Review

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Second generation direct-acting antivirals – Do we expect major improvements?

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Summary

The rapid progress in the development of direct-acting antiviral agents for hepatitis C has allowed the vast majority of patients to receive all oral therapy that will eliminate their virus. The success of the new regimens has led many to question the need for further developments in this field. Major improvements in drugs for hepatitis C are unlikely but we predict incremental improvements in the next few years. We hope that the next generation of drugs will address the unresolved issues for patients with genotype 3 infection where current treatments are still not entirely satisfactory and we anticipate improvements in the management of patients with renal failure. Shorter duration treatments, perhaps with novel modes of action, may allow simplified 'one-dose' treatments that will greatly expand our ability to treat patients who have difficulty accessing current services and we anticipate that the clinical community will better define the patients with advanced disease who will benefit from therapy prior to liver transplantation.

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Abbreviations: HCV, hepatitis C virus; G3, genotype 3; SVR, sustained virological response; NS5A, non-structural 5A; PI, protease inhibitor.

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HCV Perspectives

Introduction

The development of direct-acting antivirals (DAAs) has revolutionized the treatment of hepatitis C virus (HCV) infection. These small molecule inhibitors of different viral proteins have dramatically improved both response rates and the tolerability of treatment. The evolution of DAA therapy has moved at a remarkable pace from initial combinations with interferon (IFN) and ribavirin being replaced by extremely well tolerated single or multi-tablet regimens combining DAAs of different classes within just a few years. Current regimens deliver rates of sustained virological response (SVR) above 90% in most patient populations, raising the prospect of widespread treatment leading to local elimination or, possibly, even global eradication of HCV as a public health problem.

Despite the incredible success of the first oral DAA regimens, development of new DAAs and new DAA combinations continues at a rapid pace. Future agents hold promise to address the remaining therapeutic holes and perhaps more importantly, to further simplify therapy, a key factor if treatment is going to move out of specialty clinics. While high SVR rates are critical to the success of HCV therapy for the individual patient, major improvements in all aspects of the cascade of care right from diagnosis through engagement in treatment must improve to address HCV at the population level. Simplified, less expensive therapies hold the promise of treatment being delivered in primary care settings using novel models of care, which has the potential to lead to the increases in treatment capacity which will be required to deliver the promise of HCV elimination [1].

Here we will briefly review current drugs and discuss the remaining therapeutic challenges before examining DAAs in development, with a focus on how these regimens will address existing therapeutic and logistical gaps. Novel approaches to treatment and the future of HCV therapy will also be explored.

First generation DAAs

The first oral agents developed for HCV targeted the HCV non-structural 3 (NS3) serine protease [2]. While potent inhibitors of HCV replication, the first generation protease inhibitors (PIs), telaprevir and boceprevir, had important deficiencies including a low barrier to resistance, multiple drug-drug interactions and numerous side effects, which were

particularly problematic when combined with pegylated interferon (PegIFN) and ribavirin [3]. These agents were quickly replaced by a second wave of first generation PIs including simeprevir, asunaprevir and paritaprevir, which primarily improved the side effect profile with only modest changes in the other attributes of this class of agents.

In addition to the NS3 protease, the NS5B RNA-dependent RNA polymerase has been targeted and two approaches have been used. Classical nucleotide analogues that are incorporated into replicating HCV RNA and lead to chain termination of nascent viral genomes have been developed and differ substantially from so-called non-nucleotide polymerase inhibitors that target regions of the enzyme outside of the active site, inhibiting its function through steric hindrance [4,5]. Despite the evaluation of numerous nucleotide inhibitors (NIs) in clinical trials, only sofosbuvir has been approved to date, with other agents in the class failing for a combination of lack of efficacy (e.g. mericitabine) and/or toxicity (PSI-938) [4,5]. Sofosbuvir has proven highly effective with an excellent safety profile, pan-genotypic activity and most importantly, a very high barrier to resistance [5]. The only significant limitation to sofosbuvir is the fact that its major metabolite is renally cleared, preventing its use in patients with significant renal impairment [6]. Unlike NIs, non-nucleotide polymerase inhibitors (NNIs) have a very low barrier to resistance and a very restricted genotype specificity [7]. To date, only dasabuvir, a 'Thumb' I inhibitor, which is only active against genotype 1 HCV, has been approved for clinical use, in combination with paritaprevir (PI) and ombitasvir (NS5A inhibitor) [8].

Despite an incomplete understanding of its function, the NS5A protein has proven to be an excellent therapeutic target. Agents discovered through compound screening with potent activity against HCV replicons selected for variants with nucleotide changes in the NS5A sequence, suggesting that these novel agents were targeting this protein which is involved in viral assembly and, probably, other aspects of the replication cycle [9,10]. With extremely potent antiviral activity, wide genotypic coverage and little potential for drug-drug interactions, NS5A inhibitors quickly became an important component of most combination DAA regimens. The major limitation of the first generation agents in this class, including daclatasvir, ombitasvir and ledipasvir, is their very low barrier to antiviral resistance [11]. Variants with resistance to NS5A inhibitors are generally very fit, allowing them to emerge even in untreated patients and to persist long-term in those who have failed an NS5A-inibitor-containing regimen [12]. Some troublesome resistant variants, such as the Y93H polymorphism persist in untreated populations, albeit at low frequency, compromising the efficacy of some regimens, particularly those of short duration [13].

Combinations of the four DAA classes have been evaluated in clinical trials and proven highly effective across a wide array of patient populations, including groups that were very difficult to cure with IFN-based therapy. Combinations approved to date include: PI + NI (simeprevir + sofosbuvir), PI + NS5A + NNI (paritaprevir/r, ombitasvir and dasabuvir), PI + NS5A (grazoprevir and elbasvir) and NS5A + NI (ledipasvir/sofosbuvir and daclatasvir + sofosbuvir).

Key point

First generation DAA regimens are highly successful. However, there are specific patient populations for whom these therapies are suboptimal.

Therapeutic challenges with existing regimens

Clinical trials have reported SVR rates above 95% in most populations using the licensed combinations of first generation DAAs and remarkably, early data from real-world registries suggest that SVR rates in clinical practice are only marginally inferior [14,15]. However, despite their remarkable success, there are specific populations for whom currently approved regimens remain suboptimal.

Genotype 3

Of approved DAAs, only sofosbuvir and daclatasvir have significant activity against genotype 3 HCV, although other protease and NS5A inhibitors, such as the combination of grazoprevir and elbasvir may have clinical value, particularly in combination with a nucleotide. The combination of sofosbuvir and ribavirin for 24 weeks is highly effective for patients who do not have cirrhosis, but SVR rates drop significantly in those with cirrhosis [16]. The effect is most pronounced in patients with cirrhosis who have failed prior treatment with PegIFN and ribavirin in whom clinical trials report SVR rates of just 60% and real-world studies document SVR rates below 50% [16,17]. Even for treatment-naïve patients with cirrhosis, SVR rates from real-world studies are as low as 58%, in contrast to trial data showing SVR rates of 79% [17]. Sofosbuvir has also been evaluated in combination with daclatasvir in patients with genotype 3. When given for 12 weeks, this combination is highly effective in patients without cirrhosis, yielding SVR rates of 97% and 98% in treatment-naïve and treatment-experienced populations, respectively. However, in patients with cirrhosis, SVR rates are much less encouraging, falling to 57% and 63% in treatment-naïve and treatment-experienced cohorts [18]. A small trial extending therapy to 16 weeks and adding ribavirin resulted in SVR rates of 86% in patients with cirrhosis who had previously failed IFN-based therapies, however the small number of patients and the lack of difference compared to patients treated for 12 weeks make this trial difficult to interpret [19]. Although real-world studies extending daclatasvir and sofosbuvir with or without ribavirin have reported SVR