TRANSFORMING HCV MANAGEMENT

Summary of Presentations from the Gilead Sciences (Europe) Symposium, held at the 49th Annual EASL ILC, London, UK, on 9th April 2014

Chairperson

Graham Foster,[1] Patrick Marcellin[2]

Speakers

Ira Jacobson,[3] Heiner Wedemeyer,[4] Christophe Hézode,[5] Antonio Craxì[6]

1. Queen Mary University of London, London, UK
2. Université Paris-Diderot, Paris, France
3. Weil Cornell Medical College, New York, USA
4. Hannover Medical School, Hannover, Germany
5. Hôpital Henri Mondor, Créteil, France
6. University of Palermo, Palermo, Italy

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MEETING SUMMARY

This Gilead-sponsored satellite symposium addressed the new and exciting advent of novel therapy in the field of hepatitis C by highlighting recent important clinical trials. The scientific programme covered the history of treatment of hepatitis C and the current and future treatment landscape in the management of hepatitis C virus (HCV) infection.

Historical View – Where Have We Come From?

Professor Patrick Marcellin

Prof Marcellin introduced the delegates to a history of hepatitis C by giving an overview of the discovery of the virus and the subsequent investigation into its transmission. Identification of a new virus that was not attributable to hepatitis A or B was made in the 1970s and led to a flurry of investigation, which revealed that it is a small enveloped RNA virus.[1] Further efforts to elucidate the nature of the infection resulted in a small pilot study that involved ten patients with non-A, non-B hepatitis. Administration of daily injections of recombinant human interferon-α (IFNα) led to a normalisation of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, and subsequent novel cloning techniques allowed the identification of this elusive virus as HCV in 1989. This discovery laid the foundation for many advances including the development of diagnostic and monitoring tools used to identify HCV, as well as an increasing number of treatment targets and regimens over the years since its discovery. Of note is the first-generation ELISA and the subsequent

development of the second-generation - more sensitive - RIBA assay, both of which are used for diagnosing non-A, non-B hepatitis.[2]

Initial treatment regimens established IFNα as a stalwart in the treatment of HCV. The addition of ribavirin (RBV) to this regimen was seen to improve viral response rates, whilst the pegylation of IFNα was observed to delay its breakdown and increase drug exposure, permitting a single dose a week and therefore representing a major treatment advancement.[3,4] However, the side-effects seen with IFNα therapy and the danger of viral resistance have led to the development of direct-acting antiviral agents (DAAs) which include first-generation protease inhibitors (PIs). Although first-generation PIs improve sustained viral response (SVR), they come with further toxicities and the continued problem of emerging resistance.

Combining IFNα therapy with other DAAs has resulted in encouraging improvements in SVR in patients with HCV.[5–9] In particular, combinations with a newly approved, once daily, oral non-structural protein 5B (NS5B) nucleotide analogue polymerase inhibitor, sofosbuvir (SOF), has been shown to achieve >90% SVR across all genotypes.[10]

Prof Marcellin concluded his presentation by proposing that these results indicate a new era in the treatment of HCV, where despite concerns that only a small portion of patients are currently being treated, huge progress has already been made. High SVR rates achievable with a shorter course of therapy and IFN-free regimens were considered to represent the future of HCV management.[11]

Investigator View – Being Part of History in the Making

Professor Ira Jacobson

Prof Ira Jacobson offered his personal perspective on the field of HCV by beginning with an introduction to IFN therapy and the use of RBV as an adjunct to IFN. Although the mechanism of action of RBV in HCV remains the subject of much debate, increased understanding of the HCV lifecycle has formed the basis of the development of a number of therapeutic agents, including protease inhibitors, NS5A inhibitors, nucleotide, and non-nucleotide inhibitors.

Dr Jacobson went on to describe his personal experiences as a young clinician, working with Dr Charles Rice at Rockefeller University, whose laboratory was pivotal in overcoming several milestones in HCV biology that have been key in the development of new therapies. These included elucidating the crystal structure of NS5A and identification of the co-receptors that mediate HCV entry into the cell as well as identifying an infectious cell culture system for the study of the mechanism of disease.

A timeline of the major therapeutic breakthroughs in HCV disease history of HCV therapy was described with major landmarks including the introduction of the first-generation PIs, boceprevir and telaprevir, in 2011 and the eventual move towards potential curability of HCV without IFN. Regulatory approval of sofosbuvir for genotypes (GTs) 1-6 followed the publication of results from a Phase III trial, which showed >91% SVR rate in patients with GT 1, 4, 5, and 6 over a shorter, 12-week treatment period.[10,11] Furthermore, Dr Jacobson highlighted key clinical trials with new DAAs of different drug classes that offer high levels of efficacy and unprecedented short treatment durations, giving new hope to patients for whom treatment with IFN is not an option.[12–14] In addition, the development of oral regimens, highlighted as a pivotal topic at the EASL meeting, was emphasised as another major culmination of recent scientific investigation.

In particular, the approval of SOF for chronic HCV by the EMA, a new drug that has no clinically significant drug interactions and has a high barrier to resistance during therapy, even in the event of a post-treatment relapse, marks the advent of a new and exciting period in the field of HCV.[14]

Virological View – Understanding the Relevance of HCV Genotype

Professor Heiner Wedemeyer

In his talk, Prof Heiner Wedemeyer addressed the diversity of GTs, demonstrating differences not only in response to treatment but also portraying differences in natural history. Prof Wedemeyer stressed that the relevance of GT was not only linked to response with IFN-based therapy but has also been shown to have importance in the context of DAAs.

Initial treatment regimens with IFN have demonstrated marked differences in response to therapy between GTs that can be explained by the divergent nature of each GT, as demonstrated in patients with GT 2 who respond better to PEG-IFN than those with GT 3 and 4.[15–21] Prof Wedemeyer explained that GT 3 is associated with rapid disease progression, including accelerated fibrosis and poor long-term survival in comparison to GT 1 and 2.[22] GTs also have varied responses to DAAs, including the first HCV protease inhibitor that rapidly decreased viral load in GT 1 patients but had little effect in patients with GT 2/3.[23,24] In contrast to previous established therapies, nearly all patients treated with SOF become HCV RNA negative within 4 weeks of therapy;[11,14] however, Prof Wedemeyer pointed out that maintenance of SVR between GTs differed and that 12 weeks of SOF + RBV therapy showed higher response rates in GT 2 versus GT 3 patients.[11,25]

Methods to overcome the lower response rates in GT 3 patients were then presented with approaches including increasing the duration of treatment, combining therapy with IFN or, finally, through the potential addition of a developmental NS5A DAA, such as daclatasvir, providing potential solutions.[10,11,14,26,28] Initial data have demonstrated that all of these approaches may provide future benefit within this group and further insights are highly anticipated.

Prof Wedemeyer concluded his presentation by reiterating that GT remains a very relevant issue in HCV therapy and one that must be taken into account when addressing the treatment needs of individual patients with different HCV GTs.

Perspectives on New Candidates for Cure

Doctor Christophe Hézode

In his talk about the treatment of difficult patients, Dr Christophe Hézode began by explaining results from the real-life CUPIC study in which cirrhotic patients were given triple therapy (boceprevir or telaprevir with PEG-IFN and RBV). Patients in this study who had platelet counts <100,000 mm^3 and albumin <35 g/L were more likely to experience complications, and less likely to achieve an SVR12, indicating that triple therapy is an inefficient way to manage patients with severe complications.[29,30] In contrast, SOF therapy in combination with RBV and PEG-IFN for 12 weeks in cirrhotic patients resulted in a promising SVR of 80%, indicating that SOF may be a new standard of care in patients with severe disease.[31]

Dr Hézode presented an important clinical case study of one of his patients, a woman with GT 4, previously taking PEG-IFN + RBV therapy. The patient had cirrhosis and encephalopathy and was awaiting transplant when she was put on a regimen of SOF with RBV. After 16 weeks of treatment the patient displayed a significant improvement in biological and clinical parameters, including a significant improvement in her Child–Pugh (C11 to B7) and MELD (15 to 12) scores to the extent that there is reconsideration of whether this patient will now indeed be in need of a liver transplant.

A more pressing question about the prevention and recurrence of HCV after liver transplant was discussed. Patients on a combination of SOF + RBV for up to 48 weeks pre-liver transplant display significantly less recurrence of HCV leading up to the transplant, with a 93% viral response rate at transplant. >30 days of undetectable viral load significantly reduced recurrence. Furthermore, 69% of patients maintained this at 12 weeks post-transplant and had very few adverse effects; however, data are not final as the trial is still ongoing.[32] Early interim Phase II trial data suggest that in patients with recurrent HCV post-liver transplant, treatment with SOF + RBV results in a high SVR after 12 weeks of treatment.[33] Dr Hézode then described a second clinical case of one of his patients, a 52-year-old male with recurrent HCV GT1 following liver transplant who failed to respond to PEG-IFN + RBV + BOC. The patient was put on a regimen of SOF + RBV, quickly reaching undetectable levels of HCV RNA, and after 24 weeks of treatment, showed improvement in his Child–Pugh (A6 to A5) and MELD (14 to 11) scores.

This presentation and the clinical cases highlighted the increasing promising data and clinical experience with the use of SOF + RBV in hard-to-treat patients undergoing liver transplant as well as those who are post-liver transplant with recurrent HCV.

Perspectives on Therapy for Challenging Patients

Professor Antonio Craxì

In his talk, Prof Antonio Craxi explored the current and future therapeutic options available to clinically challenging patients, including those who are treatment-experienced cirrhotics and those with HIV/HCV co-infection.

Results from the ATTAIN study showed little benefit in response of simeprevir over telaprevir in combination with PEG-IFN + RBV in treatment non-responders with cirrhosis, suggesting that this clinical approach is insufficient in dealing with the problem of HCV in cirrhotic patients.[34] Treatment with SOF + RBV in treatment-naïve and treatment-experienced patients with GT 3 who were further stratified into cirrhotic and non-cirrhotic groups resulted in a significant improvement in SVR after 12 weeks.[26] In treatment-experienced patients with cirrhosis SVR was 60% while in treatment-naïve patients with cirrhosis SVR was 92%.[26] The combined use of PEG-IFN with SOF + RBV further improved SVR in treatment-experienced cirrhotics to 83%, suggesting that combining PEG-IFN with currently-approved agents may give an optimal viral response.

Similarly, combining SOF + RBV + PEG-IFN in treatment-naïve patients GT 1–4 with HIV co-infection resulted in 91% SVR in this difficult-to-treat population.[10,35] Prof Craxi then went on to present data on the use of all-oral therapy (SOF + RBV for 12 or 24 weeks) in cirrhotic and non-cirrhotic patients. In patients with GT 1 and 2, viral response rates were 76–88% in treatment-naïve patients and 92–94% in treatment-experienced patients. In patients with GT 3, recognised as being a more resistant GT, viral response rate was 67% after 12 weeks; however, this was still considered promising. There was no sign of viral resistance, though HCV and HIV breakthrough was observed in two patients due to non-adherence.[36] Moreover, comparison of viral response rates in HIV/HCV co-infected and HCV mono-infected treatment-naïve patients showed that these were similar between the two groups.[11,26,36,37]

In summary, this presentation showed that patients with HIV/HCV co-infection are no longer to be considered a special patient population and can be treated with SOF, which has a high efficacy. This therapy paves the way for more investigational DAAs being considered for the treatment of more difficult patient populations.

Has the Future Arrived? – Perspectives in HCV Tomorrow

Professor Graham Foster

Prof Graham Foster introduced his presentation by highlighting the hopeful future in hepatitis C. Supporting this perspective with recent data he presented an overview of the use of SOF in GT 1–4 for up to 12 weeks in order to elicit a viral response. This is especially promising in patients for whom IFN therapy is ineffective or contraindicated, where SOF can be used for 24 weeks. Results from clinical trials have shown 90–100% SVR across GT 1–6 following 12 weeks of treatment, a result that is unprecedented with any other drug that has been previously available.[11,15]

The emergence of new drugs means that the use of IFN/RBV therapy, which carries a significant adverse effects profile, will be reduced. In addition to this, newer drugs also offer reduced pill burden and shorter treatment duration for many patients, including offering an alternative IFN-free therapy option for more difficult-to-treat patient populations.[38]

Prof Foster went on to propose early treatment of HCV-infected patients in order to reduce morbidity and mortality, but especially in the treatment of those who have progressed and are now cirrhotic, offering the possibility of removing high-risk patients from the transplant list as well as vastly improving the quality of life that is directly associated with SVR.[39,40]

Furthermore, the introduction of SOF therapy for HCV may not only be beneficial for disease burden, but is also thought to have a significant financial burden on healthcare systems. Therefore, another incentive for the development of newer, more effective treatments for HCV are burgeoning HCV-related healthcare costs.[41,42] Several new IFN-free regimens are currently at an advanced stage of development; in particular, single treatment regimen (STR) therapies, consisting of a single pill that combines two or more highly effective drugs, will provide a new portfolio of therapies for HCV patients. A combination of SOF + daclatasvir (two pills) over a 12–24-week period has

demonstrated up to 98% SVR for GT1 patients in a Phase II study, while Phase III data presented at the EASL 2014 Congress showed that combining SOF with ledipasvir as an STR (one pill) without IFN or RBV has shown up to 98% SVR over a 12 or a 24-week period in GT1 patients.[27,43–46]

Prof Foster concluded that the development of newer therapies may help to eradicate HCV as a disease, not only in patients at the front line, but also in those where the virus lies nascent.

This satellite symposium provided an insight into the dynamic, rapidly changing field of HCV. It introduced data on exciting new treatment regimens that offer new hope to those with HCV, especially for patients with severe disease for whom these new treatments offer a new lease of life. The treatment of HCV has been previously stymied in more challenging cirrhotic patients and in those with HIV/HCV co-infection; however this new paradigm shift may pave the way for a brighter future with the potential of a world without HCV.

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