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REVIEW ARTICLE

Patients with HCV and F1 and F2 fibrosis stage: treat now or wait?

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Abbreviation
HCV hepatitis C virus; PEG-IFN peginterferon; RVR rapid virological response; RBV ribavirin; SOC standard of care; SVR sustained virological response.

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Abstract
The current standard of care (SOC) for patients with chronic HCV genotype 1 is a combination of either boceprevir or telaprevir with peginterferon (PEG-IFN) and ribavirin (RBV). Although it is effective in a high percentage of patients, this treatment is associated with significant adverse events (AEs). The next generation of protease inhibitors, simeprevir and faldaprevir, will also be used with PEG-IFN/RBV. Interferon-free therapy with sofosbuvir appears promising and on the horizon for patients with genotypes 2 and 3, but may still be many years away for patients with HCV genotype 1. The factors which should be considered when deciding whether to treat a patient with HCV and mild fibrosis with the current SOC now, or to delay treatment until less toxic and/or more effective therapy is available is discussed.

The current standard of care (SOC) for the treatment of chronic hepatitis C virus (HCV) genotype 1 is the combination of a protease inhibitor, peginterferon (PEG-IFN) and ribavirin (RBV) (1). Two protease inhibitors are currently available: boceprevir and telaprevir. Either of these triple therapy combinations is significantly more effective in achieving a sustained virological response (SVR) than the previous SOC, PEG-IFN/RBV (2–5). An improvement in SVR with triple therapy is observed in nearly all patient populations (treatment-naïve or prior PEG-IFN/RBV failure) and subpopulations (race, ethnicity, degree of fibrosis, viral load or IL28B status).

The main limitation of telaprevir or boceprevir triple therapy is the adverse events (AEs) associated with treatment. These are more frequent and severe than those observed with PEG-IFN/RBV dual therapy (2–5). The most significant of these AEs is anaemia, which develops in about 35–40% of patients. Approximately half of all patients treated with telaprevir also develop a rash and 25% develop gastrointestinal symptoms. Boceprevir may also cause dysgeusia. These AEs lead to somewhat higher dropout rates during treatment than observed with PEG-IFN/RBV and increase the complexity of managing HCV treatment by the practitioner.

The treatment of chronic HCV genotype 1 is evolving rapidly (6). Two new protease inhibitors simeprevir (TMC-435) and faldaprevir (BI 201335) are currently completing phase 3 clinical trials. Both of these protease inhibitors are also utilized with PEG-IFN/RBV. Although both appear to have SVR rates that are similar to current protease inhibitors, these two agents have a more favourable adverse event profile and a lower pill burden. Enrolment is also complete in the phase 3 clinical trial with the polymerase inhibitor sofosbuvir (GS-7977 formerly PSI-7977) along with PEG-IFN/RBV. In addition, preliminary studies with various combinations of protease inhibitors, polymerase inhibitors, polymerase complex inhibitors and non-nucleoside polymerase inhibitors have recently demonstrated that a combination of anti-viral agents can also lead to SVR in a high percentage of patients without interferon. Many of these studies will be summarized during the 2013 Paris Hepatitis Conference and appear in this supplement of Liver International. Based on these preliminary studies, three large clinical trials evaluating interferon-free therapy utilizing 2–3 anti-viral agents with or without RBV will be initiated before the end of 2012. The phase 3 clinical trials that are either nearing completion, fully enrolled or expected to be initiated during 2012 are summarized in Table 1.

These events have made healthcare providers question whether they should continue to treat patients with

Table 1. Phase 3 clinical trials for hcv treatments, which are either nearing completion, fully enrolled or expected to be initiated during 2012

Genotype	Anti-viral agents	Peginterferon/ ribavirin	Available
1	Simeprevir	Peginterferon + ribavirin	2013–2014
1	Faldaprevir	Peginterferon + ribavirin	2013–2014
1,4,5,6	Sofosbuvir	Peginterferon + ribavirin	2013–2014
2, 3	Sofosbuvir	Ribavirin	2013–2014
1	Sofosbuvir + GS5855	Ribavirin	Unknown
1	Faldaprevir + BI207127	± ribavirin	Unknown
1	ABT-450 + ABT-267 + ABT-333 + ritonavir	Ribavirin	Unknown

chronic HCV using our currently available therapy or wait until the next generation of medications is available. This manuscript will discuss the pros and cons of this dilemma.

Results with our current therapies – The argument to treat now

The combination of either boceprevir or telaprevir with PEG-IFN/RBV is highly effective for the treatment of chronic HCV. In general, the results observed with these two treatment regimens yield similar SVR rates (2–5). A comparison of the treatment paradigms and results for these two protease inhibitors was presented by one of these authors (MLS) at the 2012 Paris Hepatitis Conference (7).

Patients who are treatment-naïve achieve SVR rates of 70–75% (2,3). Predicting treatment success in the treatment-naïve population can be further refined by assessing the IL28B genotype. Patients with IL28B genotype CC are highly responsive to interferon and have SVR rates of about 80–90%. In contrast, patients with IL28B genotype TT are relatively insensitive to interferon and have SVR rates in the range of 50–66% (8). SVR rates are also reduced in African Americans, patients with high viral load and patients with advanced fibrosis or cirrhosis (2, 3). However, given the potency of triple therapy utilizing a protease inhibitor, the negative impact of these factors on SVR is far less when compared with that observed with peginterferon and ribavirin dual therapy (8).

Approximately 60% of patients who initiate the current SOC achieve an extended rapid virological response (RVR). These patients are HCV RNA undetectable within 4 weeks of adding the protease inhibitor and if they remain HCV RNA undetectable, their triple therapy treatment can be shortened to 24 weeks (1, 6, 9). The SVR rate in these patients exceeds 90–95%. A retrospective analysis of the telaprevir phase 2 trial has suggested that patients with IL28B genotype CC could potentially shorten treatment to as little as 12 weeks without influencing this very high SVR rate (10). A phase 4 prospective study is currently underway.

In those patients who do not achieve an RVR, a delayed virological response, where the patient becomes HCV RNA undetectable before treatment week 24, is still associated with an SVR rate of 64–75% if these patients remain HCV RNA undetectable throughout the 48-week treatment regimen (2–5, 7). A delayed virological response occurs in about 15–20% of HCV patients. This is more common in patients who are relatively interferon insensitive as determined by IL28B genetic testing or their previous virological response to interferon and ribavirin.

The success of retreatment in patients who previously failed to achieve SVR with PEG-IFN/RBV is also related to interferon responsiveness. This can be assessed by IL28B genetics but also by the virological response pattern of the previous treatment. Patients with a prior relapse have already defined themselves as being interferon responsive. These patients have the highest SVR rates during retreatment with either boceprevir or telaprevir: in the range of 75–88%. Patients with a prior partial response have SVR rates of about 50–60% and patients who are insensitive to interferon or had prior non-response achieve an SVR of only about 33% when retreated with the current triple therapy regimens (4, 5).

One of the keys to achieving an SVR is to aggressively manage the AEs of triple therapy. This is particularly important for anaemia, which occurs in nearly half of all patients whatever the protease inhibitor utilized (2–5). It is now well accepted that the best way to manage anaemia is to reduce the dose of RBV. Both retrospective and prospective controlled trials have demonstrated that RBV dose reduction has no significant impact on SVR in patients receiving IFN/RBV dual therapy or triple therapy with a protease inhibitor as long as treatment is not interrupted or prematurely discontinued (11–14). Reducing the dose of RBV and/or IFN significantly eases the AEs of treatment and helps patients to complete therapy.

Because of the effectiveness of current agents, there are very few disadvantages to treating patients with the current SOC. This is especially true in patients who have favourable response characteristics and are expected to have SVR rates that exceed 75%. These include patients with IL28B genotype CC, patients with prior relapse or a partial virological response to PEG-IFN/RBV and patients with a low viral load. It is extremely unlikely that future therapies will lead to higher SVR rates in these sub-populations.

Future protease inhibitors – The argument to wait

Two new protease inhibitors simeprevir (TMC-435) and faldaprevir (BI 201335) are currently completing phase 3 clinical trials. Like the current protease inhibitors, these agents will be utilized with PEG-IFN/RBV. In

phase 2 clinical trials, the overall SVR rates in the treatment-naïve population with either of protease inhibitors is 70–85% (15, 16). In patients with a prior partial response to PEG-IFN/RBV, SVR rates of approximately 40–70% were observed. Prior non-responders had SVR rates of only 30–50%. These results are similar to those observed with the current SOC (17, 18).

Both of these new protease inhibitors will follow the same response-guided therapy paradigm as currently employed. In phase 2 clinical trials, approximately 80% of treatment-naïve patients who received simeprevir or faldaprevir achieved an extended RVR and were treated for only 24 weeks (15, 16). The SVR rate observed in these patients was over 90%, which is also quite similar to the current SOC.

The advantages of these two new protease inhibitors are the reduced pill burden and a more favourable adverse event profile. Both faldaprevir and simeprevir are dosed once a day. In addition, neither of these two protease inhibitors appears to exacerbate anaemia compared with PEG-IFN/RBV. An increase in unconjugated bilirubin and rash has been observed with faldeprevir.

Both simeprevir and faldaprevir are expected to be available for HCV treatment in late 2013 or early 2014. The reduced pill burden and more favourable AE profile compared with telaprevir and boceprevir are the primary arguments to defer therapy until these new agents are available.

Future polymerase inhibitors – The argument to wait

The only nucleoside polymerase inhibitor which has advanced to phase 3 clinical trials is subosfovir (GS-7977). In a phase 2 clinical trial, 177 patients with HCV genotypes 1, 4 or 6 were treated with subosfovir, PEG-IFN/RBV for either 12 or 24 weeks (19). An RVR was observed in approximately 95% of patients and an SVR was achieved in 90%. No virological breakthrough was observed. Subosfovir is administered once a day and can be taken with or without food. AEs were similar to that observed with PEG-IFN/RBV. A phase 3 clinical trial evaluating 12 or 24 weeks of subosfovir, PEG-IFN/RBV in patients with genotypes 1, 4, 5 and 6 is now fully enrolled. This treatment is expected to become available for patients with chronic HCV by mid-2014.

The primary rationale for deferring therapy and waiting for subosfovir is the higher SVR rates that appear to be achieved with this polymerase inhibitor. This drug is also easier to administer. It is taken only once a day and there is no food effect. However, subosfovir will be taken with PEG-IFN/RBV in patients with HCV genotype 1.

Interferon free therapies – The argument to wait longer

The development of multiple classes of anti-viral agents for HCV has led to the use of multi-drug treatment. Phase 2 clinical trials have been performed with several of these combinations.

In a small phase 2 study, the combination of sobosfovir and RBV was administered for 12 weeks to 25 treatment-naïve patients with HCV genotype 1 and 10 prior non-responders to PEG-IFN/RBV. All 25 treatment-naïve patients were HCV RNA undetectable by treatment week 4 and 88% achieved an SVR. Nearly half of these patients were IL28B genotype CC and all had mild fibrosis. All 10 non-responders also responded well to sobosfovir and were HCV RNA undetectable by treatment week 4. However, nearly all of these patents relapsed after 12 weeks of treatment. An SVR was only achieved in 11% of the prior non-responders (20).

In a large phase 2 clinical trial, the combination of faldaprevir and BI207127 a non-nucleoside polymerase inhibitor, was used with or without RBV for 16, 28 or 40 weeks in 362 treatment-naïve patients with chronic HCV (21). An SVR of 68% was achieved with the triple oral-therapy combination. Without RBV, the SVR rate was only 39%, showing the importance of RBV for the eradication of HCV. As in previous studies using PEG-IFN, patients with IL28B genotype CC, HCV genotype 1B and patients without cirrhosis had higher SVR rates than patients with the non-CC IL28B genotypes, HCV genotype 1A and cirrhosis respectively.

Two small phase 2 clinical trials have been performed with the protease inhibitor ABT-450. This agent is dosed with ritonavir to enhance half-life and improve antiviral potency. ABT-450/ritonavir was used in combination with the non-nucleoside polymerase inhibitor ABT-333 and RBV in 23 treatment-naïve patients with HCV genotype 1 and 17 previous non-responders to PEG-IFN/RBV. All patients received 12 weeks of treatment. An RVR was achieved in 90% and an SVR in 95% of the treatment-naïve patients. In contrast, only 77% of patients who failed previous PEG-IFN/RBV therapy achieved an RVR and an SVR was observed in only 47% (22). The second study combined ABT-450/ritonavir and ABT-072, another non-nucleoside polymerase inhibitor. Eleven treatment-naïve HCV genotype 1 patients, all of whom were IL28B genotype CC, were enrolled. All achieved an RVR, and 91% achieved the classic definition of SVR, and remained HCV RNA undetectable 24 weeks after treatment was stopped. However, during long-term follow-up, 1 additional patient developed virological relapse 36 weeks after stopping treatment (23).

Three large phase 3 clinical trials using interferon-free multi-drug oral therapy will be initiated before the end of 2012. Approximately 20% of the patients enrolled in each of these studies are expected to have cirrhosis. Patients who have received prior treatment with PEG-IFN/RBV with or without a protease inhibitor will be excluded. The pharmaceutical sponsor and basic design of these three trials are as follows:

(i) Gilead: sobosfovir a nucleotide polymerase inhibitor in combination with several doses of GS-5855 an NS5A inhibitor with and without RBV for either 12 or 24 weeks.
(ii) Abbott: ABT-450 a protease inhibitor, ABT-267 an NS5A inhibitor, ABT-333 a non-nucleoside polymerase inhibitor, and RBV all administered for 12 weeks.
(iii) Boehringer Ingelheim: faldaprevir, BI207127 a non-nucleoside polymerase inhibitor, and RBV for 16 or 24 weeks.

Marketing of these treatments will depend upon the SVR rates achieved in the trials and whether companion studies in patients previously treated with PEG-IFN/RBV (with or without a protease inhibitor) are required for regulatory approval. Although these studies are very encouraging, actually deferring current HCV therapy for an interferon-free regimen may take several years, and thus waiting may not be appropriate for all patients with HCV.

Genotypes 2 and 3

The current protease inhibitors have essentially no antiviral activity against HCV genotype 3 and are minimally effective in HCV genotype 2 (24). The current SOC for these patients continues to be PEG-IFN/RBV. The SVR rates in patients with these genotypes are also influenced by the IL28B genotype, viral kinetics and based on response-guided therapy. Patients with an RVR have SVR rates that exceed 90% after 24 weeks of treatment (25, 26). In contrast, the SVR rates in patients who do not achieve an RVR are only about 50% after 24 weeks of treatment. A retrospective analysis and a recently completed randomized controlled clinical trial have shown that extending therapy from 24 to 48 weeks improves the SVR to 66–75% in these slower responders with HCV genotypes 2 and 3 (27, 28).

In a small pilot study, the polymerase inhibitor subosfovir (GS-7977) combined with RBV resulted in an SVR in 10/10 patients with just 12 weeks of treatment (29). Two phase 3 clinical trials evaluating the effectiveness of this dual combination in patients with HCV genotypes 2 and 3 are nearly completed. One study includes treatment-naïve patients, patients who have contraindications to PEG-IFN, are intolerant to PEG-IFN or refuse to be treated with PEG-IFN. The other study includes patients who failed previous treatment with PEG-IFN/RBV. Both studies include patients with cirrhosis and significant thrombocytopenia. The results of these studies are eagerly awaited.

The obvious reason to defer therapy in patients with HCV genotypes 2 and 3 is to avoid using PEG-IFN. However, for the moment, the SVR rate in patients with HCV genotypes 2 and 3 has not been confirmed in large studies, with various IL28B genotypes and cirrhosis.

Genotype 4

Genotype 4 is the most common HCV genotype in Egypt and many Middle Eastern countries (30). SVR rates in response to PEG-IFN/RBV tend to be somewhat higher in patients with genotype 4 than genotype 1. As is observed in patients with other HCV genotypes, SVR rates in patients with HCV genotype 4 are also influenced by IL28B genotype, viral load and the degree of hepatic fibrosis (31).

To date, neither current nor next-generation protease inhibitors (simeprevir and faldaprevir) have been shown to be effective in patients with HCV genotype 4 in clinical trials.

Danaprevir is a protease inhibitor with activity against genotype 4 and in a recently completed phase 2 study, 100% of genotype 4 patients achieved an SVR (32). It is unclear if additional studies with danaprevir are planned.

Subosfovir is active against HCV genotype 4 and these patients were included in a previous phase 2 study (20). However, the SVR rate in the genotype 4 subpopulation enrolled into this study has not yet been reported. Patients with HCV genotype 4 are included in the phase 3 clinical trial utilizing subosfovir, PEG-IFN/RBV.

Because of the uncertain future of daneprevir and the lack of data on subosfovir, chronic HCV genotype 4 patients should be treated now rather than delaying therapy.

The impact of disease severity

Several studies have shown that most patients with chronic HCV develop progressive fibrosis and may eventually develop cirrhosis (33). The progression of fibrosis appears to be non-linear and accelerates with increasing inflammation and fibrosis (34). For simplicity sake, fibrosis can be estimated to progress 1 Metavir unit every 5 years. Progression appears to be faster in patients who were older when they acquired HCV, who have high alcohol consumption and with HIV co-infection. Patients with advanced fibrosis and cirrhosis are at risk of hepatic decompensation and of developing hepatocellular carcinoma (35). The latter appears to be significantly increased in patients with a platelet count of less than 100 000 (36).

The ability to accurately assess liver fibrosis is less than ideal. Liver biopsy is an invasive procedure and although it is still considered the ‘gold standard’, it is subject to sampling error (37). While it is still used in the USA, it has been largely replaced in Europe and other areas of the world by serum markers of fibrosis and/or fibroscan. Although these tools are excellent at identifying patients with cirrhosis, the results to discriminate the stages of fibrosis between F1 and F3 are not accurate or reproducible.

When deciding whether to treat a patient with HCV now, or to defer treatment, most clinicians would decide to treat patients with bridging fibrosis and cirrhosis (Metavir stages 3 and 4) now because they have an increased risk of hepatic decompensation and hepatocellular carcinoma. There is a feeling by many that patients with less severe fibrosis can wait for better or less toxic therapies. The irony of this approach is that HCV treatment is more successful in patients with mild than advanced fibrosis. This is true whatever the baseline factors including genotype, race and IL28B status and whether patients are being treated with PEG-IFN/RBV dual therapy or triple therapy with a protease inhibitor (2–5). Future HCV treatments will probably also be less effective in patients with advanced fibrosis and cirrhosis. Excluding patients with mild fibrosis from treatment now will only reduce the overall SVR rate in the treated population, increase the overall cost per SVR, and most importantly increase the risk that a patient who could be 'cured' of HCV now fails to achieve SVR in the future.

Conclusions

In the past 20 years, great advances have been made in the ability to 'cure' HCV. Within the next several years, treatment will probably become more tolerable, easier to administer and lead to even higher rates of SVR. Since the first study demonstrating that an oral antiviral agent could suppress HCV, many clinicians have been telling their patients with mild disease to 'wait 5 years' until better therapy becomes available. Some clinicians are still telling their patients the same thing 5–10 years later. Unfortunately, while waiting for better therapies, many of these patients have developed advanced fibrosis and now have a lower probability of achieving an SVR.

This article has summarized the current treatment for HCV and looks ahead at treatments that may be available in the near future. The factors that should be used to decide if patients should be treated now or treatment should be delayed are presented in Table 2. There is little reason to delay treatment in most patients who can achieve a favourable response with current standard of care. An SVR now is one less thing for these patients to worry about in the future. In contrast, in patients who would have a less favourable outcome with the current standard of care, watchful waiting until treatment improves could be an option. How long these patients may need to wait for the 'perfect' therapy remains to be seen.

Table 2. Factors which affect the decision to treat now or delay therapy

	Treat now	Delay treatment
Ethnicity	Non-black	Black
Viral load	Low	High
IL28B genotype	CC	TT
Fibrosis	F0–F2	F3, F4
Previous treatment	Naïve Prior relapse Prior partial response	Prior null response
Interferon		Relative contraindication or previous intolerance

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The authors have no disclosure.

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