Merck’s Triple-Drug 8-Week Hepatitis C Regimen Shows Promise

The fixed-dose combination tablet of grazoprevir, ruzasvir and uprifosbuvir cured the virus at high rates among a diverse group.

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In a recent pair of trials, eight weeks of the triple-drug combination of Merck’s grazoprevir, ruzasvir and uprifosbuvir cured high rates of hepatitis C virus (HCV) in a diverse population of participants, including those with cirrhosis. This opens the door for more advanced research of the fixed-dose combination tablet of the three direct-acting antivirals.

The regimen includes the NS3/4A protease inhibitor grazoprevir, the NS5A inhibitor ruzasvir and the NS5B polymerase inhibitor uprifosbuvir. Grazoprevir is already approved as a component of Merck’s Zepatier (grazoprevir/elbasvir), while ruzasvir and uprifosbuvir are experimental.

Part A of C-CREST-1 and C-CREST-2 consisted of a pair of studies that were randomized, multicenter open-label trials of two triple-drug hep C regimens that enrolled 241 adult participants from 11 countries. The participants had genotypes 1, 2 or 3 of hep C and a viral load of at least 10,000, did not have cirrhosis and were first-timers to treatment.

The researchers grouped the participants by genotype and then randomly and evenly assigned them within those groups to one of four treatment groups between February and March 2015. The four regimens and their doses were as follows, with the grazoprevir dose always 100 milligrams, the ruzasvir dose always 60 mg and the elbasvir dose always 50 mg:

- grazoprevir, ruzasvir and uprifosbuvir (300 mg)
- grazoprevir, ruzasvir and uprifosbuvir (450 mg)
- grazoprevir, elbasvir and uprifosbuvir (300 mg)
- grazoprevir, elbasvir and uprifosbuvir (450 mg)

A total of 240 individuals completed eight weeks of treatment with their respective regimens as well as 12 weeks of follow-up. Of the four regimens, grazoprevir, ruzasvir and uprifosbuvir (450 mg) boasted the most consistently high rate of sustained virologic response 12 weeks after
participants completed therapy (SVR12, considered a cure). The cure rate broken down by genotype was 91 percent (21 of 23) for those with genotype 1, 94 percent (15 of 16) for those with genotype 2 and 91 percent (20 of 22) for those with genotype 3.

By comparison, among those with genotype 2, the regimen of grazoprevir, ruzasvir and uprifosbuvir (300 mg) led to a cure rate of 71 percent (10 of 14); the regimen of grazoprevir, elbasvir and uprifosbuvir (300 mg) led to a cure rate of 69 percent (11 of 16); and the regimen grazoprevir, elbasvir and uprifosbuvir (450 mg) led to a cure rate of 60 percent (9 of 15).

Overall, the most common adverse health events were headache (23 percent), fatigue (20 percent) and nausea (13 percent). Two of the participants (less than 1 percent) experienced serious adverse events, although neither was considered related to the hep C regimen.

The researchers concluded that the part A pair of studies supported further research of the regimen of grazoprevir (100 mg), ruzasvir (60 mg) and uprifosbuvir (450 mg) among a more diverse population of people with hep C, including those with compensated cirrhosis, those treated for hep C before with an interferon-based regimen, and those coinfected with HIV.

Part B of C-CREST-1 and C-CREST-2 indeed conducted further research of that triple-drug regimen, testing it as a single-pill combination tablet for different lengths of treatment. This pair of randomized Phase II open-label clinical trials enrolled 676 participants from 15 nations who had genotypes 1 through 6 of hep C and a viral load of 10,000 or higher, including those with and without compensated cirrhosis. The participants with genotypes 1, 2, 4 and 6 had not been treated for hep C before while those with genotype 3 were either first-timers to treatment or had been treated before with interferon and ribavirin.

Between February 2015 and April 2016, the participants were randomized to receive 8, 12 or 16 weeks of treatment with the fixed-dose combination tablet of grazoprevir, ruzasvir and uprifosbuvir with or without ribavirin.

A total of 675 of the participants received at least one dose of the study regimen.

The cure rate for the eight-week regimen, given with or without ribavirin, was 93 percent (39 of 42) for genotype 1a, 98 percent (45 of 46) for genotype 1b, 86 percent (54 of 63) for genotype 2, 95 percent (98 of 103) for genotype 3 and 100 percent (7 of 7) for genotype 4.

The cure rate for the 12-week regimen, given with or without ribavirin, was 99 percent (87 of 88) for genotype 1, 98 percent (61 of 62) for genotype 3 and 100 percent (4 of 4) for genotype 6.

Among those with genotype 3 and cirrhosis, the cure rate for the 12-week regimen, with or without ribavirin, was 97 percent (28 of 29) among those who were being treated for HCV for the first time and 100 percent (29 of 29) among those who had been treated before.

The cure rate for the 16-week regimen, given with or without ribavirin, was 100 percent (26 of 26) for genotype 2 and 96 percent (72 of 75) for genotype 3.
The most common adverse health events were headache (22 percent), fatigue (19 percent) and nausea (13 percent). Two percent (16) of the participants experienced serious adverse health events.

The study authors concluded that the triple-drug regimen “has the potential to provide a simplified treatment for HCV that is effective and well tolerated in most individuals infected with HCV, as well as a shorter duration of treatment in many individuals.”

The fixed-dose combination tablet of grazoprevir, ruzasvir and uprifosbuvir is now in a position to move to Phase III trials (the last step before the Food and Drug Administration can grant approval to an experimental treatment).

To read the abstract for the part A studies, click here.

To read the abstract for the part B studies, click here.