New oral drug regimens cure hardest-to-treat hepatitis C

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Two new pill-only antiviral drug regimens could provide shorter, more effective treatment options with fewer side effects for the majority of patients infected with hepatitis C, even those most difficult to treat, according to the results of two studies published in *The Lancet*.

Both studies focused on hepatitis C genotype 1, which is the most common genotype in the USA, Europe, North Asia, Australia, and South America, and one of the most difficult to treat.

Around 150 million people worldwide have chronic hepatitis C virus (HCV) infection, a condition that is a major cause of liver cirrhosis and liver cancer. In the USA, numbers of people with HCV-related liver failure and liver cancer are expected to treble by 2030 because of low treatment rates.

Until recently, the standard of care for chronic HCV genotype 1 involved a combination of three drugs; ribavirin (RBV), pegylated interferon (PEG) and a protease inhibitor, which together inhibit viral replication and enhance the body's immune response to eradicate the virus. These drugs can place a substantial burden on the patient, with complicated injection and pill regimens, which can involve up to 18 tablets a day and last for up to a year, and can also cause severe side effects including anaemia and depression. Direct-acting antiviral agents (DAAs) provide new opportunities for treatment whilst reducing the need for interferon and ribavirin and their potential side effects.

In the HALLMARK-DUAL phase 3 study, Professor Michael Manns from Hannover Medical School in Germany and colleagues randomly assigned 645 patients with HCV genotype 1b from 18 countries to receive a 6-month course of treatment with a pair of oral DAAs asunaprevir and daclatasvir [2]. A further 102 treatment-naïve patients were assigned to a placebo control group. The regimen was highly effective at clearing the virus and well tolerated even in patients who have traditionally been the hardest to treat. 90% of previously untreated patients and 82% who were intolerant of, or who had been treated unsuccessfully using standard regimens, were cured. No differences in response were seen in individuals who had characteristics such as being male, older, African American race, or having advanced liver disease—that are recognised as predictors of poor response to treatment.

According to Professor Manns, "The efficacy and safety of 24 weeks of daclatasvir plus asunaprevir represents a huge improvement on the first generation of protease inhibitor based triple therapies for HCV genotype 1b infection (up to 48 weeks of boceprevir or telaprevir in combination with PEG/RBV). This new all-oral interferon and ribavirin-free combination could provide a more effective, safer, shorter, and simpler treatment option for those traditionally hard-to-cure patients with cirrhosis or those who have failed to respond to existing therapies."[3]

In the COSMOS study, a team of US and European researchers led by Professor Eric Lawitz from the Texas Liver Institute, University of Texas Health Science Center in San Antonio, USA, randomly assigned 167 individuals with HCV genotype 1a and 1b to receive a 12-week or 24-week course of once-daily sofosbuvir plus simeprevir with or without ribavirin. After just 12 weeks of treatment without ribavirin, 93% of participants (including those with cirrhosis and previous non-responders to interferon-based treatment) were cured—with no detectable virus in their blood 3 months after treatment had stopped. Neither extending

treatment to 24 weeks or adding ribavirin provided any clear benefit. The 12-week sofosbuvir plus simeprevir regimen was well tolerated with less than 2% of participants reporting serious adverse events or discontinuing treatment due to an adverse event.

According to Professor Lawitz, "We saw a cure rate of about 93% with only 12 weeks of treatment using an all-oral regimen that did not include interferon or ribavirin. This is especially encouraging given the high proportion of participants who had multiple characteristics traditionally associated with low cure rates including cirrhosis. This is the first trial combining two DAAs that are currently on the market and supports recent American Association for the Study of Liver Diseases/Infectious Disease Society of America (AASLD/IDSA) and the European Association for the Study of the Liver (EASL) treatment recommendations." [3]

Writing in a linked Comment, Professor Ed Gane, Director of the New Zealand Liver Transplant Unit at Auckland City Hospital in New Zealand says, "In the future, very-short-duration, all-oral DAA regimens should improve treatment uptake and success, and reduce the health burden from liver-related complications. When combined with targeted testing and treatment of populations who transmit infection (ie, treatment as prevention), these DAA regimens might eventually eliminate HCV infection. The only barrier to achieving this goal will be the ability to access these new therapies. In many developing countries where HCV is endemic, interferon-based therapy will remain the first choice because of the high cost of DAAs and lack of reimbursement. As almost 75% of all patients with HCV infection reside in economically deprived regions of eastern Europe, Asia, and the Middle East, consideration should be given to discounting prices in these regions.29 Eradication of HCV infection worldwide will only be achievable through universal access to HCV testing and new DAA regimens."

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