

## Systematic review

# Treatment of hepatitis C, then, now and tomorrow

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**Commentary on:** Kohli A, Shaffer A, Kotttilil S. Treatment of hepatitis C: a systematic review. *JAMA* 2014;312:631–40.

## Context

Hepatitis C virus (HCV) infects over 185 million people worldwide and can lead to progressive liver fibrosis, cirrhosis, hepatocellular carcinoma and death. Antiviral treatment can prevent these complications and improve survival. Interferon has been the backbone of anti-HCV therapy, but has been plagued by side effects, treatment failure and relapse. HCV treatment has seen significant changes with the advent of directly acting antiviral agents with nearly 100% cure rate with all oral, interferon and ribavirin-free regimens.

## Methods

This systematic review of randomised controlled trials (RCTs) and cohort studies aimed to examine the safety, tolerability and efficacy of all Food and Drug Administration (FDA)-approved regimens against HCV genotypes 1, 2 and 3. All studies between January 2009 and May 2014 were included if they were published in English, used FDA-approved antiviral therapies, included sustained virological response (SVR) as the study outcome, and defined treatment experience according to American Association of Study of Liver Diseases (AASLD) definitions. Studies involving patients with liver transplant, acute HCV or HCV genotypes other than 1, 2 or 3 were excluded, as were dose-finding studies. Quality of clinical evidence and strength of practice recommendations were graded according to Oxford-based level of evidence-grading system. The systematic review was conducted according to PRISMA guidelines.

## Findings

Forty-one studies (33 RCTs and 8 cohort studies) met the inclusion criteria, reporting 19 063 adult patients with chronic HCV genotype 1, 2 or 3. Among patients with genotype 1, the first-generation NS3 inhibitors (telaprevir and boceprevir) were clearly more effective than the standard care (peg-interferon plus ribavirin therapy), both among treatment naïve and treatment-experienced patients (SVR range 61–75% vs 38–49% and 69–83% vs 20–29%, respectively). However, among prior null responders, only a modest improvement in SVR (39–56% vs 9–17%) was noted with the telaprevir-based therapy.

Addition of simeprevir (a second-generation NS3/4 serine protease inhibitor) was superior to peg-interferon plus ribavirin alone, both among treatment naïve and treatment-experienced patients (SVR 79–86% vs 37–65% and 67–80% vs 36%, respectively). However, prior null responders fared poorly compared to partial responders and previous relapses (SVR of 41–59% vs 65–86% and 76–89%, respectively).

Response rate was significantly lower among genotype 1a patients with NS3 Q80K polymorphisms.

Sofosbuvir, the first FDA-approved NS5B polymerase inhibitor, in combination with peg-interferon and ribavirin, showed very high SVR rates (89–90%) with only 12 weeks of therapy. Extending the treatment to 24 weeks did not improve the SVR further.

The all-oral regimen of sofosbuvir and ribavirin for 12–24 weeks showed SVR of 68–84% among treatment naïve genotype 1 patients.

Among treatment naïve genotype 2 patients, 12 weeks of sofosbuvir plus ribavirin performed much better than 24 weeks of peg-interferon plus ribavirin (SVR 97% vs 78%). Genotype 3 patients, however, did not do well with 12 weeks of sofosbuvir and ribavirin (SVR~30%). However, SVR improved further with an extension of the treatment course to 24 weeks among both treatment naïve and treatment-experienced groups (95% and 80%, respectively). Of note, patients with cirrhosis or advanced fibrosis did less well compared to those without cirrhosis. Cirrhotic genotype 3 patients with prior null response fared the worst (SVR~33%).

The addition of telaprevir or boceprevir was associated with increased side effects and treatment discontinuation, while the addition of simeprevir or sofosbuvir was associated with minimal additional side effects beyond that expected with interferon. Although drug–drug interactions were a major problem with telaprevir and boceprevir, this was not the case with simeprevir or sofosbuvir.

## Commentary

While this systemic review carefully examines and clearly summarises the rapidly evolving field of HCV therapies, unfortunately the information is already outdated as new drugs have since been approved and treatment guidelines are being updated constantly. None the less, the extraordinary effort by the authors to put together these landmark studies, concisely summarising the treatment outcomes in the tabular format is commendable and worth reading.

While small numbers of well-compensated cirrhotics were included, studies involving patients with decompensated cirrhosis, renal failure, other comorbidities and minorities are lacking. Unfortunately, these are the most difficult and complex groups of patients in the clinical practice.

## Implications for practice

The field of HCV therapy is changing at such a rapid pace that any printed guidelines will likely be outdated by the time it hits the market. Keeping this in mind, and as the authors have pointed out in their discussion, the AASLD and Infectious Disease Society of America have jointly ventured a dynamic online clinical guidance that accommodates these rapid updates. Readers are encouraged to familiarise themselves with these updates as they will impact on the care they provide. With these new highly effective and safe interferon-free oral-only agents treating hepatitis C it is going to be easier than ever—except for their prohibitive costs.

**Contributors** ND was responsible for critical review of the article and drafted the original commentary. RKS was responsible for critical review of the article, revised draft and finalised it.

**Competing interests** RKS has received grants from Roche/Genentech, Gilead, Abbvie, Merck, BMS, Boehringer Ingelheim, and sits on the advisory board of Abbvie, Gilead, Janssen, Salix, Bayer, BMS.

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## Reference

1. American Association for the Study of Liver Diseases. Recommendations for testing, managing and treating hepatitis C. <http://www.hcvguidelines.org/>