NEWS AT SIX: HEPATITIS C SPECIAL

Summary of Presentations from the Bristol Myers Squibb Symposium, held at the 49th Annual EASL ILC, London, UK, on 12th April 2014

Chairperson

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MEETING SUMMARY

This Bristol Myers Squibb-sponsored symposium was chaired by Mark Thursz, who oversaw a novel news bulletin-themed symposium with sessions provided by a distinguished, international team of roving reporters; Charles Gore from the World Hepatitis Alliance, Jean-Michel Pawlotsky from France, Alessandra Mangia from Italy, Ashley Brown and Graham Foster from London, Heiner Wedemeyer from Germany, and Rafael Esteban from Spain.

Stop the Press! A Critical Evaluation of HCV Treatment Targets for Patients of all Genotypes

Professor Jean-Michel Pawlotsky

Prof Pawlotsky began by predicting an interferon (IFN)-free future in hepatitis C virus (HCV) infection. Within his presentation he recommended four criteria through which a highly effective IFN-free regimen could be achieved. The first was potency; achieved using combinations of direct-acting antiviral (DAA) agents with differing targets and mechanisms of action; secondly, a high barrier to resistance should be achieved through the combination of DAAs without cross-resistance. The third criterion was to ensure adequate treatment duration, and the final suggestion was the inclusion of ribavirin (RBV), which has been shown to be beneficial in some settings.

Prof Pawlotsky went on to describe key therapeutic targets in the HCV lifecycle.[1] The first target, inhibition of viral polyprotein maturation, can be achieved using NS3/4A protease inhibitors (PIs).[2] While the latest generation of PIs have shown activity against infections with all HCV genotypes (GTs), it was also noted that the effectiveness of these agents is

lower against HCV GT 3 and they possess an improved barrier to resistance compared with first-generation PIs.

Representing the second target of the lifecycle, HCV ribonucleic acid (RNA)-dependent RNA polymerase (RdRp) can be targeted using nucleoside or nucleotide analogue inhibitors to block viral RNA replication. These therapies demonstrate pan-genotypic activity and a high barrier to resistance. Non-nucleoside inhibitors (NNI) also target HCV RdRp and, despite their narrow genotypic range and low barrier to resistance, they were nevertheless considered important components of some IFN-free regimens. Finally, the HCV NS5A protein can inhibit viral RNA replication, inhibition of viral particle assembly and the release of HCV particles. First-generation NS5A inhibitors have a low barrier to resistance and while some, for example daclatasvir (DCV), are effective for all GTs, new generation non-structural 5A (NS5A) inhibitors demonstrate pan-genotypic activity and an increased barrier to resistance.

Overviewing the need for informed combination choices in order to achieve high, sustained viral response (SVR) rates, Prof Pawlotsky described three ways in which DAAs could be combined within IFN-free regimens. The first uses a nucleoside/nucleotide analogue backbone together with one or two DAA agents (PI, NS5A inhibitor, NNI). Several studies supporting this approach were presented and showed high SVR rates with this combination with or without RBV in patients infected with HCV GTs 1, 2, or 3.[3-5] The combination of sofosbuvir (SOF) and the NS5A inhibitor DCV (60 mg/day) for 24 weeks, yielded SVR rates of 100%, with and without ribavirin, in treatment-naïve patients infected with GT 1; and SVR rates of 92% and 89% in treatment-naïve patients infected with GTs 2 and 3, respectively.[3]

The second combination comprised of three DAAs; several 12-week studies were presented which investigated the PI, ABT-450 with ritonavir (ABT-450/r) + the NS5A inhibitor ombitasvir, and the NNI dasabuvir, together with RBV in treatment-naïve patients infected with HCV GT 1.[6-8] Results from one of these studies, SAPPHIRE-1 showed a high SVR rate of 96% in patients infected with HCV GT 1.[6] Similarly, PEARL-III[7,8] showed that patients infected with HCV GT 1b achieved an SVR rate of 99% with or without RBV, and in PEARL-IV,[7] patients infected with HCV GT 1a achieved an SVR rate of 97% with the addition of RBV, which fell to 90% without. A 12-week Phase III study of the NS5A inhibitor DCV with the PI, asunaprevir, and the NNI, BMS-791325,[9] in treatment-naïve patients infected with HCV GT 1 showed SVR rates of 100% and 71% for five out of seven patients with liver cirrhosis and NNI 150 mg. In patients with liver cirrhosis, SVR rates of 91% and 94% were achieved for NNI 75 mg and 150 mg, respectively. Prof Pawlotsky commented that the SVR rates achieved by these triple-therapy combinations were very high and therefore represented a very valuable treatment option.

The third treatment option combines two agents with a high barrier to resistance, specifically a second-generation PI with a second-generation NS5A inhibitor. A 12-week study of the PI MK-5172 with the NS5A MK-8742, together with RBV in treatment-naïve, non-cirrhotic patients infected with HCV GT 1, showed SVR rates of 100% and 96% with 20 mg and 50 mg of MK-8742, respectively. Without RBV, 100% SVR was achieved with 50 mg MK-8742.[10]

Prof Pawlotsky closed his presentation by stating that, currently, four classes of DAAs are available for use in IFN-free combination therapy for HCV and these achieve high SVR rates; however, the audience were cautioned against potential problems of resistance, with new therapies still required in the minority of patients for whom IFN-free DAA combinations do not lead to high rates of SVR.

The Big Debate: Has the Time Come for All-Oral Interferon/Ribavirin-Free Regimens?

Professor Heiner Wedemeyer

Before the session commenced, Prof Thursz conducted a poll of the audience, revealing that 70% would vote in favour of the motion 'Has the time come for all-oral interferon/ribavirin-free regimens?'

Prof Wedemeyer adopted the pro stance and argued the case in favour of the motion. He began by stating that overall, evidence from the US FDA has shown that a high SVR rate can be achieved irrespective of the addition of IFN or RBV.[11] When deciding between treatment options, the potential for irreversible side-effects and potential deaths from IFN treatment, as well as the safety profile

of RBV, must be taken into account.[12] Careful consideration must also be given to the financial impact of working days lost to illness, the intensive monitoring required with IFN treatment, and patient preference.

Describing the scale of the HCV disease burden across European countries and further supporting the stance for IFN-free regimens, Prof Wedemeyer reported evidence supporting this perspective from the HALT-C study, which showed that mortality in patients with advanced chronic HCV infection increases with IFN treatment.[15] In addition, serious adverse events have been reported following treatment with first-generation PIs in certain populations, particularly in patients with advanced fibrosis; cohorts which reflect those commonly seen in the clinic, demonstrating the importance of adhering to recent guidance and specifically contraindications.[13–21] Evidence was also provided from several studies which showed that high SVR rates of 95-100% could still be achieved without the addition of RBV.[3,4,10,22–29] However, the issue of increased adverse events again presented a concern in comparison with placebo.[23,30]

Prof Wedemeyer concluded by stating that 100% cure rates can be achieved for the majority of patients with HCV without the use of treatments known to result in adverse events.

Professor Ashley Brown

Opposing the motion, Prof Ashley Brown stated that while the proposal of a 100% cure rate may be achievable within an 'ideal world', in some patient populations it remained inappropriate to stop using IFN or RBV at this time. He reminded the audience that IFN is pan-genotypic, whereas the high SVR rates presented by Prof Wedemeyer were exclusively from patients infected with HCV GT 1. In addition, the studies presented have used combinations of DAAs including SOF, which has a higher barrier to resistance than that seen for the majority of DAAs.

Prof Brown suggested that the evidence cited for adverse events associated with IFN and RBV did not represent the whole picture. In the HALT-C study, the duration of IFN treatment was 3 years for patients with cirrhosis, which would predict for a high rate of adverse event reporting. He proposed a case for short-term, IFN-sparing regimens, which would reduce the number of adverse events. In particular, these regimens could include IFN-lambda; a lesser known liver-specific IFN which is associated with fewer adverse events than IFN-alpha.[31]

Reflecting his own clinical experience, Prof Brown reported that 45% of patients are infected with HCV GT 3 and represent the hard-to-treat population. Studies of SOF + RBV in these patients showed SVR rates of 56% at 12 weeks, with 85% achieved after 24 weeks.[32,33] However, this increase in efficacy comes at a high cost due to the longer treatment duration required. Studies of triple therapy with SOF or DCV + RBV and IFN showed SVR rates of 83% (with SOF) and 78% (with DCV) at 12 and 16 weeks, respectively; representing a shorter treatment duration and high SVR rates in this hard-to-treat patient population.[34–36] Prof Brown also suggested that including IFN could be useful for patients who have relapsed after initial therapy.

Evidence was provided for the use of RBV in hard-to-treat patient populations with HCV GT 3, which was shown to be effective and associated with relatively little additional cost.[37]

Utilising the evidence described, Prof Brown argued for IFN and RBV to remain in the current treatment algorithm for HCV, as a pan-genotypic option with few concerns regarding resistance. In addition to providing a much needed option within a resource constrained setting, their addition to DAA combination regimens provides a valued approach in hard-to-treat patient populations.

The Expert Angle: Physician and Patient Perspectives on Key HCV Management Challenges

Mr Charles Gore

Mr Gore provided the first of four expert perspectives into HCV management. He provided a patient's view on current treatment choices and began by asserting that in most of Western Europe only 3% of patients with hepatitis C are currently treated. Reasons for this include poor diagnosis of hepatitis C, practical considerations around accessibility to treatment centres, and patient reluctance to receive treatment - particularly due to a fear of IFN treatment. Timing considerations may also reduce treatment uptake, as patients defer treatment to have a child or to wait for their circumstances to provide more support.

Discrimination and practical difficulties were described, which could prevent treatment delivery to certain groups of patients, including those in prisons, intravenous drug users, and the homeless. Difficult-to-treat patient groups were also described, including those infected with HCV GT 3, patients with cirrhosis - especially those with decompensated cirrhosis - and patients who are coinfected with HIV. Mr Gore concluded that the challenge now is to increase awareness to ensure informed therapeutic choices are made and the proportion of patients being treated is increased.

Professor Alessandra Mangia

Prof Mangia began by stating that, despite reports of SVR rates of 67–75% being achieved in registrational studies for patients infected with HCV GT 1, the TARGET study reported SVR rates of 58–61% in 1,100 previously-treated HCV GT 1 patients.[38] This lower, real-world SVR range may be due to increased adverse events resulting in treatment discontinuation, and the development of HCV resistance-associated variants.[39] In the TARGET study, 36% of patients discontinued treatment with the study drug; in 16% of cases this was attributable to the occurrence of adverse events.[38]

EASL guidelines recommend careful monitoring of the 40% of patients who do not achieve a high SVR rate with a triple DAA combination in order to determine reasons for treatment failure and to identify patients with cirrhosis who are at increased risk of developing hepatocellular carcinoma.[21] For pretreated patients, who had not responded to telaprevir (TPV) or boceprevir + pegylated IFN alpha-RBV, a combination of DCV + SOF with or without RBV led to 95–100% SVR rates after 24 weeks treatment.[3] The safety profile of this study was encouraging, with small numerical increases in non-specific adverse events such as fatigue and headache.[3] The Phase II, LONESTAR-1 study also provided promising results for this patient population, which included those with cirrhosis,[24] SVR rates of 91% or higher were achieved after treatment with SOF and ledispavir, with 100% seen when RBV was added.[24]

Prof Mangia concluded that the 40% of patients who fail after treatment with PI can now expect promising results with DAA combination therapy, also emphasising the urgent need for treatments for patients infected with HCV GT 3, suggesting they may benefit from the combinations described above after PI treatment failure.

Professor Graham Foster [guest video]

Prof Foster joined the debate via video link from London to add his thoughts on the challenges faced by patients infected with HCV GT 3 in his practice, and shared his approach to treatment for this patient group, and how this differs from those infected with HCV GT 1.

Patients infected with HCV GT 3 have, for many years, been regarded as an easy-to-treat GT, provided they do not have advanced fibrosis. Prof Foster stated that approximately 70% of patients respond to treatment with IFN and RBV; however, once patients present with cirrhosis the treatment rates plummet dramatically, and aggressive disease is then more likely. An additional challenge is that a large proportion of patients infected with GT 3 were originally born outside the UK, very often in Pakistan, Bangladesh, and the Indian subcontinent, often being infected at birth or very close to birth as a result of poor-quality vaccinations. These patients are now presenting with advanced cirrhosis, unaware that they have HCV, and all too often there is little that can be done. Prof Foster felt that an all-oral regimen for patients infected with HCV GT 3 would transform the treatment landscape for these very unfortunate patients.

Professor Rafael Esteban

Prof Esteban also shared his experience of patients in his practice with HCV and liver cirrhosis who are waiting for liver transplants and who are in urgent need of effective treatments. He presented results from several studies, which showed that the efficacy of triple-combination therapies, including IFN or RBV, is low in patients with liver cirrhosis.[16,40–43] In a subgroup analysis of ADVANCE, a study of TPV + IFN and RBV in patients infected with HCV GT 1 for 24 weeks, SVR rates were 62% in patients with liver cirrhosis compared with 81% in patients without.[16] The tolerability of these regimens is reduced in patients with liver cirrhosis; the CUPIC study showed a high proportion of serious adverse events, which led to discontinuation of treatment in these patients.[44] Several studies of IFN-free, dual DAA regimens in this patient population have, however, shown high SVR rates together with high tolerability.[24,45–49]

Prof Esteban described the urgent need of treatments for peri-liver transplant patients. A high rate of graft reinfection is seen in patients who have detectable serum HCV RNA prior to

transplantation,[50] and with current therapies the proportion of patients who achieve undetectable HCV RNA prior to transplant is 29-59%.[51,52] Relapse rates for HCV cirrhosis is also high following liver transplantation.[50] IFN-free DAA combination therapy can lead to patients remaining HCV-RNA negative for 30 days before transplant, which maximises the chances for a high post-transplantation virologic response and reduces the HCV-cirrhosis recurrence.[53] In summary, IFN-free regimens for patients with advanced liver cirrhosis, IFN-free DAA therapy combinations, are effective and well tolerated and carry a lower risk of drug–drug interactions with transplant medications.[54–56]

Prof Esteban ended by describing his experience of a patient who developed severe cholestatic hepatitis (bilirubin 25 mg/dl) soon after receiving a liver transplant. Within 11 weeks of treatment with SOF + DCV, the patient was serum HCV RNA-negative and bilirubin levels had returned to normal.[57]

Prof Thursz brought the symposium to a close, stating that a majority of the audience and panel were in support of all-oral, IFN/RBV-free treatment regimens for all patients with HCV.

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