REVIEW

Response-guided therapy in patients with genotype 1 hepatitis C virus: Current status and future prospects

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Abstract
On-treatment responses to antiviral therapy are used to determine duration of therapy in patients being treated for genotype 1 hepatitis C virus infection. Such use of response-guided therapy has successfully reduced exposure of patients to the side-effects of pegylated interferon and ribavirin without jeopardizing overall treatment success. Response-guided therapy is an integral part of treatment using the current standard treatments involving the direct-acting antiviral (DAA) agents—boceprevir or telaprevir—combined with pegylated interferon/ribavirin. Improvements in our understanding of the kinetics of viral load during antiviral therapy have shown us that more potent suppression of viral replication increases the rate of viral eradication, providing impetus for the development of more potent DAAs. Emerging results from clinical trials of these agents—including trials of interferon-free DAA combinations—suggest that very high rates of viral eradication are achievable, even in patients who failed to respond to previous courses of interferon-based therapy. Furthermore, because of these high rates of treatment success, on-treatment assessment of viral response may become unnecessary. The field of hepatitis C virus therapy is evolving rapidly and current trends indicate that the era of simple treatment regimens with high rates of success and good tolerability are near.

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**Introduction and background**

The goal of treating chronic hepatitis C is sustained virological response (SVR), historically defined as undetectable hepatitis C virus (HCV) RNA 24 weeks after the end of treatment. Among patients who achieved SVR in nine therapeutic trials, 99.1% still had undetectable HCV RNA after several years of follow-up (mean 3.9 years). SVR is associated with improvements in markers of hepatic function and strong reductions in the long-term risks of hepatocellular carcinoma and other liver-associated morbidity and mortality. For a number of years, the standard therapy for chronic hepatitis C was pegylated interferon (PegIFN) α2a or α2b in combination with ribavirin (RBV), given for 48 weeks to patients with genotype 1 or 4 HCV infection, or for 24 weeks to patients with genotype 2 or 3 HCV infection. However, PegIFN/RBV therapy is difficult to tolerate, leading to high rates of treatment discontinuation. Furthermore, only 40–50% of genotype 1 patients achieve SVR after a first course of PegIFN/RBV. The prolonged course of therapy required for treating patients with genotype 1 HCV, along with the associated relatively low SVR rates and poor tolerability, have been significant drawbacks to the use of PegIFN/RBV.

The desire to minimize exposure to PegIFN/RBV and to optimize response rates led to the development of response-guided therapy (RGT), which can be defined as determining treatment duration on the basis of viral load at a specific time after initiation of therapy. The use of RGT began in the era of PegIFN/RBV, where it was demonstrated that certain patient subgroups with favorable baseline characteristics associated with higher rates of SVR could receive a shorter duration of therapy. In patients with genotype 1 HCV infection receiving PegIFN/RBV, for example, those achieving a rapid virological response (RVR; HCV RNA < 50 IU/mL at week 4) were eligible for shortened duration of therapy (24 weeks instead of the usual 48 weeks), without experiencing a reduction in SVR rates. RVR, or on-therapy response to PegIFN, has been shown to be a better predictor of SVR than various baseline factors, including genotype, patient age, viral load, alanine aminotransferase ratios, and presence of liver fibrosis. The development and evolution of RGT greatly improved the treatment experience for patients with genotype 1 HCV, allowing shorter courses of therapy for strong responders and cessation of therapy in those unlikely to achieve SVR, decreasing exposure to adverse drug effects and costs in both types of patients. Unfortunately, only a small proportion of treatment-naïve, genotype 1 patients achieve an RVR during PegIFN/RBV therapy; the remainder must endure a full 48-week course of therapy or are discontinued because of virological failure, defined as not achieving an early virological response (Table 1) or by having detectable virus at treatment week 24.

Studies of the kinetics of viral load during antiviral therapy have provided a mechanistic underpinning for RGT and guideposts for the development of improved antiviral therapies. According to current models of viral load in patients who respond to PegIFN/RBV, HCV RNA levels decline in two phases. The first phase of decline represents suppression of virus production, and the slower second phase represents clearance of infected cells or cell cure, in which intracellular viral RNA is eliminated. A key aspect of this model and its application to RGT is that the rate of decline during the second phase is influenced by antiviral efficacy. With this underpinning, it is predicted that more rapid and effective suppression of virus production will shorten the duration of treatment necessary to achieve SVR. It should be noted, however, that pre-existing factors also influence the second phase—factors such as the host interleukin 28B (IL28B) genotype, baseline viral load, degree of fibrosis or cirrhosis, and HIV co-infection. Furthermore, durable viral suppression requires the use of antiviral therapy that prevents the development of treatment-resistant strains, generally necessitating combination therapies.

This paper gives an overview of current clinical practice regarding RGT in patients with genotype 1 HCV infection and sets the stage for how the introduction of new direct-acting antiviral agents (DAAs) will change RGT.

### Interferon-based triple therapy regimens incorporating viral protease inhibitors

In 2011, the first DAAs, boceprevir and telaprevir, became available. These agents inhibit the NS3/4A viral protease. Addition of either agent to a standard PegIFN/RBV regimen dramatically improved SVR rates among patients with genotype 1 HCV infection. Just as importantly, DAAs have increased the proportion of patients eligible for shortened duration of therapy using the principles of RGT. Between 44% and 65% of treatment-naïve, patients achieved criteria for RGT during phase 3 studies and stopped therapy after 24 weeks (telaprevir) or 28 weeks (boceprevir) without significantly increasing their risk of relapse. However, the addition of telaprevir/boceprevir to PegIFN/RBV has led to an increase in adverse events.

Boceprevir and telaprevir were studied in five phase 3 clinical trials in both treatment-naïve and treatment-experienced patients. These trials have been extensively reviewed, so we will limit our discussion to a brief overview and focus on the implications for use of RGT.

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Table 1 On-treatment response criteria and their definitions

<table>
<thead>
<tr>
<th>Response type</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Extended RVR (eRVR)‡</td>
<td>Undetectable HCV RNA at weeks 8–12 (week 8 comprises a 4-week lead-in period of PegIFN/RBV followed by 4 weeks of triple therapy)</td>
</tr>
<tr>
<td>Triple therapy with boceprevir</td>
<td>Undetectable HCV RNA at weeks 8–12 (week 8 comprises a 4-week lead-in period of PegIFN/RBV followed by 4 weeks of triple therapy)</td>
</tr>
<tr>
<td>Triple therapy with telaprevir</td>
<td>Undetectable HCV RNA at weeks 4 and 12</td>
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‡Undetectable HCV RNA historically defined as < 50 IU/mL. 
Undetectable HCV RNA defined as ≤ 25 IU/mL.
**Boceprevir.** Triple-therapy using boceprevir was studied in the SPRINT-2 trial, which enrolled treatment-naïve patients with chronic, genotype 1 HCV infection.26 This trial employed a 4-week lead-in period of PegIFN/RBV, after which treatments diverged into three groups. Group 1 received placebo plus PegIFN/RBV; group 2 (response-guided arm) received boceprevir triple therapy for 24 weeks, at which time all treatment was discontinued in those who had undetectable HCV RNA at clinic visits between weeks 8 and week 24 (not including week 24) and those with detectable HCV RNA continued treatment with PegIFN/RBV plus placebo to complete 48 weeks of therapy; and group 3 that received boceprevir plus PegIFN for a total of 44 weeks (after a 4-week lead in) even if virus levels were undetectable between weeks 8 and 24. Patients in any group who had detectable HCV RNA at week 24 were discontinued according to rules of futility.26

Forty-four percent of patients in the boceprevir response-guided arm were eligible to stop therapy at week 28 based on undetectable HCV RNA levels between weeks 8 and 24. Similarly, 44% of patients in the 48-week triple therapy arm had undetectable HCV RNA between weeks 8 and 24 but continued therapy to full 48-week duration as per the study protocol; HCV RNA levels were undetectable in only 12% of patients in the control arm between weeks 8 and 24. Ninety-six percent of patients in each boceprevir treatment arm who achieved undetectable HCV RNA between weeks 8 and 24 also achieved SVR (group 2: 156/162; group 3: 155/161).26

The SPRINT-2 trial had a 4-week lead-in of PegIFN/RBV, and 5% of patients achieved RVR (undetectable HCV RNA after 4 weeks of PegIFN/RBV) during that time. Previous guidelines recommended that these patients could be considered for a shortened duration of PegIFN/RBV therapy if baseline factors supported such a decision.4 With the addition of a DAA and the application of different RGT criteria, more patients are eligible for shortened duration of therapy with triple therapy (44%) than would have been eligible with PegIFN/RBV alone (12%).26

The RESPOND-2 trial studied boceprevir-containing triple therapy among chronically infected, genotype 1 HCV-infected patients who had prior exposure to PegIFN/RBV and were either partial responders or relapsers (prior null responders were not included in the trial).28 The RESPOND-2 trial used a lead-in of PegIFN/RBV treatment similar to the SPRINT-2 trial. To be eligible for a shortened duration of therapy, however, participants in the response-guided arm of the RESPOND-2 trial had to have undetectable HCV RNA at weeks 8 and 12. In boceprevir-containing regimens, 49% of participants had undetectable HCV RNA at weeks 8 and 12 compared with 9% of participants in the placebo (PegIFN/RBV) group. Those eligible for a shortened duration of therapy received 36 weeks of treatment (4-week lead-in followed by 32 weeks of triple therapy). There was no significant difference in SVR rates between the group that received boceprevir-containing triple therapy for 48 weeks and the group treated according to response-guided principles (odds ratio, 1.4; 95% confidence interval 0.9–2.2). The trend toward a difference may be explained by differing responsiveness of patients with cirrhosis in the two groups.29

Although SVR rates in the boceprevir-containing groups of the RESPOND-2 trial were not significantly different (59% in the response-guided group and 66% in the group that received full 48 weeks of therapy), SVR rates were substantially lower among the subgroup of patients who had a weak response to the 4-week lead-in treatment with PegIFN/RBV (< 1 log10 IU/mL decline in HCV RNA level; 33% and 34% in the two boceprevir-containing arms). Furthermore, those patients who had a weak response to the lead-in phase (who can be considered comparable with prior null responders) and who received RGT had a high rate of emergence of boceprevir-resistant variants.29 Based on these results, RGT with boceprevir was not recommended for prior null responders.

However, the PROVIDE trial retreated patients who did not achieve SVR during phase 2/3 boceprevir trials with 44 weeks of boceprevir-triple therapy. Of 168 patients, SVR was achieved in 38% of prior null responders, 67% of prior partial responders, and 93% of prior relapsers.30 Cirrhotic patients were underrepresented in the RESPOND-2 trial, and those in the boceprevir-containing groups had significantly lower SVR rates after RGT than after the full 48 weeks of treatment (35% vs 77%).29 The PROVIDE study showed SVR rates of 74% for patients with advanced fibrosis who received 44 weeks of boceprevir-triple therapy.30

**Telaprevir.** Triple therapy using telaprevir was studied in two trials of treatment-naïve patients, the ADVANCE trial27 and the ILLUMINATE trial.28 The three-arm ADVANCE trial did not employ a lead-in phase. Participants were randomized to receive 12 weeks of PegIFN/RBV in combination with telaprevir for the first 8 or 12 weeks. In those two groups, patients who satisfied the criteria for extended RVR (eRVR) (see Table 1) received another 12 weeks of PegIFN/RBV, whereas those not satisfying those criteria received an additional 36 weeks of PegIFN/RBV. A third group received PegIFN/RBV plus placebo for 12 weeks followed by 36 weeks of PegIFN/RBV. The eRVR criteria for shortened duration of therapy were satisfied by 58% of participants in the telaprevir-containing groups but only 8% of participants in the placebo (PegIFN/RBV) group. Among those who received a shortened duration of therapy, 86% achieved SVR.27

The use of RGT in a telaprevir-containing regimen was studied explicitly in the ILLUMINATE trial,28 which enrolled treatment-naïve (TN) patients with chronic HCV genotype 1 infection. All patients received telaprevir-based triple therapy for 12 weeks. Those who experienced eRVR were then randomized to receive PegIFN/RBV for either 12 or 36 more weeks (those not experiencing eRVR received PegIFN/RBV for 36 more weeks.) Sixty-five percent of participants experienced eRVR. Among those participants who had eRVR, those randomized to receive an additional 12 weeks of PegIFN/RBV achieved SVR rates of 92% and those randomized to receive an additional 36 weeks of PegIFN/ RBV achieved SVR rates of 88%. The results satisfied the criteria for non-inferiority, allowing the investigators to conclude that the shorter duration of therapy for patients who achieved eRVR was non-inferior to the longer duration. Notably, significantly more participants randomized to the longer duration of therapy discontinued treatment because of adverse events compared with those randomized to the shorter duration (12% vs 1%; \( P < 0.001 \)).28

Telaprevir was also studied in previously treated patients in the REALIZE trial.31 However, the treatment protocol for that trial did not employ RGT.

**Clinical use of RGT in patients treated with boceprevir- or telaprevir-based triple therapy.** Current guidelines note that the use of boceprevir- or telaprevir-containing therapy, in combination with PegIFN/RBV, is optimal
for treatment-naive patients with genotype 1 HCV. Treatment regimens employing boceprevir should use a 4-week PegIFN/RBV lead-in period prior to initiation of triple therapy. \(2^{32}\) Triple therapy should then be administered for 24 weeks in patients eligible for RGT (i.e. those without cirrhosis and who have undetectable HCV RNA levels at weeks 8 and 24). Patients with cirrhosis should receive triple therapy for 44 weeks. Triple therapy should be stopped if the HCV RNA level is > 100 IU/mL at treatment week 12 or detectable at treatment week 24. \(2^{34}\) Telaprevir-containing regimens do not require a lead-in period. Triple therapy with telaprevir should be administered for 12 weeks, followed by 12 weeks of PegIFN/RBV in patients eligible for RGT (i.e. those without cirrhosis and who have undetectable HCV RNA levels at weeks 4 and 12). Patients with cirrhosis should continue PegIFN/RBV therapy for a total of 48 weeks. Triple therapy should be stopped at week 12 if HCV RNA levels are > 1000 IU/mL at weeks 4 and 12 of the triple-therapy phase, or at week 24 if HCV RNA is detectable at that time.\(^2\)

For patients previously treated with PegIFN/RBV, the guidelines recommend retreatment with a boceprevir- or telaprevir-containing regimen for patients who relapsed (undetectable HCV RNA at the end of treatment but detectable during follow-up) or had a partial response (HCV RNA declined by at least 2 log\(_{10}\) IU/mL at treatment week 12 with detectable HCV RNA at week 24) during prior treatment; retreatment can be considered for prior null responders (HCV RNA declined less than 2 log\(_{10}\) IU/mL at treatment week 12 with detectable HCV RNA at week 24).\(^2\) The use of RGT can be considered in prior relapsers. In prior partial responders, RGT can be considered for boceprevir-containing but not telaprevir-containing regimens. RGT is not recommended for prior null responders, poor IFN responders, or patients with cirrhosis.\(^{2,29,32}\) The HCV RNA threshold for discontinuing therapy in retreated patients is lower for boceprevir (patients with HCV RNA ≥ 100 IU/mL at week 12 should discontinue) than for telaprevir (patients with HCV RNA ≥ 1000 IU/mL at week 4 or 12 should discontinue).\(^2\)

**Future prospects**

In patients with genotype 1 HCV infection, boceprevir and telaprevir suppress HCV RNA levels by 2–4 log\(_{10}\) units. Although this represents 99–99.99% inhibition, mounting evidence indicates that DAAs offering even more potent suppression of HCV RNA levels could yield additional improvements in SVR rates and shorter durations of therapy.\(^2\) Indeed, a number of new DAAs, or combinations of DAAs, have been approved or are in late-stage clinical development and offer more potent suppression of viral replication. These new agents target the NS3/4A protease or other viral proteins such as the NSSB RNA polymerase or NS5A.\(^3\) In addition, many of these new agents are active against other genotypes, unlike boceprevir and telaprevir, which are approved only for genotype 1 HCV.\(^3,4^4\)

As these developments unfold, the future role of RGT is becoming uncertain. With the more potent suppression of viral replication, it may become possible to shorten therapy for all patients, obviating the need to tailor therapy duration to viral response. Emerging therapies with and without IFN have now demonstrated 90% or better SVR rates with fixed durations of 12 weeks in previously untreated, non-cirrhotic patients with genotype 1 HCV.\(^3,5^7,37\) Later, we give a brief overview of selected new DAAs and DAA-containing regimens in late-stage clinical development for patients with genotype 1 HCV. It is not our intention to give a comprehensive view but to highlight important trends and key studies, particularly those with implications for the future of RGT.

**Interferon-containing regimens**

**Simeprevir.** Simeprevir (TMC435) is a recently approved inhibitor of the NS3/4A HCV protease.\(^38\) Simeprevir is a macrocyclic, non-covalent protease inhibitor, unlike boceprevir and telaprevir, which are covalent, ketoamide inhibitors.\(^2\) US Food and Drug Administration (FDA) approval was based on data from three randomized, placebo-controlled, phase 3 clinical trials of simeprevir-containing triple therapy (with PegIFN/RBV), all of which used RGT.\(^39,4^1\) In the QUEST-1 trial, previously untreated patients with genotype 1 chronic HCV infection received simeprevir-containing triple therapy (or placebo plus PegIFN/RBV) for 12 weeks, followed by 12 or 36 weeks of PegIFN/RBV.\(^39\) In this trial, 85% of participants who received simeprevir-containing therapy were eligible for the shorter duration of therapy based on RGT criteria, 91% of whom achieved SVR12. The primary outcome of the trial was SVR12, which was reported in 80% of patients in the simeprevir-containing group (vs 50% in the placebo group). In the simeprevir-containing group, 3% of patients discontinued because of adverse events. The most common side-effects were fatigue, headache, and pruritus; hyperbilirubinemia due to inhibition of OATP1B1/MRP2 transporters was also noted.\(^39\) The QUEST-2 trial, which also enrolled treatment-naive patients with genotype 1 HCV, yielded similar results; 91% of simeprevir-treated patients met RGT criteria and were eligible to stop therapy at week 24 and among those patients, 86% achieved SVR12. Overall SVR12 rates were 81% in the simeprevir-based triple therapy arm versus 50% in the placebo plus PegIFN/RBV arm \((P < 0.001)\).\(^4^0\) In a trial of previous relapsers to PegIFN/RBV (PROMISE), 93% of participants receiving simeprevir-containing therapy were eligible for the shortened duration of therapy, and overall, 79% achieved SVR12.\(^4^1\) These large phase 3 trials are consistent with phase 2 trials of simeprevir-containing triple therapy\(^4^2,4^4\) and suggest that newer protease inhibitors may be associated with substantial increases in the percentage of patients eligible to stop therapy after 24 weeks compared with the first-generation agents boceprevir and telaprevir. Simeprevir is also active against a broader set of HCV genotypes, including 2, 4, 5, and 6, although phase 3 trials were not designed to investigate non-genotype 1 patients.\(^3^8\) Simeprevir has a number of desirable properties compared with the first-wave protease inhibitors, including more tolerable adverse events, fewer drug-drug interactions, and once-daily dosing, which may favorably impact compliance relative to boceprevir (12 pills/day) and telaprevir (6 pills/day).\(^2,3^3\)

**Faldaprevir.** Faldaprevir is another macrocyclic, non-covalent inhibitor of the NS3/4A protease in late-stage clinical development for treatment of chronic HCV.\(^4^5\) Faldaprevir potently suppresses HCV RNA levels in patients with genotype 1 chronic HCV infection by about 4 log\(_{10}\) IU/mL\(^4^6\) and has pharmacokinetic properties suitable for once-daily dosing.\(^4^5\) Faldaprevir in combination with PegIFN/RBV was studied in a randomized, double-blind, phase 3
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trial (STARTVerso1) in treatment-naïve patients with chronic, genotype 1 HCV infection. All patients received PegIFN/RBV for 24–48 weeks and were also randomized to receive either placebo, faldaprevir 120 mg once daily for 12 or 24 weeks based on RGT, or faldaprevir 240 mg once daily for 12 weeks. Patients in either faldaprevir group who achieved early treatment success (defined as HCV RNA < 25 IU/mL at week 4 and undetectable HCV RNA at week 8) stopped all treatment at 24 weeks, whereas other patients continued PegIFN/RBV for a total of 48 weeks. Overall, 88% of patients receiving faldaprevir achieved early treatment success and discontinued therapy at 24 weeks; among those, 88% achieved SVR12. Overall, 80% of patients receiving faldaprevir achieved SVR12. Study medications were discontinued because of adverse events in 4–5% of patients. These results are consistent with an earlier phase 2 trial in treatment-naïve patients (SILEN-C1).

In the phase 3 STARTVerso3 study of faldaprevir in treatment-experienced patients with HCV genotype 1 infection, only relapers were eligible for RGT following results from the phase 2 SILEN-C2 trial that showed continuing PegIFN/RBV for a total of 48 weeks was significantly better than discontinuing at 24 weeks in patients with a prior non-response (SVR 72% vs 43%; P = 0.035). Among prior relaper patients in STARTVerso3, 86–87% achieved early treatment success and were eligible to stop treatment at week 24; 75% of these patients achieved SVR12. Study medications were discontinued because of adverse events in 6–7% of patients who received faldaprevir.

Sofosbuvir. Sofosbuvir (GS-7977) is a recently approved nucleotide analog inhibitor of the HCV RNA-dependent RNA polymerase (NS5B) with activity against all HCV genotypes. Sofosbuvir in combination with PegIFN/RBV was associated with high rates of SVR (87–92%) in phase 2 trials of treatment-naïve patients with genotype 1 chronic HCV. The NEUTRINO trial was a phase 3, single-arm, open-label study of sofosbuvir plus PegIFN/RBV in treatment-naïve patients with genotype 1, 4, 5, or 6 chronic HCV (69% had genotype 1a, and 20% had genotype 1b). Two notable features of this trial were that 17% of patients had cirrhosis at baseline, and total treatment duration was 12 weeks for all study drugs and all patients (RGT criteria were assessed but did not dictate course of therapy). At week 2, 91% of patients had HCV RNA < 25 IU/mL, which increased to 99% at week 4. The primary end-point, SVR12, was achieved in 90% of patients, which was significantly higher than adjusted historical controls for PegIFN/RBV alone (60%; P < 0.001). Pretreatment factors such as IL28B genotype (SVR12 98% in CC IL28B vs 87% in non-CC IL28B) and presence of cirrhosis (SVR12 80% in cirrhotic patients vs 92% in non-cirrhotic patients) were predictive of lower response rates. Only 2% of patients discontinued because of adverse events. This study, which offers the best response rate in patients with cirrhosis to date, and future trials like it may herald the onset of a new era of fixed short-duration therapy with high SVR.

Interferon-free regimens. The development of DAAs with potent antiviral efficacy has led to an evolving paradigm shift in which IFN may be eliminated from treatment regimens for HCV infection. Elimination of IFN from treatment is highly desirable because its use requires intense patient monitoring and is responsible for many of the most challenging side-effects of treatment. Furthermore, durations of therapy for highly potent, IFN-free regimens are expected to be less dependent upon on-treatment responses. Indeed, recently completed phase 2 trials and ongoing phase 3 trials of IFN-free regimens using DAAs have eliminated the use of RGT.

Two studies provided proof-of-concept support for the use of IFN-free regimens utilizing a DAA or combinations of DAAs. More recently, the combination of sofosbuvir and daclatasvir (with or without RBV) was studied in a phase 2 trial that included both treatment-naïve patients and patients who had failed a prior course of IFN-based therapy that included telaprevir or boceprevir. In both treatment-naïve patients and prior non-responders, the combination of sofosbuvir and daclatasvir (for 12 or 24 weeks) was associated with a 100% SVR24 rate, even without the use of RBV. Similar SVR rates were observed in the phase 2 LONESTAR study, in which 60 treatment-naïve, non-cirrhotic patients were given a once-daily, fixed-dose combination of sofosbuvir and ledipasvir (an NS5A inhibitor) with or without RBV. In this study, 95% of treatment-naïve patients in the no RBV arms achieved SVR12 whether they were treated for 8 or 12 weeks. In the 12-week arm with RBV, 100% of patients achieved SVR12. This study also evaluated an additional cohort of 40 patients (50% with compensated cirrhosis) who had failed previous DAAs; 100% of patients who received a 12-week course of fixed-dose sofosbuvir and ledipasvir with RBV achieved SVR12 compared with 95% in the RBV-free arm.

The phase 2 ELECTRON study included treatment-naïve patients and prior null responders with genotype 1 HCV who were treated with 12 weeks of sofosbuvir plus RBV and either ledipasvir or GS-9669 (a non-nucleoside NS5B inhibitor). Results indicate that 100% of treatment-naïve (25/25) and 100% of prior non-responders (9/9) achieved SVR12 when ledipasvir was added to the sofosbuvir plus RBV regimen. The addition of GS-9669 to sofosbuvir and RBV also yielded a 92% SVR12 rate (23/25) in treatment-naïve patients; 100% of treatment-experienced patients with F3/F4 fibrosis achieved SVR12 when sofosbuvir and ledipasvir were combined with either RBV or GS-9669. The phase 2a COSMOS trial evaluated the all-oral combination of sofosbuvir and simprevir, with and without RBV, in cirrhotic and non-cirrhotic treatment-naïve or prior null responder patients with genotype-1 (GT-1) HCV. Interim analysis of cohort 1 (non-cirrhotic prior null responders), showed that 93% and 96% of those treated with or without RBV for 12 weeks achieved SVR12 and 93% and 79% of those treated for 24 weeks achieved SVR12. Early results from cohort 2 (prior null responders and treatment-naïve, F3-F4) showed that 100% of treatment-naïve patients treated with or without RBV achieved SVR4 after 12 weeks of treatment, as did 93% and 100% of prior null responders. For both cohorts, relapse occurred only in those GT-1a patients with known Q80K mutations, and treatment was generally safe and well tolerated with approximately 3% of patients experiencing serious adverse events. Although not FDA-approved, the recent Infectious Diseases Society of America/American Association for the Study of Liver Diseases HCV treatment guidelines recommended the all-oral IFN-free combination for treatment of HCV GT1 patients who are IFN ineligible.

Two phase 2a trials (PILOT and COPILOT) investigated another potent viral protease inhibitor, ABT-450, boosted with
low-dose ritonavir in combination with RBV and a non-nucleoside inhibitor of RNA polymerase (ABT-072 or ABT-333). Both trials demonstrated SVR rates above 90% in treatment-naïve patients, whereas 47% of treatment-experienced patients achieved SVR. A larger phase 2b trial (AVIATOR) added ABT-267 (an NS5A inhibitor) and demonstrated SVR12 rates of 99% in treatment-naïve patients and 93% in previous null responders with 12 weeks of therapy. In the PEARL-1 trial, patients with genotype 1b infection achieved SVR 450/3 and ABT-267. SVR12 was achieved by 95% of treatment-naïve patients and 90% of prior null responders. A large number of phase 3 trials are now underway testing various DAAs and DAA combinations for treatment of chronic HCV. In general, these trials are designed without RGT. If the results of these trials are confirmed, treatment of HCV could become much more effective and much simpler in the near future, leading to eradication of infection in > 90% of patients without the use of RGT.

Conclusion

RGT for the treatment of genotype 1 HCV infection is the current standard of care for IFN-based therapy with telaprevir or boceprevir, and has undoubtedly spared countless patients from unnecessarily long treatment durations, as well as the side-effects and costs associated with PegIFN/RBV therapy. Despite these benefits, the need to monitor HCV RNA levels during treatment adds another layer of complexity to already complex treatment regimens. The increased potency of DAAs is allowing more rapid viral kinetics in both the first and second phases of viral load declines, reducing the need for on-treatment assessments of response for determining duration of therapy. These improvements will likely lead to the approval of IFN-free regimens in the near future. All-oral direct antiviral therapies are expected to have high cure rates with short treatment duration and limited adverse events. Furthermore, treatment regimens will likely be simpler, without requiring on-treatment measurement of response, and likely not requiring pretreatment assessment of factors that have traditionally influenced response rates—such as HCV genotype, IL28B genotype, baseline viral load, and degree of fibrosis. In the future, studies will focus on the improvement of SVR rates in special populations of patients with HCV including those with compensated and decompensated cirrhosis, prior null response (particularly those with genotype 3 infection), renal failure, and HCV recurrence after a liver transplant. The role of RGT in these groups is still to be determined.

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