Introduction

The prognosis of hepatitis C virus (HCV) infection is linked to the progression of fibrosis. Cirrhosis increases the risk of premature liver-related deaths because of complications such as hepatic decompensation and hepatocellular carcinoma (HCC). Thus the patients most in need of treatment are those with cirrhosis in whom HCV eradication could prevent liver-related complications and improve survival (1). Over the past decade, knowledge of the HCV lifecycle shows that potentially each step of the viral cycle could be a target for drug development. Understanding of the structures of HCV protease and HCV polymerase has allowed structure-based drug design to develop inhibitors of these enzymes. Two first generation protease inhibitors (boceprevir and telaprevir) were marketed in 2011. The aim of this article is to review the treatment of HCV cirrhosis in the era of new direct-acting antiviral (DAAs), according to the recent literature.

Where do we come from: HCV cirrhosis treatment-response with pegylated interferon and ribavirin

The association of pegylated-interferon (PEG-IFN) and ribavirin (RBV) has been the standard of care (SOC) for the treatment of HCV patients for the past decade. Treatment in patients with cirrhosis is less effective than in patients without, as recently shown in a real-life setting cohort study involving 2011 patients including 306 patients with cirrhosis. A sustained virological response (SVR) was achieved in 28% of treatment naive genotype 1 patients with cirrhosis vs 33% in patients with severe fibrosis, 41% in patients with moderate fibrosis, 49% in patients with mild fibrosis and 68.6% in patients without fibrosis (2). A recent review emphasizes the benefit...
of SOC in clinical trials. The rate of SVR with SOC ranged from 10% to 44% for HCV genotypes 1/4 and 33% to 72% for HCV genotypes 2/3 in compensated cirrhosis (3).

The clinical utility of treating patients with compensated cirrhosis was a matter of debate in the era of interferon (4, 5). Studies using the association of PEG-IFN and RBV definitely show the beneficial impact of successful treatment in terms of improvement of fibrosis, regression of cirrhosis and the reduction and prevention of cirrhosis-related complications such as the development of portal hypertension or HCC (6–16). However, they also report that viral eradication does not totally eliminate the risk of HCC, since it has been reported to occur years after a cure at a rate between 0.6% to 2.5% annually (17–20). Therefore HCC surveillance programmes should be maintained in all patients with cirrhosis even after the eradication of HCV. Great attention has been paid in the past decade to identifying the predictive factors of response, and on-treatment HCV viral kinetics appear to be the best tool to predict treatment outcome and individualize treatment duration. A rapid virological response (RVR), defined as HCV RNA undetectability after 4 weeks of treatment, is the most important factor of SVR in patients with cirrhosis with an odds ratio of 22.4 (95% CI 6.87–73.03) for genotype 1/4 and 11.35 (95% CI, 6.56–19.61) for genotype 2/3 (15). However, RVR is achieved by a lower percentage of patients with cirrhosis than by those without. In genotypes 2/3 patients, SVR rate was not different in patients with cirrhosis who achieved an RVR compared with those without. All studies suggest that the duration of treatment should not be shortened in patients with cirrhosis regardless of other pretreatment characteristics and on-treatment viral kinetics. Whether the type of PEG-IFN administered could influence SVR in patients with cirrhosis remains controversial. In one randomized trial assessing the effectiveness of SOC with PEG-IFN alpha 2a or 2b in 431 patients, 82 with cirrhosis, revealed that cirrhosis negatively influenced the response to PEG-IFN α2b (21). On the contrary the IDEAL study assessed the effectiveness of SOC with PEG-IFN alpha 2a or 2b in 3070 patients, 328 of whom had severe fibrosis or cirrhosis and observed no difference in SVR in relation to the type of PEG-IFN: 29.9% in patients treated with low dose PEG-IFN α2b, 20.7% in patients treated with a standard dose of PEG-IFN α2b and 23.6% in those treated with PEG-IFN α2a (22).

The safety of and tolerance to the association of PEG-IFN/RBV in HCV patients with cirrhosis does not differ from those without cirrhosis (3). Moreover, the rate of treatment discontinuation is not significantly different in patients with cirrhosis compared with those with less advanced liver disease (3). However, treatment dose modifications seem to be more frequent in patients with cirrhosis. This is mainly caused by an increase in haematological toxicity in relation with portal hypertension, thus leading to splenomegaly and increasing the risk of cytopenia – mostly anaemia and neutropenia (6, 11, 15). The reported rate of liver decompensation in patients with compensated cirrhosis enrolled in clinical trials is low, between 0 – 3% (9–11). This may reflect a bias in patient selection and the exclusion of patients at risk of decompensation. Therefore caution is recommended in real-life clinical practice.

Because of a reduced 5 year survival rate (50%) compared with patients with compensated cirrhosis (91%), (23) patients with decompensated cirrhosis are the HCV population most in need of treatment. HCV treatment has frequently been limited in this population because of the risk of infection and worsening of disease (24–26). When possible liver transplantation is the best treatment option in this population. Nevertheless, the outcome of liver transplantation is hindered by HCV recurrence in the graft and a low SVR rate in HCV transplant recipients treated with SOC (27).

In the era of interferon treatment, a few uncontrolled studies demonstrated the feasibility of antiviral treatment in patients with decompensated cirrhosis. Although treatment could prevent the recurrence of HCV after liver transplantation, it was associated with potentially severe or fatal side effects. Three prospective controlled or observational studies were performed with SOC. They confirmed results with interferon. The SVR rate ranged from 7% to 16% in genotype 1/4 patients and from 44% to 57% in genotype 2/3 patients (25, 26, 28, 29). However, treatment with SOC was associated with a higher risk of infection and deaths related to infection. The side effects were more frequent in patients with advanced liver disease (Child–Pugh class C and MELD > 18). Adverse events were counterbalanced by a lower rate of decompensation during follow-up and reduced mortality in responders compared with non-responders or untreated patients. Moreover, a retrospective study from the Barcelona group of 51 patients awaiting liver transplantation treated with SOC showed that of 15 (29%) patients who achieved SVR before liver transplantation, 10 (20%) did not experience HCV recurrence 6 months after liver transplantation (30). These studies showed that adherence to treatment and higher dosage were independent predictors of SVR. This provided a rationale for early treatment cessation in patients with a low probability of HCV eradication thus reducing the risk of complications. The safety of SOC is a major concern in decompensated cirrhosis. Child–Pugh class C patients are not candidates for treatment because there is a low probability of SVR and a high risk of potentially lethal side effects. The risk/benefit ratio should be assessed in patients with Child–Pugh class B on a case by case basis.
Where are we now: HCV cirrhosis treatment-
response with first generation protease inhibitors
in association with pegylated interferon and ribavirin

The two first protease inhibitors, boceprevir (Victrelis®) and
telaprevir (incivo®) were launched in 2011 and tri-
ple therapy with PI plus PEG-IFN/RBV (PR) has
become the new SOC for genotype 1 patients. The SVR
rate was increased by nearly 30% with triple therapy
compared with SOC in naïve genotype 1 patients and by
25% to 60%, according to previous treatment response
in treatment-experienced genotype 1 patients (31–34).
However, this progress in HCV genotype 1 treatment is
associated with an increased rate of adverse events such
as a two fold increase in anaemia and new side effects
such as dysgeusia, observed in nearly 1/3 of the patients
on the boceprevir regimen as well as a rash observed in
55% of the patients on telaprevir regimen. There was a
slight increase in severe adverse events compared with
SOC (7% vs 3% with boceprevir and 11–14% vs 5–9%
with telaprevir) as well as in treatment withdrawal
because of adverse events (8–16% vs 2–16% with boce-
previr and 8–14% vs 4% with telaprevir).

Treatment-response with boceprevir in genotype 1
patients with severe fibrosis or cirrhosis

The absence of cirrhosis is one of the baseline predictive
factors of response to triple therapy with boceprevir
with an odds ratio for SVR of 2.5 (95% CI 1.04–4.6)
(P = 0.003) in naïve genotype 1 patients (31). In a phase
III trial in naïve genotype 1 patients, 100/1097 patients
had either severe fibrosis (47) or cirrhosis (53) (31). The
baseline characteristics of patients with severe fibrosis or
cirrhosis were identical to those with milder fibrosis
except for age (mean 52 ± 8 years vs 49 ± 9 years).
Patients were randomized into three treatment groups.
PR was administered in all groups for 4 weeks (lead-in
phase). Group 1 then received PR for 44 weeks (SOC),
group 2 received boceprevir plus PR for 24 weeks, those
with detectable HCV RNA between weeks 8 and 24
received PR for an additional 20 weeks [response-
guided therapy (RGT)] and group 3 received boceprevir
and PR for 44 weeks (fixed-duration therapy (FDT)).
The SVR rates in patients with advanced fibrosis were
52% in the triple regimen FDT arm, 41% in the triple
regimen with RGT arm and 38% with SOC, whereas
SVR rates were 67% with the triple regimen and 38%
with SOC in patients with milder fibrosis stage (Fig. 1)
(35). SVR rates were increased by 14% compared with
SOC in patients with F3/F4 compared with nearly 30%
in patients with mild or moderate fibrosis. The relapse
rate was also more frequent in patients with severe
fibrosis or cirrhosis compared with patients with less
advanced fibrosis (12–18% vs 9%) (35). An RVR during
triple therapy with boceprevir (treatment week 8) was
frequent (46%) and allowed the duration of treatment
to be shortened in patients with no or low stage fibrosis
(35). However, RVR was less frequent in patients with
severe fibrosis or cirrhosis, (25%) and the SVR rate was
higher in patients achieving RVR who received 48 weeks
of treatment (92%) compared with those who received
RGT (75%), which is not the case in patients with wild
milder fibrosis (98% and 96% respectively). Overall,
naiïve genotype 1 patients with severe fibrosis or cirrho-
sis benefit from the triple regimen but should receive a
fixed treatment duration.

In a phase III trial in treatment-experienced patients
(relapsers or partial responders), 78/403 patients had
either severe fibrosis (29) or cirrhosis (49) (33). Patients
were randomized into three treatment groups. PR was
administered for 4 weeks (lead-in phase). Group 1 then
received PR for 44 weeks, group 2 received boceprevir
plus PR for 32 weeks, patients with detectable HCV
RNA at week 8 received PR for an additional 12 weeks
(RGT) and group 3 received boceprevir plus PR for
44 weeks (FDT). The SVR rates in patients with
advanced disease were 68% with the FDT triple regimen
(48 weeks), 44% with the triple regimen RGT and 13%
with SOC, while SVR rates were 67% with the triple
regimen and 23% with SOC in patients with milder stage
fibrosis (Fig. 2) (35). SVR rates were increased by 42%
compared with SOC in patients with F3/F4 and nearly
44% in patients with no, mild or moderate fibrosis.
According to previous treatment response, SVR rates
were increased in all boceprevir regimen patients com-
pared with SOC in both prior relapsers or partial
responders irrespective of stage of fibrosis (Fig. 3). The
relapse rate was more frequent in patients with severe
fibrosis or cirrhosis than in those with less advanced
fibrosis (21% vs 11%). Week 4 lead-in response was pre-
dictive of SVR. RVR under triple therapy with bocepre-
vir (treatment week 8) occurred in 53% of the patients
and allowed the duration of treatment to be shortened
in patients with no or low stage fibrosis. An RVR was
achieved in 25% of the patients with severe fibrosis or
HCV cirrhosis treatment

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Treatment-response with telaprevir in genotype 1 patients with severe fibrosis and cirrhosis

In the two phase III trials with telaprevir (32, 36) 380 naïve genotype 1 patients/1628 had either severe fibrosis (251) or cirrhosis (129).

In the ADVANCE study 1088 patients were randomized into three treatment groups (32). Group 1 received telaprevir plus PR for 12 weeks (T12PR) followed by PR alone for 12 weeks if HCV RNA was undetectable at week 4 and 12, or for 36 weeks if HCV RNA was detectable at either time point. Group 2 received telaprevir and PR for 8 weeks and placebo plus PR for 4 weeks (T8PR) followed by 12 or 36 weeks of PR on the basis of the same HCV RNA criteria. Group 3 received PR for 48 weeks (SOC). The SVR rates in patients with advanced fibrosis were 62% with the triple regimen T12PR, 53% with the triple regimen T8PR and 33% with SOC while the SVR was 76% with the triple regimen and 47% with SOC in patients with milder stage fibrosis (Fig. 4). The SVR rate in patients with F3/F4 was increased by 10–30% compared with SOC and by nearly 30% in patients with no, mild or moderate fibrosis.

In the ILLUMINATE study 540 patients received telaprevir plus PR for 12 weeks followed by PR (36). Patients who had an extended RVR (eRVR) (undetectable HCV RNA at week 4 and 12) were randomly assigned to receive PR after week 20 for 4 more weeks (T12PR24) or 28 more weeks (T12PR48). Patients without an eRVR were assigned to T12PR48. The SVR rate was 63% in patients with advanced fibrosis vs 75% in patients with mild or moderate fibrosis. An eRVR was frequent under triple therapy with telaprevir: 58% with the T12PR regimen in the ADVANCE study and 60% in the ILLUMINATE study. However, an eRVR was less frequent in patients with severe fibrosis or cirrhosis (46% and 49% respectively). Moreover, the SVR rates were higher in patients who achieved an eRVR and received 48 weeks of treatment 88% than in those who received 24 weeks of treatment 82%, which was not the case in patients with milder fibrosis (87% and 95%...
respectively) (Fig. 5). Overall, naïve genotype 1 patients with severe fibrosis or cirrhosis benefit from the triple regimen with telaprevir but should receive the T12PR48 regimen, especially patients with cirrhosis.

In the phase III trial in treatment-experienced genotype 1 patients (relapsers, partial responders or non-responders), 316 (48%)/663 patients had either severe fibrosis (147) or cirrhosis (169, 25%) (34). Patients with cirrhosis were slightly older (54 years vs 50 years) and more likely to be prior non-responders (36% vs 25%) (37). Patients were randomly assigned to three groups. Group 1 (T12PR48) received telaprevir for 12 weeks and PR for a total of 48 weeks, group 2 (lead-in T12PR48) received PR for 4 weeks followed by 12 weeks of telaprevir and PR for a total of 48 weeks and group 3 which received PR for 48 weeks. The SVR rates were identical for all telaprevir regimens. The SVR rates were increased in the telaprevir regimen compared with SOC irrespective of the stage of fibrosis, 75% vs 22% in patients with minimal or moderate fibrosis, 67% vs 7% in patients with bridging fibrosis and 47% vs 10% in patients with cirrhosis. The SVR rates were increased with the telaprevir regimen compared with SOC in previous relapsers irrespective of the stage of fibrosis (34). The SVR rates were higher with the telaprevir regimen compared with SOC for previous partial responders and non-responders. However, the benefit decreased in those with advanced fibrosis (Fig. 6). The SVR rates were lower in patients with cirrhosis than in those without, except for previous relapsers, however, the effect of telaprevir treatment was maintained compared with PR. The relapse rate was higher in patients with cirrhosis and a previous partial or null-response than in those without cirrhosis (10% vs 4%). A high baseline ALT or AST and prior PR response was predictive of an SVR in multivariate analysis in patients with cirrhosis. There was no association between the presence or level of telaprevir resistance and the stage of fibrosis in patients who failed the telaprevir regimen. Rash, pruritus and anemia were more frequent in patients with cirrhosis who received telaprevir (43%, 55% and 44% respectively) than in those who received PR (27%, 35% and 27% respectively). Adverse events led to telaprevir discontinuation in 15% of patients with cirrhosis and 11% of those without (37).

Conclusions
The first generation of protease inhibitors plus PEG-IFN/RBV treatment represents a major advancement in the treatment of both in naïve and treatment-experienced genotype 1 patients with compensated cirrhosis. The greatest benefit seems to be found with both drugs in patients with cirrhosis who are previous relapsers. There seems to be less benefit in patients with a previous null-response and this should be weighed against the increase in side effects. There are no data on the efficacy of the triple regimen in patients with decompensated cirrhosis. Patients with cirrhosis need to be carefully followed-up during treatment because of an increase in side effects that may be even greater in the real-life setting than in clinical studies.

Conflicts of interest
The authors have not declared any conflicts of interests.

References

Fig. 5. Sustained virological response with telaprevir regimen in naïve genotype 1 patients according to fibrosis stage and extended rapid virological response.

Fig. 6. Sustained virological response with telaprevir regimen in treatment-experienced genotype 1 patients according to fibrosis stage and previous treatment response.


