CLINICAL INVESTIGATION

Telaprevir in the treatment of hepatitis C infection: evidence from the ADVANCE, ILLUMINATE and REALIZE studies

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Treatment of chronic hepatitis C (HCV) infection with PEGylated IFN-α and ribavirin is suboptimal, resulting in a growing number of treatment-failure patients who are left with limited treatment options. Telaprevir, a NS3/4A HCV protease inhibitor, was shown in Phase II studies to be efficacious and safe in treatment-naive and treatment-experienced genotype 1 patients. This article reviews the results of the recently reported Phase III studies: ADVANCE, ILLUMINATE and REALIZE, which reported sustained virological response as high as 75% in treatment-naive patients and 88% in prior relapse patients. Response-guided therapy using extended rapid virological response resulted in sustained virological response rates as high as 92% in treatment-naive patients with a short course of therapy. The addition of telaprevir to the therapeutic regimen for HCV genotype 1 represents a major advance in the management of chronic HCV.

Keywords: directly acting antiviral drugs • extended rapid virological response • hepatitis C • NS3/4 protease inhibitors • response-guided therapy • telaprevir

Chronic hepatitis C (HCV) infection is a significant global health problem, afflicting more than 170 million people worldwide. The current standard of care with PEGylated IFN-α (P) and ribavirin (R) affords a sustained virological response (SVR) in approximately 40% of genotype (GT)1 patients and 80% in GT 2 and 3 patients [1]. Due to the relatively low SVR rates, many patients with HCV GT 1 have opted to defer antiviral therapy. Furthermore, the majority of patients that have been treated with HCV GT 1 have failed therapy. Options for managing these patients have been limited. Thus, there has been an impetus for the development of new therapies for chronic HCV. There are numerous compounds in many different classes currently under investigation for HCV. The most advanced area of research has involved the NS3/4A protease inhibitors, the first generation of direct acting antiviral (DAA) medications.

Telaprevir (TVR) is an HCV NS3/4A protease inhibitor that recently received US FDA approval for therapy of treatment-naive and treatment-experienced HCV GT 1 patients, based on the results of three recently reported Phase III studies: ADVANCE, ILLUMINATE and REALIZE. This review focuses on the outcomes of these three pivotal clinical trials and the subsequent FDA approval of TVR, a significant advance in the management of chronic HCV GT 1.

TVR is an orally bio-available, NS3/4A protease inhibitor belonging to the α-ketoamide derivative group, which binds the NS3/4A protease covalently but reversibly [2]. TVR has strong antiviral potency, but a low genetic barrier to resistance. Furthermore, the high rate of HCV replication and mutation rate allows for the presence of resistance at baseline in many patients. Thus, P and R are

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necessary to treat baseline-resistant virus and provide antiviral support during therapy with TVR to achieve success. TVR is active against HCV GT 1. As the amino acid sequence of the NS3/4A protease varies between genotypes, TVR has less potency in GT 2 and no significant effect in GT 3 [3,4].

The high antiviral efficacy and side-effect profile of TVR were demonstrated in several Phase I studies that also revealed a low barrier to the development of virological resistance development [5–7]. A rapid decline in HCV RNA was observed, but selection of resistant viral mutants that led to virological rebound in a majority of patients after cessation of TVR monotherapy was also identified.

PROVE 1, 2, 3; study 107 (Phase II trials)

There were three major Phase II trials with TVR that set the stage for the three large Phase III studies. PROVE 1 and 2 studied approximately 670 treatment-naive HCV GT 1 patients in the USA and Europe to determine the efficacy and tolerability of TVR. PROVE 1 enrolled 250 patients in the USA with chronic HCV GT 1 who were treatment-naive. Overall SVR was 67% in the T12PR48 arm (12 weeks of TVR with 48 weeks of PEGylated IFN-α + ribavirin [PR]), 61% in the T12PR24 arm (12 weeks of TVR with 24 weeks of PR), 35% in the T12PR12 arm (12 weeks of TVR with 12 weeks of PR) and 41% in the control PR48 arm. Relapse rates were 6, 2, 33 and 23%, respectively. The study protocol dictated that treatment was stopped after 12 or 24 weeks when a rapid virological response (RVR) was achieved. Adverse events (AEs) during the TVR/placebo phase led to treatment termination in 18% in the TVR arms versus 4% in the PR arms, mainly due to rash, anemia and diarrhea/anorectal symptoms [8].

PROVE 2 was another Phase II study enrolling 323 GT 1, treatment-naive, noncirrhotic chronic HCV patients in Europe. The protocol was similar to PROVE 1, except that treatment termination after 12 or 24 weeks was independent of achieving RVR. In addition, there was one study arm without R. SVR rates ranged between 69% in the T12PR24, 60% in the T12PR12, 36% in the T12P12 and 46% in the control PR48 arm. Relapse rates were 14, 30, 48 and 22%, respectively. The T12P12 group had higher rates of relapse, viral breakthrough and on-treatment response [9].

These two trials demonstrated that TVR-based treatment led to a dramatic increase in SVR compared with the standard of care with P and R. A total treatment regimen of only 12 weeks (TVR + P + R) was insufficient, due to a high relapse rate. RVR, undetectable HCV RNA at 4 weeks, was shown to be an important predictor of SVR. Although R's mechanism of action has yet to be fully elucidated, it was found to be necessary to improve the total antiviral efficacy and to reduce the risk of relapse by reducing resistance and viral breakthrough rates. The tolerability profile was significant for an increased frequency and severity of rash, increased anemia and diarrhea/anorectal symptoms that led to greater rates of discontinuation of medications in the TVR arms than in the control PR arm. Despite this, the change in SVR rates was significantly higher in the T12PR12 and T12PR24 treatment arms compared with control PR48.

PROVE 3 was the major Phase IIb trial that assessed the safety and efficacy of TVR-based therapy in HCV treatment-experienced patients. The trial was notable for strict stopping rules designed to minimize the risk of developing viral resistance: TVR arms had to have an RVR in order to continue treatment. Overall SVR was 51% in the T12PR24 arm (12 weeks of TVR with 24 weeks of PR), 53% in the T24PR48 arm (24 weeks of TVR with 48 weeks of PR), 24% in the T24P24 arm (no R), and 14% in the control PR48 arm (retreatment). As expected, SVR was higher among historical relapse patients (undetectable HCV RNA at end of initial course of therapy with subsequent detectable HCV RNA in follow-up) compared with historical partial (>2 log decline in HCV RNA at week 12 of initial course but not undetectable) and null responders (<2 log decline in HCV RNA at week 12 of initial course) across all study arms. AEs were again notable for rash, anemia and anorectal symptoms. Severe rash requiring treatment cessation was seen in up to 5% of the TVR arms. PROVE 3 showed that more than 12 weeks of TVR did not confer significant additional benefit in the treatment-experienced population, and that R was necessary to achieve optimal SVR. Interestingly, more viral breakthrough was observed in GT 1a patients compared with 1b (24 vs 11%) [10].

Study 107 was an open-label, rollover study of patients from the PROVE 1/2/3 studies who did not achieve SVR. 81 patients were initially enrolled, with a study design of T12PR24. Subsequently, 34 more patients were enrolled and a protocol amendment was implemented, allowing tailoring of the PR duration to 48 weeks leading to a T12PR48 regimen for those not attaining extended rapid virological response (eRVR), as well as all previous null responders. The overall SVR rate was 59% in this retreatment group, with a safety profile similar to the PROVE 1/2/3 trials. This data led to the FDA approving relapse patients for RGT even though the REALIZE trial treated all treatment-experienced patients for 48 weeks [11].

ADVANCE

The first Phase III trial with TVR was called ADVANCE, which was a randomized, double-blind, placebo-controlled trial conducted in more than 100 centers in the USA and Europe. ADVANCE had a final enrollment of 1095, in treatment-naive chronic HCV GT 1 patients. The goals were to compare the efficacy of 8 versus 12 weeks of TVR in combination with PR (RGT with either a 24- or 48-week course of PR), compared with a 48-week course of PR. Tolerability was also assessed. P-2a at 180 µg weekly and R 1000–1200 mg daily weight-based dosing were used with TVR (750 mg every 8 h). Highly sensitive HCV RNA testing (Roche TaqMan v2) was used with a LLOQ of 25 IU/ml and LLOD of ~10 IU/ml. Growth factors were not allowed. In addition, there were strict futility rules instituted to discontinue therapy to minimize the risk of virological resistance breakthrough if therapy was unsuccessful (Table 1). Precise management plans were established for AEs, such as rash, to reduce treatment discontinuation rates [12].

Table 1. ADVANCE stopping rules.

HCV RNA	Week	Action
>1000 IU/ml (TVR arms)	4	D/C TVR, continue PR
<2 log drop from baseline	12	D/C all treatment
Detectable (>25 IU/ml)	24, 28, 36, 40	D/C all treatment

D/C: Discontinued; HCV: Hepatitis C virus; PR: PEGylated IFN-α + ribavirin; TVR: Telaprevir.

Patients were randomized to one of two TVR-based treatment arms with either 8 or 12 weeks of TVR, with PR or PR48 as control. The T8PR arm was given placebo from weeks 8–12, while the T12PR arm received 12 weeks of TVR. Both TVR arms were assessed for eRVR, HCV RNA undetectable with the sensitive HCV RNA assay at weeks 4 and 12 to guide total treatment duration (RGT). For patients in the TVR arms with eRVR, an additional 12 weeks of PR were administered for a total 24-week course. For patients that did not meet criteria for eRVR or stopping rules (HCV >1000 IU/ml at week 4, discontinue TVR; less than 2 log decline in HCV RNA at week 12 or detectable HCV RNA at week 24, discontinue P/R), an additional 36 weeks were administered for a total 48-week course. The T12PR arm had 68% achieving RVR and 58% eRVR with a 9% overall relapse, while the T8PR arm had 66% achieving RVR and 57% eRVR with an overall 9% relapse rate. The T12PR arm had a total SVR of 75% (89% in the eRVR+/ T12PR24 arm and 54% in eRVR-/ T12PR48 arm). The T8PR arm had a total SVR of 69% (83% in the eRVR+/ T8PR24 arm and 50% in the eRVR-/T8PR48 arm). The control arm had a 44% SVR (97% in the eRVR+ and 39% in eRVR-). Subanalysis by RVR, eRVR, fibrosis stage, race and ethnicity showed that the T12PR arm had a greater SVR compared with the standard PR48 arm. Among African–American patients, 62% achieved SVR in the TVR-based arms, as compared with only 25% in the control PR48 arm. Moreover, 62% of cirrhotics achieved SVR with the TVR-based arms, as opposed to 33% in the PR48 arm. Although the T12PR had a slightly higher SVR than the T8PR arm across all of the subanalysis factors, the differences were not statistically significant. Figure 1 shows the study design and final results.

The ADVANCE study results showed that 12 weeks of TVR were numerically superior (although not statistically) to 8 weeks of TVR, with SVR rates of 75 and 69%, respectively. In addition, RGT using eRVR allowed nearly 60% of patients to receive a shorter duration of treatment (24 weeks), while maintaining high SVR. Clear treatment stopping rules with sequential discontinuation of medications and

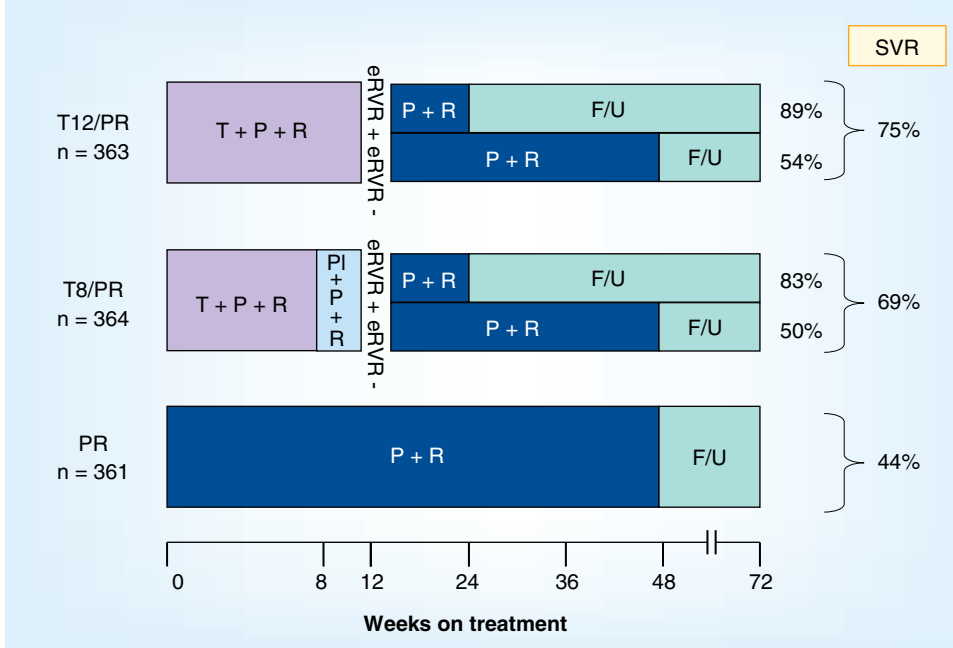

Figure 1. ADVANCE treatment of hepatitis C virus treatment-naive patients comparing 8 versus 12 weeks of TPR.

eRVR: Extended rapid virological response; F/U: Follow-up; P: PEGylated IFN-α; R: Ribavirin; SVR: Sustained virological response; TPR: Telaprevir + PEGylated IFN-α ribavirin.

side-effect management plans led to a reduction of premature treatment discontinuation.

Virological failure occurred in 8% of the T12PR arm and 13% T8PR. Overall treatment discontinuation rates during the TVR/placebo phase due to AEs were 7% in the T12PR arm, 8% T8PR and 4% in the PR48. Rash leading to treatment discontinuation was 7% in T12PR, 5% in T8PR and 1% in PR48. Table 2 shows the characteristics of the AEs and the treatment discontinuation rates. Anemia was managed by R dose reduction. A follow-up clinical virology study showed that virological failure was greater in the T8PR than T12PR arms, and using modeling showed that 12 weeks of TVR is sufficient to eradicate the wild type HCV RNA variant and the majority of lower level resistant variants. This study supported the use of 12 weeks rather than 8 weeks of TVR treatment [13].

ILLUMINATE

The follow-up study to ADVANCE was a Phase III, randomized, open-label study called ILLUMINATE. 544 treatment-naive HCV GT 1 patients were enrolled to assess RGT directly, that is, whether a truncated 24-week course of antiviral therapy in patients with eRVR who received 12 weeks of TVR (T12PR24) is sufficient compared with an extended 48-week regimen (T12PR48). Patients were treated with P-2a 180 µg weekly and weight-based R (1000–1200 mg daily). The trial was powered to assess noninferiority of 24 versus 48 weeks of total therapy in patients with eRVR. Subjects were administered 12 weeks of TVR, along with PR. HCV RNA was assessed at weeks 4 and 12. Patients with eRVR were randomized (at week 20) to receive a total of 24 weeks of therapy (T12PR24) versus 48 weeks of therapy (T12PR48). All patients who did not achieve eRVR or meet criteria for futility (same as the ADVANCE study as above) received a 48-week course of therapy (T12PR48). As in the ADVANCE study, growth factors were prohibited [14].

A total of 65% (352/540) achieved eRVR and 60% (322/540) were randomized to 24 versus 48 weeks of total PR treatment. 100 patients discontinued therapy prior to the week 20 randomization point. In the eRVR treatment arms, 92% of the T12PR24 arm achieved SVR compared with 88% in the T12PR48. 64% of the patients who did not achieve eRVR (T12PR48) also achieved SVR. The group of patients who discontinued treatment prior to week 20 had an SVR of 23%. In the eRVR groups, low relapse rates were observed (6% in the T12PR24 arm and 3% in the T12PR48 arm). By an intention to treat analysis, the overall SVR was 72%. 72% had RVR, 65% eRVR, 87% had end of treatment HCV RNA undetectability and there was an 8% relapse rate. As expected, SVR was higher in stage 0/1/2 fibrosis versus stage 3/4 fibrosis, and in whites as opposed to African–Americans or Hispanic/Latinos. However, SVR rates of 63% were reported in stage 3/4 compared with an SVR of 75% in stage 0/1/2. Figure 2 shows the study outline and results.

The AE rates were very similar to the ADVANCE and PROVE 1/2 trials with side-effects related to TVR of pruritus, anemia, rash and diarrhea. Discontinuation of TVR during the T12PR phase was 12% due to any AE, 7% due to rash and 2% due to anemia. By intention to treat analysis, 17% of all study drugs were discontinued due to AEs throughout the course of therapy (Table 3).

The ILLUMINATE trial revealed that a truncated course of therapy for patients with HCV GT 1 and eRVR (12 weeks of telaprevir + PEGylated IFN-α ribavirin [TPR] followed by 12 weeks of PR) is not inferior to a 48-week course of therapy (12 weeks of TPR followed by 36 weeks of PR) with an SVR of 92 versus 88%, respectively. ILLUMINATE provided data confirming the use of eRVR in RGT for TVR-based regimens in treatment-naive HCV GT 1 patients.

REALIZE

The final Phase III trial, REALIZE, was a randomized, double-blind, placebo-controlled trial involving patients with HCV GT 1 who had failed previous treatment with PR. 663 HCV GT 1 patients who were null responders, partial responders or relapsers to previous

Table 2. ADVANCE adverse events during overall treatment phase and treatment discontinuation during telaprevir/placebo phase†.

Adverse event	T12PR (%)	T8PR (%)	PR48 (%)
Pruritus	50	45	36
Nausea	43	40	31
Anemia	37	39	19
Rash	37	35	24
Diarrhea	28	32	22
TVR phase treatment discontinuation			
Discontinue TVR/placebo	11	7	1
Discontinue all treatment	7	8	4
Anemia associated discontinuation			
Discontinue TVR/placebo	4	2	0
Discontinue all treatment	1	3	1
Rash associated discontinuation			
Discontinue TVR/placebo	7	5	1
Discontinue all treatment	1.4	0.5	0

†Observed in >25% of patients in any group and with an incidence ≥10% in the TVR arm as compared with control.
TVR: Telaprevir.

PR treatment were randomized at a ratio of 2:2:1 to T12PR48, delayed start PR4 lead-in T12PR48 or control retreatment PR48 treatment arms. The study was constructed to assess the efficacy, safety and tolerability of TVR with or without a delayed TVR start (4 week PR lead-in) in previous treatment failure patients. Of note, RGT was not used. As with the ADVANCE and ILLUMINATE trials, highly sensitive HCV RNA testing (Roche TaqMan v2) was used and growth factors were not allowed. In addition, there were strict stopping rules (HCV RNA >100 IU/ml at week 4, 6 or 8, discontinue TVR or <2 log decline in HCV RNA at week 12 or detectable HCV RNA at week 24, discontinue PR) that were more aggressive than in the Phase III treatment-naive trials. Stepwise management of AEs, especially rash, was implemented. All patients received P-2a (180 µg weekly) and weight-based R at 1000–1200 mg daily. TVR dosage was 750 mg every 8 h in the study arms [15].

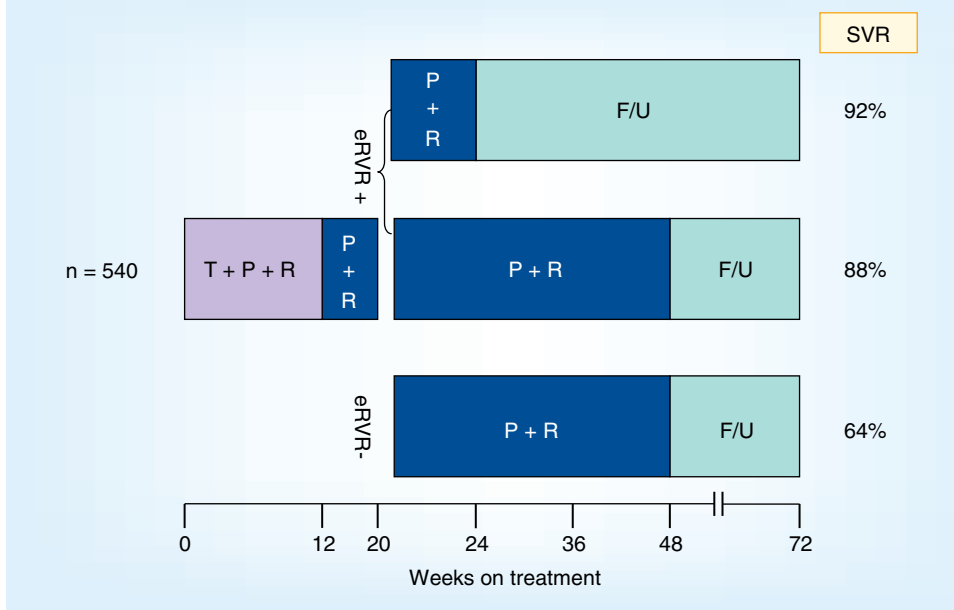

Figure 2. ILLUMINATE trial: treatment of hepatitis C virus treatment-naive patients comparing 24 versus 48 weeks total treatment in the eRVR+ groups after 12 weeks of TPR.
eRVR: Extended rapid virological response; F/U: Follow-up; P: PEGylated IFN-α; R: Ribavirin; SVR: Sustained virological response; TPR: telaprevir + PEGylated IFN-α + ribavirin.

Patients were randomized to one of three arms: T12PR48, T12PR48 with PR4 lead-in or PR48 control. Figure 3 shows the study outline and results. 266 patients were randomized to the T12PR48, with a total SVR of 64%. There was an 83% SVR in historic relapse patients, 59% in historic partial responders and 29% in historic null responders. 264 patients in the PR4 lead-in arm had a total SVR of 66%, with an 88% SVR in historic relapse patients, 54% in historic partial responders and 33% in historic null responders. The control group was comprised of 132 patients with a total SVR of 17%. There was a 24% SVR in historic relapse patients, 15% in historic partial responders and 5% in historic null responders. Overall, 26% of patients had cirrhosis and 89% had an HCV RNA >800,000 IU/ml, consistent with the 'difficult to treat' patient population in the study. Among the historic null responders, 33% had cirrhosis and 95% had HCV RNA >800,000 IU/ml. There were no significant differences in SVR, virological failure or relapse rates between the two TVR groups, indicating that there was no benefit to a 4-week lead-in with PR in treatment-experienced patients with TVR. For comparison to the control group, the TVR arms were pooled for analysis, leading to an overall SVR of 65% with 86% SVR in historic relapse patients, 57% in historic partial responders and 31% in historic null responders by an intention to treat analysis. The differences in SVR between the combined TVR arms compared with control were statistically significant.

Table 3. ILLUMINATE adverse events during overall treatment phase and treatment discontinuation during telaprevir/placebo phase[†].

Adverse event	%		
Fatigue	68		
Pruritus	51		
Nausea	47		
Anemia	39		
Headache	38		
Rash	37		
Insomnia	34		
Diarrhea	30		
Flu-like illness	26		
Treatment discontinuation due to	**Any adverse event (%)**	**Rash (%)**	**Anemia (%)**
Discontinue TVR/placebo	12	7	2
Discontinue all treatment	7	1	1

[†]Observed in >25% of patients.
TVR: Telaprevir.

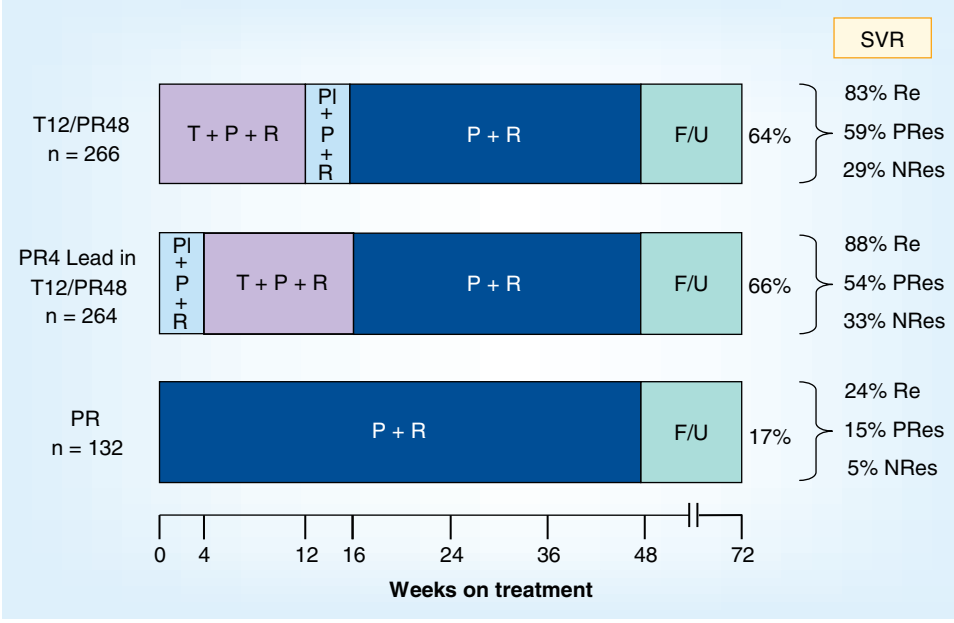

Figure 3. REALIZE treatment of hepatitis C virus treatment-experienced patients comparing 4 week PEGylated IFN-α + ribavirin lead-in versus no lead-in.
F/U: Follow-up; NRes: Null responders; P: PEGylated IFN-α; PRes: Partial responders; R: Ribavirin; Re: Relapsers; SVR: Sustained virological response.

Table 4 shows the AEs and treatment discontinuation rates. Rash was present in 37% of the T12PR48 arm, 36% in the PR4 lead-in arm and 19% in the PR arm. Grade 3 rash was present in 3% in the combined TVR arms. Treatment discontinuation was related to rash in 5% of the T12PR48 arm, 4% in the PR4 lead-in arm and 0% in the control PR48 arm. Anemia was associated with treatment discontinuation in 2% of T12PR48 subjects, 3% of PR4 lead-in T12PR48 subjects and 0% in PR48 subjects. The AE profile was similar to the ADVANCE and ILLUMINATE trials. The most common AEs included fatigue, pruritus, headache, rash, flu-like symptoms, nausea and anemia. A follow-up report showed that prior treatment response is a better predictor of SVR than the week 4 response with PR lead-in [16].

The REALIZE trial demonstrated that, although there is no benefit to a 4-week lead-in with PR in treatment-experienced patients with TVR, retreatment with a TVR-based regimen was successful in nearly two out of three cases.

Table 4. REALIZE adverse events during overall treatment phase and treatment discontinuation rates during telaprevir/placebo phase†.

	T12PR48 (%)	Lead in T12PR48 (%)	PR48 (%)
Fatigue	55	50	40
Pruritus	52	50	27
Rash	37	36	19
Flu-like illness	32	36	25
Nausea	35	33	23
Anemia	30	36	15
Diarrhea	25	26	14
TVR phase treatment discontinuation			
Discontinue all treatment	6	4	3
Discontinue TVR/placebo (due to any AE)	15	11	3
Due to rash	5	4	0
Due to anemia	2	3	0
All treatment discontinuation due to	**Combined TVR arms**		**PR48**
Any AE	4		3
Anemia	0.60		0
Rash	0.40		0

†During overall treatment phase, by preferred terms, occurring in over 25% of patients in any group, with an incidence ≥5% in TVR arm as compared with control.
AE: Adverse event; TVR: Telaprevir.

Latest developments/FDA review

The three Phase III trials with TVR defined SVR strictly as having both HCV RNA not quantified by the Roche TaqMan v2 assay (at a threshold of 25 IU/ml) and undetectable (at a threshold of ~10 IU/ml). However, the FDA determined that SVR would include patients whose HCV RNA levels were detectable, but not quantified (i.e., below the 25 IU/ml threshold), and that an undetectable HCV RNA at week 12 of follow-up (SVR12) could be used for a missing SVR24 data point. Therefore, the SVR rates were adjusted slightly upwards. The adjusted SVR for the ADVANCE study in the FDA document were 79% for T12PR, 72% T8PR and 46% for PR as opposed to the original 75, 69 and 44%, respectively. The adjusted SVR rates for the REALIZE study in the FDA document were, for historic relapse patients, 84% in T12PR48, 88% PR4 lead-in T12PR48 and 22% in PR48. For historic partial responders, SVR was 61% in T12PR48, 56% PR4 lead-in T12PR48 and 15% PR48. For historic null responders, SVR was 31% in T12PR48, 33% in PR4 lead in T12PR48 and 5% PR48 [101].

Although IL28B genotyping has been shown to be highly associated with SVR to P and R therapy, recent reports suggest that IL28B testing may have a limited role in TVR-based treatment regimens. An unplanned, *post hoc* analysis of 454 (42%) of the 1088 ADVANCE trial patients who received at least one dose of medication was performed utilizing IL28B genotyping of de-identified samples of white patients. Allele distribution was 33% CC, 49% CT and 18% TT. SVR rates in the CC group were 90% in T12PR, 84% in T8PR and 64% in PR control. In the CT allele group, SVR rates were 71% in the T12PR group, 57% in T8PR and 25% in PR control. Corresponding SVR rates in the TT allele group were 73, 59 and 23%, respectively. SVR in the CC genotype patients was highly favorable with PR therapy, as has been previously reported. Although patients with the CC genotype did best with TVR-based regimens, subjects with CT and TT also did very well, with SVR >70%. In fact, the impact of TVR appeared to be greatest in patients with a T allele [17]. A similar evaluation was performed in the REALIZE trial. SVR rates in the CC allele group were 79% for pooled T12PR patients and 29% for PR patients. In the CT allele patients, SVR was 60% in the pooled T12PR patients and 16% in the PR patients. In the TT allele subjects, SVR was 61% for pooled T12PR patients and 13% for PR patients [18]. In both studies, regardless of the IL28B genotype, the addition of TVR resulted in a significant increase in the SVR compared with PR control. Although patients with CC genotype did the best, the difference in SVR between CC and CT or TT genotypes was not substantial. This suggests that IL28B genotyping may have limited utility in patients receiving TVR.

Several groups of patients, including those with severe hepatic and renal impairment, may not be ideal candidates for treatment with TVR and will require further study. TVR has not been evaluated in patients with significant hepatic impairment, specifically in those with Child-Pugh class C. Further studies have been recommended by the FDA antiviral products advisory committee to study the extent of accumulation of TVR in patients with severe renal impairment [102].

In addition, TVR is metabolized by the CYP3A4 cytochrome system in the liver and is a substrate of P-gp. This is a common drug metabolic pathway, which means that there are many possible drug–drug interactions that must be accounted for when using protease inhibitors such as TVR. In some cases, TVR can occupy CYP3A4 and inhibit the metabolism of other medications, thereby raising levels of the other drugs and potentially causing toxicity. Many drugs are contraindicated with TVR and must be discontinued during the usage of TVR, while others must be used with extreme caution and careful monitoring. For example, a recent abstract of a Phase I study investigating the impact of TVR on cyclosporine and tacrolimus metabolism, reported that TVR increased the dose-normalized exposure to cyclosporine 4.6-fold and to tacrolimus 70-fold [19]. Therefore, the use of TVR for liver transplant patients at this time is only advised within the context of clinical trials. In other cases, lower levels of other medications such as estrogens may be observed. Theoretically, estrogen-containing oral contraceptives may be less effective. Finally, in other cases, induction of CYP3A4 may potentially result in a decrease in TVR levels leading to decreased effectiveness of TVR and possible increased development of resistance. Additional data on concomitant drug use are needed. Table 5 outlines some of the established and other potentially significant drug interactions with TVR for which the manufacturer endorses caution.

The FDA made several important changes in the prescribing information recommendations from the Phase III trials. First, based on favorable results for a T12PR24 regimen in the Phase II 107 trial for historic relapse patients, the FDA included historic relapse patients in the RGT treatment paradigm. This allows patients with eRVR to receive a 24-week course of therapy (even though the REALIZE Phase III trial only investigated a 48 course in all relapse patients). Second, the futility rules were changed. For all patients (treatment-naive or experienced), HCV RNA

Table 5. Drug–drug interactions.

Drugs class/name	Effect
Antiarrhythmics	
Lidocaine, amiodarone, bepridil, flecainide and quinidine	Inc. drug levels
Digoxin	Inc. drug levels
Antibacterials	
Clarithromycin, erythromycin and telithromycin	Inc. TVR levels Inc. drug levels
Anticoagulant	
Warfarin	Inc. or dec. drug levels
Anticonvulsants	Dec. TVR levels
Carbamazepine	Inc. drug levels
Phenobarbital	Inc. or dec. drug levels
Phenytoin	Inc. or dec. drug levels
Antidepressants	
Escitalopram	Dec. drug levels
Desipramine	Inc. drug levels
Trazodone	Inc. drug levels
Antifungals	
Ketoconazole, itraconazole, posaconazole and voriconazole	Inc. TVR levels
Voriconazole	Inc. or dec. drug levels
Benzodiazepines	
Alprazolam, midazolam	Inc. drug levels
Calcium channel blockers	Inc. drug levels
Corticosteroids	
Prednisone, methylprednisolone	Inc. drug levels
Dexamethasone	Dec. TVR levels
HIV-antiviral medications	Variable effects
Hormonal contraceptives/estrogen	
Ethinyl estradiol	Dec. drug levels
Norethindrone	No effect
Immunosuppressants	
Cyclosporine, sirolimus, tacrolimus	Inc. drug levels
Narcotic	
Methadone	Dec. drug levels
PDE5 inhibitors	
Sildenafil, tadalafil and vardenafil	Inc. drug levels

Dec.: Decrease; Inc.: Increase; TVR: Telaprevir.

>1000 IU/ml at weeks 4 or 12 constitute stopping rules. All medications, not TVR only, are discontinued if stopping rules are met [20].

Conclusion

The three Phase III studies, including the two pivotal trials (ADVANCE and REALIZE), have led to the approval by the FDA for HCV GT 1 treatment-naive and treatment-experienced patients (historic relapse, partial responders and null responders). All patients are treated with 12 weeks of TPR followed by PR therapy. Treatment-naive or historic relapse patients are treated with RGT using eRVR to determine if therapy can be limited to 24 weeks. Historic partial responders or null responders are treated with 48 weeks of therapy. Stopping rules must be strictly adhered to.

TVR cannot be used without both P and R. If R must be discontinued, TVR must also be discontinued. TVR cannot be dose reduced and it cannot be stopped and restarted. Furthermore, it must be taken every 8 h, with a snack or a meal containing approximately 20 g of fat. Side-effects were manageable, and the number of patients that discontinued all of the medications or TVR alone due to side-effects was relatively low.

Future perspective

It is possible that TVR may eventually be dosed more conveniently at every 12 h rather than every 8 h. The recently published Phase II C208 study suggests that dosing of TVR with 1125 mg twice daily (b.i.d.) is comparable to 750 mg thrice daily [21]. Data are awaited from a Phase IIIb trial (OPTIMIZE), an open-label study, evaluating b.i.d. versus thrice daily dosing of TVR in treatment-naive HCV GT 1 patients. b.i.d. dosing may lead to greater compliance with the medical regimen, which is important since noncompliance may lead to increased resistance and diminished efficacy.

The impact of resistance is poorly understood. The EXTEND study, which is enrolling patients with virological failure from the Phase II and III studies, has several objectives characterizing and assessing the durability of TVR-resistant variants. Preliminary results report that resistant virus could not be detected in approximately 89% of the participants after an average of 2 years of follow-up [22]. The final results are awaited. Durable resistant variants may have an impact on future therapeutic regimens with protease inhibitors.

Additional work must be carried out to assess the impact of drug–drug interactions and how to manage them. Many of the contraindicated medications are common ones and may present complicated management problems.

Many subpopulations of HCV patients were not included in the Phase II or III trials and must be investigated. These include HCV–HIV coinfected patients, patients with decompensated liver disease

and post-liver transplantation patients. In the future, data will provide additional patient groups with HCV the opportunity for increased SVR.

TVR is only approved for patients with HCV GT 1. Further data are awaited to determine if TVR has a role for patients with other genotypes.

This is the dawn of a new age in the treatment of HCV. However, the landscape of HCV therapy will likely continue to change over the next 5 to 10 years. There are dozens of promising medications in the research pipeline for HCV. These include DAAs in the protease inhibitor class, that offer better side-effect profiles, higher barriers to resistance and once-daily dosing. Furthermore, DAAs in other classes are under study, including nucleoside and nonnucleoside polymerase inhibitors and NS5A inhibitors. Agents that attack host components of the replication process (i.e., cyclophilin inhibitors) are also under investigation. It is likely in the foreseeable future that quadruple therapy regimens (PR and two complementary small molecules) may allow higher SVR by increasing efficacy and decreasing resistance in patients with HCV GT 1. Furthermore, some of these compounds may have pangenotypic efficacy and offer increased SVR in patients with genotypes other than GT 1.

Finally, there is promise that interferon-free regimens may be possible to achieve SVR in patients with HCV. Not only would this be important because interferon has significant toxicity and cost, but many patients with HCV have contraindications to interferon or cannot tolerate it. Although the concept has been hotly debated, a recent presentation was a proof-of-concept trial. Four out of 11 (36%) patients who were historic null responders and treated with a 24-week course of a protease inhibitor and NS5A inhibitor obtained SVR [23]. It is possible that interferon-free regimens with multiple small molecules may be available within the next 10 years.

Executive summary

- Current hepatitis C virus (HCV) treatment options lead to suboptimal responses, especially in HCV genotype 1 (GT 1).
- Telaprevir (TVR) is an NS3/4 protease inhibitor with high antiviral efficacy but risk of viral resistance.
- The ADVANCE study showed that 12 weeks of TVR with PEGylated IFN-α + ribavirin (PR) led to 75% sustained virological response (SVR) in treatment-naive HCV GT 1. Response-guided therapy using extended rapid virological response (eRVR) can lead to shortening of treatment duration in nearly 60% of treatment-naive patients.
- The ILLUMINATE study demonstrated that 24 weeks is not inferior to 48 weeks of total therapy in eRVR+, HCV GT 1 treatment-naive patients, leading to a 92% SVR in eRVR patients.
- The REALIZE study demonstrated SVR rates in treatment-experienced patients (historic relapse, partial responders and null responders) of 64–66% with no significant benefit with a 4-week lead-in PR phase.
- All three studies demonstrated that rash was a significant adverse event, but that stepwise, controlled management could limit treatment discontinuation.
- Future studies will address concerns over the impact of virological resistance with TVR.
- Future studies will examine drug–drug interactions and management strategies for medications that are metabolized by CYP3A4.
- Future studies will address the efficacy and safety of TVR in patient populations, such as HCV–HIV coinfected, decompensated liver disease patients and postliver transplantation patients.
- Future studies will determine if TVR can be dosed twice daily versus thrice daily.

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SL Flamm performs clinical research for, is a consultant for and is on the Speaker's Bureau of Vertex Pharmaceuticals. J Ahn is on the Speaker's Bureau of Vertex Pharmaceuticals. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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