Efficacy and safety of telaprevir in patients with genotype 1 hepatitis C infection

Morven Cunningham and Graham R. Foster

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Abstract: Chronic hepatitis C infection represents a significant and growing health problem worldwide. Patients with genotype 1 hepatitis C respond poorly to the current standard of care, pegylated interferon and ribavirin, which is frequently associated with unpleasant side effects. Consequently new agents with improved efficacy and tolerability are needed. The efficacy and safety of the direct-acting antiviral agent telaprevir in the treatment of genotype 1 hepatitis C infection have been demonstrated in a number of clinical trials. The addition of telaprevir to standard therapy considerably improves response rates and allows response-guided shortening of treatment duration in a substantial number of treatment-naïve patients. Side effects associated with telaprevir therapy include rash, anaemia, gastrointestinal disturbance and anorectal discomfort. Telaprevir-resistant variants have been identified in patients who have failed telaprevir-containing therapy, and whether selection of these variants will compromise future therapeutic options is currently unknown. The efficacy and safety of telaprevir in the treatment of the most challenging patients, including those with recurrent hepatitis C following liver transplantation and those co-infected with HIV, remains to be established.

Keywords: antiviral agents, hepatitis C, interferon α-2a, protease inhibitors, ribavirin

Introduction

Infection with the hepatitis C virus (HCV) represents a significant and growing global health problem, with an estimated 170 million individuals chronically infected worldwide [Marcellin, 2009]. Approximately 20–30% will progress to cirrhosis after 20 years [Alberti *et al*. 1999], and those with cirrhosis have a 3% risk of hepatocellular carcinoma and 4–5% risk of death or liver transplantation per annum [Alazawi *et al*. 2010].

HCV is classified into six genotypes, which differ by up to 30% at the nucleotide level [Simmonds *et al*. 1993]. Genotype 1 is the most common genotype in North America and Western Europe, and responds least well to present therapies. Treatment with weekly injections of pegylated interferon alpha (pegIFN) and twice-daily oral ribavirin for 48 weeks results in a sustained virological response (SVR; defined as undetectable HCV RNA 24 weeks after treatment, which probably equates to a cure) in less than 50% of patients infected with genotype 1 HCV [Fried *et al*. 2002; Hadziyannis *et al*. 2004; Manns *et al*. 2001]. This treatment is often poorly tolerated, with side effects including flu-like symptoms, fatigue, anaemia and mood disturbance. Response rates tend to be worst in patients who would benefit most from viral eradication such as those with cirrhosis [Veldt *et al*. 2007], or patients with HIV co-infection in whom HCV-related liver fibrosis progresses at a faster rate [Benhamou *et al*. 1999; Soto *et al*. 1997]. Clearly, more effective treatment strategies are required as a matter of urgency.

The drive to develop new therapies for chronic HCV infection has focused on the development of small molecules which directly inhibit viral replication (direct-acting antivirals [DAAs]) following the success of such strategies in the treatment of other chronic viral infections such as HIV and hepatitis B. A number of drugs targeting proteins essential

Correspondence to:
Graham R. Foster, FRCP, PhD
Professor of Hepatology, Queen Mary, University of London, Institute of Cell and Molecular Science, 4 Newark Street, London, E1 2AT, United Kingdom,
g.r.foster@qmul.ac.uk

Morven Cunningham, MBBS, MRCP
Queen Mary, University of London, Blizard Institute of Cell and Molecular Science, London, UK

Table 1. Summary of virological outcomes in the telaprevir phase I randomized-controlled trials. Where not otherwise stated, telaprevir was dosed at 750 mg 8-hourly after a 1250 mg loading dose. Pegylated interferon-α2a (PegIFN) and ribavirin were given at standard doses. SVR, sustained virological response; q8h, every 8 hours; q12h, every 12 hours.

Study	Patients	Duration of treatment	Dosing regimen (number of patients)	Median HCV reduction from baseline to end of treatment (log_{10} IU/mL)	Viral rebound/ breakthrough (% (number/total number of patients in group))
Reesink *et al*. [2006] and Sarrazin *et al*. [2007]	34 genotype 1 (7 treatment naïve)	14 days	Telaprevir 450 mg q8h (10) Telaprevir 750 mg q8h (8) Telaprevir 1125 mg q12h (10) Placebo (6)	–2.37 –4.41 –2.21 –0.21	60% (6/10) 13% (1/8) 40% (4/10)
Forestier *et al*. [2007] and Kieffer *et al*. [2007]	16 genotype 1; all treatment naive	14 days	Telaprevir (8) PegIFN/telaprevir (8) PegIFN/placebo (4)	–3.99 –5.49 –1.09	50% (4/8) 0% (0/8)
Lawitz *et al*. [2008]	12 genotype 1; all treatment naïve	28 days/ 44 weeks	PegIFN/ribavirin/ telaprevir for 28 days (12) Then pegIFN/ribavirin for 44 weeks	Undetectable HCV RNA at 28 days in 100% (12/12) SVR in 67% (8/12)	0% (0/12) 17% (2/12)

for viral replication are currently in clinical trials [Vermehren and Sarrazin, 2011]. Inhibitors of the viral NS3/4A serine protease, such as telaprevir and boceprevir, are at the most advanced stage of development. Both have recently been approved by the US Food and Drugs Administration and the European Medicines Agency for treatment of adults with chronic genotype 1 HCV infection.

NS3/4A serine protease inhibitors

Translation of the HCV open reading frame generates a polyprotein which is cleaved by cellular and viral proteases, yielding structural and non-structural (NS) viral proteins. The NS3/4A serine protease is required for self-cleavage during viral replication, but may also inhibit activation of interferon signalling pathways in infected cells [Morikawa *et al*. 2011]. Targeting this protease may therefore restore interferon responsiveness as well as inhibiting viral replication.

Ciluprevir, a macrocyclic noncovalent NS3/4A protease inhibitor, first demonstrated the clinical antiviral efficacy of NS3/4A protease inhibitors. Two days of dosing in patients with chronic genotype 1 HCV resulted in 2–3log_{10} decline in viral RNA. Cardiac toxicity in animals halted further development of ciluprevir, but proof of concept for the drug class was established [Hinrichsen *et al*. 2004].

Telaprevir is an orally bioavailable linear α-ketoamide NS3/4A inhibitor, which binds covalently but reversibly to the protease catalytic site. *In vitro*, using a cell line harbouring a subgenomic replicon based on a genotype 1b HCV strain, 14 days of treatment with telaprevir eliminated HCV RNA from the replicon cells with little cytotoxicity. Furthermore, an additive/ synergistic effect on RNA suppression was seen when the cells were treated with telaprevir and interferon in combination [Lin *et al*. 2006]. Similar results were obtained using a modified genotype 1a replicon [Perni *et al*. 2006].

Early clinical studies conducted in patients with chronic genotype 1 HCV confirmed the *in vivo* efficacy of telaprevir, and identified 750 mg 8-hourly as the optimum dosing regimen (Table 1). However, telaprevir monotherapy is associated with frequent virological breakthrough due to the emergence of telaprevir-resistant viral variants. The addition of interferon led to greater reductions in viral RNA during the dosing period than telaprevir alone, or placebo, and suppressed emergence of telaprevir-resistant variants [Forestier *et al*. 2007; Kieffer *et al*. 2007].

The observation that dual therapy with telaprevir and interferon reduced the emergence of telaprevir-resistant viral variants and enhanced virological decline raised the question of whether ribavirin could be omitted from the treatment regimen without adversely affecting SVR. This question was addressed in the PROVE 2 and PROVE 3 phase II clinical trials, which included ribavirin-free treatment arms [Hezode *et al*. 2009;

Table 2. Efficacy outcomes of the telaprevir phase II randomized-controlled trials in treatment-naïve patients with genotype 1 HCV. In each trial, patients were randomized to one of the featured treatment regimens: telaprevir for 12 weeks with pegylated interferon-α2a (pegIFN) and ribavirin for 12 weeks (T12PR12); 12 weeks of telaprevir with 24 weeks of pegIFN and ribavirin (T12PR24); 12 weeks of telaprevir with 48 weeks of pegIFN and ribavirin (T12PR48); 12 weeks of telaprevir with 12 weeks of pegIFN (T12P12); or 12 weeks of placebo with 48 weeks of pegIFN and ribavirin (the control group, PR48). Telaprevir was dosed at 750 mg 8-hourly after a 1250 mg loading dose. PegIFN and ribavirin were given at standard doses. Breakthrough refers to an increase of >1 $\log_{10}$ unit from nadir or >100 IU/mL of previously undetectable HCV RNA during treatment; relapse refers to undetectable HCV RNA at the end of treatment but detectable during 24 weeks of follow up. SVR, sustained virological response.

Study	Number of participants	Duration of treatment	Treatment regimen (number of patients)	SVR	Relapse	Breakthrough
PROVE 1 [McHutchison *et al*. 2009]	250	12–48 weeks	T12PR12 (17) T12PR24 (79) T12PR48 (79) PR48 (75)	35% 61% 67% 41%	33% 2% 6% 23%	7% of all telaprevir-treated patients
PROVE 2 [Hezode *et al*. 2009]	334	12–48 weeks	T12PR12 (82) T12PR24 (81) T12P12 (78) PR48 (82)	60% 69% 36% 46%	30% 14% 48% 22%	1% 5% 24% 1%

McHutchison *et al*. 2009]. These trials clearly demonstrated that ribavirin remains necessary to maintain virological response in both treatment-naïve and treatment-experienced patients (Table 2 and Figure 1). For the time being at least, telaprevir must be given in combination with both interferon and ribavirin.

Telaprevir for treatment-naïve patients

Following the demonstration of the antiviral efficacy of telaprevir in phase I trials, further studies were conducted to evaluate its efficacy and safety in larger groups of patients. These studies also addressed a number of issues regarding optimization of telaprevir-containing treatment.

An important question in the treatment of patients with genotype 1 HCV is whether the addition of novel therapies will permit shorter treatment duration. In patients receiving pegIFN and ribavirin therapy, retrospective studies suggest that those with no evidence of detectable virus after 4 weeks of treatment (i.e. those who have achieved a rapid virological response [RVR]) can be successfully treated with 24 weeks of therapy, as compared with the standard 48 weeks of treatment. However, less than 10% of treated patients usually achieve a RVR. In contrast, a large proportion of patients receiving telaprevir achieve a RVR.

The PROVE 1 and PROVE 2 phase II trials evaluated the efficacy and safety of varying lengths of pegIFN and ribavirin therapy in combination with 12 weeks of telaprevir in treatment-naïve patients with genotype 1 HCV [Hezode *et al*. 2009; McHutchison *et al*. 2009]. These trials confirmed that addition of telaprevir for 12 weeks significantly improves SVR rates and indicated that total treatment duration can be reduced to 24 weeks with no adverse impact on SVR, although further reduction to 12 weeks was associated with increased posttreatment virological relapse (Table 2).

The ADVANCE phase III trial evaluated the efficacy of a shorter duration of telaprevir therapy (8 weeks *versus* 12 weeks) and considered whether total treatment duration could be individually tailored according to viral response [Jacobson *et al*. 2011b]. Patients who achieved an extended rapid virological response (eRVR; defined as undetectable virus at week 4, sustained through to week 12) stopped pegIFN and ribavirin treatment after 24 weeks, whilst those who did not continued to 48 weeks (Table 3). Thus, 12 weeks of telaprevir treatment appeared superior to 8 weeks, with slightly lower rates of on-treatment virological failure. A substantial number of participants (58%) achieved an eRVR and were eligible for shortened treatment. The ILLUMINATE study investigated the noninferiority of 24 weeks *versus* 48 weeks total therapy in patients with an eRVR [Sherman *et al*. 2011]. Almost two thirds of participants were eligible for shortened treatment, and there was no efficacy benefit to extending treatment beyond 24 weeks for these patients

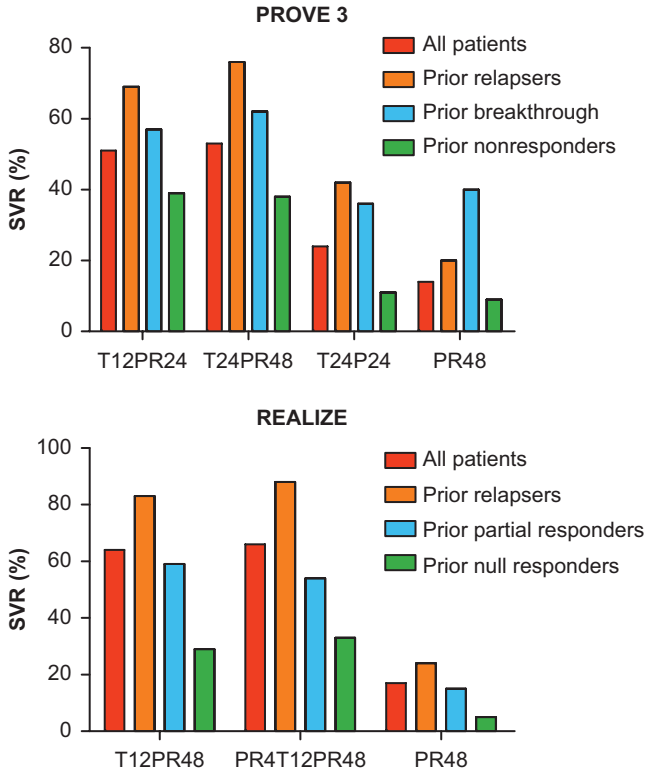

Figure 1. Efficacy outcomes overall and according to prior treatment response in the PROVE 3 and REALIZE trials of telaprevir in treatment-experienced patients with chronic genotype 1 HCV. Participants in PROVE 3 were randomized to receive: 12 weeks of telaprevir with 24 weeks of pegylated interferon-α2a (pegIFN) and ribavirin (T12PR24); 24 weeks of telaprevir with 48 weeks of pegIFN and ribavirin (T24PR48); 24 weeks of telaprevir and pegIFN (T24P24); or 48 weeks of pegIFN and ribavirin (PR48, control group). In REALIZE, participants were randomized to receive: 12 weeks of telaprevir with 48 weeks of pegIFN and ribavirin (T12PR48); a 4-week pegIFN and ribavirin lead-in, followed by 12 weeks of telaprevir with 48 weeks of pegIFN and ribavirin (PR4T12PR48); or 48 weeks of pegIFN and ribavirin (control group, PR48). SVR, sustained virological response.

(Table 3). Importantly, a considerable number of patients who were not eligible for shortened treatment duration in these trials still achieved SVR following 48 weeks of therapy (Table 3). Thus, eRVR may be useful to guide duration of therapy, but not to predict treatment outcome, as a substantial proportion of patients given telaprevir who do not have an eRVR will still achieve SVR if pegIFN and ribavirin treatment is extended to 48 weeks.

These large clinical trials have all evaluated telaprevir at a dose of 750 mg 8-hourly, in combination with ribavirin and pegylated interferon alpha-2a (pegIFN2a). Less frequent telaprevir dosing may lead to fewer missed doses and improved compliance with therapy. Furthermore, a recent meta-analysis showed a small increase in SVR in patients receiving pegIFN2a compared with pegylated interferon alpha-2b (pegIFN2b) [Awad *et al*. 2010], and so the benefits of telaprevir may differ with different pegylated interferons. To address these issues a small open-label phase II study compared 750 mg telaprevir 8-hourly with 1125 mg 12-hourly, in combination with ribavirin and either pegIFN2a or pegIFN2b [Marcellin *et al*. 2011]. SVR rates were similar between the pooled telaprevir dosing arms, and between the pooled pegIFN2a and pegIFN2b arms. The OPTIMIZE phase III study is currently underway to investigate the noninferiority of dosing telaprevir at 1125 mg 12-hourly, compared with 750 mg 8-hourly, and results are expected in 2012.

Thus, the addition of 12 weeks of telaprevir to pegIFN and ribavirin therapy substantially improves outcomes in treatment-naïve patients with genotype 1 HCV. Total treatment duration can be shortened to 24 weeks in those who achieve a satisfactory virological response, but good results can still be obtained with 48 weeks of treatment in those who do not. PegIFN and ribavirin are both

Table 3. Efficacy outcomes of the phase III telaprevir randomized-clinical trials in treatment-naïve patients with genotype 1 HCV. Patients in ADVANCE were randomized to 8 weeks of telaprevir with pegylated interferon-α2a (pegIFN) and ribavirin (T8PR); 12 weeks of telaprevir with pegIFN and ribavirin (T12PR); or 12 weeks of telaprevir-matched placebo with 48 weeks of pegIFN and ribavirin (control group, PR). Duration of pegIFN and ribavirin treatment in the telaprevir groups was allocated according to virological response; patients with undetectable HCV RNA at weeks 4 and 12 (extended rapid virological response [eRVR]) received 24 weeks of treatment, whilst patients who did not achieve eRVR received 48 weeks of treatment. All patients in the control group received 48 weeks of treatment, regardless of eRVR. All patients in ILLUMINATE received 12 weeks of telaprevir with 20 weeks of pegIFN and ribavirin. Patients with an eRVR were then randomized to 4 or 28 further weeks of pegIFN and ribavirin (T12PR24 group or T12PR48 (eRVR) group). Patients without an eRVR received 48 weeks of treatment (T12PR48 (no eRVR) group). SVR, sustained virological response.

Study	Number of participants	Treatment duration	Treatment regimen (number of patients)	SVR (% (number of patients/ number in group))
ADVANCE [Jacobson *et al.* 2010]	1088	24–48 weeks	T8PR (364)	Overall: 69% (250/364) T8PR24: 83% (171/207) T8PR48: 50% (79/157)
			T12PR (363)	Overall: 75% (271/363) T12PR24: 89% (189/212) T12PR48: 54% (82/151)
			PR (361)	Overall: 44% (158/361) eRVR: 97% (28/29) no eRVR: 39% (130/332)
ILLUMINATE [Sherman *et al.* 2011]	540	24–48 weeks	T12PR24 (eRVR) (162) T12PR48 (eRVR) (160) T12PR48 (no eRVR) (118)	92% (149/162) 88% (140/160) 64% (76/118)

required in combination with telaprevir to maintain an adequate virological response. It is likely that pegIFN2b can be used instead of pegIFN2a with equivalent outcomes. Twice-daily telaprevir dosing may also be possible, although further results in support of this are awaited.

Telaprevir for treatment-experienced patients

A significant proportion of patients treated with pegIFN and ribavirin fail to achieve SVR. The most common mode of treatment failure in genotype 1 infection is null response, where patients fail to achieve an EVR (defined as $>2\log_{10}$ decline in viral RNA at week 12 of therapy). Other patients relapse, where the virus is undetectable at the end of treatment but returns after cessation of therapy. A minority of patients show a partial response, where EVR criteria are met at 12 weeks but the virus never becomes undetectable, or virological breakthrough, where viral RNA is undetectable during treatment but becomes detectable again before the end of treatment. Retreatment of these patients with a further course of pegIFN and ribavirin is usually poorly effective. Retreatment with prolonged courses or increased doses of pegIFN and ribavirin can be effective in patients who have previously relapsed, but may be limited by patient tolerance and adverse events. Response rates in previous nonresponders to pegIFN and ribavirin remain low [Singal *et al.* 2010]. Development of new therapies for these patients is a priority to prevent progressive HCV-related liver disease.

The efficacy of telaprevir for patients who have previously failed pegIFN and ribavirin therapy was assessed in the phase II study PROVE 3 [McHutchison *et al.* 2010]. Patients with previous nonresponse (defined as undetectable HCV RNA levels never achieved during or at the end of previous treatment), relapse (undetectable HCV RNA for at least 42 weeks during previous treatment, but detectable HCV RNA during follow up with lack of SVR) or breakthrough (undetectable HCV RNA during previous treatment, but detectable levels before the end of the treatment period) were enrolled. Randomization was stratified according to previous achievement of negative HCV RNA. Whilst the addition of telaprevir clearly augmented SVR rates in all patients, regardless of prior treatment outcome, response rates were higher among previous relapsers than patients with a previous breakthrough or nonresponse (Figure 1).

REALIZE was a phase III study designed to evaluate efficacy, safety and tolerability of telaprevir in combination with pegIFN and ribavirin in patients with prior nonresponse or relapse after pegIFN

and ribavirin therapy [Zeuzem *et al.* 2011a]. Nonresponse was divided into null response (failure to achieve at least a 2 $\log_{10}$ decline in viral RNA by week 12) and partial response (achievement of 2 $\log_{10}$ decline by week 12, but viral RNA never undetectable). The study also explored the efficacy of a 4-week pegIFN and ribavirin lead-in phase. As in PROVE 3, the addition of telaprevir to therapy-enhanced treatment response in all groups, regardless of previous treatment outcome. Again, the best response rates were seen in patients with previous relapse (Figure 1).

The addition of a 4-week lead-in phase did not increase SVR rates, but it may help predict SVR by indicating a patient's interferon responsiveness. A patient who is poorly interferon responsive may be less able to suppress the emergence of telaprevir-resistant viral variants, leading to virological breakthrough on telaprevir therapy. A subanalysis of the REALIZE study compared virological response after the 4-week pegIFN and ribavirin lead-in with previous treatment response and SVR in response to telaprevir-containing treatment [Foster *et al.* 2011b]. A cut-off of <1 $\log_{10}$ or ≥1 $\log_{10}$ RNA decline was used to define response at the end of the 4-week lead-in. Overall, patients who achieved ≥1 $\log_{10}$ decline in viral load by the end of the lead-in achieved better SVR rates than those who did not. Those with <1 $\log_{10}$ decline who then received telaprevir achieved SVR rates considerably higher than those in the control arm (15–62%, depending on previous treatment response, *versus* 0% of controls). Patients with previous relapse or partial response to therapy who responded poorly to the lead-in phase still achieved SVR rates of 56–62% with subsequent telaprevir-containing therapy, and so the lead-in phase adds little useful information to guide treatment for these patients. Amongst prior null responders, only 15% with <1 $\log_{10}$ decline in viral RNA after the lead-in achieved SVR with subsequent telaprevir-containing therapy, compared with 54% of those who showed a good virological response to the lead-in.

Thus, the addition of 12 weeks of telaprevir to 48 weeks of pegIFN and ribavirin substantially improves SVR rates for patients with genotype 1 HCV who have previously failed a course of pegIFN and ribavirin therapy. Response to a lead-in phase is not a substitute for detailed knowledge of previous response to pegIFN and ribavirin, and adds little useful information to guide management of patients with prior relapse or partial response. It may help guide the management of patients with a well-documented previous null response to pegIFN and ribavirin, where poor response to a lead-in is associated with low rates of SVR following telaprevir-containing therapy.

Telaprevir for 'difficult to treat' patients

A number of factors have been identified which confer a lower likelihood of SVR in response to pegIFN and ribavirin therapy, including ethnicity, advanced fibrosis/cirrhosis, and IL28B genotype. The efficacy of telaprevir in these individuals is of particular interest.

Few patients with advanced fibrosis/cirrhosis have been included in clinical trials to date. ADVANCE appeared to show a benefit of telaprevir in treatment-naïve patients with bridging fibrosis/cirrhosis (SVR 53–62% in telaprevir-containing groups *versus* 33% in controls), although the SVR rates were lower than in patients with no/mild/portal fibrosis (SVR 73–78% in telaprevir-containing groups *versus* 47% in controls) [Jacobson *et al.* 2011b]. Regarding treatment-experienced patients, 25% of those recruited to REALIZE had biopsy-proven cirrhosis. Telaprevir improved SVR considerably in prior relapsers regardless of fibrosis stage (mild fibrosis, SVR 86% in pooled telaprevir groups *versus* 32% in controls; cirrhosis, SVR 84% in pooled telaprevir groups *versus* 13% in controls). Prior null responders with cirrhosis saw less benefit (mild fibrosis, SVR 41% in pooled telaprevir groups *versus* 6% in controls; cirrhosis, SVR 14% in pooled telaprevir groups *versus* 10% in controls) [Zeuzem *et al.* 2011a].

The impact of ethnicity (Black/African American *versus* non-Black/African American) was examined in a retrospective pooled analysis of the ADVANCE and ILLUMINATE studies [Dusheiko *et al.* 2011]. The number of Black/African American participants was small (11%). Telaprevir appeared to increase SVR in treatment-naïve Black/African American patients (61% in pooled telaprevir groups *versus* 25% of controls) although the SVR rates remained lower than in other ethnic groups (75% in pooled telaprevir groups *versus* 45% of controls).

IL28B genotype has been identified as a predictor of treatment outcome in genotype 1 hepatitis C infection [Ge *et al.* 2009; Tanaka *et al.* 2009]. The presence of the poor-risk genotype may account

for up to half of the difference in treatment response seen between Black and non-Black patients [Ge *et al.* 2009]. A subanalysis of ADVANCE indicated that amongst treatment-naïve Caucasian patients, telaprevir improved outcomes regardless of IL28B genotype, although the best outcomes were seen in those without the poor-risk T allele (SVR 90% in CC patients receiving 12 weeks of telaprevir with response-guided pegIFN and ribavirin (T12PR) and 64% in CC patients in control arm, compared with 73% in TT patients receiving T12PR and 23% in TT patients in control arm). The highest rates of RVR and eRVR were seen in CC patients [Jacobson *et al.* 2011a]. A retrospective analysis of REALIZE examined SVR according to previous treatment response and IL28B genotype [Pol *et al.* 2011]. Whilst the population included in this analysis was representative of the overall REALIZE population, the vast majority of participants were Caucasian (94%). Again, telaprevir improved SVR rates regardless of IL28 genotype, with the best rates in those without the T allele. However, poorer responses were seen in prior null responders than in prior relapsers, regardless of IL28B genotype. Thus, in both treatment-naïve and treatment-experienced Caucasian patients, telaprevir improves outcomes across all IL28B genotypes. Treatment-naïve patients with the CC genotype are more likely to achieve eRVR and be eligible for a shortened duration of treatment. Amongst treatment-experienced patients, previous treatment response is a far better predictor of outcome of telaprevir-containing therapy than IL28B genotype.

Resistance

Drugs directly targeting viral enzymes are inherently susceptible to mutations of the target site, leading to reduced drug efficacy. The HCV RNA-dependent RNA polymerase (RdRp) has no proof-reading capacity, and errors generated during rapid viral replication lead to emergence of circulating viral quasispecies within an individual. Most viral mutations lead to defective virus or virus with reduced replicative fitness, so exist in very low proportions relative to the dominant, or wild-type, virus. However, in the presence of a protease inhibitor or other direct-acting antiviral agent, variants with mutations conferring reduced susceptibility will have a selective advantage and emerge as the wild-type virus is suppressed. In this environment, further mutations may accumulate which improve viral fitness [Pawlotsky, 2011]. Pre-existing viral variants with NS3/4A mutations conferring resistance to telaprevir have been identified in the serum of 2% of naïve patients [Bartels *et al.* 2008], although the sequencing techniques used may not have been sufficiently sensitive to detect pre-existing variants present at very low levels [Verbinnen *et al.* 2010].

Protease inhibitors have a low genetic barrier to resistance, meaning that a single amino acid substitution within the target site is sufficient to confer significant drug resistance. Telaprevir monotherapy is frequently complicated by the rapid emergence of viral variants harbouring resistant mutations, suggesting selection of pre-existing viral variants [Kieffer *et al.* 2007]. A number of mutations conferring varying degrees of telaprevir resistance have been identified *in vivo* and characterized by *in vitro* assessment, particularly at positions 36, 54, 155 and 156 of the NS3 protease catalytic domain [Sarrazin *et al.* 2007]. Virological breakthrough or plateau in patients treated with telaprevir monotherapy for 14 days was associated with the emergence of viral strains harbouring mutations at these positions [Kieffer *et al.* 2007; Sarrazin *et al.* 2007]. Amino acid mutations T54A, V36A/M, R155K/T and A156S were associated with low-level resistance to telaprevir in the replicon model, whilst A156T/V and double mutations V36M+R155K and V36M+A156T conferred high-level resistance [Sarrazin *et al.* 2007]. Mutations V36M and R155K/T have only been detected in genotype 1a isolates, presumably because only one nucleotide change is required to generate these amino acid substitutions in genotype 1a viral genomes. Differences in the nucleotide composition between subtypes 1a and 1b mean that two nucleotide changes are required to generate the same amino acid substitutions in genotype 1b strains, providing a higher genetic barrier to the development of these particular resistant variants.

The addition of interferon to telaprevir reduced the emergence of resistant mutations both *in vitro* in the replicon model and *in vivo* [Kieffer *et al.* 2007; Lin *et al.* 2006]. Furthermore, patients with telaprevir-resistant viral variants following telaprevir monotherapy who then received pegIFN/ribavirin demonstrated a continued decline in viral RNA, indicating that these variants remain sensitive to pegIFN and ribavirin *in vivo* [Kieffer *et al.* 2007].

Amongst treatment-experienced patients receiving telaprevir, the highest rates of on-treatment

virological breakthrough were seen in those with a previous null response to pegIFN and ribavirin therapy [McHutchison *et al*. 2010; Zeuzem *et al*. 2011a]. Breakthrough was seen more commonly in genotype 1a than genotype 1b infection [McHutchison *et al*. 2010]. A subanalysis of REALIZE according to previous treatment response and genotype 1 subtype indicated there was no difference in SVR rates between genotype 1a and genotype 1b in previous relapsers receiving a telaprevir-containing regimen (84% *versus* 88%), but a trend for lower SVR rates in genotype 1a patients with a previous partial or null response than genotype 1b (47% *versus* 68% for prior partial responders; 27% *versus* 37% for prior null responders) [Zeuzem *et al*. 2011a]. These data may indicate that in previous nonresponders to pegIFN and ribavirin, telaprevir-resistant mutations may play a significant role in determining treatment outcome, with patients who have pre-existing mutations (or the potential for their early development) responding less well to combination therapy. This is supported by a deep sequencing study in a small series of patients in which pre-existing resistance mutations played a role in treatment outcome only in patients who had failed to respond to a previous course of pegIFN and ribavirin therapy [De Meyer *et al*. 2011].

The potential for selection of resistant variants in patients who fail telaprevir-containing therapy poses a worrying dilemma. Cross-resistance between NS3/4A protease inhibitors has been described, and persistence of selected protease-resistant variants could preclude future treatment with other agents in this class [Pawlotsky, 2011].

In general, the degree of telaprevir resistance conferred by an amino acid mutation is inversely proportional to replicative fitness of the variant. Follow-up of patients with resistant mutations after the telaprevir dosing period showed decline of resistant variants over three to seven months, replaced by the fitter wild-type virus [Sarrazin *et al*. 2007]. A sub-analysis of the ADVANCE, ILLUMINATE and REALIZE trials found that 84% of genotype 1a and 54% of genotype 1b patients who failed to achieve SVR harboured a resistant variant. Follow-up viral sequencing after treatment found it took a median of 10 months for genotype 1a patients and 0.8 months for genotype 1b patients to revert fully to wild type. Kaplan–Meier estimates of loss predicted that 98% of genotype 1b patients would revert to wild type by month 12 and 94% of genotype 1a would revert to wild type by month 16 posttelaprevir [Sullivan *et al*. 2011]. However, the population sequencing techniques used lack the sensitivity of more sophisticated deep sequencing technologies, and more detailed information on the dynamics of resistant viral strains awaits studies using these more sensitive techniques [Pawlotsky, 2011]. Whether previous exposure to telaprevir and selection of viral variants that decline with time will compromise future therapeutic options for these patients is not yet known.

Safety and tolerability

Over 2,500 individuals have now received telaprevir as part of an extensive programme of clinical trials. The most significant adverse reactions have been rash, pruritis (together with and independent of rash) and anaemia. Diarrhea, fatigue and anorectal discomfort have also been reported. Between 12% and 21% of patients receiving telaprevir discontinued treatment due to adverse events in the earlier trials, compared with 4–11% of controls [Hezode *et al*. 2009; McHutchison *et al*. 2009; McHutchison *et al*. 2010]. Later protocols incorporated a strategy of early interventions to minimize adverse events, particularly rash and anaemia. This reduced discontinuation of all medications to 4–8% of those receiving telaprevir [Jacobson *et al*. 2011b; Marcellin *et al*. 2011; Zeuzem *et al*. 2011a].

Rash is the most notable adverse event. It has been described as maculopapular or eczematous, usually appearing within the first month of telaprevir and resolving on telaprevir withdrawal. Incidence of rash appears similar amongst treatment-naïve and treatment-experienced patients, with rash of any severity reported in 36–60% of patients in telaprevir-treated groups, compared with 19–41% of controls [Hezode *et al*. 2009; Jacobson *et al*. 2011b; McHutchison *et al*. 2009; McHutchison *et al*. 2010; Zeuzem *et al*. 2011a]. The majority of rashes were classified as grade 1–2 in severity and were managed with antipruritic and anti-allergic agents at the investigators' discretion. Across all trials 3–7% of patients in telaprevir arms developed a severe (grade 3) rash, compared with 0–1% of controls [Hezode *et al*. 2009; Jacobson *et al*. 2011b; McHutchison *et al*. 2009, 2010; Zeuzem *et al*. 2011a]. Treatment of a grade 3 rash with early discontinuation of therapy and administration of potent topical steroids is essential as a handful of patients have developed rapidly progressive skin lesions with systemic

symptoms and both Stevens–Johnson and DRESS syndromes have been reported. ADVANCE adopted a protocol of drug withdrawal for moderate and severe rash, whereby telaprevir was stopped first, followed by ribavirin if necessary after 7 days, and finally pegIFN. This resulted in telaprevir discontinuation due to rash in 5–7%, but reduced discontinuation of all medications due to rash to 0.5–1.4% of those in a telaprevir arm [Jacobson *et al.* 2011b].

Anaemia is a recognized side effect of ribavirin treatment, usually managed with dose reduction. Erythropoeitin (EPO) is sometimes used as an adjunct to allow maintenance of ribavirin dosing, as SVR rates are known to be adversely affected if less than 80% of the prescribed pegIFN and ribavirin therapy is taken for less than 80% of the duration of treatment [McHutchison *et al.* 2002]. The telaprevir phase II and III clinical trials did not permit use of EPO during the telaprevir dosing period and anaemia was managed by ribavirin dose reduction alone.

Addition of telaprevir to pegIFN and ribavirin therapy appears to increase the frequency and severity of anaemia. Patients in PROVE 1 receiving telaprevir experienced a 0.5 to 1 g/dl greater decline in haemoglobin than controls [McHutchison *et al.* 2009]. Amongst patients receiving telaprevir in ADVANCE, anaemia was more common than in controls (Hb <10 in 36–40% *versus* 14%; Hb <8.5 in 9% *versus* 2%) [Jacobson *et al.* 2011b]. A total of 2–4% of patients in the telaprevir arms discontinued telaprevir due to anaemia, and 1–3% of those receiving telaprevir and 1% of controls discontinued all medications. Similar results were seen in treatment-experienced patients, with anaemia of any severity reported in 26–36% of those receiving telaprevir, compared with 8–15% of controls [McHutchison *et al.* 2010; Zeuzem *et al.* 2011a]. Following the telaprevir dosing period, haemoglobin levels in telaprevir-treated patients returned to levels similar to controls. Thus, the increased severity of the anaemia is transient and rapidly reverses when telaprevir is discontinued after 12 weeks of exposure.

As reduction in ribavirin dosing can adversely affect SVR, management of anaemia by ribavirin dose reduction may have compromised SVR rates in these trials. To address this, a retrospective pooled analysis of ADVANCE and ILLUMINATE investigated efficacy outcomes based on anaemia and ribavirin dose reductions [Sulkowski *et al.* 2011b]. Amongst patients receiving 12 weeks of telaprevir with 24 or 48 weeks of pegIFN/ribavirin there was no difference in SVR rates between those with investigator-reported anaemia and those without, or between those with ribavirin dose reductions and those without. Thus, management of anaemia by ribavirin dose reduction did not appear to compromise treatment efficacy in these trials. As to whether use of EPO might enhance SVR rates, a phase II study which permitted EPO use found no difference in SVR rates according to concomitant EPO [Marcellin *et al.* 2011]. However, this was a relatively small study and no pegIFN and ribavirin control arm was included for comparison.

In addition to gastrointestinal side effects such as nausea and diarrhea, a spectrum of anorectal disorders have been reported, including haemorrhoids, anal pruritis and proctalgia. These can be significant, for example affecting up to 28% of participants in REALIZE, and causing two patients to stop telaprevir alone and three patients to withdraw from all medications in this study [Zeuzem *et al.* 2011b].

Development of optimal management strategies for these adverse events will require further experience with telaprevir as well as close collaboration with colleagues in other disciplines. In the event of a severe adverse reaction to treatment, stepwise discontinuation of medication starting with telaprevir appears a safe strategy that may avoid the need for total discontinuation of therapy, maximizing the chance of SVR as far as possible.

Future challenges

A significant proportion of patients with HCV who present particular challenges to treatment are not represented in the current clinical trials, including patients co-infected with HIV and patients with recurrent HCV following liver transplantation. These patients have a poorer response to pegIFN and ribavirin therapy and generally faster progression of liver disease.

An interim analysis of a small phase II trial of telaprevir for treatment-naïve patients co-infected with genotype 1 HCV and HIV found considerably higher rates of RVR in patients receiving telaprevir (70% compared with 5% in those receiving pegIFN and ribavirin alone) [Sulkowski

et al. 2011a]. The full results of this study are eagerly awaited to see if this translates to improved SVR rates for these patients. A trial of telaprevir for treatment-experienced genotype 1 HCV patients co-infected with HIV is also currently underway.

A major challenge for telaprevir use in patients with HIV co-infection is the potential for drug–drug interactions. Telaprevir is a substrate and inhibitor of CYP3A, leading to significant interactions with protease inhibitors and nonnucleotide reverse transcriptase inhibitors used in the treatment of HIV. At present, this limits use of telaprevir to patients either not requiring antiretroviral therapy, or stably maintained on a limited number of treatment regimens with tested interactions with telaprevir (such as efavirenz, tenofovir and emtricitabine, or ritonavir-boosted atazanavir, tenofovir and emtricitabine or lamivudine) [Sulkowski *et al*. 2011a].

Drug interactions with immunosuppressant medications will also complicate the use of telaprevir in patients posttransplant. In healthy volunteers, co-administration of telaprevir substantially increased blood concentrations of both tacrolimus and ciclosporin [Garg *et al*. 2011]. No studies have yet been performed in organ transplant recipients, or with other commonly used immunosuppressants, so whether dose adjustment is required to allow safe co-administration with telaprevir is currently unknown.

Although telaprevir clearly enhances response to treatment in genotype 1 HCV infection, its role in treatment of other viral genotypes is not clear. Interestingly, telaprevir appears to have equivalent antiviral efficacy in treatment-naïve patients with genotype 2 infection as genotype 1, but very limited efficacy in patients with genotype 3 infection [Foster *et al*. 2011a]. Whether telaprevir will play a role in shortening treatment duration for patients with genotype 2 infection, in retreatment of genotype 2 patients who have failed previous pegIFN and ribavirin therapy, or in treatment of genotype 4 infection remains to be established.

Conclusions

The recent approval of telaprevir for treatment of chronic HCV infection is an exciting development. Although resistant viral variants emerge rapidly when telaprevir is used alone, in combination with pegIFN and ribavirin substantial increases in SVR are seen in both treatment-naïve and treatment-experienced patients. This benefit extends to those patients usually thought of as difficult to treat. The addition of telaprevir may allow shortening of treatment duration in treatment-naïve patients who show an early and sustained virological response. Knowledge of previous treatment response is important when considering telaprevir for treatment-experienced patients, as those with prior relapse have a greater chance of achieving SVR than prior null responders. A short lead-in phase of pegIFN and ribavirin could be considered for previous null responders, to estimate the likelihood of achieving SVR before commencing telaprevir-containing therapy. The efficacy and safety of telaprevir has yet to be established in some subgroups of patients who would greatly benefit from viral eradication but who respond poorly to pegIFN and ribavirin therapy, such as those co-infected with HIV or patients with recurrence of HCV infection following liver transplantation.

Telaprevir is generally well tolerated, but significant side effects include rash, pruritis, anaemia and gastrointestinal disturbance. A strategy of sequential discontinuation of therapy, starting with telaprevir, may permit management of a severe adverse event whilst maximizing SVR rates. As experience of using telaprevir grows, local multidisciplinary strategies for the management of adverse events will need to be developed.

In the majority of patients who do not achieve SVR following telaprevir-containing treatment, viral variants conferring telaprevir resistance can be detected. Although these variants are gradually replaced by wild-type virus over months following treatment, the implications of these variants on future treatment with telaprevir or other protease inhibitors is currently unknown. Successful treatment of these patients may await the development of further novel antiviral agents.

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