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Review

Performance of hepatitis C virus (HCV) direct-acting antivirals in clinical trials and daily practice

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ABSTRACT

In recent years a revolution in hepatitis C virus drug development has taken place from troublesome regimens with pegylated interferon-alfa for 24 to 48 weeks with limited success to all-oral single tablet regimens taken for 12 weeks with very high chances of success. These promising results are not available to everybody. Depending on, for example, geographical factors with limited availability of new compounds, virus factors like hepatitis C virus genotype and host factors like presence of cirrhosis, these favorable outcomes can be compromised. This review discusses the recent clinical trials (from phase 3 registration through real-world application), highlighting the different available regimens and their success rates. **J.E. Arends, CMI 2016;22:846**

Introduction

At the dawn of this millennium the combination of pegylated interferon-alfa (PEG-IFN) and ribavirin was the accepted treatment of hepatitis C virus (HCV) infections, yielding sustained virologic response (SVR) rates of at best 80% in genotypes 2 or 3, although it is less successful (40–50%) in genotype 1 [1–3]. In 2003 the study by Lamarre *et al.* paved the way for successful HCV treatment by establishing proof of concept with an investigational compound directly targeting virus replication, considerably reducing HCV RNA plasma levels [4]. These findings eventually led to a revolution in HCV treatment: the introduction of direct-acting antivirals (DAAs) in 2011. As a result, SVR rates exceeding 95% can generally be achieved with an all-oral DAA regimen for many types of patients [5–7]. For example, based on a number of different studies with different compounds, the new paradigm in HCV treatment is that antiviral therapy is equally effective in HCV monoinfected and HCV/HIV coinfected patients [8]. However, success rates are still compromised in patients with (decompensated) cirrhosis, previous DAA treatment failure and HCV genotype (GT) 3. In the near future, next-generation DAAs with high efficacy against all genotypes could be up for this challenge, as the field of anti-HCV therapeutics continues to evolve rapidly.

This review provides a comprehensive overview of performed clinical trials and elaborates on anticipated developments in the near future in the treatment of HCV infection.

Methods

A literature search was conducted in PubMed and Embase (December 2015). Search terms consisted of all currently available DAAs, including the ones for which US Food and Drug Administration approval is expected soon, with further addition of synonyms for 'real world' and 'clinical trial.' Through a snowballing strategy further publications were identified from the references of the retrieved articles. Only phase 3 studies of HCV or HCV/HIV coinfected patients were included together with the largest real-world studies.

Results

Different possible combinations

Sofosbuvir (SOF, the first-in-class NS5B nucleotide analogue with high viral potency, pangenotypic activity and high barrier to

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resistance) has become the backbone for several DAA regimens (combination with a NS3 or NS5A inhibitor) since its introduction. Together with the non-SOF-based antiviral therapeutics there are currently seven different DAA-only strategies available for treatment of HCV-infected patients (Fig. 1).

SOF-based regimens

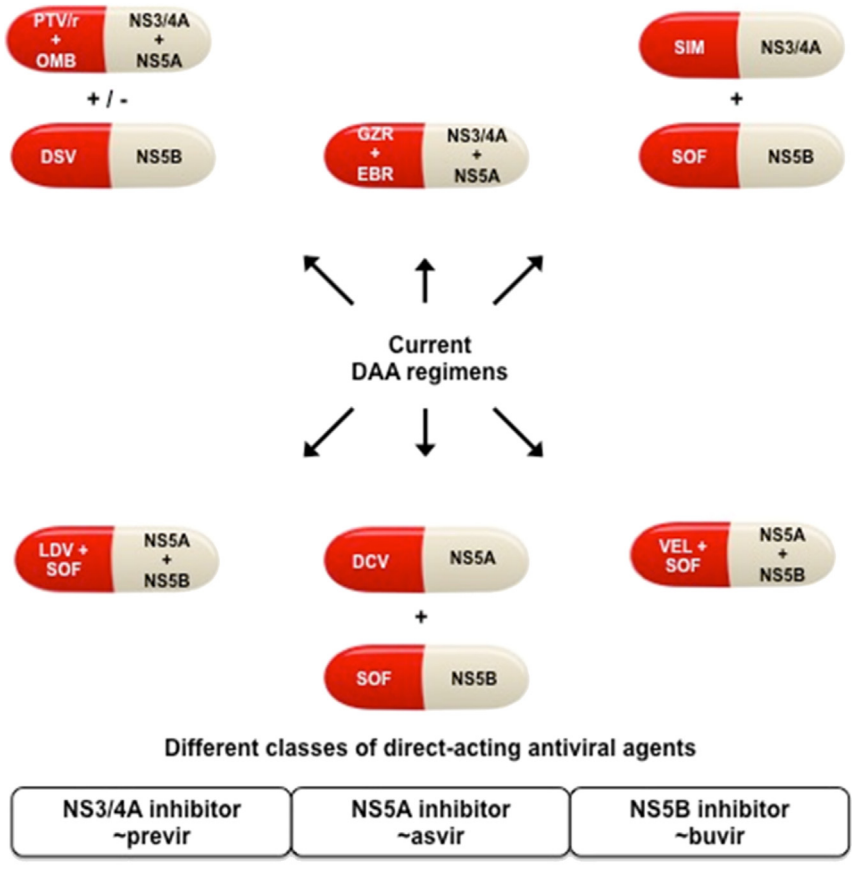
In clinical practice SOF is combined with either a NS3/4a inhibitor like simeprevir (SIM), as first explored in the phase 2 COSMOS study [9], or with a NS5A inhibitor like daclatasvir (DAC), a first-in-class potent NS5A inhibitor or ledipasvir (LDV), another first-generation NS5A inhibitor. Characteristics of phase 3 studies together with outcomes are listed in Table 1.

The randomized OPTIMIST-1 study [10] presented results at either 8 or 12 weeks of SIM/SOF treatment in 310 treatment-naive and treatment-experienced HCV GT1 noncirrhotic patients. The SVR at 12 weeks (SVR12) was 97%, which dropped substantially to 83% with a treatment course of 8 weeks. The presence of a baseline Q80K polymorphism had no impact on SVR12. Subsequently, OPTIMIST-2, an open-label single arm study, looked at response rates after 12 weeks of SIM/SOF in 103 patients with cirrhosis (METAVIR score 4). The overall SVR12 was 83%, which was higher in treatment-naive than treatment-experienced patients with cirrhosis (88% vs. 79%). In addition, subgroup analysis revealed higher responses in GT1a patients without baseline Q80K polymorphism compared to those who did harbour this particular resistance-associated amino acid variant (RAV) (92% vs. 74%) [11].

Next, the first possible combination of SOF with a NS5A inhibitor in clinical practice in Europe was SOF with DAC, due to its allowance by the European Medicines Agency as an early-access compound. Meanwhile, the ALLY-1/2/3 studies [12–14] were under way. The ALLY-2 study, a randomized two-arm study comparing 8 and 12 weeks of SOF/DAC in 151 treatment-naive and 52 treatment-experienced (no NS5A inhibitor) HCV/HIV GT1–4 coinfected patients, achieved a SVR12 rate after 12 weeks of therapy of 97% in the treatment-naive and 98% in the treatment-experienced group [13].

The two-arm ALLY-3 cohort study (101 treatment naive and 51 PEG-IFN/ribavirin experienced) achieved impressive results, with a SVR12 of 90% in difficult-to-treat GT3 patients and a slightly lower SVR12 of 86% in those whose disease previously failed to respond to a DAA (not NS5A) or PEG-IFN regimen [14]. However, success rates were still compromised in GT3 patients with cirrhosis compared to those without (SVR12 63% vs. 96%). DAC has shown activity against HCV GT1 through GT6 *in vitro* [15], and SOF/DAC is recommended by the European Association for the Study of the Liver for all HCV genotypes [16].

A fixed-dose single-tablet combination of SOF with LDV was investigated in the pivotal ION studies [5,17,18]. In the ION-1 and -3 studies 865 and 647 treatment-naive patients were treated, while the ION-2 study investigated 440 patients previously exposed to PEG-IFN and ribavirin with or without a protease inhibitor. In



Abbreviations: HCV, hepatitis C virus; DAA, direct-acting Antivirals; OBV, ombitasvir; DSV, dasabuvir; SIM, simeprevir; SOF, sofosbuvir; LDV, ledipasvir; DCV, daclatasvir, GZR, grazoprevir; EBR, elbasvir; VEL, velpatasvir; PTV/r, ritonavir boosted paritaprevir.

Fig. 1. All oral direct-acting antiviral regimens for hepatitis C virus treatment with all different classes.