Therapeutic Class Overview
Hepatitis C Antivirals

Therapeutic Class

- **Overview/Summary:** This review will focus on the hepatitis C antiviral ribavirin.[1-4] The ribavirin products are all FDA-approved for the treatment of chronic hepatitis C in combination with pegylated interferon. Two ribavirin products, Copegus® and Moderiba®, are indicated for treating patients with chronic hepatitis C who are coinfected with human immunodeficiency virus.[1,4] 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. Chronic HCV infection can lead to the development of active liver disease, and accounts for up to 40% of all patients undergoing liver transplantation.[5,6] There are six genotypes of HCV (genotypes 1 to 6).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.[7] Triple therapy with pegylated interferon, ribavirin and a direct acting hepatitis C antiviral (polymerase inhibitors and protease inhibitors) is the current standard of care for the treatment of chronic hepatitis C for most genotypes. However, with the introduction of new oral hepatitis C antivirals such as sofosbuvir, SRV can be achieved without pegylated interferon, and thus dual therapy with sofosbuvir and ribavirin has become common.[7-10] Other guidelines have not been updated to include the newer agents.[11-15] Overall, guidelines do not give preference to one specific ribavirin or pegylated interferon product over another.[7-15]

  Ribavirin is available generically in a capsule and tablet formulation, while the solution (Rebetol®) is only available as a branded product. Ribasphere® RibaPak® is a branded unit dose pack containing seven days of therapy.[1-4] Virazole®, a branded ribavirin inhalation powder, is not included in this review as it is FDA-approved for the treatment of hospitalized infants and young children with severe lower respiratory tract infections due to respiratory syncytial virus.[16]

Table 1. Current Medications Available in the Therapeutic Class[1-4,17]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Ribavirin (Copegus®*)	Treatment of chronic hepatitis C virus infection in combination with Pegasys® (pegylated interferon alfa-2a) in patients ≥5 years of age with compensated liver disease not previously treated with interferon alfa; treatment of adult chronic hepatitis C virus infection coinfected with human immunodeficiency virus	Tablet: 200 mg	✔
Ribavirin (Moderiba®*)	Treatment of chronic hepatitis C virus infection in combination with peginterferon alfa-2a in adults with compensated liver disease not previously treated with interferon alpha; treatment of chronic hepatitis C virus infection in combination with peginterferon alfa-2a in adults coinfected with HIV	Tablet: 200 mg 400 mg 600 mg	✔
Ribavirin (Rebetol®*)	Treatment of chronic hepatitis C virus infection in combination with interferon alfa-2b (pegylated and nonpegylated) in patients ≥3 years of age with compensated liver disease	Capsule: 200 mg Solution: 40 mg/mL	✔
Ribavirin (Ribasphere®*, Ribasphere® RibaPak®)	Treatment of chronic hepatitis C virus infection in combination with pegylated interferon alfa-2a in adults with compensated liver disease and not previously treated with interferon alpha	Capsule: 200 mg Tablet: 200 mg 400 mg 600 mg	✔

*Generic available in at least one dosage form or strength.

Evidence-based Medicine

Clinical trials demonstrating the efficacy of ribavirin in combination with interferon or pegylated interferon (± other agents) has consistently shown effectiveness at achieving SVR.[20-69,71,72] Ribavirin should not be used as monotherapy for the treatment of hepatitis C.[1-4] The addition of a third agent to ribavirin and peg-interferon has significantly increased the rate of SVR compared to standard therapy. Protease inhibitors were the first direct acting hepatitis C antiviral to show efficacy.[37-39,48,49] Sofosbuvir, a polymerase inhibitor against hepatitis C combinations have achieved SVR rates consistently around 90%.[68-72]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - Triple therapy with pegylated interferon, ribavirin and a direct acting hepatitis C antiviral (polymerase inhibitors > protease inhibitors) is the current standard of care for the treatment of chronic hepatitis C for most genotypes.[7-10]
    - With the introduction of new oral hepatitis C antivirals such as sofosbuvir, SRV can be achieved without pegylated interferon, and thus dual therapy with sofosbuvir and ribavirin has become more common and is currently the recommended first line regimen for certain genotypes.
    - Dual therapy with sofosbuvir and ribavirin (and/or simeprevir) is the recommended first-line alterative in most genotypes if the patient is ineligible for interferon therapy.
  - Newer guidelines no longer recommend the use of older protease inhibitors (boceprevir and telaprevir), or recommended it a last-line alternative.[7-9]
    - Older guidelines still have not been updated to include the new direct acting hepatitis C antiviral agents.[11-15]
  - No ribavirin or pegylated interferon product is preferred or recommended over another.[7-15]

- Other Key Facts:
  - Ribavirin should not be used as monotherapy for the treatment of hepatitis C.[1-4]
  - Ribavirin is available generically as a capsule and a tablet. A solution and unit dose pack (seven days of therapy) is available as a branded product only.[1-4]

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Therapeutic Class Review
Hepatitis C Antivirals

Overview/Summary

This review will focus on the hepatitis C antiviral ribavirin.[1-4] 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 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.[5,6] There are six genotypes of HCV (genotypes 1 to 6).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.[7] 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.[7] Triple therapy with pegylated interferon, ribavirin and a direct acting hepatitis C antiviral (polymerase inhibitors and protease inhibitors) is the current standard of care for the treatment of chronic hepatitis C for most genotypes. However, with the introduction of new oral hepatitis C antivirals such as sofosbuvir, SRV can be achieved without pegylated interferon, and thus dual therapy with sofosbuvir and ribavirin has become more common.[7-10] Other guidelines have not been updated to include the newer agents.[11-15] Overall, guidelines do not give preference to one specific pegylated interferon or ribavirin product over another.[7-15] Ribavirin should not be used as monotherapy.[1-4]

The ribavirin products included in this review are FDA-approved for the treatment of chronic hepatitis C in combination with pegylated interferon. Two ribavirin products, Copegus® and Moderiba®, also have the indication of treating patients with chronic hepatitis C who are coinfected with human immunodeficiency virus.[1,4] Ribavirin is available generically in a capsule and tablet formulation, while the solution (Rebetol®) is only available as a branded product. Ribasphere® RibaPak® is a branded unit dose pack containing seven days of therapy.[1-4] Virazole®, a branded ribavirin inhalation powder, is not included in this review as it is FDA-approved for the treatment of hospitalized infants and young children with severe lower respiratory tract infections due to respiratory syncytial virus.[16]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Ribavirin (Copegus®*, Moderiba®*, Rebetol®*, Ribasphere®*, Ribasphere® RibaPak®, RibaTab®†)	Antiviral agent	✔

*Generic available in at least one dosage form or strength.
†Clinical information for this product is not available.

Indications

Table 2. Food and Drug Administration-Approved Indications[1-4]

Generic Name	Indications
Ribavirin (Copegus®)	Treatment of chronic hepatitis C virus infection in combination with Pegasys® (pegylated interferon alfa-2a) in patients ≥5 years of age with compensated liver disease not previously treated with interferon alfa
	Treatment of adult chronic hepatitis C virus infection coinfected with human immunodeficiency virus
Ribavirin (Moderiba®)	Treatment of chronic hepatitis C virus infection in combination with peginterferon alfa-2a in adults with compensated liver disease not previously treated with interferon alpha
Ribavirin	Treatment of chronic hepatitis C virus infection in combination with interferon alfa-2b

Generic Name	Indications
(Rebetol®)	(pegylated and nonpegylated) in patients ≥3 years of age with compensated liver disease
Ribavirin (Ribasphere®, Ribasphere® RibaPak®)	Treatment of chronic hepatitis C virus infection in combination with pegylated interferon alfa-2a in adults with compensated liver disease and not previously treated with interferon alpha

Ribavirin has the potential to be used off-label in the treatment of herpes simplex, influenza and viral hemorrhagic fever.[17]

Pharmacokinetics

Table 3. Pharmacokinetics[17]

Generic Name	Bioavailability (%)	Metabolism (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Ribavirin	64	Site unknown (percent not reported)	61	Ribavirin mono-, di- and triphosphate	298

Clinical Trials

Clinical trials demonstrating the safety and efficacy of ribavirin combination therapy for the treatment of hepatitis C are outlined in Table 4.[18-72] The use of ribavirin in combination with interferon or peg-interferon (± other agents) has consistently shown effectiveness at achieving SVR[20-69,71,72]

As noted in the Food and Drug Administration approved package labeling, ribavirin should not be used as monotherapy for the treatment of hepatitis C. A Cochrane review demonstrated that monotherapy with ribavirin was not effective in achieving a SVR compared to monotherapy with interferon (relative risk [RR], 1.14; 95% confidence interval [CI], 0.98 to 1.33) or placebo (RR, 1.01; 95% CI, 0.96 to 1.07).[19]

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 standard of care alone. However, triple therapy is associated with more side effects. The use of a protease inhibitor with pegylated interferon and ribavirin has been evaluated in treatment naïve and experienced patients.[37-39,48,49]

Use triple therapy including ribavirin, pegylated interferon, and the hepatitis C polymerase inhibitor, sofosbuvir, has been show to provide very SVRs in up to 90% of adult patients who were treatment naïve for all genotypes.[68,69,71,72] In addition, dual oral therapy (sofosbuvir and ribavirin) and oral triple therapy (simeprevir, sofosbuvir and ribavirin) has shown similar efficacy for SVR in several genotypes without the need for pegylated interferon.[69,70,72]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Hepatitis C				
Alam et al[18] Ribavirin (Ribasphere® RibaPak®) weight-based dosing (400 or 600 mg tablets) vs ribavirin weight-based dosing (200 mg tablets)	AC, MC, PRO Patients ≥18 years of age with chronic HCV who had been prescribed Ribasphere® RibaPak® or ribavirin tablets in addition to weekly peginterferon	N=503 24 weeks	Primary: Treatment adherence Secondary: Not reported	Primary: A greater proportion of patients treated with ribavirin prematurely discontinued treatment compared to patients treated with Ribasphere® RibaPak®. Significantly more patients treated with Ribasphere® RibaPak® compare to ribavirin remained on treatment at both weeks 12 and 24 (P<0.04), the greatest discontinuation rate occurred between weeks five and 12 where 15.9% of ribavirin-treated patients discontinued treatment compared to 8.1% of patients receiving Ribasphere® RibaPak®. The most common reasons for treatment discontinuation in the Ribasphere® RibaPak® group were intolerability to medication (31.1%), loss to follow-up (30.3%) and inadequate response to treatment (15.2%). In the ribavirin group, the most common reasons were loss to follow-up (30.5%), intolerability to study medication (25.4%) and inadequate response to treatment (22.0%). For patients remaining on treatment at four weeks, an equal proportion of Ribasphere® RibaPak® (9.4%) and ribavirin (9.4%) patients had missed doses of medication. For patients who remained on treatment up to 24 weeks, a greater proportion of ribavirin-treated patients had missed doses compared to patients treated with Ribasphere® RibaPak®; however, the differences were not statistically significant at 12 weeks (13.0 vs 9.4%, respectively, P=0.31) or 24 week (13.0 vs 11.7%, respectively; P=0.77). At the four- and 12-week follow-ups, there was no significant difference in the mean number of doses missed, either by objective or self-reported measurement, between the Ribasphere® RibaPak® and ribavirin groups. At 24 weeks there was a significantly greater mean number of missed doses for ribavirin compared to Ribasphere® RibaPak® when assessed by objective measurement (1.12 vs 0.36; P=0.01). For remaining on treatment through four and 12 weeks, the mean daily milligrams missed was no significantly different between Ribasphere® RibaPak® and ribavirin; however, the mean milligrams missed per day at 24

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				weeks was significantly greater in the ribavirin compared to Ribasphere® RibaPak® (47.1 vs 14.5 mg; P=0.01). For both the Ribasphere® RibaPak® and ribavirin groups, there was a statistically significant difference observed between the self-reported number of missed doses and the objectively measured number of missed doses at four and 12-weeks. Specifically, patients in both groups underreported the number of missed doses compared to the objective measurement of missed doses. At 24 weeks, the self-reported missed doses were also less than the objectively measured missed doses; however, the difference was not statistically significant. At four weeks, a similar proportion of Ribasphere® RibaPak®- and ribavirin-treated patients took ≥80% of their prescribed doses (92 vs 89%, respectively; P=0.30). At the 12 weeks, significantly more Ribasphere® RibaPak®-treated patients took ≥80% of their prescribed dose compared to patients treated with ribavirin (94 vs 84%; P=0.02). At 24 weeks, 98% of Ribasphere® RibaPak® patients took ≥80% of the prescribed dose compared to 89% of patients treated with ribavirin (P=0.005). Secondary: Not reported
Brok et al[19] Ribavirin vs placebo or no intervention vs interferon	MA Patients with chronic hepatitis C with the presence of HCV RNA plus elevated transaminases for >6 months or chronic hepatitis documented on liver biopsy	N=594 (13 RCTs) Duration varied	Primary: Failure of SVR, liver-related morbidity plus all-cause mortality Secondary: Failure of end of treatment response, failure of sustained biochemical response, failure of end of treatment biochemical	Ribavirin monotherapy seems without beneficial effects for patients with chronic hepatitis C. Primary: Ribavirin vs placebo or no intervention Ribavirin had no significant effect on SVR (RR, 1.01; 95% CI, 0.96 to 1.07). No significant difference in liver morbidity plus all-cause mortality was observed (OR, 1.96; 95% CI, 0.20 to 19.01). Ribavirin vs interferon Compared to ribavirin, interferon therapy did not significantly improve SVR (RR, 1.14; 95% CI, 0.98 to 1.33).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			response, failure of histologic response, quality of life, adverse events	None of the patients in the evaluated trials developed liver morbidity or died. Secondary: Ribavirin vs placebo or no intervention Ribavirin had no significant effect on end of treatment response (RR, 1.00; 95% CI, 0.94 to 1.07). No significant effect on sustained biochemical response was observed (RR, 1.00; 95% CI, 0.93 to 1.07). Ribavirin had a significant beneficial effect on end of treatment biochemical response (RR, 0.75; 95% CI, 0.68 to 0.81). Ribavirin had a significant beneficial effect on liver histology scores including inflammation and fibrosis assessment (RR, 0.70; 95% CI, 0.70 to 0.98). There was an increased risk of anemia seen with ribavirin therapy (RR, 6.99; 95% CI, 2.87 to 17.03), treatment discontinuations (RR, 2.19; 95% CI, 1.04 to 4.60) and dose reduction (RR, 6.61; 95% CI, 2.16 to 20.27). Ribavirin vs interferon Interferon therapy significantly improved the number of patients with end of treatment response (RR, 1.91; 95% CI, 1.36 to 2.66). Interferon therapy significantly improved the number of patients with sustained and end of treatment biochemical response. No significant differences in adverse events or treatment discontinuations were observed. No trials reported histological response or quality of life.
Brok et al[20] Interferon	MA (72 RCTs) Hepatitis C patients	N=9,991 Duration	Primary: Failure of SVR ≥6 months, liver-related	Primary: Compared to interferon, combination therapy significantly reduced the number of patients with failure of SVR (RR, 0.73; 95% CI, 0.71 to 0.75; P

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs interferon plus ribavirin	without HIV who were randomized to receive interferon monotherapy or a combination of ribavirin and interferon	varied	morbidity plus all-cause mortality Secondary: Failure of end of treatment virologic response, failure of histological response, quality of life, adverse events	value not reported). For the combined total of all patients evaluated, combination therapy significantly reduced morbidity plus mortality (OR, 0.46; 95% CI, 0.22 to 0.96; P value not reported); however, morbidity plus mortality was not significantly reduced compared to patients classified as naïve alone, nonresponders alone or relapsers alone (P values not reported). Secondary: Combination therapy significantly reduced the number of patients with failure of virologic response at end of treatment (RR, 0.70; 95% CI, 0.67 to 0.72; P value not reported). Failure of histological response was significantly reduced with combination therapy. Combination therapy significantly reduced the number of patients with failure with grading (RR, 0.84; 95% CI, 0.80 to 0.87; P value not reported) and staging (RR, 0.95; 95% CI, 0.92 to 0.97; P value not reported). Where measured, combination therapy was found to significantly increase quality of life, including measures of general health, social functioning and mental health (P values not reported). Anemia was reported in 22.0% of patients receiving combination therapy compared to 0.8% of patients receiving interferon (RR, 18.22; 95% CI, 12.92 to 25.70; P value not reported). Rates of leukopenia were significantly higher with combination therapy (RR, 4.32; 95% CI, 1.56 to 11.90; P value not reported). Rates of dermatological and gastrointestinal adverse events also occurred significantly more often with combination therapy.
McHutchison et al[21] Interferon alfa-2b 3 MIU three times a week vs	DB, PC, RCT Adult patients diagnosed with hepatitis C	N=912 24 to 48 weeks	Primary: SVR Secondary: ALT and histologic improvement	Primary: SVR rates were significantly higher with combination therapy (31 to 38%) compared to interferon (6 to 13%; P<0.001). Secondary: ALT levels normalized at the end of treatment in 58 to 65% of patients

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
interferon alfa-2b 3 MIU three times a week plus ribavirin 1,000 to 1,200 mg/day				receiving combination therapy compared to 24 to 28% of patients receiving interferon (P value not reported). Histologic improvement was significantly higher in patients receiving combination therapy (57 to 61%) compared to those receiving interferon (41 to 44%; P value not reported). Anemia necessitating a reduction in ribavirin dose occurred in eight percent of patients receiving combination therapy. Dyspnea, pharyngitis, pruritus, rash, nausea, insomnia and anorexia were more common with combination therapy (P value not reported). Dose reductions due to an adverse event occurred in 13 to 17% of patients receiving combination therapy compared to 9 to 12% of patients receiving interferon (P value not reported).
Poynard et al[22] Interferon alfa-2b 3 MIU three times a week plus ribavirin 1,000 to 1,200 mg/day for 24 weeks vs interferon alfa-2b 3 MIU three times a week plus ribavirin 1,000 to 1,200 mg/day for 48 weeks vs interferon alfa-2b 3 MIU three times a week for 48 weeks	MC, PC, RCT Adult patients with compensated hepatitis C not previously treated	N=832 48 weeks	Primary: SVR Secondary: ALT and histological improvement	Primary: SVR rates were significantly higher for both combination therapy regimens compared to interferon (P<0.001). SVR was observed in 43, 35 and 19% of patients receiving combination therapy for 48 weeks, for 24 weeks and patients receiving interferon. Secondary: ALT normalization was significantly higher with 48 weeks of combination therapy (50%) compared to 24 weeks of combination therapy (39%; P=0.02) and interferon (24%; P<0.001). Inflammation improvement was significantly higher with 48 weeks of combination therapy (63%) compared to 24 weeks of combination therapy (52%; P=0.05) and interferon (39%; P<0.001). Twenty four weeks of combination therapy had significantly greater improvement compared to interferon (52 vs 39%; P=0.007). Significantly more patients treated for 48 weeks (combination therapy and interferon) discontinued therapy due to an adverse reaction compared to those treated for 24 weeks (P value not reported).
Rodriguez-Torres et al[23] LATINO Study	MC, nonrandomized, OL, PRO	N=569 48 weeks	Primary: SVR	Primary: The SVR rate was significantly lower in Latino patients compared to non-Latino patients (34 vs 49%; absolute difference, -16%; 95% CI, -24 to -8;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Peginterferon alfa-2a 180 µg weekly plus ribavirin 1,000 or 1,200 mg/day	Patients 18 to 65 years of age with chronic HCV genotype 1 infection with no history of treatment for HCV infection	(plus 24 weeks follow up)	Secondary: Virologic response during the treatment period, relapse	P<0.001). Secondary: The rate of virologic response was lower among Latino patients at every time point at which data were available (week four; 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[24] 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; 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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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 regard 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 five to six vs zero to two and an Ishak fibrosis score of three to four vs zero to two 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 three to four vs zero to two and steatosis scores ≤5% vs >5% were significantly predictive of SVR. Baseline HCV RNA titers >400,000 and an Ishak fibrosis score five to six vs zero to two 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
Dinges et al[25] 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-	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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	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 six months after liver transplant and within the 12 months before the trial			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% in patients infected with HCV genotypes 2 or 3 and was 33% 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% 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 scheduled duration (P=0.02). Secondary: Not reported
Hakim et al[26] Peginterferon alfa-2a 135 µg weekly plus ribavirin 200 mg three 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% had a significant drop in their HCV levels at some point during treatment. Secondary: Not reported
Makhzangy et al[27] 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	N=95 24 weeks (treatment was	Primary: SVR Secondary: End of treatment	Primary: Fifty eight out of 95 patients (61.1%) achieved a SVR (95% CI, 50.5 to 70.9). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	chronic hepatitis C genotype 4, with positive HCV antibodies, detectable HCV RNA, elevated aminotransferases in the preceding six months and a liver biopsy showing Metavir score of ≥A1 and >F or >A1 and ≥F1	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)	response, safety, liver biopsy	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.
Lam et al[28] 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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Kainuma et al[29] 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[30] Peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 800 to 1,400 mg/day	RETRO (data from two clinical trials) Patients of Scandinavian origin with HCV genotype 3 and had been treated	N=281 24 weeks (patients who achieved a rapid virologic	Primary: Relationship between the IL28B genotype and viral response to therapy Secondary:	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 TT (77 vs 96%; P=0.038).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	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)	Relationship between the IL28B genotype and natural history of infection	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).
Escudero et al[31] 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				patients receiving peginterferon alfa-2b discontinued treatment early; 10 patients due to treatment related adverse events.
Ascione et al[32] 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 at least six months, negative pregnancy test, using contraception and no alcohol use for six 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 requiring hospitalization) were reported with either treatment.
Rumi et al[33] Peginterferon alfa-2a 180 µg weekly vs peginterferon alfa-2b 1.5 µg/mg weekly All patients received ribavirin.	OL, RCT Patients 18 to 70 years of age with hepatitis C previously untreated with serum HCV RNA, higher than normal ALT activity and a diagnostic liver biopsy done in the previous 24 months	N=431 24 (genotypes 2 and 3) or 48 weeks (genotypes 1 and 4) (plus 24 weeks of follow up)	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). 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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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
McHutchison et al[340] 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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 with peginterferon alfa-2a group (31.5 vs 23.5 and 20.0%; P values not reported).
Muir et al[35] 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).
Fried et al[36] Interferon alfa-2b 3 MIU three time a week plus ribavirin 1,000 to 1,200 mg/day vs peginterferon alfa-2a 180 µg weekly vs	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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
peginterferon alfa-2a 180 µg weekly plus ribavirin 1,000 to 1,200 mg/day				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[37] Interferon alfa-2b 3 MIU three 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 (high dose) vs peginterferon alfa-2a 1.5 µg/kg weekly for four weeks then 0.5 µg/kg weekly plus ribavirin 1,000 to 1,200 mg/day (low dose)	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). The side effect profiles were comparable among the treatments.
Zhao et al[38] Peginterferon (peginterferon alfa-2a, peginterferon alfa-2b)	MA (18 RCTs) Chinese patients with chronic hepatitis C infection	N=1,148 24 (genotypes 2 and 3)	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

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vs interferon (interferon alfa-2a, interferon alfa-2b, interferon alfa-1b) All patients received ribavirin.		or 48 weeks (plus 24 weeks of follow up)		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[39] SPRINT-2 Group one (control): Peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 600 to 1,400 mg/day for 44 weeks vs Group two (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 eight to	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 ≥10,000 IU/mL	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 one, two and three (P<0.001 vs Group one for both Group two and three). The corresponding numbers in black patients were 23, 42 (P=0.04 vs Group one) and 53% (P=0.004 vs Group one). 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 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 one, two and three, respectively. There were six deaths during the trial; four deaths in Group one and two deaths from boceprevir-containing regimens. Two suicides (one in Group one and one in Group two) 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
24 vs Group three (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 four-week lead in period in which peginterferon alfa-2b and ribavirin were administered. The trial consisted of two cohorts enrolling nonblacks and blacks separately. Treatment was considered complete in Group two if the HCV RNA level was undetectable from week eight through week 24 (total duration, 28 weeks). In all three treatment groups, treatment was discontinued for all				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
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[40] 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 plus ribavirin for 12 or 36 weeks. Patients who achieved an extended rapid virologic response (undetectable HCV RNA levels at weeks four and 12) after 20 weeks were randomized to continue peginterferon alfa-2a plus ribavirin for an additional four (24 weeks total treatment; T12PR24) or 28 weeks (48 total weeks of treatment; T12PR48). Patients who did not achieve an extended rapid virologic response	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
after 20 weeks received peginterferon alfa-2a plus ribavirin for an additional 28 weeks (48 total weeks of treatment).				
Jacobson et al[41] ADVANCE Telaprevir 750 mg three times a day plus 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 four 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 eight weeks, followed by an additional 16 or 40 weeks of peginterferon alfa-2a plus ribavirin based on HCV RNA levels weeks four and 12 (T8PR)	DB, PC, PG, RCT Patients 18 to 70 years of age with chronic HCV genotype 1 infection with no previous treatment	N=1,088 48 weeks (plus 24 weeks of follow up)	Primary: SVR Secondary: Proportion of 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	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). 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, pruritus, 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs peginterferon alfa-2a 180 µg weekly plus ribavirin 1,000 or 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 four 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 four or 12 received an additional 36 weeks of peginterferon alfa-2a plus ribavirin (48 total week of treatment).				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.
Lawitz et al[66] Cohort A (HCV genotype 1 patients): sofosbuvir 200 mg, sofosbuvir 400 mg, or placebo (randomized 2:2:1) for 12 weeks in combination with	DB, RCT Treatment-naive patients aged 18 to 70 with HCV genotypes 1, 2, and 3 and no cirrhosis	N=122 (Cohort A) N=25 (Cohort B)	Primary: Safety and tolerability Secondary: SVR12, SVR24	Primary: The most common adverse events during sofosbuvir dosing (up to week 12) were fatigue, headache, nausea, chills, pain, and insomnia. Most adverse events were mild or moderate in severity. Eight patients in cohort A discontinued treatment because of an adverse event, six within the first 12 weeks of treatment (three in the placebo group and three in the 400 mg sofosbuvir group). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
peginterferon (180 µg per week) and ribavirin (1000 to 1200 mg daily), followed by peginterferon and ribavirin for an additional 12 weeks or 36 weeks (depending on viral response) Cohort B (genotypes 2 or 3): open-label sofosbuvir 400 mg plus peginterferon and ribavirin for 12 weeks				In cohort A, compared with the placebo group, SVR12 and SVR24 were more common in the 200 mg sofosbuvir group (differences of 30%; 95% CI, 12 to 49; P=0.001, and 28%, nine to 46; P=0.0017, respectively) and in the 400 mg sofosbuvir group (differences of 32%; 13 to 51; P=0.0005, and 30%, 11 to 49; P=0.0006, respectively). Of the 25 patients in cohort B, most achieved both SVR12 and SVR24 (23 patients (92%) for both SVR12 and 24; 95% CI, 74 to 99).
Gane et al[67] Group 1: Sofosbuvir 400 mg and ribavirin 1,000 mg/day (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) for 12 weeks Group 2: Group 1 treatment plus 4 weeks of concomitant peginterferon alfa-2a 180 µg once weekly Group 3: Group 1 treatment plus 8 weeks of concomitant peginterferon alfa-2a 180 µg once weekly Group 4: Group 1	OL Patients19 years of age or older, who had chronic HCV infection without cirrhosis	N=95	Primary: Serum HCV RNA levels, safety Secondary: Not reported	Primary: Viral suppression was rapid in all patients, regardless of genotype, status with respect to previous treatment, baseline viral load, race or ethnic group, interleukin-28B status, and presence or absence of interferon in the regimen. All 95 patients had an undetectable level of HCV RNA by week four, with viral suppression sustained through the end of treatment. All 40 patients with HCV genotype 2 or 3 infection who received sofosbuvir and ribavirin for 12 weeks had an undetectable level of serum HCV RNA at two, four, eight, 12, 24, and 48 weeks after treatment. The presence or absence of peginterferon alfa-2a appeared to have no effect on viral kinetics or rate of sustained virologic response. Six of the 10 patients in the sofosbuvir monotherapy group had a sustained virologic response at 12 and 24 weeks after treatment. All 95 patients completed treatment. The most common adverse events were headache, fatigue, insomnia, nausea, rash, and anemia. Hematologic abnormalities were more common among patients who received interferon than among those who did not. Neutropenia and thrombocytopenia were not observed in the groups that did not receive interferon. However, sofosbuvir monotherapy was associated with a modest decrease in the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
treatment plus 8 weeks of concomitant peginterferon alfa-2a 180 µg once weekly (additional groups amended): Group 5: Sofosbuvir 400 mg daily monotherapy for 12 weeks Group 6: Sofosbuvir plus peginterferon and ribavirin for 8 weeks				hemoglobin level. Secondary: Not reported
Zeuzem et al[68] VALENCE Sofosbuvir 400 mg once daily for 12 weeks and ribavirin 1,000 mg/day (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) for 12 weeks vs placebo After study initiation, on the basis of emerging data from phase 3 trials, the study was unblinded, treatment for all patients with genotype 3 infection was extended to 24	DB, MC, PC, R Patients ≥18 years of age with confirmed diagnosis of chronic HCV infection (genotypes 2 or 3) and serum HCV RNA levels of ≥10,000 IU/mL during screening	N=419 12 weeks (genotype 2) or 24 weeks (genotype 3)	Primary: SVR12 Secondary: Not reported	Primary: Treatment with sofosbuvir plus ribavirin achieved a SVR12 in 93% (95% CI, 85 to 98) of patients with HCV genotype 2 receiving 12 weeks of therapy and 85% (95% CI, 80 to 89) of patients with HCV genotype 3 receiving 24 weeks of therapy. Among patients with genotype 2 infection receiving sofosbuvir plus ribavirin, high SVR12 rates were observed in treatment-naïve non-cirrhotics (96.7%; 95% CI, 82.8 to 99.9), treatment-naïve cirrhotics (100%; 95% CI, 15.8 to 100), and treatment-experienced non-cirrhotics (93.8%; 95% CI, 79.2 to 99.2), whereas lower SVR12 rate was observed in treatment-experienced cirrhotics with genotype 2 infection (77.8%; 40.0 to 97.2). Similarly, among patients with genotype 3 infection receiving sofosbuvir plus ribavirin, high SVR12 rates were observed in treatment-naïve non-cirrhotics (94.6%; 95% CI, 86.3 to 97.6), treatment-naïve cirrhotics (92.3%; 95% CI, 64.0 to 99.8), and treatment-experienced non-cirrhotics (86.7%; 95% CI, 78.4 to 92.7), whereas lower SVR12 rate was observed in treatment-experienced cirrhotics with genotype 3 infection (61.7%; 46.4 to 75.5).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
weeks, the placebo group was terminated, and the goals of the study were redefined to be descriptive and not include hypothesis testing.				Secondary: Not reported
Hepatitis C – Retreatment				
Enriquez et al[42] Interferon alfa-2b 3 MIU three times a week plus ribavirin 1,000 to 1,200 mg/day for 24 weeks vs interferon alfa-2b 3 MIU the times a week plus ribavirin 1,000 to 1,200 mg/day for 48 weeks	RCT Adult patients with hepatitis C who had previously received at least one courses of interferon alfa without achieving a sustained response	N=120 24 to 48 weeks (plus 24 weeks of follow up)	Primary: End of treatment response, SVR Secondary: Not reported	Primary: End of treatment response rates were 44.8 and 46.8% with 24 and 48 weeks of treatment (P=0.85). SVR rates were significantly higher with 48 weeks of treatment compared to 24 weeks (37.1 vs 15.5%; P=0.013). Dose adjustments due to decreased hemoglobin levels occurred in 5% of patients treated for 48 weeks and 3% in those treated for 24 weeks (P value not reported). Influenza-like symptoms were reported in most patients for both treatment groups during the first two to four weeks. Secondary: Not reported
Rustgi et al[43] 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Husa et al[44] 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 and detectable HCV RNA	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: 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[45] 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	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	N=950 (Total) N=318 (Group A) N=158 (Group B) N=158 (Group C) N=316	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
alfa-2a 180 µg weekly for 36 weeks (Group B) vs peginterferon alfa-2a 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.	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 detectable serum HCV RNA after baseline assessment; treatment must have been discontinued ≥12 weeks before enrollment	(Group D) 48 to 72 weeks (plus 24 weeks of follow up)		
Poynard et al[46] 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	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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	for women and ≥13 g/dL for men, absolute neutrophil count ≥1,500/mm^3, platelet count ≥80,000/mm^{3}and body weight of 40 to 125 kg			Secondary: Not reported
Camma et al (abstract)[47] 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
Bacon et al[48] RESPOND-2 Group one (control): Peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 600 to 1,400 mg/day for 44 weeks vs Group two (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,	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 one, two and three, respectively (P<0.001). The increase observed with Groups two and three 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 one. The absolute difference between Groups two and one was 34.7 percentage points (95% CI, 25.7 to 49.1), and between Groups three and one it was 45.2 percentage points (95% CI, 33.7 to 56.8). There was no difference in SVR rates between Groups two and three (OR, 1.4; 95% CI, 0.9 to 2.2). Overall, the most common adverse events were flu-like 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
followed by an additional 12 weeks of peginterferon alfa-2b plus ribavirin in detectable HCV RNA levels at week eight but undetectable at week 12 vs Group three (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 four-week lead in period in which peginterferon alfa-2b and ribavirin were administered. Treatment was considered complete in Group two if the HCV RNA level was undetectable at weeks eight and 12 (total duration, 36 weeks). In addition, in all three treatment groups, treatment was				receiving boceprevir. Secondary: The proportion of patients with an undetectable HCV RNA level at week eight in Groups two and three (46 and 52%) was approximately six times the proportion in Group one (9%). Early response was associated with a high rate of SVR in all three treatment groups (100, 86 and 88% in Groups one, two and three; 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 one, two and three; 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 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 two and three vs Group one, 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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
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.				
Zeuman et al[49] REALIZE Telaprevir 750 mg 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 four 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)	DB, PC, RCT Patients 18 to 70 years of age with chronic HCV genotype 1 infection, no SVR to one previous course of peginterferon alfa and ribavirin despite receiving at least 80% of the intended dose	N=662 48 weeks (plus 24 weeks of follow up)	Primary: SVR Secondary: 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	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 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.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs peginterferon alfa-2a 180 µg weekly and ribavirin 1,000 to 1,200 mg/day for 48 weeks (control) Patients could have one of three 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).				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.
Hepatitis C - Varying Treatment Duration				
Ho et al[50] Interferon alfacon-1 15 µg/day plus ribavirin 1,000 to 1,200 mg/day for 52 weeks (Group A) vs	MC, OL, RCT Adult patients with HCV genotype 1 infection and "difficult-to-treat" characteristics (male, 92%; African American, 33%; Veterans Affairs, 78%; high viral load,	N=64 52 or 72 weeks (plus 24 weeks of follow up)	Primary: Efficacy, tolerability Secondary: Not reported	Primary: Pooled ITT analysis demonstrated that 31% (20/64) of patients achieved a rapid virologic response after four weeks. Twenty percent (13/64) of patients were complete early virologic responders between weeks eight and 12 and 14% (9/64) of patients were late virologic responders between weeks 12 and 24. Fifty two percent of patients overall were viral negative after 12 weeks, 52% of patients were viral negative after 24 weeks and 42% of patients were viral negative after 52 weeks. Based on ITT data, the final SVR rate was 33%. Separately there was no difference in viral

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
interferon alfacon-1 15 µg/day plus ribavirin 1,000 to 1,200 mg/day for 52 to 72 weeks, depending on the time to achieving viral negativity (Group B)	67%; stage three to four fibrosis and mean body weight of 204 lbs)			negativity rates between Groups A and B (36 [12/33] vs 48% [15/31]) through 52 weeks. Final SVR rates were not different between the two groups (33 [11/33] vs 32% [10/31]) (P values not reported). Overall, patients with a rapid virologic response demonstrated a 75% (15/20) SVR. Rates among patients with complete early and late virologic responses were 29 (6/21) and zero percent (0/1), respectively. Overall, 61 (39/64) and 41% (26/64) of patient required an interferon alfacon-1 and ribavirin dose reduction. Reasons for dose reduction included neutropenia, anxiety/depression, flu-like syndromes, unknown side effect, tremor, headache/pain, retinopathy, dyspnea, weight loss, skin rash, anemia and dizziness/fatigue. Secondary: Not reported
Mecenate et al[51] Peginterferon alfa-2a 180 µg week plus ribavirin 800 to 1,200 mg/day If HCV RNA after four weeks of treatment was <50 IU/mL (rapid virologic response), patients were randomized to 12 (Group one) or 24 weeks of treatment (Group two); those with HCV RNA ≥50 IU/mL after four weeks were treated for 24 weeks (Group three).	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 received 12 weeks of treatment, 71 patients achieved rapid virologic	Primary: SVR Secondary: Safety	Primary: SVR rates were the following: Group one, 83% (60/72 patients); Group two, 75% (53/71 patients) and Group three, 49% (33/67 patients; P values not reported). Secondary: From Group two, five patients (7%) withdrew from the trial due to adverse events and seven patients (10%) from Group three withdrew due to adverse events. Significantly more patients in Group three (seven patients) discontinued the medication due to adverse events than Group one (zero patients; P<0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
		response and received 24 weeks of treatment and 67 patients did not achieve rapid virologic response and received 24 weeks of treatment)		
Liu et al[52] 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 at least months, HCV genotype 1 infection, ALT level greater than the upper limit of normal and liver histologic characteristics consistent with chronic viral hepatitis within the previous three 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.
Shiffman et al[53] Peginterferon alfa-2a 180 µg weekly for 16 weeks	MC, NI, RCT Patients ≥18 years of age diagnosed with HCV genotype 2 or 3	N=1,465 16 or 24 weeks (plus 24	Primary: SVR Secondary: Rapid virologic	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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs peginterferon alfa-2a 180 µg weekly for 24 weeks All patients received ribavirin 800 mg/day.	infection, HCV RNA level >600 IU/mL, elevated ALT and liver biopsy consistent with chronic HCV infection	weeks of follow up)	response, virologic relapse, safety	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[54] Peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 800 to 1,200 mg/day	Pooled analysis of 1 RCT and 1 non-RCT Treatment-naïve patients with HCV genotype 2 or 3 infection, elevated ALT levels and rapid virologic response	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. 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Mangia et al (abstract)[55] 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 four 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
Nagaki et al[56] 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 mg/day for 48 weeks (96 weeks total treatment)	MC, OL, PG, RCT Patients >18 years of age with HCV genotype 1 infection who were late responders (HCV RNA positive after eight 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
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.				
Buti et al[57] SUCCESS Peginterferon alfa-2b 1.5 µg/kg weekly for 48 weeks vs peginterferon alfa-2b 1.5 µg/kg weekly for 72 weeks All patients received ribavirin 800 to 1,400 mg/day. Patients with detectable HCV RNA at week 12 (slow responders) were randomized to continue treatment for a total of 48 or 72 weeks.	MC, OL, PRO, RCT Patients 18 to 70 years of age with compensated chronic hepatitis C infection who were considered slow responders based on HCV RNA levels after 12 weeks of standard of care	N=159 48 or 72 weeks (plus 24 weeks of follow up)	Primary: SVR, relapse Secondary: Safety	Primary: SVR rates were 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% with 72 and 48 weeks (P value not reported). Relapse rates were similar with 48 and 72 weeks of treatment (47 vs 33%; P=0.169). Secondary: The safety profile was similar in both 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.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Dalgard et al[58] 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 four 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.
Singal et al[59] 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
Kowdley et al[64] ATOMIC Cohort A: sofosbuvir 400 mg orally once daily, peginterferon 180 µg subcutaneously once a week, and ribavirin orally as a divided weight-based daily dose (<75 kg received 1000 mg and those ≥75 kg received 1200 mg) for 12 weeks vs Cohort B received the same drugs at the same doses for 24 weeks vs Cohort C received the same regimen as individuals in cohort A followed by an additional 12 weeks of sofosbuvir monotherapy for half the patients, or sofosbuvir plus ribavirin for the other half (with patients randomly allocated to these subcohorts)	MC, OL, R Patients with chronic HCV infection (genotypes 1, 4, 5, or 6),18 years of age or older, and had not previously received treatment for HCV infection	N=316 12 to 24 weeks (plus 24 weeks of follow up)	Primary: SVR24 Secondary: Safety	Primary: The portion of patients that achieved SVR24 were 89 % in Cohort A (46/52; 95% CI, 77 to 96%), 89% in Cohort B (97/109; 95% CI, 82 to 94%) and 87% in Cohort C (135/155; 95% CI, 81 to 92%). No difference was found in the proportions of patients achieving SVR24 between cohorts A and B (P=0.94) or between cohorts A and C (P=0.78), suggesting no additional benefit of treatment durations longer than 12 weeks. Secondary: Most patients (97 to 99%) had at least one adverse event during the study. The most common adverse events were those consistent with the known safety profile for peginterferon and ribavirin: fatigue, headache, and nausea.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Lawitz et al[65] NEUTRINO and FISSION NEUTRINO: Sofosbuvir 400 mg once daily for 12 weeks, peginterferon alfa-2a 180 µg once weekly for 12 weeks, and ribavirin 1,000 mg/day (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) for 12 weeks FISSION: Sofosbuvir 400 mg once daily for 12 weeks and ribavirin 1,000 mg/day (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) for 12 weeks vs peginterferon alfa-2a 180 µg once weekly for 24 weeks and ribavirin 800 mg/day in two divided doses for 24 weeks	NEUTRINO: MC, OL, SG Patients ≥18 years of age with confirmed diagnosis of chronic HCV infection (genotypes 1, 4, 5, or 6), serum HCV RNA levels of ≥10,000 IU/mL during screening, and who had never received treatment for HCV infection FISSION: AC, MC, OL, R Patients ≥18 years of age with confirmed diagnosis of chronic HCV infection (genotypes 2 or 3), serum HCV RNA levels of ≥10,000 IU/mL during screening, and who had never received treatment for HCV infection	NEUTRINO: N=327 12 weeks FISSION: N=499 24 weeks	NEUTRINO: Primary: SVR12 Secondary: Not reported FISSION: Primary: SVR12 Secondary: Not reported	NEUTRINO: Primary: Treatment with sofosbuvir added to peginterferon alfa-2a and ribavirin achieved a SVR12 in 90% of patients (95% CI, 87 to 93). In addition, this regimen was found to be more effective in achieving a SVR12 compared to an adjusted historical response rate of 60% (P<0.001) observed in studies of telaprevir and boceprevir. The rate of SVR12 was 92% (95% CI, 89 to 95) among patients without cirrhosis and 80% (95% CI, 67 to 89) among those with cirrhosis. A SVR12 occurred in 98% of patients with the CC genotype of IL28B, as compared to 87% of patients with the non–CC IL28B genotype. Rates of SVR12 were similar among various HCV genotypes: 89% for patients with genotype 1 (92% for genotype 1a and 82% for genotype 1b) and 96% for those with genotype 4. The single patients with genotype 5 and all six patients with genotype 6 achieved SVR12. Secondary: Not reported FISSION: Primary: A SVR12 was achieved in 67% of patients in both sofosbuvir plus ribavirin group and peginterferon alfa-2a plus ribavirin group. Response rates in patients receiving sofosbuvir plus ribavirin were lower among patients with genotype 3 infection than among those with genotype 2 infection (56 vs 97%). Among patients with cirrhosis at baseline, 47% of patients receiving sofosbuvir plus ribavirin had a SVR12 compared to 38% of those receiving peginterferon alfa-2a plus ribavirin. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Hepatitis C - Pediatric Patients				
Sokal et al[60] Peginterferon alfa-2a 100 µg/m^2 weekly plus ribavirin 15 mg/kg/day	MC, OL, PRO Children six 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[61] 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 two to eight 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 events. Three others withdrew due to administrative reasons.
Schwarz et al[62] Peginterferon alfa-2a 180	MC, PC, RCT Children five to 18	N=114 48 weeks	Primary: SVR	Primary: SVR rates were 53 and 21% with combination and monotherapy (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
µg/1.73 m^2 weekly plus ribavirin 15 mg/kg/day vs peginterferon alfa-2a 180 µg/1.73 m^2 weekly	years of age with chronic HCV infection documented by the presence of HCV RNA in plasma on two occasions at least six months apart and chronic liver disease as indicated by inflammation and/or fibrosis consistent with chronic HCV infection on liver biopsy specimen obtained within the past 36 months	(plus 24 weeks of follow up)	Secondary: Safety	Secondary: Influenza-like, headache and gastrointestinal symptoms occurred in almost all patients. Therapy was discontinued in five (4%) of the 114 patients, four patients receiving combination therapy and one patient receiving monotherapy.
Baker et al[63] 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.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Jara et al[64] Peginterferon-alfa-2b 1 µg/kg weekly plus ribavirin 15 mg/kg/day	OL Children three 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 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[65] 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[66] Peginterferon alfa-2b 60 µg/m^2/week plus ribavirin 15 mg/kg/day	MC, OL Children three to 17 years of age with previously untreated chronic hepatitis C, absolute neutrophil count ≥1,500/m^3,	N=107 24 (genotypes 2 or genotype 3 with a low viral load) or	Primary: SVR Secondary: Early virologic response, end of treatment response, relapse, ALT	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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	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	48 weeks (genotypes 1, 4 or 3 with a high viral load) (plus 24 weeks of follow up)	normalization	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[67] Peginterferon alfa-2b plus ribavirin vs peginterferon alfa-2b	MC, PC, PRO, RCT Children five to 18 years of age with documented HCV viremia on two tests at least six months apart and/or one 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	N=114 24 or 48 weeks (plus 24 weeks of follow up)	Primary: CHQ-Parent Form 50 scores, CBCL scores, BRIEF scores Secondary: Not reported	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 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 regard 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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. Secondary: Not reported

Drug regimen abbreviations: MIU=million international units
Study abbreviations: CI=confidence interval, DB=double-blind, ITT=intention to treat analysis, MA=meta-analysis, MC=multicenter, NI=non-inferiority, 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, HCV=hepatitis C virus, HIV=human immunodeficiency virus, IU=international units, NASH=nonalcoholic steatohepatitis, RNA=ribonucleic acid, SVR=sustained virologic response

Special Populations

Table 5. Special Populations[1-4,17]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Ribavirin	No dosage adjustment required in the elderly. Safety and efficacy in children have not been established (Moderiba®, Ribasphere®, Ribasphere® RibaPak®). Safety and efficacy in children <5 years of age have not been established (Copegus®). Safety and efficacy in children <3 years of age have not been established (Rebetol®).	Not recommended with creatinine clearances <50 mL/minute.	No dosage adjustment required. Use of ribavirin tablets is contraindicated with hepatic decompensation.	X	Unknown; use with caution.

Adverse Drug Events

Adverse events outlined in Table 6 are reported from clinical trial data in which ribavirin was administered in combination with a nonpegylated interferon or pegylated interferon. [1-4,17]

Table 6. Adverse Drug Events (%)[1-4,17]

Adverse Drug Event	Ribavirin
Central Nervous System	
Agitation	8 to 5
Anxiety	10 to 11
Anxiety/emotional lability/irritability	6 to 47
Concentration impairment	5 to 21
Depression	19 to 37
Dizziness	13 to 26
Headache	39 to 69
Insomnia	9 to 41
Irritability	14 to 32
Irritability/anxiety/nervousness	33 to 38
Nervousness	2 to 38
Memory impairment	5 to 6
Mood alteration	9
Endocrine Disorders	
Hypothyroidism	4 to 5
Flu-like Symptoms and Signs	
Chills	21 to 39
Fatigue/asthenia	4 to 68
Fatigue	25 to 72

Adverse Drug Event	Ribavirin
Fever	21 to 80
Influenza-like illness	13 to 91
Malaise	4 to 6
Pain	9 to 10
Pyrexia	41 to 55
Rigors	25 to 48
Gastrointestinal	
Abdominal pain, upper	12
Abdominal pain/discomfort/cramping	8 to 21
Anorexia	11 to 51
Constipation	5
Diarrhea	10 to 22
Dry mouth	4 to 7
Dyspepsia/heartburn	<1 to 16
Gastrointestinal disorder	44 to 49
Nausea	18 to 47
Vomiting	8 to 42
Hematologic Disorders	
Anemia	11 to 35
Leukopenia	5 to 10
Lymphopenia	12 to 14
Neutropenia	8 to 40
Thrombocytopenia	<8
Metabolic and Nutritional	
Weight decrease	10 to 29
Musculoskeletal	
Arthralgia	15 to 36
Back pain	5
Musculoskeletal pain	19 to 35
Myalgia	17 to 64
Respiratory	
Cough	7 to 23
Dyspnea	5 to 26
Dyspnea, exertional	4 to 7
Pharyngitis	12 to 13
Rhinitis	8 to 6
Sinusitis	<1 to 14
Skin and Subcutaneous Tissue	
Alopecia	17 to 36
Dermatitis	13 to 16
Dry skin	10 to 24
Eczema	4 to 5
Pruritus	4 to 29
Rash	5 to 34
Sweating increased	5 to 11
Other	
Chest pain	4 to 9
Conjunctivitis	4 to 5
Decreased appetite	11 to 29
Flushing	3 to 4
Hepatomegaly	4

Adverse Drug Event	Ribavirin
Injection site erythema	29
Injection site inflammation	6 to 25
Injection site reactions	3 to 58
Menstrual disorder	6 to 7
Resistance mechanism, fungal infection	1 to 6
Resistance mechanism, viral infection	12
Resistance mechanism disorders, overall	10 to 12
Right upper quadrant pain	6 to 12
Taste perversion	<1 to 9
Unspecified pain	9 to 13
Vision blurred	2 to 6

Contraindications

Table 7. Contraindications[1-4,17]

Contraindication	Ribavirin
Autoimmune hepatitis	✔
Combination treatment with didanosine	✔
Creatinine clearance <50 mL/minute	✔
Hepatic decompensation in cirrhotic patients monoinfected with chronic hepatitis C before treatment	✔
Hepatic decompensation in cirrhotic patients with chronic hepatitis C who are coinfected with the human immunodeficiency virus before treatment	✔
Known hypersensitivity reactions such as Stevens-Johnson syndrome, toxic, epidermal necrolysis and erythema multiforme	✔
Men whose female partners are pregnant	✔
Patients with hemoglobinopathies (e.g., thalassemia major or sickle-cell anemia)	✔
Women who are or may become pregnant	✔

Black Box Warnings for Copegus® (ribavirin), Moderiba® (ribavirin Rebetol® (ribavirin) and Ribasphere®/Ribasphere® RibaPak® (ribavirin)[1-4]

WARNING
Ribavirin monotherapy is not effective for the treatment of chronic hepatitis C virus infection and should not be used alone 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.

As mentioned previously, ribavirin should not be used as monotherapy for the treatment of hepatitis C. Standard of care for the treatment of hepatitis C remains pegylated interferon and ribavirin; however, nonpegylated interferon products are also available for use in certain clinical situations.

Black Box Warning for Pegasys® (peginterferon alfa-2a) and PegIntron® (peginterferon alfa-2b)[64]

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 Intron® (interferon alfa-2b)[64]

WARNING
Alpha interferons, including interferon alfa-2b and alfacon-1, may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic and infectious disorders. Monitor patients closely with periodic clinical and laboratory evaluations. Withdraw therapy from patients with persistently severe or worsening signs or symptoms of these conditions. In many but not all cases these disorders resolve after stopping interferon alfa-2b or alfacon-1 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. Ribavirin is genotoxic and mutagenic and should be considered a potential carcinogen.

Black Box Warning for Infergen® (interferon alfacon-1)[64]

WARNING
Alpha interferons, including interferon alfa-2b and alfacon-1, may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic and infectious disorders. Monitor patients closely with periodic clinical and laboratory evaluations. Withdraw therapy from patients with persistently severe or worsening signs or symptoms of these conditions. In many but not all cases these disorders resolve after stopping interferon alfa-2b or alfacon-1 therapy.

Warnings/Precautions

Table 8. Warnings and Precautions[1-4,17]

Warning/Precaution	Ribavirin
Anemia; fatal and nonfatal myocardial infarction have been reported	✔
Bone Marrow Suppression; pancytopenia has been reported following the initiation of treatment with ribavirin and pegylated interferon with coadministered azathioprine; discontinue azathioprine for pancytopenia	✔
Contraception; two forms of contraception and monthly pregnancy tests should be used throughout treatment and for six months following completion of therapy	✔
Dental and periodontal disorders; patients should brush teeth twice daily and have regular dental exams while on treatment	✔ (Rebetol®, Ribasphere®)
Growth velocity in pediatric patients; may be reduced while receiving concomitant	✔

Warning/Precaution	Ribavirin
treatment with pegylated interferon	(Copegus®, Rebetol®, Ribasphere®)
Hemolytic anemia; monitor hemoglobin prior to treatment and at two and four weeks after initiating therapy	✔
Laboratory abnormalities; hematological and blood chemistries should be performed at baseline and periodically thereafter	✔
Monotherapy; ribavirin is not effective as monotherapy	✔
Ophthalmic disorders; patients should receive ophthalmologic exams at baseline	✔
Pancreatitis; discontinue treatment in cases of confirmed pancreatitis	✔
Pregnancy; withhold until a negative pregnancy test has been confirmed	✔
Pulmonary disorders; closely monitor patients with evidence of pulmonary infiltrates or pulmonary function impairment	✔

Drug Interactions

Table 9. Drug-Drug Interactions[1-4,17,64]

Drugs	Interaction	Mechanism
Hepatitis C antivirals (ribavirin)	Didanosine	Systemic exposure to the active metabolite of didanosine increased, raising the risk of toxicity. Fatal hepatic failure has been reported with concurrent use.
Hepatitis C antivirals (ribavirin)	Azathioprine	Induction of severe pancytopenia and increased risk of azathioprine-related myelotoxicity. has been reported when coadministered.

Dosage and Administration

Table 10. Dosing and Administration[1-4]

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Ribavirin (Copegus®)	Treatment of chronic hepatitis C virus infection in combination with Pegasys® (pegylated interferon alfa-2a) in adults with compensated liver disease not previously treated with interferon alpha: Tablet: 800 to 1,200 mg/day administered in two divided doses for 24 (genotypes 2 and 3) to 48 weeks (genotypes 1 and 4) Treatment of adult chronic hepatitis C virus infection coinfected with human immunodeficiency virus: Tablet: 800 mg/day for 48 weeks	Treatment of chronic hepatitis C virus infection in combination with Pegasys® (pegylated interferon alfa-2a) in patients ≥5 to 18 years of age with compensated liver disease not previously treated with interferon alpha: Tablet: 400 to 1,200 mg/day administered in two divided doses for 24 (genotypes 2 and 3) or 48 weeks (genotypes 1 and 4)	Tablet: 200 mg
Ribavirin (Moderiba®)	Treatment of chronic hepatitis C virus infection in combination with peginterferon alfa-2a in adults with compensated liver disease not previously treated with interferon alpha: Tablet: 800 to 1,200 mg/day administered in two divided doses	Safety and efficacy in children have not been established.	Tablet: 200 mg 400 mg 600 mg

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
	for 24 weeks (genotypes 2 and 3) to 48 weeks (genotypes 1 and 4) Treatment of chronic hepatitis C virus infection in combination with peginterferon alfa-2a in adults coinfected with HIV: Tablet: 800 mg once daily for 48 weeks		
Ribavirin (Rebetol®)	Treatment of chronic hepatitis C virus infection in combination with interferon alfa-2b in adults with compensated liver disease: Capsule: 1,000 to 1,200 mg/day administered in two divided doses for 24 to 48 weeks in patients previously untreated with interferon Capsule: 1,000 to 1,200 mg/day administered in two divided doses for 24 weeks in patients who relapsed after interferon monotherapy Treatment of chronic hepatitis C virus infection in combination with pegylated interferon alfa-2b in adults with compensated liver disease: Capsule: 800 to 1,400 mg/day for 24 (genotypes 2 and 3) or 48 weeks (genotype 1) in patients previously untreated with interferon Capsule: 800 to 1,400 mg/day administered in two divided doses for 48 weeks in previous treatment failures to pegylated interferon and ribavirin therapy	Treatment of chronic hepatitis C virus infection in combination with interferon alfa-2b (pegylated and nonpegylated) in patients ≥3 to 18 years of age with compensated liver disease: Capsule, solution: 15 mg/kg/day to 1,200 mg/day administered in two divided doses for 24 (genotypes 2 and 3) or 48 weeks (genotype 1)	Capsule: 200 mg Solution: 40 mg/mL
Ribavirin (Ribasphere®, Ribasphere® RibaPak®)	Treatment of chronic hepatitis C virus infection in combination with pegylated interferon alfa-2a in adults with compensated liver disease and not previously treated with interferon alpha: Tablet: 800 (patients co-infected with human immunodeficiency virus) to 1,200 mg/day administered in two divided doses for 24 (genotypes 2 and 3) or 48 weeks (genotypes 1 and 4 and patents co-infected with human immunodeficiency virus)	Safety and efficacy in children have not been established.	Capsule: 200 mg Tablet: 200 mg 400 mg 600 mg

Clinical Guidelines

Table 11. Clinical Guidelines

Clinical Guideline	Recommendation(s)
American Association for the Study of Liver Diseases, Infectious Diseases Society of America, and International Antiviral Society-USA: **Recommendations for testing, managing, and treating hepatitis C (2014)**[7]	• It may be advisable to delay treatment for some patients with documented early fibrosis stage (F0 to 2), because waiting for future highly effective, pangenotypic, direct-acting antiviral combinations in interferon-free regimens may be prudent. Potential advantages of waiting to begin treatment will be provided in a future consensus guideline update. • A regimen is classified as either "recommended" when it is favored for most patients or "alternative" when optimal in a particular subset of patients in that category. When a treatment is clearly inferior or is deemed harmful, it is classified as "not recommended." • Recommendations for peginterferon alfa and ribavirin relapsers are the same as for treatment-naïve persons as described below. • Interferon ineligible criteria: o Intolerance to interferon alfa. o Autoimmune hepatitis and other autoimmune disorders. o Hypersensitivity to peginterferon alfa or any of its components. o Decompensated hepatic disease. o Major uncontrolled depressive illness. o A baseline neutrophil count below 1,500/µL, a baseline platelet count below 90,000/µL, or baseline hemoglobin below 10 g/dL. o A history of preexisting cardiac disease. When and in whom to initiate HCV therapy • Treatment is recommended for patients with chronic HCV infection. • Liver-related complications in which HCV treatment is most likely to provide the most immediate and impactful benefits are assigned “highest” and “high” priorities. • Highest priority due to highest risk for severe complications: o Advanced fibrosis (F3) or compensated cirrhosis (F4) o Organ transplant recipients o Severe extrahepatic hepatitis C (type 2 or 3 essential mixed cryoglobulinemia with end-organ manifestations e.g., vasculitis) o Proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis • High priority due to high risk for complications: o Fibrosis (F2) o Human immunodeficiency virus (HIV) or hepatitis B virus (HBV)-coinfection o Other coexistent liver disease (e.g., non-alcoholic steatohepatitis) o Debilitating fatigue o Type 2 Diabetes mellitus (insulin resistant) o Porphyria cutanea tarda • Persons whose risk of HCV transmission is high and in whom HCV treatment may yield transmission reduction benefits: o Men who have sex with men with high-risk sexual practices

Clinical Guideline	Recommendation(s)
	o Active injection drug users o Incarcerated persons o Persons on long-term hemodialysis • Factors associated with accelerated fibrosis progression: o Fibrosis stage o Inflammation grade o Older age at time of infection o Male sex o Organ transplant o Alcohol consumption o Nonalcoholic fatty liver disease o Obesity o Insulin resistance o Genotype 3 o HIV or HBV-coinfection <u>Treatment of HCV genotype 1 in treatment-naïve patients and relapsers with prior peginterferon alfa and ribavirin</u> • Recommended treatments: o Interferon eligible: sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. o Interferon ineligible: sofosbuvir plus simeprevir with or without ribavirin for 12 weeks. • Alternative treatments: o Interferon eligible: simeprevir for 12 weeks plus peginterferon alfa and ribavirin for 24 weeks (for genotype 1a, baseline resistance testing for Q80K should be performed and alternative treatments considered if this mutation is present). o Interferon ineligible: sofosbuvir plus ribavirin for 24 weeks. • Treatments that are not recommended: o Boceprevir or telaprevir plus peginterferon alfa and ribavirin for 24 or 48 weeks. o Peginterferon alfa and ribavirin for 48 weeks. o Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral. <u>Treatment of HCV genotype 2 in treatment-naïve patients and relapsers with prior peginterferon alfa and ribavirin</u> • Recommended treatments: o Sofosbuvir plus ribavirin for 12 weeks. • Alternative treatments: o None. • Treatments that are not recommended: o Peginterferon alfa and ribavirin for 24 weeks. o Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral. o Any regimen with boceprevir, telaprevir, or simeprevir. <u>Treatment of HCV genotype 3 in treatment-naïve patients and relapsers with prior peginterferon alfa and ribavirin</u>

Clinical Guideline	Recommendation(s)
	• Recommended treatments: o Sofosbuvir plus ribavirin for 24 weeks. • Alternative treatments: o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. • Treatments that are not recommended: o Peginterferon alfa and ribavirin for 24 to 48 weeks. o Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral. o Any regimen with boceprevir, telaprevir, or simeprevir. Treatment of HCV genotype 4 in treatment-naïve patients and relapsers with prior peginterferon alfa and ribavirin • Recommended treatments: o Interferon eligible: sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. o Interferon ineligible: sofosbuvir plus ribavirin for 24 weeks. • Alternative treatments: o Simeprevir for 12 weeks plus peginterferon alfa and ribavirin for 24 to 48 weeks. • Treatments that are not recommended: o Peginterferon alfa and ribavirin for 48 weeks. o Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral. o Any regimen with boceprevir or telaprevir. Treatment of HCV genotype 5 or 6 in treatment-naïve patients and relapsers with prior peginterferon alfa and ribavirin • Recommended treatments: o Interferon eligible: sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. • Alternative treatments: o Peginterferon alfa and ribavirin for 48 weeks. • Treatments that are not recommended: o Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral. o Any regimen with boceprevir or telaprevir. Recommendations for patients with HCV genotype 1 with prior null or partial response to peginterferon alfa and ribavirin • Recommended treatments: o Sofosbuvir plus simeprevir with or without ribavirin for 12 weeks. • Alternative treatments: o Sofosbuvir for 12 weeks plus peginterferon alfa and ribavirin for 12 to 24 weeks. o Sofosbuvir plus ribavirin for 24 weeks. o Simeprevir for 12 weeks plus peginterferon alfa and ribavirin for 24 weeks (for genotype 1a, baseline resistance testing for Q80K should be performed and alternative treatments considered if this mutation is present).

Clinical Guideline	Recommendation(s)
	• Treatments that are not recommended: o Boceprevir or telaprevir plus peginterferon alfa and ribavirin. o Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral. Recommendations for patients with HCV genotype 1 with prior null or partial response to peginterferon alfa and ribavirin plus either boceprevir or telaprevir • Recommended treatments: o Sofosbuvir for 12 weeks plus peginterferon alfa and ribavirin for 12 to 24 weeks. • Alternative treatments: o Interferon eligible: Sofosbuvir for 12 weeks plus peginterferon alfa and ribavirin for 24 weeks. o Interferon ineligible: Sofosbuvir plus ribavirin for 24 weeks. • Treatments that are not recommended: o Boceprevir, simeprevir, or telaprevir plus peginterferon alfa and ribavirin. o Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral. o A recommendation for simeprevir use for patients with previous telaprevir or boceprevir exposure has not been provided due to potential risk of preexistent resistance to protease inhibitor treatment. Recommendations for patients with HCV genotype 2 with prior null or partial response to peginterferon alfa and ribavirin • Recommended treatments: o Sofosbuvir plus ribavirin for 12 weeks; ▪ In treatment-experienced cirrhotics only, the decision to extend therapy to 16 weeks should be made on a case-by-case basis. • Alternative treatments: o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks (cirrhotics only) • Treatments that are not recommended: o Boceprevir or telaprevir plus peginterferon alfa and ribavirin. o Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral. Recommendations for patients with HCV genotype 3 with prior null or partial response to peginterferon alfa and ribavirin • Recommended treatments: o Sofosbuvir plus ribavirin for 24 weeks. • Alternative treatments: o Sofosbuvir plus ribavirin for 16 weeks (cirrhotics only). o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. • Treatments that are not recommended:

Clinical Guideline	Recommendation(s)
	o Peginterferon alfa and ribavirin with or without protease inhibitor. o Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral. <u>Recommendations for patients with HCV genotype 4 with prior null or partial response to peginterferon alfa and ribavirin</u> • Recommended treatments: o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. • Alternative treatments: o Sofosbuvir plus ribavirin for 24 weeks. • Treatments that are not recommended: o Peginterferon alfa and ribavirin with or without protease inhibitor o Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral. <u>Recommendations for patients with HCV genotype 5 or 6 with prior null or partial response to peginterferon alfa and ribavirin</u> • Recommended treatments: o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. • Alternative treatments: o None. • Treatments that are not recommended: o Peginterferon alfa and ribavirin with or without protease inhibitor. o Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral. <u>Initial treatment of human immunodeficiency virus (HIV)/HCV co-infected patients with HCV genotype 1 who are treatment-naïve or prior peginterferon alfa and ribavirin relapsers</u> • Recommended treatments: o Interferon eligible: sofosbuvir plus peginterferon and ribavirin for 12 weeks. o Interferon ineligible: ▪ Sofosbuvir plus ribavirin for 24 weeks. ▪ Sofosbuvir plus simeprevir with or without ribavirin for 12 weeks. • Alternative treatments: o Interferon eligible: simeprevir for 12 weeks plus peginterferon alfa and ribavirin for 24 weeks (for genotype 1a, baseline resistance testing for Q80K should be performed and alternative treatments considered if this mutation is present). o Interferon ineligible: none. • Treatments that are not recommended: o Boceprevir or telaprevir plus peginterferon alfa and ribavirin for 24 or 48 weeks.

Clinical Guideline	Recommendation(s)
	o Peginterferon alfa and ribavirin for 48 weeks. o Simeprevir for 12 weeks plus peginterferon alfa and ribavirin for 48 weeks. • Allowable antiretroviral therapy: o For sofosbuvir use: all except didanosine, zidovudine, or tipranavir. o For simeprevir use: limited to raltegravir, rilpivirine, maraviroc, enfuvirtide, tenofovir, emtricitabine, lamivudine, abacavir. <u>Recommendations for HIV/HCV co-infected patients with HCV genotype 1 with prior null or partial response to peginterferon alfa and ribavirin</u> • Recommended treatments: o Sofosbuvir plus simeprevir with or without ribavirin for 12 weeks. • Alternative treatments: o Interferon eligible: sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. o Interferon ineligible: sofosbuvir plus ribavirin for 24 weeks. • Treatments that are not recommended: same as for treatment-naïve or prior peginterferon alfa and ribavirin relapsers above. • Allowable antiretroviral therapy: same as for treatment-naïve or prior peginterferon alfa and ribavirin relapsers above. <u>Treatment of HIV/HCV co-infected patients with HCV genotype 2</u> • Recommended treatments (regardless of treatment history): o Sofosbuvir plus ribavirin for 12 weeks. • Alternative treatments: o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks (only in prior nonresponders to peginterferon alfa and ribavirin eligible for peginterferon alfa). • Treatments that are not recommended: o Peginterferon alfa and ribavirin for 24 to 48 weeks. o Any regimen with boceprevir, telaprevir, or simeprevir. o Allowable antiretroviral therapy: same as above. <u>Treatment of HIV/HCV co-infected patients with HCV genotype 3</u> • Recommended treatments (regardless of treatment history): o Sofosbuvir plus ribavirin for 24 weeks. • Alternative treatments: o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks (only in prior nonresponders to peginterferon alfa and ribavirin eligible for peginterferon alfa). • Treatments that are not recommended: o Peginterferon alfa and ribavirin for 24 to 48 weeks. o Any regimen with boceprevir, telaprevir, or simeprevir. o Allowable antiretroviral therapy: same as above. <u>Treatment of HIV/HCV co-infected patients with HCV genotype 4</u> • Recommended treatments (regardless of treatment history):

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	o Interferon eligible: sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. o Interferon ineligible: sofosbuvir plus ribavirin for 24 weeks. • Alternative treatments: o None. • Treatments that are not recommended: o Peginterferon alfa and ribavirin for 48 weeks. o Any regimen with boceprevir, telaprevir, or simeprevir. o Allowable antiretroviral therapy: same as above. Treatment of HIV/HCV co-infected patients with HCV genotype 5 or 6 • Recommended treatments (regardless of treatment history): o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. • Alternative treatments: o None. • Treatments that are not recommended: o Peginterferon alfa and ribavirin for 48 weeks. o Any regimen with boceprevir, telaprevir, or simeprevir. o Allowable antiretroviral therapy: same as above. Treatment of patients with cirrhosis • Treatment-naive patients with compensated cirrhosis, including those with hepatocellular carcinoma, should receive the same treatment as recommended for patients without cirrhosis. • Patients with decompensated cirrhosis (moderate or severe hepatic impairment; Child Turcotte Pugh class B or C) should be referred to a medical practitioner with expertise in that condition (ideally in a liver transplant center). • Recommended regimen for patients with any HCV genotype who have decompensated cirrhosis (moderate or severe hepatic impairment; Child Turcotte Pugh class B or C) who may or may not be candidates for liver transplantation, including those with hepatocellular carcinoma. o Sofosbuvir plus weight-based ribavirin (with consideration of the patient's creatinine clearance and hemoglobin level) for up to 48 weeks. o This regimen should be used only by highly experienced HCV provider. • The following regimens are not recommended for patients with decompensated cirrhosis (moderate or severe hepatic impairment; Child Turcotte Pugh class B or C): o Any interferon-based therapy. o Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral. o Telaprevir, boceprevir, or simeprevir-based regimens. Treatment of patients who develop recurrent HCV infection post-liver transplant • Recommended regimen for treatment-naive patients with HCV genotype 1 in the allograft liver, including those with compensated

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	cirrhosis. o Sofosbuvir plus simeprevir with or without dose-adjusted ribavirin for 12 to 24 weeks. • Alternate regimen for treatment-naive patients with genotype 1 HCV in the allograft liver, including those with compensated cirrhosis. o Sofosbuvir and dose-adjusted ribavirin (with consideration of the patient's creatinine clearance and hemoglobin level), with or without peginterferon alfa, for 24 weeks. • Recommended regimen for treatment-naive patients with HCV genotype 2 or 3 in the allograft liver, including those with compensated cirrhosis. o Sofosbuvir plus dose-adjusted ribavirin (with consideration for creatinine clearance and hemoglobin level) for 24 weeks. • Treatment-naive patients with decompensated allograft HCV infection should receive the same treatment as recommended for patients with decompensated cirrhosis (moderate or severe hepatic impairment; Child Turcotte Pugh class B or C).
European Association for the Study of the Liver: **Treatment of Hepatitis (2014)**[8]	Goals and endpoints of HCV therapy • The goal of therapy is to eradicate HCV infection, to prevent hepatic cirrhosis, decompensation of cirrhosis, hepatocellular carcinoma, and death. • The endpoint of therapy is SVR, defined by undetectable HCV RNA 12 and 24 weeks after the end of treatment; SVR usually equates to cure of infection in more than 99% of patients. • Both SVR 12 and SVR 24 have been accepted in the US and Europe, given that their concordance is 99%. Indications for treatment • All treatment-naïve and -experienced patients with compensated disease due to HCV should be considered for therapy. • Treatment should be prioritized for patients with significant fibrosis (F3 to F4). • Treatment is justified in patients with moderate fibrosis (F2). • In patients with no or mild disease (F0 to F1), the indication for and timing of therapy can be individualized. • Patients with decompensated cirrhosis who are on the transplant list should be considered for interferon-free, ideally ribavirin-free therapy. Treatment considerations for HIV/HCV-coinfection • Indications for HCV treatment and treatment regimens in HCV/HIV co-infected persons are identical to those in patients with HCV mono-infection. • The use of cobicistat-based regimens, efavirenz, delavirdine, etravirine, nevirapine, ritonavir, and any HIV protease inhibitor, boosted or not by ritonavir, is not recommended in HIV-infected patients receiving simeprevir. • Daclatasvir dose should be adjusted to 30 mg daily in HIV-infected patients receiving atazanavir/ritonavir and to 90 mg daily in those

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	receiving efavirenz. • No drug-drug interaction has been reported between sofosbuvir and antiretroviral drugs. Treatment options for HCV genotype 1 infection • Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. o The most efficacious and the easiest to use interferon alfa-containing option, without the risk of selecting resistant viruses in case of treatment failure. • Simeprevir for 12 weeks plus peginterferon alfa and ribavirin for 24 weeks (in treatment-naïve and prior relapsers, including cirrhotics) or 48 weeks (in prior partial and null responders, including cirrhotics). o Not recommended for HCV genotype 1a with Q80K polymorphism. o HCV RNA levels should be monitored on treatment. Treatment should be stopped if HCV RNA level is ≥25 IU/mL at week four, 12, or 24. • Daclatasvir plus peginterferon alfa and ribavirin for 24 weeks (HCV genotype 1b only). o Not recommended for HCV genotype 1a given the preliminary data available, pending results of on-going large-scale studies. o Daclatasvir should be given for 12 weeks in combination with peginterferon alfa and ribavirin. Daclatasvir, in combination with peginterferon alfa and ribavirin, should be continued for an additional 12 weeks (24 weeks total) in patients who do not achieve an HCV RNA level <25 IU/mL at week 4 and undetectable at week 10. Peginterferon alfa and ribavirin should be continued alone between week 12 and 24 (24 weeks total) in patients who achieve an HCV RNA level <25 IU/mL at week 4 and undetectable at week 10. • Sofosbuvir plus ribavirin for 24 weeks. o Due to suboptimal SVR rates, reserve for interferon alfa ineligible patients when no other interferon-free option is available. • Sofosbuvir plus simeprevir for 12 weeks. o The addition of ribavirin should be considered in patients with predictors of poor response to anti-HCV therapy, especially prior non-responders and/or patients with cirrhosis. • Sofosbuvir plus daclatasvir for 12 weeks (treatment-naïve) or 24 weeks (treatment-experienced, including prior telaprevir or boceprevir failures). o The addition of ribavirin should be considered in patients with predictors of poor response to anti-HCV therapy, especially prior non-responders and/or patients with cirrhosis. Treatment options for HCV genotype 2 infection • Sofosbuvir plus ribavirin for 12 weeks (or 16 to 20 weeks in

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	cirrhotics, especially treatment-experienced). • Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks is an option for cirrhotic and/or treatment-experienced patients. <u>Treatment options for HCV genotype 3 infection</u> • Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks • Sofosbuvir plus ribavirin for 24 weeks o Suboptimal in treatment-experienced cirrhotics, who should be proposed an alternative treatment option. • Sofosbuvir plus daclatasvir for 12 weeks (treatment-naïve) or 24 weeks (treatment-experienced, pending data with 12 weeks of therapy). o The addition of ribavirin should be considered in patients with predictors of poor response to anti-HCV therapy, especially prior non-responders and/or patients with cirrhosis. <u>Treatment options for HCV genotype 4 infection</u> • Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. • Simeprevir for 12 weeks plus peginterferon alfa and ribavirin for 24 weeks (in treatment-naïve and prior relapsers, including cirrhotics) or 48 weeks (in prior partial and null responders, including cirrhotics). o HCV RNA levels should be monitored on treatment. Treatment should be stopped if HCV RNA level is ≥25 IU/mL at week four, 12, or 24. • Daclatasvir plus peginterferon alfa and ribavirin for 24 weeks. o Daclatasvir should be given for 12 weeks in combination with peginterferon alfa and ribavirin. Daclatasvir, in combination with peginterferon alfa and ribavirin, should be continued for an additional 12 weeks (24 weeks total) in patients who do not achieve an HCV RNA level <25 IU/mL at week four and undetectable at week 10. Peginterferon alfa and ribavirin should be continued alone between week 12 and 24 (24 weeks total) in patients who achieve an HCV RNA level <25 IU/mL at week four and undetectable at week 10. • Sofosbuvir plus ribavirin for 24 weeks. o Should be reserved for interferon alfa intolerant or -ineligible patients. • Sofosbuvir plus simeprevir for 12 weeks. o The addition of ribavirin should be considered in patients with predictors of poor response to anti-HCV therapy, especially prior non-responders and/or patients with cirrhosis. • Sofosbuvir plus daclatasvir for 12 weeks (treatment-naïve) or 24 weeks (treatment-experienced). o The addition of ribavirin should be considered in patients with predictors of poor response to anti-HCV therapy, especially prior non-responders and/or patients with cirrhosis.

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	Treatment options for HCV genotype 5 or 6 infection • Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. • Sofosbuvir plus ribavirin for 24 weeks. o Should be reserved for interferon alfa intolerant or -ineligible patients. Treatment monitoring • A real-time polymerase chain reaction-based assay with a lower limit of detection of <15 IU/mL should be used to monitor HCV RNA levels during and after therapy. • In patients treated with sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks, HCV RNA should be measured at baseline and at weeks 4, 12, and 12 or 24 weeks after the end of therapy. • In patients treated with simeprevir for 12 weeks plus peginterferon alfa and ribavirin for an additional 24 or 48 weeks, HCV RNA should be measured at baseline, week four, 12, 24 (end of treatment in treatment-naïve and prior relapsers), week 48 (end of treatment in prior partial and null responders), and 12 or 24 weeks after the end of therapy. • In patients treated with daclatasvir for 12 to 24 weeks plus peginterferon alfa and ribavirin for 24 weeks, HCV RNA should be measured at baseline, week four, 10, and 24 (end of treatment), and 12 or 24 weeks after the end of therapy. • In patients treated with sofosbuvir plus simeprevir with or without ribavirin for 12 weeks; sofosbuvir plus daclatasvir with or without ribavirin for 12 or 24 weeks; and sofosbuvir plus ribavirin 12 or 24 weeks, HCV RNA should be measured at baseline, week 2 (assessment of adherence), week four, week 12 or 24 (end of treatment), and 12 or 24 weeks after the end of therapy. Stopping (futility) rules • Treatment with simeprevir plus peginterferon alfa and ribavirin should be stopped if HCV RNA level is ≥25 IU/mL at treatment week four, 12 or 24. • No futility rules have been defined for other treatment regimens. Virological response-guided triple therapy • With the triple combination of daclatasvir plus peginterferon alfa and ribavirin, patients who do not achieve an HCV RNA level <25 IU/mL at week 4 and undetectable at week 10 should receive the three drugs for 24 weeks. • Patients who achieve an HCV RNA level <25 IU/mL at week four and undetectable at week 10 should stop daclatasvir at week 12 and continue with peginterferon alfa and ribavirin dual therapy until week 24. • No response-guided therapy is used in other treatment regimens. Measures to improve treatment adherence • HCV treatment should be delivered within a multidisciplinary team

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	setting, with experience in HCV assessment and therapy. • Counseling on the importance of adherence is recommended. • In persons who actively inject drugs, access to harm reduction programs is mandatory. • Patients should be counseled to abstain from alcohol during antiviral therapy; patients with on-going alcohol consumption during treatment should receive additional support during antiviral therapy. • HCV treatment can be considered also for patients actively using drugs if they wish to receive treatment and are able and willing to maintain regular appointments. Retreatment of non-sustained virological responders • Patients who failed on a regimen containing sofosbuvir as the only direct-acting antiviral can be retreated with a combination of sofosbuvir and simeprevir (HCV genotypes 1 or 4 only), or a combination of sofosbuvir and daclatasvir (all genotypes). • Patients who failed on a regimen containing simeprevir, telaprevir or boceprevir as the only direct-acting antiviral can be retreated with a combination of sofosbuvir and daclatasvir. • Patients who failed on a regimen containing daclatasvir as the only direct-acting antiviral can be retreated with a combination of sofosbuvir and simeprevir (HCV genotypes 1 or 4 only). • Patients who failed on a regimen containing sofosbuvir and simeprevir can be retreated with a combination of sofosbuvir and daclatasvir. • Patients who failed on a regimen containing sofosbuvir and daclatasvir can be retreated with a combination of sofosbuvir and simeprevir (HCV genotypes 1 or 4 only). • Alternatively, patients who failed on any of the new treatment regimens including sofosbuvir, simeprevir and/or daclatasvir can wait until new treatment combinations are available if they do not need urgent therapy. • The utility of HCV resistance testing prior to retreatment in patients who failed on any of the new treatment regimens including sofosbuvir, simeprevir and/or daclatasvir is unknown. 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 mid-term complications; interferon-free regimens are preferred. • If a 12 to 24 week interferon-based direct-acting antiviral regimen is considered tolerable in patients with compensated cirrhosis and good liver function and without cytopenia, these patients can be treated as recommended above across genotypes. • Patients with cirrhosis should undergo regular surveillance for hepatocellular carcinoma, irrespective of SVR. Patients with an indication for liver transplantation • In patients awaiting liver transplantation, antiviral therapy is indicated, because it prevents graft infection if HCV RNA has been undetectable at least 30 days prior to transplantation.

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	• Patients with conserved liver function (Child Pugh class A) in whom the indication for transplantation is hepatocellular carcinoma should be treated with sofosbuvir plus ribavirin until liver transplantation. • Patients with conserved liver function (Child Pugh class A) in whom the indication for transplantation is hepatocellular carcinoma can also be treated with sofosbuvir, peginterferon alfa and ribavirin for 12 weeks. • In patients with conserved liver function (Child Pugh class A) in whom the indication for transplantation is hepatocellular carcinoma, the addition of another direct acting antiviral drug is likely to improve the prevention of HCV recurrence post-transplant; therefore, patients awaiting liver transplantation with genotype 1 to 4 infection can be treated with sofosbuvir, daclatasvir and ribavirin for 12 weeks prior to transplantation. • Patients with decompensated cirrhosis awaiting liver transplantation (Child Pugh class B and C) can be treated with sofosbuvir plus ribavirin until liver transplantation in experienced centers under close monitoring. Interferon alfa is contraindicated in these patients. • The addition of another direct-acting antiviral drug is likely to improve the prevention of HCV recurrence post-transplant; therefore, patients with decompensated cirrhosis awaiting liver transplantation (Child Pugh class B and C) with genotype 1 to 4 infection should be treated with sofosbuvir, daclatasvir and ribavirin until liver transplantation in experienced centers under close monitoring. • Patients with decompensated cirrhosis not on transplant waiting list should only be offered an interferon-free regimen within a clinical trial, an expanded access program or within experienced centers, because the efficacy, safety and outcomes have not yet been established for this group. <u>Post-liver transplantation recurrence</u> • Patients with post-transplant recurrence of HCV infection should be considered for therapy. • Patients with HCV genotype 2 infection must sofosbuvir plus ribavirin for 12 to 24 weeks, pending more data in this population. • Patients with HCV genotype 1, 3, 4, 5 or 6 infection can be treated with sofosbuvir plus daclatasvir for 12 to 24 weeks, with or without ribavirin, pending more data in this population. • Patients with HCV genotype 1 or 4 infection can be treated with sofosbuvir plus simeprevir for 12 to 24 weeks, with or without ribavirin, pending more data in this population. • No dose adjustment is required for tacrolimus or cyclosporine with any of the above combinations. Careful monitoring is important in the absence of safety data in this population. <u>Hepatitis B virus (HBV) co-infection</u> • Patients should be treated with the same regimens, following the same rules as HCV mono-infected patients. • If HBV replicates at significant levels before, during or after HCV

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	clearance, concurrent HBV nucleoside/nucleotide analogue therapy is indicated. Hemodialysis patients • Hemodialysis patients, particularly those who are suitable candidates for renal transplantation, should be considered for antiviral therapy. • Hemodialysis patients should receive an interferon alfa-free and ribavirin-free regimen. • Due to the lack of safety and efficacy data, the need for dose adjustments for sofosbuvir, simeprevir and daclatasvir is unknown. • Given the lack of data, extreme caution is recommended and sofosbuvir should not be administered to patients with an estimated glomerular filtration rate <30 mL/min/1.73 m^2 or with end-stage renal disease. Non-hepatic solid organ transplant recipients • HCV treatment before kidney transplantation may avoid liver-related mortality in the post-transplant patient, and may prevent HCV-specific causes of renal graft dysfunction. • Where possible, interferon-free and ribavirin-free antiviral regimen should be given to potential transplant recipients before listing for renal transplantation; however, no safety and efficacy data is available in this population. • Given the lack of data, extreme caution is recommended and sofosbuvir should not be administered to patients with an estimated glomerular filtration rate <30 mL/min/1.73 m^2 or with end-stage renal disease. • In non-hepatic solid organ transplant recipients, patients with an indication for anti-HCV therapy should receive an interferon-free regimen. • Patients with HCV genotype 2 infection must be treated with sofosbuvir plus ribavirin for 12 to 24 weeks, pending more data in this population. • Patients with HCV genotype 1, 3, 4, 5 or 6 infection can be treated with sofosbuvir plus daclatasvir for 12 to 24 weeks, with or without ribavirin, pending more safety data in this population. • Patients with HCV genotype 1 or 4 infection can be treated with sofosbuvir plus simeprevir for 12 to 24 weeks, with or without ribavirin, pending more data in this population. • No dose adjustment is required for tacrolimus or cyclosporine with any of these combinations. Careful monitoring is important in the absence of safety data in this population. Active drug addicts and patients on stable maintenance substitution • HCV treatment for people who inject drugs (PWIDs) should be considered on an individualized basis and delivered within a multidisciplinary team setting. • Sofosbuvir and simeprevir can be used in PWIDs on opioid substitution therapy. They do not require specific methadone and buprenorphine dose adjustment, but monitoring for signs of opioid

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	toxicity or withdrawal should be undertaken. More data is needed with daclatasvir. • Consideration of interferon-containing or interferon-free therapy in PWIDs should be undertaken on an individualized basis, but those with early liver disease can be advised to await further data and/or potential development of improved therapies. • The regimens that can be used in PWIDs are the same as in non-PWIDs. • Awareness should be raised that liver transplantation is a therapeutic option in those with a history of injection drug use. • Opioid substitution therapy is not a contraindication for liver transplantation and individuals on opioid substitution should not be advised to reduce or stop therapy. Treatment of acute hepatitis C • Peginterferon alfa monotherapy for 24 weeks can be used in patients with acute hepatitis C, who will achieve SVR in as many as 90% of cases. • Peginterferon alfa plus ribavirin for 24 weeks is recommended in patients with acute hepatitis C who are HIV-coinfection. • Although no data is available yet, interferon-free regimens can theoretically be used in patients with acute hepatitis C and are expected to achieve high SVR rates. Note: Daclatasvir is not currently Food and Drug Administration-approved in the United States.
Department of Veterans Affairs National Hepatitis C Resource Center Program and the Office of Public Health: **HCV Infection: Treatment and Considerations (2014)**[9]	Treatment considerations • The urgency of treating HCV should be based on the risk of developing decompensated cirrhosis or dying from liver or liver-related disease, and prolonging graft survival in liver transplant recipients. • Urgent treatment should be considered in patients with advanced cirrhosis, selected patients with hepatocellular carcinoma awaiting liver transplant, post-transplant recipients with cirrhosis, and patients with serious extra-hepatic manifestations of HCV. • Patients with mild liver disease (F0 to F2) may consider waiting until newer therapies are available that may improve the chance of treatment success and reduce treatment-related adverse effects; approval is anticipated over the next 12 to 24 months. • Factors that may complicate adherence, such as active substance abuse, neurocognitive disorders, and lack of social support, should be addressed before initiating medications. • Sofosbuvir or simeprevir should not be used as monotherapy or in reduced dosages; neither drug should be restarted if discontinued. • Interferon ineligible or intolerant criteria: o Platelet count <75,000/mm^3. o Decompensated liver cirrhosis (Child Turcotte Pugh class B or C). o Severe mental health conditions that may be exacerbated by interferon or may respond poorly to medical therapy. o Autoimmune diseases that may be exacerbated by

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	interferon-mediated immune modulation. o Inability to complete a prior treatment course due to documented interferon-related adverse effects. • Treatment of patients with HCV/HIV co-infection is similar to that of HCV mono-infected patients. Drug-drug interactions must be carefully considered. Treatment of HCV genotype 1 in treatment-naïve, non-cirrhotic or cirrhotic interferon eligible patients • Preferred regimen: o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. • Alternative regimen: o Simeprevir for 12 weeks plus peginterferon alfa and ribavirin for 24 weeks (do not use in genotype 1a with Q80K polymorphism). Treatment of HCV genotype 1 in treatment-naïve, non-cirrhotic interferon ineligible patients • Preferred regimens: o Sofosbuvir plus ribavirin for 24 weeks. o Sofosbuvir plus simeprevir with or without ribavirin for 12 weeks. • Alternative regimen: o None. Treatment of HCV genotype 1 in treatment-naïve, cirrhotic interferon ineligible patients • Preferred regimen: o Sofosbuvir plus simeprevir with or without ribavirin for 12 weeks. • Alternative regimen: o None. Treatment of HCV genotype 1 in treatment-experienced, non-cirrhotic interferon eligible patients • Preferred regimen: o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. • Alternative regimen: o Simeprevir for 12 weeks plus peginterferon alfa and ribavirin for 24 weeks (relapsers) or 48 weeks (prior partial or null responders); do not use in genotype 1a with Q80K polymorphism or previous failure of boceprevir- or telaprevir-based therapy. Treatment of HCV genotype 1 in treatment-experienced, cirrhotic interferon eligible patients • Preferred regimen: o Sofosbuvir plus peginterferon alfa and ribavirin for 12

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	weeks. • Alternative regimen (peginterferon alfa and ribavirin null responders only): o Sofosbuvir plus simeprevir with or without ribavirin for 12 weeks. Treatment of HCV genotype 1 in treatment-experienced, non-cirrhotic or cirrhotic interferon ineligible patients • Preferred regimen: o Sofosbuvir plus simeprevir with or without ribavirin for 12 weeks. • Alternative regimen: o None. Treatment of HCV genotype 2 in treatment-naïve patients • Preferred regimen: o Sofosbuvir plus ribavirin for 12 weeks. • Alternative regimen: o None. Treatment of HCV genotype 2 in treatment-experienced patients • Preferred regimens: o Sofosbuvir plus ribavirin for 12 to 16 weeks. o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks (interferon eligible only). • Alternative regimen: o None. Treatment of HCV genotype 3 in treatment-naïve patients • Preferred regimens: o Sofosbuvir plus ribavirin for 24 weeks. • Alternative regimen: o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks (interferon eligible only). Treatment of HCV genotype 3 in treatment-experienced cirrhotic patients • Preferred regimens: o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks (interferon eligible only). • Alternative regimen: o Sofosbuvir plus ribavirin for 24 weeks (interferon ineligible only). Treatment of HCV genotype 1, 2, 3, or 4 in patients with hepatocellular carcinoma • Preferred regimens: o Sofosbuvir plus ribavirin for 24 to 48 weeks or until liver transplant, whichever occurs first. • Alternative regimen:

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	o None. Treatment of patients with HCV genotype 1, 2, 3, or 4 infection post-liver transplant • Sofosbuvir plus ribavirin with or without peginterferon for 24 weeks Treatment of patients with HCV genotype 1, 2, 3, or 4 infection post-other solid organ transplant (kidney, heart, or lung) • Discuss with transplant center. Do not use peginterferon-containing regimens. Sofosbuvir has not been studied in non-liver transplant recipients. Discontinuing HCV treatment based on lack of virologic response • Patients receiving sofosbuvir-based regimen should have HCV ribonucleic acid (RNA) assessed at week 4 of treatment; if the HCV RNA is detectable at week 4 or at any time point thereafter, reassess HCV RNA in 2 weeks. If the repeated HCV RNA increased (i.e., >1 $\log_{10}$ IU/mL from nadir) or if the HCV RNA is ≥25 IU/mL at week 8 of therapy, discontinuation of all treatment should be strongly considered. • Patients receiving simeprevir plus peginterferon and ribavirin regimen should have HCV RNA levels assessed at week 4, 12, and 24; if the HCV RNA is ≥25 IU/mL at any of these time points, all treatment should be discontinued. Use in renal insufficiency • Sofosbuvir use is not recommended if creatinine clearance <30 mL/min or end-stage renal disease due to insufficient safety and efficacy data. • No simeprevir dose adjustment is needed if creatinine clearance <30 mL/min. • Peginterferon alfa-2a dosage should be reduced to 135 µg/week once weekly for creatinine clearance <30 mL/min, including hemodialysis. • Peginterferon alfa-2b dosage should be reduced by 25% for creatinine clearance 30 to 50 mL/min and by 50% for creatinine clearance <30 mL/min, including hemodialysis. • Ribavirin should be dosed at 200 mg daily alternating with 400 mg daily for creatinine clearance 30 to 50 mL/min and 200 mg daily for creatinine clearance <30 mL/min, including hemodialysis. Use in hepatic impairment • No simeprevir dosage recommendation can be provided in moderate to severe hepatic impairment (Turcotte Pugh Class B or C) due to higher simeprevir exposures. • No sofosbuvir dosage adjustment in required for patients with any degree of renal impairment. • Peginterferon alfa use is not recommended in patients with moderate or severe hepatic impairment (Turcotte Pugh Class B or C).

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	Mental health and substance-use disorders • Patients with severe mental health conditions (e.g., psychotic disorders, bipolar disorder, major depression, posttraumatic stress disorder) who are engaged in mental health treatment should be considered for therapy on a case-by-case basis; interferon use may worsen these conditions. Substance or alcohol use • The presence of current heavy alcohol use (>14 drinks per week for men or >7 drinks per week for women), binge alcohol use (>4 drinks per occasion at least once per month), or active injection drug use warrants referral to an addiction specialist before treatment initiation. • There are no published data supporting minimal length of abstinence as an inclusion criterion for HCV antiviral treatment. Patients with active substance- or alcohol-use disorders should be considered for therapy on a case-by-case basis and care should be coordinated with substance-use treatment specialist.
World Health Organization: **Guidelines for the Screening, Care and Treatment of Persons with Hepatitis C Infection (2014)**[10]	Recommendations for treatment of HCV infection • All adults and children with chronic HCV infection, including people who inject drugs, should be assessed for antiviral treatment. • Peginterferon alfa in combination with ribavirin is recommended for the treatment of chronic HCV infection rather than standard non-peginterferon alfa with ribavirin. • Where access to treatment for HCV infection is limited, priority for treatment should be given to patients with advanced liver disease (F3 and F4). • Treatment with the direct-acting antivirals telaprevir or boceprevir, given in combination with peginterferon alfa and ribavirin, is suggested for genotype 1 chronic HCV infection rather than peginterferon alfa and ribavirin alone. • In high-income settings, HCV treatment with peginterferon alfa and ribavirin and with boceprevir or telaprevir plus peginterferon alfa and ribavirin has been evaluated as being cost–effective. • Sofosbuvir, given in combination with ribavirin with or without peginterferon alfa (depending on the HCV genotype), is recommended in genotypes 1, 2, 3 and 4 HCV infection rather than peginterferon alfa and ribavirin alone (or no treatment for persons who cannot tolerate peginterferon alfa); recommendation made without taking resource use into consideration. • Simeprevir, given in combination with peginterferon alfa and ribavirin, is recommended for persons with genotype 1b HCV infection and for persons with genotype 1a HCV infection without the Q80K polymorphism rather than peginterferon alfa and ribavirin alone; recommendation made without taking resource use into consideration. • Absolute contraindications to peginterferon alfa: o Uncontrolled depression, psychosis, or epilepsy. o Uncontrolled autoimmune disease. o Decompensated cirrhosis (Child–Pugh ≥B7 or B6 in

Clinical Guideline	Recommendation(s)
	HCV/HIV coinfection). o Pregnancy or unwillingness to use contraception. o Breastfeeding women. o Severe concurrent medical disease including severe infections. o Poorly controlled hypertension, cardiac failure, or diabetes. o Solid organ transplant (except liver transplant recipients). o Chronic obstructive pulmonary disease. o Age <2 years old. • Relative contraindications to peginterferon alfa: o Abnormal hematological indices: ▪ Hemoglobin <13 g/dL in men or <12 g/dL in women. ▪ Neutrophil count <1.5x10^9/L. ▪ Platelet count <90x10^9/L. o Serum creatinine >1.5 mg/dL. o Hemoglobinopathies (sickle cell disease or thalassemia). o Significant coronary artery disease. o Untreated thyroid disease. • Treatment for HCV infection is both efficacious and cost-effective in people who inject drugs and is therefore recommended. • Specialist care needs to address the additional needs of special populations of patients, including people who inject drugs, persons coinfected with (or at risk for infection with) HIV, children and adolescents, and those with cirrhosis. • The decision to initiate treatment for HCV/HIV-coinfection is more complex than in those with HCV monoinfection, as response rates are lower, risk of potential toxicities is higher and treatment is complicated by a high pill burden, overlapping toxicities, and interactions between drugs used for treating HCV and HIV.
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])**[11]	• 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

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	(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. Treatment experienced patients • 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 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

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	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. Interleukin (IL) 28B 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.
European Association for the Study of the Liver: **Management of Hepatitis C Virus Infection (2013)**[12]	Goals and endpoints of HCV therapy • The goal of therapy is to eradicate HCV infection. • The endpoint of therapy is SVR, defined by undetectable HCV RNA 24 weeks after the end of therapy; SVR usually equates to cure of infection in more than 99% of patients. • Undetectable HCV RNA at 12 weeks after the end of therapy (SVR 12) has been accepted in the US and Europe given concordance with SVR 24 is 99%; however, this concordance needs to be further validated in ongoing clinical trials. Indications for treatment • All treatment-naïve patients with compensated disease due to HCV should be considered for therapy. • Treatment should be scheduled, not deferred, for patients with significant fibrosis (F3 to F4). • In patients with less severe disease, indication for and timing of therapy can be individualized. First line treatment of chronic hepatitis C genotype 1 • Triple therapy with boceprevir or telaprevir added to peginterferon alfa and ribavirin is the approved standard of care for chronic hepatitis C genotype 1. There is no head-to-head comparison to allow recommendation of boceprevir or telaprevir as preferred therapy. • Patients with cirrhosis should never receive abbreviated treatment with boceprevir or telaprevir regimens. • Selected patients with high likelihood of SVR to peginterferon alfa and ribavirin or with contraindications to boceprevir or telaprevir can be treated with dual therapy. • When lead-in is used to identify patients with peginterferon alfa sensitive infection, the possibility of continuation of dual therapy should have been discussed with the patient prior to initiation of treatment. • Both peginterferon alfa-2a (180 µg/week) and peginterferon alfa-2b (1.5 µg/kg/week) can be used in dual or triple therapy. • Ribavirin should be dosed following the peginterferon alfa label for triple therapy. • Ribavirin should be administered at a weight-based dose of 15 mg/kg/day in dual therapy

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	First line treatment of chronic hepatitis C genotypes 2, 3, 4, 5, and 6 • The combination of peginterferon alfa and ribavirin is the approved standard of care for chronic hepatitis C genotypes 2, 3, 4, 5, and 6. • Ribavirin should be administered at a weight-based dose of 15 mg/kg/day for genotypes 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 • A real-time polymerase chain reaction-based assay with a lower limit of detection of <15 IU/mL should be used to monitor triple therapy. • During triple therapy in HCV genotype 1 patients, HCV RNA measurements should be performed at weeks four, eight, 12, 24, and end of treatment when administering boceprevir, and at weeks four, 12, 24, and end of treatment when administering telaprevir. • During dual therapy in any HCV genotype, HCV RNA levels should be assessed at baseline, weeks four, 12, 24 and end of treatment. • The end-of-treatment virological response and the SVR at 12 or 24 weeks after the end of treatment must be assessed. • Whether the baseline HCV RNA level is low or high may be a useful criterion to guide treatment decisions during dual therapy. The safest threshold level for discriminating low and high baseline HCV RNA is 400,000 IU/mL. • Dual therapy 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. • Triple therapy with boceprevir should be stopped if HCV RNA is >100 IU/mL at treatment week 12 or if HCV RNA is detectable at treatment week 24. • Triple therapy with telaprevir should be stopped if HCV RNA is >1,000 IU/mL at weeks four or 12 of therapy. • Dual therapy duration should be tailored to the on-treatment virological response at weeks four and 12. The likelihood of SVR is directly proportional to the rapidity of HCV RNA disappearance. • For patients receiving dual therapy who achieve an RVR and who have low baseline viral titre (<400,000 IU/mL), treatment for 24 weeks (genotype 1) or 16 weeks (genotype 2 or 3) can be considered. If negative predictors of response (i.e., advanced fibrosis/cirrhosis, metabolic syndrome, insulin resistance, hepatic steatosis) are present, published evidence for equal efficacy of shortened treatment is lacking. • Patients receiving dual therapy with genotypes 2 or 3, and with any adverse predictor of SVR, and who achieve an early virological response or a delayed virological response without an RVR, can be treated for 48 weeks. • Genotype 1 patients receiving dual therapy who demonstrate a delayed virological response can be treated for 72 weeks, provided that their HCV RNA is undetectable at week 24.

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	Treatment dose reductions and stopping rules • The peginterferon 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. Peginterferon 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 rise, treatment can be restarted, but at a reduced peginterferon 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. • Boceprevir or telaprevir doses should not be reduced during therapy due to the risk of the development of antiviral resistance. If boceprevir or telaprevir have been stopped, they should never be reintroduced in the same course of treatment. Measures to improve treatment success rates • Full adherence to all antiviral drugs should be the aim in order to optimize SVR rates and to reduce the risk of emergence of specific drug resistance. • Body weight adversely influences the response to peginterferon 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 for dual therapy; 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. • In dual therapy, recombinant erythropoietin can be administered when the hemoglobin level falls <10 g/dL in order to reduce the need for ribavirin dose reduction. • In patients receiving boceprevir or telaprevir-based triple therapy, ribavirin dose reduction should be the initial response to significant anemia. • There is no evidence that neutropenia during peginterferon alfa and ribavirin therapy 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. Post treatment follow up of patients who achieve an SVR • Noncirrhotic patients with SVR should be retested for alanine

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	transaminase and HCV RNA at 48 weeks post-treatment, and then discharged if alanine transaminase is normal and HCV RNA is negative. • Cirrhotic patients with SVR should undergo surveillance for hepatocellular carcinoma every six months by means of ultrasound. • If present, portal hypertension and esophageal varices should be managed, though index variceal bleed is seldom observed in low-risk patients after the achievement of SVR. • Patients with ongoing drug use should not be excluded from HCV treatment on the basis of perceived risk of reinfection. • Following SVR, monitoring for HCV reinfection through annual HCV RNA assessment should be undertaken on people who inject drugs with ongoing risk behavior. <u>Retreatment of nonsustained virological responders to peginterferon alfa and ribavirin</u> • Patients infected with HCV genotype 1 who failed to eradicate HCV in prior therapy with peginterferon alfa and ribavirin should be considered for retreatment with the triple combination of peginterferon alfa, ribavirin and a protease inhibitor. • The previous response to interferon-based therapy is an important predictor of success of triple therapy. If the pattern of prior response to dual therapy is not clearly documented, the patient should not be treated with abbreviated response-guided therapy. • Patients with cirrhosis and prior null responders have a lower chance of cure and should not be treated with response-guided therapy with either boceprevir or telaprevir. • Patients infected with HCV genotypes other than 1 and who failed on prior therapy with non-pegylated interferon alfa, with or without ribavirin, can be re-treated with pegylated interferon alfa and ribavirin. <u>Treatment of patients with severe liver disease</u> • Patients with compensated cirrhosis should be treated, in the absence of contraindications, in order to prevent short to midterm complications. • Monitoring and management of side effects, especially those linked to portal hypertension, low platelet count, and low serum albumin should be done particularly carefully. Growth factors may be 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 while awaiting liver transplantation, with the goal of achieving SVR or HCV RNA negativity before transplantation. • In patients with 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

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	current interferon alfa-based antiviral regimens due to a high risk of life-threatening complications. • Treatment can be started at low doses of peginterferon 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. • For patients with HCV genotype 1, protease inhibitor-based therapy can be used, but frequent monitoring and dose adjustment of tacrolimus and cyclosporine are required. • Graft rejection is rare but may occur during peginterferon alfa treatment. A liver biopsy should be performed whenever liver tests worsen on antiviral therapy. Treatment of special groups • Indications for HCV treatment in patients with HIV coinfection are identical to those in patients with HCV monoinfection. The same peginterferon alfa regimen should be used in HIV coinfected patients. Longer treatment duration may be considered for patients with genotype 2 and 3 who exhibit slow early viral kinetics. • Patients coinfected with HIV and HCV genotype 1 should be considered for telaprevir or boceprevir triple therapy regimen, but special care should be taken to minimize or avoid potential drug-drug interactions. • HIV patients with a diagnosis of acute HCV infection should be treated with peginterferon and ribavirin, with duration dependent on viral kinetics independent of HCV genotype. • Patients coinfected with hepatitis B should be treated with telaprevir or boceprevir triple therapy regimen, 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 therapy is indicated. • Patients on hemodialysis, particularly those who are suitable candidates for renal transplantation, should be considered for antiviral therapy. • Antiviral treatment should comprise peginterferon alfa at an appropriately reduced dose. • Ribavirin can be used at very low doses, but with caution. • Boceprevir or telaprevir can be used with caution in patients with impaired creatinine clearance, and dose adjustment is probably unnecessary. • 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. • Interferon alfa-based antiviral treatment is associated with a significant risk of renal graft rejection, and it should be avoided

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	unless there is a powerful indication for antiviral treatment (e.g., aggressive cholestatic hepatitis). • 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 patients with treatment failure • Untreated patients with chronic hepatitis C and those who failed prior treatment should be followed regularly. • Non-invasive methods for staging fibrosis are best suited for follow-up assessment at intervals. • Hepatocellular carcinoma screening must be continued indefinitely in patients with cirrhosis. Treatment of acute hepatitis C • Peginterferon alfa monotherapy for 24 weeks is recommended in patients with acute hepatitis C and achieves SVR in >90% of patients. • Patients failing to respond to monotherapy should be retreated according to the standard of care for chronic hepatitis C.
Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program Office: **Update on the management and treatment of hepatitis C virus infection (2012)**[13]	Recommendations in patients being considered for HCV therapy • All patients with chronic HCV infection should be evaluated for HCV antiviral treatment. • Patients should be counseled on their likelihood of achieving SVR, based upon individual factors such as body mass index, genotype, race, stage of fibrosis, and viral load before initiating therapy. • IL28B genotype testing can be performed before peginterferon-ribavirin therapy with or without a protease inhibitor, if the results would alter treatment decisions. Recommendations for treatment-naïve patients with genotype 1 infection • Peginterferon alfa and ribavirin, in combination with boceprevir (800 mg three times daily with food) or telaprevir (750 mg three times daily with 20 grams of fat), is the standard of care for most treatment-naïve genotype 1-infected patients. • If a telaprevir-containing regimen is used in treatment-naïve noncirrhotic patients who achieve an extended rapid virologic response (eRVR), telaprevir should be discontinued at week 12 and peginterferon-ribavirin should be continued for an additional 12 weeks. If HCV RNA is detectable at week four, but <1,000 IU/mL and remains <1,000 IU/mL or becomes undetectable at week 12, telaprevir should be discontinued at week 12, and peginterferon-ribavirin can be continued for another 36 weeks. • If a telaprevir-containing regimen is used in treatment-naïve cirrhotics who achieve an HCV RNA that is undetectable or <1,000 IU/mL at treatment weeks four and 12, telaprevir should be discontinued at week 12, and peginterferon-ribavirin can be continued for 36 more weeks.

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	• If a boceprevir-containing regimen is used in treatment-naïve noncirrhotics, if HCV RNA declines by ≥1 $\log_{10}$ during the four-week lead-in, and HCV RNA is undetectable at weeks eight to 24, treatment with boceprevir-peginterferon-ribavirin for 24 weeks is sufficient. If HCV RNA is detectable at week eight, but <100 IU/mL at week 12, and negative at week 24, boceprevir-peginterferon-ribavirin should be continued until week 36, followed by peginterferon-ribavirin alone for 12 more weeks. If HCV RNA declines by <1 $\log_{10}$ during the lead-in, boceprevir-peginterferon-ribavirin can be continued for 44 weeks. • If a boceprevir-containing regimen is used in treatment-naïve cirrhotics, 44 weeks of boceprevir-peginterferon-ribavirin is required after the four-week lead-in. <u>Recommendations for treatment of nonresponders and relapsers with genotype 1 infection</u> • For patients who previously failed peginterferon-ribavirin, retreatment with boceprevir or ribavirin and peginterferon-ribavirin may be considered, particularly in patients who were relapsers. • If a boceprevir-containing regimen is used for retreatment of noncirrhotic prior partial responders or relapsers, the treatment duration is 36 weeks if HCV RNA is undetectable from weeks eight to 24. If HCV RNA is detectable at week 12, but <100 IU / mL and is undetectable from weeks 24 to 36, boceprevir can be discontinued at week 36 and peginterferon-ribavirin can be continued for an additional 12 weeks. • If a boceprevir-containing regimen is used for re-treatment in cirrhotics, the treatment duration is 48 weeks if HCV RNA is detectable at week 12, but <100 IU/mL, and becomes undetectable from weeks 24 to 36. • If a boceprevir-containing regimen is used for retreatment of prior null responders, the treatment duration is 48 weeks if HCV RNA is detectable at week 12, but <100 IU/mL, and becomes undetectable from weeks 24 to 36. • If a telaprevir-containing regimen is used for retreatment of prior relapsers, and HCV RNA is undetectable from weeks four and 12, telaprevir should be discontinued at week 12 and peginterferon-ribavirin should be continued for an additional 12 weeks. If HCV RNA is detectable, but <1,000 IU/mL at week four and/or 12, telaprevir can be discontinued at week 12, and peginterferon-ribavirin can be continued for an additional 36 weeks. • If a telaprevir-containing regimen is used for re-treatment of prior partial responders or null responders, and HCV RNA is <1,000 IU/mL at weeks four and 12, telaprevir should be discontinued at week 12 and peginterferon-ribavirin should be continued for an additional 36 weeks. <u>Recommendations for dose modification</u> • Peginterferon alfa and ribavirin doses should be reduced in response to decreases in white blood cells, neutrophils, hemoglobin or platelets.

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	• If ribavirin is stopped for seven or more days in patients concomitantly receiving boceprevir or telaprevir, then the protease inhibitor should also be permanently discontinued. The protease inhibitors should be either continued at full dose or discontinued. • A ribavirin dose reduction should be used as initial management of HCV treatment-related anemia in a symptomatic patient with a hemoglobin <10 g/dL. Erythropoietin may be administered in patients with symptomatic anemia related to peginterferon-ribavirin therapy with or without protease inhibitors to limit anemia-related ribavirin dose reductions or dose discontinuations. • A peginterferon dose reduction should be used as initial management of HCV treatment-related neutropenia (an absolute neutrophil count of <750, or as clinically indicated). Granulocyte colony-stimulating factor should not be given as primary therapy to prevent peginterferon alfa dose reductions. <u>Recommendations for treatment monitoring</u> • Patients should be monitored for treatment-related adverse effects at least every two weeks early in the course of therapy, and every one to two months during treatment as clinically indicated. • Assessment of treatment adherence and screening for depression, suicidal ideation, alcohol, and illicit drug use should be performed at every visit. • Patients should be counseled about avoiding pregnancy through the use of two forms of contraception during treatment and for six months posttreatment. If a patient is receiving a boceprevir- or telaprevir-containing regimen, two alternative effective methods of contraception, such as intrauterine devices and barrier methods, should be used in at-risk patients and partners during and for at least six months after treatment. • In patients receiving telaprevir-peginterferon-ribavirin, all treatment should be stopped if any of the following occur: o HCV RNA level >1,000 IU/mL at week four or 12. o Detectable HCV RNA levels at week 24 or at any time point thereafter. o HCV RNA rebounds at any time point (≥1 $\log_{10}$ increase from the nadir HCV RNA). • In patients receiving boceprevir-peginterferon-ribavirin, all treatment should be stopped if any of the following occur: o HCV RNA level ≥100 IU/mL at week 12 with a boceprevir-containing regimen. o Detectable HCV RNA levels at week 24 or at any time point thereafter. o HCV RNA rebounds at any time point (≥1 $\log_{10}$ increase from the nadir HCV RNA). • Do not switch to the other protease inhibitor if virologic failure occurs with one protease inhibitor. <u>Recommendations for groups with special considerations for therapy</u> • Peginterferon alfa monotherapy may be used to treat patients with contraindications to ribavirin.

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	• For patients who achieve RVR and have a low baseline viral load (HCV RNA <400,000 IU/mL), 24-weeks of treatment with peginterferon-ribavirin may be sufficient. • Treatment can be deferred in patients with minimal inflammation and/or minimal portal fibrosis on liver biopsy. • HCV genotype 1-infected patients with compensated cirrhosis (Child-Pugh Class <7), adequate neutrophils (>1.5 k/mm^3), and adequate platelet counts (>75 k/mm^3) should be considered for treatment with boceprevir (for 44 weeks) or telaprevir (for 12 weeks) combined with peginterferon-ribavirin at standard doses for 48 weeks. • Patients with cirrhosis continue to be at risk for hepatocellular carcinoma and should undergo routine screening regardless of viral clearance status. <u>Recommendations for treatment-naïve and -experienced patients with genotype 2 or 3 infection</u> • Treatment-naïve patients should be treated with peginterferon-ribavirin for 24 weeks. • For patients with low viral load (HCV RNA <600,000 IU/mL) and mild fibrosis who achieve a RVR, 12 to 18 weeks of treatment may be sufficient. • For patients with genotype 3 infection and a high HCV RNA (>600,000 IU/mL), steatosis or advanced fibrosis, treatment beyond 24 weeks may improve response. • Retreatment duration is 48 weeks. <u>Recommendations in patients with genotype 4 infection</u> • Appropriate candidates with HCV genotype 4 infections should be treated with peginterferon alfa-2a 180 µg per week or peginterferon alfa-2b 1.5 µg / kg per week, plus ribavirin up to 1,400 mg per day for 48 weeks. <u>Recommendations in patients with decompensated cirrhosis</u> • Liver transplantation is the treatment of choice in patients with decompensated cirrhosis. • Antiviral therapy is contraindicated in most patients with decompensated cirrhosis. • Interferon-based therapy in combination with ribavirin can be considered for patients awaiting liver transplantation if they have a Child-Pugh score <7 and a Model for End-Stage Liver Disease score ≤18. • If beginning antiviral therapy, the interferon dose should be reduced and growth factors may be used to for treatment-associated cytopenias. <u>Recommendations in patients following solid organ transplantation</u> • Interferon-based antiviral therapy is contraindicated in patients who have received a heart, lung or kidney transplant. • In patients with biopsy-proven chronic HCV disease following liver

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	transplantation, peginterferon-ribavirin for 48 weeks may be considered. • Monitor antiviral therapy in post-liver transplant patients on antiviral therapy and discontinue if rejection is documented. Pre-emptive antiviral therapy early post-transplantation in patients without histological recurrence should be avoided. Recommendations in patients with renal disease • Considered modified doses of antiviral therapy with interferon (standard or pegylated). • Antiviral therapy for HCV treatment is not recommended in patients following renal transplant; however, it may be considered if patients develop fibrosing cholestatic hepatitis. Recommendations in patients with comorbid conditions • Antiviral therapy is not recommended in patients with a limited life expectancy. In addition, peginterferon-ribavirin, treatment should be avoided in comorbid conditions that may be exacerbated by treatment. Recommendations for patients on methadone • Antiviral therapy should be offered to patients enrolled in a methadone maintenance program who meet criteria for therapy. Coordinated HCV treatment between providers and substance abuse specialists should occur. Recommendations in patients with ongoing alcohol use • Encourage patients to decrease alcohol consumption or to abstain, and refer for behavioral intervention to reduce alcohol use. Antiviral therapy may be used in patients who are otherwise appropriate candidates, regardless of prior alcohol use. Alcohol reduces adherence and treatment response. Recommendations in obese patients and those with hepatic steatosis • Patients with a body mass index >30 should be considered for antiviral treatment. Control comorbid conditions prior to initiation of antiviral therapy. Recommendations in patients with human immunodeficiency virus (HIV)/HCV coinfection • Patients with controlled HIV infection and evidence of liver disease on biopsy should be considered for HCV antiviral therapy. Treatment should consist of peginterferon-ribavirin at doses similar to those with HCV for a duration of 48 weeks. Recommendations in patients with acute HCV infection • Observe patients for eight to 20 weeks from time of initial exposure to monitor for spontaneous resolution of infection. • In patients who fail to resolve infection spontaneously, treatment with peginterferon alfa, with or without ribavirin for 24 to 48 weeks

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	should be used, based on genotype and HCV RNA response during therapy.
Centers for Disease Control and Prevention: **Hepatitis ABC Fact Sheet (2012)**[14]	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.
American Gastroenterological Association: **Medical Position Statement on the Management of Hepatitis C (2006)**[15]	• 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: o 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. o Twelve weeks of therapy suffices in patients in whom HCV RNA levels are undetectable at week four. o Patients with genotype 3, with high levels of HCV RNA or advanced fibrosis on liver biopsy, may require treatment for 48 weeks.

Conclusions

The ribavirin products included in this review are FDA-approved for the treatment of chronic hepatitis C in combination with pegylated interferon. Two ribavirin products, Copegus® and Moderiba®, also have the indication of treating patients with chronic hepatitis C who are coinfected with human immunodeficiency virus.[1,4] Ribavirin is available generically in a capsule and tablet formulation, while the solution (Rebetol®) is only available as a branded product. Ribasphere® RibaPak® is a branded unit dose pack containing seven days of therapy.[1-4]

Clinical trials demonstrating the efficacy of ribavirin in combination with interferon or pegylated interferon (± other agents) has consistently shown effectiveness at achieving SVR.[20-69,71,72] Ribavirin should not be used as monotherapy for the treatment of hepatitis C.[1-4] The addition of a third agent to ribavirin and peg-interferon has significantly increased the rate of SVR compared to standard therapy. Protease inhibitors were the first direct acting hepatitis C antiviral to show efficacy.[37-39,48,49] Sofosbuvir, a polymerase inhibitor against hepatitis C combinations have achieved SVR rates consistently around 90%.[68-72]

Triple therapy with pegylated interferon, ribavirin and a direct acting hepatitis C antiviral (polymerase inhibitors and protease inhibitors) is the current standard of care for the treatment of chronic hepatitis C for most genotypes. However, with the introduction of new oral hepatitis C antivirals such as sofosbuvir, SRV can be achieved without pegylated interferon, and thus dual therapy with sofosbuvir and ribavirin has become common.[7-10] Other guidelines have not been updated to include the newer agents.[11-15] Overall, guidelines do not give preference to one specific pegylated interferon or ribavirin product over another.[7-15]

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