Short communication

Sustained virological response after 14-day treatment with danoprevir and 48-week treatment with pegylated interferon-α2a (40 KD) plus ribavirin

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Introduction

Danoprevir (RG7227) is a potent macrocyclic orally administered inhibitor of the HCV NS3/4A protease that is active against HCV genotypes 1, 4 and 6 [1,2]. The drug has been studied in HCV genotype 1 patients as monotherapy, in triple combination with pegylated interferon (PEG-IFN) plus ribavirin (RBV), and in combination with the HCV polymerase inhibitor mericitabine (RG7128) with and without RBV in an interferon-free regimen [3–5]. In Phase Ib studies in treatment-naïve HCV genotype 1 patients, the median maximum reduction in serum HCV RNA level was 3.8 log_{10} IU/ml during 14 days of danoprevir monotherapy, and the median reduction in HCV RNA was 5.7 log_{10} IU/ml after 14 days of combination therapy with danoprevir, PEG-IFN-α2a (40 KD) and RBV [3,4]. The objective of this pooled retrospective analysis was to report the sustained virological response (SVR) rates in treatment-naïve genotype 1 patients who elected to continue treatment with PEG-IFN-α2a (40 KD) plus RBV after completion of the Phase Ib study protocols.

Methods

Patients aged 18 to 65 years with a body mass index between 18 and 30 kg/m², HCV genotype 1 infection, a serum HCV RNA concentration >1×10⁴ IU/ml and
no evidence of cirrhosis on liver biopsy or non-invasive scan were eligible for the Phase Ib studies [3,4]. Individuals coinfected with HBV and/or HIV were excluded as were those patients with decompensated liver disease [3,4]. Although both treatment-naive and previous non-responders were eligible for the monotherapy study, only treatment-naive patients were included in this analysis [3,4].

Patients enrolled in the monotherapy study received one of four danoprevir dosage regimens (Figure 1A), and those enrolled in the triple therapy study received one of six danoprevir dosage regimens in combination with PEG-IFN-α2a (40 KD) 180 µg/week and RBV 1,000 or 1,200 mg/day (Figure 1B). After completion of 14 days of danoprevir treatment, patients had the option of continuing treatment with PEG-IFN-α2a (40 KD) plus RBV (roll-over) to a full 48 weeks if they had been enrolled in the 14-day monotherapy study, or a further 46 weeks if they had been enrolled in the 14-day triple therapy study. There was no interruption between the end of protocol and the commencement of dual therapy with PEG-IFN-α2a (40 KD) plus RBV.

For the purposes of this analysis the primary outcome was SVR, defined as undetectable HCV RNA (<15 IU/ml) in serum at the end of a 24-week untreated follow-up period (week 72) as determined by COBAS® Ampliprep/COBAS® Taqman® HCV assay (Roche Molecular Diagnostics, Pleasanton, CA, USA).
The analysis was conducted according to the intention-to-treat principle; all patients who elected to continue therapy after completing the Phase Ib study protocols were included in SVR calculations.

Results

In French centres, among 32 patients enrolled in the monotherapy study [4], we excluded several patients who did not meet the criteria for this analysis: 6 previous non-responders, those patients who received placebo instead of danoprevir and 6 patients who declined to continue therapy with PEG-IFN/RBV after the protocol-defined 14-day period. Among the 40 patients enrolled in French centres in the triple therapy study [3], we excluded 7 patients who received placebo and 8 patients who declined to continue therapy with PEG-IFN/RBV. This analysis includes a total of 15 patients who had received danoprevir monotherapy for 14 days and 24 patients who received danoprevir-based triple therapy for 14 days, and who elected to continue treatment and were included in this analysis. The baseline characteristics of the 39 patients included in this analysis are presented in Table 1.

In total, 7 of 39 (17.9%) patients discontinued treatment with PEG-IFN-α2a (40 KD) plus RBV. Four individuals (two in the monotherapy group and two in the combination therapy group) discontinued treatment because of insufficient therapeutic response (<2 log₁₀ decrease in HCV RNA by week 12). Two patients were lost to follow-up: one from the monotherapy group who was HCV-RNA-negative at weeks 4 and 12, and one from the combination therapy group who was HCV-RNA-negative at week 6. One individual in the combination therapy group withdrew at week 11 because of an adverse event (skin reaction).

At weeks 2 and 4 of PEG-IFN-α2a (40 KD) plus RBV roll-over, virological response rates were numerically higher in patients who had received danoprevir-based triple therapy (Figure 2A), while at week 12 and at end of roll-over treatment, virological response rates were numerically higher in patients who had received previous danoprevir monotherapy. The final SVR rate was 70.8% in those who had received danoprevir-based triple therapy and 60.0% in those who had received danoprevir monotherapy (Figure 2A), corresponding to an overall SVR rate of 66.7%.

To determine whether early viral kinetics might be predictive of SVR, we compared HCV RNA levels at the end of the protocol phase at week 2 for danoprevir monotherapy and danoprevir-based triple therapy (Additional file 1). In the danoprevir monotherapy group, the mean week 2 HCV RNA level was 91,678 IU/ml (median 11,600 IU/ml), with 1/15 patients achieving an undetectable HCV RNA level. In the triple therapy group, the mean week 2 HCV RNA level was 686 IU/ml (median 365 IU/ml), with 11/24 patients achieving undetectable HCV RNA. In the triple therapy group, all but two patients with undetectable HCV RNA at week 2 achieved an SVR: one patient discontinued dual therapy...

Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Danoprevir monotherapy (n=15)</th>
<th>Danoprevir-based triple therapy (n=24)</th>
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<tbody>
<tr>
<td>Male:female gender, n</td>
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<td>22:2</td>
</tr>
<tr>
<td>Median age, years</td>
<td>50</td>
<td>45</td>
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<tr>
<td>Median serum ALT, IU/l (range)</td>
<td>71 (37–207)</td>
<td>73 (25–193)</td>
</tr>
<tr>
<td>Median HCV RNA, log₁₀ IU/ml (range)</td>
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<td>6.6 (4.3–7.4)</td>
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*The necroinflammatory activity and extent of fibrosis were evaluated by liver biopsy and/or elastometry (Fibroscan®) and were expressed according to the METAVIR scoring system [3,4]. ALT, alanine aminotransferase.
at week 6 because of a skin reaction and one patient was lost to follow-up after week 6 (but did achieve a rapid virological response [RVR] at week 4).

We also compared week 2 HCV RNA levels in patients who achieved an SVR and in non-responders to danoprevir treatment. In the monotherapy group, the mean week 2 HCV RNA level was 36,665 IU/ml in patients with SVR (9/15) versus 200,300 IU/ml in non-responders (6/15). In the triple therapy group, 17/24 patients achieved SVR; week 2 HCV RNA levels were undetectable in 11/17 patients and ranged from 55–637 IU/ml in the six patients with detectable HCV RNA levels. By contrast, none of the non-responders were undetectable at week 2 and HCV RNA levels in these seven patients ranged from 65–10,300 IU/ml (Figure 2B).

HCV RNA at week 4 was also analysed. Among the 22 patients who achieved an RVR, 19 went on to achieve an SVR (86.4%) in both treatment groups (Figure 2B). Among the three patients who did not, two were lost to follow-up and one had a virological relapse after treatment was discontinued.

Therefore, week 2 and 4 (RVR) HCV RNA levels were both highly predictive of SVR in this population. There was no difference observed in SVR rates between patients with HCV subgenotype 1a and 1b (1a pooled SVR rate 12/18 [66.6%], 1b pooled SVR rate 13/19 [68.4%], 1a/1b SVR rate [monotherapy group only] 1/2 [50.0%]), however, this analysis is limited by the small numbers of patients in each group.

Transaminase levels either normalized or did not increase during exposure to danoprevir or within the
month after this exposure. There was no indication of any liver toxicity.

Discussion

Inhibitors of the NS3/4A protease of HCV are the first direct-acting antiviral agents to be approved for the treatment of chronic hepatitis C [6,7]. The protease inhibitors boceprevir and telaprevir have the potential to increase SVR rates and decrease treatment duration for HCV genotype 1 patients when used in combination with PEG-IFN plus RBV [8–11]. The promising results of the current analysis provide further evidence that protease-inhibitor-based triple therapy, even for as little as 2 weeks, can increase cure rates in treatment-naive genotype 1 patients. A regimen of 14 days of danoprevir-based triple therapy followed by 46 weeks of PEG-IFN-α2a (40 KD) plus RBV produced an SVR rate of 71% in treatment-naive genotype 1 patients. This result is considerably higher than the SVR rates achieved in treatment-naive genotype 1 patients who received 48 weeks of treatment with the combination of PEG-IFN-α2a (40 KD) plus RBV in a number of large randomized clinical trials conducted over the past decade (range 41–52%) [8,12–16]. Moreover, an SVR rate of 71% is numerically similar to that achieved in genotype 1 patients with the two commercially available protease inhibitors in Phase II and III trials. SVR rates of 61–75% were achieved with 12 weeks of telaprevir-based triple therapy followed by 12 to 36 weeks of PEG-IFN plus RBV combination therapy [8,15,16]. Similarly, SVR rates of 56–75% were obtained after a 4-week PEG-IFN plus RBV lead-in phase and then 24 to 44 weeks of boceprevir-based triple therapy [9,17]. However, the 71% SVR rate achieved with danoprevir-based triple therapy must be interpreted with some degree of caution because of the retrospective nature of this study, the small number of patients involved in the analysis and the lack of a control group.

The commercially available protease inhibitors have certain limitations, encouraging the further development of new direct-acting antiviral agents to address these limitations. The signature toxicities of boceprevir are anaemia and dysgeusia, and of telaprevir, anaemia, skin rash and gastrointestinal disorders [8–11]. Thus, alternative direct-acting antiviral agents, including protease inhibitors with an improved tolerability profile, broader spectrum of activity against other HCV genotypes and a non-overlapping resistance profile, would be welcome. Preliminary data suggest that danoprevir is well-tolerated [3–5]. Dose-related grade 3 and 4 increases in serum alanine aminotransferase levels have been reported in a small number of individuals (4 out of 122) treated with danoprevir doses of 600 and 900 mg/day [18]. Any changes in transaminase levels in patients included in this analysis were reversible and there was no indication of any liver toxicity. Current and future studies of danoprevir-based triple therapy are being conducted with much lower doses of danoprevir boosted with ritonavir. Ritonavir boosting of danoprevir maintains danoprevir trough concentrations while decreasing overall exposure, and may enable less frequent dosing [19]. Resistance to danoprevir was not analysed in those patients who had replicating virus (lower limit of quantification 25 IU/ml, limit of detection 9.3 IU/ml) at the end of 14 days of treatment with danoprevir.

Danoprevir is a macrocyclic protease inhibitor that binds to the same pocket as linear protease inhibitors, such as telaprevir and boceprevir [1]. While there is cross-resistance among protease inhibitors, some amino acid substitutions affect drug susceptibility to some protease inhibitors more than to others.

In conclusion, the results of this long-term follow-up study show that 14 days of treatment with danoprevir-based triple therapy followed by 46 weeks of PEG-IFN-α2a (40 KD) plus RBV achieves SVR rates that are comparable to those obtained with commercially available protease inhibitors. Future studies will determine the optimal dose of danoprevir, the required duration of triple therapy, and whether the overall treatment duration can be shortened. The results of these and other larger confirmatory studies are awaited with great interest.

Acknowledgements

All authors have contributed to the work and writing of the manuscript and they have all read and approved the paper. Support for third-party writing assistance for this manuscript, furnished by Blair Jarvis, was provided by F Hoffmann-La Roche Ltd.

Disclosure statement

The authors declare no competing interests.

Additional file

Additional file 1: Supplementary Figure 1 illustrating virological response over time for patients enrolled in the danoprevir monotherapy and triple therapy studies can be accessed via http://www.intmedpress.com/uploads/documents/AVT-11-SC-2294_Larrey_Add_file1.pdf

References


Accepted 5 February 2012; published online 18 May 2012