Hepatitis C

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Abstract

The first report of a blood-borne virus that caused hepatitis (inflammation or swelling of the liver) that was not either of the 2 well-known viruses, hepatitis A or hepatitis B, was published in 1975. The new virus proved very difficult to isolate by the means then currently available, but in 1988, the hepatitis C virus was finally identified. It was not until 1993 that a specific test was developed that could reliably and rapidly identify the virus.

In the United States, approximately 1.4 % of the population has antibodies to hepatitis C, but this percentage is higher in developing countries. Hepatitis C is transmitted primarily through contaminated blood. Risk factors for contracting the virus include intravenous drug use (the most common source in the US), receiving a transfusion of infected blood (not a very common source in developed countries, where testing of donated blood for hepatitis C is now routine, but this source continues to be of concern in third-world countries), hemodialysis, and tattooing. There are now a number of very accurate tests available to diagnose hepatitis C, but testing is nonetheless a complicated process for 2 reasons. The first is that the blood levels of virus rise and fall over time. The second is that the hepatitis C virus exists as 6 different genotypes, more than 30 subtypes, and each of these mutates rapidly into what are called quasispecies. These factors make treatment difficult, too.

People with acute (newly infected) hepatitis C tend to have mild infections. Most people have no symptoms at all, with only 25 % developing jaundice. Very few people with acute hepatitis have liver injury or failure. Unfortunately, 80% of people with acute hepatitis C do not fight off the virus and they go on to develop chronic hepatitis C. Chronic hepatitis C is associated with a number of complications, including fibrosis and cirrhosis of the liver and liver cancer. Nevertheless, a majority of those infected with hepatitis C virus live a normal life span without apparent liver disease. The diagnosis is often made when laboratory studies obtained during a routine physical examination are not normal.

The decision to treat infected individuals is a complex one. Pretreatment factors that help conclude whom to treat include the amount of virus in the blood, the viral genotype, and the number of viral quasispecies. Another consideration is the amount of liver injury as measured by how much of a liver enzyme, ALT, has been leaked into the bloodstream, as well as the presence of cirrhosis or liver decompensation. This means that all patients have a liver biopsy before starting therapy. Other medical problems the patient has, their ability to adhere to treatment recommendations, and any previous treatment failures are also factors in whom to treat. Treatment has the potential to eradicate the virus because this virus does not incorporate itself into the human DNA. Treatment has proved difficult, however, because the virus replicates and mutates so quickly. Currently available therapies are inconvenient (they involve an injection three times a week, as well as daily pills), lengthy (12 months), and have side effects. Thus, only patients who show signs of liver injury and are willing to undergo this rigorous regimen are candidates for treatment.

The treatment of hepatitis C is constantly being improved. In 1986, a pilot study reported that therapy with interferon a led to remission in a proportion of patients with non-A, non-B hepatitis and this was confirmed in a series of randomized clinical trials. From the results of these studies, a standard interferon a regimen was defined. Three forms of interferon a are currently approved in the US for the treatment of HCV infection, and a fourth interferon a is approved for this use in other countries. Side effects include initial flu-like symptoms, fatigue, bone marrow suppression, and neuropsychiatric disorders including depression and psychosis. Side effects are dose-dependent, and while dose reduction is helpful, can lead to withdrawal of therapy in 15% of patients.

The standard interferon a regimen leads to normalization of liver function studies and a loss or decrease in the amount of hepatitis C RNA in the blood at end of treatment for 50% of patients, and a sustained response for one year or more in 25% of patients. This means that only one quarter of patients given this regimen have long-term remission or cure. Attempts to improve the sustained response rate have included increasing the dosage, the dose frequency, and the duration of treatment. Increased duration of therapy significantly increases the sustained response rate, but the long-term results of increased dosage and dose frequency have been disappointing.

Other agents have been used for the treatment of hepatitis C infection, although none as successfully as interferon a . Amantadine and rimantadine are both oral drugs that are used to treat influenza A. Trials using these drugs have had some success in producing sustained responses in patients infected with hepatitis C virus. Ribavirin is an oral drug that has been effective against a range of viruses. Ribavirin used alone for the treatment of hepatitis C virus infection decreases the amount of ALT in the blood and improves the liver cell structure in 30% to 50% of patients, but does not affect serum hepatitis C virus levels: that is, it helps the symptoms but doesn't cure the infection.

The limited efficacy of using one drug alone led to studies assessing combination therapies. Multiple agents given simultaneously may block viral replication by acting at different target sites. Combinations of 2 and 3 different drugs have been studied. The most commonly used involves standard interferon a plus ribavirin. This leads to a sustained response in 42% of patients. Triple therapy using interferon a , ribavirin, and amantadine was recently studied in a small pilot study. Triple therapy led to a response in 70% of patients who had not responded to standard interferon a therapy, and was well tolerated.

Other recent efforts to develop a more successful treatment for HCV have focused on altering the interferon a molecule by attaching one or more chains of polyethylene glycol (PEG) to it, forming a selectively protective barrier around the base molecule. This increases the amount of time the drug remains in the bloodstream, making it more effective. Modifying interferon with polyethylene glycol has recently shown great success in increasing the percentage of sustained responders with no change in safety.

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