HARVONI – FDA

New Indications
On February 16, 2016, Gilead Sciences, Inc., announced that the Food and Drug Administration (FDA) approved additional indications for Harvoni in genotype 1 and 4 patients with advanced liver disease.

The approval for the use of Harvoni plus ribavirin for a treatment duration of 12 weeks is indicated for:
- liver transplant patients without cirrhosis - genotype 1 & 4
- compensated cirrhosis patients – genotype 1 & 4 (Child-Pugh A)
- genotype 1 decompensated patients (Child-Pugh B or C) including those who have undergone liver transplantation

Listed below is the table from the Highlights of Prescribing Information that details data from the SOLAR studies.

Table 16: Studies SOLAR-1 and SOLAR-2: SVR12 and Relapse Rates After 12 Weeks of Treatment with HARVONI and Ribavirin in Subjects with Genotype 1 HCV Who Were Post Liver Transplant and/or Who Had Decompensated Liver Disease

<table>
<thead>
<tr>
<th>Pre-Transplant</th>
<th>SVR12/Cure 300 patients</th>
<th>Relapse (288 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT B</td>
<td>87% (45/52)</td>
<td>12% (6/51)</td>
</tr>
<tr>
<td>CPT C</td>
<td>88% (35/40)</td>
<td>5% (2/37)</td>
</tr>
<tr>
<td>Post-Transplant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metavir Score FO-F3</td>
<td>95% (94/99)</td>
<td>3% (3/97)</td>
</tr>
<tr>
<td>CPT A</td>
<td>98% (55/56)</td>
<td>0% (0/55)</td>
</tr>
<tr>
<td>CPT B</td>
<td>89% (41/46)</td>
<td>2% (1/42)</td>
</tr>
<tr>
<td>CPT C</td>
<td>57% (4/7)</td>
<td>33% (2/6)</td>
</tr>
</tbody>
</table>

--- CONTINUED ON PAGE 2 ---
a. Five subjects transplanted prior to post-treatment Week 12 with HCV RNA<LOQ at last measurement prior to transplant were excluded.

b. Two subjects were excluded due to failure to meet the inclusion criteria for any of the treatment groups (i.e., did not have decompensated cirrhosis and had also not received a liver transplant).

c. Twelve subjects were excluded from relapse analysis because they died (N=11) or withdrew consent (N=1) prior to reaching the 12 week posttreatment follow-up visit.

There were 7 subjects with fibrosing cholestatic hepatitis (a reduction or stoppage in the flow of bile); all of the patients were cured.

Note: It was also listed in the package labeling that twelve genotype 4 patients who were post-transplant without cirrhosis or with compensated cirrhosis who were treated with Harvoni plus ribavirin for 12 weeks achieved similar cure rates as those with genotype 1 (above). In the studies, there was not enough data on people with decompensated cirrhosis—either pre- or post-liver transplant to make dosage recommendations.

---

Child-Pugh score is used to determine the survival time, the need for a liver transplant and type of treatment for someone with cirrhosis. The score is based on certain measurements including blood markers that may include bilirubin, albumin, and/or prothrombin time. It also takes into account certain conditions that occur as the result of worsening liver disease such as ascites and encephalopathy.

The Child-Pugh classes have estimated survival times of:

- **One year survival:** Class A: 100%; Class B: 81%; Class C: 45%
- **Two-year survival:** Class A: 85%; Class B: 57%; Class C: 35%

Note: This is a very simple overview of the Child-Pugh scoring system. There are many variables involved such as the type of liver disease (alcoholic liver disease, or hepatitis B could affect the estimated survival times).

---

Source: Company Press Release

Harvoni - HIGHLIGHTS OF PRESCRIBING INFORMATION


---

RG-101

On February 17, 2016, Regulus Therapeutic Inc. announced mid-stage results from their interim 8-week Phase II study of the combination of RG-101 plus approved direct-acting antiviral medications. The study included 79 treatment naïve genotype 1 and 4 patients.

RG-101 is a GalNAc-conjugated anti-miR targeting miR-122, a host factor for HCV infection. It is an injectable medication given at Day 1 and Day 29 plus 4 weeks of a once-a-day direct-acting antiviral medication:

- Harvoni (27 patients)
- Olysio (27 patients)
- Daklinza (25 patients)

Thirty-eight of the patients were evaluated through week 8 of follow-up. Ninety-seven percent (37 of 38 patients) had HCV RNA (viral load) that was undetectable. The majority of the side effects were considered mild to moderate. There were no treatment discontinuations.

---

— CONTINUED ON PAGE 3
In March 2016, Regulus also announced that it was starting a new Phase II study to evaluate the combination of RG-101 and GSK2878175 to treat genotype 1 and 3. GSK2878175 is a HCV polymerase inhibitor that will be dosed at 20mg for 12 weeks. “Concurrently, GSK will work on developing a “LAP” formulation of GSK2878175 as a single intra-muscular injection, providing the potential for a single-visit therapeutic treatment for HCV that could improve patient compliance through reduced dosing intervals and potentially extend opportunities for HCV therapeutic interventions.”

Now wouldn’t that be a breakthrough – two shots and be done with treatment!

Resources:
The Treatment section of the HCV Advocate Website includes the following information: highlights of the prescribing labels of all of the FDA-approved medications to treat hepatitis C, a Quick Reference Guide and expanded guide to drugs in development to treat hepatitis C, fact sheets about FDA approved HCV medications. http://hcvadvocate.org/treatment/

Hepatitis C Treatment and Cirrhosis

By Lucinda K. Porter, RN

In October 2015, the FDA issued this disturbing headline: “FDA Drug Safety Communication: FDA warns of serious liver injury risk with hepatitis C treatments Viekira Pak and Technivie.” The problem with that headline, is it needlessly scared patients who were taking Viekira Pak and Technivie, when in fact the warning pertained to patients who had advanced cirrhosis. In fact, doctors shouldn’t have been prescribing these drugs for their patients with that level of cirrhosis in the first place.

Treating cirrhotic hep C patients is tricky business. Cirrhosis is a serious medical condition, and although it can remain stable for a long time, it can also go south quickly. Patients with hep C-related cirrhosis clearly need to be treated, and treated soon. This article will discuss some of the risks and benefits of hepatitis C treatment in cirrhotic patients.

Some Words about Cirrhosis

Chronic hepatitis C virus (HCV) causes inflammation of the liver, eventually leading to tissue damage. Cirrhosis is the result of extensive scarring of the liver. The Centers for Disease...
Control and Prevention state that HCV typically causes cirrhosis in 5 to 20 percent of infected people over a period of 20 to 30 years. Overall, cirrhosis develops 20 to 30 percent of the time. Progression to cirrhosis may be accelerated in people who are older, obese, drink alcohol, or are immune-suppressed (such as people who are coinfected with HIV).

Cirrhosis has two levels: compensated and decompensated. Compensated cirrhosis means that the liver is still functioning relatively well. At this stage, the early symptoms may still be vague and some people may be unaware that they have cirrhosis.

Decompensated cirrhosis means that the liver is not functioning well. About one in five of those with HCV-induced cirrhosis will progress to a decompensated stage. Some serious complications that occur with decompensated cirrhosis are:

- Ascites, which is bloating from fluid build-up in the abdomen.

- Hepatic encephalopathy (HE) is a brain disorder that develops when the liver is unable to remove ammonia and other toxins in the body. HE may cause impaired concentration, sleep disturbances, confusion, or coma.

- Variceal hemorrhage is severe bleeding from enlarged veins in the esophagus and upper stomach.

Society of America offer clear treatment guidelines for people who have cirrhosis. Treatment recommendations for those with compensated cirrhosis are a bit different than the recommendations for noncirrhotic patients, depending on the medication and if this is a first treatment or retreatment.

Treatment for those with decompensated cirrhosis gets its own section in the HCV Guidelines. More importantly, the Guidelines recommend referring patients with decompensated cirrhosis to specialists, ideally in a liver transplant center. In other words, your local naturopath is not qualified to treat you if you have advanced liver disease. And if you think I am being overdramatic here, let me assure you that I am not. I failed in my effort to get a friend to let someone other than her naturopath treat her cirrhosis. When the naturopath eventually referred my friend to a liver transplant specialist, it was too late.

In general, the Guidelines advise proceeding cautiously. Generally, ribavirin is used with a combination of other drugs, such as daclatasvir and sofosbuvir or ledipasvir/sofosbuvir. The initial ribavirin dose is low and the amount is increased as tolerated. There are alternatives for those who aren’t able to tolerate ribavirin. For specific treatment recommendations based on genotype, visit the HCV Guidelines.
Risk and Benefits
Simply stated, if you have cirrhosis and you aren’t treated, you may live a long time with cirrhosis, get liver cancer, have kidney failure, need a liver transplant, or die. If you get treated, the treatment may or may not work or you may have complications during treatment. These complications are much like the ones people have from cirrhosis, and sometimes it isn’t the medication that caused the complication but the cirrhosis. However, patients and their families are quick to blame the treatment because it is human nature to connect the dots, even if there are other dots that can be connected.

However, if treatment works, you have a shot at a better life. As I mentioned before, studies indicate that cirrhosis may reverse in up to half of those who are cured, although it may take a year or two. And as wonderful as that is, there is something else that is wonderful—feedback from patients. In a large study conducted by Zobair M. Younossi and colleagues administered questionnaires to HCV patients with cirrhosis who underwent treatment that included sofosbuvir (Patient-Reported Outcomes in Chronic Hepatitis C Patients with Cirrhosis Treated with Sofosbuvir-Containing Regimens, *Hepatology*, November 2015). Researchers measured patient-reported outcomes (PROs), such as health-related quality of life, productivity, and fatigue.

HCV patients with cirrhosis showed significant impairment of PROs before initiation of treatment. No surprise there. PROs declined during treatment; again, no surprise, especially among patients whose treatment used peginterferon. But, the encouraging outcome, was patients who achieve a cure (SVR-12) had improved PROs, even if they had cirrhosis.

When HCV Treatment Fails
Sadly, HCV treatment doesn’t always work. And in some cases, it may fail not just once, but multiple times. Fortunately, new treatments are in the pipeline, and they just keep getting better. While you are waiting, devote your time to staying healthy. Avoid alcohol, eat a nutritionally-rich diet, and aim for a healthy weight. Don’t take vitamins or other dietary supplements unless prescribed by your doctor. Tell your doctor all the medications you take, and be sure you know how to take them. If you take acetaminophen (Tylenol), ask your doctor what a safe amount is, and check all products for added acetaminophen so you don’t take extra by mistake.

A cirrhosis diagnosis means more frequent regular medical tests and check-ups. Your doctor will monitor you for signs of liver cancer, kidney failure and worsening of your liver disease along with indications that you may need a liver transplant. In addition to office visits, expect more frequent lab and ultrasound tests. Keep your immunizations current.

Lastly, talk to your doctor about the benefits of drinking coffee, specifically the caffeinated kind. Many studies show that caffeinated coffee use is associated with improvement in liver tissue. At last, something delicious that might be good for us!

Resources
An Overview of HCV Disease Progression

A Guide to Understanding Hepatitis C

Lucinda K. Porter, RN, is a long-time contributor to the HCV Advocate and author of *Free from Hepatitis C* and *Hepatitis C One Step at a Time.* She blogs at www.LucindaPorterRN.com and HepMag.com
**Article: Cohort study of the impact of direct acting antiviral therapy in patients with chronic hepatitis C and decompensated cirrhosis—G R Foster et al.**


**Study Aims and Results**

The study was a retrospective study that analyzed data from 2014 in genotype 1 and 3 patients treated in an Expanded Access Programme (EAP). The clinicians were able to use their treatment of choice—sofosbuvir, ledipasvir or daclatasvir, with or without ribavirin. There was also a group of patients who were not treated that was the comparator group. Cure and improvement in MELD scores were deemed as successful outcomes. MELD is the standard employed by the Organ Procurement and Transplant Network (OPTN) and determines who is the highest priority to receive liver transplants in the US—scores were taken before and after treatment to find out if successful treatment improved scores.

There were 467 patients treated of whom 409 had decompensated cirrhosis.

**Conclusions**

The cure rates were for genotype 1 - 91% and 69% for genotype 3. Importantly, the MELD scores improved in treated patients on average -0.85, but worsened in untreated patients on average + 0.75).

**Editorial Comment**

In the days of pegylated interferon and ribavirin therapy, the chances of successfully treating people with hepatitis C, who had decompensated cirrhosis and in those who had a liver transplant was slim to very slim. The side effects could take up the entire newsletter. Also, the side effects could have led to an accelerated decompensation process and death.

It is amazing how far hepatitis C treatment has come in such a short period. These ‘miracle’ direct-acting antiviral medications have very good to excellent cure rates and the side effects are mostly tolerable even for this vulnerable population.

Hopefully, we can treat and cure more people before HCV disease progression reaches this stage! Don’t forget to check out the two related articles in this issue in HealthWise and HCV Drugs.

---

*The side effects could take up the entire newsletter. Also, the side effects could have led to an accelerated decompensation process and death.*

—Alan Franciscus, Editor-in-Chief
Statins are known to decrease portal pressure in patients with cirrhosis and increase survival times of patients who have had bleeding episodes from varices. Statins have also been known to cause damage to the liver. Many physicians are reluctant to prescribe statins because of the potential risk to patients with liver disease.

The current study reviewed data from the Veteran Affairs Clinical Case Registry to determine if long-term use of statins is safe in patients with hepatitis C-related decompensated cirrhosis and if statins improve the survival time in patients with compensated cirrhosis. A total of 685 people who were statin users were matched with 2062 people who were nonusers for comparison.

Based on the current study, the risk of liver decompensation and death was more than 40% lower for the group of people that used statins. The authors did not recommend the use of statins for patients with liver disease or hepatitis C but importantly, they did not state that statins should be avoided.

This is good news! As the hepatitis C population ages, the use of statins will be more of an issue. It’s good to know that these studies are showing that statin use is safe. If people have compensated cirrhosis, it’s even more good news. Of course, one study doesn’t make it a fact—more studies are needed. A larger study that proves that statin use is safe, effective and proves to be protective as well would be a boom to people living with hepatitis C.
Study Aims and Results
The current study analyzed the ION phase 3 clinical trials of the cure rates of black patients compared to non-black patients. Ledipasvir plus sofosbuvir with and without ribavirin was given for 8, 12 and 24 weeks.

A total of 1,949 patients were treated in the ION studies. Of these 308 (16%) were black—on average the black patients were older, had a higher body mass index and were more likely to be IL28B non-CC—all of these are typically negative predictors of treatment response.

Conclusions
The overall cure rate in black patients was 95% and 97% in non-black patients. The rate of relapse was 3% compared to 2% in non-black patients.

The most common side effects were fatigue, headache, nausea, and insomnia. The majority of adverse events occurred in the groups who received ribavirin.

Editorial Comment
These are impressive results especially when you consider that previous studies with pegylated interferon plus ribavirin had inferior cure rates among Blacks compared to Caucasians.

However, in the ION-4 trial, the cure rate in the Black patients was 90% compared to 99% in the non-black patients. It was the first direct-acting antiviral clinical study to find a difference in cure rates between Blacks and non-black patients. More studies are needed to determine why this occurred.

These are impressive results especially when you consider that previous studies with pegylated interferon plus ribavirin had inferior cure rates among Blacks compared to Caucasians.
WE HAVE UPDATED THE BASICS!

The purpose of this “Basics” is to provide easy to understand information for those who want to learn the basics about hepatitis C.

UPDATED FACT SHEETS

We have also updated and reposted our fact sheet:
Acetaminophen in English and Spanish

HAVE AN EVENT?

Do you have an event you’d like us to list? If you fill out the online form, we will get you on our calendar.

© 2016 Hepatitis C Support Project