Effective Health Care Program

Comparative Effectiveness of Treatments for Chronic Hepatitis C Virus Infection in Adults

Research Focus for Clinicians

In response to a request from the public regarding antiviral regimens for the treatment of chronic hepatitis C virus (HCV) infection, a review was undertaken to evaluate the evidence regarding the potential benefits and adverse effects associated with currently available antiviral treatment regimens. This review did not address antiviral treatment for hepatitis C in pregnant women, or in patients receiving hemodialysis, or in those infected with HIV, or in patients after transplantation. The systematic review included 77 reports of eligible studies published from 1947 through April 2012. The full report, listing all studies, is available at www.effectivehealthcare.ahrq.gov/hepctreatment.cfm. This summary is provided to inform discussions with patients of options and to assist in decisionmaking along with consideration of a patient's values and preferences. However, reviews of evidence should not be construed to represent clinical recommendations or guidelines.

Background

Approximately 1.6 percent of U.S. adults over the age of 20 have antibodies to HCV, indicating previous acute HCV infection. About 70 to 85 percent of patients with acute HCV infection develop chronic HCV infection.[1] Of these, about 75 percent have HCV genotype 1 infection, and about 20 percent have HCV genotype 2 or 3 infection.

Chronic HCV infection has a variable course and can result in complications of the liver including cirrhosis, liver failure, and hepatocellular cancer. The risk of developing cirrhosis ranges from 5 to 25 percent over 25 to 30 years. Identifying individuals at risk of progressive disease is challenging. Currently, the preferred strategy is to evaluate the degree of fibrosis by liver biopsy; however, indications for liver biopsy continue to evolve. Modalities such as blood tests and indices have been evaluated as alternatives.[2]

The goal of treating chronic HCV infection is to prevent long-term health complications and death. The sustained virologic response (SVR) rate is a key marker of successful treatment, because it is strongly associated with long-term absence of viremia. HCV genotype 1 infection is associated with a substantially lower response to antiviral treatment than infection with genotypes 2 and 3.[1] Other factors suggested to be associated with lower SVR rates are pretreatment viral load >600,000 IU/mL, male sex, age >40 years, race (partly linked to polymorphisms in the interleukin-28B gene), and insulin resistance.

In the early 2000s, the combination of ribavirin with either pegylated interferon alfa-2a or alfa-2b became the standard antiviral treatment for HCV infection. Both combinations are associated with a high rate of adverse effects.

[1] www.cdc.gov/hepatitis/HCV
[2] Ghany MG, Strader DB, Thomas DL, et al. Hepatology 2009;49(4): 1335-74. PMID: 19330875.

In 2011, the U.S. Food and Drug Administration approved the first direct-acting antiviral agents, boceprevir and telaprevir, for treating chronic HCV genotype 1 infection. Each drug is administered in combination with pegylated interferon (alfa-2a or alfa-2b) plus ribavirin.

Decisions about treatment strategies for patients with chronic HCV infection who are treatment naive are based on various disease- and patient-related factors such as hepatitis C genotype, the presence of liver disease and its severity, the presence of comorbidities, and demographic characteristics. The continued development of new treatment strategies, including testing of the all-oral interferon-sparing therapies that might be available in the coming years, also impacts treatment decisions. Understanding the comparative benefits and harms of dual- and triple-therapy antiviral regimens—and whether they are affected by medication dose, treatment duration, and dosing strategy (fixed treatment vs. response-guided therapy)—is critical for making informed treatment decisions. Having this understanding is particularly important, given the availability of new treatment options (telaprevir and boceprevir) for chronic HCV infections.

Conclusions

Although direct evidence on the comparative effectiveness of current antiviral regimens on long-term clinical outcomes is lacking, both dual and triple therapies were found to produce SVRs in treatment-naive patients. Triple therapy with pegylated interferon (alfa-2a or alfa-2b), ribavirin, and either boceprevir or telaprevir induced substantially higher responses in patients with HCV genotype 1 when compared with dual therapy with pegylated interferon plus ribavirin. Triple-therapy regimens were associated with increased risk of harms including anemia (both boceprevir and telaprevir) and rash (telaprevir). Recent cohort studies provided moderate-strength evidence that achieving an SVR is associated with a decreased risk of all-cause mortality.

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Clinical Bottom Line

Evidence of Benefits

Triple therapy with ribavirin + pegIFN alfa (2a or 2b) + boceprevir versus dual therapy with ribavirin + pegIFN alfa in patients with HCV genotype 1 infection

The likelihood of achieving SVR was higher with 48 weeks of triple therapy containing boceprevir versus dual therapy, with an absolute increase in the SVR rate of 31 percent. ●●○
- The pooled RR was 1.8 (95% CI, 1.6–2.1).
- SVR rates were 66–75 percent for triple therapy versus 38 percent for dual therapy.

In patients treated with 48 weeks of triple therapy containing boceprevir, absolute SVR rates were lower in patients of black race when compared with patients of nonblack race; no clear differences in RR estimates for SVR were found. ●●○

Triple therapy with ribavirin + pegIFN alfa (2a or 2b) + telaprevir versus dual therapy with ribavirin + pegIFN alfa in patients with HCV genotype 1 infection

The likelihood of achieving SVR was higher with 24 weeks of triple therapy containing telaprevir versus 48 weeks of dual therapy, with an absolute increase in the SVR rate of 22 percent. ●●○
- The pooled RR was 1.5 (95% CI, 1.3–1.8).
- SVR rates were 60–73 percent for triple therapy versus 41–49 percent for dual therapy.

In patients treated with response-guided triple therapy containing telaprevir (initial triple therapy for 12 weeks followed by dual therapy) versus 48 weeks of dual therapy, characteristics associated with lower SVR rates were:
- Older age or black race ●●○
- Advanced fibrosis or cirrhosis and higher body mass index (based on limited evidence) ●○○

Dual therapy with ribavirin + pegIFN alfa-2b versus ribavirin + pegIFN alfa-2a*§

The likelihood of achieving an SVR was similar for dual therapy with ribavirin + pegIFN alfa-2b versus pegIFN alfa-2a (although the likelihood appeared to be slightly lower for dual therapy with ribavirin + pegIFN alfa-2b). ●●○
- The pooled RR was 0.87 (95% CI, 0.80–0.95).
- SVR rates were 38–62 percent versus 41–71 percent for dual therapy with pegIFN alfa-2b versus alfa-2a.

When comparing dual-therapy regimens, no clear differences in RR estimates for SVR in patients stratified by genotype were found, although rates of SVR were lower by 24–42 percent for HCV genotype 1 infection when compared with HCV genotypes 2 and 3. ●●○

In patients treated with dual-therapy regimens, absolute SVR rates were lower in those who were older, were black, had advanced fibrosis or cirrhosis, and had a high baseline viral load. ●○○

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Evidence of Benefits *(Continued)*

Dual therapy with ribavirin + pegIFN alfa (2a or 2b) in patients with HCV genotype 2 or 3 infection

Likelihood of achieving SVR was higher with dual therapy for 24 weeks when compared with dual therapy for 12–16 weeks. ●●○
- The pooled RR was 1.2 (95% CI, 1.0–1.3).
- SVR rates were 67–78 percent (24 weeks of therapy) versus 57–62 percent (12–16 weeks of therapy).
- In patients with rapid virologic response,** SVR rates did not differ between 24 weeks and 12–16 weeks of therapy. ●●○
- Lower doses (0.75–1.0 mcg/kg or 50 mcg) of pegIFN alfa-2b were less effective than standard doses (1.5 mcg/kg or 100–150 mcg) in dual-therapy regimens. ●●○
- No difference in likelihood of achieving SVR was observed with lower doses (a 400–800 mg/day flat dose or a 600–800 mg/day weight-based dose) versus higher doses (a 800–1,200 mg/day flat dose or a 800–1,400 mg/day weight-based dose) of ribavirin. ●●○

SVR after antiviral therapy and clinical outcomes

Evidence from cohort studies suggests that achieving an SVR after antiviral therapy might be associated with lower risk of all-cause mortality when compared with not achieving an SVR; however, the smaller supporting studies had some methodological shortcomings. ●●○

Other key findings of this review
- No studies were identified that evaluated the relative effectiveness of antiviral therapies on long-term clinical outcomes and on clinical outcomes in patients stratified by HCV genotype, age, race, sex, stage of disease, or other factors. ○○○
- Limited evidence suggested that achieving an SVR was associated with greater improvement in measures of quality of life 24 weeks after the end of antiviral therapy versus no SVR. ●○○

* The population included patients infected with HCV genotypes 1, 2, 3, or 4.
§ Duration of therapy in these studies was fixed (48 weeks in patients with HCV genotypes 1 or 4 and 24 weeks in patients with HCV genotypes 2 or 3) or response guided (24 or 48 weeks based on HCV RNA negativity between weeks 4 and 20).
**HCV RNA was undetectable by 4 weeks.

Evidence of Harms

Triple therapy with ribavirin + pegIFN alfa (2a or 2b) + telaprevir versus dual therapy with ribavirin + pegIFN alfa

Triple therapy with telaprevir for 24 weeks was associated with increased risk of anemia and rash when compared with dual therapy; there was no difference in risk of withdrawal due to adverse events between the two groups. ●●○
- The pooled RR for anemia was 1.3 (95% CI, 1.1–1.5), and the pooled RR for rash was 1.4 (95% CI, 1.1–1.7).
- In patients on triple therapy, the incidence of anemia was 27–91 percent, rash was 33–66 percent, severe anemia was 4–11 percent, and severe rash was 7–10 percent.

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Clinical Bottom Line *(Continued)*

Evidence of Harms

Triple therapy with ribavirin + pegIFN alfa (2a or 2b) + boceprevir versus dual therapy with ribavirin + pegIFN alfa

Triple therapy with boceprevir for 48 weeks was associated with increased risk of neutropenia, anemia, dysgeusia, and thrombocytopenia when compared with dual therapy; there was no difference in risk of withdrawal due to adverse events between the two groups. ●●○

- The pooled RR for neutropenia was 1.8 (95% CI, 1.5–2.3), the pooled RR for anemia was 2.0 (95% CI, 1.4–2.8), the pooled RR for dysgeusia was 2.5 (95% CI, 2.0–3.2), and the pooled RR for thrombocytopenia was 3.3 (95% CI, 1.3–8.6).
- In patients on triple therapy, incidence of anemia was 50 percent, neutropenia was 25 percent, severe neutropenia was 8–15 percent, and severe anemia was 4–5 percent.

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Evidence of Harms *(Continued)*

Dual therapy with ribavirin + pegIFN alfa-2a versus ribavirin + pegIFN alfa-2b*

- Withdrawals due to adverse events did not differ between dual therapy with ribavirin + pegIFN alfa-2b versus ribavirin + pegIFN alfa-2a. ●●○
- There was a lower risk of neutropenia, rash, and serious adverse events[†] with ribavirin + pegIFN alfa-2b versus ribavirin + pegIFN alfa-2a. ●●○

* The population included patients infected with HCV genotypes 1, 2, 3, or 4.
† Serious adverse events included gastrointestinal disorders, cardiovascular disorders, other infections, neoplasms, and psychiatric disorders.

Abbreviations: 95% CI = 95-percent confidence interval; pegIFN = pegylated interferon; RR = relative risk

Strength of Evidence Scale

High: ●●● High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.

Moderate: ●●○ Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.

Low: ●○○ Low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate.

Insufficient: ○○○ Evidence either is unavailable or does not permit a conclusion.

Key Information Issued by the U.S. Food and Drug Administration on Medications Used To Treat Hepatitis C Virus Infection[‡]

Medication	Information
Boxed Warnings	
Pegylated interferon (alfa-2a or alfa-2b)	May cause or aggravate fatal or life-threatening: ■ Neuropsychiatric disorders ■ Autoimmune disorders ■ Ischemic disorders ■ Infectious disorders
Ribavirin	■ Ribavirin monotherapy is not effective for treating chronic HCV infection. ■ Hemolytic anemia associated with ribavirin may result in worsening of cardiac disease and lead to fatal and nonfatal myocardial infarctions. ■ Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. 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 6 months after completion of therapy in both female patients and in female partners of male patients who are taking ribavirin therapy.
Other Information	
Boceprevir	■ Its use is contraindicated in coadministration with other drugs that are highly dependent on CYP3A4/5 for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events. ■ Its use is contraindicated in coadministration with potent CYP3A4/5 inducers, where significantly reduced boceprevir plasma concentrations may be associated with reduced efficacy.
Telaprevir	■ Its use is contraindicated in coadministration with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events. ■ Its use is contraindicated in coadministration with drugs that strongly induce CYP3A, which may lead to lower exposure and loss of efficacy of telaprevir.

‡ Source: www.fda.gov

Additional Information

- The findings of the review are also relevant to screening recommendations. Important new evidence that may affect assessments of the potential benefits of screening include:
  - ☐ Stronger evidence of the link between achieving an SVR and improvement in clinical outcomes
  - ☐ Evidence showing substantially higher SVR rates with newer triple-therapy regimens with boceprevir or telaprevir in patients with HCV genotype 1 infection

Applicability of the Findings of This Report

The applicability of the findings of this report are limited by the following factors:

- All the studies included in this review were conducted only in treatment-naive patients.
- The trials assessed in this report included a broad range of patients as indicated by the severity of baseline liver disease in the enrolled patients.
- The trials included in this review generally met criteria for efficacy studies, based on the exclusion of patients with common comorbidities such as serious psychiatric conditions or recent or ongoing substance abuse.
- Populations such as patients with HIV coninfection, transplant recipients, or patients requiring hemodialysis were excluded from this review.

Gaps in Knowledge

- No trials directly compared regimens containing boceprevir with regimens containing telaprevir. Given the increased efficacy of these regimens in patients with HCV genotype 1 infection, trials directly comparing their effects would be helpful for informing treatment choices between these drugs.
- Few trials have evaluated the specific drug regimens approved by the U.S. Food and Drug Administration for use in clinical practice, limiting confidence in conclusions about estimates of their benefits and adverse effects.
- Few methodologically rigorous studies conducted in settings applicable to U.S. populations evaluated the association between achieving an SVR and improvements in clinical outcomes or quality of life.
- Trials that enroll broader populations with medical and psychological comorbidities, as encountered in clinical practice, and studies designed according to an effectiveness paradigm that reflect real-world effects are lacking.

What To Discuss With Your Patients

- The disease management strategy (considering no treatment vs. immediate treatment) that would be most appropriate for the individual patient based on the severity of liver disease
- The type of treatment regimen that might be most suitable for the patient given the HCV genotype, severity of disease, likelihood of treatment response, and presence of comorbid conditions

- The different types of therapeutic regimens currently available for treating chronic HCV infection
- The available evidence for the effectiveness of the various regimens for treating chronic HCV infection
- The available evidence for the adverse effects associated with the various regimens for treating chronic HCV infection, and what should be done if adverse effects develop
- The potential new therapies on the horizon, and their possible impact on the treatment approach for the patient
- The possibility that other specialists might be involved in the patient's care during the treatment process
- The potential out-of-pocket costs that the patient might incur for the various treatments based on his/her insurance coverage

Resource for Patients

Treating Chronic Hepatitis C, A Review of the Research for Adults is a free companion to this clinician research summary. It can help patients with chronic HCV infection talk with their health care professionals about the many options for treatment.

Ordering Information

For electronic copies of *Treating Chronic Hepatitis C, A Review of the Research for Adults*, this clinician research summary, and the full systematic review, visit www.effectivehealthcare.ahrq.gov/hepctreatment.cfm. To order free print copies, call the AHRQ Publications Clearinghouse at 800-358-9295.

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