

# Telaprevir: evidence and guidance for use in clinical practice

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## Practice Points

- Triple therapy with pegylated interferon, ribavirin (PR) and telaprevir significantly increases sustained viral response rates in patient with genotype 1 hepatitis C virus compared with PR treatment alone.
- Sustained viral response rates with telaprevir combination therapy are significantly improved in 'hard-to-treat' patients, including those with cirrhosis and who have previously failed treatment.
- Patients treated with telaprevir and PR who achieve an extended rapid virological response can have the duration of PR treatment shortened from 48 to 24 weeks.
- Adverse events are increased in patients treated with telaprevir compared with those treated with PR alone; the most common adverse events are fatigue, pruritis, nausea, diarrhea and rash.
- Treatment discontinuation occurs in 8–12% of patients, and the most common reasons for treatment discontinuation with telaprevir are anemia and rash.

**SUMMARY** Hepatitis C virus (HCV) is the leading cause of chronic liver disease and liver transplantation worldwide, with an estimated 170 million people chronically infected. Pegylated interferon and ribavirin (PR) have been the mainstay of treatment for the past 10 years with sustained viral response rates of 41–82%. The use of PR is limited by its side-effect profile, the prolonged treatment course required and its relatively low efficacy. Recently, two new therapies have been approved for the treatment of chronic genotype 1 HCV in combination with PR, the first-generation protease inhibitors telaprevir (TVR) and boceprevir. Phase III clinical trials show that triple therapy with these agents significantly improves sustained viral response rates over PR, but with an increase in adverse events. In this article, we discuss the development of TVR, the current evidence supporting its use in genotype 1 HCV and give practical guidance on the use of TVR in clinical practice.

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### Background to the therapy

#### ■ Hepatitis C virus epidemiology

Hepatitis C virus (HCV) has been estimated by WHO to affect 3% of the world's population – approximately 170 million people [1]. The most serious consequences are the development of cirrhosis, end-stage liver disease and hepatocellular carcinoma (HCC). Cirrhosis occurs in an estimated 7–24% of patients with HCV [2] and once cirrhosis has occurred, the risk of development of HCC or hepatic decompensation is 1.5–7.1% and 6.7% per year, respectively [3].

#### ■ HCV virology

HCV is a single-stranded genome, enveloped RNA virus with a single open reading frame, that is flanked by noncoding 5' and 3' regions. After the HCV virus enters a hepatocyte, genome replication occurs in the cytoplasm. The first step in this process involves translation into a large polyprotein consisting of nearly 3000 amino acids. This is then cleaved by viral and host cellular proteases into structural (core and envelope protein 1 and 2) and nonstructural (NS2, NS3, NS4A, NS4B, NS5A and NS5B) proteins. The nonstructural proteins and viral RNA form membrane-associated replication complexes, and replication occurs. The RNA and capsid proteins then assemble into nucleocapsids, which travel through the intracellular membranes into cytoplasmic vesicles [4–6].

Telaprevir (TVR) is a small molecule that is a direct inhibitor of the NS3/4A serine protease [7]. The function of the NS3/4A serine protease in the HCV lifecycle is to catalyze the cleavage of the post-translational HCV polyprotein at multiple junctions [8]. The NS3/4A serine protease may also inhibit antiviral response of the host by preventing activation of interferon regulatory factor 3 (a factor that induces expression of IFN- $\beta$ , leading to an antiviral state) and by reducing intrahepatic production of IFN- $\gamma$  (leading to reduction in the hepatic inflammatory response). Therefore, inhibition of NS3/4A has the potential to suppress viral replication and improve the host immune response against HCV by restoring interferon pathways [9].

#### ■ Current treatment

Dual therapy with pegylated IFN- $\alpha$  (pegylated IFN- $\alpha$ 2a [Pegasys<sup>®</sup>, Roche] or pegylated IFN- $\alpha$ 2b [ViraferonPeg<sup>®</sup>, Schering-Plough]) and ribavirin (Copegus<sup>®</sup>, Roche or Rebetol<sup>®</sup>,

Schering-Plough) has been the standard of care in the treatment of chronic HCV infection for the last 10 years [10,11]. In genotype 1 (G1) HCV, a treatment course of 48 weeks is required in most patients and a sustained viral response (SVR) of 41–51% can be achieved, although this is substantially lower in African-American patients, those with cirrhosis and those who have previously failed treatment [12–14]. Both pegylated interferon and ribavirin have a significant side-effect profile, and discontinuation due to adverse events occurs in up to 10% of patients. Pegylated interferon causes influenza-like symptoms, fatigue, depression and hematological abnormalities and ribavirin causes anemia and is teratogenic [12,14]. These considerations have led to the search for new therapies for G1 HCV. The first to have been approved for use are the protease inhibitors TVR and boceprevir. In this article, we examine the evidence for the use of TVR in G1 HCV in more detail.

### Clinical evidence

#### ■ Phase II trials

##### PROVE 1

The PROVE 1 study took place at 37 centers in the USA and was a Phase IIb, randomized parallel-group, double-blind, placebo-controlled trial in previously untreated patients with G1 HCV (Table 1) [15]. Patients were assigned to four treatment groups: a control group who received 48 weeks of pegylated IFN- $\alpha$ 2a (180  $\mu$ g/week) and ribavirin (1000 or 1200 mg/day dependent on bodyweight) and TVR placebo for 12 weeks; a T12PR12 group who received TVR 1250 mg on day 1, and then TVR 750 mg every 8 h for 12 weeks and pegylated interferon and ribavirin (PR) for 12 weeks; a T12PR24 group who received TVR at the same dose for 12 weeks and 24 weeks of PR; and a T12PR48 group who received 48 weeks of PR and 12 weeks of TVR. The control group had an SVR rate of 41%, the T12PR12 group had a 35% SVR rate, the T12PR24 group had a 61% SVR rate and the T12PR48 group had a 67% SVR rate. Rates of discontinuation were higher in the TVR-containing groups (21% in TVR groups vs 11% in control group) [15].

##### PROVE 2

The PROVE 2 trial was a further Phase IIb, randomized, partially double-blind placebo-controlled trial (Table 1) [16]. There was random assignment of previously untreated patients with G1 HCV into four treatment groups. Two

**Table 1. Phase II trials of telaprevir.**

Study (n)	Arms	SVR (%) <sup>†</sup>	Relapse (%) <sup>‡</sup>	Viral breakthrough (%) <sup>§</sup>	Ref.
PROVE 1 (263 patients: not previously treated)	Control (n = 75)	41	23	–	[15]
	T12PR12 (n = 17)	35	33	7 in TVR patients	
	T12PR24 (n = 79)	61	2	–	
	T12PR48 (n = 79)	67	6	–	
PROVE 2 (334 patients: not previously treated)	Control (n = 82)	46	22	1	[16]
	T12PR12 (n = 82)	60 (p = 0.12)	30	1	
	T12PR24 (n = 81)	69 (p = 0.004)	14	5	
	T12P12 (n = 78)	36	48	24	
PROVE 3 (465 patients: previously treated)	Control (n = 114)	14	53	–	[17]
	T12PR24 (n = 115)	51 (p ≤ 0.001)	30	12–13 in TVR arms	
	T24PR48 (n = 113)	53 (p ≤ 0.001)	13	–	
	T24P24 (n = 111)	24 (p ≤ 0.02)	53	–	

<sup>†</sup>SVR was defined as an undetectable hepatitis C virus RNA 24 weeks after the end of therapy.

<sup>‡</sup>Relapse was defined as a detectable hepatitis C virus RNA during the 24-week post-treatment period in patients who had undetectable hepatitis C virus RNA at the end of the treatment period.

<sup>§</sup>Viral breakthrough was defined as an increase of >1 log unit of hepatitis C virus RNA as compared with the lowest value during the treatment period, or if the hepatitis C virus RNA level had become undetectable, an increase to an hepatitis C virus RNA value of >100 IU/ml.

SVR: Sustained viral response; TVR: Telaprevir.

groups were identical to PROVE 1 and investigated the efficacy of 12 weeks of TVR with 12 and 24 weeks of PR (T12PR12 and T12PR24, respectively). A third group (T12P12) examined 12 weeks of TVR and 12 weeks of pegylated interferon without ribavirin, and the control group received 48 weeks of PR in combination with TVR placebo for the first 12 weeks. The dosing of each of the drugs was identical to the PROVE 1 study. In the T12PR24 group, the SVR rate was 69%, which was significantly higher than the PR group (46%;  $p \leq 0.004$ ). The SVR rate in the T12PR12 was 60%, and the lowest rate of SVR occurred in the T12P12 group at 36%. Neither of these were significantly better than the control group. Viral breakthrough was higher in the T12P12 group at 24% than it was in all other groups (1% in PR48, 1% in the T12PR12 and 5% in the T12PR24 group). This study showed the importance of ribavirin as part of combination treatment to maintain increased SVR rates and reduce relapse rates [16].

### PROVE 3

The PROVE 3 Phase II study examined 453 previously treated patients with G1 HCV (Table 1) [17]. There were four treatment arms: a T12PR24 group (as previously described); a T24PR48 group (where subjects received 24 weeks of TVR and 48 weeks of peg interferon plus ribavirin); a T24P24 group (where 24 weeks of TVR and peg interferon were given without ribavirin) and a PR48 group (where patients received PR for

48 weeks with 24 weeks of placebo). Previous relapsers and null responders were stratified evenly between the groups. The SVR rates in each TVR-treated arm were significantly higher than placebo with SVR rates in the T12PR24 arm of 51%, 53% in the T24PR48 arm and 24% in the T24P24 arm versus 14% in the control arm. All TVR-treated patients had at least a 2 log drop in HCV RNA levels at week 12. SVR rates were higher in patients who had had a previous relapse (defined as undetectable HCV RNA levels during treatment for at least 48 weeks, with detectable HCV RNA during follow-up and a lack of SVR), than in those who had been previous null responders (undetectable HCV RNA never achieved). SVR rates were 69 versus 39% in the T12PR24, 76 versus 38% in the T24PR48, 42 versus 11% in the T24P24 arm, in previous relapsers and null responders, respectively. Relapse rates were 53% in the PR48 and T24P24 groups and 30% in the T12PR24 group and 13% in the T24PR48 arm. The T12PR24 regime had a lower rate of discontinuation of treatment due to adverse events than the T24PR48 group and similar rates as SVR [17].

### Phase III trials

#### ADVANCE

The ADVANCE trial examined outcomes of response-guided treatment with triple therapy in previously untreated patients with G1 HCV (Table 2) [18]. In the response-guided treatment arms, the duration of treatment with PR could be reduced to 24 weeks (rather than 48 weeks)

if an extended rapid viral response (eRVR) was achieved. eRVR was defined as a negative HCV RNA at week 4 and 12. The three arms were: a T12PR12 group, where 12 weeks of TVR and PR were given, followed by 12 weeks of PR if eRVR was achieved, or 36 weeks PR if eRVR was not achieved; a T8PR group, who received 8 weeks of TVR followed by 4 weeks of TVR placebo in combination with PR, with response-guided therapy in those who achieved eRVR; and a control arm where 12 weeks of TVR placebo was given with 48 weeks of PR. The SVR at 24 weeks was significantly higher in both TVR treatment arms (75% in the T12PR group and 69% in the T8PR group, versus 44% in the PR group;  $p \leq 0.001$ ) and 58% of patients were eligible for a shortened treatment duration of PR. Stopping rules were implemented in this study whereby patients treated with TVR who had HCV RNA levels of  $>1000$  IU/ml at week 4 stopped TVR and continued PR alone, and patients who had a less than 2 log drop in HCV RNA from baseline at week 12 stopped all treatment as per national guidelines for standard treatment [18].

### REALIZE

In the REALIZE trial, 633 previously treated patients were treated (Table 2) [19]. Subgroup analysis was undertaken on those who were previous relapsers, partial responders or null responders. The arms consisted of a T12PR48 arm; a lead-in T12PR48 arm where a lead in of 4 weeks of PR was given followed by 12 weeks of TVR and 48 weeks of PR; and a control group where a TVR placebo was given for 12 weeks with 48 weeks of PR. SVR rates of 83, 88 and 24% were seen in patients with a previous relapse in the T12PR, lead-in T12PR48 and control groups, respectively. In previous partial responders, SVR rates of 59, 54 and 15% were seen in the same groups, respectively. In previous null responders the SVR rates were 29, 33 and 5%, respectively. Of note, there were no significant differences in response in patients who did, or did not, undergo the PR lead in phase [19].

### ILLUMINATE

The response-guided treatment concept was further elaborated in the ILLUMINATE Phase III

Table 2. Phase III trials of telaprevir.

Study (n)	Arms	SVR (%) <sup>†</sup>	Relapse (%) <sup>‡</sup>	Virologic failure <sup>§</sup> /viral breakthrough <sup>¶</sup> (%)	Ref.
ADVANCE (1088 patients: not previously treated)	Control group	44	28	32	[18]
	T12PR12 then RGT with PR for 12 or 36 weeks	75 ( $p \leq 0.001$ )	9	8	
	T8PR12, then RGT with PR for 12 or 36 weeks	69 ( $p \leq 0.001$ )	9	13	
REALIZE (633 patients: previously treated)	Control	Overall: 17 Previous relapsers: 24 Partial responders: 15 Null responders: 5	65	Previous relapsers: 26 Partial responders: 70 Null responders: 84	[19]
	T12PR48	Overall: 64 Previous relapsers: 83 Partial responders: 59 Null responders: 29	7	Previous relapsers: 1 Partial responders: 18 Null responders: 57	
	Lead-in 4/52 TVR then T12PR48	Overall: 66 Previous relapsers: 88 Partial responders: 54 Null responders: 33	7	Previous relapsers: 1 Partial responders: 19 Null responders: 47	
ILLUMINATE (540 patients: not previously treated)	T12PR24 (RGT)	92	6	2	[20]
	T12PR48 (RGT)	88	3	–	
	T12PR48	88	11	–	

<sup>†</sup>SVR was defined as an undetectable hepatitis C virus RNA 24 weeks after the end of therapy.

<sup>‡</sup>Relapse was defined as a detectable hepatitis C virus RNA during the 24 week post-treatment period in patients who had undetectable hepatitis C virus RNA at the end of the treatment period.

<sup>§</sup>Virologic failure was defined as either viral breakthrough or discontinuation of study drug because of meeting a virological stopping rule.

<sup>¶</sup>For the ILLUMINATE study only, viral breakthrough was defined as an increase of  $>1$  log unit of hepatitis C virus RNA as compared with the lowest value during the treatment period, or if the hepatitis C virus RNA level had become undetectable, an increase to an hepatitis C virus RNA value of  $>100$  IU/ml.

PR: Pegylated interferon and ribavirin; RGT: Response-guided treatment; SVR: Sustained viral response; TVR: Telaprevir.

noninferiority trial (Table 2) [20]. A total of 540 previously untreated patients were included. All patients received 12 weeks of TVR in combination with PR for 12 weeks. Those who had an eRVR were randomly assigned at week 20 to receive a total of 24 or 48 weeks of PR. Those who did not achieve an eRVR had 48 weeks of PR. A total of 65% of patients had an eRVR and were eligible for shortened treatment. The SVR rate was 92% in the T12PR24 group and 88% in the T12PR48 arms, so the noninferiority rule was fulfilled. Relapse rates were not significantly higher in the T12PR24 arm than in the T12PR48 arm [20].

### Place in therapy

#### ■ Patient selection

TVR was approved for the treatment of G1 chronic HCV by the US FDA and by the EMA in 2011 [101,102].

Consideration of treatment with TVR for all patients with G1 HCV with or without cirrhosis and previously untreated or treated is recommended by the American Association for the Study of Liver Diseases (AASLD) [21] and by NICE [22].

Recent UK guidelines for the use of TVR and boceprevir state that where resource constraints mean that there may be delays in therapy then those with the greatest clinical need should be prioritized for treatment. This includes patients who have a high likelihood of developing cirrhosis or HCC within the next 5 years, and those with additional urgent considerations, such as disabling extra hepatic consequences of HCV or fertility concerns [23].

#### ■ Special circumstances

##### Patients with hepatic impairment/cirrhosis

In the ADVANCE study, subgroup analysis was carried out on patients with bridging fibrosis and cirrhosis. A total of 21% of patients in this study had cirrhosis or bridging fibrosis with 73 (20%), 86 (23%) and 73 (20%) cirrhotic patients in the T12PR, T8PR and PR groups, respectively. SVR rates were 62% in the T12PR and 53% in the T8PR group, versus 33% in the PR group. While rates were significantly better with TVR than with PR, they were still lower than in patients with minimal or low fibrosis (SVR: 81% in patients with minimal/low fibrosis vs 62% for those with cirrhosis) [18]. In the REALIZE trial, 48% of patients had cirrhosis. The SVR rate in

patients with cirrhosis, similar to other patients in the trial, was dependent on their previous response to therapy. In the T12R48 arm SVR rate was 84% (54/64) in cirrhotic patients with previous relapse versus 13% in the PR group. In patients with a previous partial response to PR treatment an SVR rate of 44% was seen in the T12PR48 versus 10% in the PR group. In previous null responders SVR rates of 14 and 5% were seen in each group [19]. The REALIZE study reports that no specific safety and tolerability issues were identified in patients with advanced fibrosis and cirrhosis.

In the ILLUMINATE study, 149 patients (28%) had bridging fibrosis or cirrhosis, and overall, 63% of these had a SVR, but in those with an eRVR the SVR rates were 82% in the T12PR24 arm and 88% in the T12PR48 arm. This compares with 75% of patients with no or minimal portal fibrosis [20].

Cirrhotic patients traditionally have a low response rate to PR and so the increased response rates seen are encouraging, but the numbers treated in Phase II and III studies are still relatively low. The data presented so far indicate that patients with compensated cirrhosis should all be considered for treatment. However, a note of caution is appropriate as postmarketing data presented in 2012 examined 169 patients with HCV cirrhosis who were treated with triple therapy including TVR and showed high rates of serious adverse events (51%) and discontinuation of therapy (12%). The most common serious adverse event was anemia [24]. These figures are considerably higher than those seen in the Phase III studies. Given that patients with portal hypertension are at high risk of developing complications of cirrhosis, these outcomes are not unexpected and, in our view, the data should not be interpreted as indicating that such patients should not be treated, but that they should be monitored very closely during their treatment for adverse events. As deaths have occurred following the cessation of TVR, it is probable that the consequences of PR therapy play an important role in side effects. In the past, PR therapy has been ineffective in patients with advanced cirrhosis and hence, patients have not been exposed to prolonged courses of these medications.

##### African–American patients

African–American patients with G1 HCV have a lower response rate to PR than other ethnicities, with a reported SVR rate of 28% in the

VIRAHEP-C study [25]. Thus, they are a group where better therapy is more urgently required. Subgroup analysis was undertaken in these patients in the ADVANCE study where SVR rates of 62 and 58% in the T12PR and T8PR groups, respectively, versus 25% in the PR group were observed; however, there were low numbers of African-American patients in each group (T12PR: 26/363 [7%]; T8PR: 40/364 [11%] PR: 28/361 [8%]) and so the results may not be reproducible [18]. In ILLUMINATE, the SVR was 60% among African-American patients and 67% in Hispanic and Latino patients, with an overall SVR rate of 74% in Caucasian patients, which was significantly higher than in the other races ( $p = 0.02$ ). There were 73 African-American patients (14%) and 54 Hispanic and Latino patients (10%) included in the study, therefore numbers were small, with approximately 20 patients in each arm [20]. In the PROVE 1 study in a small subset of African-American patients, SVR rates were 44% (eight of 18 patients) in the TVR-treated groups and 11% in the PR group (one of nine patients). Although the numbers are small the significantly higher response rates in African-American patients treated with TVR should be taken into consideration when deciding on the appropriate treatment for patients with G1 HCV.

### Pregnancy

TVR is given in combination with PR, which are both contraindicated in pregnancy due to the teratogenic effects of ribavirin and the antiproliferative effects of pegylated interferon [26].

### HIV-coinfected patients

HIV-coinfected patients have lower SVR rates than those infected with HCV alone. A small Phase II study (13 patients) has examined TVR in combination with PR in HIV/HCV coinfecting G1 treatment-naive patients, and week 24 interim analysis has been presented showing increased response rates in TVR- and PR-treated patients versus those treated with placebo and PR (undetectable HCV RNA at week 24 of 86 vs 33%) in patients who were not concurrently treated with antiretroviral therapy [27]. At present, HIV-coinfected patients should be considered for treatment on a case-by-case basis by expert physicians [23].

### ■ Dosing & administration

TVR is an oral medication that is taken three-times daily at a dose of 750 mg for 12 weeks.

It should always be taken with fatty food and be delivered in conjunction with PR. Pegylated interferon is a weekly injection of 180 µg and ribavirin is an oral tablet taken once daily at a dose of 800–1200 mg, dependent on weight.

UK and US guidelines on the treatment of TVR in G1 HCV have recently been published that differ slightly in their recommendations [21,23]. Both guidelines state that, in previously nontreated patients without cirrhosis, response-guided therapy should be considered. Patients should receive 12 weeks of TVR and if eRVR is achieved 24 weeks of PR should be given. If the HCV RNA is detectable at weeks 4 or 12 then a full treatment course of 48 weeks of PR should be taken.

The AASLD guidelines state that response-guided therapy can also be considered in prior relapsers or partial responders with an undetectable HCV RNA at 4 and 12 weeks [21], whereas the UK guidelines state that all previously treated patients should be treated with 12 weeks of TVR and 48 weeks of PR [23]. All other patients should be treated with 48 weeks of PR in addition to 12 weeks of TVR and the UK guidelines state that when considering prior null responders with cirrhosis for treatment a discussion should be had about waiting for future therapies due to the low chance of response [21,23].

### Stopping rules

TVR should be stopped in all patients where the HCV RNA level is over 1000 IU/ml at week 4 or 12. In this situation continuing PR therapy is unlikely to be beneficial and this should also be discontinued. All treatment should be stopped if HCV RNA is detectable between weeks 24 and 48. The AASLD guidelines state in addition that in previously treated patients who have a HCV RNA of over 1000 IU/ml at 4 or 12 weeks, triple therapy should be stopped as they have a high chance of developing viral resistance [21,23].

### Resistance-associated variants

Due to its high rate of viral replication and fault-prone RNA polymerase activity there is a large amount of genetic diversity within the HCV genome. This viral diversity includes mutated and wild-type viral variants with reduced susceptibility to TVR and other direct-acting antiviral therapies. The mechanism of action of direct-acting anti-virals can lead to the emergence of pre-existing mutant variants with a low susceptibility

to direct-acting anti-virals as the principal viral strain, by selective inhibition of other viral variants during treatment. This has been shown in clinical trials where rapid selection of resistant viral strains was observed with TVR and boceprevir monotherapy. In clinical practice, the presence of resistance variants has a number of significant implications. Most importantly, futility stopping rules should be strictly adhered to in order to prevent the expansion of resistant variants. In addition, TVR should not be given as monotherapy as, due to its low barrier to resistance, HCV eradication is not possible without combination therapy with PR. Patient compliance with the drug regime is also very important as missed doses may lead to prolonged drug trough levels and the emergence of resistant variants [28].

### Tolerability, safety & adverse events

#### ■ Adverse events

All the Phase II and III trials assessing TVR in addition to PR have shown an increase in discontinuation rates of between 8 and 12% in the TVR-containing arms (Table 3). The most common adverse events associated with TVR therapy were fatigue, pruritus, nausea, diarrhea and rash. Most discontinuations were related to anemia and rash. TVR-associated rash was serious in approximately 5% in each study and caused 4–5% of patients to discontinue treatment over all. Anemia was seen in up to 39% of TVR-treated patients and caused discontinuation in 1–3% of patients [15–20].

#### ■ Treatment of common adverse events

A mild or moderate rash over a small body surface area should initially be treated with antihistamines, topical steroids and avoidance of sun exposure. If the rash progresses with this treatment then TVR should be stopped, and if it continues to progress or does not improve within 7 days then consideration should be given to stopping ribavirin and pegylated interferon. All patients who develop a severe rash should have all medications stopped and a dermatology opinion should be sought urgently. Oral corticosteroids can be used in the treatment of a severe rash after TVR has been stopped [23,29].

Anemia due to TVR is treated with a combination of ribavirin dose reduction, interferon dose reduction if there is evidence of bone marrow suppression, erythropoietin administration and, in rare cases, blood transfusion [23,30].

#### ■ Drug interactions

TVR is metabolized by the CYP450 system, leading to the potential for many drug–drug interactions. A thorough drug history should be taken and databases such as Hep Drug Interactions [103] should be reviewed for potential drug interactions prior to prescribing TVR [23].

### Conclusion

TVR therapy significantly increases SVR rates in G1 HCV in previously treated and untreated patients, and in hard to treat patients such as those with cirrhosis and African–American

**Table 3. Adverse events associated with telaprevir.**

Adverse event		PROVE 1 <sup>†</sup>		PROVE 2 <sup>‡</sup>		PROVE 3 <sup>§</sup>		ADVANCE <sup>¶</sup>	
		TVR (%)	PR (%)	TVR (%)	PR (%)	TVR (%)	PR (%)	TVR (%)	PR (%)
Rash	Overall	–	–	44–49	35	41–60	20	17–35	24
	Severe	7	1	3–7	0	–	–	–	–
	Moderate	15	8	–	–	–	–	–	–
	Mild	37	32	–	–	–	–	–	–
Anemia		29–37	27	9–27	17	8–27	8	37–39	19
Nausea		56–65	29	31–48	40	24–48	34	40–43	31
Vomiting		18–24	12	–	–	–	–	–	–
Diarrhea		24–42	28	25–32	28	26–43	19	28–32	22
Pruritus		10–18	0	51–63	35	34–44	15	45–50	36
Asthenia		–	–	38–52	32	46–67	56	–	–
Discontinued treatment due to adverse event		21	11	12	7	9–26	4	–	–

<sup>†</sup>Data taken from [15].  
<sup>‡</sup>Data taken from [16].  
<sup>§</sup>Data taken from [17].  
<sup>¶</sup>Data taken from [18].  
 PR: Pegylated interferon and ribavirin; TVR: Telaprevir.

patients. This is achieved at the cost of a higher rate of adverse events and discontinuation than with standard therapy. It is an important additional therapy for the treatment of G1 HCV and should be considered for use in all patients.

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