EASL: GS-7977, Daclatasvir, and Asunaprevir Look Good in Interferon-Free Regimens for Hepatitis C

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by Liz Highleyman

Fumitaka Suzuki (Photo: Liz Highleyman)

Most previously untreated people with chronic hepatitis C virus (HCV) infection achieved an early cure with an all-oral combination of the HCV NS5A replication complex inhibitor daclatasvir (formerly BMS-790052) plus the nucleotide NS5B polymerase inhibitor GS-7977, researchers reported this week at the 47th International Liver Congress (EASL 2012) in Barcelona. Another study confirmed that daclatasvir plus the HCV protease inhibitor asunaprevir (formerly BMS-650032) produces a long-term cure for a large proportion of difficult-to-treat patients.

Last year's approval of the first direct-acting antiviral (DAA) agents for hepatitis C ushered in a new era of treatment, but many patients and clinicians await all-oral regimens that do not include interferon. Several interferon-free regimens are currently under study; these resemble antiretroviral therapy for HIV, combining drugs that target different steps of the viral lifecycle.

Daclatasvir + GS-7977

Mark Sulkowski from Johns Hopkins Medical School and colleagues tested various oral combinations of daclatasvir plus GS-7977, with or without ribavirin, in an open-label Phase 2a trial (AI-444040).

The study included 88 treatment-naive participants, half with difficult-to-treat hepatitis C virus (HCV) genotype 1a or 1b and half with genotype 2 or 3. Participants, divided by genotype (1 vs 2/3), were randomly allocated to receive 3 regimens, for a total of 6 study arms:

400 mg once-daily GS-7977 alone for 7 days, then add 60 mg once-daily daclatasvir through week 24; 400 mg once-daily GS-7977 plus 60 mg once-daily daclatasvir for 24 weeks; 400 mg once-daily GS-7977 plus 60 mg once-daily daclatasvir plus ribavirin (weight-based 1000-1200 mg/day for genotype 1 or 800 mg/day fixed-dose for genotype 2 or 3) for 24 weeks. Across all study arms, about half of participants were men, about 80% were white, and the median age was about 52 years. Among genotype 1 patients, 73% had 1a and 27% had 1b; among the rest, 59% had genotype 2 and 41% had genotype 3. Proportions of participants with the favorable IL28B "CC" gene pattern ranged from 27% to 57%. People with liver cirrhosis or HIV coinfection were excluded.

Sulkowski reported interim sustained virological response rates at 4 weeks after completion of treatment, or SVR4. The study will continue evaluation to see how many participants maintain

undetectable viral load 12 weeks after the end of treatment (SVR12), which is considered a cure. Safety and tolerability were assessed through week 12 of treatment.

Results

Among genotype 1 patients, all 3 regimens produced early viral load decreases. Rates of rapid virological response (RVR), or undetectable HCV RNA (< 10 IU/mL) at treatment week 4, ranged from 73% to 93%. At the end of treatment, 87% of people taking the GS-7977 lead-in regimen, 86% taking the dual combination for 24 weeks, and 93% taking the triple combination achieved undetectable HCV viral load. Even after finishing treatment, a few patients achieved further viral suppression, resulting in SVR4 rates of 100% in all 3 arms. Among genotype 2/3 patients, early viral suppression was also good, with RVR rates ranging from 64% to 88%. 24-week end-of-treatment response rates were 93% for people taking either the GS-7977 lead-in regimen or the dual combination for 24 weeks, and 86% for those taking the triple combination. SVR4 rates were 88%, 100%, and 79%, respectively. Adding ribavirin -- which is known to help prevent relapse -- did not improve response rates at this early post-treatment time point. Sustained response rates were independent of IL28B gene pattern. Daclatasvir and GS-7977 in combination were generally well-tolerated. The most common adverse effects were fatigue, nausea, and headache. 2 people (6%) in the GS-7977 lead-in group, 5 (18%) in the dual combination group, and 3 (10%) in the triple combination group experienced serious adverse events. 1 person each in the latter 2 arms stopped treatment early for this reason. Serious laboratory abnormalities, including anemia, were only seen in the group that took ribavirin. Overall, in this first report of data on an interferon-free regimen containing a NS5A inhibitor plus a NS5B nucleotide polymerase inhibitor, the combination of daclatasvir plus GS-7977 cured more than 95% of genotype 1, 2, and 3 treatment-naive patients, including all of those with genotype 1, the researchers concluded.

"Ribavirin contributed adverse effects but had no effect on virologic response," they added.

These findings were discussed at an EASL opening press conference, where it was noted that daclatasvir developer Bristol-Myers Squibb and GS-7977 developer Gilead Sciences do not currently have plans to further test this regimen in Phase 3 studies. Gilead is testing GS-7977 in combination with several of its own compounds.

Daclatasvir + Asunaprevir

Another study provided further data on the combination of daclatasvir plus asunaprevir. This regimen was previously shown to be effective in small early studies of a difficult-to-treat population, genotype 1 patients with null response to prior interferon-based therapy. Results were especially promising for people with genotype 1b.

Fumitaka Suzuki from Toranomon Hospital in Tokyo and colleagues provided further data on 60 mg once-daily daclatasvir plus 200 mg twice-daily asunaprevir for 24 weeks in 21 prior

interferon null responders and 22 people who were ineligible for or intolerant of pegylated interferon/ribavirin.

Participants were older on average (median age about 65 years) than those in most European and U.S. hepatitis C studies and all had genotype 1b -- both characteristics reflective of the hepatitis C patient population in Japan. About two-thirds were women. None had cirrhosis at study entry.

Results

Overall, 70% of participants achieved RVR at week 4 of treatment. At the end of the 24-week course of therapy, 88% had undetectable HCV RNA. The overall SVR4 rate was 81%. This fell to 77% at post-treatment weeks 12 and 24. By patient group, 91% of prior null responders and 64% of ineligible/intolerant participants achieved a cure. 3 patients experienced viral breakthrough while on therapy. 4 people relapsed after finishing treatment. Again, IL28B gene pattern had no apparent effect. Adverse events were common, but there were only 3 treatment discontinuations. Based on these findings, the researchers concluded, "The dual oral DAA combination of daclatasvir and asunaprevir, without [pegylated interferon/ribavirin], may offer a needed therapeutic alternative to [pegylated interferon/ribavirin]-containing regimens for many patients, including some difficult-to-treat groups."

They noted that almost all patients who were not cured showed low plasma concentrations of the 2 drugs, although many others with low levels nevertheless achieved SVR.

While side effects were common, the researchers emphasized that the adverse event profile was generally more favorable than that of pegyalted interferon/ribavirin for this difficult-to-treat patient population.

M Sulkowski, D Gardiner, E Lawitz, et al. Potent Viral Suppression with All-Oral Combination of Daclatasvir (NS5A Inhibitor) and GS-7977 (NS5B Inhibitor), +/-Ribavirin, in Treatment-Naive Patients with Chronic HCV GT1, 2, or 3. 47th Annual Meeting of the European Association for the Study of the Liver (EASL 2012). Barcelona, April 18-22, 2012. Abstract 1422.

F Suzuki, K Ikeda, J Toyota, et al. Dual Oral Therapy with the NS5A Inhibitor Daclatasvir (BMS-790052) and NS3 Protease Inhibitor Asunaprevir (BMS-650032) in HCV Genotype 1b-infected Null Responders or Ineligible/Intolerant to Peginterferon. 47th Annual Meeting of the European Association for the Study of the Liver (EASL 2012). Barcelona, April 18-22, 2012. Abstract 14.