Interferon-Free BMS Combo Yields 77% Cure Rate in Geno 1 Hep C

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A 24-week, interferon-free regimen pairing two drugs from Bristol-Myers Squibb—60 milligrams (mg) of daclatasvir, a once-daily NS5a inhibitor, and 200 mg of asunaprevir, a twice-daily hepatitis C protease inhibitor—is highly effective for first-time treatment takers and prior null responders with genotype 1b hepatitis C virus (HCV) infection.

According to Fumitaka Suzuki, MD, from Toranomon Hospital in Tokyo and his colleagues, who presented their data Thursday, April 19, at the 47th Annual Meeting of the European Association for the Study of the Liver (EASL) in Barcelona, the overall cure rate was 77 percent, which included 91 percent of prior null responders and 64 percent of people who could not tolerate or were ineligible for interferon.

Suzuki and his colleagues' trial builds on the initial success of this interferon-free regimen in Japanese prior null responders with HCV genotype 1b, as reported by Kazuaki Chayama, MD, PhD, at the 62nd annual meeting of the American Association for the Study of Liver Diseases (AASLD) in November in San Francisco. According to that study, 90 percent of the 10 study participants were cured.

Results originally reported by Chayama were combined with those involving additional null responders and were reviewed by Suzuki at EASL.

The participants in this study mirrored Japan's HCV epidemic, which is almost exclusively genotype 1b and concentrated among older people. The average age among the 21 null responders was 61. The average age among the 18 people who were not eligible for interferon therapy, along with four people who could not tolerate prior therapy containing interferon, was 68. More than half of the participants were female. None of them had cirrhosis.

Among null responders, three had the IL-28B CC genotype, which is linked with higher cure rates from interferon-based treatment; the remaining 18 people had the IL-28B CT genotype. Among interferon-intolerant/ineligible participants, 16 had the IL-28B CC genotype and six had the IL-28B CT genotype.

Ultimately, 74 percent of CC and 79 percent of TT genotype patients were cured.

The two-drug combo worked quickly. By week four, HCV was undetectable in 70 percent. Specifically, a rapid virologic response (RVR) was documented in 52 percent of prior null responders and 86 percent of the interferon-ineligible/intolerant group.

By week 12, 91 percent of people in both groups were undetectable. This percentage remained stable among prior null responders, yielding a 91 percent cure rate.

In the interferon-ineligible/intolerant group, 86 percent were undetectable at the end of treatment, dropping to 64 percent 12 weeks later. There were three viral breakthroughs during treatment and four relapses in this group, bringing the breakthrough rate to 7 percent and the relapse rate to 9 percent.

To explain the treatment failures, Suzuki and his team looked at both drug resistance and drug concentrations in people who were not cured. Overall, 10 of the 43 study participants (23 percent) had the Y93H mutation, which is associated with resistance to daclatasvir, before treatment. Five of them were cured, possibly because the effect of this mutation is minor without additional mutations.

In regard to drug concentrations, almost everyone who was not cured had lower drug concentrations, although treatment remained effective for some people despite having lower levels of both drugs in their bloodstream.

Suzuki and his colleagues noted that the potential association of virologic failure with pre-treatment NS5a mutations and lower drug levels requires additional study.

There were six serious adverse events in five patients: three cases of moderate to severe fever, a single case of health anxiety and symptoms that doctors could not find the cause of, and a single case of gastroenteritis with extremely elevated bilirubin levels, which led to treatment discontinuation at week two.

Two additional discontinuations because of elevated liver enzymes occurred at week 12 and week 16. One late discontinuation at week 52, during follow-up, was attributed to an abnormally low white blood cell count in a patient who was also treated with pegylated interferon and ribavirin.

During treatment, at least three patients experienced headache, upper respiratory infection, liver enzyme elevations, decreased eosinophils (infection-fighting white blood cells), mild diarrhea, fever, stomach and back pain, constipation and appetite loss.

The laboratory abnormalities that were considered severe to life-threatening—although there were no deaths during the study—were elevations in liver enzymes and total bilirubin, along with alterations in white blood cell (lymphocytes and leukocytes) and phosphorous levels. Most were a single case, and none of these occurred in more than four study participants.

Suzuki and his team considered the drug combination as “generally well tolerated.”

In conclusion, the combination of daclatasvir and asunaprevir is an effective option for people with HCV genotype 1b, and is also effective for people with HCV genotype 1a when it is used with pegylated interferon and ribavirin.

Current or Planned Daclatasvir and Asunaprevir Trials

Also presented at EASL were exciting results from a trial of daclatasvir and GS-7977, a trial that remains open to first-time treatment takers with HCV genotypes 1, 2 and 3.

Additional trials are evaluating daclatasvir with pegylated interferon and ribavirin in first-time treatment takers with HCV genotype 4, and in first-time treatment takers living with HIV and HCV genotype 1.

A trial is also comparing pegylated interferon-lambda plus ribavirin with either daclatasvir or asunaprevir—or both drugs—in first-time treatment takers with HCV genotype 1.

A trial comparing the combination of pegylated interferon, ribavirin and telaprevir to pegylated interferon, ribavirin and daclatasvir is open to first-time treatment takers with HCV genotype 1.

An additional trial open to people who were in the control arm of earlier Bristol-Myers Squibb trials is studying pegylated interferon, ribavirin and daclatasvir in treatment-experienced people with HCV genotypes 2 and 3, and pegylated interferon, ribavirin, daclatasvir and asunaprevir in treatment experienced people with HCV genotypes 1 and 4.

Another trial is looking at cure rates after treatment with pegylated interferon, ribavirin and daclatasvir in black, Latino and white first-time treatment takers with HCV genotype 1.

Also for first-time treatment takers with genotype 1 HCV is a study combining daclatasvir, asunaprevir and an experimental non-nuculeoside polymerase inhibitor, BMS-791325.

For prior null responders with HCV genotypes 1 and 4, HALLMARK QUAD is set to launch soon and will be evaluating a four-drug regimen consisting of pegylated interferon, ribavirin, daclatasvir and asunaprevir. Another upcoming study, HALLMARK DUAL, will look at daclatasvir and asunaprevir—with pegylated interferon and ribavirin added if treatment is not working—in prior partial and null responders; people who are interferon-ineligible/intolerant will be treated with daclatasvir and asunaprevir, and first-time treatment takers will be treated with daclatasvir and asunaprevir.

To learn more about clinical trials involving daclatasvir and asunaprevir, search clinicaltrials.gov.

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