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## **Sofosbuvir + velpatasvir + voxilaprevir (Vosevi) for HCV re-treatment**

Most people with chronic hepatitis C virus (HCV) infection will likely be cured when they take modern all-oral treatments (otherwise known as direct-acting antivirals, or DAAs) for their infection. Combination therapy with DAAs usually results in cure rates ranging between 90% and 95%. However, the remaining proportion of patients who are not cured will require re-treatment. The best combination for re-treatment is not clear.

DAAs work by impairing the activity of proteins and/or enzymes needed by HCV-infected cells to make more copies of this virus. One HCV protein that is impaired by DAAs is called NS5A. In cases where treatment has failed, a person's HCV can develop resistance to NS5A inhibitors. Examples of drugs that are inhibitors of NS5A include the following:

- daclatasvir (Daklinza)
- elbasvir (in Zepatier)
- ledipasvir (in Harvoni)
- ombitasvir (in Holkira Pak)

Pharmaceutical companies are developing combinations of drugs that may be suitable for re-treating people whose initial DAA regimen failed. One experimental combination is made by Gilead Sciences and consists of the following drugs in one pill:

- sofosbuvir – 400 mg
- velpatasvir – 100 mg
- voxilaprevir (formerly GS-9857) – 100 mg

As the brand name for this trio is not yet available, we will shorten the combination to sof-vel-vox.

Results from well-designed clinical trials of people with HCV whose previous regimens had failed suggest that when this trio of drugs is taken once daily for 12 consecutive weeks, it is effective against a broad range of genotypes, with cure rates ranging between 96% and 98%. Commonly reported adverse effects included headache, fatigue, diarrhea and nausea.

This trio of drugs is expected to be licensed in Canada by the end of the summer of 2017.

### **Study details**

Researchers in Canada, Western Europe, New Zealand, Australia and the U.S. recruited participants for a trial called Polaris-1. In this study, participants were randomly assigned to receive one of the following taken daily:

- sof-vel-vox – 263 participants
- placebo – 152 participants

The average profile of participants upon entering the study was as follows:

- 80% men, 20% women
- age – late 50s
- participants with severe scarring of the liver – 40%
- HCV viral load – 2 million IU/mL
- genotypes – the most common was genotype 1 (60%), followed by genotype 3 (30%). There were smaller proportions of participants with genotypes 2, 4, 5 and 6.

- 67% of participants had undergone one course of treatment in the past with other drugs
- about 50% of participants had previously used an NS5A inhibitor combined with an NS5B inhibitor
- most treated participants (80%) had experienced a relapse of HCV on their previous regimen

Participants underwent extensive laboratory and clinical assessments before, during and after the cessation of treatment.

## Results—Overall

Twelve weeks after the cessation of pill taking, the proportions of participants cured were distributed as follows:

- sof-vel-vox – 96% cured
- placebo – 0% cured

Most of the people cured with sof-vel-vox (253 of 263 participants) returned 24 weeks after they stopped taking the medication and blood tests continued to show that they were cured.

## Results—Focus on subgroups

Genotype 1 can be subdivided into different strains, or genotypes, such as 1a and 1b. Of these two strains, subtype 1a generally does not respond as well to treatment. Rates of cure distributed by genotype were as follows:

- 1a – 96% cured
- 1b – 100% cured

## Results—Focus on cirrhosis

In past clinical trials of earlier DAAs with people with extensive scarring of the liver, treatment failure occurred in some patients. In Polaris-1 there were participants with cirrhosis, however, none of them had the severe symptoms that can accompany cirrhosis. The distribution of cure rates in the present study were as follows:

- no cirrhosis – 99% cured
- cirrhosis – 93% cured

## Results—Focus on pre-existing resistance

In Polaris-1, researchers had viral resistance data on 248 participants who received sof-vel-vox. Of these people, researchers found that 205 (83%) had a strain of HCV at the start of the study that was resistant to previously used inhibitors of NS3 or NS5A. Most of these participants (97%) were cured after they completed their course of sof-vel-vox. This compares to a cure rate of 98% among people who entered the study without such resistant viruses.

## Results—Safety issues

In general, the combination of sof-vel-vox was well tolerated by participants.

The term *adverse events* is used by researchers to describe unfortunate events that can occur during a clinical trial. These events can include issues and symptoms that arise from exposure to treatment (side effects) and/or the underlying disease process or from factors that have nothing to do with the clinical trial, such as accidents, injuries and other trauma.

The overall distribution of adverse effects reported by participants was as follows:

- sof-vel-vox – 78%
- placebo – 70%

The most common adverse events reported by participants who received sof-vel-vox were as follows:

- headache – 25%
- fatigue – 21%

- diarrhea - 18%
- nausea - 14%

The most common adverse events reported by placebo users was as follows:

- fatigue - 20%
- headache - 17%
- diarrhea - 12%
- dizziness - 9%

Based on this reporting, it is likely that some adverse events were related to the underlying disease process but some were also caused by the drugs. For instance, it is likely that some of the following symptoms were related to exposure to study medicines:

- headache
- fatigue
- diarrhea

Similar side effects have been seen with other combinations of HCV treatments. Usually the side effects are temporary and fade after several weeks or, at worst, after the course of treatment ends.

Adverse events graded as serious occurred in only seven people (2%) who took sof-vel-vox. Serious adverse events also occurred in seven people who took placebo.

## **Lab test results**

Very unusual lab tests results were not common during the study, affecting a total of 7% of participants who received sof-vel-vox. Note that a total of 14% of participants who took placebo had similarly abnormal lab tests. The grading and distribution of abnormal or very abnormal blood tests affected the following substances measured:

- creatine kinase (elevated levels of this enzyme are possibly suggestive of muscle injury)
- blood sugar (consistently elevated levels can indicate the development of pre-diabetes or worsening of pre-existing diabetes)
- lipase (elevated levels of this enzyme are possibly suggestive of an inflamed pancreas gland)

Despite these lab test results, no participants developed symptoms of any of the issues associated with these tests.

## **Bear in mind**

Overall, the results from Polaris-1 show that the combination of sof-vel-vox is highly effective at curing people of chronic HCV whose prior regimen failed. In this and other clinical trials, sof-vel-vox was effective against a range of genotypes.

There were several shortcomings to the study, as follows:

Only a small proportion of participants had been treated with the latest DAAs, such as Zepatier (a fixed-dose combination of elbasvir and grazoprevir) or Epclusa (a fixed-dose combination of sofosbuvir and velpatasvir). So, the effectiveness of sof-vel-vox against strains of HCV that are resistant to these drugs is not clear.

Certain populations were excluded from the study, including people co-infected with HIV or hepatitis B virus and people who had symptoms of cirrhosis. As such, it is not clear how effective sof-vel-vox will be in these populations.

—Sean R. Hosein

## **REFERENCE:**

Bourlière M, Gordon SC, Flamm SL, et al. Sofosbuvir, velpatasvir, and voxilaprevir for previously treated HCV infection. *New England Journal of Medicine* . 2017; *in press* .

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