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Editorial

Telaprevir, peginterferon alfa-2a, and ribavirin for 28 days in chronic hepatitis C patients ☆

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The first potent and specific inhibitor of the NS3/4A serine protease to be tested in a randomized, placebo-controlled pilot study in patients with chronic hepatitis C was ciluprevir (BILN 2061). In previously untreated patients with genotype 1 infection, treatment with ciluprevir for 2 days resulted in HCV RNA reductions of 2–3 $\log_{10}$ copies/mL in most of the patients, thus providing proof-of-concept that HCV NS3/4A protease inhibitors are a therapeutic option for patients with chronic hepatitis C [1]. However, further clinical development of ciluprevir was suspended following reports of cardiotoxicity in animal studies [1].

The NS3/4A protease inhibitors telaprevir and boceprevir have been shown to reduce serum HCV RNA levels when used alone [2,3] and to produce additive reductions in levels when administered with peginterferon (PEG-IFN) [3,4]. Telaprevir monotherapy for 2 weeks was associated with a more than 4 $\log_{10}$ median reduction of HCV RNA in patients with chronic hepatitis C genotype 1 infection [2]. When used as monotherapy, current protease inhibitors show a low barrier to genetic resistance, a potential problem for antivirals given the high rate and error-prone nature of HCV replication [5].

The study by Lawitz et al. [6] in the current issue of this Journal assessed the safety and antiviral effects of telaprevir (750 mg q8h) in combination with peginterferon alfa-2a and ribavirin (RBV). Previously untreated patients infected with HCV genotype 1 received triple therapy for 28 days and could then start off-study treatment with PEG-IFN alfa-2a and RBV for up to 44 weeks at the discretion of the investigator and patient. All patients had undetectable HCV RNA levels by day 28, indicating that the addition of PEG-IFN and RBV may be able to inhibit the rapid selection of resistant strains as observed in the telaprevir monotherapy trials. Eight patients completed 44 weeks of off-study standard of care combination therapy. Eight patients achieved a sustained virologic response, including one patient who received only 22 weeks of treatment. In general, triple therapy was well tolerated, however, rash or pruritus occurred in 5 of the 12 patients [6].

Based on these data, larger phase II clinical trials have been initiated and very recently completed [7,8]. The PROVE 1 trial in the US enrolled patients into 4 treatment groups: (i) group 1: telaprevir 750 mg q8h, with PEG-IFN and RBV for 12 weeks; (ii) groups 2 and 3: patients received the same triple combination for 12 weeks, followed by treatment with PEG-IFN plus RBV alone for 12 or 36 weeks, respectively; (iii) group 4: 48 weeks of PEG-IFN plus RBV (controls). The PROVE 2 trial was conducted in Europe and had a similar design as PROVE 1, with an extra arm evaluating the PEG-IFN/telaprevir combination without RBV.

In PROVE 2 HCV RNA was undetectable at week 4 in 122 of 163 patients (75%) receiving triple therapy [8]. Thus, compared to the 12 patients of the study of Lawitz et al. (100% RVR), the RVR in the PROVE 2 study was apparently lower. Certainly, patients in the first pilot study of triple therapy were under very careful surveillance. Compliance with drug doses and intervals may

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have been less stringent in larger patient cohorts of the PROVE studies. Other factors may comprise adverse events leading to premature discontinuation, the development of viral resistance and breakthrough, perhaps due to different PEG-IFN and/or RBV sensitivities in the respective patient populations.

With the addition of direct antivirals to PEG-IFN/RBV several questions must be addressed in the future:

(i) Will every HCV-1 infected patient need the addition of a protease inhibitor to improve changes for SVR?

Probably not because patients with a low baseline viral load and a rapid virologic response comprising approximately 15% of the overall HCV-1 infected population already have SVR rates around 90% with only 24 weeks of PEG-IFN and RBV combination therapy [9].

(ii) What is the minimum Peg-IFN and RBV sensitivity to avoid functional monotherapy?

An "ideal" direct antiviral drug or drug combination which does not select for resistant strains may not require combination with PEG-IFN and RBV. However, drugs with a low genetic barrier such as protease inhibitors currently require the combination with PEG-IFN and RBV to eradicate the mutant viral strains. Whether substantial reduction of HCV RNA replication can restore innate immunity and IFN sensitivity *in vivo* (as it has been shown in vitro [10]) remains to be proven. Such effects would most likely enhance SVR rates.

(iii) Is RBV needed? Is PEG-IFN needed?

The RBV sparing arm of PROVE 2 clearly shows that RBV is required in particular to reduce virologic relapse rates after the end of therapy. Furthermore, preliminary data from the SPRINT1 trial [11] suggest that RBV doses cannot even be reduced to 400–800 mg without reducing the chances to achieve a virologic response. The question whether (peg)interferon is ultimately required cannot be answered at present. However, proof-of-concept pilot trials using potent protease and polymerase inhibitors in combination with RBV may provide an answer in the near future.

(iv) Is there a potential value of a PEG-IFN/RBV lead-in phase?

Hypothetically, achieving steady-state levels for peginterferon and ribavirin may (quantitatively) reduce the selection and expansion of resistant strains after the addition of a protease inhibitor. However, virologic response rates 12 weeks after the end of therapy in patients treated for 24–28 weeks with peginterferon alfa-2b, ribavirin and boceprevir were similar but independent of a 4-week lead-in phase with PEG-IFN/RBV (57% vs. 55%) [11]. The benefit of a lead-in phase remains to identify patients who do not require the addition of a protease inhibitor (low baseline viral load and RVR) and those who do not respond at all to PEG-IFN/RBV and would be exposed to functional monotherapy by addition of a protease inhibitor.

(v) How long must a potent direct antiviral be given and how long should be the overall treatment duration?

Direct antiviral agents may eradicate the sensitive wild-type population rapidly, perhaps within 8–12 weeks, which is reflected in the design of forthcoming phase III trial with telaprevir. So far, in patients with virologic breakthrough or relapse treated with telaprevir only resistant but not wild-type variants were identified supporting the concept that approximately 8–12 weeks may suffice to eradicate the sensitive viral population. The question of how long PEG-IFN/RBV therapy must be continued to eradicate the mutant variants is quite unclear. Data suggest that overall PEG-IFN/RBV should be continued longer in patients not achieving a RVR (e.g. 36 vs. 12 additional weeks). On the other hand, in PROVE 2 62% and 68% of HCV-1 infected patients achieved an SVR with 12-week triple therapy and 12-week triple therapy followed by another 12 weeks of PEG-IFN/RBV combination, respectively. This implies that more than 90% of patients achieving an SVR in the latter group were apparently overtreated. The crucial question how patients who require more than 12-week triple therapy can be identified will need further attention. Possibly, pretreatment and on-treatment predictors of SVR may differ with triple therapy compared to PEG-IFN/RBV standard combination therapy.

(vi) How important is the pharmacokinetic profile of an antiviral drug?

Several HCV NS3/4A protease inhibitors are currently dosed every 8 h. Experience from the treatment of HIV shows that compliance and adherence to such dosing intervals is impaired and affects antiviral responses. A major difference between HIV and HCV, however, is the overall duration of combination therapy. Patients should be able to adhere to strict dosing intervals for a limited period of time better than if treatment is required indefinitely. Nevertheless, there is no doubt that antiviral drugs which require only once (qd) or twice (bid) a day dosing will be preferred. Pharmacokinetics may also affect the emergence of resistant strains. So far, little information is published and more com-

bined data on pharmacokinetics, pharmacodynamics, and the emergence of resistant strains are required.

(vii) Will the improvement in SVR rates be the only parameter to consider?

In the past, progress in the treatment of chronic hepatitis C was defined by improvement of SVR rates. Patients who failed PEG-IFN and RBV treatment were generally not considered to have endured any harm beyond the side effects they suffered during therapy. However, in the era of drugs rapidly selecting for resistance, the question needs to be answered, whether selected HCV strains in non-responders will persist and impair the chances for patients to be cured in the future with the development of antiviral combination therapies of, e.g., protease and polymerase inhibitors. Data for how long resistant strains can persist and whether these mutants can improve viral fitness by compensatory mutations are largely lacking.

(viii) What are the short and long-term side effects of the new direct antiviral drugs?

Relevant clinical and laboratory side effects of protease inhibitors comprise rash (telaprevir), anemia (telaprevir, boceprevir) and gastrointestinal side effects. Cardiotoxicity – as described for ciluprevir in monkeys – has yet not been observed in clinical trials in patients with chronic hepatitis C. All adverse events so far described were fully reversible after drug discontinuation. The safety data base, however, is still too small to definitely exclude the risk of life-threatening or irreversible side effects.

The data of the study by Lawitz et al. [6] as well as the recently presented data for telaprevir from the PROVE studies [7,8] clearly show the tremendous potential of new direct antiviral drugs. Many patients are desperately waiting for improved treatment modalities for chronic hepatitis C. Representatives from the industry developing these new compounds together with those from academic centers performing phase 1–3 clinical trials and regulatory agencies must carefully balance the urgent need for these new drugs on one hand with the responsibilities and requirements of a thoughtful and comprehensive clinical development program on the other hand [12] that should answer most of the questions raised above.

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