Targeted Therapies for Hepatitis C Reach the Clinic

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DOI 10.1016/j.chembiol.2012.04.005

Chronic hepatitis C infections have been difficult to clear from the body because the virus has found so many ways to coexist with humans. The genome of the hepatitis C virus (HCV) contains features that allow for quick mutations that scoot around medications. Easy mutations also make vaccine development and drug design especially problematic. For the past 20 years or so, the six main HCV genotypes have been treated with the same drug regimen, but genotype I, the most common in Europe and North America, has proven the most problematic to treat. What's more, the health care community in the United States can only estimate the total number of people with chronic HCV infections.

In 2011, the Food and Drug Administration approved two new treatments. Both are protease inhibitors that target molecular features in genotype 1. Telaprevir (ICIVEK) is manufactured by Vertex Pharmaceuticals, Incorporated, in Cambridge, Massachussets, and Boceprevir (VICTRELIS), from Merck of Whitehouse Station, New Jersey. When the new therapies are given in combination with peginterferon and ribavirin, the cure rates reach 70%–80% for genotype I.

"These drugs certainly mean an improvement in outcome and potentially shorter therapy for patients with genotype 1. They can also be used for patients who failed previous therapy. So overall they are an important step forward, although there will still be a substantial minority (perhaps a quarter) of patients who go through the therapy and still fail to clear the virus," Paul Klenerman, M.D., Ph.D., a clinician and immunologist at University of Oxford, England, wrote in an email.

Fortunately, the HCV therapy pipeline is transporting targeted therapies for genotype I to the clinic.

Until recently, the standard of care for HCV has been pegylated interferon (peginterferon) and ribavirin (Virazole), which help dampen the immune response in a general way. Although neither drug specifically targets HCV, around 80% of people with most genotypes respond well enough to achieve what physicians call a sustained virological response, meaning that the virus can't be detected in the bloodstream for 6 months or longer. Such patients are considered cured.

Unfortunately, response rates to peginterferon and ribavirin for those infected with genotype I are much lower—about 40%–50%. For those infected patients who didn't respond at all, there was nothing physicians could offer, at least from a treatment standpoint.

Fortunately, the HCV therapy pipeline is transporting targeted therapies for genotype I to the clinic. Additional targeted therapies are in various stages of clinical trials. These therapies have already boosted the sustained virological response for genotype I.

Silent Disease, Costly Therapy

The peak years for HCV infections were the 1960s and 1970s. At the time, doctors knew the infections were a form of hepatitis but the virus hadn't been identified; they just knew that it wasn't hepatitis A or B, so HCV was called, "non-A" or "non-B." In 1989, with the discovery of the virus, came the serologic means to establish a diagnosis.

By the late 1980s, the virus was treated with the immune glycoprotein interferon. Once HCV was identified as a flavivirus, a family of RNA viruses that includes West Nile, the antiviral ribavirin was added to the treatment regimen because it worked against flaviviruses. Shortly after, interferon was chemically altered with polyethylene glycol to last longer in the bloodstream. Injections of peginterferon could be given weekly rather than three times a week.

Worldwide, more than 170 million people are estimated to be chronically infected with HCV. In the United States, around 700,000 cases are known; an estimated 3 million cases are suspected. Pinning down that number is difficult because HCV attacks the liver slowly and silently for two to three decades. Those infected don't know they carry a deadly virus until the liver is nearly destroyed. Often, the only symptom is fatigue—a warning easily attributed to other conditions.

The potentially millions of people who unknowingly carrying the virus makes hepatitis C "a gigantic health issue because hepatitis C is responsible for most liver transplants and for most cases of liver cancer," says Mauricio Lisker-Melman M.D., a gastroenterologist at Washington University School of Medicine in St. Louis, Missouri.

HCV has a high tendency to become chronic if the infection persists beyond 6 months. Because the virus is indolent, once a chronic infection establishes itself, HCV slowly damages the liver decade after decade without stopping, unless a blood test detects the virus and a treatment regimen begins. If undetected, the path to liver destruction can take 20 to 30 years, or more.

At first, HCV triggers inflammation, then fibrosis, a scarring and thickening of the tissue that slowly spreads throughout the liver. Unchecked fibrosis leads to cirrhosis. By the time cirrhosis occurs, most of the healthy liver tissue has been replaced with scarring. Patients with cirrhosis go on to develop liver cancer at rate of 3%–5% per year.

HCV doesn't incorporate its genetic material into the host genome (unlike HIV and hepatitis B), so the aim of treatment is eradication of the virus. Once the virus is cleared, it's gone, says Adrian Di Bisceglie, M.D., a gastroenterologist at Saint Louis University in St. Louis, Missouri.

Clearing the virus involves lengthy treatment in addition to plenty of money. Treatment lasts for about 45 weeks and costs around $60,000 per year. Side effects can include decreased ability to concentrate, depression, suppression of bone marrow, and flu-like symptoms. Patients are then monitored closely by a physician for five years.

Once the virus is gone, the fibrosis and even cirrhosis can start reversing itself. "That was a novelty here, because we used to think that the fibrosis and scarring didn't go away, but we've seen that it can decrease substantially and even go away after a few years," says Di Bisceglie.

Treating Nonresponders

Helping those who have never responded to standard therapy has been difficult for physicians. Telaprevir and boceprevir are providing such patients with another chance. Such patients are good candidates for new therapies, but their response to the new drugs isn't as strong as those who have never received any treatment, says Darius Moradpour, M.D., a hepatologist at the University of Lausanne, Switzerland. New drugs in clinical trials may provide new options.

Anna Lok, M.D., a gastroenterologist at the University of Michigan Health System in Ann Arbor, led a preliminary study that tested the safety and efficacy of two new antivirals on patients who had received previous treatment with peginterferon and ribavirin but had not responded. This exploratory study included 21 men and women ages 18–70 years old with chronic HCV genotype I. The patients had no cirrhosis. Patients were randomly assigned to receive either daclatasvir, which keeps the virus from replicating, or asunaprevir, a protease inhibitor; both are manufactured by Bristol-Meyers Squibb, based in Hopewell, New Jersey. The experimental drugs were given in combination either with or without peginterferon and ribavirin, (Lok et al., 2012).

The aim was to figure out whether treatment for 24 weeks would eliminate most traces of the virus from the bloodstream. Although the virus broke through in some patients and resistance to the antivirals occurred in 11 patients, 36% receiving the two oral antivirals without peginterferon and ribavirin achieved a sustained virological response 24 weeks after the therapy stopped, which Lok says provides proof of concept that it is possible to eliminate hepatitis C virus without peginterferon and ribavirin. Lok emphasizes that the study showed that the four drug regimen with two new oral antivirals plus peginterferon and ribavirin achieved sustained virological response in 9 of 10 patients that are very difficult to treat.

"For 10 years, we had only peginterferon and ribavirin. Retreating patients who had failed to respond with the same treatment is, as expected, futile in most cases. Now that we have new drugs, it opens up all sorts of possibilities," says Lok.

Identifying Those Infected

With new treatments in hand and the specter of millions silently infected, the health care community is trying to identify as many people with HCV as possible. That's not an easy task. The Centers for Disease Control and Prevention has a long list of screening recommendations, including those in contact with blood or blood products, those who have had blood transfusions or a transplant prior to 1990, and those who've had multiple sexual partners, used intravenous drugs, or have tattoos.

A specific blood test for HCV exists but doctors need a medical reason for the test to be administered. That's not as straightforward as it could be, as screening recommendations rely on physicians to ask sensitive questions about drug use and sexuality that patients may be reluctant to answer or doctors may be reluctant to ask. Also, tests for liver enzymes may not be included in routine physicals. If they are, says Lisker-Melman, a slight increase in liver enzymes may or may not mean the presence of HCV.

"When you combine both the ability of doctors to ask those questions and the reluctance of patients to answer them you recognize that the situation is less than ideal," says Lisker-Melman. "But if we don't recognize this disease, and we don't start treating patients early on in their natural history, we will see more patients affected in the later stages with little possibility of a cure."

Currently, the CDC is refining recommendations based on birth cohort screening, rather than relying on doctors to ask questions that patients may not answer in an honest fashion. The recommendations are expected to advise testing baby boomers, those born between 1945 and 1965.

If baby boomers are screened and such screening dramatically increases the numbers of those with HCV, Lisker-Melman says that the newly diagnosed patients would need to go on the new treatment regime, which would save lives. However, such treatment costs $60,000 per year, which would be difficult to afford for people without health insurance or a good health support system.

"A lot of patients with HCV in the west are in marginalized groups, especially intravenous drug users, who may not have optimal access to health care, or other medical and social issues which mean they cannot access these complex treatments. In other countries, including Egypt, where there is a huge burden of disease, much of the disease is non-genotype 1, which means the new drugs will not be useful. But also importantly, the cost of the treatment and the complexity of delivery means it is not really yet affordable in many countries," Klenerman wrote in an email.

REFERENCE

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