Editorial

Direct-acting antiviral agents for the treatment of HCV

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Introduction

Chronic infection with the HCV is a global epidemic, affecting 130–170 million individuals worldwide. It may cause cirrhosis, liver failure and hepatocellular carcinoma, and is the leading indication for liver transplantation worldwide. In the United States, HCV-related mortality now exceeds that of HIV [1]. Without intervention, the healthcare burden is predicted to increase as the HCV population ages [2,3]. Viral eradication has been shown to prevent disease progression and related morbidity and mortality. The standard-of-care treatment for HCV for the past decade has been pegylated interferon (PEG-IFN)-α and ribavirin (RBV), which was able to cure at best 50% of patients with genotype 1 HCV, the most prevalent HCV genotype in the West. In this context, there has been an urgent need for more effective antiviral therapy.

The past year has seen two landmark milestones in the field of HCV therapeutics. The first two direct-acting antiviral (DAA) agents, boceprevir and telaprevir, were approved for the treatment of genotype 1 HCV. Used in combination with PEG-IFN-α and RBV, these NS3 protease inhibitors increase sustained virological response (SVR) rates twofold compared to the former standard-of-care. Furthermore, NS3 protease inhibitors are the first of multiple classes of DAAs in development that target different steps in the viral life cycle, and are suitable for combination therapy. Indeed, 2011 also saw proof-of-concept that HCV could be cured by combination DAA therapy alone, without IFN-α, the backbone of therapy for the past 20 years. An era of effective IFN-free therapy is within reach. In this special edition, authors consider the journey so far, the progress made and the lessons learnt, and how this may inform the future development of highly effective, well-tolerated oral therapies for all patients with chronic hepatitis C.

Viral targets for antiviral therapy and rational drug design

The evolution of DAA therapy represents a success story for rational drug design. Two key advances in the late 1990s made this possible. The description of the 3-dimensional structure of the NS3 protease and the NS5B polymerase HCV proteins through X-ray crystallography [4–8], and the development of the subgenomic replicon system [9–11] allowed high throughput screening of candidate HCV inhibitors for high in vitro antiviral activity. This has led to the identification of multiple promising compounds. More recent efforts have identified agents that potently inhibit the NS5A phosphoprotein, as well as drugs that target the host cell protein cyclophilin, which interacts with the HCV replication complex and is required for efficient viral replication. Indeed, in theory, every step of the HCV life cycle could be targeted for antiviral development. In this issue, Jean-Michel Pawlotsky reviews the science underpinning the development of DAA therapies for HCV [12].

A new standard-of-care for genotype 1 HCV: NS3 protease inhibitors

The first two DAAs for the treatment of HCV were approved by regulatory authorities in North America and Europe in 2011. Boceprevir and telaprevir are peptidomimetic inhibitors of the HCV NS3/4a protease. Both agents are approved only for individuals who are chronically infected with genotype 1 HCV. Triple therapy regimens of telaprevir or boceprevir with PEG-IFN-α and RBV have been associated with SVR rates of up to 80% in treatment-naïve patients, compared to 40–45% with PEG-IFN-α and RBV alone [13,14] (note...
that SVR is defined as an undetectable HCV RNA 24 weeks after stopping antiviral therapy. Treatment is also effective for patients who have previously failed PEG-IFN-α-based therapy [15,16]. This clearly represents a significant advance, highlighted in an article by Marks and Jacobson [17]. Treatment is not without new challenges however. Boceprevir and telaprevir are both associated with drug-specific toxicity, have a high pill burden, and the potential for drug–drug interactions. Treatment failure is associated with selection of resistant variants, a risk that is higher in genotype 1A versus 1B HCV, as discussed by Aloia et al. [18]. David Thomas [19] describes how many of these hurdles were predictable from HIV experience, and how this experience might inform current and future development. One important parallel is cost – DAA therapy is expensive, and Gellad et al. [20] point out that this may restrict access in certain regions. One strategy to maximize cost effectiveness might be to triage access according to host IL28B genotype, recently identified as the strongest baseline determinant of IFN sensitivity in patients infected with genotype 1 HCV [21–23]. Ahlenstiel et al. [24] discuss the relevance of IL28B polymorphism to current and future DAA regimens.

**Future treatment paradigms**

The development of DAA regimens continues at pace. The next step for genotype 1 HCV will be triple therapy regimens involving PEG-IFN-α and RBV plus DAAs that have minimal side effects, have single daily dosing schedules, with improved potency that allows shorter treatment duration according to response-guided criteria. Mathematical modelling of viral kinetics during telaprevir therapy suggests that the minimum treatment duration necessary for protease inhibitors might be only 10 weeks. Chatterjee et al. [25] report on how mathematical modelling might inform design of short duration regimens. The NS5B nucleotide inhibitor sofosbuvir, the NS5A inhibitor daclatasvir (BMS-790052) and the NS3 protease inhibitor simeprevir (TMC-435) are all in the advanced stages of Phase III development with treatment durations as short as 12 weeks. An even shorter duration may be feasible in IFN-sensitive individuals. Quadruple therapy regimens involving combination DAA plus PEG-IFN-α and RBV are in development, but will likely be reserved for more difficult-to-treat individuals, particularly prior null responders to PEG-IFN-α and RBV. The ultimate goal is IFN-free therapy that is highly effective, pan-genotypic, well-tolerated, and has a daily dosing schedule with short treatment duration. For genotype 2 and 3 HCV, very high response rates have been observed with 8–12 weeks of the nucleotide inhibitor sofosbuvir (GS-7977) plus ribavirin [26]. Phase III results for this regimen are expected at the end of 2012. This regimen has not been as successful for genotype 1 HCV, particularly in those patients who are prior non-responders to PEG-IFN-α and RBV. This was a little surprising and remains unexplained; it may relate to intrahepatic innate immunity, advanced liver fibrosis, or even ribavirin resistance. Emergence of resistance-associated variants to this agent has not been observed clinically. Combinations of best-in-class regimens may be required for these patients, and the combination of sofosbuvir and daclatasvir ±RBV was recently associated with undetectable HCV RNA 4 weeks after stopping antiviral therapy (SVR4) rates of 100% in a small cohort of treatment-naive patients, even in the RBV-free arm [27]. Ed Gane reviews the breakneck journey towards IFN-free therapy [28].

**Eradication of HCV**

The treatment landscape for HCV is changing rapidly and dramatically. We are very confident that within 5–10 years clinicians will have highly effective regimens that will be suitable for most patients. Eradication of HCV can now be considered. The barrier to eradication will not be the efficacy of treatment, but rather access to treatment [29]. This will require substantial review of current models of care, and concerted advocacy from interest groups on behalf of both the developed and developing world. This vital process should begin now.

**Disclosure statement**

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**References**


