EDITORIAL

TREATMENT OF HEPATITIS C IN 2011

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New knowledge on the treatment of Hepatitis C is accruing at an extraordinarily rapid rate and my aim in this editorial based on a talk I gave at the Pakistan Society of Gastroenterology Annual International Congress this year, is to outline how patients may be treated both currently and over the next two to three years.

One aspect is certain, namely, that careful documentation is essential in determining the optimal course of therapy for an individual patient. The first key event to be documented in a patient being given treatment is whether a rapid virological response (RVR) is obtained with a negative HCV RNA at 4 weeks. Seen in around 20% only of genotype I infections, frequencies are considerably higher with genotype II and III. A RVR predicts an 80–90% chance of obtaining a sustained virological response (SVR) which is the ultimate goal of treatment. The next key measurement is at 12 weeks —the early virological response (EVR). A complete EVR with RNA negativity is also highly predictive of an SVR whereas with a partial EVR will achieve this. No response makes later clearance of the virus very unlikely and in clinical practice is usually taken as an indication for discontinuing therapy. Slow and non-responders with either some or no reduction in viral load at 24 weeks are also important to define as even a partial response to antiviral therapy may lead to improvement in histological appearances and to reduced frequency in later life of HCC.[1]

Being able to confidently predict the chances of, or of not, obtaining an SVR before starting on treatment with all the attendant side effects, would represent a major advance. Distinct gene signatures in liver tissue and blood have been reported and there are many papers currently on IL-28B gene polymorphisms involved in regulation of the host's innate immune responses. The chances of an SVR are much higher for the CC genotype than for CT and TT genotypes.[2] Response rates are even less with the combination of an unfavourable IL-28B and a high serum level of interferon gamma inducible protein which interferes with Interferon signalling pathways in the liver. Such pre-treatment prediction may still be helpful with the higher responses obtainable from the new protease and polymerase inhibitor drugs.

Whether IFN alpha-2a or 2b is used marks little difference. What is important in the current standard of care treatment regime is an adequate dosage of Ribavirin as this agent has a major influence in preventing relapse after cessation of treatment. Overall SVR's in genotype I naive patients are around 50–55%, but when there is a RVR as well as a low level of viraemia (<600,000 IU/ml) pre-treatment, SVR's as high as 80% can be obtained and the period of treatment shortened from 48 to 24 weeks. Similarly for genotypes II and III —with overall SVR's higher at 70% to 90%, when an RVR is obtained, treatment can be shortened —from 24 weeks to 12 weeks. If risk factors for impaired responsiveness, namely, obesity and severe fibrosis/cirrhosis are present, the duration of the first course of treatment should be extended from 24 to 48 weeks. For slow responders extending the duration of treatment from 48 to 72 weeks gave a substantial increase in SVR from 19% to 38% consequent on a marked reduction in relapses from 59% to 20%.[3]

A difficult question is whether retreatment is of value in genotype I non-responders or relapsers. Identifiable reasons for the initial failure of treatment may be correctable such as inadequate Ribavirin dosage and interruptions in therapy. Weight reduction in the obese should be attempted but is often difficult to achieve and in one trial of subjects weighing >85 Kg, increasing the dose of Ribavirin to 1600mg daily gave an improvement in SVR of 28% to 47%.[4] In the EPIC 3 retreatment trial, SVR's were 38% for the relapsers and 14% for non-responders.[5] In the REPEAT trial, treatment duration was extended from 48 to 72 weeks with a doubling of SVR in non-responders —8% to 16%.[6] Both the EPIC 3 and the REPEAT trials had a high percentage of cirrhotics —the hardest to treat category which emphasises the need for early diagnosis and treatment of chronic hepatitis C infection. Both trials showed that further treatment was pointless if there was no EVR at 12 weeks.

The new and encouragingly potent antiviral drugs, namely, Telaprevir and Boceprevir specifically inhibit protease activity of the virus. Late 2011 is the projected date for release onto the market. Early trials of Telaprevir as monotherapy showed that a rapid fall in viral titre over the first week was followed by a high breakthrough rate from development of viral resistance. This could be prevented by giving

additional PegIFN and Ribavirin with Telaprevir being discontinued after 12 weeks and the PegIFN/Ribavirin continued for a further 12 weeks. The PROVE phase 2b trials of this triple therapy regime in genotype I naive subjects showed over 80% achieving a RVR giving an SVR rate of 61% at 24 weeks versus 41% in the control arm of PegIFN/Ribavirin given for 48 weeks.[7] Thus not only is a higher SVR obtainable with Telaprevir but treatment duration is shortened. In the PROVE 3 trial of non-responders and prior relapsers, SVR's of 39% and 69% were obtained compared with 9% and 20% respectively in control arms. Viral breakthrough in the non responders was high at 22% which is not surprising as these patients were essentially on Telaprevir monotherapy. Side-effects of rash and anaemia lead to a discontinuation rate for severe adverse events of around 20%. The drug has to be given in tds dosage at exactly 8 hour intervals and as it is metabolised through the P450 enzyme system, drug interactions may occur with the commonly used statins.

Boceprevir similarly has significant side effects including anaemia requiring Epoetin support, gastrointestinal disturbances and unpleasant taste in the mouth (dysgeusia) with discontinuation of therapy in around 25% of cases. In contrast to Telaprevir, the drug is started after a lead in period of Peg IFN/Ribavirin for 4 weeks. By obtaining steady state concentrations prior to the start of Boceprevir, the emergence of resistant mutations to the drug is reduced. Depending on level of RNA reduction during the lead in period, Boceprevir is given for a further 24 or 44 weeks along with PegIFN/Ribavirin. In the Sprint-I phase 2 study, the SVR was nearly double that in the control arm —75% vs 39%.[8] With a RVR achieved in nearly two thirds of the cases, the SVR was 82% and treatment duration can be shortened.

There is progress too in what we are all hoping for, namely, an antiviral regime without Interferon and based on oral medication only. Gane *et al*, reported at the AASLD Meeting in 2009 that combining the protease inhibitor drug Danoprevir with a polymerase inhibitor R7128 resulted in rapid viral suppression over 14 days without the emergence of resistance to either compound, and confirmatory results of this approach were published recently.[9] Targeting different steps of viral replication concurrently, as we have learnt from HIV infection, may prevent or delay the emergence of drug resistance.

Many other compounds targeting different areas of the virus and with potentially less severe side effects are in Phase 1–2 trials and the reader is referred to the abstract book of the recent EASL meeting in Berlin. One can but hope that the lead time in their introduction to clinical practice will be less than the 10 years interval between introduction of current standard of care —PegIFN & Ribavirin and release of the new Protease inhibitors.

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