internet]. Fort Washington (PA): NCCN. 2012. Version 2 [cited 2013 Jul 17]. Available from: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp.