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Commentary

Current race in the development of DAAs (direct-acting antivirals) against HCV

Erik De Clercq *

Rega Institute for Medical Research, KU Leuven, Minderbroedersstraat 10, B-3000 Leuven, Belgium

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Simeprevir (PubChem CID: 24873435)
Daclatasvir (PubChem CID: 25154714)
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ABSTRACT

The direct-acting antivirals (DAAs) currently in development for treatment of hepatitis C fall into four categories: (i) NS3/4A protease inhibitors: ABT-450/r, faldaprevir, asunaprevir, GS-9256, vedroprevir (GS-9451), danoprevir, MK-5172, vaniprevir, sovaprevir, ACH-2684, narlaprevir and simeprevir, in addition to those that are already developed [telaprevir (Incivek®) and boceprevir (Victrelis®)], (ii) NS5A protein inhibitors: ABT-267, daclatasvir, ledipasvir, ACH-2928, ACH-3102, PPI-668, AZD-7295, MK-8742, and GSK 2336805; (iii) NS5B (nucleoside-type) polymerase inhibitors: sofosbuvir (now approved by the FDA since 6 December 2013), GS-0938, mericitabine, VX-135, ALS 2158 and TMC 649128; (iv) NS5B (non-nucleoside-type) polymerase inhibitors: VX-222, ABT-072, ABT-333, deleobuvir, tegobuvir, setrobuvir, VCH-916, VCH-759, BMS-791325 and TMC-647055. Future drug combinations will likely exist of two or more DAAs belonging to any of the 4 categories, with the aim to achieve (i) pan-genotypic hepatitis C virus (HCV) activity, (ii) little or no risk for resistance; (iii) short duration (i.e. 12 weeks) of treatment, and (iv) a sustained viral response (SVR) and definite cure of the disease.

1. Introduction

For more than a decade, the standard of care (SOC) for hepatitis C virus (HCV) treatment existed of the combination of pegylated interferon with ribavirin [1–3]. This combination was generally looked upon as a combination of an antiviral (ribavirin) with an immunomodulating agent (interferon), whereas, in fact, interferon acted as an antiviral, while ribavirin behaved as an immunomodulatory agent. The combination of pegylated interferon with ribavirin achieved a sustained virus response (SVR) in *circa* 40% of the genotype 1 HCV patients upon a treatment duration of 48 weeks. With the introduction of telaprevir (Incivek®) and boceprevir (Victrelis®), in combination with pegylated interferon and ribavirin the percentage of genotype 1 HCV patients witnessing an SVR was increased to *circa* 75% and the duration of treatment was shortened to 24 weeks [4–9]. With the advent of

* Tel.: +32 16 337367; fax: +32 16 337340.
E-mail address: erik.declercq@rega.kuleuven.be

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the new direct-acting antivirals (DAAs) [10], as has already been shown for sofosbuvir [11–13], the percentage of patients with an SVR may be increased to 100%, the duration of treatment may be shortened to 12 weeks, and, more importantly, this beneficial outcome may eventually be achieved in the absence of interferon and ribavirin as well.

2. NS3/4A protease inhibitors

Among the NS3/4A protease inhibitors, two congeners have been approved for clinical use: telaprevir (Incivek®) and boceprevir (Victrelis®). Twelve others are in one or another stage of clinical development: ABT-450/r, faldaprevir, asunaprevir, GS-9256, GS-9451 (vedroprevir), danoprevir, MK-5172, MK-7009 (vaniprevir), sovaprevir (ACH-1625), ACH-2684, narlaprevir and simeprevir (Table 1A, Fig. 1).

ABT-450/r: ABT/450-/r (ABT-450 boosted with ritonavir) has so far been used only in combinations with ABT-267, ABT-072 and/or ABT-333 with or without ribavirin (see section on Combinations).

Faldaprevir: Treatment-experienced patients treated with faldaprevir plus pegylated IFN plus ribavirin showed higher viral load reductions, lower rates of breakthrough and less frequent emergence of resistance-associated mutations (R155 K and D168 V) compared with faldaprevir monotherapy [14]. Patients receiving faldaprevir (400 mg or 600 mg three times daily) for 4 weeks could be further treated with pegylated interferon α-2a/ribavirin to week 24 or 48 [15].

Asunaprevir is specifically taken up by the liver, thus displaying a selective hepatotropic disposition [16]. Asunaprevir is active against genotypes 1 and 4. Its target dose is 200 mg twice-daily: at this dose it achieved higher response rates than placebo when combined with peginterferon and ribavirin [17].

GS-9256: The phosphinic acid derivative GS-9256 has potent activity against genotype 1 [18]; like tegobuvir it provides additive antiviral activity when combined with peginterferon and ribavirin [19]. *GS-9451* (vedroprevir), not a phosphinic acid derivative, also acts synergistically with peginterferon and ribavirin against genotype 1 [20].

Danoprevir was selected as the clinical development candidate for a number of reasons: (i) its potency profile across multiple HCV genotypes; (ii) its activity against key mutant strains and (iii) its favorable *in vitro* ADME profile and (iv) its *in vivo* liver exposure in multiple animal species [21].

MK-5172 is anticipated to be broadly active against multiple HCV genotypes and clinically important resistance variants [22]. Compared to other NS3/4A protease inhibitors (i.e. telaprevir, danoprevir and vaniprevir), MK-5172 retains potency against two multi-drug-resistant variants, R155K and D168A [23].

Vaniprevir (MK-7009) [24], while leading to the emergence of resistance (due to the R155K and D168A mutations) [25,26], has, nevertheless, been advocated for QD and BID administration [27]. It may be particularly useful in cirrhotic patients [28] and prior non-responders [29].

ACH-1625 (sovaprevir) has been reported to affect a rapid and sharp decline in HCV upon monotherapy in both fasted and fed states [30]. It was accredited with a high pharmacological barrier to viral resistance [31]. At the same meeting, *ACH-2684* (*deldeprevir*) (neceprevir) was reported to achieve a potent viral suppression in genotype 1 HCV patients with and without cirrhosis [32].

Narlaprevir (SCH 900518), in combination with peginterferon and ribavirin, achieved a sustained virologic response (SVR) that was durable for up to 32 months after the end of treatment [33].

Simeprevir (TMC435) has been jointly developed by Janssen and Medivir AB, and submitted by Janssen to the European Medicines Agency for marketing authorization for the treatment of adult patients with HCV genotype 1 or genotype 4. Simeprevir, at present, still needs combination with peginterferon and ribavirin [34], but it is intended, in the future, to be combined with other direct-acting antivirals (DAAs) without interferon to treat HCV infection [35]. Simeprevir QD (once-daily), in combination with peginterferon and ribavirin significantly improved the SVR rates compared with peginterferon and ribavirin alone, and allowed the majority of patients (treatment-naïve patients with genotype 1) to

Table 1A
Target: NS3/4A protease.

Compound
Telaprevir (Incivek®)
Boceprevir (Victrelis®)
ABT-450/r
Faldaprevir (BI-201335)
Asunaprevir (BMS-650032)
GS-9256
Vedroprevir (GS-9451)
Danoprevir (ITMN-191, RG7227)
MK-5172
Vaniprevir (MK-7009)
Sovaprevir (ACH-1625)
Deldeprevir (Neceprevir) (ACH-2684)
Narlaprevir (SCH 900518)
Simeprevir (TMC 435)

Table 1B
Target: NS5A protein.

Compound
ABT-267
Daclatasvir (BMS-790052)
Ledipasvir (GS-5885)
ACH-2928 → ACH-3102
PPI-1301, PPI-461 → PPI-668
AZD-7295
MK-8742
GSK 2336805

Table 1C
Target: NS5B polymerase (nucleoside-type).

Compound
BMS-986094 (INX-189)
Sofosbuvir (GS-7977)
GS-0938
Mericitabine (RG7128, RO5024048)
BCX-5191
IDX-184
ALS-2200 → VX-135
ALS 2158
TMC 649128

Table 1D
Target: NS5B polymerase (non-nucleoside type).

Compound
VX-222
ABT-072
ABT-333
Deleobuvir (BI-207127)
Tegobuvir (GS-9190)
Setrobuvir (ANA-598)
Filibuvir (PF-868554)
VCH-916
VCH-759
BMS-791325
TMC-647055