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## Treatment of Hepatitis C in the Pre-DAA's Era: Treat Now or Wait for New Medications?



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### INTRODUCTION

The development of small molecules that specifically target the hepatitis C protease has entered phase 3 clinical development and holds great promise in enhancing the treatment response rate. Telaprevir and boceprevir, which belong to a class of agents that will be known as DAA's (Direct-Acting Anti-virals), are the two products currently in phase 3 development. While these products will likely increase the number of patients who are able to achieve viral clearance, their use will be associated with increased toxicity and cost, as well as complexity of treatment.

With the promise of new therapies on the horizon, physicians and patients often wonder: Is it best to proceed with the available therapy or wait for the new medications to be approved for general use? The decision to treat now or wait is not always easy and should be individualized. This paper presents the advantages and disadvantages of treating now versus waiting and provides a framework for physicians to discuss treatment alternatives with their patients.

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### GENERAL APPROACH TO THE PATIENT

New information regarding the natural history of hepatitis C and factors affecting response to therapy suggest that postponing antiviral therapy may not be the best strategy, even in patients with mild disease at presentation.

Previously, it was believed that fibrosis progression in hepatitis C infection was linear and patients who did not progress over the initial 20 to 25 years of infection were likely to remain with mild disease. Recent information challenges that concept and shows that the rate of progression to advanced fibrosis is not linear (1) and may rapidly increase after ages 40–45 years (2,3) even in patients who previously progressed slowly. Thus, a slow progression of fibrosis over several decades is no longer a guarantee that future progression will also be slow. This should be taken into account when counseling patients 40–55 years of age who were infected in early adulthood, have mild disease on biopsy, and are unsure whether to proceed with treatment now or assume a wait-and-see attitude.

The second development that questions the strategy of delaying treatment initiation is the realization that over time, patients become older, are more likely to gain weight, or become insulin resistant and could progress to more advanced stages of fibrosis—all of

**Table 1.**  
**Negative Predictors of Response to Peginterferon and Ribavirin Therapy for Hepatitis C.**

**Patient-related factors**

- Non-white ethnicity
- High BMI\*
- Older age\*
- Male gender
- Metabolic syndrome\*
- Diabetes\*

**Disease-related factors**

- Genotype 1 HCV
- Advanced fibrosis (stages 3–4)\*
- High baseline viral load
- Steatosis on liver biopsy\*
- HCV/HIV co-infection

\*These factors are less likely to be present if treatment is started early.

BMI = body mass index; HCV = hepatitis C virus;

HIV = human immunodeficient virus

which decreases the chance of a sustained response to antiviral therapy (4).

With these caveats in mind, when approaching a newly diagnosed hepatitis C patient, the physician should balance the urgency of treatment versus the likelihood of response. Patients who have advanced fibrosis (stages 3–4) should be strongly encouraged to promptly undergo therapy regardless of the likelihood of response. In contrast, patients with milder disease (stages 0–2) should be encouraged to undergo therapy but can decide whether to proceed now or wait 2 to 3 years for future therapeutic options, according to their likelihood of response. Those with multiple negative-predictive factors may decide to wait for newer therapies that may enhance their response, while those with greater likelihood of response may opt for current therapy that is likely to yield attractive response rates and may be less toxic than future regimens. Both the physician and patient, however, should recognize that waiting too long to initiate therapy may result in a decreased likelihood of response after therapy is finally initiated, as many of the negative predictive factors of response appear with increasing age.

### ASSESSING PREDICTORS OF RESPONSE PRIOR TO TREATMENT

Several disease-related and patient-related factors affect response to treatment (5) (Table 1). Patient-related factors that cannot be controlled include ethnicity (eg, African-Americans and Hispanics have a lower response rate), and gender (ie, response rate in males tends to be less than in females). Other patient-related factors, however, can be minimized by early treatment, as many of these factors become more prevalent as the patient ages. Among these factors, a high body mass index (BMI) (6), metabolic syndrome (7), and diabetes are all negative predictive factors and are more likely to occur the longer treatment is postponed and the older the patient becomes.

Likewise, disease-related negative predictive factors may be non-modifiable or may become more prominent as treatment initiation is delayed. Non-modifiable factors include genotype 1 infection and baseline viral load. One negative disease-related predictive factor that can worsen with time is the degree of hepatic fibrosis; the longer treatment is postponed, the higher the likelihood that a patient may progress to advanced fibrosis and will be less responsive to therapy. Hepatic steatosis, another factor that has recently been identified as a marker for progression of fibrosis (8) and lower response to antiviral therapy (9), usually worsens with age and weight gain, two factors that could be avoided by initiating early treatment.

Genotype is perhaps the strongest disease-related predictor of response. Patients infected with genotype 2 or 3 of HCV are much more likely to achieve a response with pegylated interferon and ribavirin therapy than genotype 1 patients. It is not clear if the new drugs likely to become available in the near future will be effective for treating genotype 2 or 3 infection. As the current research has concentrated mainly on genotype 1 patients, it is unlikely that these new medications will come to market with approval for the treatment of genotypes 2 or 3. For that reason, patients infected with genotypes 2 or 3 should undergo therapy with currently available options and should not wait for the approval of new medications.

Another group of patients that should be treated now are those co-infected with HCV and the human immunodeficiency virus (HIV). These patients

progress to fibrosis faster than HCV-monoinfected patients (10) and end-stage liver disease has now become one of the leading causes of death among HIV patients (11). The new drugs under development have not been tested in HCV/HIV-infected patients and their efficacy, interaction with HIV anti-viral drugs, and effect on HIV disease are not known. For these reasons, it is likely that these drugs will not be used in co-infected patients for several years after their introduction into clinical practice. Therefore, this patient group should be treated now, with currently available drugs.

In summary, initiating treatment early in patients with hepatitis C infection—before progression of disease occurs—is more likely to result in sustained viral response. This is, therefore, a strong stimulus for considering treatment with currently available therapies in younger individuals with milder disease and few negative predictive factors; they are likely to have a very good response to current therapy.

### PREDICTORS OF RESPONSE DURING THERAPY FOR GENOTYPE 1 INFECTION

One of the most important advances in the treatment of hepatitis C has been the recognition that sustained response rates can be predicted relatively early into therapy based on virologic response (12). The ability of predicting non-response or an enhanced possibility of response as early as 4 to 12 weeks into therapy makes initiation of therapy more attractive to patients.

Generally, patients infected with HCV genotype 1 are reluctant to initiate a therapy that has approximately a 35% to 40% likelihood of sustained viral response (SVR), that will take a year to complete, and has significant side effects. On the other hand, when patients are informed that by 4 to 12 weeks of therapy the likelihood of response may be predicted more accurately, many are willing to initiate therapy.

Rapid virologic response (RVR) is defined as non-detectable virus at week 4 of therapy. Approximately 20% of genotype 1 patients achieve this milestone and have a 90% chance of sustained response with completion of therapy (13). Selected genotype-1 infected patients who achieve an RVR could be treated for only 24 weeks (short-duration therapy). Short-duration therapy is only recommended for genotype 1 patients with a low baseline viral load (<400,000 IU/mL), who have no cirrhosis on biopsy, become virus-negative in blood by week 4, and are experiencing significant side effects with therapy. For others, the standard 48-week treatment course is recommended, even if an RVR is achieved (14).

A decrease of  $\geq 2_{\log}$  in viral load by week 4 of therapy is a powerful predictor of response and significantly increases chances of SVR in patients who are able to complete the 48-week course of treatment. This is a powerful, positive reinforcement for patients who at week 4 are likely experiencing significant side effects from interferon and wondering if continuation of therapy is a worthwhile endeavor.

**Table 2.**  
Virologic-Response Guided Therapy with Peginterferon and Ribavirin for Genotype 1 HCV Infection

<i>Response</i>	<i>Definition</i>	<i>SVR</i>	<i>Duration of therapy (weeks)</i>
RVR	Negative HCV-RNA at week 4	90%	24 to 48
cEVR	Negative HCV-RNA at week 12	66%	48
pEVR	$\geq 2_{\log}$ decrease in viral load from baseline, but positive HCV-RNA at week 12	45%	Extend to 72
Non-response	$< 2_{\log}$ drop in viral load from baseline at week 12 <b>OR</b> detectable virus at week 24	$< 2\%$	Discontinue

SVR=sustained viral response; RVR=rapid virologic response; cEVR=complete EVR; pEVR=partial EVR

In contrast, patients who have a  $<2_{\log}$  decrease in viral load by week 4 are much less likely to achieve a sustained response, particularly if the viral load at week 4 exceeds  $5.5_{\log}$  IU/mL (15). In this situation, consideration should be given to stopping therapy, particularly in patients with mild disease on liver biopsy who are experiencing significant side effects from therapy.

Treatment-week 12 response, or early virologic response (EVR), has emerged as an important determinant of SVR and duration of therapy. Previously, either non-detectable virus or a  $>2_{\log}$  decrease in viral load from baseline was considered an adequate response; up to 80% of genotype 1 patients achieve this milestone. Because not all patients who achieve an EVR have the same chance of SVR, the EVR is now divided into two types: 1) Complete EVR (cEVR) defined as no detectable virus at week 12 of therapy or 2) Partial EVR (pEVR), defined as a  $>2_{\log}$  decrease in viral load from baseline, but the virus is still detectable (12). Complete EVR can be achieved by 65% of genotype 1 patients treated with peginterferon and ribavirin

and is a much more desirable milestone, as patients that achieve a cEVR have a 66% chance of achieving SVR with 48 weeks of therapy. In contrast, patients achieving a pEVR are less likely to achieve SVR with 48 weeks of therapy (SVR rates of 45%) due to increased rates of relapse (12). These patients could benefit from extending therapy to 72 weeks to maximize the chances of achieving SVR (16). Thus, given the reduced chance for SVR, patients with mild disease on liver biopsy who are unable to achieve a cEVR could consider stopping therapy and waiting for new drugs to reach the market. In contrast, those patients with more advanced fibrosis should continue therapy despite the pEVR and, to maximize response, should consider extending duration of treatment to 72 weeks.

Lack of response to treatment is defined as a  $<2_{\log}$  decrease in viral load by week 12 or any detectable virus at week 24. These patients have  $<2\%$  chance of achieving SVR and treatment should be discontinued at that point. Patients falling into these groups are likely to benefit from re-treatment once newer medications are approved. Table 2 lists the types of response, chance of SVR, and suggested treatment duration based on virologic response to treatment.

**Table 3.**  
**Factors that Should Be Considered When Deciding Timing of Therapy for HCV Infection**

#### Factors that Favor Treating Now

- Stages 3–4 fibrosis
- Genotype 2 or 3 infection
- HCV/HIV co-infection
- None or few negative predictors of response to peginterferon/ribavirin
- Ability to predict response early in treatment course
- Current treatment is less toxic
- Current treatment is less costly
- No concerns about emergence of viral resistance
- Less complex regimen, better adherence

#### Factors that Favor Waiting for New Therapies

- Prior non-response to peginterferon/ ribavirin combination therapy
- Mild fibrosis (Stages 0–1)
- Multiple negative predictors of response to peginterferon/ribavirin
- Shorter duration of therapy more likely with triple-drug regimen
- Increased probability of SVR with triple-drug regimens

### NEW THERAPIES FOR HCV INFECTION ON THE HORIZON

The development of drugs that specifically inhibit HCV replication by inhibiting either the HCV protease or polymerase promises to change the treatment of hepatitis C in the future. Many compounds are currently under development. At the time of this writing, only two of these, telaprevir and boceprevir have reached phase 3 in development and may become available for general use in the next few years. Others are still in early stages of development and it is too soon to predict which ones will emerge as potential therapies.

While both telaprevir and boceprevir are potent inhibitors of HCV replication, resistance emerges promptly and these compounds must be used together with pegylated interferon and ribavirin. The importance of ribavirin was highlighted in the PROVE-2

*(continued on page 18)*

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study of telaprevir, in which patients in the ribavirin-free arm had a relapse rate of 29% compared with 2% in the ribavirin-containing arm; treatment duration was similar in the two groups (17). Thus, it is clear that the next generation of small molecules will be added to currently available therapies, increasing toxicity and cost while hopefully increasing efficacy as well.

New therapies promise to increase the SVR rates for genotype 1 patients and possibly shorten duration of treatment. Triple-therapy regimens of telaprevir in combination with pegylated interferon alfa-2a and ribavirin can achieve SVR rates of 61% to 68% with only 24 weeks of therapy (18). Boceprevir, in combination with pegylated interferon alfa-2b and ribavirin can achieve SVR rates of 56% and 74% for patients in the 28- and 48-week treatment arms, respectively (19). Patients who achieve viral negativity after 4 weeks of triple therapy have the best response rates.

This enhancement in response, however, comes with an increased incidence of side effects. In the PROVE-1 and PROVE-2 trials of telaprevir, gastrointestinal events (such as nausea and diarrhea), skin rashes, and anemia were more frequent in the triple-therapy arm compared with peginterferon and ribavirin alone (17,20). In PROVE-1, a trial conducted in the United States, discontinuation rates were 18% in the triple-therapy arm compared with 4% in the peginterferon/ribavirin arm. In the boceprevir trials, rates of anemia and dysgeusia (altered taste) were higher in the triple-therapy arm than with standard therapy, as were discontinuation rates (26%–28% vs. 14%) (19). It is now evident that there is both an upside and a downside to the newer therapies: efficacy may be higher, treatment duration may be shorter, but discontinuation rates are higher due to toxicity. These factors must be taken into account when deciding whether to treat patients now rather than wait for a more toxic, yet potent, cocktail of medications.

A new concern that emerges with newer therapies is that of viral resistance. With current peginterferon and ribavirin therapy, emergence of resistant variants has not been observed. With the new protease inhibitors, however, *in vitro* analyses have shown that resistant mutations in the NS5B gene are selected in response to protease inhibitors. In general, virologic breakthrough with emergence of resistance appears to

be associated with lower trough serum levels of telaprevir and/or peginterferon (21), highlighting the importance of adherence.

Adherence to the new triple-therapy regimens can be problematic. Both protease inhibitors currently in phase 3 development must be taken every 8 hours, with a “window of opportunity” of 7 to 9 hours between doses. In practice, it is difficult for patients to adhere to such a strict protocol, particularly for the middle-of-the day dose that is often forgotten by patients during a busy work day. It remains to be seen if emergence of resistance and, thus, lower rates of SVR will be noted when these regimens are used in the “real-world” where patients are not as likely to be as compliant in taking their medications compared to research subjects.

The consequences of resistance remain unknown. In the case of telaprevir-resistant mutants, it appears they remain susceptible to interferon and ribavirin; however, only a minority of these patients goes on to achieve a sustained response. It is unknown, however, if the presence of these resistant variants will influence the rate of disease progression and whether patients who develop resistance after treatment with one protease inhibitor will also be resistant to other drugs in the same or different class. Preliminary data suggests that there is considerable overlap in resistance between telaprevir and boceprevir. The concern regarding emergence of resistance will add to the complexity of treatment. Not only will there be a need to monitor for treatment response (as we currently do), but, in addition, new procedures and recommendations will need to be in place to monitor for the emergence of resistance as well as guidelines on how to manage resistance.

## CONCLUSION

In summary, promising new therapeutic compounds may become available for the treatment of HCV on the horizon. These drugs will be added to currently available medications to enhance response, resulting in triple-therapy cocktails of variable duration. While the number of patients reaching SVR is likely to be higher, toxicity and cost will also be increased. The number of patients discontinuing therapy due to toxicity will double or triple compared to current therapy. Development

of resistance is a concern and may have unknown effects on the long-term natural history of the disease. These considerations highlight the fact that triple therapy is not a panacea and may not be the best option for all patients who are in need of therapy at present. Consideration should be given to treating patients now, many of whom will be able to achieve a sustained response without the added concerns of triple therapy.

## PRACTICAL RECOMMENDATIONS

When making the decision whether to treat now or wait, the clinician must balance the benefits of the current less toxic, simpler regimen with a possibly lower SVR rate versus a potentially higher SVR rate with higher toxicity, complexity, adherence issues, and risk of resistance development associated with the new therapeutic cocktails. The ability of early prediction of response with current therapy makes a therapeutic trial with current medications appealing to many patients, particularly those with few or no negative predictors of response.

Patients with advanced fibrosis or with disease characteristics that increase the likelihood of response to current therapy should probably be treated now. Newer treatments may be best reserved for those who have failed currently available therapy, do not achieve an acceptable EVR with current therapies, or are less likely to achieve a response to current therapy based on pre-treatment characteristics. Table 3 lists the considerations that should be reviewed with patients when deciding whether to embark on therapy with options available today, or wait for newer therapies that are in development. ■

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