ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

Section Editor: Eugene R. Schiff, MD

Exploring the Possibility of an Interferon-Free Treatment Regimen for Hepatitis C Virus Infection

Mark Sulkowski, MD
Associate Professor of Medicine
Medical Director, Viral Hepatitis Center
Johns Hopkins University School of Medicine
Baltimore, Maryland

G&H What are the disadvantages of interferon-based therapy for hepatitis C virus infection?

MS There are 2 main limitations to interferon-based therapy. One is that patients' response to interferon is heterogeneous; some patients respond well to interferon, but others do not respond very well to this therapy. The second problem is that interferon is associated with significant side effects, ranging from fatigue to mood disorders. Even in patients for whom interferon is effective, its side effects can make it very challenging to take.

G&H Will the launch of boceprevir and telaprevir facilitate a shift toward interferon-free treatment for hepatitis C virus infection?

MS Telaprevir and boceprevir will not facilitate a shift to interferon-free treatment in and of themselves; once these drugs become available, they will be used in combination with pegylated interferon (peginterferon) and ribavirin. However, it is important to note that the addition of telaprevir and boceprevir will markedly improve the hepatitis C cure rate, both in patients who respond well to interferon and in those who do not. However, since these drugs will be used in combination with interferon and ribavirin, patients will still experience the side effects associated with interferon, plus the side effects associated with the new drugs.

Nonetheless, boceprevir and telaprevir will take us a large step closer to where we want to be with respect to hepatitis C virus (HCV) treatment. These drugs are the first in what promises to be a wave of new direct-acting antiviral (DAA) agents that will target HCV in different ways. Some of these drugs, like boceprevir and telaprevir, will focus on the protease, but other drugs will focus on the polymerase, NS5A, or other targets.

G&H Could an interferon-free treatment regimen be developed using these new drugs?

MS Clinical trial investigators are currently testing the concept of an interferon-free HCV treatment regimen by combining hepatitis C protease inhibitors with other DAA agents. For example, the INFORM-1 study, published in *The Lancet*, combined a protease inhibitor with a nucleoside analogue polymerase inhibitor. While this study was relatively small and treated patients for only 14 days, it showed that an interferon-free treatment combination could achieve viral suppression in HCV patients, including those who had previously failed to respond to peginterferon and ribavirin.

Other studies have looked at other interferon-free drug combinations. To date, however, these have been relatively small, proof-of-concept studies. Three such studies were presented at the 2010 meeting of the American Association for the Study of Liver Diseases: One study tested a non-nucleoside polymerase inhibitor plus a protease inhibitor with or without ribavirin; another study looked at a non-nucleoside polymerase inhibitor plus a protease inhibitor with ribavirin; and a third study examined an NS5A inhibitor plus a protease inhibitor.

Overall, these studies were very interesting. First, they demonstrated that ribavirin has an important role in the suppression of HCV replication in the absence of interferon. Second, they demonstrated that viral suppression could be achieved in some patients over a 28-day period. Interestingly, the most impressive results in these studies were seen in patients who received a regimen that has been termed "QUAD" therapy: a combination of peginterferon, ribavirin, and 2 DAA agents.

G&H If an interferon-free regimen is developed, which patients would be the best candidates for such treatment?

MS We do not yet know which patients might be candidates for interferon-free HCV therapy. Interferon works very well for some patients, particularly individuals with a favorable interleukin (IL)-28B genotype, so some clinicians may want to continue using interferon in certain patient groups. On the other hand, nearly 100% of patients who receive interferon experience side effects. If the side effect profile of a DAA combination regimen is more favorable than that of interferon and the response rate is high, then I would anticipate that almost all patients would want to switch to a more easily tolerated regimen.

G&H Are there some patients who will always require interferon as part of their treatment regimen?

MS Whether we would need to continue interferon-based therapy in select patients is the subject of much debate, but the hope among researchers is that we can develop a regimen that would be highly effective across a wide range of patients and HCV genotypes: A single, all-oral regimen for most HCV-infected patients is the goal.

G&H What might an interferon-free DAA treatment combination look like?

MS Most of the combinations being considered consist of multiple drugs that target HCV via different mechanisms of action. Drugs currently in development include polymerase inhibitors, both drugs that directly target the active site of the nucleos(t)ide and non-nucleoside polymerase inhibitors; protease inhibitors, such as telaprevir and boceprevir; NS5A inhibitors that bind to and block replicase function; medications that target cyclophilins, a host factor that the virus uses in its replication cycle; and entry-inhibitor drugs that block HCV entry into the liver cell. In order to prevent viral resistance, these drugs will almost certainly be used in combination. However, we do not yet know which drugs will be used or in which combinations, nor do we know whether ribavirin will remain a necessary part of the treatment regimen. Answering these questions will require more studies and is currently the focus of many researchers.

G&H Would it be possible to shorten the duration of treatment with some of these combinations?

MS When telaprevir and boceprevir are added to peginterferon and ribavirin, we will be able to shorten the duration of treatment from 48 weeks to 24 weeks in approximately two thirds of HCV genotype 1–infected patients. Currently, we are very focused on duration of therapy because interferon is difficult to tolerate over a long period of time. If an interferon-free regimen were easy to tolerate, however, the emphasis on treatment duration may not be as significant.

G&H If interferon cannot be completely eliminated from the treatment regimen, would shortening the course of therapy benefit patients?

MS Absolutely. Minimizing exposure to interferon will reduce side effects and make treatment more tolerable. Also, I have so far been discussing interferon α, but there is a new type of interferon being developed called interferon λ. Interferon λs are type-3 interferons, which include IL-28A, IL-28B, and IL-29. IL-28 or peginterferon λ is currently undergoing phase II studies. While interferon λ is still early in development, available data suggest that it is better tolerated than interferon α, with a marked decrease in flu-like symptoms and other toxicities such as bone marrow suppression. Thus, there is the possibility that switching from interferon α to interferon λ may allow us to achieve the benefits of interferon with less toxicity. It will be very interesting to see how this agent fares in clinical studies.

G&H How soon do you think interferon-free treatment for HCV might become a reality?

MS I think we are still many years away from an interferon-free HCV treatment regimen. We anticipate the approval of telaprevir and boceprevir in 2011. Other DAA agents are further behind in development, however, so we would not expect to see a US Food and Drug Administration–approved, interferon-free regimen for, optimistically, at least 3–5 years. Frankly, we have much research to do before this is a reality.

G&H How do you think the launch of DAA medications will affect HCV treatment?

MS Given the higher effectiveness of these drugs combined with their acceptable tolerability, I believe combination therapy with telaprevir or boceprevir plus peginterferon and ribavirin will rapidly become the standard of care for genotype 1 HCV infection. These regimens will offer patients infected with HCV genotype 1 a substantially higher likelihood of success.

Suggested Reading

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