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Review

# Hepatitis C virus therapy: No one will be left behind

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ABSTRACT

The advent of oral direct-acting antiviral agents (DAAs) has dramatically improved the hepatitis C treatment landscape in the last 4 years, providing cure rates over 95% with shorter duration of treatment and a very good safety profile. This gave access to treatment to almost all Hepatitis C virus (HCV)-infected patients. The launch of two pangenotypic fixed-dose combinations (FDCs) in 2017 was a step forward in hepatitis C treatment, by slightly increasing efficacy and more importantly allowing the treatment of patients without HCV genotyping, and in some cases without fibrosis assessment. New triple regimens have solved the issue of retreatment of the few patients who present failure to DAAs therapy. In the present review we describe the current HCV landscape that allows almost all HCV-infected patients to be cured.


## 1. Introduction

Hepatitis C virus (HCV) is a hepatotropic RNA virus that causes progressive liver disease that may result in liver cirrhosis and hepatocellular carcinoma. The latest assessment from the World Health Organization suggests that roughly 71 million people are chronically infected by HCV worldwide [1]. The major routes of contamination for this blood-borne infection are unsafe drug injections and unsafe medical procedures. Sexual transmission is rare except in men who have sex with men with high-risk sexual behavior.

Originally, Feinstone et al. identified post-transfusion non-A non-B hepatitis in 1975 [2]. The HCV viral genome was identified from plasma containing the uncharacterized non-A non-B hepatitis agent in 1989 [3]. Subsequently HCV antibodies assays were developed and thereafter HCV RNA testing became available in 1991. Then HCV genotypes and subtypes were characterized in 1993.

From 1986 to 2011, treatment of chronic HCV hepatitis was based on the use of interferon, at first alone, then in combination with ribavirin and thereafter on the use of the combination of pegylated interferon plus ribavirin (PR) for 24 or 48 weeks. According to genotype and fibrosis stages, the sustained virological response (SVR) rate with PR varied from 40% up to 70% in HIV-negative patients and lower in HIV-coinfected patients [4,5]. Those treatments were associated with numerous side effects and a deterioration in the quality of life of patients.

Since 2011, several direct-acting antiviral agents (DAAs) have been developed which targeted three proteins involved in different key steps of the HCV life cycle: the NS3/4A protease, the NS5A protein and the NS5B RNA-dependent RNA polymerase. The first DAAs were two NS3/4A protease inhibitors boceprevir and telaprevir that in combination with PR were able to shorten treatment duration and increase the SVR rate, 12 weeks after the completion of treatment, by 30% up to 70–80% [6,7].

Since 2013, other DAAs have been launched targeting the three proteins. The combination of several DAAs improved the SVR rate over 90%, with even a shorter duration of treatment of 8, 12, 16 or 24 weeks and a very good safety profile. Patients who could not be treated with PR, such as patients with ongoing intravenous use, severe renal impairments, inherited blood disorders and patient with advanced cirrhosis, were finally able to be treated with those combinations [8,9].

## 2. Current hepatitis C treatment landscape

Since 2013 only oral DAAs regimens have been used for HCV treatment. Therapies were based on several associations: (1) combinations using sofosbuvir (SOF) the only potent nucleotide NS5B inhibitor as a backbone combined with either a protease inhibitor such as simeprevir (SIM) or NS5A inhibitors such as daclatasvir (DCV) or ledipasvir (LDV); (2) a triple combination with a NS3/4A protease inhibitor boosted by ritonavir (paritaprevir) plus a NS5A inhibitor (ombitasvir) plus a non-nucleoside NS5B inhibitor

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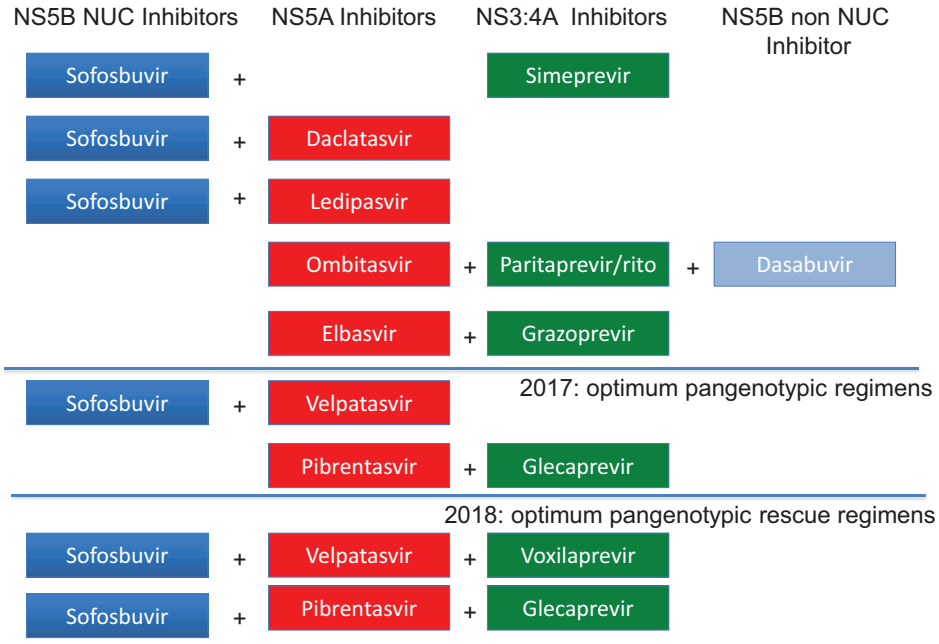


**Fig. 1.** Treatment options with DAAs combination since 2013.

**Table 1**
SVR12 according to genotype and fibrosis stage in phase 3 trials and large real-life (RL) studies [7–25].

| | GT-1 | GT-2 | GT-3 | GT-4 | GT-5/GT-6 |
|---|---|---|---|---|---|
| SOF+SIM | 97% (FO–F3),<br>83–92% (F4)<br>84% (RL) | | | 100% (F0–F4)<br>91–92% (RL) | |
| SOF+DCV | 98% (F0–F4)<br>95–98%(RL) | 92% (F0–F4)<br>100% (RL) | 96% (F0-F3)<br>63–90%**(F4)<br>89–92%(RL) | 95–97% (RL) | |
| SOF+LDV | 94–99%(F0–F4)<br>91-95%(RL) | 96%(F0–F4) | 89%**(F0–F4)<br>78% (RL) | 93% (F0–F4)<br>97% (RL) | GT-5: 95%<br>GT-6: 96%<br>GT-6: 95% (RL) |
| PrOD | 96–99% (F0–F3)<br>91–96%*(F4)<br>92–98%(RL) | | | | |
| PrO | | | | 94-98%**(F0–F4)<br>98–100%** (RL) | |
| GZR/EBR | 92–99% (F0–F4)<br>93-99% (RL) | 73–80%** | 45–57%**(F0–F3)<br>100% +SOF(F4) | 90–100%**<br>95–97% (RL) | GT-5: 25–100%**<br>GT-6: 75–80% |

* 24 weeks; **± ribavirin; DCV, daclatasvir; EBR, elbasvir; F0–F3, fibrosis stage 0–3; F4, cirrhosis; GT, genotype; GZR, grazoprevir; LDV, ledipasvir; Pr0, paritaprevir boosted by ritonavir plus ombitasvir; RL, real-life data; SIM, simeprevir; SOF, sofosbuvir.

(dasabuvir) (PrOD)); (3) a combination using a potent NS3/4A protease inhibitor grazoprevir (GZR) plus a second wave NS5A inhibitor elbasvir (EBR) (Fig. 1).

The SVR rate of phase 3 studies and large real-life data according to genotype and fibrosis stage are reported in Table 1. The first, all oral, DAAs combination was SOF and SIM that achieve high SVR rates only in patients with genotype 1 and 4 both in clinical trials and in real-life cohorts [8,9]. However the SVR rates were slightly disappointing in patients with cirrhosis, especially in patients with genotype 1a who harbored baseline Q80K mutation. The second combination of SOF and DCV was the first pangenotypic combination achieving SVR rates over 90–95% in patients infected by genotypes 1–4, across all studies, except in patients with genotype 3 and cirrhosis in whom SVR rates, with or without ribavirin (RBV), did not achieve 90% threshold [10,11]. The third association available was the triple combination PrOD. This combination achieved a very high SVR rate over 95% in patients with genotype 1, with a lower SVR in patients with cirrhosis or subtype 1a and in those who harbored baseline resistance-associated substitutions (RASs) [12]. The double combination paritaprevir boosted by ritonavir plus ombitasvir (PrO) was also highly potent in patients with genotype 4 in clinical trial and in real-life data [13,14].

Subsequently, a second wave of NS5A inhibitors became available with two new, single-pill, fixed-dose combinations (FDCs). The combination of SOF plus LDV was the first single-pill FDC available and was highly potent in patients with genotypes 1, 4, 5 and 6, whatever the fibrosis stage [15–19]. Moreover, this combination was the first that demonstrated potent activity in genotype 1 and 4 patients with decompensated cirrhosis [20,21]. This combination was suboptimal for patients with a genotype 3 infection [22]. The FDC of GZR plus EBR was highly potent in patients with genotype 1 and 4 both in studies and in real-life, even if patients with subtype 1a and baseline RASs may need longer duration of treatment (16 weeks) in order to achieve the highest SVR rate [23]. The GZR/EBR FDC demonstrated suboptimal SVR rate in patients with genotypes 2, 3,

**Table 2**
SVR12 according to genotype and fibrosis stage in phase 3 trials for pangenotypic combinations [27].

| | GT-1 | GT-2 | GT-3 | GT-4 | GT-5 | GT-6 |
|---|---|---|---|---|---|---|
| SOF/VEL<br>12 weeks<br>F4dc=SOF/VEL+RBV | 99%<br>(F0–F4)<br>F4dc*: 94% 1a<br>100%1b | 100%<br>(F0–F4)<br>F4dc*: 100% | 97%<br>(F0-F3)<br>91% F4<br>F4dc*: 85% | 100%<br>(F0–F4)<br>F4dc: 100% | 97% (F0–F3)<br>100% F4 | 100% (F0–F4) |
| GLE/PIB<br>F0–F3: 8w<br>F4: 12w | 99.8% (F0–F3)<br>99% (F4) | 99%<br>(F0–F3)<br>100% (F4) | 97%<br>(F0-F3)<br>96%** (F4) | 100%<br>(F0–F4) | 100% (F0–F4) | 100% (F0–F4) |

F4dc, decompensated cirrhosis; GLE, glecaprevir; GT, genotype; PIB, pibrentasvir; RBV, ribavirin; SOF, sofosbuvir; VEL, velpatasvir.
* SOF/VEL+RBV, ** GLE/PIB for 16 weeks

**Table 3**
Sustained virological response rates in direct-acting antiviral agents treatment naïve patients (F0–F4) except GT-3 patients with cirrhosis [32].

| | GT-1a | GT-1b | GT-2 | GT-3 | GT-4 | GT-5 | GT-6 |
|---|---|---|---|---|---|---|---|
| Triple FDC 8 weeks | 92%(155/169) | 97%(61/63) | 97%(61/63) | 99%(91/92) | 95%(59/63) | 94%(17/18) | 100%(30/30) |
| Dual FDC 12 weeks | 99%(170/172) | 97%(57/59) | 100%(53/53) | 97%(86/89) | 98%(56/57) | 0 | 100%(9/9) |

FDC, fixed-dose combination; GT, genotype.

5 and 6 [24,25]. In contrast. the combination of SOF+GZR/EBR demonstrated high efficacy rates in patients with genotype 3 and this option was, at least, endorsed by American Association for study of liver disease (AASLD) guidelines but not by the European Association for study of the liver (EASL) guidelines [26].

Since 2017, two pangenotypic FDCs SOF/velpatasvir (VEL) and glecaprevir (GLE)/pibrentasvir (PIB) were approved and launched in the USA by the Food and Drug Administration (FDA) and in some of the European union countries by the European Medicines Agency (EMA). SOF/VEL is the first single-pill FDC, given for a 12-week regimen regardless of genotype and fibrosis stage [27]. This combination for 12 weeks with RBV achieved very high SVR rates in patients with decompensated cirrhosis, whatever their genotype [28]. GLE/PIB offer a three-pills-daily FDC regimen for 8 weeks in naïve patients without cirrhosis regardless of genotype and for a 12-week regimen in patients with cirrhosis [29,30]. However, patients with genotype 3 and compensated cirrhosis need to be treated for 16 weeks [31]. Nevertheless, GLE/PIB could not be used in patients with decompensated cirrhosis, due to the presence of NS3/4A protease inhibitors. These treatments provided over 95% of SVR in the phase 2 and 3 pivotal studies (Table 2).

A new combination of SOF/VEL plus voxilaprevir (VOX), a pangenotypic HCV NS5A inhibitor with antiviral activity against HCV replicon in genotypes 1 through 6 was recently evaluated in treatment-naïve HCV patients. This combination was evaluated as a single-pill FDC daily regimen [32].

The POLARIS-2 study enrolled patients infected with all HCV genotypes with or without compensated cirrhosis, except patients with genotype 3 and cirrhosis. It was designed to test non-inferiority of 8 weeks triple FDC to 12 weeks of dual FDC (SOF/VEL) using a non-inferiority margin of 5%. The SVR rates were 95% for patients treated with 8 weeks triple FDC and 98% for those treated for 12 weeks with dual FDC. Those results did not meet the criteria to establish non-inferiority (Table 3). The difference in the efficacy was due primarily to a lower rate of SVR (92%) among US patients with HCV genotype 1a infection receiving 8 weeks of triple FDC. Baseline RASs to NS3 and/or NS5A inhibitors were found in 50% of patients. Of these, 94% had SVR as compared with 98% for patients without RASs [32].

The POLARIS-3 study enrolled only HCV genotype 3 patients with cirrhosis. It was designed to compare rates of SVR between a group treated with 8 weeks of triple FDC and another group treated with 12 weeks of dual FDC with a performance goal of 83%. Ninety-six percent of patients achieved an SVR in both treatment groups, which was significantly superior to the performance goal (Table 4). All 46 patients with baseline RASs achieved an SVR. Neither of the two patients who relapsed after triple FDC for 8 weeks had treatment-emergent RAS [32].

Overall, none of the 611 patients receiving 8 weeks of triple FDC in both studies discontinued study treatment owing to adverse events; the safety profile was fine. The most common adverse events with triple FDC were headache (26%), fatigue (22%), diarrhea (17%) and nausea (16%). Mild gastrointestinal adverse events were associated with the regimen including VOX [32].

## 3. Treatment options in case of DAAs treatment failure

Despite the overall high success rate of the new DAAs therapies, a small proportion of treated patients did not achieve SVR, mainly due to relapses and rarely due to viral breakthrough under treatment [33]. Several factors may favor DAAs failure to the first generation of DAAs such as cirrhosis, virological factors, genotypes 1a and 3 and RASs either pre-existing as natural polymorphisms or induced by a previous DAAs regimen. A recent study using the HCV disease burden model (HEP-SIM) suggested that according to the number of patients treated with DAAs between 2014 and 2020 in five European countries (France, Germany, Italy, Spain and United Kingdom), we could expect to have 47,000 DAAs failure patients during this period and nearly all patients treated since 2015 will be NS5A-failure [34]. In the guidelines, several retreatment options according to genotype were proposed [8].

In patients with genotype 1 or 4 who failed on the DAAs regimen containing NS5A inhibitors, four options were available. The first combined SOF with PrOD for genotype 1 or PrO for genotype 4 plus RBV either for 12 weeks in patients with mild fibrosis or for 24 weeks in patients with subtype 1a and in patients with severe fibrosis or compensated cirrhosis. This option achieved an SVR rate of 95% [35]. The second option combined SOF with GZR/EBR plus RBV for 12 weeks in patients with mild fibrosis or for 24 weeks in patients with subtype 1a and in patients with severe fibrosis or compensated cirrhosis. Data demonstrated that this combination was highly effective achieving SVR in all patients with mild disease treated for 12 weeks and in all patients with NS5A RASs treated for 16 weeks [36,37]. The third option combined SOF with DCV and SMV plus RBV for 12 weeks in patients with mild fibrosis or for 24 weeks in patients with subtype 1a and in patients with severe fibrosis or compensated cirrhosis. This option was not endorsed by any real-life data [38]. This combination in DAAs failure patients, some with advanced compensated cirrhosis, demon-

**Table 4**
Sustained virological response rates in direct-acting antiviral agents treatment-naïve patients with genotype 3 and cirrhosis [32].

| | GT-3 | GT-3 with baseline RASs | GT-3 Treatment-naive | GT-3 Treatment-experienced |
|---|---|---|---|---|
| Triple FDC 8 weeks | 96%(106/110) | 100%(23/23) | 96%(72/75) | 97%(34/35) |
| Dual FDC 12 weeks | 96%(105/109) | 100%(23/23) | 99%(76/77) | 91%(29/32) |

FDC, fixed-dose combination; GT, genotype; RAS, resistance-associated substitution.

**Table 5**
Sustained virological response in direct-acting antiviral agents treatment-experienced patients (F0–F4) who previously failed a direct-acting antiviral agents regimen with NS5A inhibitors [42,43].

| | GT-1a | GT-1b | GT-2 | GT-3 | GT-4 | GT-5 | GT-6 |
|---|---|---|---|---|---|---|---|
| Triple FDC 12 weeks | 96%(97/101) | 100%(45/45) | 100%(5/5) | 95%(74/78) | 91%(20/22) | 100%(1/1) | 100%(6/6) |
| Triple FDC deferred 12 weeks | 97%(109/113) | 100%(30/30) | | | | | 100%(2/2) |

FDC, fixed-dose combination; GT, genotype.

**Table 6**
Sustained virological response in direct-acting antiviral agents (DAAs) treatment-experienced patients (F0–F4) who previously failed a DAAs regimen without NS5A inhibitors [42].

| | GT-1a | GT-1b | GT-2 | GT-3 | GT-4 | No RASs | Any RASs |
|---|---|---|---|---|---|---|---|
| Triple FDC 12 weeks | 98%(53/54) | 96%(23/24) | 100%(31/31) | 94%(51/54) | 100%(19/19) | 94%(84/89) | 100%(83/83) |
| Dual FDC 12 weeks | 89%(39/44) | 95%(21/22) | 97%(32/33) | 85%(44/52) | | 89%(67/75) | 90%(63/70) |

FDC, fixed-dose combination; GT, genotype.

strated a high rate of adverse, even fatal, events and a lower response rate [39]. The last option is the association of GLE/PIB plus RBV for 12 or 16 weeks. The study demonstrated a high SVR rate of 96% and above in patients treated either for 12 weeks in those who harbored at baseline only NS3 RASs or for 16 weeks in those who harbored at baseline only NS5A RASs. For patients who have both baseline NS3 and NS5A RASs the SVR rate was suboptimal [40]. Therefore, this combination was not recommended in this situation at least in the EMEA label and in the last EASL guidelines [9].

For patients with genotype 2, 3, 5 and 6 who failed a DAAs combination with an NS5A inhibitors, the recommended retreatment option was the combination of SOF/VEL with RBV for 24 weeks [8]. This recommendation was supported by a small multicenter trial in which sixty-nine patients with genotype 1, 2 or 3, who previously failed a NS5A containing DAAs regimen, were retreated with SOF/VEL and RBV for 24 weeks. SVR rate was 97% in genotype 1 and 93% in genotype 2 patients regardless of NS5A RASs, but only 78% in patients with genotype 3 [41]. Therefore there was an urgent need for a pangenotypic rescue regimen for patients who failed previous NS5A-containing DAAs regimens.

## 4. New salvage regimen for DAAs failure

POLARIS 1 and 4 studies assessed the efficacy of 12 weeks' treatment with the triple FDC SOL/VEL/VOX in HCV DAAs treatment–experienced patients with or without compensated cirrhosis [42].

The POLARIS-1 study enrolled patients, infected with all HCV genotypes, who previously failed a regimen containing an NS5A inhibitor. Genotype 1 patients were randomly assigned at a 1:1 ratio to receive either the triple FDC or matching placebo once daily for 12 weeks. Patients who were infected by other genotypes were enrolled in the triple FDC once daily for 12 weeks. Forty-six percent of patients had compensated cirrhosis. Thirty nine percent of patients had received at least two or more previous HCV treatments. The rate of SVR was 96% as compared with 0% with placebo. Overall the rate of SVR was 99% among patients without cirrhosis and 93% among patients with cirrhosis (Table 5). Baseline RASs were present in 83% of patients and 79% harbored NS5A RASs. SVR rate was similar between patients with baseline RASs (96%) as compared with those without RASs (99%). Six patients with cirrhosis had a relapse (one genotype 1a, 4 genotype 3 and one genotype 4). One patient with genotype 4 had treatment-emergent RASs.

Patients with genotype 1, who received placebo, were subsequently treated with triple FDC once daily for 12 weeks [43]. One-third of patients had cirrhosis. Overall the SVR rate was 97%. Patients with cirrhosis had an SVR rate of 98% and those without cirrhosis had an SVR rate of 97%. Four genotype 1a patients, one with cirrhosis, experienced relapse. All had baseline RASs and two developed treatment-emergent RASs. Combining the data in the primary and sub-study of POLARIS-1, the overall SVR rate was 97%.

The POLARIS-4 study enrolled patients who previously failed a DAA regimen without an NS5A inhibitor. HCV genotype 1, 2 and 3 patients were randomly assigned at a 1:1 ratio to receive triple FDC or dual FDC (SOF/VEL) for 12 weeks. Additional genotype 4 patients were enrolled in the triple FDC regimen for 12 weeks [42]. Forty-six percent of patients had compensated cirrhosis. Thirty-nine percent of patients had received at least two or more previous HCV treatments. Overall, the rate of SVR was 98% in patients receiving triple FDC and 90% in those receiving dual FDC (Table 6). Among patients without cirrhosis the rate of SVR was 98% among those receiving triple FDC and 94% among those receiving dual FDC as compared with 98% and 86%, respectively, among patients with cirrhosis. Forty-nine percent of enrolled patients had baseline RASs to NS3 or NS5A inhibitors. Only one patient relapsed in those treated with triple FDC as compared to 14 patients of those treated with dual FDC. The patient who failed with triple FDC had no baseline RASs and no treatment-emergent RAS. The safety profile in POLARIS-1 and 4 studies was good.

An alternative option is the combination of SOF plus GLE/PIB ± RBV for 12–16 weeks based on two small studies involving patients who had failed previous DAAs regimens including GLE/PIB regimen [44,45]. The SVR rate was 96% [44].

## 5. Conclusions

Currently two pangenotypic DAAs regimens are able to cure either treatment-naïve or treatment-experienced HCV patients with an SVR rate over 97%. The duration of treatment is 12 weeks with

the single pill dual FDC SOF/VEL whatever fibrosis stage and 8 or 12 weeks with the three pills FDC GLE/PIB according to the absence or presence of cirrhosis. Patients with decompensated cirrhosis should be treated with SOF/VEL plus RBV for 12 weeks. Among the few patients who failed this combination, both the single-pill triple FDC SOF/VEL/VOX for 12 weeks or the triple combination SOF plus GLE/PIB with or without ribavirin for 12 weeks are able to achieve an SVR rate of 96%. The objective of curing all HCV patients has almost been achieved and no one has therefore been left behind.

## Declarations

## Funding

None

## Competing Interests

M. Bourlière is a member of the advisory board and a speaker for: Gilead, AbbVie, MSD, BMS, Janssen, Boehringer- Ingelheim. Olivia Pietri has no conflicts of interest to declare.

## Ethical Approval

Not required.

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