Good progress with novel therapies for hepatitis C

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New antiviral agents look set to shorten treatment times for hard to treat hepatitis C infection, and may be most effective when started after patients have shown an early response to initial treatment with a standard combination of pegylated IFN- α (peg-IFN- α) and ribavirin. However, attempts to drop ribavirin from the new combinations have so far proved unsuccessful.

These were the key conclusions to emerge from the growing body of evidence surrounding novel hepatitis C protease and polymerase inhibitors, presented at this year's largest ever European Association for the Study of the Liver (EASL) congress, as this new generation of small molecule treatments start to reach Phase III clinical trials.

Stefan Zeuzem (Saarland University Hospital, Homburg/Saar, Germany) predicted that the success of future approaches to hepatitis C treatment will depend on whether cross-resistance can be avoided by combining different small molecules with peg-IFN- α , hopefully without the need for ribavirin. However, it could be 10 years or more before novel antiviral agents take the place of current combinations. Zeuzem said: "We don't yet know whether we will be able to get rid of the hepatitis C virus without peg-IFN- α and, at the present time, we can't even reduce the dose of ribavirin. So I would urge patients with hepatitis C not to delay treatment in the hope of better results with the newer agents".

Protease inhibitors

PROVE studies of telaprevir

Data reported from two key studies of the HCV protease inhibitor telaprevir (PROVE 1 and 2) suggest that treatment duration for genotype 1 patients can be halved from 48 to 24 weeks when the drug is added to the peg-IFN- α /ribavirin combination.

Presenting final data from PROVE 1, John McHutchison (Duke University, Durham, USA) reported that patients treated with telaprevir, together with peg-IFN- α 2a and ribavirin (triple therapy) for 12 weeks, followed by peg-IFN- α 2a and ribavirin (dual therapy) for a further 12 weeks achieved a sustained virological response (SVR) of 61% compared with an SVR of 41% in patients who had a standard 48-week course of dual therapy.

There was little advantage to following 12 weeks of triple therapy with a more prolonged 36-week course of dual therapy, as the SVR in this group was 67%.

McHutchison reassured delegates that the relapse rate was low in patients who only had 12 weeks of follow-up peg-IFN- α 2a and ribavirin – just 2% compared with 6% in the group who had 36 weeks of follow-up dual therapy, and 23% in those who had a standard 48 weeks of dual therapy.

A total of 7% of patients taking triple therapy had severe rash requiring discontinuation of treatment, while 13% suffered modest rash and 35% mild rash. McHutchison explained that the rash was maculopapular and more

severe than that seen with interferon, but that it was not associated with mucosal involvement and was usually delayed; appearing a mean 73 days after the start of treatment (range: 60–80 days).

Interim results were also presented from the PROVE 2 study of treatment-naïve genotype 1 patients treated with combinations of telaprevir and peg-IFN- α 2a, with or without ribavirin, or standard peg-IFN- α 2a and ribavirin.

Geoffrey Dusheiko (Royal Free Hospital, London, UK) reported an SVR rate of 68% in patients who had 12 weeks of triple therapy followed by 12 weeks of peg-IFN- α 2a and ribavirin, versus 62% in patients who had 12 weeks of triple therapy with no further treatment. This compared with only 36% in patients who had 12 weeks of telaprevir/peg-IFN- α 2a, without ribavirin.

Amongst the patients who had triple therapy for 12 weeks, there was a relapse rate of 29%, compared with 14% in those who followed 12 weeks of triple therapy with 12 weeks of dual therapy. By contrast, there was a relapse rate of 48% in patients who had an additional 12 weeks of peg-IFN- α 2a but no ribavirin and 20% in those who had standard 48 weeks of treatment with peg-IFN- α 2a and ribavirin.

Most patients who relapsed had not achieved a rapid virological response (RVR), so it was suggested that the more prolonged regimen may be most suitable for those who do not achieve a rapid response.

Addressing telaprevir resistance during a sponsored symposium on the drug, Christophe Sarrazin (JW Goethe University Hospital, Frankfurt, Germany) explained that viral breakthrough is associated with resistance. He reported that resistance was demonstrated in 5% of patients treated with

triple therapy in PROVE 1 and 2, and in 24% of patients treated with telaprevir and peg-IFN- α 2a. So it appears that resistance can be reduced by using combination treatment. He added that there is a reversion to wild-type virus after telaprevir is stopped, but that the long-term effects are not yet known.

SPRINT-1 suggests benefits of staged use of triple therapy

Initial results from the ongoing SPRINT-1 study of the protease inhibitor boceprevir, suggest that establishing hepatitis C patients on peg-IFN- α 2b and ribavirin for 4 weeks before adding the new antiviral agent may reduce the risk of resistance, and make it easier to predict who will achieve a SVR.

Paul Kwo (Indiana University School of Medicine, Indianapolis, USA) reported comparable response rates 12 weeks after the end of treatment (SVR12) whether patients were treated with peg-IFN- α 2b and ribavirin for 4 weeks before boceprevir was added for a further 24 weeks, or triple therapy for the full 28 weeks (57 vs 55%). Relapse rates were also similar (18 vs 19%), but were lowest in patients who had an RVR at week 4 of boceprevir treatment (8 vs 12%).

Rapid virological response was highly predictive of SVR12, with up to 85% of patients with undetectable virus at 4 weeks achieving a SVR12. RVR rates were highest in patients who received peg-IFN- α 2b and ribavirin prior to boceprevir treatment (60 vs 39%), supporting the idea that achieving steady-state peg-IFN- α 2b and ribavirin levels before adding a protease inhibitor may produce optimal outcomes with triple therapy.

Boceprevir treatment was well tolerated, with the incidence of skin rash or pruritus similar to that seen with peg-IFN- α and ribavirin alone. As with other protease inhibitors, there was an increased rate of anemia in patients who received boceprevir. Kwo suggested that the triple therapy combination could

prove particularly useful in African-American patients. A subanalysis of data showed an SVR12 of approximately 45% in this group; superior to the less than 25% seen in earlier studies of combination peg-IFN- α and ribavirin treatment. Other arms of the trial, with extended treatment for 48 weeks, with or without boceprevir, are continuing.

Polymerase inhibitors

At the 2007 EASL meeting, disappointing Phase IIb trial results were reported with valopicitabine, which was, at that time, the polymerase inhibitor at the most advanced stage of development. No patients achieved an SVR when the drug was used with peg-IFN- α 2a alone, and research with the drug has subsequently been stopped. However, a series of other polymerase inhibitors continue to be researched, as part of triple therapy with peg-IFN- α and ribavirin.

David Nelson (University of Florida, Gainesville, USA) reported promising end of treatment (EOT) virological responses with the polymerase inhibitor R1626, although these were associated with significant levels of grade IV neutropenia at some doses.

A total of 84% of genotype 1 patients who received triple therapy with R1626 1500 mg, peg-IFN- α 2a and ribavirin for 4 weeks, followed by 44 weeks of peg-IFN- α 2a and ribavirin, achieved an EOT response. This compared with EOTs of 66 and 52%, respectively, in patients treated with dual therapy of R1626 3000 mg or 1500 mg and peg-IFN- α 2a for the first 4 weeks, followed by 44 weeks of peg-IFN- α 2a and ribavirin, and 65% in patients who received standard peg-IFN- α 2a and ribavirin for the full 48 weeks.

Nelson added that the majority of patients treated with R1626 1500 mg had undetectable virus within 2–3 weeks of starting treatment, and maintained that status.

A promising RVR was also reported with a second polymerase inhibitor, R7128. A total of 85% of 20 genotype 1

patients treated with R7127 1500 mg combined with peg-IFN- α 2a and ribavirin had undetectable virus at 4 weeks, with an accompanying 5.1 log₁₀ reduction in viral load.

Lower RVRs were achieved with R7128 500 mg or standard peg-IFN- α 2a and ribavirin (30 and 10%, respectively). The preliminary safety profile was similar to that of standard therapy.

Moving forward

The best way to combine the new generation antiviral agents with standard combination treatment was the subject of considerable discussion at this year's EASL congress, and much will depend on the results of upcoming Phase III trials, and emerging data on viral mutations and resistance to the new agents.

The picture could be further complicated if and when significant progress is made with agents designed to boost patients' immune systems to combat their hepatitis C infection. The idea that a combination of immunostimulants and protease and polymerase inhibitors could ultimately make peg-IFN- α and ribavirin redundant in hepatitis C therapy has been tantalizing researchers for a number of years. But, judging by the results presented at EASL in 2008, the antiviral approach continues to have the upper hand.

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