Efficacy of new direct acting antivirals in transplant recipients and patients with advanced disease

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A R T I C L E   I N F O

Article history:
Received 4 August 2014
Accepted 6 October 2014
Available online 6 November 2014

Keywords:
Antiviral treatment
Cirrhosis
Hepatitis C
Liver transplantation

A B S T R A C T

The development of new direct acting antivirals constitutes a clinical revolution in the field of hepatitis C therapy and, most probably, in the history of Hepatology. Difficult-to-treat patients, such as cirrhotics or patients in the peri-transplant setting, will clearly benefit from these therapies, particularly from interferon-free all-oral combinations. However, despite the substantial improvement of the hepatitis C drug market, access to these therapies will likely be different around the world due to economic restrictions. This review aims to clarify the current stage of different antiviral strategies (with or without interferon) in these difficult populations by analysing specific efficacy and safety results in patients with cirrhosis, patients on the waiting list for liver transplantation and recipients with hepatitis C recurrence after liver transplantation. Hitherto, some important challenges still remain unanswered in these patients and will need to be assessed in clinical practice, such as the evaluation of safety and efficacy in advanced cirrhotic patients with portal hypertension, the impact (if any) of viral clearance on clinical outcomes in patients with decompensated liver disease, the role of ribavirin in all-oral combinations, the relevance of the development of multi-drug viral resistant strains and the drug–drug interaction profiles of these drugs, especially after liver transplantation.

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1. Introduction

In the last few years, the development and use of direct-acting antivirals (DAAs) have been a major step forward in the management of chronic hepatitis C (HCV). Several combinations of new molecules have been reported to cure more than 90% of hepatitis C infections in many different patient populations in Phase-2 and 3 trials, with and without pegylated interferon-α (PEG-IFN) and/or ribavirin (RBV). The safety and efficacy profile of these DAA combinations is particularly relevant in so-called difficult-to-treat patients, namely those with advanced liver disease and those with HCV recurrence after liver transplantation (LT). Interferon containing therapies are frequently contraindicated in this group of patients, and previous antiviral regimens resulted in a very low efficacy and poor tolerance. This review aims to summarize the current status and strategies regarding antiviral therapy in these patients.

2. Efficacy of new DAAs in patients with advanced disease

2.1. Compensated cirrhotic patients

2.1.1. Interferon-based therapy

Patients with chronic hepatitis C and advanced cirrhosis are one of the most difficult-to-treat populations, and at the same time they are at high risk of developing decompensation or hepatocellular carcinoma (HCC). Interferon-based therapy can only be administered in cirrhotics with good liver function, and efficacy results are far from optimal, especially in genotype 1 patients (GT1). However, IFN-free regimens are not yet available or efficacious enough in some subsets of patients and, in addition, these all-oral combinations are usually more expensive. Therefore, IFN containing regimens will remain as first-line therapies in some settings, at least, in the short term.

The addition of first-generation protease inhibitors (PI), boceprevir and telaprevir, to pegylated interferon and ribavirin (PR) has clearly been associated with an increase in response rates in GT1 infected patients. Sustained virological response (SVR) rates increase by nearly 30% with triple therapy as compared to PR in naïve patients and by 25–60% in treatment-experienced patients (depending on previous treatment response) [1–5]. Nonetheless, PI-based regimens in real-life compensated cirrhotics may be
associated with serious adverse events (SAEs), such as severe infections (4–6%), clinical decompensation (3–4%) and even death [6]. These serious side effects were not reported in the registration trials because patients included in these studies were mostly very well compensated cirrhotics without significant portal hypertension (low platelet count <90,000 for telaprevir and <100,000 for boceprevir was an exclusion criterion). The main predictive factors of severe complications in cirrhotics undergoing triple therapy (severe infections, clinical decompensation or death) were a low platelet count (<100,000/mm^3) and low serum albumin levels (<35 g/L) [6,7]. Importantly, the risk for severe complications was 44% in patients with both factors, as compared to 3.4% in patients with normal platelet count and serum albumin levels [6].

With the current approval of sofosbuvir and simprevir in the US and Europe, and the recent approval of daclatasvir in September 2014, new interferon-based combinations will be available for eligible cirrhotic patients.

Sofosbuvir (SOF) is a nucleotide analogue with potent activity against HCV genotypes 1–6. The combination of PR plus SOF 400 mg/d for 12 weeks seems to offer the highest efficacy and the best safety profile. This regimen was evaluated in the NEUTRINO Phase-3 trial in treatment-naïve GT1, 4, 5 and 6 patients (mainly GT1) [8] providing an overall SVR rate of 90%. Cirrhotic patients (n = 54) had a lower SVR rate than non-cirrhotics (80% versus 92%, respectively). Regrettably, data on interferon-based therapy in treatment-experienced cirrhotics are only available in a small number of GT2 and GT3 infected patients, with SVR rates over 80% [9].

Simeprevir (SMV) is a once-daily dosed NS3/4A protease inhibitor with the added benefit of a more convenient dose regimen and a more favourable side-effect profile. Phase-3 trials in naïve patients QUEST1 [10] and QUEST 2 [11] assessed the combination of SMV for 12 weeks and PR (response-guided therapy 24–48 w). Pooled data demonstrated overall SVR12 rates of 60% in patients with cirrhosis (n = 48) compared to 82% in patients without cirrhosis and to 34% in the placebo group [12]. The PROMISE [13], ASPIRE [14] and ATTAIN [15] studies assessed the efficacy of the combination SMV with PR in treatment-experienced patients; the number of cirrhotic patients included in each study receiving SMV was 39, 73 and 88, respectively. Pooled data showed SVR rates of ~50%, higher in previous relapers to PR (74%) than in partial or null responders, as expected. It should be noted that in the package insert, testing the Q80K mutation prior to initiating SMV treatment is recommended in patients with GT1a due to the lower chance of response if the mutation is present.

Daclatasvir (DCV) is a first-in-class HCV NSSA replication complex inhibitor. The Phase-2b COMMAND [16] study evaluated the efficacy of the combination of DCV+PR in GT1 and GT4 naïve patients. Patients were randomly assigned to receive DCV 20 or 60 mg or placebo once daily in combination with PR. At Week 12, DCV recipients achieving protocol-defined response were re-randomized to continue triple therapy for a total duration of 24 weeks (24 triple) or to continue therapy with placebo+PR during weeks 13–24 (12 triple+12). SVR12 rates were 8/13 (62%) and 4/7 (57%) in GT1 cirrhotic patients on 20 or 60 mg, respectively, compared with 2/8 (25%) receiving PR. The COMMAND-GT2/3 study assessed the combination of DCV+PR 12–16 w in GT2 and 3 patients. Only 11 patients with cirrhosis (all GT3) were included. More frequent relapses occurred in cirrhotics (4/11, 36%) than in non-cirrhotics (8/39, 21%) [17].

Efficacy results in cirrhotic patients treated with PR plus sofosbuvir, simprevir or daclatasvir are summarized in Fig. 1A (naïve) and B (treatment-experienced).

2.1.2. Interferon-free therapies

2.1.2.1. Genotype 1 cirrhotic patients. For GT1 cirrhotics, the combination of SOF and RBV for 24 w appears to be suboptimal. In the group of 13 patients with advanced fibrosis (F3/4) [18], SVR rates were 50% and 29% in weight-based and low-dose RBV, respectively. Data from Phase-2 studies strongly suggest that the addition of simprevir or daclatasvir to sofosbuvir (with or without RBV) significantly increases SVR rates up to 90% (Fig. 1A and B). The combination of SOF + SMV ± RBV 12–24 w in cohort 2 of the COSMOS study [19] evaluated 41 GT1 patients with F3–F4 scores who were prior null-responders or naïve. Preliminary data indicated that rates of SVR at week 4 were 100% (7 of 7 and 12 of 12 with and without RBV, respectively) in treatment-naïve patients, and 100% (7 of 7) and 93% (14 out of 15) with and without RBV, respectively, in prior null responders. Thirty-two patients with significant fibrosis, GT1–3, naïve or treatment-experienced (including Ps) received the combination of SOF + DCV ± RBV 12–24 w [20]. SVR12 rates were >95%, although specific analysis in the cirrhotic population is not available.
Other drugs are likely to be approved later in 2015; these include the fixed dose combination of Sofosbuvir and Ledipasvir (LDV), the triple combination of co-formulated paritaprevir, ombitasvir plus dasabuvir, and the protease inhibitor asunaprevir (ASV). The main results of the registered trials with these molecules are summarized below and in Fig. 2.

Two registered Phase-3 studies have assessed the safety and efficacy of SOF and LDV (with or without RBV) for 12 versus 24 weeks in GT1 infected patients. In the first study (ION-1), which included naive patients, there were 136 cirrhotics and SVR rates were 100% in the RBV arms and 97% in the non-RBV arms [21]. In the second study (ION-2), which included treatment-experienced patients (with a significant number of failures to PI), there were 88 cirrhotics: SVR rates were 100% in the 24-week regimen, but the figure decreased to ~85% in the 12-week arms [22]. The latter suggests that a regimen containing Sofosbuvir and Ledipasvir is excellent in compensated cirrhotics and extension of treatment to 24 weeks may be necessary in previous non-responders.

A large randomized clinical trial (TURQUOISE-II) performed specifically in cirrhotic patients with an all-oral DAA combination has recently evaluated the safety and efficacy of paritaprevir boosted with ritonavir, ombitasvir and dasabuvir co-administered with RBV for 12 or 24 weeks in HCV GT1 infected patients (both treatment-naïve and -experienced) [23]. SVR rates reached 92% and 96% in the 12-week and 24-week arms, respectively. A trend towards slightly lower SVR rates were observed in GT1a previous null responders, as well as in patients with more significant portal hypertension (platelets <100,000/mm³) or more advanced cirrhosis (albumin <35 g/L) in the 12-week arm.

A combination of daclatasvir and asunaprevir for 24 weeks was evaluated in 223 GT1b cirrhotics: SVR rates were 91% in naive, 81% in ineligible/intolerant patients and 87% in treatment-experienced individuals [24].

Preliminary data on the Phase-2 C-WORTHY study [25] were presented at the latest EASL meeting. Treatment-naïve patients with cirrhosis or null responders were randomized to receive MK-5172 (PI, 100 mg/d) and MK-8742 (NS5A complex inhibitor, 50 mg/d) with or without RBV (weight-based) for 12 or 18 weeks. Around 96% of cirrhotic patients (n = 164) achieved undetectable RNA levels on treatment, reflecting the potency of the combination. Final data on SVR rates are expected soon.

2.1.2.2. Non-genotype 1 cirrhotic patients. For GT2 and 3-infected patients, Sofosbuvir 400 mg/d plus RBV represents the only active treatment available. Results from four Phase 3 trials assessing this combination have been published (FISSION, FUSION, POSITRON and VALENCE). Overall, SVR rates in GT2 were consistently lower in cirrhotics compared to non-cirrhotics, but 12 or 16-week regimens achieve SVR rates of around 80% [8,26]. In GT3 patients, it became clear that a 12-week regimen of Sofosbuvir and RBV was insufficient for cirrhotic patients, and treatment extension up to 24 weeks increased SVR rates to 92% in naïve patients and to 62% in previous non-responders to PR [8,27,28].

Sofosbuvir, simeprevir, ledipasvir, daclatasvir, paritaprevir and ombitasvir also have antiviral effectiveness against GT4 [29]. Sofosbuvir is also effective for GT5 and 6. However, for GT4–6 infected patients there are very little data on interferon-free regimens, and no solid recommendations can be given in case of cirrhosis.

2.2. Decompensated cirrhotic patients

In the era of interferon-free oral combinations, cirrhotic patients with more advanced liver disease in whom IFN-based therapy is contraindicated may be candidates for antiviral therapy. Nonetheless, data on the potential impact of significant portal hypertension in the achievement of SVR are lacking. On the other hand, the impact of SVR in patients with decompensated cirrhosis may be heterogeneous, since it encompasses a wide spectrum of disease, ranging from patients with relatively well-preserved liver function (mild ascites or recent variceal bleeding) to patients with very poor liver function and a short life expectancy (Child–Pugh C >10 points) [30,31]. Several studies have found that fibrosis regression/reversal might be more likely in early cirrhosis than established cirrhosis and that the absence of portal hypertension may be a determinant of reversibility [32].

Hitherto, most studies have included very well compensated cirrhotic patients probably with, although not measured, a low degree of portal hypertension. Indeed, in the Phase-3 Turquoise II study [23] the median platelet count (as an indirect marker of portal hypertension) was 140,000/mm³ (n = 380); and in the studies evaluating the combination of Sofosbuvir and Ledipasvir [21,22] less than 5% of the cirrhotic patients included (n = 224) had platelet counts below 90,000/mm³.

Preliminary data are available in a small cohort of 25 compensated or decompensated cirrhotic patients with portal hypertension (mean HVPG 16.9 mmHg) who were randomized to Sofosbuvir and Ribavirin for 48 weeks, versus an observational arm (after 6 months these patients crossed over to the treatment arm) [33]. From a virological point of view, it was interesting to learn that at weeks 2 and 4 after treatment initiation, 56% and 100% of Child–Pugh A patients had undetectable HCV-RNA; figures for Child–Pugh B patients were only 44% and 75%, respectively. This might be explained by changes in drug PK; Sofosbuvir exposure was 2-fold higher in HCV-infected patients without hepatic impairment, compared with patients with advanced liver disease [34]. Regarding clinical outcomes, after a 24-week period, the data suggest a reduction of clinical events in patients included in the treatment arm, but importantly, data on portal pressure were not yet available. From a safety point of view, exposure to some new compounds (such as paritaprevir [35], asunaprevir [36] and simeprevir [37]) is significantly increased in Child–Pugh C patients and its use is currently not recommended until more data are available. Whether achieving SVR in patients with decompensated cirrhosis is associated with a further reduction in HVPG and protection from liver decompensation, and, finally, lower mortality, needs to be investigated.
Other studies assessing the efficacy of interferon-free combinations in patients with cirrhosis are currently ongoing (Table 1).

### 3. Efficacy of new DAAs in the peri-transplant setting

HCV-related cirrhosis constitutes the leading indication for LT in the Western world and Japan [38]. Unfortunately, HCV infection of the new graft occurs in all patients with detectable viremia at the moment of LT [39]. The main characteristic of HCV recurrence after LT is the accelerated course of the disease [40–44]. In fact, fibrosis progression in the transplant population has been estimated to be 2–4 times faster than the HCV-infected immune competent patients [45]. This accelerated fibrosis rate negatively impacts both on the allograft and recipient survival, which are significantly reduced in HCV recipients when compared to non-HCV transplanted patients [40,44,46].

Preventing the allograft HCV infection by eradicating the virus before LT is the best strategy to avoid HCV recurrence and its consequences after LT. However, HCV-infected patients enlisted for transplantation are often the sickest, and the waiting list exhibits some peculiarities that may hamper the applicability of these antiviral therapies. In those patients in whom treating pre-LT is not feasible, and who develop viral recurrence after LT, eradicating the virus after LT is the only alternative. The different HCV therapies specifically evaluated in the LT setting, both before or after LT, are summarized in Fig. 3 and will be discussed herein.

#### 3.1. Antiviral treatment before LT: the waiting list

Two clinically different patterns of enlisted patients have to be considered for the purposes of HCV treatment. This difference will be relevant in terms of virological response, safety profiles and pharmacokinetics. Firstly, patients in whom the indication for LT is the development of HCC often have compensated cirrhosis and preserved liver function. The second group would be those patients with decompensated cirrhosis, who exhibit progressive liver impairment. With the new DAAs, treatment of patients on the waiting list is expected to radically change in the coming years. However, it is relevant to mention the results of all the different antiviral regimens used in this population to date.

#### 3.1.1. Interferon-based regimens

Interferon-based therapy has been shown to be suboptimal in patients awaiting LT from both virological and safety perspectives. Interferon can only be administered in cirrhotic patients with good liver function (Child–Pugh ≤ 7 or MELD ≤ 18) (on the waiting list, typically referred to patients in whom the indication for LT is HCC) [47]. In those patients with more advanced disease, IFN should not be used, since SAEs (i.e., bacterial infections [48], grade 3 and 4 cytopenias and clinical decompensation) have been shown to be frequent and potentially life threatening. However, prevention of graft HCV infection was shown to be feasible in different studies some years ago, in those patients on the waiting list who achieved undetectable HCV-RNA when PR was administered [48–51].

Global virological responses, maintained after LT, were around 25% (slightly higher, as expected, in HCV GT2/3 patients with IL28B CC genotype) [52], but safety profiles were poor.

Data on PIs-based therapy (boceprevir or telaprevir plus PR) in GT1 cirrhotic patients awaiting LT are anecdotic. Verna et al. [53] reported preliminary results of triple therapy in a very small cohort of 29 HCV-infected cirrhotic patients on the waiting list for LT (Child

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**Table 1**: Ongoing clinical trials including cirrhotic patients and hepatitis C Virus transplant recipients.

<table>
<thead>
<tr>
<th>Identifier</th>
<th>Regimen</th>
<th>Treatment duration</th>
<th>Genotype</th>
<th>Child–Pugh class</th>
<th>Trial Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01938430</td>
<td>SOF + LDV + RBV</td>
<td>12–24w</td>
<td>1,4</td>
<td>Pre-LT: B, C</td>
<td>2</td>
</tr>
<tr>
<td>NCT01973049</td>
<td>DVC + ASV + BMS-791325 + RBV</td>
<td>12w</td>
<td>1</td>
<td>A</td>
<td>3</td>
</tr>
<tr>
<td>NCT02032875</td>
<td>DCV + SOF + RBV</td>
<td>12w</td>
<td>1</td>
<td>A</td>
<td>3</td>
</tr>
<tr>
<td>NCT02115321</td>
<td>MK-5172 + MK-8742</td>
<td>12w</td>
<td>1–6</td>
<td>Pre- &amp; post-LT: A</td>
<td>3</td>
</tr>
<tr>
<td>NCT02105454</td>
<td>MK-5172 + MK-8742</td>
<td>12w</td>
<td>1,4–6</td>
<td>B</td>
<td>2</td>
</tr>
<tr>
<td>NCT02114151</td>
<td>MK-5172 + MK-8742</td>
<td>12w</td>
<td>1</td>
<td>A</td>
<td>2</td>
</tr>
<tr>
<td>NCT01909804</td>
<td>SOF + GS-5516 + RBV</td>
<td>12w</td>
<td>3</td>
<td>A</td>
<td>3</td>
</tr>
<tr>
<td>NCT01962441</td>
<td>SOF + RBV</td>
<td>16–24w</td>
<td>2,3</td>
<td>A</td>
<td>3B</td>
</tr>
<tr>
<td>NCT01936625</td>
<td>SMV + DCL + RBV</td>
<td>24w</td>
<td>1b</td>
<td>Post LT</td>
<td>2</td>
</tr>
<tr>
<td>NCT01782495</td>
<td>Paritaprevir/Ombitasvir (ABT-267) + Dasabuvir (ABT-333) + RBV</td>
<td>12w</td>
<td>1</td>
<td>Metavir F1-F3 (Child A)</td>
<td>2</td>
</tr>
</tbody>
</table>

w, weeks; SOF, sofosbuvir; LDV, ledipasvir; RBV, ribavirin; LT, liver transplantation; DVC, daclatasvir; ASV, asunaprevir; SMV, simeprevir.

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**Fig. 3**: Results of treatment strategies within the peri-transplant setting. Pre-LT treatments: Treatments while on the waiting list. PR: PEG-interferon plus ribavirin up to liver transplantation (LT) [48–52]; PR + PI: PR plus protease inhibitor [53]; SOF + RBV: sofosbuvir 400 mg/d plus ribavirin up to 48 weeks or LT. SVR12 rates are referred to undetectable HCV RNA 12 weeks after LT [54]. Sibutrin monotherapy is not shown (SVR12, 0%) [55]. Post-LT treatments: PR: PEG-interferon plus ribavirin for 48 weeks (historical cohort), PR + PI: PR plus protease inhibitor (telaprevir or boceprevir) for 48 weeks (* pooled data from case studies and REPLACE study) [72,82]; SOF + RBV: sofosbuvir 400 mg/d plus ribavirin for 24 weeks [83]; SOF + RBV (+IFN): sofosbuvir 400 mg/d plus ribavirin (with or without interferon) (Compassionate use in severe HCV recurrence including FCH) [84]; Paritaprevir + Ombitasvir + Dasabuvir + RBV: Paritaprevir/ritonavir plus ombitasvir plus dasabuvir ribavirin for 24 weeks (** patients included had fibrosis stage Metavir F0-2). SVR12 rates refer to undetectable HCV RNA 12 weeks after the end of treatment [79].
A 62%, Child B 38%). Overall SVR12 was 52%; 67% when considering only those who underwent LT (n = 12). However, SAEs were frequent (31%) and included one death (3%) and 8 hospitalizations (28%). Moreover, SVR rates with PIs-based therapy are very low in cirrhotic patients who are previous null responders to PR, a common situation in patients awaiting LT. Therefore, in real life, the proportion of patients on the waiting list that may benefit from triple therapy with telaprevir or boceprevir is very small.

Importantly, with the recent approval of the new DAAs (sofosbuvir, simeprevir, and daclatasvir), the use of boceprevir and telaprevir are no longer recommended in this population, due to their poor safety profile [29].

3.1.2. IFN-free regimens
Very little data are available to date for use of IFN-free regimens on patients on the waiting list. Fortunately, as previously mentioned, some clinical trials are currently evaluating different combinations in this patient population (Table 1), and we will presumably have results soon.

• Sofosbuvir and ribavirin
This combination was the first all-oral IFN-free regimen with DAAs to be assessed in patients awaiting LT. A Phase-2 open-label study was conducted, in which 61 HCV-infected patients (GT1–4) awaiting LT received sofosbuvir and ribavirin until LT or up to 48 weeks [54]. The indication for LT was HCC; nearly 75% of patients were Child–Pugh A, all had MELD score below 15 and most individuals were previous non-responders to IFN-based regimens (75%). The median duration of therapy was 17 weeks. Forty-six patients underwent LT and of these, 43 (92%) had HCV-RNA < 25 IU/mL at time of LT. Of these, 42 reached 12 weeks of follow-up after transplantation and 29 (69%) remained free of recurrence and reached SVR12. The strongest predictor of post-LT SVR was the number of consecutive days with undetectable HCV RNA prior to transplant. Treatment with SOF + RBV was generally well tolerated. These results are encouraging. Longer treatment duration and/or the addition of a second DAA (currently under evaluation with ledipasvir, see Table 1) may reduce the rate of virological failures.

• Silibinin
Some years ago, the antiviral efficacy of silibinin monotherapy for patients awaiting LT was explored in a proof-of-concept Phase-2 trial [55], as this natural flavonoid has been shown to exert potent antiviral properties [55–57]. The study included a very small number of patients (n = 14), but demonstrated a consistent antiviral effect of intravenous silibinin and a good safety profile in these very ill patients (43% Child A, 57% Child C). Although some patients reached undetectable HCV-RNA during therapy, none of them achieved SVR following LT. The main problems of this study were the short-treatment duration and the fact that the drug needs to be administered intravenously. It is unknown whether the use of silibinin could be helpful in patients treated with new DAAs on the waiting list and this could be explored in the future, especially considering the favourable economic profile of this drug.

Peculiarities of treatment while on the waiting list:

• Relevance of treatment duration before LT
As the moment of LT is unpredictable (unless when considering living donor LT recipients), one of the main difficulties of treating patients on the waiting list is to know when to start antiviral treatment to guarantee a minimal effective duration. Different studies to date have shown the impact of treatment duration on SVR rates after LT.

Everson et al. [50] treated 56 well-compensated cirrhotic patients on the waiting list with PR. In this study, the strongest predictor of virologic response after LT was duration of treatment. In fact, SVR rates were significantly higher (50%) in those patients who received pre-transplant therapy for >16 weeks than in those receiving <16 weeks and other historical treated cohorts [48,49,51] (although this specific analysis of treatment duration was not performed in these studies).

Treatment duration was also relevant in another trial, in which patients on the waiting list were treated with sofosbuvir and ribavirin [54]. The strongest predictor of post-LT SVR for this IFN-free combination was the number of consecutive days with undetectable HCV RNA prior to transplant. In fact, only one relapse occurred among the 25 individuals with undetectable HCV-RNA for >28 days while on treatment.

• Possibility of delisting
Given the short supply of organs available, a potential additional benefit of treating patients before LT would be to improve liver function, and perhaps regain compensation for final delisting. This has been shown in some patients with HBV-related cirrhosis treated with nucleos(t)ide analogues [58,59], but in HCV-infected cirrhotic patients this has not yet been demonstrated [60]. However, HCC patients will need a LT anyway, and those patients with severely impaired liver function are probably less likely to re-compensate.

• Relevance of virological failures
Another distinct feature of patients awaiting LT is the potential risk of viral breakthrough or relapse during or after treatment, which may theoretically induce flares that could trigger liver decompensation. It is thus extremely important to choose the best treatment combination (high potency and high genetic barrier) in order to minimize the possibility of virological relapse or the selection of resistant-associated viral strains (RAVs). The fitness of resistant strains is usually lower than that of the wild-type viruses, which tend to replace RAVs progressively. This issue is important, since the potential presence of multi-resistant strains may hamper antiviral efficacy if urgent treatment is required.

3.2. Antiviral treatment after LT
Recurrence of HCV after LT will be inevitable in viraemic patients. If preventive treatment before transplantation fails or is not possible, the graft will be immediately infected [39] and treatment after LT will have to be considered.

3.2.1. Why should we treat?
The main characteristic of hepatitis C recurrence after LT, as already mentioned, is the accelerated course of the disease [40,42–44,46,61,62]. The presence of significant fibrosis beyond the portal tract (METAVIR F ≥ 2), portal hypertension (HVPG > 6 mmHg) or high liver stiffness (>8.6 kPa) one year after LT accurately identify patients who are in urgent need of treatment due to a higher risk for clinical decompensation and death [63,64]. In patients with a severe recurrence occurring during the first months after LT (i.e. fibrosing cholestatic hepatitis, FCH), antiviral therapy and viral clearance is critical, otherwise patients will die or need re-transplantation.

Eradicating the virus after LT may have beneficial effects. Several studies have shown a significant histological improvement or stabilization of fibrosis after SVR in the transplant setting, compared to non-responders [65,66]. Similarly, portal pressure measurements and determinations of transient elastography also suggest the beneficial effect of antiviral treatment on liver fibrosis when SVR is achieved [66].
3.2.2. How can we treat?

3.2.2.1. Interferon-based regimens. The overall SVR rates with PR are low; ranging between 30% and 40% across different series [65,67,68]. These modest virological results are mainly explained by high rates of treatment discontinuation (20–38%) and dose reductions (66–73%) due to adverse events. Liver transplant recipients are prone to haematological toxicity, particularly anaemia, which is almost universal in these patients [69]. The risk of rejection is small (~5%) [70,71].

Regarding triple therapy with PI in the post-LT setting, several studies have evaluated the safety and efficacy of such regimens in >300 patients with hepatitis C recurrence [72–75]. Two thirds of these received telaprevir and the rest were treated with boceprevir. Most of the patients had an advanced fibrosis (METAIVIR F ≥ 2) or FCH. Approximately half of the patients had received a previous course of antiviral therapy. SVR rates ranged between 48% and 62% [72–75]. Despite the increased efficacy, the major concern of triple therapy in LT recipients is the high rate of SAEs leading to treatment discontinuation. Drug–drug interactions (DDI) are an additional challenge when using telaprevir and boceprevir. First generation PIs are not only substrates, but also inhibitors of the CYP3A4 system, thus strongly interacting with many drugs. Due to the narrow therapeutic range of cyclosporine and tacrolimus, dose adjustments are crucial and require very close monitoring when combined with PIs (Table 2, [37,76,77,78,81]).

The only Phase 3 clinical trial assessing the safety and efficacy of telaprevir in the liver transplant setting [82] was performed in Europe, and included 74 naive patients with GT1 hepatitis C recurrence with a METAIVIR score of F0–F3. Treatment consisted of 12 weeks of triple therapy, followed by 36 weeks of PR. Tacrolimus or cyclosporine doses were adjusted on telaprevir initiation and discontinuation. Final data from 61 of the 74 patients were available and presented in the last European Meeting, showing SVR rates of 67%. Eight (11%) patients had 11 SAEs, and there were no rejection episodes during the study period.

3.2.2.2. Interferon-free regimens.

- Sofosbuvir and ribavirin

Sofosbuvir plus RBV is the first interferon-free combination to be evaluated for hepatitis C recurrence in a clinical trial [83]. A pilot single-arm study assessed the safety and efficacy of sofosbuvir 400 mg/d and RBV (dose escalating regimen starting at 400 mg/d) for 24 weeks in 40 patients with HCV recurrence (any genotype) at least 6 months after LT.

Of the 40 patients, 33 were infected with GT1. The study included treatment-naive and treatment-experienced patients (some even with PI); 40% were compensated cirrhotic patients. Despite these characteristics, all individuals had HCV RNA <25 IU/mL at week 4 of treatment initiation. SVR12 was achieved in 28 (70%) of the 40 patients (Fig. 3). These results can be considered excellent, particularly due to the good tolerance; most side effects were mild and no rejection episodes occurred during therapy.

- Compassionate use of DAs after LT

Results from 104 HCV-infected LT recipients included in the Sofosbuvir compassionate use programme were presented at the last European meeting [84]. The antiviral regimen included sofosbuvir 400 mg/d for up to 48 weeks, with appropriate doses of RBV. PEG-IFN was added at the investigator’s discretion. The patients included in this programme differed substantially from those included in the pilot study described above: approximately half of these patients had severe cholestatic hepatitis (some of them well-documented FCH) or were rapid fibrosers; the remaining half had compensated or decompensated cirrhosis. Sixty patients (58%) presented an improved clinical condition (decrease of hepatic encephalopathy episodes and/or improvement/disappearance of ascites). Although clinical improvement was subjectively assessed by the investigators, liver function tests improved remarkably over time. The other 23 patients (22%) remained stable, while in 21 (20%) the disease progressed or the patient died (n = 18). Of the 93 patients on which HCV-RNA testing was carried out at the end of treatment, 76 (82%) had undetectable HCV-RNA; 53 (62%) of 85 patients with more than 12 weeks of follow-up after LT achieved SVR. SAEs were frequent, but they were mostly attributable to disease progression. Overall, the preliminary results of this programme indicate that a regimen containing sofosbuvir is able to inhibit hepatitis C replication in most patients, and that this is associated with an improvement in the clinical condition of a significant number of patients. Although longer follow-up is obviously needed, these results are encouraging. A particularly relevant result of this study was the excellent response in patients with cholestatic hepatitis (including FCH), in which liver tests improved significantly only a few weeks after treatment initiation and viral clearance. SVR in patients with acute cholestatic hepatitis/FCH was 70%, whereas SVR in those with established cirrhosis was 48% (Forns, personal communication). The latter strongly suggests the benefit of early treatment in severe forms of hepatitis C recurrence.

Data from a small compassionate use programme with sofosbuvir and daclatasvir were also recently presented [85]. This study included 12 GT1/4 recipients with severe HCV recurrence (METAIVIR F3–4, including 3 FCH) in whom PEG-IFN-based therapy was unfeasible, who were treated with sofosbuvir 400 mg/d and daclatasvir 60 mg/d either with or without RBV for 24 weeks. All patients achieving 12 and 24 weeks of treatment had undetectable HCV-RNA, although results of follow-up are still lacking. No adverse events were directly attributable to the drugs. In patients who completed the treatment, mean Child–Pugh score and serum albumin concentration showed a significant improvement compared to baseline.

- Paritaprevir, Ombitasvir plus Dasabuvir and ribavirin in HCV-infected LT recipients

In this Phase 2 study [79] the safety and efficacy of this 3-drug combination, plus ribavirin administered for 24 weeks, were assessed in 34 HCV-infected liver transplant patients. The included patients were GT1 infected, naive after transplantation and had mild fibrosis in the graft (METAIVIR ≤F2). Preliminary analysis has shown that all 34 patients had undetectable HCV-RNA at end of treatment, and 25 (96%) of 26 with sufficient follow-up achieved SVR. The only patient who experienced relapse had RAVs (R155K in NS3 protease, M28T+Q30R in NS5A, and G554S+G537R in NS5B); none of these mutations were present at baseline. Tolerance of this regimen was good; no episodes of rejection were reported. A number of other clinical trials, using different DAA combinations in the peri-transplant setting, are currently recruiting patients and this is summarized in Table 1.

- Specific features of interferon-free regimens in HCV-infected liver transplant recipients

Renal failure is common in liver transplant recipients. Most patients have decreased glomerular filtration rate (GFR) due (at least in part) to the long-term use of cyclosporine or tacrolimus. Sofosbuvir, for instance, is not recommended if GFR is below 30 ml/min [86]. Another issue that needs particular consideration in the LT setting is that these patients usually have high viral loads, making it easier to select for drug resistant strains. The latter might be particularly relevant in those patients with FCH, who exhibit the highest viremias.
Table 2
Drug–drug interactions between direct acting antivirals and calcineurin inhibitors.

<table>
<thead>
<tr>
<th>DAA</th>
<th>Cyclosporine</th>
<th>Tacrolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Healthy volunteers Dose adjustment</td>
<td>Healthy volunteers Dose adjustment</td>
</tr>
<tr>
<td>Boceprevir [76,77]†</td>
<td>AUC ↑ 2.7 fold ↓ 2 fold</td>
<td>AUC ↑ 17 fold ↓ 5 fold</td>
</tr>
<tr>
<td>Telaprevir [77,69]†</td>
<td>AUC ↑ 4.6 fold ↓ 4 fold</td>
<td>AUC ↑ 70 fold ↓ 35 fold</td>
</tr>
<tr>
<td>Paritaprevir [79]</td>
<td>AUC ↑ 5.8 fold ↓ 5 fold</td>
<td>AUC ↑ 58 fold ↓ 100 fold</td>
</tr>
<tr>
<td>Simeprevir [37]</td>
<td>AUC ↑ 19% Under investigation. Not</td>
<td>AUC ↓ 17% Not necessary</td>
</tr>
<tr>
<td></td>
<td>recommended</td>
<td></td>
</tr>
<tr>
<td>Sofosbuvir [80]†</td>
<td>No change Not necessary</td>
<td>No change Not necessary</td>
</tr>
<tr>
<td>Daclatasvir [81]</td>
<td>No change Not necessary</td>
<td>No change Not necessary</td>
</tr>
</tbody>
</table>

† AUC is given; AUC↓ is given.
DAA, direct acting antiviral; AUC, area under curve.

3.2.3. When should we treat?

The most common approach to treat hepatitis C after LT so far has been to start antiviral therapy once the histological damage (in particular liver fibrosis) is confirmed in the graft. This assumption was made in the interferon era, in which treatment in the very early phases of LT was not recommended for different reasons. In the early period after LT, individuals are still under strong immunosuppression, at risk of opportunistic infections, not uncommonly recovering or being treated for surgical complications and undergoing treatment with multiple drugs.

However, with the new DAAs, this recommendation will probably need to be reviewed. Although caution is needed, experiences to date regarding treatments with DAAs of very early severe HCV recurrences (i.e. FHC) suggest that treatment is feasible and safe at very early phases after transplantation. In addition, fortunately the many new anti-HCV compounds do not seem to have clinically significant interactions with cyclosporine and tacrolimus, which makes treatment much easier (Table 2).

4. Conclusions

In 2014 and 2015, the new IFN-containing and IFN-free regimens will become available. Starting in 2015 and onwards, IFN-based therapies will be replaced by all-oral DAA combinations, especially in difficult-to-treat populations, and at least in those areas of the world in which these molecules have been approved and are affordable (Fig. 4). However, despite a large HCV drug market, treatment options will likely be very different, depending
on the regions and their wealth. Indeed, real-life treatment will depend on the local recommendations, reimbursement strategies and economic restrictions.

Conflict of interest
XF has received unrestricted grant support from Roche and MSD and has acted as advisor for Gilead, Jansen and Abbvie. The other authors have no conflicts of interest to declare.

This article is part of a supplement supported by an unrestricted educational grant from Gilead Sciences Europe Ltd. Gilead has had no editorial control or involvement in the content of this article. The views and opinions within this supplement are those of the authors and not necessarily those of Gilead.

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