Undetectable or Bust: Reevaluating Prolonged Hep C Treatment

The goal of hepatitis C virus (HCV) treatment is to drop-kick HCV levels to undetectable while on interferon and ribavirin therapy for a year and maintain it for six months after treatment stops. But this only occurs in a minority of people coinfected with HIV and HCV. While it was originally believed that continued treatment might help protect the liver, a large clinical trial suggests that interferon maintenance therapy yields no additional benefit—or does it?

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For all of the debilitating side effects of hepatitis C treatment, it is a curable infection. Treatment is dubbed a success if a person is able to achieve and maintain undetectable hepatitis C virus (HCV) levels while taking weekly pegylated interferon injections and daily ribavirin pills for one year and then stays undetectable for at least six months after treatment is stopped. This is called a sustained virologic response, or an SVR.

About 30 to 40 percent of people coinfected with HIV and HCV achieve this desired outcome. For the remaining 70 to 60 percent, options include trying a second round of treatment or waiting for new experimental drugs to be approved. A third option, called maintenance therapy, involves continuous treatment with low-dose pegylated interferon.

Despite earlier observations to the contrary, a large clinical trial called HALT-C recently reported that maintenance therapy failed to protect most people from the possible long-term effects of hepatitis C infection, notably liver function impairment, cancer and death—despite reducing liver enzymes and HCV levels. While the study volunteers were infected with only HCV, and not HIV as well, experts say there's no reason to believe that maintenance therapy would work any better in people infected with both viruses.

Jules Levin, a longtime HCV and HIV activist, isn't ready to give up on maintenance therapy though. He recalls a presentation that Mitchell Schiffman, MD, gave earlier this year at the European Association for the Study of the Liver (EASL) in Hamburg, Germany. In that presentation, Schiffman, who is professor of medicine and chief of hepatology at Virginia Commonwealth University in Richmond, showed that a very small group of HALT-C patients did appear to benefit from maintenance therapy. These were individuals who initially responded to treatment, experienced HCV viral load rebounds after stopping interferon/ribavirin and were able to once again reduce their viral loads to undetectable for most of the three and a half years of the study. For similar patients in the real world, Schiffman says, maintenance therapy remains a rational

approach.

For people who were unable to reach and maintain undetectable HCV levels on standard treatment, however, the HALT-C results indicate that maintenance therapy merely increases the risk of side effects—including flu-like symptoms, anemia and depression—without the possibility of long-term benefits. Because of this, Schiffman says, HCV maintenance should definitely not be routine practice for the majority of people who fail to benefit from standard treatment.

A Promising Start

Maintenance therapy once had a fairly bright future. It grew out of small studies showing that, even when people failed to achieve an SVR from standard treatment, continuing therapy was associated with measurable improvements in liver function, including lower HCV levels and reduced liver enzymes. There were even hints that progression of liver damage and scarring (fibrosis) may be slowed or halted.

The large HALT-C study was conducted to confirm these initial observations. According to Adrian Di Bisceglie, MD, chief of hepatology at the Saint Louis University School of Medicine in St. Louis and a member of the HALT-C team, the study set out "to see if maintenance therapy would reduce the risk of clinical outcomes—in other words bad things happening, like people dying, needing liver transplantation, having liver decompensation [functional deterioration], or developing liver cancer."

The study investigators enrolled 1,050 people infected with HCV, with advanced fibrosis, who'd failed to achieve an SVR from standard therapy with pegylated interferon and ribavirin. Some of the patients in the study had never reached an undetectable HCV level on treatment, while others had reached undetectable, but saw their HCV levels come back after stopping treatment. The patients were randomized to receive either 90 micrograms of pegylated interferon per week or no treatment for three and a half years.

"What we found," Di Bisceglie explains, "was that there was no difference in outcomes between the treated group and the control group." Although patients receiving maintenance therapy were more likely to see reductions in their liver enzymes and HCV viral load and improvements in their liver biopsy results, they were no more likely to avoid the major clinical outcomes of the study. Based on these results, Di Bisceglie says, "We concluded that maintenance therapy, at least this form of maintenance therapy, really didn't seem to give the benefit that we had hoped."

Di Bisceglie doesn't reckon the results would be any more favorable in people coinfected with HIV and HCV. "As it happens, we excluded patients who are HIV positive [from HALT-C]," he said, "though I'm not sure that would change the ultimate message."

Douglas Dieterich, a professor of medicine at Mount Sinai School of Medicine in New York City and an HIV/HCV-coinfection specialist, concurs. "There are two other studies that have also been completed in HIV patients on maintenance [therapy], and neither one of them showed any

benefit," he says.

The results of HALT-C were published by Di Bisceglie and his colleagues in the December 4 issue of The New England Journal of Medicine (NEJM) and were eventually picked up by media outlets. That upset Levin, who felt that the story was more complicated and deserved a more nuanced approach.

Levin is worried that such attention could put the kibosh on further maintenance therapy research. In particular, he points to a lesser-known analysis of the HALT-C study presented earlier this year at EASL by Schiffman and wishes that Di Bisceglie and his coauthors had mentioned it in the NEJM article.

While Schiffman agrees that the EASL analysis is important, and is hoping to publish the findings in a scientific journal next year, he also says that HALT-C was never designed to measure the impact of getting and keeping a person's HCV levels undetectable. Fewer than 70 people who entered HALT-C and got maintenance therapy were able to achieve and maintain undetectable HCV viral loads while on standard therapy.

Schiffman's EASL presentation involved a group of 35 who also managed to achieve undetectable HCV levels on maintenance therapy, 22 of whom kept their HCV viral loads undetectable for the three and a half years they remained on treatment. Of those 22 patients, 75 percent of them ended up having an SVR when they stopped maintenance therapy.

"That's a positive outcome," Schiffman says. Unfortunately, the numbers are so small—22 out of a study of more than 1,000 patients—that they did not reach statistical significance, meaning that the benefit can't be readily tied to maintenance therapy. However, Schiffman still considers this an encouraging finding in his own clinical practice. "I have about 25 patients on maintenance therapy, the goal of which is to keep [their HCV undetectable]," he says, "If we can't keep them [undetectable], we stop maintenance therapy…. The goal of maintenance therapy should be to suppress virus, and to keep virus undetectable. Do we have data that shows that is effective? Except for the 22 patients in the HALT-C study, no."

While many HALT-C patients who received maintenance therapy saw reductions in their HCV viral loads, they rarely reached the goal of undetectable. It is for this reason that Schiffman says maintenance therapy probably didn't work. "It doesn't make sense that it would be effective. If you don't drop the virus, how is it going to be helpful?" he asks.

Levin hopes that word gets out about Schiffman's small group of patients, and that more research is conducted to validate maintenance therapy's potential in people who manage to achieve undetectable HCV levels.

While Dieterich acknowledges the Schiffman EASL data, he doesn't expect that providers will continue recommending maintenance therapy for people who don't respond to standard treatment. "Most people won't bother with that," he says.