Treatment of hepatitis C in difficult-to-treat patients

Peter Ferenci

Abstract | Interferon-free regimes are now the treatment of choice for patients with chronic hepatitis C; previously patients who were 'difficult-to-treat' using interferon-containing treatments can now safely be treated with such therapies. More than 90% of patients infected with HCV genotype 1 or 4, compensated cirrhosis, or who have had liver transplantation, can be cured with the use of sofosbuvir combined with simeprevir, daclatasvir or ledipasvir, or by the combination of paritaprevir with ritonavir, ombitasvir and with or without dasabuvir. Addition of ribavirin seems to shorten treatment duration. However, the safety of these drugs is not fully explored in patients with decompensated cirrhosis (that is, those with Child–Pugh class C disease), and protease inhibitors should not be used in this group. The optimal use of interferon-free regimes in patients with renal failure or after kidney transplantation is currently being studied. However, new and improved drugs are needed to treat patients infected with HCV genotype 3. Unfortunately, the broad application of new HCV treatments is limited by their high costs. In this Review, I discuss the treatment of patients with hepatitis C with compensated and decompensated cirrhosis, before and after orthotopic liver transplantation and in patients with impaired kidney function.

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Introduction

Chronic hepatitis C is the leading cause of cirrhosis and hepatocellular carcinoma in the USA and Europe[1,2] and has become the leading cause of mortality due to viral infections in the USA (4.4 per 100,000 per year).[3] The natural history of hepatitis C reveals a slow progressing liver disease, with cirrhosis occurring ~20–30 years after infection, followed by the ocurrence of late complications such as variceal bleeding, hepatic decompensation and hepatocellular carcinoma. Once a patient reaches this late stage, only liver transplantation can improve survival. Since the first publication of the use of interferon treatment for hepatitis C,[4] a slow, but continuous improvement in the options for treatment has occurred, including the combination of interferon with ribavirin, the introduction of PEG-IFN and of the first generation of protease inhibitors.[5–8] However, these interferon-based regimes could not be used safely in patients with advanced liver diseases.[9] A high incidence of serious adverse events (40.0%) and death and/or life threatening infections (6.4%) was observed, and anaemia was difficult to manage in these patients.[9] In 2010, investigators conducting a first proof-of-concept study indicated that an interferon-free treatment was possible.[10] Within 3 years interferon-free treatments became a clinical reality and the treatment of choice for patients with chronic hepatitis C. In this Review, I describe and assess the application of interferon-free treatment in previously untreatable patients.

Definition of 'difficult-to-treat patients'

The rapid evolution of direct-acting antiviral (DAA)-based interferon-free treatment regimens changed our perception of how to treat patients with chronic hepatitis C. The term 'difficult-to-treat' was first used when interferon-based regimes were standard of care[11] and described patients who did not respond to treatment or who did not tolerate interferon (such as those with advanced cirrhosis, psychiatric problems, comorbidities). This issue was highlighted in the French CUPIC trial[9] in which PEG-IFN and ribavirin was used in combination with a first-generation protease inhibitor (telaprevir or boceprevir). In the CUPIC study, a low platelet count and low serum albumin level identified patients who were at risk of developing serious adverse effects on treatment, and some of these patients even died. Similar problems were described in the HCV-TARGET database in the USA.[12] Whether these patients remain 'difficult-to-treat' with the new interferon-free treatments is the subject of ongoing studies. Patients who do not respond to interferon-free regimes constitute a group we might term 'very difficult-to-treat'.

The 'difficult-to-treat' group of patients also includes individuals with end-stage renal failure or those who have a kidney transplant and are infected with HCV. Interferon cannot be used in the post-renal

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Key points

- The availability of potent and safe direct-acting antiviral agents has substantially improved the treatment of chronic hepatitis C
- Patients who are 'difficult-to-treat' can now be cured, including those with advanced cirrhosis before and after liver transplantation; studies in patients with kidney failure and after kidney transplantation are underway
- Combinations of NS5B inhibitors (sofosbuvir, dasabuvir) with new protease inhibitors (simeprevir, paritaprevir) and NS5A inhibitors (ledipasvir, daclatasvir, ombitasvir) are becoming the standard of care for all patients with HCV
- In patients post-liver transplantation, sofosbuvir, ledipasvir and daclatasvir are safe but protease-containing regimes should be avoided in patients with decompensated liver disease
- The optimal treatment duration and the need for ribavirin require further studies
- More effective antiviral agents than those currently available are needed for patient with cirrhosis who are infected with HCV genotype 3a

transplantation setting because it might lead to transplanted graft rejection.[13,14] Furthermore, individuals infected with HCV genotype 3a are a subgroup of patients with suboptimal response to interferon-free regimes, especially in those with cirrhosis.

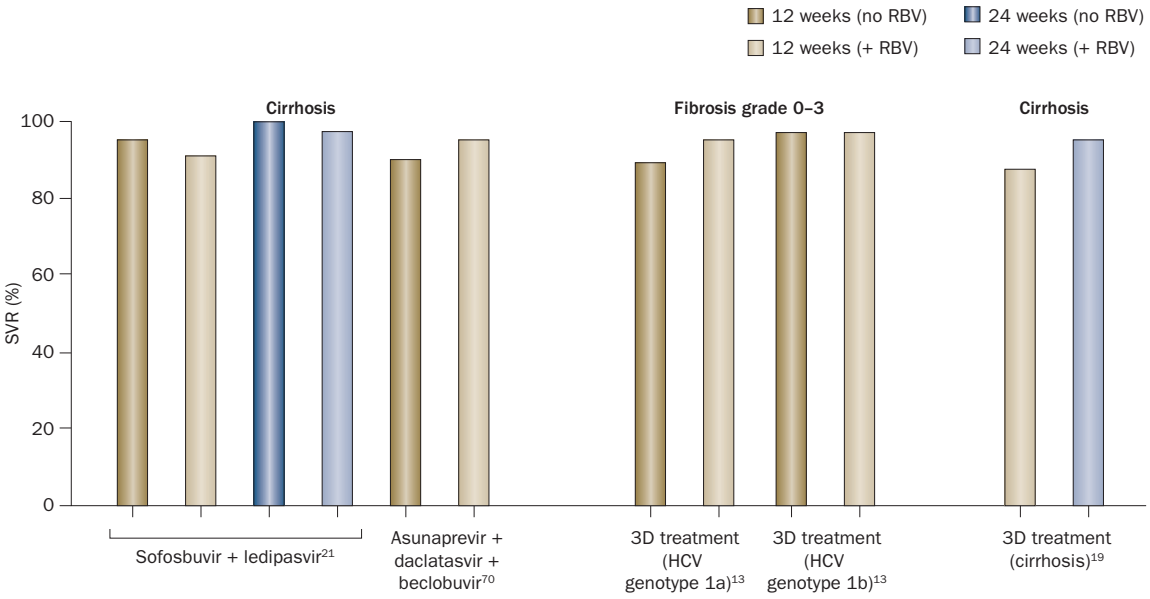
Finally, the term 'special populations' refer to patients coinfected with HIV and/or HBV, elderly patients or intravenous drug users; however, this term but does not imply that these patients are difficult to treat and, therefore, is not discussed in this Review.

Cirrhosis

Compensated cirrhosis

In most phase II and phase III studies either patients who have cirrhosis with Child–Pugh classes B and C,[15–17] or in some cases all patients with cirrhosis [18–22] are excluded. Even Child–Pugh class A cirrhosis does not represent a homogeneous cohort of patients.[23] Cirrhosis is not a single, irreversible, end stage of disease but rather a spectrum characterized by progressive increases in hepatic venous pressure gradient, and decreases in liver function finally leading to hepatic decompensation.[23] Only one phase III trial (the Turquoise-II trials[24]) has been conducted in patients who had cirrhosis, but also well-compensated liver disease. Consequently, the efficacy, safety and dosage of DAAs are unknown in patients with decompensated liver disease. Currently, one randomized controlled study with sofosbuvir and ledipasvir (NS5B and NS5A polymerase inhibitors, respectively) in patients with decompensated liver disease is ongoing (Solar 2[25]).

In a meta-analysis of patients with compensated cirrhosis who participated in phase III clinical trials with sofosbuvir and ledipasvir[26] and paritaprevir plus ritonavir (paritaprevir/r) with ombitasvir and dasabuvir (known as the 3D regime),[27] interferon-free therapy was highly efficacious and well-tolerated.[26] No predictive factor for sustained virologic response (SVR) was identified, but was not expected because SVR rates were between 95% and 98%. No statistically significant differences were identified regarding patient characteristics for both drug combinations, except a nonsignificant trend towards to lower SVR rates in patients infected with HCV genotype 1a compared with HCV genotype 1b by the 3D regime (Figure 1). With the 3D regime, SVR rates for HCV genotype 1a are lower than that for HCV genotype 1b.[18,24] For sofosbuvir and ledipasvir neither length of treatment (12 or 24 weeks) nor the addition of ribavirin had an effect on treatment outcome.[26] In a randomized controlled study in patients with cirrhosis who did not respond to triple therapy with PEG-IFN, ribavirin and first-generation protease inhibitors, 24 weeks



SVR	113	188	133	57	133	188	185	97	207	209	191	165
n	118	204	133	58	118	204	205	100	209	210	208	172

Figure 1 | SVR rates with or without ribavirin in phase III studies of interferon-free treatments. Sofosbuvir containing treatments.[9–11] 3D treatment consists of paratapravir combined with ritonavir plus ombitasvir plus dasabuvir).[12–15,18,21] Abbreviations: RBV, ribavirin; SVR, sustained virologic response.

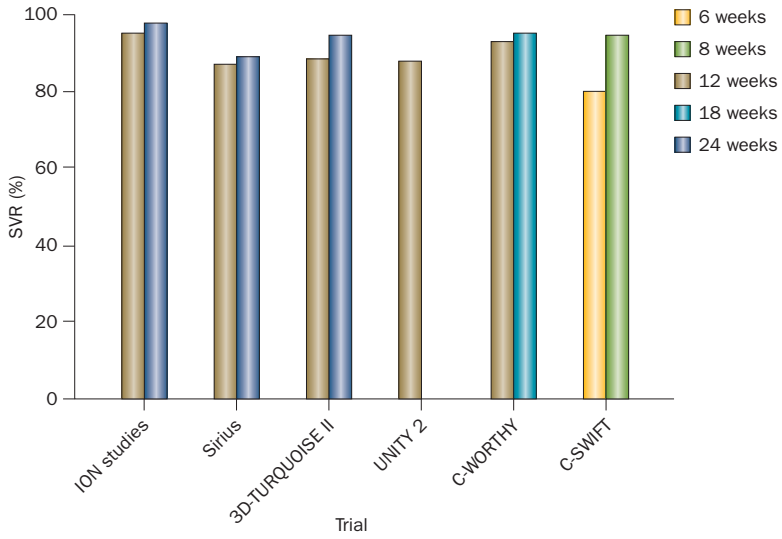


Figure 2 | SVR rates in patients with compensated cirrhosis. Data for groups treated with or without ribavirin are combined. ION studies: sofosbuvir and ledipasvir ± ribavirin,[21] Sirius: sofosbuvir, ledipasvir and ribavirin in patients with cirrhosis who did not respond to triple therapy,[13] Turquoise-II, 3D treatment (paratapreviri/r plus ombitasvir plus dasabuvir) in compensated patients with cirrhosis,[19] UNITY 2: asunapreviri, daclatasvir and beclobuvir,[58] C-WORTHY: grazoprevir and elbasvir ± ribavirin,[56] C-SWIFT, grazoprevir, elbasvir and sofosbuvir.[59] Abbreviation: SVR, sustained virologic response.

of sofosbuvir and ledipasvir and 12 weeks of sofosbuvir and ledipasvir plus ribavirin were equally effective (SVR 97% and 96%, respectively).[28] Unfortunately the investigators in this study did not include a 12-week sofosbuvir and ledipasvir treatment arm, which makes a proper comparison difficult.

HCV genotype 3

HCV genotype 3 has emerged as a particularly difficult HCV genotype to treat. Not all of the newly available DAAs have activity against HCV genotype 3, which further limits treatment choices in this patient group. HCV genotype 3 is the second most prevalent genotype worldwide (accounting for ~30% of all patients infected with HCV) and particularly common in the Indian subcontinent (72%).[29] Finding the most effective treatment is, therefore, urgently needed.

In one study, an SVR rate of 86% was achieved in patients with HCV genotype 3 and compensated cirrhosis using a combination of sofosbuvir with ribavirin given for 24 weeks.[30] In Ally-3,[31] the efficacy and safety of the combination of daclatasvir (a potent pangenotypic NS5A inhibitor) and sofosbuvir for 12 weeks were evaluated in patients with chronic HCV genotype 3 infection. Although SVR rates in patients without cirrhosis were 91–95%, the response rates are substantially lower, just 73% and 63%, in treatment-naive and treatment-experienced patients with cirrhosis, respectively.[31] However, because no patient in this study received ribavirin, the effect of this drug on SVR rates in these patients was not studied. By contrast, all patients with cirrhosis treated with sofosbuvir and ledipasvir received ribavirin.[32] The need for ribavirin in HCV genotype 3 patients remains to be studied.

Decompensated cirrhosis

The interim results of a prospective study of 108 patients infected with HCV genotype 1 or HCV genotype 4 who were either treatment-naive or treatment-experienced with decompensated cirrhosis (Child–Pugh class B [score 7–9] or C [score 10–12]) have been reported. Patients were randomly assigned to receive 12 weeks or 24 weeks of treatment with sofosbuvir and ledipasvir plus ribavirin.[25] The overall SVR rate was 87% and 89% in patients treated for 12 or 24 weeks, respectively. No difference in the outcome of patients with Child–Pugh class B or C was apparent. Of these patients, 28 (26%) experienced serious adverse events, but only three discontinued treatment in response to these events. These results suggest that even in a patient population with advanced disease, 12 weeks of sofosbuvir and ledipasvir plus ribavirin are sufficient in individuals with Child–Pugh class B and C to control cirrhosis. The clinical benefit was evident by an improvement in model for end-stage liver disease (MELD) score by 1–6 points in 77 of 108 included patients. Achieving SVR might even result in the delisting of patients from an orthotopic liver transplantation waiting list.[33]

However, many issues remain unresolved. For example, the optimal length of treatment has not been studied. In preliminary data, viral clearance on interferon-free and ribavirin-free regimes is slower in patients with cirrhosis than in patients without cirrhosis, but in these studies the interim data was compared with nonspecified historical controls so a definitive conclusion cannot be made.[34,35] The level of portal hypertension does not affect viral clearance in patients treated with an interferon-free regime.[36]

Furthermore, the pharmacokinetics of most DAAs, either alone or in combination, has not been sufficiently addressed in patients with advanced liver diseases; consequently, the optimal dose of each drug in this patient group is unknown. The differences of SVR rates in patients treated for 12 weeks or longer were small in a number of different trials (Figure 2). A suggestion for the selection of treatment duration following the principles of response-guided therapy is shown in Figure 3.

The NS34A protease inhibitors simeprevir, asunaprevir and paritaprevir are primarily metabolized by the liver and might, therefore, accumulate in patients with advanced liver failure.[37,38] The mean steady-state area under the curve (AUC) of simeprevir was 2.4-fold and 5.2-fold higher than in healthy individuals not infected with HCV for patients with cirrhosis and moderate hepatic impairment (Child–Pugh class B) and/or with severe hepatic impairment (Child–Pugh class C), respectively.[37] Relative to individuals with normal hepatic function, paritaprevir, ritonavir and dasabuvir AUC values increased by 945%, 13% and 325%, respectively, and ombitasvir AUC values decreased by 54% in patients with severe hepatic impairment.[38] In the absence of safety data, therefore, simeprevir and the 3D drug combination are not recommended for use in patients with severe hepatic impairment (Child–Pugh class C). By contrast, NS5A inhibitors and sofosbuvir[39,40] need no dose adjustment in these patients. However, in patients with

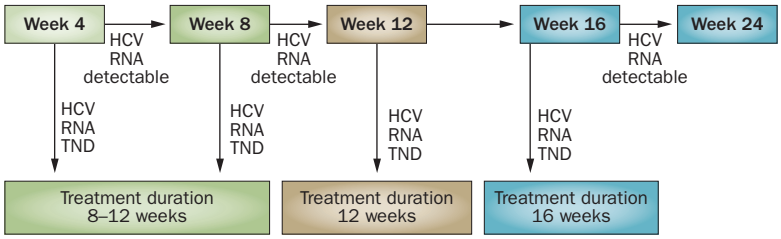


Figure 3 | Selection of optimal treatment duration in patients with cirrhosis. This proposed algorithm is based on interim data in which all patients with advanced liver diseases and undetectable HCV (and who completed 12 weeks follow-up) at week 8 had an SVR12.[29] TND by One Signal Amplification (Versant® HCV RNA 3.0, Siemens Corp. USA). The predictive value of HCV-RNA by One Signal Amplification (Versant® HCV RNA 3.0, ART) at week 4 was low in patients without cirrhosis.[80] Using this system, undetectable HCV RNA rates were lower than with the COBAS® AmpliPrep/Cobas TaqMan (Roche Molecular Systems Inc., USA).[80–82] Abbreviations: SVR12, sustained virologic response at 12 weeks; TND, target not detected.

impaired renal function the dose of sofosbuvir might have to be adjusted.[36]

Finally the role of ribavirin has not been investigated in patients with decompensated cirrhosis. Ribavirin is associated with substantial toxicities,[41] thus a ribavirin-free regime would lessen the adverse effect profile of interferon-free regimes. Overall, ribavirin provided no additional benefit with the combination of sofosbuvir and ledipasvir, irrespective of HCV genotype or treatment duration,[26] but slightly increased SVR rates in the subgroup of patients with cirrhosis who did not respond to PEG-IFN and ribavirin. No data have been reported for the use of a combination of ribavirin, sofosbuvir and ledipasvir in patients with decompensated cirrhosis.[25] In studies that included a protease inhibitor, addition of ribavirin increases SVR rates slightly in patients without cirrhosis (Figure 1), but these differences were not statistically significant and only detectable in patients infected with HCV genotype 1a.[42] In treatment-naive patients who did not have cirrhosis and participated in the Pearl IV study,[16] all those infected with HCV genotype 1a from Europe were cured by the 3D combination treatment irrespective whether they received placebo or ribavirin. All 17 patients who did not respond to treatment were from the USA, suggesting that small geographical differences in pre-existing resistance mutations exist, such as those shown in studies using simeprevir.[43] SVR rates for patients infected with HCV genotype 1b patients were identical.[16,17] The same observation was made in the Unity 1 trial,[44] with a high proportion of patients from USA. Owing to the only slight benefit of adding ribavirin to treatments, treating all patients with this drug would overtreat ~90% of the patients for a difference of only 5–7% SVR.[18]

Liver transplant

Reinfection of the graft is unavoidable after successful liver transplantation for hepatitis C. Antiviral therapies before DAAs were available were not very successful and poorly tolerated.[45] With protease-inhibitor-based triple therapy of PEG-IFN, ribavirin, boceprevir or telaprevir, SVR rates of ~50–60% could be achieved in patients with recurrent HCV genotype 1 infection after liver transplantation, but significant adverse effects were reported.[43,44,46–50] For example, in one study 38% of patients developed renal dysfunction, 21% had a decline in haemoglobin levels to <8 g/dl (4.96 mmol/l) and 57% required blood transfusion,[46] in another study 11% died and 22% experienced hepatic decompensation.[47] Only four studies on interferon-free treatment of patients with hepatitis C undergoing transplantation have been published.[51–54]

In the CORAL-1 trial, 34 recipients of a liver transplant, who had either no fibrosis or mild fibrosis received ombitasvir (25 mg, once daily), paritaprevir/r (150 mg paritaprevir coformulated with 100 mg of ritonavir, once daily), dasabuvir (250 mg, twice daily), and ribavirin for 24 weeks.[51] Only patients with mild fibrosis were included (fibrosis grade 0–2). Of the 34 study participants, 33 had an SVR at post-treatment weeks 12 and 24 (97%). The most common adverse events were fatigue, headache and cough. Five patients (15%) required erythropoietin and no patients required blood transfusion. One patient discontinued treatment due to adverse events after week 18, but also had an SVR. Blood levels of calcineurin inhibitors were monitored, and dosages were modified to maintain therapeutic levels; no episode of graft rejection was observed during the study.

In a prospective, multicentre, open-label pilot study,[52] 40 patients with recurrent HCV infection of any genotype and compensated liver disease received 24 weeks of sofosbuvir (400 mg daily) and ribavirin (starting at 400 mg daily). SVR 12 weeks after treatment was achieved by 28 of 40 patients (70%). Relapse accounted for all cases of SVR failure. No patients had detectable viral resistance during or after treatment. The most common adverse events were fatigue (30%), diarrhoea (28%) and headache (25%). 20% experienced anaemia. No deaths, graft losses or episodes of rejection occurred. No interactions with any concomitant immunosuppressive agents were reported.

A phase II, open-label study has evaluated sofosbuvir plus ribavirin in the pretransplant setting to prevent recurrent HCV infection.[55] Patients infected with HCV ($n=61$) of all genotypes and cirrhosis (Child–Pugh scores ≤7) listed for liver transplantation for HCC received up to 48 weeks of therapy. In total 46 patients received a liver transplant. Of the 43 patients who had HCV RNA <25 IU/ml at transplantation, 30 (70%) achieved SVR12 after transplantation, 10 (23%) had recurrent infection, and three (7%) died (two owing to nonfunctioning of the primary graft and one from hepatic artery thrombosis). Recurrence was inversely related to the number of consecutive days of undetectable HCV RNA before liver transplantation. The most frequently reported adverse events were fatigue (38%), headache (23%) and anaemia (21%).[55]

In a compassionate use programme, patients with severe recurrent hepatitis C, including those with fibrosing cholestatic hepatitis and decompensated cirrhosis who had a life expectancy of ≤1 year were treated with sofosbuvir and ribavirin for between 24 and 48 weeks.[53] Investigators could add PEG-IFN at their discretion.

Table 1 | Treatment of recurrent post liver transplant hepatitis C with interferon-free regimes

Trial	Regime	Fibrosis grade	Treatment duration (weeks)*	Patients (*n*)‡	SVR12 (*n*, %)	Study type
Charlton[52]	Sofosbuvir + ribavirin	2–4	24	40	28 (70)	Case series
CORAL-1[51]	Paritaprevir/r + ombitasvir + dasabuvir + ribavirin	≤2	12	34	33 (97)	Prospective
Forns[53]	Sofosbuvir + ribavirin	FCH, 4	24–48	92	54 (59)	Case series
SOF/LDV Phase 3[56]	Sofosbuvir + ledipasvir	0–3	12	55	53 (96)	Prospective
SOF/LDV Phase 3[56]	Sofosbuvir + ledipasvir	0–3	24	56	55 (98)	Prospective
SOF/LDV Phase 3[56]	Sofosbuvir + ledipasvir	4	12	57	50 (88)	Prospective
SOF/LDV Phase 3[56]	Sofosbuvir + ledipasvir	4	24	46	41 (89)	Prospective
Mayo Clinic[55]	Sofosbuvir + simeprevir ± ribavirin	24% 3–4	12	66	60 (91)	Case series
HCV-TARGET[83]	Sofosbuvir + ledipasvir	Any	Physicians choice	68	61 (90)	Case series
University of Massachusetts[84]	Sofosbuvir + ledipasvir	17.5% with 4	12§	22	22 (100)	Case series
Emory University[85]	Sofosbuvir + simeprevir ± ribavirin	22% with 4	12	37	34 (92)	Case series
Daclatasvir NPP[86]	Sofosbuvir + daclastasvir	4	24	12	9 (75)	Case series
CUPILT[87]	Sofosbuvir + daclastasvir ± ribavirin	FCH	12	15	15 (100)	Case series
AISF-SOFOLT [88]	Various sofosbuvir-based	FCH, 4	24	39	31 (79)	Case series
Lahey Clinic[89]	Sofosbuvir + simeprevir	6% with 4	12	16	13 (81)	Case series
University of Louisville[90]	Sofosbuvir + simeprevir ± ribavirin	<4	12	18	16 (89)	Case series

*Unless otherwise stated. ‡Patients who completed treatment and follow-up. §Addition of ribavirin possible at the discretion of treating physician.
Abbreviations: FCH, fibrosing cholestatic hepatitis; SVR12, sustained virologic response at 12 weeks.

Of the 104 patients assessed, 52 had an early severe recurrence (diagnosed <12 months after orthotopic liver transplantation) and 52 had cirrhosis (diagnosed >12 months after orthotopic liver transplantation). 22 patients did not complete treatment (eight owing to liver retransplantation, 10 died and four discontinued treatment). 12 patients with reorthotopic liver transplantation before week 12 were excluded from further analysis. Of the final 92 patients assessed, 54 (59%) achieved SVR12 with an increased rate (73%); 35 of 48 in patients with early severe recurrence. 123 serious adverse events occurred in 49 patients (47%), and those events associated with hepatic decompensation were the most frequent (26 occurring in 19 patients; 18%).

Investigators for the Mayo Clinic study reported 128 patients treated postorthotopic liver transplantation with sofosbuvir plus simeprevir with or without ribavirin, 25 of them had fibrosis stage F3–4.[54] The overall SVR rate was 91%, with lower rates in patients infected with HCV genotype 1a than in those infected with genotype 1b. Ribavirin had no effect on the outcome.

In addition, interim results of ongoing studies have also been reported at the American Association for the Study of Liver Diseases, The Liver Meeting 2014 in Boston, USA (Table 1). In total, 575 of 627 patients (91.7%) who completed therapy and 12 weeks of treatment-free follow-up achieved an SVR (Table 1). These preliminary results are extremely encouraging and will revolutionize liver transplantation for hepatitis-C-associated cirrhosis. Graft and overall survival will be substantially improved (in the same way that hepatitis B survival was improved after polymerase inhibitors were introduced). However, most of these data were derived from patients who did not have cirrhosis. Those studies that included patients only with advanced fibrosis post-liver transplantation had worse SVR rates and most of these patients were treated with sofosbuvir and ribavirin (Table 1). Nevertheless, the available data in patients with decompensated cirrhosis[20] indicate that even patients with Child–Pugh class C cirrhosis will benefit from this treatment.

Antiviral treatment of individuals waiting for a liver transplant might lead to a delay in organ allocation as the patient's MELD score can improve by 1–6 points in response to treatment within a few weeks.[56] One can speculate that eradicating HCV will even improve the condition of a patient with decompensated cirrhosis to the point where they can be removed from the transplantation waiting list.[57] By contrast, some patients continue to have further increases in MELD score despite treatment for HCV indicating that there might be a point-of-no-return in late liver disease presentation.[57] Consequently, owing to the lack of safety data in patients with Child–Pugh class C, antiviral treatment might be safer after successful liver transplantation, given the high efficacy of interferon-free combinations post-liver transplantation.

Tolerance of ribavirin has always been a major issue after liver transplantation. The adverse events of ribavirin, mainly anaemia and renal impairment, are well known, especially in patients who have received a liver transplant.[46,47] When potent DAAs can be combined as a treatment, ribavirin should be abandoned in this population of patients. However, ribavirin-based regimens

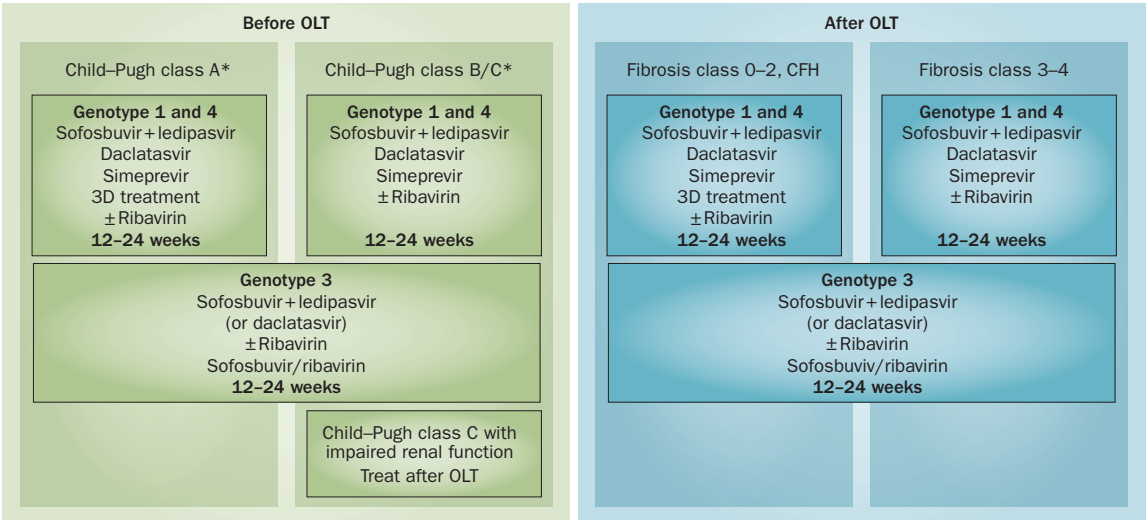


Figure 4 | Treatment selection in patients before and after OLT. These recommendations are based on currently available evidence. 3D treatment consists of paritaprevir combined with ritonavir plus ombitasvir plus dasabuvir. *Treatment can be deferred until after OLT. Abbreviations: CFH, fibrosing cholestatic hepatitis; OLT, orthotopic liver transplantation.

are still prevalent in most ongoing studies and more investigation is needed to clarify this issue.

Drug interactions will be less important when regimes without protease-inhibitors are used. With the exception of nucleoside NS5B inhibitors (such as sofosbuvir), second-generation protease inhibitors, and to a lesser degree NS5A inhibitors, are substrates and inhibitors of the CYP3A4 and P-glycoprotein metabolic pathways, which can interact with immunosuppressive drugs, mainly calcineurin inhibitors. Sofosbuvir and ledipasvir do not interact with commonly used immunosuppressants such as ciclosporin A or tacrolimus.[58] No adjustments need to be made with sofosbuvir or daclatasvir because they do not interact with calcineurin inhibitors. Using protease inhibitors with or without ritonavir requires monitoring of immunosuppressive drugs, mainly for calcineurin inhibitors, but dose adjustments are easy to complete.[59] A recommendation for the use of these drugs in patients before and after liver transplantation, and based on currently available data, is outlined in Figure 4.

Renal failure and kidney transplantation

Treatment of HCV infection in patients with renal insufficiency also requires more research. The 10-year survival rate in patients infected with HCV after successful kidney transplantation was poorer than in patients without hepatitis C (65% versus 80%; $P<0.001$).[60] Furthermore, HCV infection might lead to membraneous glomerulonephritis and consequently to renal failure.[14,61] The use of interferon-based therapies in kidney transplant recipients might result in rejection of the graft and is, therefore, not recommended. Ribavirin augments anaemia owing to kidney failure and is also poorly tolerated in patients on haemodialysis.[14] Data on the use of interferon-free regimes are preliminary and, presently, do not permit clear recommendations.

The use of new DAAs also has to be adjusted to the degree of renal impairment. The AUC_{0-inf} of sofosbuvir is 2.7-fold higher in patients with severe renal impairment (creatinine clearance <30 ml/min), and the AUC_{0-inf} of GS-331007, the renally excreted major sofosbuvir metabolite, is 5.5-fold higher than in patients without renal impairment.[62] According to the manufacturer's instructions, patients with creatinine clearance ≤30 ml/min or ≤15 ml/min should not be treated with full dose sofosbuvir or simeprevir, respectively, and a combination of both drugs should be avoided. Nevertheless, according to preliminary data, sofosbuvir can improve SVR in patients on haemodialysis or after kidney transplantation but the dose of sofosbuvir should be reduced to 200 mg daily or 400 mg every other day.[63] The 3D treatment combination seems to be safe in patients with renal failure without the need for dose adjustments.[64]

Nonresponders

Although most patients with hepatitis C can be cured, 2–5% will not achieve a SVR. Other therapies that can be offered to patients who do not respond to treatment are currently unclear. A combination of PEG-IFN with sofosbuvir and ribavirin might be effective in patients with HCV genotype 3a who do not have advanced cirrhosis (Child–Pugh class A).[65] Several studies with next-generation DAAs are underway. For example, in contrast to all other marketed DAAs, the failure of sofosbuvir treatment does not seem to be associated with viral resistance.[66] Rescue regimens based on sofosbuvir could be the preferred choice for patients who did not respond to DAA treatment. Patients who relapse, or do not respond to sofosbuvir and ribavirin, can be treated with sofosbuvir and ledipasvir either with or without PEG-IFN.[67] However, no data has been presented on how best to treat infection with HCV genotype 1 in patients who did not respond to combinations of sofosbuvir with other DAAs.

New developments

Several phase II and III studies are being conducted with new combinations of DAAs, such as the pangenotypic

protease inhibitor grazoprevir combined with the NS5A inhibitor elbasvir,[68] or the protease inhibitor asunaprevir with daclatasvir and a non-nucleoside NS5B polymerase inhibitor beclabuvir.[36,69,70] Although these study outcomes are impressive, improving the SVR rates of currently licensed drug combinations (which are between 95% and 99%) is not possible. Whether these new regimes will have any additional benefit for patients is unknown at present. Further shortening of the treatment duration is far less important than efficacy and safety. Shortening of treatment with elbasvir, grazoprevir and sofosbuvir for fewer than 8 weeks seems to increase the risk of post-treatment relapse by 50% (Figure 2).[71] Better drugs for patients infected with HCV genotype 3a who have cirrhosis are, therefore, needed.

Conclusions

The availability of interferon-free treatment regimes has changed the approach to treating chronic hepatitis C. These treatments are highly effective, well-tolerated and enable clinicians to treat patients who cannot be treated with interferon-based regimes. Eradicating HCV in the transplant setting will improve survival and graft preservation and treating patients with advanced stages of cirrhosis might even decrease the need for liver transplantation. In general, achieving SVR by any treatment effectively reduces hepatic decompensation and occurrence of hepatocellular carcinoma.[72–76] However, an improvement in drug selection, treatment duration and the need for ribavirin, are all badly needed. On the basis of currently available data, both the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver have issued and regularly update recommendations on how to use these agents.[77,78] Currently, the main nonmedical hurdle is improving access to these effective but expensive therapies.[79] Even in developed countries, economic pressure limits the number of patients who might receive interferon-free regimens. Within each country diverse insurance and reimbursement systems necessitate an individualized approach, but changing health-care policy and reimbursement strategies is not the role of physicians. In 2015, prioritization of treatment for patients with advanced liver disease makes sense, but treatment should become available to all those infected with HCV irrespective of the fibrosis stage.

Review criteria

Interferon-free therapies to treat hepatitis C only became available from 2013, consequently, this Review is based on a Medline searches between 2012 and 2015. The search terms used were “cirrhosis”, “liver transplantation”, “interferon-free therapy”, “HCV”, and “DAA”. Relevant abstracts presented at the 65th Annual Meeting of the American Association for the study of Liver Diseases, Boston, MA, USA, November 3–6, 2014 were also evaluated. Single case studies were not considered.

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