

REVIEW

## Telaprevir: An Emerging Protease Inhibitor for the Treatment of Hepatitis C

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**Abstract:** Current standard anti-HCV therapy with peginterferon/ribavirin is effective in only half of the patients and limited by side-effects that often necessitate discontinuation. Therefore, new treatments are being developed including specifically targeted antiviral therapy for HCV (STAT-C). Clinical development is most advanced for telaprevir, a HCV NS3/4A protease inhibitor. Phase 1 trials demonstrated potent antiviral effect but rapid emergence of resistance mutations which could be controlled by simultaneous administration of peginterferon. Phase 2 clinical trials (the PROVE trials) demonstrated superior efficacy of a telaprevir-based triple combination regimen for 24 weeks as compared to standard of care at an acceptable safety profile in chronic HCV genotype 1 infection both in the treatment-naïve (SVR 65% vs. 44%) and treatment-experienced (SVR 51% vs. 14%) setting. Phase 3 trials are currently ongoing in treatment-naïve as well as treatment-experienced HCV genotype 1 patients and SVR data are expected for the second half of 2010.

**Keywords:** specifically targeted antiviral therapy for HCV (STAT-C), protease inhibitors, resistance mutations, peginterferon, ribavirin

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*Clinical Medicine Reviews in Therapeutics* 2010:2 31–40

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## Introduction

The global burden of hepatitis C virus (HCV) infection is estimated at 2.2%–3.0% of the world's population.<sup>1</sup> In developed countries, chronic hepatitis C is the leading cause for cirrhosis, hepatocellular carcinoma, and liver transplantation.<sup>2</sup> Following infection with HCV, the rate of chronicity varies from 55% to 85%. Sequelae of chronic HCV infection include cirrhosis (10%–20% after approximately 20 years) and hepatocellular carcinoma complicating cirrhosis (approximately 3% per year).<sup>3</sup>

Antiviral treatment of chronic HCV infection has been improved considerably since the introduction of interferon- $\alpha$  treatment of chronic non-A-non-B hepatitis in 1986.<sup>4</sup> Current peginterferon/ribavirin treatment provides a cure rate of approximately 20%–90%, depending on HCV genotype,<sup>5–8</sup> viral interferon sensitivity<sup>9</sup> and host factors such as age, gender, race<sup>10</sup> or genetic diversity.<sup>11,12</sup> Besides its limited efficacy, peginterferon/ribavirin treatment is associated with significant side effects that frequently necessitate its discontinuation. Treatments with higher efficacy and/or better tolerability are therefore needed.

Elucidation of the HCV genome has enabled the identification of new targets and approaches for anti-HCV drugs. The availability of a sub-genomic replicon system and, more recently, of a full-length HCV genome that replicates and produces infectious viral particles now facilitates screening of candidate drugs.<sup>13–15</sup> Consequently, many new antiviral compounds have been synthesized, some of which have entered the stage of clinical trials. This review is focused on telaprevir, the first HCV-specific protease inhibitor that has entered the stage of phase 3 clinical trials.

## Specifically Targeted Antiviral Therapy for HCV (STAT-C)

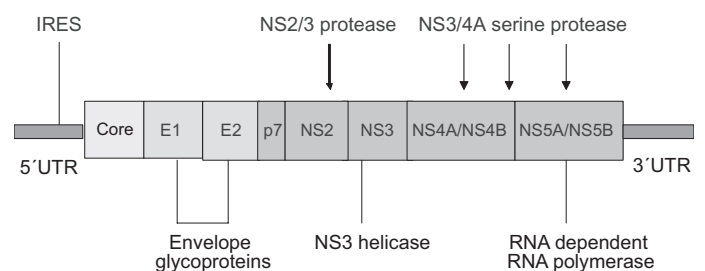
HCV, a member of the Flaviviridae family, contains a single-stranded RNA of about 9600 nucleotides encoding a precursor polypeptide of approximately 3000 amino acids. The 5' untranslated region contains an internal ribosome entry site (IRES) that initiates translation of the polypeptide by host enzymes which is subsequently processed by host and viral proteases into 10 proteins, including structural (C, E1, E2, p7) and non-structural (NS2, NS3, NS4A, NS4B, NS5A, NS5B) proteins (Fig. 1).<sup>15</sup> Nonstructural proteins essential for viral replication and maturation include the protease enzymes (NS2 and the N-terminal domain of NS3), the helicase/ATPase (C-terminal domain of NS3) and a RNA-dependent RNA polymerase (NS5B).<sup>16,17</sup>

Several potential targets have been identified for HCV-specific antiviral drugs, including IRES, E1/E2, p7, NS2, NS3, NS5A, and NS5B<sup>18,19</sup> and many orally administered small-molecule inhibitors of these targets are being developed including protease inhibitors and nucleoside and non-nucleoside polymerase inhibitors.<sup>20–24</sup> At present, development is most advanced for NS3/4A protease inhibitors.<sup>25</sup>

## NS3/4A Protease Inhibitors

The HCV NS3 serine protease is a heterodimeric enzyme requiring NS4A as a cofactor for optimal catalytic function. The NS3/4A complex cleaves four out of five junctions between the nonstructural protein regions along the HCV polyprotein. This enzyme is also involved in silencing the signalling of interferon production by the host by blocking the phosphorylation of interferon regulatory factor-3 (IRF-3).<sup>26</sup> The NS3/4A protease thus represents a dual therapeutic target as its inhibition may (i) block viral replication and (ii) restore IRF-3 control of HCV infection.<sup>27,28</sup>

Ciluprevir (BILN-2061; Boehringer Ingelheim, Ingelheim, Germany) was the first specific NS3/4A serine protease inhibitor evaluated in clinical trials in patients with chronic hepatitis C. Oral short-term administration for 2 days was well tolerated and produced 2–3 log decrease in viremia in treatment-naïve patients with HCV genotype 1.<sup>29,30</sup> While these studies provided proof-of-concept that protease



**Figure 1.** Schematic representation of the HCV genome and targets for current drug development.

**Abbreviations:** UTR, untranslated region; IRES, internal ribosome entry site.

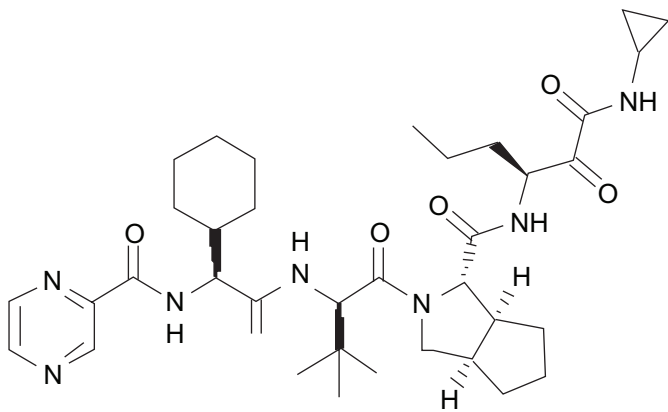


Figure 2. Chemical structure of telaprevir.

inhibitors are effective in patients with chronic hepatitis C, further development of ciluprevir was stopped because of cardiac toxicity.<sup>31</sup>

Protease inhibitors can be classified on the basis of their mechanism of action into (i) non-covalent product-based inhibitors such as BILN-2061 and (ii) covalent reversible inhibitors such as telaprevir and boceprevir.<sup>16</sup> All HCV-specific protease inhibitors currently in development are substrate-based peptidomimetic agents, i.e. small protein-like chains designed to mimic the HCV polypeptide.<sup>17</sup>

## Telaprevir (VX-950)

Development of HCV-specific protease inhibitors is most advanced for telaprevir with currently three ongoing phase 3 clinical trials.<sup>32</sup>

## Chemistry/Pharmacology

Telaprevir (VX-950; Vertex, Cambridge, MA) (Fig. 2) is an  $\alpha$ -keto amide that inhibits NS3/4A protease through covalent but reversible binding to its active site with a dissociation half-life of approximately 1 hour.<sup>16,25</sup>

## Preclinical and pharmacokinetic studies

*In vitro* experiments in the HCV replicon system demonstrated a time- and dose-dependent antiviral effect. Incubation of replicon cells with telaprevir for 14 days resulted in a 4.7 log decline of HCV RNA levels.<sup>33</sup> Previous experiments with protease inhibitor 1 (PI-1; Vertex, Cambridge, MA) revealed that HCV NS3/4A protease inhibition and interferon- $\alpha$  exhibit a synergistic antiviral effect in replicon cells.<sup>34</sup> Likewise, the combination of telaprevir and interferon- $\alpha$  showed

additive to moderately synergistic suppression of HCV RNA which was sustained.<sup>33</sup>

Preclinical studies in animals showed that telaprevir is orally bioavailable and taken up by the liver on first pass metabolism resulting in a favorable pharmacokinetic profile with high exposure in the liver. Average plasma half-life of orally administered telaprevir was 3.3 hours in rats and 3.1 hours in dogs, respectively.<sup>35</sup> Pharmacokinetic studies in humans confirmed oral bioavailability and achievement of steady state plasma levels within 24–48 hours.<sup>16</sup>

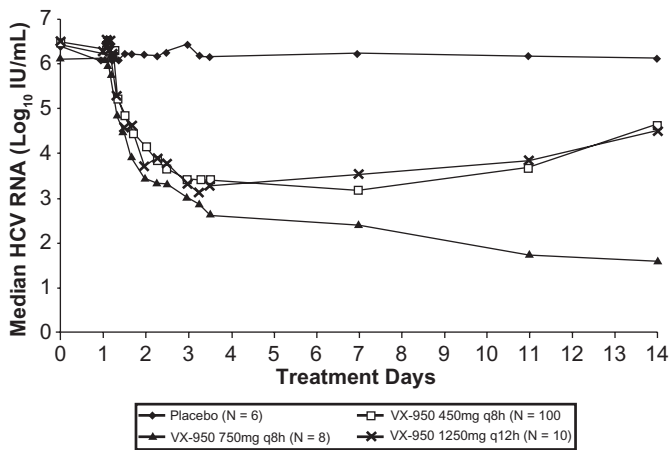
Telaprevir is metabolized in the liver primarily by cytochrome P450 3A4. Drug-drug interactions were reported for telaprevir (as well as boceprevir) with ritonavir, a potent inhibitor of cytochrome P450 3A, which may serve for ‘pharmacokinetic boosting’.<sup>36</sup> Similar interactions with telaprevir are likely for a variety of drugs, many of which may be of clinical relevance in HCV infected or HCV-HIV co-infected patients. Ongoing studies investigate the interaction of telaprevir with methadone, darunavir/ritonavir, fosamprenavir/ritonavir, efavirenz plus tenofovir, and escitalopram (<http://www.clinicaltrials.gov/ct2/results?term=Telaprevir+Drug+interaction>, accessed on 31-DEC-2009).

Information on the dosing of telaprevir in renal insufficiency is still limited. An ongoing study investigates the effect of severe renal impairment on single-dose pharmacokinetics of telaprevir (<http://clinicaltrials.gov/ct2/show/NCT00903773?term=Telaprevir&rank=3>, accessed on 31-DEC-2009). Synergistic anemic side effects of telaprevir and ribavirin following accumulation in renal insufficiency are of concern.

## Clinical trials

### Definitions of treatment response

The following definitions of virologic response to antiviral treatment are being used by convention: Rapid virologic response (RVR) denotes undetectable HCV RNA at week 4, indicating a very high chance of cure. Extended RVR (eRVR) means undetectable HCV RNA at week 4 and week 12. Early virologic response (EVR) denotes a decline of viremia by at least 2 logs at week 12, indicating a high chance of cure. Undetectable HCV RNA at week 12 is referred to as complete EVR (cEVR). Sustained virologic response (SVR) denotes undetectable HCV RNA 24 weeks after the end of treatment, which is considered a cure.



**Figure 3.** Antiviral effect of telaprevir monotherapy in treatment-naïve HCV genotype 1 infection (reprinted from Reesink et al. [ref. 37] with permission from Elsevier).

### Phase 1 trials

Phase 1a and 1b data on the use of telaprevir in humans were reported in 2006 by Reesink et al.<sup>37</sup> Administration of telaprevir at various doses up to 1250 mg q8h for 5 days was tolerated well in 24 healthy volunteers (phase 1a). Subsequently, in phase 1b 34 patients with chronic genotype 1 HCV infection (27 of whom were treatment-experienced) received placebo or telaprevir at three different doses (450 mg q8h, 750 mg q8h, 1250 mg q12h) for 14 days.<sup>37</sup> Telaprevir monotherapy led to a biphasic decline of HCV RNA by 3.5–4.8 logs in a dose-dependent fashion (Fig. 3). At the 750 mg q8h dose (the dose with the highest average trough plasma concentrations), HCV RNA dropped markedly by 4.4 log after 14 days. Mild GI symptoms were noted as adverse events. However, early viral breakthrough—starting between days 3 and 7 of dosing—was observed in some patients in the 450 mg and 1250 mg dose groups and was found to be related to the selection of viral mutants.<sup>38,39</sup>

Given the synergistic effect of telaprevir and interferon *in vitro* (see above), it was quite obvious to use combination treatment of peginterferon plus telaprevir in HCV patients. In another 2-week phase 1b trial, 20 treatment-naïve patients with chronic HCV genotype 1 infection were randomized to receive either telaprevir alone 750 mg q8h (n = 8), weekly peginterferon- $\alpha$ 2a 180  $\mu$ g (n = 4), or telaprevir plus peginterferon (n = 8). Combined peginterferon/telaprevir yielded a median 5.5 log reduction in HCV RNA after 14 days<sup>40,41</sup> indicating additive effects of telaprevir and peginterferon. Importantly, viral breakthrough

was not detected in the peginterferon/telaprevir group since HCV mutants resistant to telaprevir remained sensitive to peginterferon.<sup>40</sup>

Viral dynamic analyses performed in both phase 1b trials mentioned above indicate a 10-fold acceleration of the second phase decrease of wild-type HCV in telaprevir-based regimens enabling higher SVR rates and/or shorter duration of treatment.<sup>42</sup>

The first study of triple combination treatment enrolled 12 treatment-naïve HCV genotype 1 patients who received peginterferon- $\alpha$ 2a, ribavirin and telaprevir 750 mg q8h for 28 days.<sup>43</sup> All patients achieved RVR (undetectable HCV RNA at week 4) and continued off-study peginterferon/ribavirin for an additional 44 weeks with resulted in SVR in 8 patients (67%).

Preliminary data were recently reported on the use of telaprevir in HCV genotype *non-1* infection. In 49 treatment-naïve genotype 2 and 3 HCV patients randomized to (A) telaprevir 750 mg q8h alone, (B) telaprevir plus peginterferon/ribavirin, or (C) peginterferon/ribavirin for 15 days, mean HCV RNA decline for genotype 2/3 was  $-4.0/-0.8$  log in group A,  $-5.5/-4.7$  log in group B, and  $-4.0/-4.5$  log in group C, indicating good efficacy of telaprevir against HCV genotype 2 but not against HCV genotype 3.<sup>44</sup> Application of the same protocol in 24 treatment-naïve genotype 4 HCV patients showed a mean HCV RNA decline of  $-1.4$  log in group A,  $-3.5$  log in group B, and  $-2.0$  log in group C indicating modest efficacy of telaprevir against HCV genotype 4.<sup>45</sup>

### Phase 2 trials

The efficacy of adding telaprevir to current peginterferon/ribavirin standard treatment was evaluated in the PROVE (Protease Inhibition for Viral Evaluation) phase 2 trials in treatment-naïve (PROVE-1&2) and treatment-experienced (PROVE 3) HCV genotype 1 patients.

In the PROVE-1 trial, 250 treatment-naïve HCV genotype 1 patients enrolled in 37 US centers were randomized into 4 groups: 3 groups with telaprevir 750 mg q8h plus peginterferon- $\alpha$ 2a 180  $\mu$ g/week plus ribavirin 1000–1200 mg/day for 12 weeks followed by peginterferon/ribavirin for 0 weeks (T12PR12), 12 weeks (T12PR24), or 36 weeks (T12PR48), and a control group with peginterferon/ribavirin for 48 weeks (PR48). In the telaprevir-containing arms, RVR and cEVR were substantially higher than in



**Table 1.** Major clinical trials evaluating telaprevir in HCV genotype 1 infection.

Acronym	Stage of development	Design	n	Ref.
PROVE-1	Phase 2, treatment-naïve	T12PR12 / T12PR24 / T12PR48 / PR48	250	46
PROVE-2	Phase 2, treatment-naïve	T12PR12 / T12PR24 / T12P12 / PR48	323	47
PROVE-3	Phase 2, treatment-experienced	T12PR24 / T24PR48 / T24P24 / PR48	453	49,50
ADVANCE	Phase 3, treatment-naïve	T12PR24 / T8PR24 / PR48	1050	ongoing
ILLUMINATE	Phase 3, treatment-naïve	TPR12 → PR12-36*	500	ongoing
REALIZE	Phase 3, treatment-experienced	T12PR48 / T12PR48 lead-in / PR48	650	ongoing

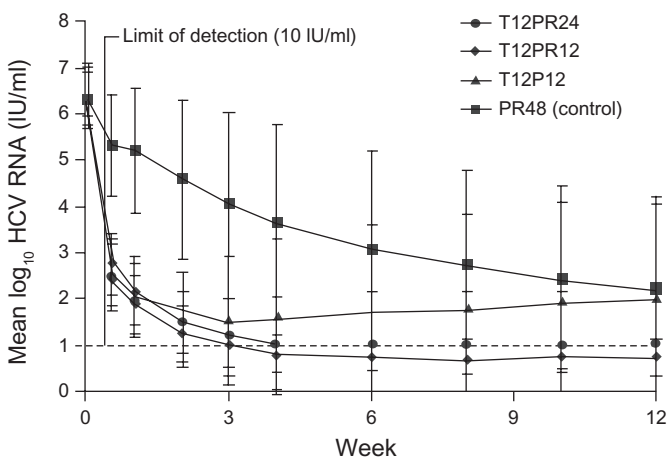
T, telaprevir 750 mg q8h; P, peginterferon- $\alpha$ 2a (standard dose); R, ribavirin (standard dose).  
 \*Depending on antiviral response (presence of eRVR).

the control group (79% vs. 11% and 70% vs. 39%, respectively). Likewise, SVR was superior in groups T12PR24 and T12PR48 as compared to control (PR48) (Table 2).<sup>46</sup>

The PROVE-2 trial in 323 European treatment-naïve HCV genotype 1 patients had a similar design except for inclusion of a no-ribavirin 12-week dual combination group (T12P12) instead of the T12PR48 group. Again telaprevir-containing regimen provided RVR in the majority of patients (Fig. 4). Both triple combination groups but not the peginterferon/telaprevir (no ribavirin) dual combination group showed superior SVR rates as compared to control (Table 2).<sup>47</sup> It should be noted that ribavirin is important for sustaining the virologic response also in peginterferon/ribavirin standard treatment of HCV genotype 1 infection.<sup>48</sup>

Thus, in HCV genotype 1 patients, 24-weeks of telaprevir-based triple combination therapy resulted in a 20% higher SVR rate than 48-week standard treatment with peginterferon/ribavirin.

The PROVE-3 trial enrolled relapsers and nonresponders to previous peginterferon/ribavirin standard treatment and final results were recently presented in abstract form.<sup>49,50</sup> A total of 453 patients were randomized into 4 groups (T12PR24, T24PR48, T24/P24 and PR48). Both telaprevir-containing triple therapy regimens achieved markedly higher SVR rates than the ribavirin-free regimen or standard of care, respectively (Table 2). With T12PR24, SVR was 39% for prior nonresponders and 69% for prior relapsers. Thus telaprevir-based triple combination retreatment may provide sustained response in about half of patients failing prior peginterferon/ribavirin treatment.



**Figure 4.** Antiviral effect of triple combination treatment with telaprevir/peginterferon/ribavirin in treatment-naïve HCV genotype 1 infection (PROVE-2 trial, reprinted from Hezode et al. [ref. 47] with permission. Copyright 2009 Massachusetts Medical Society. All rights reserved.).

**Table 2.** Efficacy of telaprevir in HCV genotype 1 infection (phase 2 trials).

	SVR		
	PROVE-1	PROVE-2	PROVE-3 Overall SVR (NR, REL)
T12PR12	35%	60%	
T12PR24	61%	69%	51% (39%, 69%)
T12PR48	67%	–	
T24PR48			53% (38%, 76%)
T12P12	–	36%	
T24P24			24% (11%, 42%)
PR48 (SOC)	41%	46%	14% (9%, 20%)

T, telaprevir 750 mg q8h; P, peginterferon- $\alpha$ 2a (standard dose); R, ribavirin (standard dose); PROVE-1 and PROVE-2: treatment-naïve patients; PROVE-3: treatment-experienced patients; SOC, standard of care; NR, nonresponders to previous SOC; REL, relapsers to previous SOC.



The open-label study C208 compared triple combination treatment with telaprevir 750 mg q8h versus a twice-daily regimen, i.e. telaprevir 1125 mg q12h, and reported similar high SVR rates for both regimens (83% vs. 82%).<sup>51</sup>

### Phase 3 trials

Currently telaprevir is tested in three large phase 3 trials in treatment-naïve and treatment-experienced HCV patients (<http://www.vrtx.com/current-projects/drug-candidates/telaprevir-VX-950.html>, accessed on 15-NOV-2009).

The ADVANCE trial (ClinicalTrials.gov # NCT00627926) has enrolled approximately 1050 treatment-naïve HCV genotype 1 patients who were randomized to telaprevir/PR for 12 weeks followed by PR for 12 weeks, telaprevir/PR for 8 weeks followed by PR for 16 weeks, and PR for 48 weeks. In patients who do not achieve eRVR (extended RVR), PR is continued until week 48.

The ILLUMINATE trial (ClinicalTrials.gov # NCT00758043) has enrolled approximately 500 treatment-naïve HCV genotype 1 patients who received telaprevir/PR for 12 weeks followed by PR for variable duration: Patients achieving eRVR were randomized to PR for 12 weeks vs. 36 weeks, whereas patients without eRVR uniformly received PR for 36 weeks.

The REALIZE trial (ClinicalTrials.gov # NCT00703118) has enrolled approximately 650 HCV genotype 1 patients who failed previous peginterferon/ribavirin standard treatment. Patients were randomized 2:2:1 to telaprevir/PR for 12 weeks followed by PR for 36 weeks, PR for 4 weeks followed by telaprevir/PR for 12 weeks followed by PR for 32 weeks, and PR for 48 weeks.

According to a press release of 10-JUL-2009, SVR data from telaprevir phase 3 trials are expected to be available in mid-2010 and the filing of Marketing Authorization Applications in the USA and Europe is planned in the second half of 2010 (<http://investors.vrtx.com/releasedetail.cfm?ReleaseID=395529>, accessed on 15-NOV-2009).

### Safety

Short-term administration of telaprevir was generally well tolerated. The most common side effects observed in the PROVE 1&2 trials included rash, pruritus, anemia, nausea and diarrhea. Treatment

discontinuation due to adverse events was more frequent in telaprevir-containing study arms than in the control arm (PROVE-1: 21% vs. 11%; PROVE-2: 12% vs. 7%). Severe rash necessitating discontinuation occurred more often in the telaprevir arms vs. controls (PROVE-1: 7% vs. 1%; PROVE-2: 7% vs. 0%). All cases of severe rash were reversible upon cessation of telaprevir. The median time to treatment discontinuation due to rash was 73 days (PROVE-1). Because of severe rashes arising after 8 weeks of treatment and tending to increase in severity thereafter, administration of telaprevir has been limited to 12 weeks both in phase 2 and phase 3 trials.

Telaprevir aggravated ribavirin-induced anemia and reduced hemoglobin levels by 0.5–1.0 g/dl (PROVE-1&2). Severe anemia was reported more often in the T12PR24 group than with standard of care (PROVE-1: 37% vs. 27%; PROVE-2: 27% vs. 17%). In addition, gastrointestinal events (nausea/vomiting, diarrhea), asthenia, and pruritus were observed more frequently in the telaprevir-based regimens (PROVE-1&2). Importantly, rashes as well as anemia may necessitate discontinuation of telaprevir and thus tolerability will represent a major limiting factor for the efficacy of telaprevir-based triple combination treatment.

### Special populations

Telaprevir-based regimens appear to maintain high efficacy in ‘difficult-to-cure’ HCV genotype 1 infection associated with older age, high body mass index, black race, advanced fibrosis stage, and high baseline viremia.<sup>52</sup> An ongoing study investigates the safety and efficacy of telaprevir plus peginterferon/ribavirin in HCV-HIV co-infected patients (<http://clinicaltrials.gov/ct2/show/NCT00983853?term=Telaprevir&rank=16>, accessed on 31-DEC-2009). No data currently exist on the use of telaprevir in HCV infected liver transplant recipients.

### Other NS3/4A Protease Inhibitors

**Boceprevir** (SCH 503034; Schering-Plough, Kenilworth, NJ) is another peptidomimetic NS3/4 protease inhibitor with high antiviral activity *in vitro* in the replicon system. In a phase 1b study in HCV genotype 1 nonresponders to previous peginterferon/ribavirin therapy, boceprevir 400 mg q8h plus weekly peginterferon- $\alpha$ 2b 1.5  $\mu$ g/kg given for 2 weeks produced a 2.9 log decline in HCV RNA as compared to a 1.6 log decline with boceprevir



alone and a 1.3 log decline with peginterferon alone.<sup>53</sup> In this study, detailed virologic testing revealed an additive effect of boceprevir over peginterferon. Final results of the SPRINT-1 study, a phase 2 trial with boceprevir in 595 treatment-naïve HCV genotype 1 patients, were recently presented at the EASL 2009 meeting.<sup>54</sup> As seen with telaprevir, addition of boceprevir to peginterferon/ribavirin markedly enhanced SVR rates in HCV genotype 1 infection (Table 2) and an excellent SVR of 75% was achieved with a unique lead-in period of peginterferon/ribavirin dual combination for 4 weeks followed by boceprevir 800 mg TID plus peginterferon  $\alpha$ -2b 1.5  $\mu$ g/kg plus ribavirin 800–1400 mg/day for 44 weeks. Gastrointestinal events, anemia and dysgeusia were the most common adverse events.

TMC435 (Tibotec, Mechelen, Belgium), BI 201335 (Boehringer Ingelheim, Ingelheim, Germany) and MK-7009 (Merck, Whitehouse Station, NJ) are currently being studied in phase 2 trials. Addition of TMC435 (25–200 mg/day) to peginterferon/ribavirin in treatment-naïve HCV genotype 1 patients was well tolerated and demonstrated potent antiviral activity.<sup>55</sup> In an ongoing phase 2 trial, triple combination treatment containing BI 201335 (240 mg once daily) yielded cEVR in 80%–90% (Sulkowski MS et al., AASLD 2009 abstract LB3). Likewise, 4-week triple combination treatment with MK-7009 (600–1200 mg/day), peginterferon and ribavirin increased RVR rates to approx. 80%.<sup>56</sup> In a phase 1 trial, ITMN-191 (R7227; Roche, Basel, Switzerland) combined with peginterferon/ribavirin produced marked HCV RNA declines up to  $-5.7$  log after 14 days.<sup>57</sup>

## Resistance Mutations

Emergence of resistance is a major limiting factor for the efficacy of STAT-C drugs in general and for protease inhibitors specifically. Due to the rapid replication rate of HCV (up to  $10^{12}$  virions per day with a half-life of 2–3 hours) and the low fidelity of its polymerase that lacks proofreading capacity, mutations accumulate rapidly throughout the viral genome.<sup>58</sup> These variants can pre-exist as minor viral populations, so-called quasispecies. During antiviral treatment, when viral suppression is incomplete, mutants conferring resistance to protease inhibitors may be rapidly selected.<sup>59,60</sup> Using sensitive assays, such resistance mutations can be detected even at baseline in patients never treated with protease inhibitors.<sup>61–63</sup> However, the clinical

significance of such baseline variants is unclear at present and will require further research.

Mutations conferring various levels of resistance to telaprevir were initially identified *in vitro* within HCV NS3/4A at residues 36, 54, 155, 156, and 170, and include single and double mutations<sup>64,65</sup> (Table 3). Most resistance mutations to telaprevir also confer resistance to boceprevir *in vitro*. During telaprevir monotherapy, nearly all patients with detectable viremia developed resistance mutations within a few days. Development of resistance with viral breakthrough after initial viral suppression has been reported during 14 days of treatment with telaprevir and a correlation between the trough plasma drug concentration and the degree of viral suppression was observed.<sup>66</sup> Importantly, resistance was infrequent (2/8 patients) when telaprevir was combined with peginterferon indicating that resistant variants remain sensitive to interferon.<sup>40,41</sup> Likewise, during triple combination treatment with telaprevir/peginterferon/ribavirin, viral breakthrough due to resistance mutations occurred in a minority of patients (PROVE-1: 7%; PROVE-2: 3%).<sup>46,47</sup>

An essential feature of the variants is their fitness, i.e. their capacity to replicate. Generally the replicative fitness of viral variants is inversely correlated with their degree of resistance (most high-level mutations show a low replicative fitness). Although the replicative fitness of resistant variants seems to be diminished,<sup>40,66</sup> minor populations of pre-existing resistant variants may have a fitness advantage over the wild type virus in the presence

**Table 3.** Resistance mutations against telaprevir.<sup>40,66</sup>

<i>In vitro</i> mutations	<i>In vivo</i> mutations
<i>Low-level resistance*:</i>	
T54A	T54A
V36A/M	V36M/A
R155K/T	R155K/T
A156S	A156S
V170A	
<i>High-level resistance*:</i>	
A156V/T	A156V/T
V36(M/A)/R155(K/T)	
V36(M/A)/156VT	

\*The degree of resistance correlates inversely with viral fitness.



of an antiviral drug and become the dominant viral species.<sup>67</sup> Resistance may be overcome by combining inhibitors of different targets and/or including immune-based therapy. In addition, maintenance of trough plasma concentrations by timely intake of antiviral drugs is essential to prevent the emergence of resistance.

## Concluding Remarks

During the last few years, many new STAT-C drugs have been designed and tested in clinical trials. However, the development of several drugs that showed high efficacy in phase 1 trials had to be stopped because of safety issues. At present, adding a STAT-C drug on to peginterferon/ribavirin standard treatment seems to be the most promising strategy. Based on the results of phase 2 trials, triple therapy with telaprevir/peginterferon/ribavirin represents a milestone in anti-HCV treatment providing (i) improved SVR in the difficult-to-treat HCV genotype 1 infection of approximately 70% with a shortened treatment duration of 24 weeks and (ii) a chance for cure in approximately 50% of patients not responding to a previous course of peginterferon/ribavirin.<sup>68</sup> In treatment-naïve patients, triple combination treatment may be especially useful for those not achieving RVR. Further studies are required to define the optimal timing and duration of telaprevir administration in various clinical settings.

Drawbacks of telaprevir include (i) its dermatological side effects which have so far precluded prolonged administration beyond 12 weeks, (ii) anemia which aggravates this already limiting hematologic side effect of ribavirin and (iii) the necessity for timely dosing every 8 hours which may hamper patient compliance outside of clinical trials. The latter limitation may be overcome by a twice-daily telaprevir regimen (according to study C208) or by newer HCV protease inhibitors such as TMC435 or BI 201335 which allow a once daily dosing interval. Future trials will define the role of telaprevir among the increasing pipeline of other STAT-C drugs currently in clinical development.<sup>69</sup>

Recently, the INFORM-1 (Interferon-Free Regimen for the Management of HCV Infection) study, the first clinical trial of dual combination treatment with oral virostatic drugs, demonstrated synergistic antiviral efficacy of HCV-specific protease and polymerase

inhibition and thus provided proof-of-concept for interferon-free anti-HCV treatment.<sup>70</sup> While such non-interferon regimens appear very promising, the focus of research in the near future will rely on “add-on” triple-therapy designs adding a new STAT-C drug to peginterferon/ribavirin standard of care.<sup>71</sup>

## Abbreviations

HCV, hepatitis C virus; SVR, sustained virological response; EVR, early virological response; cEVR, complete EVR; RVR, rapid virological response; eRVR, extended RVR.

## Disclosures

This manuscript has been read and approved by the author. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The author reports no conflicts of interest.

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