Direct-acting antivirals (DAAs) in combination with pegylated IFN-α and ribavirin drastically improve the rates of rapid virological response (RVR) and sustained virological response (SVR) in the treatment of chronic hepatitis C virus infection, specifically in difficult-to-cure hepatitis C virus genotype 1. At present, RVR is an important milestone highly predictive of SVR. Response-guided therapy based on RVR is important to shorten the treatment duration whilst preserving the greatly improved SVR rate, given that DAA-based treatments are costly and could produce serious adverse events and antiviral-resistant variants. Because strong factors other than RVR independently influence SVR, more highly personalized treatments should be developed through a combination of several robust factors. The advent of more potent DAAs may change the concept of RVR and SVR.

Keywords: chronic hepatitis C virus infection • direct-acting antivirals • pegylated IFN-α • response-guided therapy • ribavirin

According to the WHO, approximately 170 million people are chronically infected with hepatitis C virus (HCV) worldwide and are at risk of developing cirrhosis and life-threatening complications, including portal hypertension, hepatic failure, and hepatocellular carcinoma. More than 350,000 people die from HCV-related liver diseases every year. Antiviral therapy for chronic hepatitis C can lead to a sustained virological response (SVR), defined as an undetectable serum HCV RNA level (using a qualitative PCR assay) 24 weeks after treatment cessation, which provides short- and long-term clinical benefits by improving quality of life, lessening hepatic fibrosis, and reducing the incidence of hepatocellular carcinoma and liver disease-related mortality [1–8]. Over the past decade, pegylated IFN-α (peg-IFNα)-2a or -2b in combination with weight-based doses of ribavirin (RBV) has been used as the standard-of-care treatment for chronic hepatitis C, leading to improvement in the overall SVR rate from <20 to >60%: 40–60% of difficult-to-cure HCV genotype 1/4-infected patients who are treated with 48-week treatment, and 70–90% of easy-to-cure HCV genotype 2/3-infected patients who are treated with 24-week treatment [9–15]. However, more than 50% of patients infected with HCV genotype 1, the most prevalent genotype worldwide, fail to eradicate HCV with dual combination of peg-IFNα and RBV (peg-IFNα/RBV). Efforts to improve the treatment outcomes have focused on the development of antiviral therapy specifically and directly targeted to HCV, especially HCV genotype 1.

Numerous novel therapeutic approaches are being developed and assessed [16–18]. Direct-acting antivirals (DAAs) directly inhibit specific replication processes in the HCV life cycle, targeting the HCV polyproteins including the nonstructural 3/4A (NS3/4A) protease, NS5A phosphoprotein and NS5B polymerase. The NS3/4A serine protease is required for RNA replication and virion assembly. The first-generation NS3/4A serine protease inhibitors (PIs), boceprevir (BOC) and/or telaprevir.
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(TVR), have been approved for use by each government organization in several European and North American countries and in Japan in 2011. When used in combination with peg-IFNα/RBV for HCV genotype 1 infection, Phase II and III clinical trials have proven that both PIs greatly improve viral response rates in both treatment-naïve patients and patients who have had virological failure on previous treatment [19–29]. Furthermore, in Japan, where TVR, but not BOC, is available by medical insurance and subvention, a post-marketing investigation of 10,000 subjects showed that TVR-based combination therapy for 24 weeks yielded an SVR rate of approximately 90% in treatment-naïve patients and patients who had virological relapse after previous peg-IFNα/RBV treatment [30]. High rates of early viral suppression and low rates of relapse suggested that treatment duration could potentially be shortened to 24 weeks in patients who achieve a rapid virological response (RVR; defined as an undetectable serum HCV RNA level at week 4 of treatment) or extended RVR (eRVR; defined as an undetectable serum HCV RNA level at both weeks 4 and 12 of treatment) [19–22,24]. RVR has been used as the most important on-treatment milestone to shorten treatment duration from the era of dual combination therapy with peg-IFNα/RBV [14,15,31–36].

The treatment strategy for chronic HCV infection is personalized on the basis of strong predictors of SVR to IFN-based therapy, such as HCV genotype [9–12,15,37,38], the initial virological response to treatment [32,39–41], and previous treatment response (treatment-naïve, or previous relapse or no virological response) [21,23,27–29,42]. This manuscript addresses the impact of newly available DAAs on RVR and SVR in the combination therapy for chronic HCV infection and discusses the potential of response-guided therapy (RGT) based on RVR in DAA-based combination therapy to explore more optimal and highly personalized therapeutic strategies.

Contribution of factors to SVR

Identification of factors highly predictive of SVR, including host-, virus-, and treatment-related and on-treatment components, can tailor treatment to individual needs, helping to make decisions regarding which treatment regimens are suitable or whether treatment should be initiated, continued or stopped. Personalized medicine determined by using robust factors can reduce unnecessary physical/economic burdens and social loss on the patient without adversely affecting treatment outcomes.

A number of host-related factors, such as older age, African–American or Hispanic race, presence of advanced fibrosis or cirrhosis, overweight, obesity, insulin resistance, diabetes, hepatic steatosis and low levels of hemoglobin, platelet count and cholesterol, have been reported to decrease the likelihood of SVR to IFN-based therapy [9,11,43–53]. Among these factors, single nucleotide polymorphisms (SNPs) near the IL 28B (IL28B) gene, which resides on chromosome 19 and encodes IL28B or IFN-λ-3, have a stronger impact on treatment response to peg-IFNα/RBV combination alone and TVR-based triple combination therapy in HCV genotype 1-infected patients [42,53–57]. Patients with favorable genotypes at the IL28B SNPs (such as rs12979860 genotype CC and rs8099917 genotype TT) are more likely to achieve SVR than those with unfavorable genotypes (rs12979860 CT or TT and rs8099917 TG or GG).

HCV genotype (1 and 3 rather than 1 and 4), pre-treatment viral load (low rather than high), and initial virological response are significantly strong independent predictors of SVR to IFN-based therapy [9,11,12,32,37–41,45,51–53,58–64]. Thus, easy-to-cure genotype-infected patients with favorable factors have a greater chance to achieve SVR with abbreviated treatment duration and/or less potent treatment. Conversely, for difficult-to-cure genotype-infected patients with unfavorable factors, more intensive therapy is recommended including the use of DAAs or a longer treatment duration. Strictly speaking, HCV genotypes can be ranked in a decreasing order of susceptibility to IFN-based therapy as follows: genotypes 2, 3, 4, and 1 [9]. Moreover, genotypes 1b and 2a are likely to respond better to IFN-based therapy than 1a and 2b, respectively [53,65]. Of note, TVR-resistant variants and viral breakthrough occur more frequently in 1a than in 1b in TVR-based treatment [19,66,67]. For instance, the substitution of R with K at amino acid position 155 of the NS3 protease region (R155K) or V36M, which is frequently related to TVR resistance, requires only one nucleotide substitution in 1a, whereas two substitutions are required in 1b. Similarly, the emergence of the BOC-resistant mutant differs between 1a and 1b [68]. When anti-HCV treatment is initiated or treatment outcomes are interpreted, the HCV subgenotype as well as the HCV genotype should be taken into consideration.

A virological response at critical time points or HCV kinetics during the early phase of treatment are closely associated with SVR or non-SVR [32,33,39,41]. Absence of an early virological response at week 12 of treatment is the best negative predictor of non-SVR. Conversely, RVR is an important milestone highly predictive of SVR and one of the strongest independent on-treatment predictors [15,32–34,42,53,57,62,69,70]. Patients with RVR can have an SVR rate as high as 80–90% when treated for 48 weeks, although RVR is achieved in a small percentage of HCV genotype 1-infected patients (<20%) who receive peg-IFNα/RBV alone [15,31–34,53,69,71–73]. The addition of TVR greatly improves the RVR rate to 66–84% in treatment-naïve patients, and patients with RVR show an SVR rate of approximately ≥90%
In contrast, the probability of SVR is <5% in patients with a minimal fall in a viral load of <1 log₁₀ from the baseline level at treatment week 4, when peg-IFNα/RBV are combined with DAAAs [19]. With advances in antiviral treatment, RVR has become a more important milestone for tailoring treatment regimens and predicting SVR.

Although early viral kinetics are influenced by various factors, RVR is an independent predictor of SVR, irrespective of other strong predictors including HCV genotype and the *IL28B* SNP [15,42]. The proportion of patients achieving RVR with peg-IFNα/RBV alone varies greatly among HCV genotypes (16% in genotype 1, 71% in genotype 2, 60% in genotype 3 and 38% in genotype 4) [15]. Importantly, the probability of SVR is consistently high across HCV genotypes (88% in genotype 1, 86% in genotype 2, 86% in genotype 3 and 100% in genotype 4). With regard to race and host genetic variations, Caucasians and/or patients with the favorable *IL28B* genotype are more likely to achieve RVR with peg-IFNα/RBV alone than African-American and/or those with an unfavorable genotype [74]. The RVR rates appear to differ among Caucasians, East Asians, and African Americans with the same favorable *IL28B* genotype CC (28, 19 and 12%, respectively) [53,74]. Although the racial and genetic disparities are apparent, patients with RVR appear to have consistently high SVR rates, irrespective of the *IL28B* genotype and race. Taken together, these findings highlight the accepted notion that RVR is strongly linked to a high likelihood of SVR and the most reliable milestone in RGT across HCV genotypes, *IL28B* SNP genotypes and races.

Among patients who have failed to achieve SVR with previous IFN-based therapy, previous virological response has an impact on SVR with retreatment. Patients who did not have a virological response to previous treatment have a limited chance of successful outcome with retreatment [6,33,34,75–77]. The addition of DAA to peg-IFNα/RBV apparently increases the SVR rates in patients who had a previous virological relapse, which is defined as an undetectable HCV RNA level at the end of treatment, but re-emergent HCV RNA thereafter (designated as previous relapers) [21,23,27]. Phase III studies conducted in Japan showed that the SVR rate for previous relapers was 88–93% [29,42]. Previous relapers are one of the most suitable candidates for DAA-based treatment, followed by patients with a partial response to previous treatment, which is defined as a decline of ≥2 log₁₀ IU/ml in viral load at 12 weeks of treatment but with constantly detectable HCV RNA during treatment [78]. Patients with a null response to previous treatment experience little benefit from TVR-based triple combination therapy [21,23]; a null response is defined as a decline of <2 log₁₀ IU/ml in viral load at 12 weeks of treatment [78].

**Clinical trials for treatment-naive patient**

The PROVE 1 trial was a randomized, double-blind, placebo-controlled Phase IIb trial [19]. Treatment-naive HCV genotype 1-infected patients were randomly assigned to one of the three TVR groups or to the control group. The control group received peg-IFNα-2a (180 µg per week) and RBV (1000 or 1200 mg/day for body weight) for 48 weeks, plus TVR-matched placebo for the first 12 weeks (PR48 group, 75 patients). The TVR groups received TVR (1250 mg on day 1 and 750 mg every 8 h thereafter) for 12 weeks, as well as peg-IFNα-2a/RBV (at the same doses as in the PR48 group) for the same 12 weeks (T12PR12 group, exploratory 17 patients) or for 24 weeks (T12PR24 group, 79 patients) or 48 weeks (T12PR48 group, 79 patients). The RVR rates (Figure 1) were much higher in the T12PR24 (81%) and T12PR48 (81%) groups than in the PR48 (control) group (11%). The SVR rates (Figure 1) were 61%
in the T12PR24 group and 67% in the T12PR48 group compared with 41% in the PR48 group. In another Phase IIb trial (PROVE 2) of 323 treatment-naive HCV genotype 1-infected patients [20], the RVR rates (Figure 1) were 69% in the T12PR24 group, 80% in the T12PR12 group and 50% in the T12P12 group (that did not receive RBV) compared with 13% in the PR48 (control) group (p < 0.001 for each). The SVR rate (Figure 1) was significantly higher in the T12PR24 group (69%) than in the PR48 group (46%). The SVR rate was not significantly higher in the T12PR12 or T12P12 group than in the PR48 group, although the rates were significantly different between the T12PR12 and T12P12 groups (60 vs 36%), suggesting that RBV is required as an essential component in TVR-based combination therapy. Taken together, the two Phase IIb trials indicated that the addition of TVR greatly increases the RVR rate, resulting in a shortened duration of treatment from 48 to 24 weeks in most treatment-naive patients. The 24-week treatment duration is sufficient in patients who achieve RVR. Overall, the 12-week duration lowers the SVR rate, but may be sufficient for a certain subpopulation of patients with favorable robust factors. From Japan, a Phase III study for treatment-naive patients infected exclusively with HCV genotype 1b showed that RVR was 84% and SVR was 73% with the 24-week treatment regimen [28]. When treatment outcomes are compared between trials conducted in the west and east, the distribution of HCV genotype (1a versus 1b), IL28B SNP genotype, and race should be taken into consideration. To clarify the variations, multi-national/racial trials are required on a worldwide scale.

RGT

The degree of viral load decay and rapidity of virological response during the first 12 weeks of peg-IFNα/RBV treatment can predict the likelihood of achieving SVR [11,15,31,32,36,38–41,58,72]. The time points usually used to decide whether treatment should be shortened, stopped or continued/extended are treatment weeks 4, 12 and 24 [14,32]. A dynamic modification of treatment duration based on the virological response is known as RGT. As described above, RVR is a critical milestone for RGT with SVR rate maintenance. When RVR is achieved, the treatment duration of 48 weeks can be shortened to 24 weeks with peg-IFNα/RBV dual therapy alone [12,33,34] for genotype 1 or 4 or TVR-based triple combination [19,20] for genotype 1. In patients who achieved RVR with 24-week peg-IFNα/RBV alone, the SVR rates were 79–89% for genotype 1 and 86–87% for genotype 4 [33,34,63,73,75,79].

The current recommendation for genotype 2 or 3 advocates a 24-week treatment course [12,31,45,59,61,80]. Patients with RVR have a high probability of SVR despite the shortened treatment duration from 24 to 16 weeks [45,61,62,80–82], but the risk of relapse increases with abbreviated treatment, resulting in the reduction of the SVR rates [62,80,83]. Conversely, there is little information on the most suitable duration of treatment for genotype 2- or 3-infected patients who do not achieve RVR [69]. To shorten the treatment duration, whether RVR is appropriate for the decision needs to be verified, because the susceptibility to IFN-based therapy apparently differs between genotypes, subgenotypes or baseline viral loads within an identical genotype. Genotype 2- or 3-infected patients may benefit from the ongoing development of DAAs, although there are limited data for the use of DAAs in such patients [84,85].

In a randomized, double-blind, placebo-controlled Phase III trial (ADVANCE) [22], 1088 treatment-naive HCV genotype 1-infected patients were randomly assigned to one of the three groups:

- TVR combined with peg-IFNα-2a/RBV for 12 weeks (T12PR group), followed by peg-IFNα-2a/RBV alone for 12 weeks if eRVR was achieved or for 36 weeks if HCV RNA was detectable at either time point;
- TVR for 8 weeks and 4-week placebo with peg-IFNα-2a/RBV (T8PR group), followed by 12 or 36 weeks of peg-IFNα-2a/RBV on the basis of the same criteria; or
- 12-week placebo with 48-week peg-IFNα-2a/RBV (PR group).

The SVR rates were significantly higher in the T12PR (75%; Figure 2) or T8PR (69%) group than in the PR group (44%). The RVR and eRVR rates in the T12PR group were 68 and 58%, respectively (Figure 2). The SVR rates were 84 and 56% in the T12PR with and without RVR, respectively (Figure 2). The SVR rate of 89% in the T12PR24 with eRVR was the highest among all subgroups (Figure 2). Taken together, the 24-week treatment duration is sufficient for treatment-naive patients who achieved eRVR. A longer duration of peg-IFNα/RBV therapy is indicated for patients who do not achieve eRVR.

In an open-label, randomized, Phase III noninferiority trial (ILLUMINATE) [24], treatment-naive HCV genotype 1-infected patients who had eRVR were randomly assigned to the T12PR24 or T12PR48 group. Of 540 patients, 72% had RVR and 65% had eRVR; the overall SVR rate was 72%. Among the 322 patients with eRVR, 92% in the T12PR24 group and 88% in the T12PR48 group achieved SVR (Figure 2). A total of 118 patients without eRVR were assigned to the T12PR48 group and 64% achieved SVR (Figure 2). This study also showed that the 24-week treatment duration
is sufficient for patients who achieve eRVR, even if they have refractory factors such as high viral loads, bridging fibrosis or African race. Collectively, triple combination therapy yielded an RVR rate of 68–81% and an eRVR rate of 58–65% in treatment-naive HCV genotype 1-infected patients (Figures 1 & 2), and the 24-week treatment course for patients with eRVR generated an SVR rate of 89–92% (Figure 2). RGT based on eRVR permits a shorter treatment duration while preserving high SVR rates, improves the overall tolerability, and reduces exposure to unnecessary medication. However, there were a small number of cirrhotic patients in the clinical trials. Cirrhotic patients may not comply with RGT and should receive treatment for 48 weeks [78]. Treatment should be stopped if HCV RNA levels are >1000 IU/ml at week 4 or 12 of treatment and/or detectable at week 24 of treatment.

Clinical trials for treatment-experienced patients
In a Phase II study for previously treated HCV genotype 1-infected patients (PROVE 3) [21], 453 patients who had failed to achieve SVR with previous peg-IFNα-2a/RBV therapy were randomly assigned to one of four treatment groups. The SVR rates in the three TVR groups (51% in the T12PR24 group, 53% in the T24PR48 group and 24% in the T24P24 group) were significantly higher than the rate in the PR48 (control) group (14%; Figure 3). The RVR rates were 61, 50 and 47% in the TVR groups, respectively, and 0% in the control group (Figure 3). The SVR and RVR rates were higher in previous relapers than in previous nonresponders. The SVR rates were similar between the T12PR24 and T24PR48 groups (Figure 3), and treatment discontinuation because of adverse events was less common in the T12PR24 group than in the T24PR48 group. Therefore, the T12PR24 regimen appeared to provide a better risk–benefit profile. The higher termination rates and the lower relapse rates in the T24PR48 group suggest that an optimal retreatment regimen may consist of a 12-week treatment duration with TVR combined with a longer duration with peg-IFNα-2a/RBV. Of note, the SVR rates in previous relapers were 69% in the T12PR24 group and 76% in the T24PR48 group. Furthermore, in Phase III studies from Japan, the SVR rates in relapers were 88–93% with the T12PR24 regimen [29,42]. Relapers appear to be the most suitable for the 24-week treatment regimen. In contrast, previous nonresponders were less likely to achieve SVR, with the rates of 39% in the T12PR24 group and 38% in the T24PR48 group. However, these SVR rates were more than four-times the rate in the control group (9%).

In a Phase III study for previously treated HCV genotype 1-infected patients (REALIZE) [23],...
663 patients were randomly assigned to one of the three groups: the T12PR48 group, the lead-in T12PR48 group, which received 4 weeks of peg-IFNα/RBV followed by 12 weeks of TVR and peg-IFNα/RBV for a total of 48 weeks, and the PR48 (control) group. The SVR rates were significantly higher in the two TVR groups than in the control group among patients with relapse (83% in the T12PR48 group, 88% in the lead-in T12PR48 group and 24% in the PR48 group), partial response (59, 54 and 15%, respectively), and null response (29, 33 and 5%, respectively). Figure 3 shows the RVR and SVR rates in the T12PR48 group alone. Among patients with RVR in the T12PR48 group, the SVR rates were 90% in relapers, 72% in partial responders and 53% in null responders. When no virological response to previous treatment was categorized into partial and null responses, viral response rates with the T12PR48 regimen were apparently different between the partial and null responders. Of note, among patients with RVR, the SVR rates were influenced by the previous treatment response (Figure 3). These results suggest that there may be independent factors (other than RVR) associated with the final treatment outcome. To more accurately predict or completely attain SVR, other variables (such as previous treatment response, cirrhosis and the IL28B SNP) may be better used for RGT in combination with RVR. Unfortunately, the REALIZE study was not a randomized-controlled trial to compare the treatment duration of 24 weeks versus 48 weeks for patients with RVR. Therefore, RGT for treatment-experienced patients can be considered for relapers, may be considered for partial responders, but cannot be recommended for null responders [78].

Impact of the IL28B SNP

The favorable IL28B SNP genotype (rs12979860 CC) significantly increases viral response rates during the first 12 weeks of treatment, as well as the SVR rate, in peg-IFNα/RBV combination alone for HCV genotype 1-infected patients [74]. Among patients with RVR, however, IL28B genotype is not associated with SVR [74,86]. In treatment-naive HCV genotype 1-infected Caucasian patients (a part of the ADVANCE trial, available for 454/1088 [42%] participants), the addition of TVR greatly increased RVR, eRVR, and SVR rates across all IL28B genotypes (Figure 4) [22]. Although patients with favorable IL28B CC still had higher SVR rates in each treatment arm (Figure 4), the largest increasing rates were observed in those with unfavorable CT or TT, suggesting that this closeness in the SVR rate between IL28B genotypes lowers the significance of IL28B SNP as a predictor. In another study using a part of the REALIZE cohort, the RVR rates were numerically higher in genotype CC than in CT/TT [84]. Previous relapers achieved RVR rates of 77–82% regardless of the IL28B genotype. Previous partial responders and null responders somewhat differed according to the IL28B genotype (88% [CC], 66% [CT] and 64% [TT] in partial responders; and 50, 33, and 34%, respectively).

Figure 3. Rapid virological response and sustained virological response rates for treatment-experienced HCV genotype 1 patients in randomized controlled Phase II and III trials (PROVE 3 and REALIZE).

RVR: Rapid virological response; SVR: Sustained virological response.

Data taken from [21,23].
respectively, in null responders). However, SVR rates were similar across all IL28B genotypes (85, 85 and 88% in relapers; 63, 58, and 71% in partial responders; and 40, 29, and 31% in null responders, respectively) [87]. In the REALIZE study, only data of 48-week treatment regimens were available and did not include 24-week regimens. Several studies from Japan reported different results; both RVR and IL28B were independent factors significantly associated with SVR in the 24-week regimen for treatment-naive and -experienced patients [42,57]. In the REALIZE study, only data of 48-week treatment regimens were available and did not include 24-week regimens. Several studies from Japan reported different results; both RVR and IL28B were independent factors significantly associated with SVR in the 24-week regimen for treatment-naive and -experienced patients [42,57]. In Japan, the SVR rates were 90–97% in patients with the favorable IL28B SNP (rs8099917) genotype TT versus 56% in those with unfavorable genotype TG/GG and 89–92% in those with RVR versus 35–55% in those without RVR. The IL28B SNP and RVR were prominently significant in treatment-naive patients, neither was significant in previous relapers, and IL28B alone was significant in previous partial responders. Taken together, the addition of TVR appears to alter or attenuate the impact of IL28B SNPs on SVR. In treatment-naive patients and previous relapers, however, the IL28B SNP genotype can certainly identify those with a high likelihood of SVR through a shortened treatment duration. The CONCISE interim analysis suggested that non-cirrhotic IL28B CC patients with RVR could shorten the treatment duration to 12 weeks [88]. In treatment-experienced patients, the impact of the IL28B SNP genotype is limited and less informative for SVR once early viral response (such as RVR) is known. More potent DAA regimens will further attenuate the importance of the IL28B SNP genotype as a determinant of the likelihood of a response.

**Changing concept of RVR & SVR**

The remarkable development of DAAs may change the concept of RVR and SVR. More recent Phase II and III studies showed that sofosbuvir, an NS5B polymerase inhibitor, in combination with peg-IFNα-2a/RBV for only 12 weeks generated RVR rates of 94–99% and an SVR rate of approximately 90% in treatment-naive patients mainly infected with HCV genotype 1 [85,89]. More potent DAAs will increase the RVR rate up to almost 100%. RVR could no longer be an important milestone predictive of SVR or RGT. US FDA has recently approved SVR at 12 weeks after cessation of treatment (SVR12) as an end point of treatment outcome [90]. The previously approved SVR was designated as SVR24. However, a small minority of patients who achieve SVR12 appear to have virological relapse thereafter and fail to achieve SVR24. For the time being, the conventional concept will be used until a new concept is acceptable for the next-generation of treatment.

**Future perspective**

SVR indicates a permanent eradication of HCV from individuals because HCV seldom reappears in patients who achieve SVR. In peg-IFNα/RBV combination alone and DAA-based combination therapy for chronic HCV infection, SVR is closely associated with several robust pretreatment and on-treatment predictors, that is, HCV genotype, pre-existence of cirrhosis, treatment-naive or viral response to previous treatment, IL28B SNP genotype and early viral kinetics including RVR or non-RVR. To date, RVR has been a critical on-treatment milestone of RGT. However, more potent DAAs in combination with peg-IFNα/RBV or DAA combinations without IFN may attenuate the importance of RVR because more potent anti-HCV therapy greatly increases the RVR rate up to almost 100%. Currently, there is no perfect variable or model for prediction of SVR with individual treatment tailoring. To
develop more optimal and highly personalized treatment strategies, RVR should be used in combination with other robust predictors or currently unidentified factors. Alternatively, a viral response during the extremely early phase (e.g., day 2, week 1 or week 2) of treatment may be required to develop much shorter treatment durations (<12 weeks) with the advent of more potent DAAs. It will be important to reconsider the value of the currently identified robust predictors.

The next wave of DAAs are appearing in Phase I–III trials, such as second-generation NS3/4A PIs, NS5A inhibitors, and NS5B polymerase inhibitors (nucleos[t]ide inhibitors and nonnucleos[t]ide inhibitors), and represents amazing progress in the management of difficult-to-cure patients, such as prior null responders, with promising results [16–18, 85, 89, 91, 92]. These exciting developments emphasize the importance of thoughtful use of TVR or BOC, closely following the recommended regimens and stopping rules, so as to not negatively influence the possibility of treatment when the next-generation DAAs become available. Patients with a cluster of difficult-to-cure features might benefit from awaiting for the next-generation of treatments. In the near future, these ceaseless efforts will relieve a large number of HCV-infected patients worldwide.

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Executive summary

- Treatment regimens for chronic hepatitis C virus (HCV) infection are tailored according to independent robust factors predictive of sustained virological response (SVR; HCV genotype, treatment combined with or without direct-acting antivirals [DAAs], treatment-naive or viral response to previous treatment, early viral kinetics such as rapid virological response [RVR], IL28B SNP, and presence or absence of cirrhosis).
- The addition of telaprevir, one of the approved NS3/4A protease inhibitors, substantially increases RVR, extended RVR, and SVR rates in combination with peg-IFNa/ribavirin for treatment-naive and -experienced patients infected with difficult-to-cure HCV genotype 1.
- RVR and/or extended RVR are further important milestones of response-guided therapy.
- Among treatment-experienced patients who achieve RVR, SVR rates may differ according to a previous treatment response or presence of cirrhosis.
- Previous relapers are the most suitable for the 24-week treatment regimen.
- The importance of IL28B SNP is attenuated or less informative for SVR in treatment-experienced patients but still controversial.
- In treatment-naive patients, IL28B SNP can certainly identify those with a high likelihood of achieving SVR with RGT.
- With the advent of more potent DAAs, even difficult-to-cure patients will achieve SVR with a further shorter treatment duration. More potent DAAs may attenuate the importance of RVR and change the concept of RVR and SVR. We should reconsider how valuable the currently identified robust predictors are, including RVR.

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