Introduction

The European Association for the Study of the Liver’s 50th International Liver Congress presented a range of exciting new data in viral hepatitis. Several successful applications of novel direct-acting antivirals (DAA; Table 1) in previously ‘hard-to-treat’ patient populations were reported and the arrival of further DAAAs was heralded with impressive efficacy data. With success in the HCV domain now well established, greater attention is being focused on methods of clearing HBV infection. Results of novel combinations of existing therapies in the clinical domain were presented, while a proliferation of experimental approaches for targeting infected hepatocytes in vitro and in vivo show great promise.

Not so hard to treat

Decompensated liver disease

Patients with decompensated liver disease are unable to receive interferon-based therapy without risk of fatal deterioration. Some of the most striking data presented at the Congress demonstrated efficacy and safety of DAA in this patient group, including two observational cohort studies (English Expanded Access Programme, EAP, and the French Compassionate Use Program) and the ALLY-1 and SOLAR-2 trials [1-4]. In the English EAP, patients received 12 weeks of sofosbuvir/ledipasvir or sofosbuvir/daclatasvir, with or without ribavirin (RBV), at the discretion of the treating physician [1]. Rates of sustained virological response at week 12 after treatment (SVR12) were comparable amongst patients with genotype (GT)1 HCV treated with sofosbuvir/ledipasvir/RBV or sofosbuvir/daclatasvir/RBV (86% vs 82%, respectively). SVR12 rates were much lower amongst patients with GT3 HCV with decompensated disease, and this remains the most challenging population to cure in the DAA era. In the EAP, 70% of GT3 patients achieved an SVR12 with sofosbuvir/daclatasvir/RBV (59% with sofosbuvir/LDV/RBV, difference not significant), which corresponds well with the French Compassionate Use Program in which patients with GT3 HCV and compensated cirrhosis were treated with 12 weeks of SOF/DCV/RBV. This study reported an SVR4 of 76%, rising to 88% with 24 weeks of treatment, suggesting extended therapy may be prudent in GT3 disease with cirrhosis [2]. By contrast, data on outcomes in decompensated disease from SOLAR-2 suggested no benefit in extending SOF/LDV/RBV treatment in GT1 HCV, although there was a trend towards better outcomes with 24 weeks of therapy in a small group of GT4 patients [3]. GT1 HCV patients with decompensated cirrhosis were also treated in ALLY-1 (SOF/DCV/RBV 12 weeks) with a marked drop-off in SVR 12 rates between Child–Pugh B (92%) and C (50%) disease [4]. Finally, real-world data were presented from the US TARGET database including patients with advanced liver disease (MELD score >10) who had received SOF-based therapy (SOF/SIM, SOF/RBV or SOF/SIM/RBV). Amongst patients with GT1 HCV, outcomes were best amongst patients treated with SOF/SIM (SVR12 74% with SOF/SIM, 66% with SOF/SIM/RBV and 54% with SOF/RBV). SVR12 rates in GT2 HCV patients treated with SOF/RBV were good (81%), but the majority of GT3 patients receiving this combination relapsed after treatment (SVR12 39%) [5].

Importantly in all these studies, treatment was safe and well tolerated with no treatment-related deaths and few adverse events. What happens to patients after treatment is less clear. SOLAR-2 assessed disease severity in patients with decompensated cirrhosis 4 weeks post-treatment. While some patients showed considerable recompensation, a small number deteriorated despite achieving an SVR [3]. Further work is required to identify the ‘point of no return’ at which patients may be better served by transplantation.

Post-transplantation patients

In patients post-transplantation, questions remain regarding the optimum regimen, duration and timing of treatment. The ALLY-1 and SOLAR-2 trials included post-transplant patients confirming that both SOF/LDV/RBV and SOF/DCV/RBV are viable options here. Efficacy outcomes were excellent and treatment well tolerated in both (SVR12 94% in ALLY-1, 95–98% in post–transplant patients without decompensated cirrhosis in SOLAR-2) [3,4].

Renal impairment

Patients with severe renal impairment have been unable to benefit from the first wave of sofosbuvir-based DAA regimens due to uncertainty about the potential toxicity of the sofosbuvir metabolite, GS-331007, which is renally excreted. The US TARGET database has recorded outcomes of over 1800 patients with renal impairment treated with sofosbuvir-based therapy. Overall SVR rates were similar across all degrees of renal impairment. However, the vast majority of patients had eGFR >60 [6]. The incidence of adverse events, particularly further
deterioration in renal function, was increased in patients with a GFR <30, but the causal relationship between this and therapy is unclear in this retrospective observational cohort.

A promising alternative to sofosbuvir-based regimens in renal failure is ombitasvir, ritonavir-boosted paritaprevir and dasabuvir, given with RBV (GT1a) or without RBV (GT1b). RUBY-1 investigated this regimen in treatment-naive, non-cirrhotic patients with renal impairment. Most participants had advanced renal disease (95% eGFR <30, 65% haemodialysis). In this interim analysis, efficacy results were impressive but available for very few patients (SVR4 10/10, SVR12 2/2). Treatment was generally well tolerated, although RBV-related toxicity remains problematic and frequent RBV dose reductions were required [7].

Genotype 3 HCV

Patients with GT3 disease have benefited least from the DAA revolution, which probably represents the lower priority given to commercial drug development of agents active against this less prevalent genotype rather than any intrinsic viral characteristic. To investigate optimisation of sofosbuvir-based treatment for this patient group, BOSON compared sofosbuvir plus pegylated interferon and RBV (peg-IFN/RBV) for 12 weeks, sofosbuvir plus RBV for 16 weeks, or sofosbuvir plus RBV for 24 weeks in treatment-experienced, cirrhotic GT2 patients and treatment–naïve and experienced, cirrhotic and non-cirrhotic GT3 patients. In patients with GT3 HCV, sofosbuvir/peg-IFN/RBV for 12 weeks was superior to sofosbuvir/RBV regimens of 16 or 24 weeks (SVR12 93%, 71% and 84%, respectively). The peg-IFN–containing regimen was superior regardless of treatment experience or cirrhosis [8]. In the future, sofosbuvir-based regimens may be superseded for GT3 but for now, inclusion of peg-IFN in sofosbuvir-based treatment should remain an option.

Rare genotype HCV

Patients with rare genotypes, such as GT5, have not been studied in significant numbers in DAA trials. A study by Abergel et al. was therefore of interest, reporting outcomes in an unusually large cohort of GT5 patients (n=41) receiving SOF/LDV, with 95% achieving SVR [9].

Cirrhosis and HIV/HCV co-infection

Patients with cirrhosis co-infected with HIV and HCV are another group with historically poorer SVR rates in the era of interferon–based therapies. Early results from a cohort of HIV–co–infected cirrhotic patients treated with SOF–based regimens were excellent, with treatment generally well tolerated and SVR12 achieved in 93% of patients who had reached this endpoint [10]. The ALLY-2 trial compared 8 and 12 weeks of SOF/DAC in HIV/HCV co-infected patients. SOF was given at standard dose (400 mg once daily) while DAC was dose–adjusted according to concomitant antiretrovirals; 12 weeks of treatment was superior to 8 weeks (SVR12 97–98% with 12 weeks vs 76% with 8 weeks of treatment). Importantly, treatment was generally well tolerated with no impairment of HIV control during treatment [11].

Relapse following DAA treatment

Patients who have relapsed after DAA treatment represent a new and growing population of ‘hard-to-treat’ patients for whom there is a shortage of information regarding best management. One option is to retreat with extended duration of therapy. Lawitz et al. reported results from retreatment of patients with GT1 HCV who had previously failed 8–12 weeks of sofosbuvir/ledipasvir-based therapy with 24 weeks’ sofosbuvir/ledipasvir retreatment. Overall, 71% of retreated patients achieved SVR12. Retreatment success was influenced by duration of previous therapy (80% SVR12 in patients previously treated for 8 weeks vs 46% in those previously treated for 12 weeks) and the presence of NS5A RAVs at retreatment baseline (100% SVR12 if no RAVs vs 60% if RAVs present). Furthermore, a small number of patients with NS5A RAVs acquired the sofosbuvir resistance–conferring NS5B RAV S282T during retreatment [12]. The duration of follow–up of these patients is limited, but it is emerging that while NS3 RAVs diminish over time (in keeping with previous data), NS5A RAVS remain present at 48 weeks post-treatment [13]. In patients who have failed ledipasvir–containing treatment, NS5A RAVs have persisted beyond 96 weeks of follow-up [14].

Patients who had previously failed therapy with IFN-RBV and one of telaprevir, boceprevir or simeprevir were treated with grazoprevir, elbasivir and RBV for 12 weeks in the C-SALVAGE study [15]. There is no known cross–resistance to grazoprevir conferred by NS3 RAVs and this was borne out by 96% of patients achieving SVR12. However, amongst patients failing therapy, new NS3 and NS5A RAVs were identified.

Treatment simplification strategies

The high cost of DAAs has prompted searches for the shortest possible duration of effective treatment. Amongst non-cirrhotic patients with GT1 HCV, 12 weeks of simeprevir/sofosbuvir was superior to 8 weeks (SVR12 97% vs 83%, respectively). However, good outcomes with 8 weeks of therapy (SVR12 >90%) were seen in: patients with GT1b infection; the IL–28B CC genotype; and baseline viral load <4x10^6 IU/mL; although the numbers in each subgroup were relatively small [16]. Excitingly, the combination of sofosbuvir with two investigational DAAs may permit successful therapy in just 6 weeks in carefully selected patients. GT1 patients received sofosbuvir plus GS-5816 and GS-9857 for 4–6 weeks, depending on presence of cirrhosis or previous treatment experience. Six weeks of treatment was superior to 4 weeks in all patient groups (SVR12: 93% in non–cirrhotic treatment–naïve; 87% in cirrhotic treatment–naïve; 67% in treatment–experienced, all treated for 6 weeks; 27% in non-cirrhotic treatment–naïve treated for 4 weeks) [17].

Emerging treatment regimens

Several Phase II/III studies were presented on the efficacy, safety and tolerability of grazoprevir/elbasivir in patients with chronic HCV. 12–16 weeks of this novel combination therapy, with or without RBV, was highly efficacious in patients with GT1, 4 or 6 HCV (overall SVR12 95% in treatment–naïve patients, 92–97% in peg–IFN/RBV–experienced patients, 96% in protease inhibitor–experienced patients) [15,18,19]. Good outcomes were also seen in GT1, 4 or 6 patients co-infected with HIV (overall SVR12 95%) [20] and in GT1 patients with renal failure (94% SVR12) [21].

In common with other NS5A-containing regimens, SVR12 rates were influenced by pre-existing NS5A mutations which conferred reduced susceptibility to elbasivir [18]. Furthermore, this combination may be less effective in viral genotypes other than GT1 and GT4, although numbers studied were relatively small [22]. For example in GT3 HCV, grazoprevir/elbasivir was combined with sofosbuvir for 8 or 12 weeks and resulted in SVR12 rates of 91–100% [23]. These new agents therefore represent a highly useful addition to a growing armamentarium of DAAs.
The pursuit of HBV surface antigen clearance

Although treatment of chronic HBV infection (CHB) with nucleotide analogues (NUC) effectively suppresses viral replication, clearance of infection with loss of surface antigen (sAg) is uncommon. Following observational reports that addition of peg-IFN may enhance sAg loss in patients on NUC therapy, HBV e-antigen-negative patients with undetectable HBV DNA on NUC therapy were randomised in the PEGAN study to receive 48 weeks’ peg-IFN in addition to NUC, or no additional therapy. By week 48, 20% of patients randomised to peg-IFN had discontinued the drug due to adverse events and only 8% of patients treated with peg-IFN cleared HBV sAg [24]. In a multivariate analysis of patients treated for 48 weeks with tenofovir, peg-IFN or combination therapy, the factors that predicted sAg loss were: peg-IFN/tenofovir dual therapy; HBV genotype A; early ALT flare on therapy; and decline in sAg by >1log₁₀ IU/mL by treatment week 12. Therefore, it may be possible to use decline in sAg at week 12 to guide therapy according to response for patients where therapy with NUC/peg–IFN is being considered [25].

Long-term viral suppression with NUC may restore host immune function, such that NUC may be stopped. In a study by Berg et al., patients with e-antigen-negative CHB, stably maintained on NUC for over 4 years, were randomised to continue or stop therapy. After 48 weeks, two patients (9.5%) who stopped NUC had cleared sAg, compared to none of the patients who continued NUC. The majority who stopped maintained low viral loads off NUC therapy. A small number of patients (14%) restarted NUC due to a significant flare and regained virological control, indicating that with close follow-up this strategy is safe, although sAg clearance remains modest [26].

Finally, intriguing data were presented on clinical factors associated with development of hepatocellular cancer (HCC) in treatment-experienced patients with CHB. At multivariate analysis, peg-IFN treatment was found to be associated with a longer time to the development of HCC compared with NUC therapy, despite poorer viral control over the intervening period. This counterintuitive protective effect may warrant further study [27].

Progress in novel approaches to HBV therapy

The high specificity and efficacy of CRISPR/Cas9 genome editing is having a revolutionary impact in the field of gene therapy and, unsurprisingly, is now being applied to the difficult problem of removing both cccDNA and chromosomally integrated HBV copies in order to achieve HBV clearance. The CRISPR/Cas9 system has been identified as a novel method to target HBV cccDNA. Shlomi et al. screened in vivo CRISPR/Cas9 guide RNAs specific for highly conserved regions of the HBV genome, and identified three that inhibited HBV replication with high potency. Further testing in vitro confirmed reduced cccDNA in both HBV-expressing and HBV-infected cells with no significant off-target editing detected [28]. Pan et al. confirmed a reduction in HBV protein production in vitro and in mice transduced in vivo with an adenovirus-delivered HBV1.3 genome. A combination of three cleavage sites significantly enhanced inhibition of HBV e-antigen production [29]. It remains to be seen whether this gene therapy approach, with its costly limitations and risks, will prove a viable solution for the vast majority of patients with HBV.

Chronic HBV infection is characterised by functional exhaustion of HBV-specific effector T cells. One promising immunotherapeutic approach, popular in cancer immunotherapy, is to circumvent both exhaustion and antigen specificity by using bi-specific antibodies to cross-link an antigen target with the CD3 T cell receptor. Bohne et al. report the use of antibodies specific for both HBsAg on the surface of infected cells and human CD3. This led to killing of HBV-infected hepatoma cell lines in co-culture with peripheral blood monocytes (PBMC), and also in vivo shrinkage of HBV-infected hepatomas in immunodeficient mice into which human PBMC were adoptively transferred [30].

While restoration of effector T cell function has clear antiviral and antitumour potential, widespread cytotoxicity may ultimately prove harmful in patients with chronic HBV infection. Koh et al. presented data overcoming this potential limitation by RNA electroporation of an HBV-specific T cell receptor into human lymphocytes. Amongst the resulting HBV-specific T cells, a population was identified that produced antiviral cytokines but inhibited HBV replication in vitro without cytotoxicity [31]. Whether replacing, or adjunctive to, current therapies, these are exciting developing areas for future HBV therapeutic.

Summary and conclusions

Much of the data presented at EASL 2015 will have a significant impact on future HCV and HBV treatment strategies, particularly in patient groups that have previously been difficult to treat. However, this impact is unlikely to be felt for many years by the largest group of ‘hard-to-treat’ patients – those who reside in resource-limited areas. It was fitting that the 50th International EASL congress acknowledged this with a number of sessions dedicated to global public health strategies for the eradication of HCV and HBV, including the WHO-EASL symposium. The challenges here are great and wearily familiar to those who have been working to improve global access to HIV diagnosis and treatment. These sessions starkly highlighted how a disproportionate amount of our endeavours are focused upon achieving relatively small improvements in treatment efficacy for the few, while the many go without any treatment at all.

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