Sofosbuvir + velpatasvir for hepatitis C genotypes 2 and 3

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Hepatitis C virus (HCV) infects the liver, causing inflammation. Chronic infection with this virus results in healthy liver tissue being replaced with scar tissue. Over time, as scarring spreads throughout this vital organ, cirrhosis sets in and the liver becomes increasingly dysfunctional. If HCV is left untreated, serious complications can develop and the risk of liver cancer is increased.

There are many strains, or genotypes, of hepatitis C virus, such as 1, 2, 3, 4, 5 and 6. These genotypes can be further divided into subtypes, such as 1a, 1b and so on.

Genotype 1 is relatively common among people with HCV in Canada and other high-income countries. Due to travel and immigration, other genotypes can also be found in high-income countries.

Focus on genotype 3

Researchers have found that infection with genotype 3 can result in a more rapid pace of liver injury compared to other genotypes. Furthermore, infection with genotype 3 is not as easily cured as genotype 2 and other strains.

Over the past several years, the standard treatment for genotype 2 or 3 infections in high-income countries has been the combination of two drugs: sofosbuvir (Sovaldi and also in Harvoni) together with ribavirin for between 12 and 20 weeks in the case of genotype 2 and for 24 weeks in the case of genotype 3. Sofosbuvir is designed to attack HCV-infected cells and cripple an enzyme (called NS5B) needed to make new copies of HCV. Ribavirin is a broad-spectrum antiviral drug.

However, ribavirin can have many side effects, including nausea, vomiting, diarrhea, rash and difficulty falling asleep and staying asleep. Ribavirin can also cause anemia and can temporarily weaken the bone marrow.

The pharmaceutical company Gilead Sciences has developed a pill containing the following two drugs that can be taken once daily:

- sofosbuvir 400 mg + velpatasvir 100 mg

Velpatasvir, formerly code-named GS-5816, is designed to impair the activity of an enzyme (called NS5A) needed by HCV-infected cells. The combination of sofosbuvir and velpatasvir has potent activity against all genotypes of HCV in lab experiments with cells and HCV. Large trials are needed to confirm this combination’s effectiveness against genotypes 2 and 3.

Recent clinical trials

In two randomized, controlled clinical trials code-named Astral-2 and Astral-3, researchers from high-income countries tested the combination of sofosbuvir + velpatasvir in more than 800 participants. This combination resulted in a greater rate of cure (99%) than the combination of sofosbuvir + ribavirin (94%) in cases of genotype 2. In these same studies, participants with genotype 3 achieved higher cure rates when using sofosbuvir + velpatasvir (94%) than they did with sofosbuvir + ribavirin (80%). Common side effects associated with sofosbuvir + velpatasvir included tiredness or lack of energy, headache and nausea.

Study details
Researchers recruited participants for the two trials from the following countries:

- Australia
- Canada
- France
- Germany
- Italy
- New Zealand
- U.K.
- U.S.

We will provide the study details pertaining to each trial separately.

Researchers considered participants cured if the HCV viral load in their blood was less than 15 IU/mL (undetectable) 12 weeks after the cessation of therapy. This is called a sustained virological response and is written as SVR$_{12}$.

**Astral-2**

Researchers assigned 266 participants with genotype 2 to receive one of the following regimens:

- sofosbuvir + velpatasvir for 12 weeks
- sofosbuvir + ribavirin for 12 weeks

The average profile of participants when they entered Astral-2 was as follows:

- age – 57 years
- 60% men, 40% women
- major ethno-racial groups: white – 88%; black –7%; Asian – 2%

Participants had the following HCV-related factors:

- viral load – 6.5 log
- presence of cirrhosis – 14% (note that all participants who had cirrhosis did not have symptoms associated with this condition)
- previous HCV treatment – 86%

**Astral-3**

Researchers assigned 552 participants with genotype 3 to receive one of the following regimens:

- sofosbuvir + velpatasvir for 12 weeks
- sofosbuvir + ribavirin for 24 weeks

The average profile of participants upon entering Astral-3 was as follows:

- age – 50 years
- 62% men, 38% women
- major ethno-racial groups: white – 90%; black – 1%; Asian – 9%

Participants had the following HCV-related factors:

- viral load – 6.3 log
- presence of cirrhosis – 30% (note that all participants who had cirrhosis did not have symptoms associated with this condition)
- previous HCV treatment – 74%

**Results—Astral-2**

Cure rates (SVR$_{12}$) differed by regimen as follows:
- sofosbuvir + velpatasvir for 12 weeks - 99% cured
- sofosbuvir + ribavirin for 12 weeks - 94% cured

Statistical analysis found that sofosbuvir + velpatasvir was superior to a regimen of sofosbuvir + ribavirin.

**Virological failure**

There were no cases of virological failure among participants who received sofosbuvir + velpatasvir. In contrast, in 5% of participants who took sofosbuvir + ribavirin, HCV was initially suppressed with treatment but then became detectable after treatment ended.

**Results—Astral-3**

Cure rates (SVR\textsubscript{12}) were distributed as follows:

- sofosbuvir + velpatasvir for 12 weeks - 95% cured
- sofosbuvir + ribavirin for 24 weeks - 80% cured

Statistical analysis found that sofosbuvir + velpatasvir was superior to a regimen of sofosbuvir + ribavirin.

**Virological failure**

Among 277 participants who received sofosbuvir + velpatasvir, 4% developed virological failure after treatment cessation. In contrast, among 275 participants who received sofosbuvir + ribavirin, rates of virological failure were 14%.

Since genotype 3 does not always respond well to treatment, it may be useful to examine cure results by the following subgroups:

*Examining outcomes whether cirrhosis was present or not*

sofosbuvir + velpatasvir

- cirrhosis – 91% cured
- without cirrhosis – 97% cured

sofosbuvir + ribavirin

- cirrhosis – 66% cured
- without cirrhosis – 87% cured

*Examining the effect of prior treatment on outcomes*

sofosbuvir + velpatasvir

- previous treatment - 90% cured
- no previous treatment – 97% cured

sofosbuvir + ribavirin

- previous treatment – 63% cured
- no previous treatment – 86% cured

**Pre-existing degrees of resistance**

Like all viruses, every time new copies of HCV are made, small changes or mutations in its genetic material can inadvertently occur. Sometimes, these mutations may be advantageous for HCV, as the virus can use these mutations to help resist the effect of treatment.

In Astral-2, there were no cases of treatment failure in participants with genotype 2 despite the presence of
mutations that conferred resistance to sofosbuvir + velpatasvir prior to treatment.

In Astral-3, researchers had data from blood samples taken before and after treatment from 274 participants with genotype 3. Analysis of HCV found in the blood samples of some participants before they began taking study drugs found that a minority (43 participants, or 16%) had a degree of naturally occurring resistance to treatment. Among these 43 participants, 88% were cured when treated with sofosbuvir + velpatasvir. Among 231 participants who did not have mutations in HCV that conferred resistance to treatment, 97% were cured.

**Adverse events (including possible side effects and complications related to liver disease)**

**Premature discontinuation** - distribution by regimen

- sofosbuvir + velpatasvir - according to researchers, one person left on the first day of the study due to “anxiety, headache and difficulty concentrating”
- sofosbuvir + ribavirin - nine people (3%) left over the course of the study for a broad range of reasons

**Side effects**

Common side effects in Astral-2 and Astral-3 were as follows:

- tiredness and/or lack of energy
- headache
- nausea

People who used ribavirin also had these side effects:

- difficulty falling asleep and staying asleep
- irritability
- cough

Such side effects have been reported in other clinical trials of ribavirin-containing regimens.

**Serious adverse events**

Bear in mind that it is not clear what relationship, if any, serious adverse events had to the study medications. In some cases, such events may have arisen because of the course of liver disease or for other reasons.

**Astral-2**

Four participants reported serious adverse events distributed by regimen as follows:

sofosbuvir + velpatasvir

- pneumonia
- intestinal inflammation and abdominal pain

sofosbuvir + ribavirin

- bone and/or joint pain
- depression

**Astral-3**

Below are some examples of reported serious adverse events distributed by regimen:

sofosbuvir + velpatasvir

- heart attack
- food poisoning
- bulging blood vessels (aneurysm) in the brain
ruptured cyst in an ovary

sofosbuvir + ribavirin

- bacterial infection of the skin
- stroke
- depression
- attempted suicide
- rash
- psychosis
- lung infection

**Bone marrow issues**

Decreased levels of the protein hemoglobin (found in red blood cells) occurred only among ribavirin users in Astral-2 and Astral-3 and were distributed as follows:

- sofosbuvir + ribavirin for 12 weeks - 5%
- sofosbuvir + ribavirin for 24 weeks - 4%

**Deaths—Astral-2**

There were two deaths, both of which occurred in people who received sofosbuvir + velpatasvir and subsequently died under the following circumstances:

- a 56-year-old woman died 131 days after cessation of treatment because her heart stopped beating
- a 58-year-old man died 112 days after cessation of treatment due to complications from tumours in his lung that had spread

**Deaths—Astral-3**

There were three deaths, all occurring in participants who received sofosbuvir + ribavirin. Two deaths occurred during treatment (one cause was unknown and the other was from violence). One death occurred after the cessation of treatment from an unknown cause.

**Key points**

In two studies with participants who had genotype 2 or 3, researchers found higher rates of cure in participants who used sofosbuvir + velpatasvir compared to those who used sofosbuvir + ribavirin. Furthermore, sofosbuvir + velpatasvir was associated with generally fewer side effects.

In cases where people had strains of HCV genotype 3 that had some pre-existing degree of resistance to treatment, researchers are not sure which approach to treatment is best. For instance, in such cases, would a longer course of treatment be appropriate? Would the addition of a third potent direct-acting antiviral be helpful? These are issues that need to be explored in future clinical trials.

**Resources**

- The debut of velpatasvir for hepatitis C - CATIE News
- Sofosbuvir + velpatasvir—Very high rates of cure against major strains of hepatitis C - CATIE News
- Sofosbuvir and velpatasvir for cirrhosis in hepatitis C - CATIE News
- CATIE’s hepatitis C information
- Understanding cirrhosis of the liver: First steps for the newly diagnosed - Canadian Association of Hepatology Nurses (CAHN), CATIE

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REFERENCES:


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