

Hepatitis C virus directly acting antivirals: current developments with NS3/4A HCV serine protease inhibitors

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Chronic hepatitis C virus (HCV) infection is a global health problem, but the current therapy is effective in <50% of patients infected with genotype 1. With advances in cell culture systems over the past decade, the development of directly acting antivirals (DAAs) for HCV has become possible. There are currently >50 active clinical trials in this therapeutic area and NS3/4A protease inhibitors are now entering Phase III study. To date, we have learned that DAAs are potent inhibitors of HCV replication, resulting in rapid declines in serum HCV RNA levels, and have the potential to allow shortening of therapy. However, these agents drive selective pressure for mutant viruses that can develop rapidly and have reduced susceptibility to the drug. Therefore, for now, the current standard of care including pegylated interferon α (pegIFN) and ribavirin remains a crucial part of new drug development. Furthermore, the adverse event profile for the early DAAs has added to the concerns of tolerability that are so common for the current standard of care. Ongoing issues include the optimal duration of therapy, how and when to combine DAAs, and the long-term role of pegIFN and ribavirin. Here, we summarize the current information regarding the effectiveness of protease inhibitors in treating chronic HCV and discuss the key challenges now facing the field.

Keywords: targeted therapy, STAT-C, polymerase inhibitors, interferon, ribavirin, resistance

Introduction

The WHO has declared hepatitis C virus (HCV) infection a global health problem, citing the estimated 130–170 million people chronically infected worldwide.¹ Recent estimates from the US Centers for Disease Control and Prevention report that 3.2 million Americans (1.8%) are chronically infected with HCV and ~10000 die annually as a result of this persistent infection.² It is estimated that up to 20% of HCV-infected persons will develop complications of their liver disease, including cirrhosis, end-stage liver disease and hepatocellular carcinoma. Furthermore, current estimates of the disease burden in the USA report a peak of associated liver disease complications and deaths between 2015 and 2030.³ Thus, access and alternatives for more effective treatment will be crucial in coming years.

Although antiviral therapy is available for this infection, the standard of care (SOC) has not changed for almost a decade. Furthermore, current treatment [pegylated interferon α (pegIFN) and ribavirin] has variable results depending on the viral genotype, is not suitable for all patients, and is lengthy, expensive and accompanied by significant adverse effects. Sustained virological response (SVR) rates in patients with genotype 1 infection, the predominant genotype in North America, are <50% with a prolonged duration of therapy (48–72 weeks).^{4,5} Additionally, response rates

to pegIFN and ribavirin are lower for African and Latino Americans, and for those co-infected with HIV.^{6–8} Thus, there is a clear need for more effective and tolerable therapies. The development of directly acting antivirals (DAAs) against hepatitis C is a major therapeutic advance that promises to fill this void. While many new compounds directed towards multiple viral targets at many steps of the HCV viral life cycle (Figure 1) are currently in development, this review will focus on the NS3/4A protease inhibitors, which are currently the most advanced in clinical study.

What are specifically targeted therapies for hepatitis C?

HCV is a flavivirus with a positive-sense RNA genome of ~9.6 kb. This genome codes for a single polyprotein that is co- and post-translationally cleaved into 10 major structural (capsid, envelope glycoproteins) and non-structural (NS2–NS5B) proteins [step (c) in Figure 1].⁹ Many of the non-structural proteins have been identified as potential targets for antiviral development (Figure 2).^{10,11} Owing to the absence of a small animal model of HCV infection, the ability to study the viral life cycle and identify potential therapeutic targets was not possible until the last decade, when a major scientific breakthrough developed the

subgenomic HCV replicon model. This cell culture system has subsequently been modified to support full-length autonomous HCV RNA replication in a hepatoma cell line that can be readily quantified.¹² Owing to the availability of only genotype 1 replicons until recently, and the overall burden of genotype 1 infection in the USA and Western Europe, the development of DAAs was initially restricted to this genotype. However, the expansion of drug development to other HCV genotypes is now occurring. Furthermore, while the replicon system has allowed the study of RNA replication, recent infectious virus production in tissue culture has also allowed the identification of other targets in the viral life cycle (Figure 1) and the screening of potential compounds.¹³

The non-structural proteins that remain the primary target for directly targeted therapy include the viral RNA-dependent RNA polymerase (NS5B) and the serine protease (NS3) with its cofactor (NS4A). The NS3/NS4A protease is required for viral replication, with its principal function in post-translational processing.¹⁴ *In vitro*, it also has been shown to play a primary role in the regulation of intracellular type I IFN pathways, thus suppressing the innate immunological response to HCV infection.^{15,16} Highly selective inhibitors of these functional proteins are the primary focus of drug development, although other sites of action, including viral receptor binding/entry and viral assembly/release, cyclophilin B inhibitors and other immunomodulatory agents have shown promise in early phase investigations (Table 1). However, the genetic variability of HCV, which is in most part due to the high rate of spontaneous error generation (approximately one nucleotide per genome per replication cycle) during viral replication and poor fidelity of the RNA polymerase, facilitates the rapid development of antiviral resistance and will remain a major challenge to the clinical development of DAAs.

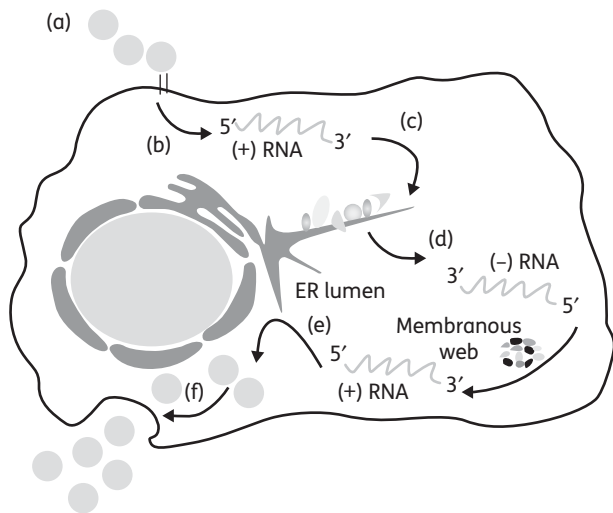


Figure 1. Life cycle of hepatitis C virus: (a) virus particle–receptor binding and endocytosis; (b) cytoplasmic release and uncoating; (c) translation and polyprotein processing with structural and non-structural proteins shown at the endoplasmic reticulum (ER); (d) RNA replication occurring in the membranous web; (e) virion packaging and assembly; and (f) virion maturation and release.

How effective are DAAs?

To date, the peptidomimetic inhibitors of the NS3/4A serine protease have been the most extensively studied DAAs. The first protease inhibitor, BILN 2061, provided ‘proof of concept’ data and clearly showed that protease inhibition is associated with a rapid decline of viral load in genotype 1-infected patients; however, clinical development was halted due to cardiac toxicity in animals.¹⁷ Two potent NS3/4A protease inhibitors have now progressed to Phase III of clinical development, telaprevir (VX-950) and boceprevir (SCH-503034).

The Phase IIb Protease Inhibition for Viral Evaluation 1 (PROVE1) ($n=250$, US sites) and PROVE2 ($n=334$, European sites) randomized, controlled trials were undertaken and completed in genotype 1, treatment-naïve, HCV-infected patients, using telaprevir in combination with pegIFN and ribavirin or with pegIFN alone (ribavirin sparing), compared with the SOC (pegIFN and ribavirin for 48 weeks) (Figure 3).^{18,19} The PROVE

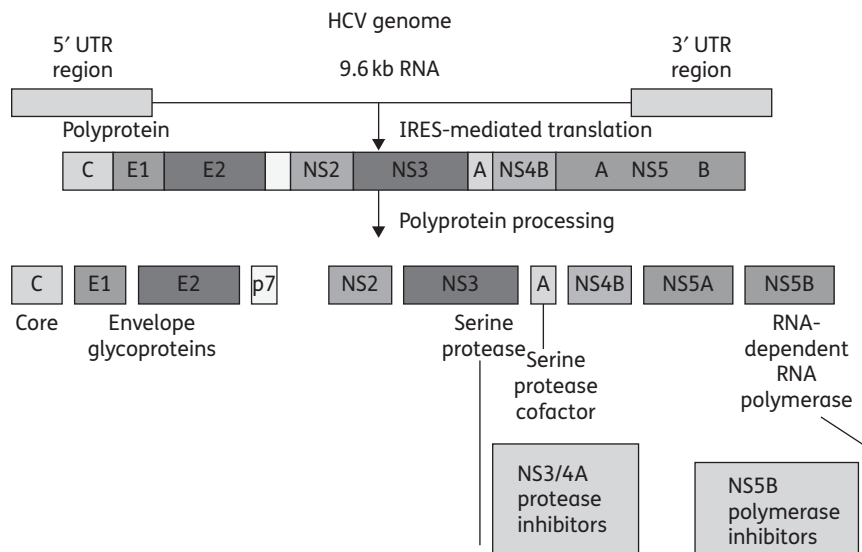


Figure 2. HCV polyprotein processing. IRES, internal ribosome entry site.

Table 1. Directly acting antivirals in development

Directly acting antiviral	Mechanism	Phase of study
GS 9132	protease inhibitor	withdrawn
BILN 2061	protease inhibitor	withdrawn
SCH 900518	protease inhibitor	withdrawn
Telaprevir	protease inhibitor	Phase III
Boceprevir	protease inhibitor	Phase III
TMC-435	protease inhibitor	Phase II
MK-7009	protease inhibitor	Phase II
BI 201335	protease inhibitor	Phase II
R7227	protease inhibitor	Phase II
VX-985	protease inhibitor	Phase I
ABT-333	protease inhibitor	Phase I
BMS-650032	protease inhibitor	Phase I
ACH-1625	protease inhibitor	Phase I
GS 9256	protease inhibitor	Phase I
Valopicitabine	polymerase inhibitor	withdrawn
R1626	polymerase inhibitor	withdrawn
GS 9190	polymerase inhibitor	Phase II
IDX184	polymerase inhibitor	Phase II
R7128	polymerase inhibitor	Phase II
ABT-072	polymerase inhibitor	Phase I
VX-222 and 759	polymerase inhibitor	Phase I
MK-3281	polymerase inhibitor	Phase I
PSI-7851	polymerase inhibitor	Phase I
PHX1766	polymerase inhibitor	Phase I
VCH-916	polymerase inhibitor	Phase I
ITX5061	HCV entry inhibitor	Phase II
SCY-635 ^a	cyclophilin inhibitor	Phase II
Debio 025 ^a	cyclophilin inhibitor	Phase II

Please note this is not a comprehensive list; for other DAAs in development see NIH clinical trials at www.clinicaltrials.gov.

^aCyclophilin B inhibitors are not classified as DAAs. Cyclophilin inhibitors exhibit antiviral activity by competitively binding NSSB at a non-catalytic site, inhibiting the binding cyclophilin B, which is required for HCV RNA replication.

studies were designed to evaluate the feasibility of a shorter course of therapy with the addition of telaprevir to the SOC and, also, of ribavirin-sparing regimens. PROVE1 reported an SVR rate (undetectable serum HCV RNA 24 weeks after the end of treatment) of 61% in the 24 week arm (telaprevir plus pegIFN and ribavirin for 12 weeks followed by pegIFN and ribavirin consolidation for 12 weeks) as compared with 41% in the SOC arm ($P=0.02$) and 67% in the 48 week arm (telaprevir plus pegIFN and ribavirin for 12 weeks followed by pegIFN and ribavirin consolidation for 36 weeks; $P=0.51$).¹⁸ The SVR rate was lower (35%) in patients treated with a shortened course of all three drugs for 12 weeks. Rates of rapid virological response (undetectable HCV viral load at week 4), a strong positive predictor of SVR, were higher with telaprevir-based therapy (81% in the 24 week arm) than without telaprevir (11% in the SOC arm). The PROVE2 trial also included a ribavirin-sparing arm (telaprevir plus pegIFN and ribavirin) and assessed shortened courses of therapy (12 and 24 weeks).¹⁹ The 24 week arm (telaprevir plus pegIFN and ribavirin for 12 weeks followed by pegIFN and ribavirin consolidation for 12 weeks) achieved a superior SVR of 69% (SOC 46%, $P=0.004$) with minimal virological breakthrough (2%). The ribavirin-sparing arm (telaprevir plus pegIFN for 12 weeks) performed poorly, with an SVR of only 36%, which was primarily due to a higher relapse rate of 48% and virological breakthrough of 26%. The study arm with a shortened course of all three drugs for 12 weeks achieved an SVR of 60%, which was not statistically different to the control arm ($P=0.12$), although it appeared higher than the SVR achieved by the same regimen in PROVE1. The difference in SVR in the 12 week arms between studies is probably due to differences between the two study populations, including the host pharmacogenomic profile. In addition, the role of telaprevir in chronic infection with genotypes 2–4 has been investigated in Phase IIa studies (C209 and C210). Considerable activity was reported against genotypes 2 and 4, but there was only limited activity against genotype 3 virus.^{20,21} Further experience with the DAAs is necessary in non-genotype 1 infections, as activity is not consistent across drug classes.

As with the telaprevir studies, the Phase IIb study of boceprevir, HCV Serine Protease Inhibitor Therapy-1 (SPRINT-1, $n=595$),

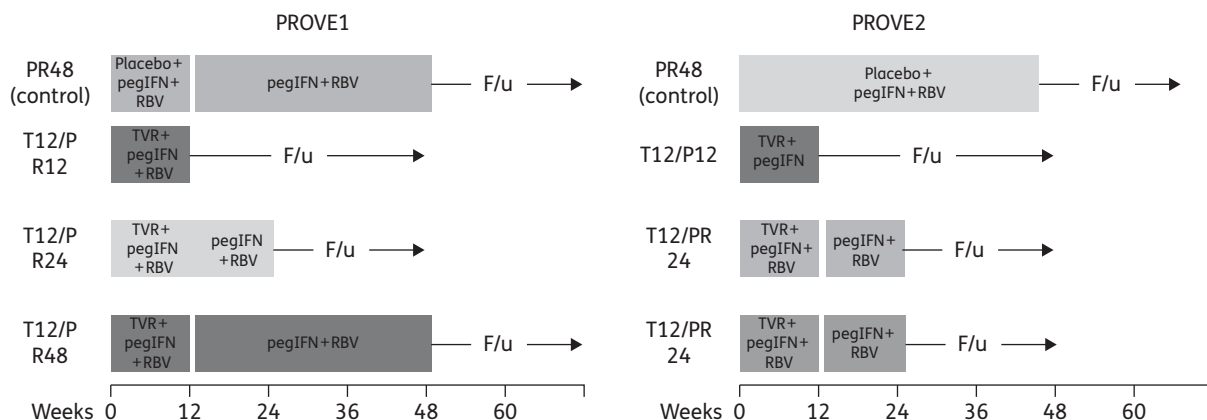


Figure 3. PROVE1 and PROVE2 study design. PROVE1 dosing: pegIFN at 180 $\mu\text{g}/\text{week}$; ribavirin (RBV) at 1000 or 1200 mg/day; and telaprevir (TVR) at 750 mg every 8 h. PROVE2 dosing: pegIFN at 180 $\mu\text{g}/\text{week}$; RBV at 1000 or 1200 mg/day; and TVR at 750 mg every 8 h. F/u, follow-up to sustained virological response.

conducted in genotype 1 treatment-naive HCV-infected patients, has confirmed that SVR rates are higher in the boceprevir treatment arms (Figure 4).²² However, a shorter course of 28 weeks of therapy (boceprevir plus pegIFN and ribavirin) did not appear to achieve the same SVR (55%) as 48 weeks of therapy (boceprevir plus pegIFN and ribavirin) (66%). The SPRINT-1 study also investigated the role of a 4 week SOC lead-in phase, which may theoretically decrease the risk of resistant mutants to DAAs by decreasing the viral burden prior to the initiation of the DAA and allow better discrimination of non-responders. There was no difference between the lead-in (4 weeks of pegIFN and ribavirin followed by 24 weeks of boceprevir plus pegIFN and ribavirin) and no lead-in arms with the 28 week course of therapy (56% versus 55%), but there did appear to be a difference between the lead-in (4 weeks of pegIFN and ribavirin followed by 44 weeks of boceprevir plus pegIFN and ribavirin) and no lead-in arms for the 48 week course of therapy (74% versus 66%).²² At this time, the lead-in strategy (both length and duration) requires further study before its role in the treatment of HCV can be determined.

Many other NS3/4A protease inhibitors are currently in clinical development. Protease inhibitors that are currently either entering or are in ongoing Phase II study include TMC-435 (Tibotec, Mechelen, Belgium and Medivir, Huddinge, Sweden), MK-7009 (Merck, NJ, USA), BI 201335 (Boehringer Ingelheim Pharmaceuticals, Ingelheim, German), R7227 (formerly ITMN-191; Intermune, CA, USA and Roche Pharmaceuticals, Basel, Switzerland), VX-985 (Vertex Pharmaceuticals, MA, USA) and ABT-333 (Abbott Pharmaceuticals, IL, USA).

Will DAAs allow interferon-sparing alternative regimens?

With the development of DAAs comes the hope that interferon-sparing regimens might be effective and possible, thus improving the tolerability of treatment. In a Phase Ib study assessing telaprevir monotherapy in patients with genotype 1 HCV infection, 14 days of therapy at three different doses (450 mg every 8 h, 750 mg every 8 h and 1250 mg every 12 h) reduced HCV viral load by $\geq 2 \log_{10}$ IU/mL in all patients, with a median decrease of $\sim 4 \log_{10}$.²³ However, viral breakthrough was noted in a

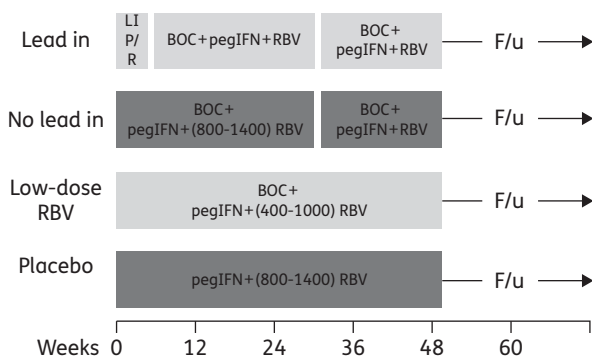


Figure 4. SPRINT-1 study design. Dosing: pegIFN at 1.5 μ g/kg/week; boceprevir (BOC) 800 mg every 8 h; ribavirin (RBV) 800–1400 mg daily in total, but given in two doses. LI, 4 week lead-in period; P/R, pegIFN+ribavirin; F/u, follow-up to sustained virological response.

significant number of patients and this correlated with the development of amino acid substitutions in the catalytic site of the enzyme.²⁴ In the absence of selective pressure from continued telaprevir exposure, the majority of resistant mutants were replaced by wild-type virus within 3–7 months, although in a minority of patients mutations were detectable for up to 2 years.²⁴ These data indicate that monotherapy with DAAs is not effective due to the rapid selection of viral resistance mutations. Thus, the addition of DAAs to other antiviral compounds, including interferon, or combination therapy with other DAAs will be necessary to achieve long-term sustained viral eradication.

Synergistic antiviral activity does exist between telaprevir and pegIFN.²⁵ The combination of telaprevir and pegIFN exhibited a greater antiviral effect than either drug alone, with a median decrease in the HCV viral load of 5.5 \log_{10} .²⁵ Furthermore, viral sequence analysis identified fewer resistance mutations (2/7) with the combination therapy compared with DAA monotherapy (7/8); thus, pegIFN appears to partially protect from selection for resistant mutants. In the Phase IIB PROVE studies, 7%–10% of telaprevir-treated patients had virological breakthrough.^{18,19} High-level resistance mutations (combination of V36M and R155K or A156T) were dominant in the viral population at the time of breakthrough. Also, in these studies, baseline analysis of the HCV virus identified low-level resistance to telaprevir at baseline in 1% of patients.¹⁸ Thus, single DAAs in combination with pegIFN will remain a necessary component of the regimen.

Although preliminary, there is also early evidence of the efficacy of DAA combinations that may offer the advantage of reducing the emergence of resistance, and potentially eliminate the need for pegIFN and/or ribavirin. INFORM-1 was designed to assess the efficacy of DAA combination therapy including R7128 (nucleoside analogue polymerase inhibitor) and R7227 (protease inhibitor) for 14 days followed by pegIFN and ribavirin consolidation.²⁶ This Phase I ascending-dose study in treatment-naive and treatment-experienced genotype 1 patients showed rapid HCV viral decline at day 13, with 4–5 \log_{10} decreases in all patients and viral suppression in a majority of treatment-naive patients [88% for lower limit of quantification (LLOQ) <43 IU/mL and 63% for LLOQ <15 IU/mL]. One patient did experience virological rebound, although sequence analysis of the NS3 region did not show evidence of resistance to R7227. Baseline population sequencing of one patient revealed the presence of E168 in NS3, a codon change associated with R7227 resistance; however, this patient experienced continuous viral decline on combination therapy (viral load of 139 IU/mL on day 14) and achieved viral suppression with the consolidation phase. Thus, the combination of two or more DAAs may provide success in terms of interferon sparing, although further study will be necessary to determine the long-term success of such regimens and in what proportion of patients such a strategy could potentially result in SVR.

The selection for resistant mutations is common among all protease inhibitors (Figure 5) and *in vitro* studies have identified variants cross-reactive to both telaprevir and boceprevir, suggesting a class effect. Both *in vitro* and *in vivo* data have demonstrated that resistant mutants have reduced replication capacity compared with the wild-type virus.²⁷ Drug-resistant mutants remain susceptible to interferon therapy, both *in vitro* and in clinical studies. It is now recognized that the natural

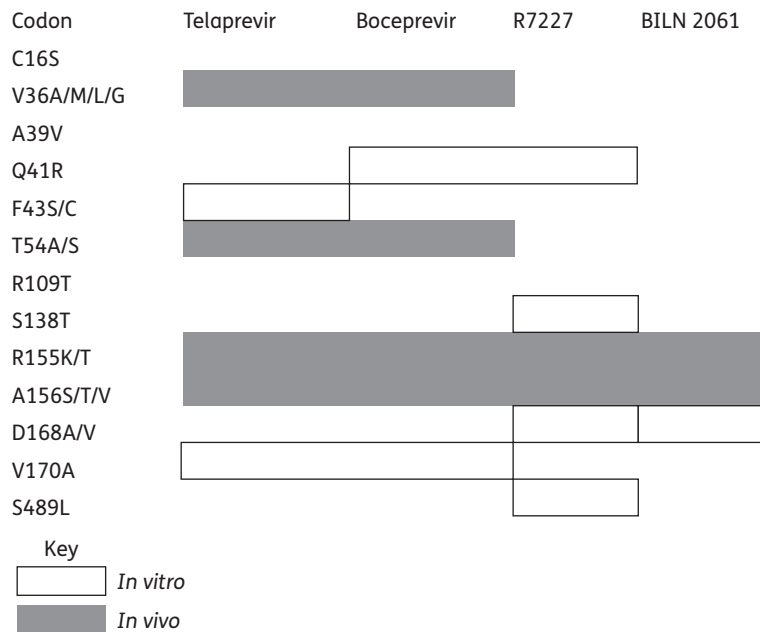


Figure 5. Amino acid substitutions found with protease inhibitors.

presence of codon changes that can confer resistance to DAAs results in baseline mutations that may be selected in the presence of drug pressure, with 1% of patients in PROVE2 having evidence of low-level resistance mutations at baseline.¹⁹ Furthermore, whether viral mutants are archived is unknown; thus, the long-term consequences of viral resistance remain to be determined. While at this time the role of sequencing analyses both of baseline mutations and of mutations developed on therapy remains unclear, based on the role that similar testing plays in guiding therapy in HIV and hepatitis B virus (HBV) treatment, it is likely that sequencing will play a role in HCV once DAAs are available outside of clinical trials. Furthermore, while baseline viral sequencing may have less of a role with combination regimens including pegIFN and ribavirin, it will become more relevant if pegIFN-sparing regimens are developed.

What role will ribavirin play in the treatment of HCV with DAAs?

Despite its modest antiviral effect on HCV replication, ribavirin, when combined with pegIFN, has been shown to increase the number of patients with an end-of-treatment response and to prevent relapse after the treatment period by accelerating the second phase of viral decline (a strong predictor of SVR).^{28,29} The mechanism of action by which ribavirin has this viral effect remains under debate, but it appears to continue to play a role in the setting of DAA therapy. The PROVE2 study included a study arm without ribavirin (telaprevir in combination with pegIFN for 12 weeks) and this showed that the ribavirin-sparing arm achieved similar rates of SVR (36%) as the SOC treatment arm (46%, $P=0.20$).¹⁹ The ribavirin-sparing arm also had a higher virological breakthrough rate (26%) as compared with the study drug treatment arms (2%). Furthermore, the ribavirin-

sparing arm had a relapse rate of 48% versus 14% in the optimal 24 week drug treatment arm. SPRINT-1 also evaluated the role of ribavirin by including a low-dose ribavirin arm, boceprevir in combination with pegIFN and 400–1000 mg of ribavirin daily (versus standard weight-based dosing of 800–1400 mg of ribavirin daily).²² Similarly, the low-dose ribavirin arm of the study achieved an SVR rate of only 36%, compared with 38% in the SOC arm and 55%–74% in the other boceprevir study arms. These lower SVR rates were also associated with an increased risk of viral breakthrough during treatment and a higher relapse rate after the end of treatment.

These data suggest that ribavirin will remain an essential component of HCV therapeutic regimens for the foreseeable future; not only because of its important effect in limiting the emergence of resistant variants, but also due to the decreased rates of relapse in the drug's presence. The role of ribavirin has also been confirmed in early studies of HCV polymerase inhibitor compounds. Therefore, while future combinations of DAAs and other newly developed compounds may ultimately limit the therapeutic role of ribavirin, for now it remains an important component of any HCV treatment regimen.

Will DAAs improve the tolerability of HCV treatment regimens?

In addition to low efficacy in many patient groups, a primary issue related to the current SOC for HCV treatment remains poor tolerance of the therapy, including flu-like symptoms, depression and anaemia. In the Phase II studies of the protease inhibitors telaprevir and boceprevir, treatment discontinuation rates were higher in the DAA arms: PROVE1, 21% versus 11%; PROVE2, 12% versus 7%; and SPRINT-1, 27% versus 8%.^{18,19,22} Furthermore, telaprevir was more commonly associated with rash, pruritis, nausea/diarrhoea and anaemia, while boceprevir

was more commonly associated with anaemia and dysgeusia (altered taste), when compared with the SOC arm. Thus, the combination of DAAs with pegIFN and ribavirin to date appear to increase the side effect profile and treatment discontinuation rates of HCV treatment regimens. In further drug development and future early phase clinical trials, there will need to be continued attention to the balance of drug toxicity and efficacy.

Will DAAs allow us to shorten the course of HCV therapy?

The length of therapy for the treatment of hepatitis C depends on the viral genotype and early viral kinetic parameters, but, currently, for chronic infection with genotype 1, 48 weeks remains the standard length of therapy. All Phase IIb studies of protease inhibitors have assessed the efficacy of a shortened course of therapy. For telaprevir, results of PROVE1 suggest 24 weeks of therapy (12 weeks triple therapy followed by 12 weeks SOC) is similar to 48 weeks (12 weeks triple therapy followed by 36 weeks SOC) and superior to both 12 weeks of triple therapy and to the SOC (48 weeks).¹⁸ The PROVE2 study confirmed that 24 weeks of therapy (12 weeks triple therapy followed by 12 weeks SOC) was superior to both 12 weeks of ribavirin-sparing therapy (telaprevir in combination with pegIFN) and to the SOC (48 weeks), and while it had similar efficacy to the 12 week course of triple therapy, it had lower relapse rates (14% versus 29%).¹⁹

For boceprevir, shortening the course of therapy did not appear feasible. Results of SPRINT-1 (discussed previously) suggest 48 weeks of triple therapy is needed to maximize rates of SVR.²² Given the potential observed differences in the optimal length of treatment between different protease inhibitor compounds, the duration of therapy for DAAs may not be generalizable and will require individual evaluation in comparative clinical trials. Furthermore, different durations of therapy in treatment-experienced patients will need to be addressed in future clinical trials in these patient populations.

Are DAAs an option for treatment-experienced patients?

PROVE3 is a randomized Phase IIb study assessing the efficacy of telaprevir in combination with either pegIFN and ribavirin or pegIFN alone (ribavirin sparing) in treatment-experienced genotype 1 patients.³⁰ Rates of SVR were similar (51%–53%) for two treatment arms [triple therapy for 12 weeks followed by SOC for 12 weeks (24 week arm) and triple therapy for 24 weeks followed by SOC for 24 weeks (48 week arm)] when compared with SOC (14%). Those patients with the most favourable response were prior relapsers with SVR rates of 69% and 76% in the 24 and 48 week arms, respectively. The most difficult to treat population, non-responders, achieved SVR rates of 38%–39% in both the 24 and 48 week arms, as compared with 9% in the SOC arm. These latter rates are similar to current SVR rates for SOC in treatment-naïve genotype 1 patients. The fourth treatment arm included triple therapy for 24 weeks followed by SOC for 24 weeks, but did not achieve superior SVR rates as compared with SOC in the non-responder patients and was inferior to other triple treatment arms in all patients, including relapsers. These

data are encouraging for all patients, but are especially exciting for patients who experience breakthrough or relapse with their prior course of therapy. A Phase II study evaluating boceprevir in prior non-responders yielded low SVR rates (7%–14%); however, a further study is under way with higher doses of boceprevir.³¹

What more needs to be done in the study of DAAs?

We are still in the early stages of drug development, with limited published data, but DAAs hold great promise for improving SVR and shortening treatment duration. However, much needs to be done to improve the tolerability, decrease the risk of resistance, standardize resistance testing, determine the optimal doses and duration of pegIFN and ribavirin consolidation, and establish more efficacious combinations of the various therapeutic options. The efficacy of DAAs needs to be evaluated in other HCV genotypes and in difficult-to-treat populations, including patients with cirrhosis, decompensated liver disease, transplantation, renal failure and HIV or HBV co-infections.

What does the future hold in the treatment of hepatitis C infection?

Within the next few years, it is likely that the first DAAs will be approved for use in combination with pegIFN and ribavirin in treatment-naïve genotype 1 HCV-infected patients, thus increasing the current achievable SVR from 40% to 60%–70%. A recent landmark discovery of an *IL28B* gene single nucleotide polymorphism (SNP; rs12979860) found an association with this SNP and response to current HCV therapy (pegIFN and ribavirin), and has provided further insight into the mechanism of the innate immune response to HCV infection, suggesting a role for IFN- λ in the HCV immune response.³² This finding has now been validated in other populations and has been further implicated in the natural clearance of HCV infection.^{33–35} This polymorphism has been shown to enhance viral kinetics, with more rapid rates of viral decay at 2 weeks and higher rates of RVR in those homozygous for the SNP.³⁶ The role of this SNP and of IFN- λ is unknown in the setting of DAAs. It is possible that due to the rapid viral decline seen with DAAs, the association of this polymorphism will be attenuated or that patients who carry the polymorphism will be able to achieve an SVR with combination DAA alone and possibly with a shorter course of therapy. While we do not know exactly what the future holds, there are likely to be different combinations of DAA- and IFN-based regimens as part of individualized therapy for chronic HCV infection. The complexity of the regimens, duration of therapy, risk of resistance and the role of resistance sequence analysis as well as the long-term role of our current therapies remain to be determined.

Transparency declarations

J. M. has received in the past or currently receives grant/research support from: Anadys Pharmaceuticals, Inc., Biolex Therapeutics, Glaxo-SmithKline, Human Genome Sciences, Inc., Idera Pharmaceutical, Inc., Abbott Laboratories, Gilead, Globeimmune, Inc., Hoffman-La Roche,

Intarcia Therapeutics, Inc., Novartis Pharmaceuticals, Inc., Pfizer Pharmaceuticals, Inc., Pharmasset, Inc., Roche Pharmaceuticals, Schering-Plough Corporation, Vertex Pharmaceuticals and Wyeth. J. M. has been or is currently a consultant/advisor for: Anadys Pharmaceuticals, Inc., Abbott Laboratories, Alnylam, Biologix Therapeutics, Biocryst, Epiphany, Glaxo-SmithKline, Gilead, GlobeImmune, Inc., Hoffman-La Roche, Human Genome Sciences, Inc., Idera Pharmaceutical, Inc., Intarcia Therapeutics, Inc., ItheRx, National Genetics Institute, Novartis Pharmaceuticals, Inc., Peregrine, Pfizer Pharmaceuticals, Inc., Pharmasset, Inc., Sanofi-Aventis, Schering-Plough Corporation, Vertex Pharmaceuticals, Wyeth and XL. The remaining authors have none to declare.

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