THE END OF THE BEGINNING FOR HEPATITIS C TREATMENT

"Now this is not the end. It is not even the beginning of the end. But it is, perhaps, the end of the beginning." Winston Churchill.

These are extraordinary times in the history of HCV drug development. We waited 13 years between the approval of ribavirin in 1998 and the approval of telaprevir and boceprevir in 2011. The trajectory of drug discovery and clinical trials has gone from exponential to warp speed since the EASL meeting in April 2011, and these two articles are perfect examples of what has changed the world of hepatitis C; interferon-free combination therapy and in one of the trials, leading to eradication of the virus.

The first demonstration in man of IFN-free combination therapy with direct acting antivirals (DAA's) was the INFORM-1 trial presented first at EASL 2009 and published in 2010(1) It showed that a nucleoside analogue polymerase inhibitor (now known as mericitabine) and a protease inhibitor (now known as danoprevir (now boosted with ritonavir) together without PEG or RBV could reduce HCV viral load by 5·1 $\log_{10}$ IU/mL in 14 days with no sign of resistant virus. This was the proof of principle that two DAA's by themselves could render most patients undetectable without PEG or RBV. This combination hit a snag with some danoprevir toxicity issues, and development has slowed. Those issues were successfully resolved with ritonavir boosting and the follow up study to INFORM is now proceeding apace and data will be forthcoming from that trial in 2012 or 2013.

The Zeuzem study published in this journal (2) compared an all-oral combination of tegobuvir a nonnucleoside polymerase inhibitor given twice daily plus GS 9256 an NS3 serine protease inhibitor with and without ribavirin in two arms for 28 days, at which point they received peginterferon and ribavirin standard of care. The third arm used quadruple therapy with both DAA's plus peginterferon and ribavirin for 28 days and then peginterferon and ribavirin alone. All patients with viral rebound of >.5 $\log_{10}$ from nadir or non response defined as < 2.0 $\log_{10}$ decline at day 5 received peginterferon and ribavirin immediately. Median maximal reductions in HCV RNA were -4.1$\log_{10}$ IU/ml, -5,1 $\log_{10}$ IU/ml and -5.7 $\log_{10}$ IU/ml for tegobuvir plus GS 9256, tegobuvir , GS9256 plus ribavirin and the tegobuvir, GS9256, peg and ribavirin arms. The results were quite instructive. RVR for the two DAA's alone was 7%, for the two DAA's plus ribavirin 38% and for the quadruple therapy arm 100%. The importance of ribavirin in preventing resistance is very clear with this combination and reemphasizes the continuing value of using ribavirin in all oral regimens of DAA's. It also demonstrates the real, but weak antiviral activity of ribavirin (3). Why was this result so much different than that of INFORM where virtually all patients were undetectable at 14 days of dual therapy? The answer lies in the barrier to resistance (4). The nucleoside/nucleotide analogues in general have a very high barrier to resistance and the INFORM study used the nucleoside mericitabine. The barrier to resistance for protease inhibitors is relatively low, and lower still for genotype 1a as opposed to genotype 1b, since the 1a virus only requires one mutation to generate resistance to protease inhibitors, while the 1b virus requires two. Most nonnucleoside polymerase inhibitors have a relatively low barrier to resistance. When you combine two DAA's with relatively low barriers to resistance, it is easy for the virus to produce the double mutants that are resistant to both drugs. Ribavirin slows this down somewhat, but does not add enough antiviral activity to prevent resistance over 60% of the time with tegobuvir and GS 9256. There is one other factor involved in preventing resistance and that is the activity of the DAA. Extremely potent agents, which drop the viral load down to undetectable rapidly, also prevent resistance. A good example of this is the combination study of BI 201335 and BI 207127 (5). This study compared two groups: BI201727 400 mg or 600 mg given thrice daily plus BI 201335 and ribavirin 1000-1200 mg for 4 weeks. In the 400 mg group, the RVR was 73 %(with better response in genotype 1b than 1a, as one would expect with a protease inhibitor in the regimen). In the 600 mg group, the RVR was 100% and did not differ between genotype 1a and 1b. From this data one can infer that the potency of either the protease inhibitor or the nonnucleoside

polymerase inhibitor was different, since the same two classes of drugs, **plus ribavirin** yielded a much higher RVR. To be fair, there was no arm without ribavirin in this study and, of course, it is hard to compare results between studies. The designs of both studies are elegant, simple and easy to understand and advance the field enormously. Gilead is now aggressively addressing the issue of potency by adding a third DAA to tegobuvir and GS 9256 with and without ribavirin. (6)

The other study in this issue of Hepatology (7) advances the field dramatically further. Not only does it move us from RVR without interferon to SVR, but it does it in **null responders!** This represents a giant step towards the "Holy Grail" of HCV therapy: once daily, oral interferon-free treatment.

The world of HCV treatment changed forever in April of 2011 when the first interferon-free SVR's were presented using an NS5A inhibitor and a protease inhibitor, the same two drugs used in the Chayama paper. (8) The 100% SVR with quadruple therapy was overshadowed by the all-oral double DAA combination, without ribavirin that resulted in a 36% SVR. This was the long awaited proof of principle that HCV could be eradicated without interferon. Of note in the all-oral arm was that both of the genotype 1b patients achieved an SVR, but only 2/9 of the genotype 1a patients achieved an SVR demonstrating the differences in activity of protease inhibitors in genotypes 1a and 1b.

The Chayama study in this issue examined the combination of the NS5A BMS-790052 60 mg qd (now called daclatasvir) and the protease inhibitor BMS-650032 600mg (now called asunaprevir) in null responders, but only in genotype 1b, the most common genotype in Japan. Ten patients received both drugs for 24 weeks. Of the nine patients who completed the study, all achieved an SVR. HCV RNA remained undetectable in the patient who discontinued treatment after two weeks. This is truly a remarkable achievement in the field of HCV treatment. It is only partially applicable to genotype 1a patients around the world, but nonetheless brings us closer to what we seek in HCV therapy: all oral highly effective treatment. This publication marks a turning point in the HCV drug development world. It demonstrates that a protease and an NS5A inhibitor together can achieve an extremely high SVR in null responders, at least in genotype 1b. It is the second trial to show that an SVR is possible without either interferon or ribavirin in null responders.

In the patois of HCV drug development, we often speak of an all-oral regimen as the "Holy Grail" we all seek. In history that term has had many meanings, particularly in Arthurian legends beginning in the late 12th century. The meaning that comes closest, though to what we really intend, is in Wolfram von Eschenbach's *Parzival*. In it he portrays the grail as a stone that prevents anyone who sees it from dying. The development of an oral regimen of DAA's that can produce SVR in a high proportion of patients is the grail that we seek. It will prolong life and prevent death from liver disease, just as the epidemic reaches crisis proportions. The two studies in this issue of Hepatology bring us much closer to providing the answer to the epidemic.

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