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. 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.

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. 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.

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 naïve 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-naïve 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.

References:
1 www.cdc.gov/hepatitis/HCV

Agency for Healthcare Research and Quality
Advancing Excellence in Health Care • www.ahrq.gov
Clinical Bottom Line

Evidence of Benefits

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<tr>
<th>Clinical Bottom Line</th>
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<tr>
<td><strong>Triple therapy with ribavirin + pegIFN alfa (2a or 2b) + boceprevir versus dual therapy with ribavirin + pegIFN alfa in patients with HCV genotype 1 infection</strong></td>
<td><strong>Dual therapy with ribavirin + pegIFN alfa (2a or 2b) in patients with HCV genotype 2 or 3 infection</strong></td>
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<td>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.  • • •</td>
<td>Likelihood of achieving SVR was higher with dual therapy for 24 weeks when compared with dual therapy for 12–16 weeks.  • • •</td>
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<td>The pooled RR was 1.8 (95% CI, 1.6–2.1).</td>
<td>• The pooled RR was 1.2 (95% CI, 1.0–1.3).</td>
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<td>SVR rates were 66–75 percent for triple therapy versus 38 percent for dual therapy.</td>
<td>SVR rates were 67–78 percent (24 weeks of therapy) versus 57–62 percent (12–16 weeks of therapy).</td>
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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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<table>
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<td><strong>Triple therapy with ribavirin + pegIFN alfa (2a or 2b) + telaprevir versus dual therapy with ribavirin + pegIFN alfa</strong></td>
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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).

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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

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: ●● O 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: ● O 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: O O O 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
Few methodologically rigorous studies conducted in populations such as patients with HIV co-infection, trials directly comparing regimens containing newer triple-therapy regimens with boceprevir or telaprevir in patients with HCV genotype 1 infection were excluded from this review.

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 coinfection, 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