Review

Future directions in therapy for chronic hepatitis C

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The development of new antiviral therapies in the treatment of hepatitis C virus (HCV) is reviewed, including a discussion of the potential advances that this treatment will bring. Data from new molecules in Phase I and II clinical trials, specifically polymerase and protease inhibitors, will be discussed. The potential for resistance has been reported when these have been used as monotherapy. However, their use in combination with pegylated interferon, particularly in the presence of ribavirin, has resulted in significant improvements in antiviral activity. Preliminary studies have confirmed that the new molecules are well tolerated and further clinical studies are underway to evaluate their efficacy. Nevertheless, because of its critical role at all stages of therapy, pegylated interferon is likely to remain the cornerstone of HCV therapy.

Introduction

The combination of pegylated interferon (PEG-IFN) plus ribavirin is the current standard of care for patients with chronic hepatitis C and is likely to remain the backbone of treatment for this condition for the foreseeable future [1,2]. Optimizing therapy with the standard of care is an effective strategy that will improve outcomes over the next few years (see articles by Lee and Ferenci and by Berg and Carosi in this supplement [3,4]). The development of novel agents with enhanced efficacy and/or better tolerability may lead to considerable improvements in outcomes over the long term. Therapeutic classes with clinical potential within the next 5 years are shown in Table 1.

Modified IFNs

An avenue that is being actively pursued is enhancing the activity of IFN. One approach is to produce novel IFN-α analogues with improved antiviral and Th1-inducing activity through ‘gene shuffling’. This approach has led to the development of interferon compounds with more than 10-fold greater antiviral activity than IFN alfacon-1 [5]. Clinical trials in patients with chronic hepatitis C are awaited with great interest.

Another ongoing programme is dedicated to producing an IFN with a longer elimination half-life than the commercially available PEG-IFNs. Alb-IFN-α2b (Albuferon®; Human Genome Sciences, Rockville, MD, USA) is a long-acting preparation that comprises IFN-α2b linked to human albumin. In a randomized, multicentre, Phase II trial, the drug was combined with ribavirin and was administered at doses of 1,000 or 1,200 mg/day at 2- and 4-week intervals for a total of 48 weeks. There was no significant improvement in sustained virological response (SVR) rates in patients treated with alb-IFN-α2b plus ribavirin compared with a control group treated with the combination of PEG-IFN-α2a (40 kDa; Pegasys®; Roche, Basel, Switzerland) plus ribavirin (Copegus®; Roche; 51–59% versus 58%) [6]. Only after the intent-to-treat population was limited to those patients with >75 kg bodyweight and >80% adherence could superiority of the alb-IFN-α2b treatment arms over PEG-IFN-α2a be demonstrated. The rate of discontinuations because of adverse events was consistently higher in patients treated at 2- and 4-week intervals with alb-IFN-α2b (9–18%) than with PEG-IFN-α2a (6%) [6].

Specifically targeted antiviral therapy for chronic hepatitis C

A number of compounds with direct activity against hepatitis C virus (HCV) are under clinical development. The most advanced compounds are those that target HCV polymerase or HCV protease enzymes. Rather than attempting to replace the existing standard of care, the best way to make use of these compounds,
at least in the near future, is to use them in combination with PEG-IFN and ribavirin. The main reason for this is to reduce the risk of resistance. Resistance has been reported with both polymerase and protease inhibitors when administered as monotherapy [2,7,8]. The ultimate goal is to significantly improve SVR rates and/or enhance patient convenience by decreasing the total duration of treatment required to eradicate the virus. The greatest need is in patients infected with HCV genotype 1, in whom SVR rates are lowest, and in those who have failed previous IFN-based therapy because the chance of a cure is <20% with existing therapy.

Resistant variants of the virus have been detected in patients treated with protease inhibitors and polymerase inhibitors. As monotherapy, this resistance would likely develop before viral eradication could be accomplished. It is unlikely that cross-resistance will occur between agents of different classes because of their distinct therapeutic targets, but, at present, few data are available on which to base combination therapy. Measures to delay or prevent the emergence of resistant HCV variants are mandatory for ensuring the clinical usefulness of experimental therapies [8]. Potential strategies include administering newer antiviral agents with low barriers to genetic resistance against the background of the current standard of care (that is, PEG-IFN plus ribavirin) or in combinations that do not demonstrate cross-resistance. The former strategy is currently viable, whereas the latter will remain theoretical until the efficacy, safety and resistance profiles of several agents have been fully characterized.

The ideal PEG-IFN for use in combination with the newer agents should have a rapid onset of action and show consistent activity throughout the dosing interval in order to minimize the likelihood of resistance. The agents used in combination with new antivirals have included both PEG-IFN-α2a and PEG-IFN-α2b. The more sustained serum levels of PEG-IFN-α2a are a distinct advantage in achieving steady viral load reduction without fluctuations, which can give rise to viral rebound.

HCV protease inhibitors

The NS3-4A serine protease of HCV is a multifunctional protein that is essential for post-translational processing of viral proteins. This protein is the target of several development programmes. Development of BILN 2061 (Boehringer Ingelheim, Ingelheim, Germany), the first of these agents to show promising antiviral activity and the first to enter the clinic, was discontinued because of cardiotoxicity in animals [9]. When used alone, protease inhibitors promote the emergence of resistant variants [10,11]; therefore, all ongoing development programmes are evaluating protease inhibitors in combination with PEG-IFN.

Telaprevir

Telaprevir (VX-950; Vertex, Cambridge, MA, USA) is in Phase II of development and is presently the best characterized protease inhibitor and the furthest down the road to market. An understanding of the efficacy, toxicity and resistance profile of the drug is emerging. Mutations were detected at four positions in the NS3 serine protease gene in HCV RNA isolated from the serum of patients after 14 days of monotherapy with oral telaprevir (750 mg every 8 h or 1,250 mg every 12 h). One variant conferred high-level resistance with a 781-fold increase in 50% inhibitory concentration (IC50) compared with wild-type HCV [8]. After withdrawal of the drug, wild-type virus re-emerged and became predominant; however, variants with low-level resistance to telaprevir (four- to sevenfold increase in IC50) were still detectable 3–7 months after treatment [8]. Rapid and sustained reductions in serum HCV RNA levels were obtained in patients with HCV genotype 1 infection given telaprevir three times daily in combination with PEG-IFN-α2a 180 μg once weekly. After 14 days of treatment, median reductions in HCV RNA were greater in patients treated with the combination (5.5 log10 IU/ml) than monotherapy with either PEG-IFN-α2a (1.1 log10 IU/ml) or telaprevir (4.0 log10 IU/ml) [12].

Telaprevir has now advanced to Phase II clinical trials in which it is being studied in treatment-naive and
treatment-experienced patients infected with HCV genotype 1. In the Phase II PROVE-1 trial in treatment-naive patients, telaprevir 750 mg every 8 h has been combined with a therapeutic backbone of PEG-IFN-α2a (40 kDa) 180 μg/week plus ribavirin 1,000 or 1,200 mg/day [13]. The study involved four treatment groups, three of which were treated with the triple-therapy regimen for 12 weeks followed by 0, 12, or 36 weeks of PEG-IFN-α2a plus ribavirin combination therapy. The control group was treated with the standard of care: 48 weeks of treatment with PEG-IFN-α2a plus ribavirin.

An interim analysis of data collected at the end of the triple-therapy phase of the trial (week 12) showed that significantly more patients treated with telaprevir had undetectable HCV RNA at week 12 (<10 IU/ml; 70% versus 39% receiving PEG-IFN-α2a plus ribavirin; P<0.001; Figure 1) [13]. Corresponding rates of rapid virological response (RVR; undetectable HCV RNA [<10 IU/ml] at week 4) were 79% and 11% (P<0.001). Through the first 12 weeks of the trial, the discontinuation rate was higher in patients treated with triple therapy (19/175; 11%) than with the standard of care (2/75; 3%). Rash was the most common cause of withdrawal in patients treated with telaprevir (7/19 patients) [13]. One arm of the trial investigated whether 12 weeks of triple therapy would be sufficient to eradicate the virus. At week 20 of follow-up, 35% of the intent-to-treat population had undetectable HCV RNA (<10 IU/ml), with the rate rising to 67% of patients who achieved an RVR.

Final SVR data are now available for patients in two of the four treatment groups in PROVE-1. Among patients treated for 12 weeks with telaprevir-based triple therapy followed by 12 weeks of PEG-IFN-α2a (40 kDa) plus ribavirin (24 weeks total) 61% (48 of 79) achieved an SVR; among those treated with 12 weeks of triple therapy alone 35% (6 of 17) achieved an SVR [14].

In the European PROVE-2 trial, which is generally similar to PROVE-1, SVR rates of 59% were reported in patients treated for a total of 12 weeks with telaprevir-based triple therapy and 65% in patients treated for 24 weeks, the first 12 of which comprised telaprevir-based triple therapy followed by 12 weeks of PEG-IFN-α2a (40 kDa) plus ribavirin therapy. The SVR rate in patients treated with telaprevir plus PEG-IFN-α2a (40 kDa) for 12 weeks was 29% [15].

Virological breakthrough during the first 12 weeks of therapy occurred in 24 of 78 patients treated with telaprevir plus PEG-IFN-α2a (40 kDa) and in just 5 of 163 patients treated with triple therapy. A viral sequence analysis showed that breakthrough was associated with selection of telaprevir-resistant mutants [16].

Collectively the results of PROVE-1 and PROVE-2 demonstrate that ribavirin is essential to maximize SVR rates in patients treated with telaprevir and that SVR rates of 60–65% may be possible with a 24-week triple-therapy regimen in genotype 1 patients.

**Boceprevir**

Boceprevir (SCH 503034; Schering-Plough Corporation, Kenilworth, NJ, USA) is less potent than telaprevir. Mean reductions in serum HCV RNA were 1.08 log_{10} and 1.61 log_{10} after 1 week of treatment with boceprevir 200 mg and 400 mg three times daily, respectively, in patients with HCV genotype 1 infection who had not responded to previous IFN-based therapy [17]. The mean maximum reductions in HCV RNA level after 2 weeks of combination therapy with PEG-IFN-α2b plus boceprevir 200 mg and 400 mg three times daily were 2.45 log_{10} and 2.88 log_{10} respectively (Figure 2). The effects of the two agents were strictly additive and the addition of boceprevir did not abrogate the characteristic fluctuations in serum HCV RNA levels that occur with PEG-IFN-α2b [17]. Boceprevir is in Phase II of clinical development.

**HCV polymerase inhibitors**

Most polymerase inhibitors are nucleoside analogues that require conversion to an active triphosphate form, and cause chain termination when incorporated into a nascent viral RNA chain. They are active against HCV
of all genotypes. Non-nucleoside polymerase inhibitors are active at non-catalytic sites and do not require triphosphate conversion.

R1626
R1626 (Roche) is an oral prodrug of the potent and selective nucleoside analogue polymerase inhibitor R1479, and is currently in Phase II trials [18]. To date, it is currently the most advanced compound in this class. Viral load reductions obtained with the drug are the highest reported to date with a polymerase inhibitor, and are of the same order of magnitude as those observed with potent protease inhibitors. The drug produced dose-dependent reductions in HCV RNA of $1.6 \log_{10}$, $2.6 \log_{10}$ and $3.7 \log_{10}$ after 14 days when given as monotherapy at a twice-daily dose of 1,500 mg, 3,000 mg and 4,000 mg, respectively, in an ascending-dose Phase IB trial in patients infected with HCV genotype 1 (Figure 3) [18]. Five out of nine patients treated with the highest dose had undetectable HCV RNA (<50 IU/ml) after 14 days of treatment. No evidence of viral resistance was detected during the trial and the drug was well tolerated. Headache was the most common adverse event in each dosage group. Reversible reductions in haemoglobin levels and white blood cell counts were detected in patients treated with the drug.

Phase II trials are now underway in which the drug is being studied in combination with a backbone of PEG-IFN-α2a plus ribavirin. An interim analysis showed that 4 weeks of treatment with the combination of R1626 1,500 mg twice daily plus PEG-IFN-α2a (40 kDa) 180 mg/week plus ribavirin 1,000/1,200 mg/day produced additive or synergistic reductions in serum HCV RNA levels compared with the combination of R1626 plus PEG-IFN-α2a (40 kDa; $5.2 \log_{10}$ versus $3.6 \log_{10}$). The standard of care (PEG-IFN-α2a [40 kDa] plus ribavirin) produced a 2.4 $\log_{10}$ reduction in HCV RNA over 4 weeks. A total of 81% of patients had undetectable HCV RNA after 4 weeks of treatment with R1626-based triple therapy. There was no evidence of resistance to R1626 during the study [19].

Valopicitabine
Valopicitabine (NM283; Idenix, Cambridge, MA, USA) is an oral prodrug of an NSSB polymerase inhibitor. Valopicitabine is being investigated in Phase II trials in combination with PEG-IFN-α2a in treatment-naive genotype 1 patients [20] and in patients with HCV genotype 1 infection who are non-responders to previous PEG-IFN plus ribavirin combination therapy [21]. The combination of valopicitabine 200 or 800 mg/day plus PEG-IFN-α2a 180 μg/week produced rapid reductions in serum HCV RNA in treatment-naive patients (Figure 4). The maximum dose of valopicitabine was subsequently reduced from 800 mg/day to 400 mg/day because of gastrointestinal adverse events that occurred during the first 2 weeks of treatment. After 24, 36 and 48 weeks, mean reductions in serum HCV RNA were on the order of $4 \log_{10}$ [20].

The combination of valopicitabine plus PEG-IFN-α2a did not produce an SVR in previous non-responders to PEG-IFN plus ribavirin in another study [21]. This suggests that it is too early to abandon...
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Figure 4. Mean reductions in serum HCV RNA levels in treatment-naive patients with HCV genotype 1 infection treated with oral valopicitabine plus subcutaneous PEG-IFN-α2a 180 μg/week [20]

- PEG-IFN-α2a + valopictabine 200 mg
- PEG-IFN-α2a + valopictabine 800 mg (pooled)

Dose reduction implemented

Study week

Mean log10 absolute HCV RNA IU/ml

PEG-IFN-α2b
HCV-796 100 mg bid + PEG-IFN-α2b*
HCV-796 250 mg bid + PEG-IFN-α2b*
HCV-796 500 mg bid + PEG-IFN-α2b*
HCV-796 1,000 mg bid + PEG-IFN-α2b*

Figure 5. Change in serum HCV RNA levels during treatment with orally administered HCV-796 plus PEG-IFN-α2b in treatment-naive patients with HCV infection [22]

Lower limit of quantification for Amplicor (Roche Molecular Diagnostics, Pleasanton, CA, USA) <600 IU/ml and the lower limit of detection for Taqman (Roche) <20 IU/ml. HCV, hepatitis C virus; PEG-IFN, pegylated interferon.

The use of small molecules in chronic hepatitis C treatment should involve the addition of an investigational agent together with the current standard of care (PEG-IFN-α2a and ribavirin). The valopicitabine clinical programme has recently been placed on hold in the US because of a high incidence of severe gastrointestinal adverse events.

HCV-796

HCV-796 (ViroPharma, Exton, PA, USA) produced additive reductions in HCV RNA levels when administered orally twice daily at a dose of 100–1,000 mg in combination with once weekly PEG-IFN-α2b (mean reductions of 3.3–3.5 log₁₀ were obtained after 14 days of treatment) [22]. The intraweek rebounds in HCV RNA levels, typical of PEG-IFN-α2b, were observed during treatment with this combination (Figure 5). Dosing of HCV-796 has recently been discontinued in this Phase II study due to safety issues [23].

Conclusion

Clinical data are still pending in order to define the best use of small molecules for the treatment of chronic hepatitis C. Available data suggest that both protease and polymerase inhibitors produce additive or synergistic effects when given with a PEG-IFN-α backbone and will need to be used with this combination to prevent the emergence of resistance. A balanced perspective of these new compounds will have to take the following two points into consideration: the first is whether the high rates of early responses (79% of patients treated with telaprevir triple therapy achieved an RVR) translate into SVR rates with shorter treatment durations that are comparable to those seen in patients treated with standard of care; and the second is that longer treatment durations with small molecules will be necessary for superiority studies, with higher cost, less convenience, more drug–drug interactions, less tolerability with higher discontinuation rates and an enhanced risk of resistance development. Two or more small molecules may be required in order to spare the IFN or ribavirin component of combination therapy, for example, in patients who are previous non-responders to PEG-IFN-α plus ribavirin. Further studies are needed to define possible strategies for future success, for example, PEG-IFN plus ribavirin plus small molecule, a combination of one or several small molecules with PEG-IFN without ribavirin or a combination of several small molecules without PEG-IFN. However, we have a long way to go before these therapeutic options become a reality.

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