

ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

Section Editor: Eugene R. Schiff, MD

New Treatments for Chronic Hepatitis C

Gary L. Davis, MD
Director, Division of Hepatology
Baylor University Medical Center
Medical Director, Liver Transplantation
Baylor Regional Transplant Institute

G&H What is the standard treatment approach for chronic hepatitis C?

GD The treatment of chronic hepatitis C has been based on interferon. The first studies of interferon in this setting were reported in 1989, with interferon given 3 times per week for 6 months. Since then, the duration of therapy has been extended, ribavirin has been added, and longer-acting pegylated interferons were developed. Each of these developments has brought incremental increases in the eradication of the virus (sustained virologic responses [SVR]) from less than 10% of patients in 1989 to greater than 50% of patients today, with the current standard regimen of pegylated interferon plus ribavirin.

However, challenges remain. First, a 50% rate of SVR leaves much room for improvement. More importantly, for a variety of reasons most patients with hepatitis C are either not diagnosed or, if they are diagnosed, not treated. Therefore, the treatment of hepatitis C does not have a significant impact on societal health and does not significantly reduce the complications associated with hepatitis C virus now, or that may occur in the future.

G&H Why are so many patients not treated?

GD Interferon and ribavirin in combination are associated with a number of side effects that some patients cannot tolerate. For example, ribavirin is associated with anemia and therefore should not be administered to patients with chronic anemia or coronary artery disease. Interferon may have psychological side effects, and must be used with caution in patients with severe psychiatric disease or ongoing depression. Among populations with a high incidence of hepatitis C, such as veterans in the VA

hospital system, only about 30% of patients are candidates for interferon/ribavirin therapy.

G&H What new types of interferon are being studied?

GD Several types of interferon are currently in development. Consensus interferon is a synthetic interferon that has greater affinity for the interferon receptor and therefore shows more activity than other interferons. There is a great deal of interest in this agent, particularly for patients who do not respond to current interferon regimens. Phase III trials are ongoing. Other interferons include agents that are easier to administer due to less-frequent dosing schedules, for example, and others that affect the virus differently than the interferons currently available. A phase III trial of a long-acting albumin-interferon fusion protein will be initiated in the next few months.

G&H Are varieties of ribavirin being explored?

GD Yes. A prodrug of ribavirin called viremagine (Valeant) is currently in development. This agent is given by mouth and is transported by the blood to the liver, where it is converted into ribavirin. By producing ribavirin directly in the liver it may be possible to preserve its antiviral effect while decreasing the hemolytic anemia associated with high drug levels in the systemic circulation. A phase II trial confirmed that viremagine is associated with a lower incidence of anemia compared with ribavirin. Viremagine is now in phase III trials that will demonstrate whether viral responses are the same as with standard ribavirin.

G&H What other strategies are being developed for the treatment of chronic hepatitis C?

GD Other treatment strategies being investigated comprise 4 categories. The first category focuses on using antibodies to prevent the virus from reaching liver cells. Immune globulin containing high titers of antibodies to the hepatitis C virus may prevent reinfection of the liver after transplantation in much the same way as antibodies are used in the treatment of hepatitis B. Two studies conducted thus far, one in the United States and one in

Canada, did not demonstrate encouraging results in preventing reinfection after transplantation; however, these were early-phase studies and further research is needed in order to determine whether it is possible to administer enough antibodies to elicit the desired result and whether this strategy has potential for the treatment of hepatitis C. Interestingly, it is possible to prevent and neutralize the infection in chimpanzees, but the same activity has not yet been observed in humans.

The second strategy entails augmenting a patient's immune response to the virus. Interferon, which is an immune stimulant, accomplishes this to some degree. Several other drugs, such as some interleukins, have been investigated for this purpose, although none have yet proven to be very effective. Therapeutic vaccines represent another avenue of therapy in this category, but research in this area is in very early stages.

Researchers are also investigating ways to block inflammation and formation of fibrosis and scar tissue in the liver. This approach does not address the virus, focusing instead on how the liver becomes damaged. A great deal of basic research has been conducted and some agents being studied for pulmonary fibrosis might be effective in liver diseases. One of the agents currently being investigated is IDN6556, which inhibits caspase, an enzyme that causes apoptosis in liver cells. IDN6556 is an anti-inflammatory agent and has shown activity in reducing cell injury in animal models, decreasing liver enzyme levels by approximately 30–50%. These findings are encouraging, but still preliminary.

Finally, drugs that inhibit the ability of hepatitis C to replicate once it is inside a cell are another promising approach. Such agents target enzymes that aid viral replication, including protease and polymerase. Studies of a protease inhibitor reported in 2003 found that viral levels were decreased to 1% of their baseline level after the drug was administered for 2 days. Unfortunately, longer dosing was associated with toxicity and development of the drug was stopped. Currently, 2 new protease inhibitors, one by Vertex and one by Schering, are entering phase II studies, with many other agents in preclinical studies.

The advantage of protease inhibitors is that they have marked activity against the virus, blocking it fairly dramatically. Since the protease of the virus blocks the ability of interferons to combat the virus, it is likely that patients will become more sensitive to the effects of interferon after administration of a protease inhibitor. The disadvantage to this approach is that when a specific part of the virus is targeted, the virus will find a way to get around this, and drug resistance is likely to develop. Therefore, it is likely that protease inhibitors would be used as part of combination therapy, and not as monotherapy. Once protease inhibitors that are active and well tolerated are

identified, the next challenge will be to find how best to integrate them into current treatment regimens in order to achieve the best responses.

Polymerase, which synthesizes RNA for replication and incorporation into virus particles, is another potential target for polymerase inhibition. However, polymerase inhibitors do not have as dramatic an effect on viral replication as the protease inhibitors. Valopicitabine (NM283, Idenex), a polymerase inhibitor currently in phase III studies in combination with interferon, was found to decrease the virus to approximately 10% of baseline levels in initial single-agent studies. However, its combination with interferon is likely to increase this response.

G&H How long might it be before some of these new agents are widely available?

GD It will be at least a few years before these new agents are widely available. If the agents currently in phase III trials prove to be effective, it will take approximately 3 years for the studies to be completed, reviewed, and presented to the US Food and Drug Administration.

G&H What attention is being paid to improving acute hepatitis C treatment as a way to prevent chronic hepatitis C?

GD There has been quite a bit of activity in this area. The major drawback to this strategy is that it is difficult to identify patients with acute hepatitis C, which is fairly uncommon (approximately 30,000 new infections occur per year in the United States). However, individuals who may have contracted hepatitis C, such as a healthcare worker stuck with a needle from a hepatitis C patient, can be followed prospectively and treated if hepatitis C develops. Studies of acute-phase patients have found fairly good responses with short courses of interferon (3–6 months), even without ribavirin; in this setting, the virus is eradicated in approximately 70% of patients. Thus, identifying patients during the acute stage could be extremely beneficial; the challenge is finding these patients.

Suggested Reading

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