Meeting report

News in hepatitis C: report from the 39th Annual Meeting of the European Association for the Study of the Liver

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Between 3 and 4 million new cases of hepatitis C are diagnosed each year and there are an estimated 170 million carriers worldwide. Morbidity and mortality from HCV-related advanced liver disease are predicted to rise over the next decade, with all the medical, social and economic consequences that go with any large-scale health problem.

The Annual Meeting of the European Association for the Study of the Liver (EASL) is an important opportunity to discuss progress in basic and clinical research in hepatitis C, and the meeting in Berlin in 2004 was no exception. From the treatment perspective, it has become clear that combination therapy with pegylated interferon and ribavirin will remain the gold standard for at least the next 3–5 years. However, clinical trials are establishing optimal regimens as well as investigating novel antiviral drugs, such as protease and polymerase inhibitors, which will begin to find their proper place in the clinic over the next few years.

Shorter courses of combination treatment may be possible for patients chronically infected with HCV genotypes 2 or 3 – currently responsible for approximately 30% of HCV infection in European patients. In a recently published study, a 24-week course of peginterferon α-2b and ribavirin was associated with sustained virological responses (SVRs) of 93% and 79% in genotype 2 and 3 patients, respectively [1]. These figures were comparable with those seen in historical controls undergoing 48 weeks of treatment [2], but the shorter course of treatment was better tolerated and fewer patients needed dose reductions or had to withdraw from treatment.

At EASL, Dr Alessandra Mangia from IRCSS-CSS Hospital, San Giovanni Rotondo, Italy, showed that some patients infected with HCV-2 or HCV-3 may be able to reduce the duration of treatment still further to 12 weeks [3]. In a randomized, controlled trial of 283 patients infected with genotypes HCV-2 or HCV-3, those who had cleared the virus after 4 weeks of treatment with peginterferon α-2b and ribavirin did just as well with 12 weeks as with 24 weeks of treatment.

A total of 85% of those who were negative for HCV RNA by RT-PCR after 4 weeks of combination treatment achieved an SVR with 12 weeks of treatment, compared with 89% of those who continued for 24 weeks. The relapse rate was slightly higher with 12 weeks than with 24 weeks of treatment, but fewer patients on the short course of treatment dropped out because of adverse events. Dr Mangia suggested that early viral clearance at week 4 might serve as a useful algorithm to decide the length of treatment for patients with chronic hepatitis C infected with genotypes HCV-2 or HCV-3.

Early viral response at week 12 is already being used to identify patients with chronic hepatitis C infected with genotype HCV-1 who are unlikely to achieve an SVR and should prematurely discontinue therapy, thus avoiding side effects and costs. A number of studies reported at the conference showed that for determining viral clearance, HCV core antigen (Ag) concentration is just as accurate as measuring HCV RNA by molecular techniques [4–6]. Dr Maria Buti and colleagues in Barcelona, Spain [4], compared the two techniques using 268 serum samples from 46 genotype HCV-1-infected patients collected after 12 weeks of treatment with peginterferon α-2b and ribavirin. They found that the negative predictive value of HCV core Ag testing in
predicting non-response at week 12 was 100% compared with 88% for a 2 log drop in HCV RNA, using two quantitative tests. Similarly, Dr V Gonzales and a second Spanish group [5] reported negative predictive values at 1 and 3 months after combination treatment with peginterferon α-2a and ribavirin of 76.5% and 100% with the HCV core Ag test, compared with 69.6% and 80%, respectively, with HCV RNA testing.

Response to antiviral therapy tends to be worse in black patients with chronic hepatitis C than in white patients, and it was originally assumed that this is because genotype HCV-1 is more prevalent in the black population. However, Dr Norbert Brau [7] from the VA Medical Center in the Bronx, New York, presented data suggesting that genotype is not the only reason. A quarter of the 813 HCV-infected patients in his multicentre US study were black and 85.3% of them had genotype HCV-1 infection. After standard therapy with interferon α-2b and ribavirin, the SVR in the black patients was 7.9% compared with 21.5% in the white patients (63.2% of whom were infected with genotype HCV-1). Amongst genotype HCV-1-infected patients, SVR rates were lower in black than white patients, 5.8% versus 14.1%, respectively, but amongst patients infected with genotypes HCV-2 and HCV-3, there was no significant difference in SVR between the black and white patients. Preliminary data from a small pharmacokinetic study of 75 HCV patients suggest that weight-based treatment with pegylated interferon α-2b in combination with ribavirin may produce a faster and greater viral response than a flat-dose regimen with pegylated interferon α-2a, especially in genotype HCV-1-infected patients [8]. A large US trial of nearly 3000 patients with chronic hepatitis C infected with genotype HCV-1 is to test this hypothesis further, by comparing the safety and efficacy of weight-based versus flat-dosing regimens of pegylated interferon α in combination with ribavirin.

For patients co-infected with HIV and HCV, a 48-week course of combination treatment remains the most effective option. Final data from the AIDS Pegysys Ribavirin International Co-infection Trial (APRICOT) showed promising results with a pegylated interferon combination in this difficult-to-treat patient group. Dr Francesca Torriani from the University of California, San Diego, reported an SVR of 40% in co-infected patients treated with peginterferon α-2a and ribavirin for 48 weeks, compared with 20% for peginterferon α-2a treatment alone and 12% for non-pegylated interferon α-2a and ribavirin [9].

Interesting data on liver fibrosis progression in HIV/HCV-coinfected patients were reported by the Puerto Rico-New York Hepatitis C Study Group. They found that HIV viral load is strongly correlated and the CD4+ cell count only weakly correlated with the fibrosis progression rate in co-infected patients [7]. The fibrosis progression rate was slow in patients with undetectable HIV viral load and not different to the rate in patients with HCV monoinfection. These data are provoking and suggest that immediate treatment of chronic hepatitis C in co-infected patients may not be that necessary based on the better prognosis of chronic hepatitis C when HIV infection is effectively controlled by highly active antiretroviral therapy (HAART).

Adherence to treatment continues to be a major challenge for physicians treating patients with chronic hepatitis C. Optimal side effect management is essential if patients are to be dissuaded from discontinuing their drugs and losing the advantages gained from their treatment up to that point.

Psychiatric side effects are common with interferon and responsible for treatment discontinuation in 10–20% of cases. Dr Laurent Castera and colleagues from hospitals in Pessac and Bordeaux, France, reported psychiatric events in 35 out of 86 patients (41%) who completed 24 weeks’ follow-up after a course of peginterferon-α plus ribavirin for 24–48 weeks [10]. A total of 86% of affected patients experienced events – all of them mood disorders – within the first 12 weeks of treatment, and 14% between weeks 12 and 24. No patients experienced events after week 24. Irritable hypomania occurred in 22% and major depression with manic features in 19% of cases. Symptoms were most common in patients who had a past history of depression. In 25 cases (71%), an antidepressant or neuroleptic drug was prescribed and this enabled all patients except one to continue their antiviral treatment.

In this series, early recognition and treatment of mood disorders were clearly helpful. However, a review of antidepressant prescribing in patients treated for chronic hepatitis C in a US healthcare plan showed little evidence of prophylactic prescribing, even in those with a history of depressive conditions [11]. Dr Jeff Markowitz from Health Data Analytics in New Jersey, concluded that a more systematic evaluation of the potential benefits of prophylactic antidepressant therapy is required.

Prophylactic management of other adverse effects of antiviral treatment is also worth considering. Anaemia associated with ribavirin tends to start earlier than mood disorders and gradually worsens with continued treatment. However, symptoms can be relieved or prevented with judicious use of epoetin α to increase serum haemoglobin levels.

There is growing evidence that patients with chronic hepatitis C – particularly those infected with genotype HCV-1 – should adhere to the so-called ‘80/80/80 rule’, that is, they should take at least 80% of their
interferon dose and 80% of their ribavirin dose at least 80% of the time. Results presented at EASL by Dr Rajender Reddy from the University of Pennsylvania in Philadelphia, suggest that it may be especially important to maintain the 80% rule for ribavirin [12]. Pooled SVR data from 569 patients infected with genotype HCV-1, randomized to 48 weeks of peginterferon α-2a and ribavirin in two Phase III clinical trials, were analysed.

For peginterferon α-2a, there was a non-significant difference in SVR for those who achieved 100% exposure to treatment compared with those who achieved less than 80% exposure: 65% versus 59%, respectively (P=0.2590). In contrast, there was a significant difference in SVR between those who achieved 100% exposure to ribavirin treatment compared with those who achieved less than 80% exposure: 72% versus 49%, respectively (P<0.001).

In an effort to reduce the risk of dose-limiting haemolytic anaemia, researchers are investigating alternatives to ribavirin in combination treatment. One of these is viramidine, a liver-targeting prodrug of ribavirin. In a US study reported by Dr Robert Gish from the California Pacific Medical Center in San Francisco, 180 patients were randomized to pegylated interferon α-2a with viramidine 400, 600 or 800 mg orally twice a day or ribavirin 1000/1200 mg daily [13]. After 24 weeks of treatment, there was no significant difference between viramidine (800-1600 mg/day) versus ribavirin in the proportion of patients with undetectable HCV RNA or a log decrease in viral load of 2 or more (83% vs 83%, respectively). However, only 2% of the viramidine group had anaemia (defined as haemoglobin below 10 g/dl) compared with 24% of the ribavirin group (P<0.001). Other adverse events were similar for the two treatment groups.

There is continuing debate over the potential advantages of triple therapy over current dual therapy regimens. The antiviral agent, amantadine, is one of the agents that has been added to standard combinations. A recent meta analysis of six controlled trials of amantadine in combination with interferon-α suggested a small but significant benefit [14]. However, larger trials are needed to confirm the role of amantadine in triple therapy, especially in the era of peginterferons. Results of a study of amantadine in triple therapy in 185 non-responders to interferon/ribavirin presented by Dr Silvia Fargion, showed an overall SVR of 22% [15]. As might be expected, those infected with genotype HCV-1 did less well than other patients. Younger patients, less than 40 years old, and those with a higher viral load, did better with a triple therapy regimen that included pegylated interferon α-2a than one using non-pegylated interferon.

Another option for inclusion in triple therapy is the novel selective inhibitor of inosine monophosphate dehydrogenase, merimepodib (VX-497). In a Phase II study carried out in France and Belgium, 31 patients infected with genotype HCV-1 who had not responded to interferon and ribavirin were randomized to receive merimepodib 25 or 50 mg every 12 hours or placebo in combination with pegylated interferon and ribavirin for 24 weeks [16]. Patients with no detectable virus at 24 weeks continued treatment for a further 24 weeks. At 24 weeks, 86% of those patients on triple therapy including merimepodib 50 mg had undetectable levels of HCV RNA, compared with 33% of those on the 25 mg dose or in the placebo group. The authors reported that merimepodib was well tolerated.

In a multicentre, double-blind, placebo-controlled, dose-ranging study, the anti-apoptotic caspase inhibitor IDN-6556 was given to 48 patients with chronic hepatitis C for 14 days [17]. While aminotransferases remained unchanged in patients who received placebo, a decrease of ALT from baseline to day 14 was observed at all doses (−40% at 25 mg daily, −33% at 100 mg daily, −35% at 200 mg daily, −49% at 5 mg twice daily, −42% at 50 mg twice daily and −56% at 100 mg twice daily). However, in all but one patient, serum HCV RNA levels remained unchanged. Oral IDN-6556 was reported to be well tolerated and adverse events were generally considered as mild and brief. Further clinical development of the compound is not only planned in patients with chronic hepatitis C but also in patients with chronic hepatitis B, primary biliary cirrhosis and non-alcoholic steatohepatitis.

A number of other interesting compounds, including the NS3/NS4A serine protease inhibitors BILN 2061 and VX-950, are in early-stage clinical or preclinical development. Preliminary research with BILN 2061 suggests that it has a rapid initial effect on HCV RNA levels [18]. Doses of 500 mg and 200 mg resulted in a 3 log reduction in HCV RNA during 2 days of treatment. Blockage of viral production reached higher levels than can be achieved with interferon-based treatments, but larger and longer studies are clearly required.

In vitro resistance studies of BILN 2061 and VX-950 suggest that resistance to the two drugs develops via different mechanisms, a valuable finding if they are to prove useful against HCV infection [19]. The major BILN-2061 resistant mutations remained fully susceptible to VX-950, while the primary resistant mutation against VX-950 remained sensitive to BILN-2061.

First clinical results were presented for NM283, a new nucleoside HCV RNA polymerase inhibitor [20]. Dose escalation studies performed over 15 days, with a 2-week follow-up, showed dose-related decreases in serum HCV RNA ranging from a mean 0.15 log_{10} at 50 mg/day to 0.73 log_{10} at 400 mg/day. Dr Na Brown from Idenix Pharmaceuticals in Cambridge, Massachusetts, pointed out that an expanded research...
programme with NM283 alone and in combination with pegylated interferon is planned.

The HCV internal ribosomal entry site (IRES) is another potential target for future anti-HCV drugs because it is a highly conserved region of the HCV genome. Small interfering RNAs (siRNAs) developed by researchers in Hannover, Germany, have been shown to reduce IRES activity by up to 30%. Northern and Western blot analyses revealed inhibition of HCV replicon RNA and NS5B protein levels by up to 65% [21]. Dr M Korf and colleagues concluded that the development of siRNAs is a promising strategy for combating HCV infection.

Research into a vaccine against HCV infection has lagged behind that for new drug treatments. Potential candidates investigated in vaccine research have included the viral envelope proteins, E1 and E2, which are involved in host cell entry and viral particle assembly and release. Another approach, described by Dr L Arribillaga and colleagues in Pamplona, Spain [22], has focused on a replication-deficient recombinant adenovirus expressing HCV NS4a protein (RadNS4a). Mice immunized with the adenovirus mounted anti-NS4a T helper and T cytotoxic responses. Immunized mice were also protected against challenge with a recombinant vaccinia virus expressing HCV-polyprotein. Such results offer some new promise in prophylactic and/or therapeutic immunization against HCV.

These and many other promising leads discussed at EASL must now be subjected to rigorous and appropriate clinical trial programmes. Their efficacy and tolerability will need to be assessed and compared with those of the current gold standard treatments for chronic hepatitis C.

Important progress has already been made in the management of this challenging infection, but significant numbers of non-responders, particularly those infected with genotype HCV-1 and those co-infected with HIV and HCV, are still awaiting interventions. Important progress has already been made in the management of this challenging infection, but significant numbers of non-responders, particularly those infected with genotype HCV-1 and those co-infected with HIV and HCV, are still awaiting interventions. Important progress has already been made in the management of this challenging infection, but significant numbers of non-responders, particularly those infected with genotype HCV-1 and those co-infected with HIV and HCV, are still awaiting interventions. Important progress has already been made in the management of this challenging infection, but significant numbers of non-responders, particularly those infected with genotype HCV-1 and those co-infected with HIV and HCV, are still awaiting interventions. Important progress has already been made in the management of this challenging infection, but significant numbers of non-responders, particularly those infected with genotype HCV-1 and those co-infected with HIV and HCV, are still awaiting interventions. Important progress has already been made in the management of this challenging infection, but significant numbers of non-responders, particularly those infected with genotype HCV-1 and those co-infected with HIV and HCV, are still awaiting interventions. Important progress has already been made in the management of this challenging infection, but significant numbers of non-responders, particularly those infected with genotype HCV-1 and those co-infected with HIV and HCV, are still awaiting interventions. Important progress has already been made in the management of this challenging infection, but significant numbers of non-responders, particularly those infected with genotype HCV-1 and those co-infected with HIV and HCV, are still awaiting interventions. Important progress has already been made in the management of this challenging infection, but significant numbers of non-responders, particularly those infected with genotype HCV-1 and those co-infected with HIV and HCV, are still awaiting interventions. Important progress has already been made in the management of this challenging infection, but significant numbers of non-responders, particularly those infected with genotype HCV-1 and those co-infected with HIV and HCV, are still awaiting interventions.

Such issues will undoubtedly be the subject of further detailed review and lively discussion at EASL in 2005, to be held in Paris on 13–17 April (www.easl.ch).

References


