New agents for the treatment of hepatitis C virus – focus on telaprevir

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Abstract: Antiviral therapy for hepatitis C virus (HCV) is rapidly evolving with the advent of direct-acting antiviral agents. Telaprevir is a first-generation linear ketoamide inhibitor of HCV NS3 protease. Approved in 2011 as standard-of-care for the treatment of patients chronically infected with HCV genotype 1, telaprevir represents a major therapeutic advance. Used in combination with PEGylated interferon-alfa and ribavirin, telaprevir-based regimens cured > 75% of treatment-naïve patients in the Phase III registration studies. Telaprevir is also effective for patients who have previously failed interferon-based therapy. Telaprevir presents a number of new challenges for clinicians, including a more demanding dosing schedule, telaprevir-specific adverse events, potential for drug–drug interactions, and selection of drug-resistant HCV variants.

Keywords: telaprevir, HCV, NS3, protease inhibitor, resistance

Introduction

There are up to 170 million individuals chronically infected with hepatitis C virus (HCV) worldwide, all of whom are at risk of the long-term complications of cirrhosis, liver failure, and hepatocellular carcinoma.¹ Chronic HCV infection is currently the leading indication for liver transplantation in the Western world. Furthermore, without intervention, the burden of disease secondary to HCV infection is projected to increase over the coming decades as the HCV population ages. The complications of chronic HCV may be prevented by viral eradication.

The standard-of-care treatment for the past decade has been the combination of PEGylated interferon- α (pegIFN) and ribavirin. Unfortunately this treatment will only cure at best 50% of individuals infected with HCV genotype 1, which is the most prevalent HCV genotype in the US and Europe. Furthermore, pegIFN and ribavirin therapy is poorly tolerated by many patients and must be taken for 12 months.

The past decade has seen great investment in the development of direct-acting antiviral agents, culminating in the regulatory approval in 2011 of telaprevir and boceprevir, the first anti-HCV protease inhibitors. This review summarizes the evidence supporting the use of telaprevir for the treatment of chronic HCV.

Microbiology, pharmacology, mode of action, and pharmacokinetics

Microbiology

HCV is a 9.6 kB single-stranded RNA virus, and is a member of the *Flaviviridae* family. The HCV encodes a polyprotein approximately 3000 amino acids long,

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which is cotranslationally and post-translationally processed into 10 mature proteins, both structural and nonstructural (NS). The NS proteins are necessary for viral replication and include HCV_NS3/4a protease, HCV_NS5a phosphoprotein, and HCV_NS5b RNA-dependent RNA polymerase. Inhibitors of NS3/4a protease, NS5a protein, and NS5B polymerase have all been shown to have potent antiviral activity.

The HCV NS3 protein is a multifunctional protein consisting of an N-terminal serine protease and a C-terminal helicase/NTPase domain.² The NS3 serine protease catalyzes cleavage of the HCV polyprotein at the NS3/NS4a, NS4a/NS4b, NS4b/NS5a, and NS5a/NS5b junctions, to generate components of the viral RNA replication complex. The catalytic site consists of a triad of key residues, ie, Ser139, His57, and Asp81. NS4a is a cofactor that facilitates NS3 protease activity. The NS3 protease also has host cell targets, inhibiting the cellular response to double-stranded RNA by cleaving IPS-1 (the IFN β promoter stimulator-1, also known as MAVS, CARDIF, and VISA) and TRIF (Toll-IL-1 receptor domain-containing adaptor inducing IFN β), the cellular adaptors for retinoic acid inducible gene-I and Toll-like receptor 3, respectively. Double-stranded RNA structures are generated during replication of HCV, and both retinoic acid inducible gene-I and Toll-like receptor 3 signaling have been shown to inhibit HCV replication in vitro.^{3–5} Therefore, inhibition of NS3/4a protease directly inhibits HCV replication, and in addition may stimulate the intrahepatic innate immune response by restoring hepatocyte interferon signaling.

Pharmacology of telaprevir

Telaprevir is a linear ketoamide that acts as a reversible covalent peptidomimetic inhibitor of the active site of the HCV NS3 protease (Figure 1).^{6,7} Telaprevir competes with the NS5a/5b substrate for the substrate binding site, ie, the serine-139 residue of the catalytic triad of protease, and is therefore often referred to as a “serine trap” inhibitor. Binding of telaprevir to the NS3/4a protease is thought to

occur in at least two stages. Telaprevir first binds weakly to NS3 to form a “collision” complex held together weakly by van der Waal’s forces. This complex is slowly rearranged to form a more tightly bound, covalent complex between the ketoamide group on the N-terminus of telaprevir and the Ser-139 residue. The dissociation of the covalent complex is a slow process, with a half-life of 58 minutes.

The pharmacokinetic properties of telaprevir have been evaluated in healthy adult subjects as well as in subjects with chronic HCV genotype 1. In treatment-naïve subjects with chronic HCV treated with multiple doses of telaprevir (750 mg every 8 hours) in combination with pegIFN and ribavirin, the mean $\pm$ standard deviation peak plasma concentration was 3510 ± 1280 ng/mL, the trough plasma concentration was 2030 ± 930 ng/mL, and the area under the concentration-time curve (AUC, 8 hours) was $22,300 \pm 8650$ ng $\times$ hour/mL.

Telaprevir has a highly crystalline nature and its aqueous solubility is very poor. A novel formulation strategy was required to produce an orally bioavailable final drug product.⁸ Telaprevir is most likely absorbed in the small intestine, with no evidence for absorption in the colon. Telaprevir is a substrate for P-glycoprotein. After a single dose of telaprevir, the peak plasma concentration is achieved after 4–5 hours. Telaprevir must be dosed with a meal containing at least 20 g of fat. A standard fat meal (533 kcal and 21 g fat) increases the systemic exposure (AUC) by 237% compared with dosing under fasting conditions. The amount of fat is important, and systemic exposure to telaprevir is suboptimal if taken with a low-fat meal (<20 g fat). After oral administration, the apparent volume of distribution of telaprevir is 252 L (interindividual variability 72%). The drug is 60%–75% bound to plasma proteins, primarily alpha 1-acid glycoprotein and albumin. It is the unbound (free) concentration of telaprevir that is critical for the liver-specific effect on HCV replication.

Telaprevir is extensively metabolized in the liver, and multiple metabolites can be detected in feces, plasma, and urine. The predominant metabolites are the R-diastereomer of telaprevir (30-fold less active), pyrazinoic acid, and an inactive metabolite resulting from reduction at the α -ketoamide bond. Telaprevir is a substrate for cytochrome P450 (CYP), and the major isoform responsible for metabolism is CYP3A4. Non-CYP-mediated metabolism may play a role following multiple doses. Therefore, telaprevir is a substrate and inhibitor of both CYP3A4 and P-glycoprotein, with a potential for drug–drug interactions (see below). The elimination of telaprevir is mainly via the fecal route (following a single oral dose of 750 mg of ¹⁴C-telaprevir

Figure 1 Chemical structure of telaprevir.

in healthy subjects, the median recovery of the radioactive dose was 82% in feces, 9% in exhaled air, and 1% in urine; the respective contributions of unchanged ^{14}C -telaprevir and the R-diastereomer to total radioactivity recovered in feces were 32% and 19%). Renal excretion is minimal, and dose reduction is not required in the setting of renal impairment. The mean elimination half-life following a single oral dose is 4.0–4.7 hours, and the effective half-life is 9–11 hours at steady state.

Telaprevir for treatment of HCV genotype 1

The antiviral efficacy of telaprevir was first demonstrated in experimental models. In an HCV subtype 1b replicon assay, the 50% inhibitory concentration (IC_{50}) of telaprevir was 354 nM, and in a subtype 1a infectious virus assay, the IC_{50} was 280 nM.^{6,7} In biochemical enzymatic assays, the median IC_{50} values of telaprevir for genotypes 1a and 1b were 20 nM. In a Phase Ib study of telaprevir monotherapy in patients with chronic HCV genotype 1, 14 days of dosing with 450 mg every 8 hours, 750 mg every 8 hours, or 1250 mg every 12 hours reduced the HCV viral load by at least 2 $\log_{10}$ IU/mL in all patients.⁹ The 750 mg treatment group had the highest trough plasma drug concentration and maximal median viral load reduction of 4.4 $\log_{10}$ IU/mL.⁹ However, viral breakthrough was common during the second week of treatment, associated with variants that had reduced sensitivity to telaprevir. Therefore, telaprevir is not effective as monotherapy. Combination therapy with pegIFN and ribavirin is synergistic in terms of antiviral effect and reduces the emergence of telaprevir resistance. The addition of pegIFN and ribavirin to telaprevir leads to an additional 0.5–2.0 $\log_{10}$ IU/mL reduction of HCV RNA after 14–28 days.^{10–13} Therefore, telaprevir was taken forward as combination therapy with pegIFN and ribavirin for genotype 1 HCV. Telaprevir was developed using experimental models of HCV genotype 1, and the antiviral effect of telaprevir is consequently relatively specific for HCV genotype 1 both in vitro and in vivo. Telaprevir does have activity in vitro against HCV genotype 6.¹⁴ Telaprevir has intermediate activity against HCV genotypes 2 and 3 in vitro (activity for genotype 2 > genotype 3). In a small Phase IIa study, telaprevir was shown to have antiviral activity for HCV genotype 2 in patients, but not for genotype 3.⁹ However, telaprevir is not currently indicated for HCV genotype 2 because the virological cure rate with dual pegIFN and ribavirin therapy is greater than 70%.¹⁵ HCV genotypes 4 and 5 are resistant to telaprevir.¹⁴

Telaprevir was approved for the treatment of HCV genotype 1 infection in the US and Europe in 2011, on the basis of the results of three pivotal Phase III registration studies (Figure 2). The ADVANCE and ILLUMINATE studies evaluated the use of telaprevir in treatment-naïve patients, and the REVEAL study evaluated the efficacy of telaprevir in patients previously treated with pegIFN and ribavirin.

In the ADVANCE study, patients were randomized to treatment with telaprevir for 12 or 8 weeks in combination with pegIFN and ribavirin (T12PR/T8PR), compared with pegIFN and ribavirin alone (Table 1).¹⁶ The active treatment arms included response-guided therapy, whereby the telaprevir phase was followed by a further 12 (T12PR24) or 36 weeks (T12PR48) of pegIFN and ribavirin depending on the achievement of an extended rapid virological response (eRVR), defined as an undetectable HCV RNA (<25 IU/mL) at weeks 4 and 12 of treatment. The overall virological cure rates were 75% in T12PR and 69% in T8PR versus 44% in the control pegIFN and ribavirin arm ($P < 0.0001$ for both comparisons with control, Table 1).¹⁶ More recently, the US Food and Drug Administration (FDA) has recognized virological cure rates defined according to SVR24, as well as SVR12 in the case of patients missing data after week 12 of follow-up. Using this definition, overall virological cure rates were 79% and 72% in the T12PR and T8PR treatment arms, respectively.¹⁷ Telaprevir was more effective than pegIFN and ribavirin alone for the treatment of patients with “hard-to-cure” characteristics, including patients with advanced fibrosis and those with a high baseline HCV RNA level, as well as patients of African ancestry (Table 1). Further, 58% and 57% of patients achieved an eRVR in the T12PR and T8PR arms, respectively, and were eligible for short-duration therapy. The virological cure rate in patients who attained an eRVR was 89% and 83%, respectively.¹⁸ Although there was no significant difference in the response rates between the T12PR and T8PR treatment arms, virological cure rates were numerically higher in the T12PR arm, due to a lower rate of breakthrough of telaprevir-resistant variants. T12PR has been approved by the FDA and European Medicines Agency as the optimal treatment duration.

The ILLUMINATE study¹⁹ was designed to confirm the efficacy of response-guided treatment for patients who attain an eRVR (Table 1). All patients received telaprevir-based therapy. Patients who achieved an eRVR were randomized to T12PR24 or T12PR48. Patients who did not achieve an eRVR received T12PR48. The overall virological cure rate was 72%. The overall rate of eRVR was 65%.

Figure 2 Approved telaprevir treatment regimens (US product labeling). **(A)** Response-guided therapy. Suitable for treatment-naïve patients and prior relapsers following pegIFN and ribavirin dual therapy. Telaprevir is administered for 12 weeks in combination with pegIFN and ribavirin (T12PR/T8PR), followed by a further 12 (T12PR24) or 36 weeks (T12PR48) of pegIFN and ribavirin according to the achievement of an eRVR (extended rapid virological response, defined as an undetectable HCV RNA [<25 IU/mL] at weeks 4 and 12 of treatment). Patients with cirrhosis may benefit from a total treatment duration of 48 weeks even if they have undetectable HCV RNA at weeks 4 and week 12. Note stopping rules = HCV RNA > 1000 IU/mL at week 4 or week 12 of treatment. **(B)** A 48-week treatment course (not response-guided).

Notes: Suitable for cirrhotic patients and prior partial responders/null responders to pegIFN and ribavirin therapy. Telaprevir is administered for 12 weeks in combination with pegIFN and ribavirin (T12PR/T8PR), followed by a further 12–36 weeks (T12PR48) of pegIFN and ribavirin. Note stopping rule = HCV RNA > 1000 IU/mL at week 4 or week 12 of treatment, or a detectable HCV RNA level at week 24 of treatment.

Abbreviations: HCV, hepatitis C virus; pegIFN, pegylated interferon.

Among eRVR patients, the virological cure rate was not different between patients treated for 24 versus 48 weeks (92% versus 88%, absolute difference 4%, 95% confidence interval $[-2$ to $11]$). Therefore, noninferiority of 24 versus 48 weeks' duration therapy was confirmed.

The REALIZE study investigated telaprevir for the treatment of patients with HCV genotype 1 who had previously failed treatment with pegIFN and ribavirin (Table 2). Patients were classified according to prior IFN response as relapsers, partial responders, or null responders according to standard definitions^{15,20} (Table 2). The study compared three treatment arms, ie, T12PR48, 4 weeks of lead-in pegIFN and ribavirin alone plus T12PR44, and PR48 control. There was no response-guided protocol. Virological cure rates were higher in the telaprevir-containing arms compared with control: overall 64% and 66% versus 17%; prior relapsers 83%/88% versus 24%; partial responders 59%/54% versus 15%; and null responders 29%/33% versus 5% ($P < 0.001$ for all comparisons). Cirrhotic null responders remain very difficult to cure (Table 2). Virological cure rates were not significantly different between the two telaprevir-containing arms, and lead-in pegIFN and ribavirin alone did

not increase virological cure rates. The strongest predictor of treatment outcome was the prior response to interferon (Table 2). The lead-in phase did have clinical utility for stratifying the likelihood of response in prior null responders. A $<1 \log_{10}$ IU/mL reduction in viral load at the end of week 4 was predictive of treatment outcome in prior null responders (virological cure rate 15% versus 54% in the setting of a lead-in reduction in HCV RNA $\geq 1 \log_{10}$ IU/mL).²¹ Therefore, a $<1 \log_{10}$ reduction might be considered a futility rule in these patients. The lead-in had less clinical utility in prior relapsers or partial responders, where 18 of 31 (58%) prior relapsers/partial responders still achieved a virological cure despite a $<1 \log_{10}$ reduction at week 4. Although response-guided therapy was not explored in this study, the FDA recommended that response-guided therapy is suitable for noncirrhotic relapsers on the basis of the very high virological cure rates observed (Figure 2).

Host *IL28B* genotype has recently been identified to be a critical predictor of response to pegIFN and ribavirin therapy for chronic HCV genotype 1.^{22–25} The most common polymorphism tested is rs12979860 (CC being a good response genotype, CT and TT being poor response genotypes).

Table 1 Summary of Phase III clinical studies of telaprevir in treatment-naïve patients

Study	Patient population	n	Study design ^a	eRVR ^b	SVR ^c	SVR ^d	SVR rate (subgroup analysis)			HCV-1A vs HCV-1B	HCV RNA < 800K vs HCV RNA > 800K	
							eRVR vs no eRVR	White vs Black	F0-2 vs F3-4			
ADVANCE ¹⁶	Naïve	1088	PR48 T8PR T12PR	8% 57% 58%	44% 69% 75%	46% ^d 72% ^d 79% ^d	97/39% 83%/50% 89%/54%	46% versus 25% } 75% versus 62% ^e	47% versus 33% } 78% versus 62% ^e	41% versus 48% } 71% versus 79% ^e	70% versus 36% } 78% versus 74% ^e	
ILLUMINATE ¹⁹	Naïve	540	eRVR + T12PR24 eRVR + T12PR48 eRVR - T12PR48	100% ^f 100% 0%	92% ^g 88% 64%	92% ^g 90% ^d N/A	* * *	93% versus 88% 87% versus 88% 65% versus 65%	95% versus 82% 87% versus 88% 70% versus 55%	90% versus 98% 88% versus 86% 58% versus 79%	Patients with HCV RNA > 800K: - overall SVR 69% - SVR if eRVR 90%	

Notes: ^aADVANCE: PR48 = pegylated interferon- α and ribavirin for 48 weeks (control); ^bT8PR = telaprevir with pegylated interferon- α and ribavirin for 8 weeks and placebo with pegylated interferon- α and ribavirin for 4 weeks followed by pegylated interferon- α and ribavirin for 12 or 36 weeks according to eRVR (extended rapid virologic response, HCV RNA undetectable at weeks 4 and 12); T12PR = telaprevir with pegylated interferon- α and ribavirin for 12 weeks followed by pegylated interferon- α and ribavirin for 12 or 36 weeks according to eRVR; in ILLUMINATE, all patients received T12PR; patients who attained an eRVR were randomly assigned at week 20 to T12PR24 versus T12PR48; patients who did not attain eRVR all received T12PR48; ^cSVR, sustained virologic response, defined by undetectable HCV RNA at 24 weeks post-treatment; ^dSVR rates as presented in the label approved by the Food and Drug Administration (SVR defined according to: the last HCV RNA assessment in the 72-week window (in case of missing data, the last HCV RNA data point from week 12 of follow-up onward was used); with HCV RNA threshold defined by the lower limit of quantitation (<25 IU/mL)); ^ecomparison of pooled data from telaprevir treatment arms versus control; ^foverall rate of RVR was 72%, eRVR was 65%; ^goverall rate of SVR was 72%. ^hThere are no data for these cells.

Abbreviations: HCV, hepatitis C virus; NR, no response; SVR, sustained virologic response; N/A, not available; RVR, rapid virologic response; vs, versus.

Table 2 Summary of Phase III REALIZE study of telaprevir in treatment-experienced patients^{38,46}

Patient population ^a n = 663	Study design	SVR	SVR rate (subgroup analysis) ^b					
			Relapsers		Partial		NR	
			F0-2 (n = 205)	F3 F4 (n = 77)	F0-2 (n = 64)	F3 F4 (n = 23)	F0-2 (n = 47)	F3 F4 (n = 60)
Relapsers 53%	PR48	24%	22% ^c	15%	18%	0%	6%	10%
Partial 19%	Lead-in T12PR48	88%	86% ^c	54%	72% ^c	56%	41%	39%
NR 28%	T12PR48	83%	59%	59%	56%	34%	39%	14%

Notes: ^aRelapse defined as undetectable HCV RNA at the end of a previous course of therapy, with HCV RNA positivity thereafter; partial response defined as a <2 log₁₀ IU/mL reduction in HCV RNA after 12 weeks of prior pegylated interferon and ribavirin therapy, but with detectable HCV RNA; no response defined by a <2 log₁₀ IU/mL reduction in serum HCV RNA at week 12 of prior pegylated interferon and ribavirin therapy; ^bcomparison of pooled data from telaprevir treatment arms versus control; ^cSVR rates for pooled telaprevir treatment arms as presented in the labeling approved by the US Food and Drug Administration (SVR defined according to the last HCV RNA assessment in the 72 week window, in case of missing data, the last HCV RNA data point from week 12 of follow-up onward was used; the HCV RNA threshold used to define SVR was the lower limit of quantitation (<25 IU/mL)).

Abbreviations: HCV, hepatitis C virus; NR, no response; SVR, sustained virologic response.

The good response CC IL28B genotype has been associated with a 2–3-fold increase in virological cure rate compared with patients who carry the poor response genotypes. Caucasians who carry the good response IL28B genotype have been shown to have an overall virological cure rate > 70%.²³ The association between IL28B genotype and treatment response is attenuated when telaprevir is combined with pegIFN and ribavirin, largely because of the large increment in the virological cure rate that has been observed in patients who carry the poor response IL28B genotypes (ADVANCE, rs12979860: CC patients, virological cure rate 90% [T12PR] versus 64% [pegIFN and ribavirin]; CT patients 71% versus 25%; TT patients 73% versus 23%).²⁶ The increment in virological cure rate for CC patients is smaller, and the cost-effectiveness of telaprevir as first-line treatment for these patients is not clear.^{27–29} One major advantage of telaprevir for CC patients is that they are much more likely to qualify for short-duration therapy (78% versus 45%–57% of non-CC patients). The IL28B genotype is a host marker of responsiveness to interferon. It is much less useful in treatment-experienced patients in whom prior treatment response is well documented.³⁰

Viral resistance

Monotherapy with all HCV protease inhibitors in clinical development has been complicated by the rapid emergence of resistant variants. The high replication rate of HCV, and the error-prone nature of the replication cycle, allow resistant

variants to be generated spontaneously. The rate of spontaneous mutation is such that all possible single and double amino acid substitutions associated with reduced sensitivity to protease inhibitor therapy are likely to be generated every day.^{31,32} The enzyme also has an unusually shallow substrate-binding pocket, such that minor structural modifications interfere with substrate binding, but have limited impact on replication fitness. Most resistant variants do have impaired replication fitness relative to wild-type HCV, and are present as minor variants in HCV quasispecies, but can rapidly emerge under antiviral selection pressure. This occurs during monotherapy with telaprevir, and virological breakthrough has been observed within 3 days.¹⁰ The success of current telaprevir regimens is therefore dependent on an effective pegIFN and ribavirin backbone. However, not all individuals are responsive to pegIFN and ribavirin therapy, placing them at high risk for treatment failure on telaprevir due to functional monotherapy. Both pegIFN and ribavirin have important and independent effects to limit the emergence of resistance-associated variants.³³ Ribavirin in particular is indispensable, and has been shown to limit the emergence of resistance-associated variants in interferon-free regimens also.^{33–35}

The key amino acid residues associated with reduced sensitivity to telaprevir are highlighted in Table 3. The most common HCV_NS3 substitutions observed in the Phase III telaprevir cohorts were V36M/A, T54A/S, R155K/T, and A156S/T (Table 3). These substitutions have been associated with reduced sensitivity to telaprevir in cell culture or

Table 3 HCV NS3 substitutions associated with reduced sensitivity to telaprevir therapy

		V36 A/L	V36M	V36M + R155K	T54 A/S	R155 K/T	A156 S/T	A156 V/F/N	D168 N	V170 A
Linear ketoamides	Telaprevir									
	– Overall	12%	33%	27%	13%	38%	9%	<2%		In vitro only
	– Subtype 1A ¹⁷	10%	49%	40%	9%	56%	8%	<2%		–
	– Subtype 1B	17%	3%	0%	22%	0.6%	12%	<2%		–
Macrocyclic compounds	Boceprevir ¹⁷									
	1st generation									
	– Danoprevir									
	– MK7009									
	Next wave									
	– TMC435									
	– GS-9256									
	– ABT 450									
	– BMS-791325									
	2nd generation									
	MK5172									

Notes: HCV_NS3 amino acid substitutions associated with resistance to telaprevir, as well as other NS3 protease inhibitors currently in development, based on mutations selected in patients from clinical studies and/or from *in vitro* studies. Gray squares indicate substitutions associated with a ≥ 5 -fold increase in IC_{50} compared with wild-type virus. The frequency of treatment-emergent substitutions observed in participants of the Phase III telaprevir studies who did not achieve SVR (Sustained Virological Response) in telaprevir combination treatment arms is presented.¹⁷

Abbreviation: HCV, hepatitis C virus.

biochemical assays: low-level resistance V36M/A (3.5–7.0-fold), T54A/S (6–12-fold), R155K/T (8.5–11.0-fold); intermediate-level resistance V36A/M + R155K/T (55–70-fold), A156S (80–100-fold); and high-level resistance A156T (100–400-fold), V36A/M + A156V/T (>700-fold).^{10,12} Enrichment of variants carrying resistance-associated substitutions is observed in all patients who fail telaprevir treatment. The long-term clinical significance of the HCV resistance-associated variants that emerge in this setting is not yet known. Long-term follow-up studies have shown gradual reversion to wild-type HCV in most patients over time, although this may take several years. It is not known whether these variants will re-emerge more rapidly on rechallenge with an NS3 protease inhibitor, particularly in the setting of interferon-free regimens. It should be noted that telaprevir-resistant variants are cross-resistant to boceprevir, the second HCV protease inhibitor that has recently been approved.

Triple therapy containing telaprevir is less effective for HCV genotype 1a (HCV-1a) versus HCV genotype 1b (HCV-1b), and a higher rate of virological breakthrough in HCV-1a patients is observed¹⁶ (Table 1). HCV-1a has a lower genetic barrier to protease inhibitor resistance than HCV-1b. The selection of the R155K variant requires one nucleotide substitution in HCV-1a (AGG → AAG), whereas two nucleotide substitutions are required for HCV-1b (CGG → AAG). Similarly, a single nucleotide substitution allows selection of V36M in HCV-1a (GTG → ATG), whereas two substitutions are required for HCV-1b (GTC → ATG). Therefore, differences in resistance profiles are observed according to HCV-1 subtype. HCV-1a has been associated with the R155K and/or V36M mutations, whereas HCV-1b is more likely to be associated with the A156S/T, V36A, and T54A variants (Table 3). Reversion to wild-type HCV has been observed to occur more rapidly in HCV-1b infection.

The genetic heterogeneity of HCV means that resistance-associated variants may be detected as minor variants in the serum of patients prior to the onset of telaprevir therapy. Indeed, preliminary data suggest that resistance-associated variants may be detected in most patients using ultrasensitive next-generation sequencing techniques. However, the clinical significance of these low frequency variants remains unclear, and they have not yet been shown to predict failure of licensed telaprevir regimens. Whether they predict treatment failure in high-risk patients with poor responsiveness to interferon remains unclear. Next-generation sequencing cannot be recommended as a routine pretreatment test, and remains a research tool.

Safety and tolerability of telaprevir in practice

The introduction of telaprevir represents a major therapeutic advance. Unfortunately, the drug is associated with adverse events that are additive to the toxicity of pegIFN and ribavirin. The major adverse events of telaprevir include pruritus, rash, anemia, and gastrointestinal upset (nausea, diarrhea, perianal discomfort/pruritus, hemorrhoids).

In the Phase II/III studies, rash of all grades was reported in 56% of patients receiving telaprevir compared with 34% of patients receiving pegIFN and ribavirin alone. Telaprevir rash is typically eczematous, and 90% of reported cases have been of mild/moderate severity. Fifty percent of cases occur during the first 4 weeks of treatment, but may occur at any time point during telaprevir therapy. Mild-to-moderate rash can be managed with topical measures, including steroid creams. Severe rash (defined as a generalized rash, or rash with vesicles or bullae or ulcerations other than Stevens Johnson syndrome) was reported in 4% of subjects receiving telaprevir regimens in the registration studies, compared with <1% of patients receiving pegIFN. Such reactions require discontinuation of telaprevir. Serious skin reactions, including Stevens Johnson syndrome, DRESS (drug rash with eosinophilia and systemic symptoms), and toxic epidermal necrolysis have been described, with a reported frequency < 1%. These serious skin reactions require cessation of all therapy.³⁶

Telaprevir is associated with additive hematological toxicity. The incidence of anemia (hemoglobin < 10 mg/dL) was 36% for telaprevir combination treatment compared with 17% for pegIFN and ribavirin in the registration studies (use of growth factor was not permitted). The median incremental decline in hemoglobin was approximately 1 mg/dL. Anemia events were associated with permanent discontinuation of telaprevir in 3% of patients compared with 0.5% of controls. Hemoglobin gradually increased to control levels after discontinuation. In clinical practice, anemia is managed by reduction in the ribavirin dose and/or growth factor support. The ribavirin dose can be safely reduced to levels ≤ 600 mg per day without compromising virological response rates.³⁷ Telaprevir therapy was also associated with increased rates of lymphopenia (lymphocyte counts fell to ≤499/mm³ in 15% versus 5%) and thrombocytopenia (3% of subjects on telaprevir combination treatment had platelet counts < 50,000/mm³ in 3% versus 1%) compared with pegIFN and ribavirin control.

Telaprevir therapy has also been associated with anorectal adverse events. Anorectal adverse events, including anorectal discomfort, rectal burning, anal pruritus, and hemorrhoids

were reported for 29% of patients who received telaprevir compared with 7% for controls. The majority of these events were of mild-to-moderate severity, and did not require discontinuation. All resolved after stopping telaprevir. It has been hypothesized that fecal pyrazinoic acid may contribute to these symptoms. However, the cause of these symptoms remains unclear. Telaprevir therapy has also been associated with elevation of uric acid levels (73% versus 29% with pegIFN and ribavirin alone; levels ≥ 12.1 mg/dL in 7% versus 1%). However, $<1\%$ of telaprevir-treated patients experienced symptomatic gout/gouty arthritis during therapy and no patients required discontinuation of treatment.

A final cautionary note is that experience of telaprevir in patients with advanced liver disease remains limited. Less than 25% of patients in the registration program were cirrhotic,^{16,19,38} and all had well compensated liver disease (Child-Pugh class A). Recent data from the French CUPIC study suggests that telaprevir may be less well tolerated in patients with advanced liver disease.³⁹ CUPIC was a compassionate use program designed to provide early access to telaprevir and boceprevir for cirrhotic patients in France before marketing authorization. Although eligibility criteria included compensated cirrhosis, 15%–16% of patients had esophageal varices (representing a group that did not qualify for inclusion in Phase III trials). All patients had failed prior pegIFN and ribavirin therapy; only prior relapsers or partial responders were enrolled, and null responders were excluded. The study is ongoing, and interim analysis of patients receiving at least 16 weeks of therapy has recently been presented.³⁹ As expected, adverse events were more common than was reported in the registration program. Serious adverse events were reported for 48.6% of patients and led to premature discontinuation of therapy in 14.5%. Anemia was more common than would be expected with pegIFN and ribavirin alone, with erythropoietin used in 56.8% of patients and blood transfusion required for 15% (note that ribavirin dose reduction was not widely used). Grade 3–4 neutropenia was reported in 4.7%. Grade 3–4 sepsis was reported in 8.8, and hepatic decompensation events in 4.4%. Of more concern, 2% ($n = 6$) of patients died, with sepsis being the most common cause of death. The relative contribution of telaprevir versus pegIFN and ribavirin to these serious adverse events is not clear. This was not a controlled study, and significant morbidity, particularly related to sepsis and hepatic decompensation, is associated with pegIFN and ribavirin therapy alone in this patient population. The risk of therapy must also be balanced against the annual risk of decompensation events in this high-risk population, estimated at 4%–7.5%.^{40,41}

However, the data are instructive, and suggest that careful monitoring of patients receiving triple therapy is required in cirrhotic patients.

Drug–drug interactions

Telaprevir is a substrate and inhibitor of both CYP3A4 and P-glycoprotein, with a potential for drug–drug interactions. No inhibition by telaprevir of CYP1A2, CYP2C9, CYP2C19, and CYP2D6 isozymes has been observed in vitro. The in vitro studies also suggest that telaprevir has a low potential to induce CYP2C, CYP3A, and CYP1A. Clinical studies have been conducted and are ongoing to evaluate the effect of drugs that can affect or be affected by telaprevir. Common drugs that should not be coadministered with telaprevir include atorvastatin, lovastatin, and simvastatin (HMG CoA reductase inhibitors), clarithromycin and erythromycin (macrolide antibiotics), ketoconazole and itraconazole (antifungals), and the herbal product *Hypericum perforatum* (St John's wort). Oral contraceptives may be less effective, and two forms of barrier contraception are recommended during the period of telaprevir dosing (and for 2 weeks afterwards). Methadone may be safely continued during treatment with telaprevir, and no dose adjustment is required at the time of initiation (although telaprevir may reduce total serum concentrations of R-methadone, the unbound effective fraction remains stable). Clinical monitoring of methadone dose during treatment with telaprevir is recommended. Telaprevir is predicted to interact with calcineurin inhibitors, making treatment of post-transplant HCV complicated. Recent data suggest that telaprevir may be safe and effective in this setting, but that close monitoring and reduction of cyclosporine/tacrolimus levels as required is necessary.⁴² Detailed discussion of drug–drug interactions is contained in the product insert.¹⁷ Online tools for checking the potential for drug–drug interactions are also available.⁴³

Future perspectives

The clinical development of telaprevir is ongoing. Studies are currently evaluating a twice-daily dosing schedule for telaprevir, the role of telaprevir as a treatment for coinfection with HCV and human immunodeficiency virus,⁴⁴ the efficacy of telaprevir therapy post-liver transplantation,⁴² the efficacy of telaprevir in patients with renal impairment, and telaprevir regimens of very short duration in patients with the IL28B genotype who are good responders. Telaprevir is also being evaluated as a component of interferon-free treatment regimen(s). It should be noted that multiple HCV NS3/4a protease inhibitors have now entered Phase III

development (eg, TMC435).⁴⁵ A number of these promising agents are likely to offer similar or increased efficacy, with improved tolerability and single-daily dosing schedules. Therefore, telaprevir is likely to be replaced as a first-line protease inhibitor in the relatively near future. In fact, the treatment landscape for HCV is changing dramatically and at a rapid rate. Direct inhibitors of multiple steps in the viral lifecycle are in the advanced stages of clinical development, with potent inhibitors of HCV NS5B polymerase (nucleo(s)ide, non-nucleoside inhibitors), and HCV_NS5A already in Phase II/III development. It is conceivable that, within the decade, clinicians will be able to choose between one of a number of interferon-free combination regimes with pan-genotypic activity.

Summary

The registration of the first direct-acting antiviral agents for the treatment of HCV in 2011 represented an important therapeutic milestone. Telaprevir, used in combination with pegIFN and ribavirin, significantly increases the likelihood for cure of HCV genotype 1, and allows a shortened treatment duration in more than 50% of patients. Treatment-related side effects remain an issue, and for the first time, HCV clinicians must consider the possibility and clinical significance of drug-resistant HCV variants, as well as drug–drug interactions. Further advances are required to increase cure rates, particularly in patients with poor responsiveness to interferon and/or cirrhosis, and to improve tolerability. It is hoped that treatment regimens involving the combination of multiple direct-acting antiviral agents targeting different steps in the viral life cycle will achieve this goal in the not too distant future.

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