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I HEPATITIS C VIRUS

A. HCV treatment in advanced liver disease

Hepatitis C virus (HCV) infects the liver, and in many cases this infection becomes established in that organ. Despite this setback, the immune system continually attempts to clear the liver of this infection, and in the process of doing so, it triggers a state of chronic low-level inflammation in the liver. Chronic immune-related inflammation in the liver slowly degrades this organ. Over time, healthy liver tissue is replaced with useless scar tissue. Eventually, most of the liver becomes scarred—a state called cirrhosis.

Initially, cirrhosis may be symptom free, a situation called compensated cirrhosis. However, over time, symptoms associated with cirrhosis can appear; this is called decompensated cirrhosis. Such symptoms can include the following:

- difficulty falling asleep or staying asleep
- difficulty thinking clearly and problems with concentration
- unexpected mood changes
- enlarged veins in the stomach and throat that can sometimes burst, leading to internal bleeding
- buildup of fluid in the abdomen
- swelling in the legs and/or feet
- abdominal infections
- itchy skin
- yellowing of the skin

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Over the past several years, randomized clinical trials conducted by pharmaceutical companies have shown that all-oral therapy, commonly called direct-acting antivirals (DAAs), can cure many people of HCV. Examples of DAAs used in Canada and other high-income countries include the following:

- Epclusa (sofosbuvir + velpatasvir)
- Harvoni (sofosbuvir + ledipasvir)
- Maviret (glecaprevir + pibrentasvir)
- Zepatier (elbasvir and grazoprevir)

As a general rule, pharmaceutical companies tend to pick young and relatively healthy adults for trials of their drugs, including DAAs. Although it is true that some participants in clinical trials with DAAs had cirrhosis, the vast majority of people who entered these trials did not have cirrhosis and/or symptoms of cirrhosis. Therefore, now that DAAs have been approved by regulatory authorities, it is important that clinics conduct further clinical trials, called observational studies, to try to understand the ability of these drugs to treat people with cirrhosis.

Enter the Target consortium

Researchers in Canada, Germany, Israel and the U.S. have collaborated in studies of DAAs; this collaboration is called Target. Clinics that are a part of Target prescribe DAAs according to the local standard of care and share their data with other clinics so that large numbers of participants can be assessed and trends can be examined. Target has produced previous analyses that have been useful with older DAAs.

In their most recently released analysis, researchers with Target focused on data collected from people who had cirrhosis and severe liver disease.

MELD

More than a decade ago, researchers at the Mayo Clinic in Rochester, New York, developed a scoring system to help predict the risk of death over the 90 days after a person with severe liver injury was admitted to hospital. The scoring system is called MELD (Model for End-stage Liver Disease) and is useful for assessing patients with severe liver disease, including those awaiting a liver transplant. The greater the MELD score, the greater the risk of death within 90 days. To calculate a MELD score, the values of several blood tests are put into an equation.

Study details

In the present study, researchers focused on data collected from 488 people. A brief summary of the different genotypes of HCV and the treatments used are as follows:

Genotype-1 (GT-1) – 352 people
- commonly used medicines were: Epclusa, Harvoni and Zepatier

GT-2 – 32 people
- commonly used medicines were: Epclusa and the combination of sofosbuvir + daclatasvir

GT-3 – 85 people
- commonly used medicines were: Epclusa and the combination of sofosbuvir + daclatasvir

Note that regardless of the genotype, in about 30% of cases, physicians chose to add the broad-spectrum antiviral drug ribavirin to each regimen in the hope of increasing the chances of cure.

The average profile of all participants is as follows:

- 67% men, 33% women
- major ethno-racial groups: 71% white, 15% black
- 48% of participants were treatment experienced, with 20% having previously used a second-generation DAA
- 67% of participants had symptoms of cirrhosis
- MELD score – 12; this suggests that there was about a 6% chance of death over the subsequent 90 days for the group as a whole

Results

Overall, 90% of participants were cured regardless of the regimen used.

Factors associated with being cured included the following:

- infected with HCV genotype 1a
- having a body mass index (BMI) of 25 or less (suggestive of normal weight or being underweight)
- using ribavirin

Adverse events

About 73% of participants reported adverse events. In clinical trials, the term *adverse events* covers a broad range of unfortunate events that occurred, including drug-related side effects and symptoms associated with the underlying disease process. Common adverse events in the present study were as follows:

- lack of energy – 25%
- headache – 16%
- nausea – 13%
- problems with sleep – 9%

Focus on MELD

Since MELD can predict the chances of death in the short-term, it is important to find out if there were any changes with this score after people were cured. However, in the present study, in which most participants had symptoms associated with cirrhosis, MELD scores generally showed only a modest decline, suggesting a small decrease in the risk of death over the short-term after cure. Bear in mind that since most patients had extensive liver disease, it will take years for that organ to recover from HCV-associated injury even though cure was achieved. However, for about 26% of participants, MELD scores decreased by three or more points. Researchers found that people who had a decrease of three or more points in their MELD score were more likely to have the following profile:

- women
- GT-1a
- having a high MELD score at the start of the study
- having a high level of bilirubin in their blood at the start of the study

Deaths

Five people died during the study from complications associated with the following:

- heart disease
- severe inflammation associated with bacterial infections
- failure of several organs
- other causes that were unstated

There was no evidence that DAAs and/or ribavirin caused deaths seen in this study.

Ten other people died after the end of their course of treatment, mostly of cirrhosis-related complications, including liver cancer.

Despite being cured, "patients with advanced liver disease may still be at considerable risk of [developing symptoms associated with cirrhosis] and liver cancer," stated the Target researchers.

REFERENCE:

Verna EC, Morelli G, Terrault N, et al. Direct-acting antiviral HCV therapy is safe and effective in patients with decompensated cirrhosis: Real-world experience from the HCV-Target cohort. *International Liver Congress*, 11-15 April 2018, Paris, France. Presentation PS-033.

B. HCV cure and the long road to recovery

Chronic hepatitis C virus infection (HCV) results in abnormalities in the way the body processes cholesterol and how it regulates blood sugar levels. HCV also causes inflammation within the liver.

Researchers at the University of Maryland in Baltimore have been monitoring participants infected with HCV or co-infected with HCV and HIV for several years, both before, during and after their treatment with direct-acting antivirals (DAAs) for HCV and subsequent cure of this virus. For many participants, blood tests did not immediately normalize after cure but took several years to do so.

Study details

The distribution of viral infections among participants in this study was as follows:

- HCV alone – 194 people
- HCV and HIV – 75 people

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

- 57 years
- 67% men, 37% women
- most (93%) did not have severe scarring of the liver (cirrhosis)

Participants were monitored for up to four years after being cured.

We now focus on the trends in certain blood tests, particularly those concerning fatty substances, over time.

Results

LDL-C ("bad" cholesterol)
Levels of LDL-C in the blood were low prior to treatment. Initiating DAA therapy was associated with a significant increase in LDL-C levels. However, a year after achieving cure, LDL-C levels began to decrease. By the fourth year after cure, LDL-C levels had decreased significantly, and in some cases approached the low levels seen prior to treatment. No significant changes occurred in levels of "good" cholesterol (HDL-C) during the study.

Triglycerides
Prior to DAA therapy, levels of triglycerides in the blood were significantly elevated. Upon initiating DAA therapy, triglyceride levels fell modestly. However, four years after cure, triglyceride levels became relatively low.

Liver enzymes
Levels of the liver enzymes AST (aspartate aminotransferase) and ALT (alanine transaminase) are usually elevated in people with chronic HCV infection. This elevation occurs because of ongoing inflammation and injury to the liver. However, after initiation of DAA therapy, levels of these liver enzymes in the blood fell significantly and stayed relatively low. This change provides evidence that the livers of participants in this study are recovering.

Average blood sugar levels
The average red blood cell lives for about four months. During this time, sugar binds to a protein in the red blood cell, and, when measured, this protein can reveal the average blood sugar level over the past four months. To get an idea of the average blood sugar level over the previous four months, a blood test measures the level of sugar that is bound to a protein called hemoglobin A1c (HbA1c). In the present study there were no apparent effects of DAAs on HbA1c.

Putting it all together

Taken together, the results of the Baltimore research show that changes in lipids and liver enzyme levels can occur as soon as DAA therapy is initiated. Over time, these measurements show a trend to improvement and, in many cases, normalization. People co-infected with HCV and HIV also had similar trends in the blood tests mentioned.

REFERENCE:

Emmanuel B, Stafford KA, Magder LS, et al. Sustained virologic response leading to improved long-term metabolic and inflammatory outcomes. *International Liver Congress*, 11-15 April 2018, Paris, France. Poster FRI-390.

C. Vancouver—providing a broad spectrum of care helps reduce the risk of re-infection after HCV cure

Undiagnosed, untreated or poorly managed mental health conditions can drive some people to substance use. In some cases, substance use can become problematic and can destabilize the lives of users. Some people who share equipment for substance use may become infected with hepatitis C virus (HCV) and HIV. In order to help people begin the process of recovering from problematic substance use and, in some cases, hepatitis C virus—and to help them remain free of HCV re-infection—a range of support services is needed.

Doctors at the Vancouver Infectious Disease Centre have been caring for people who use substances and who also have viral infections such as HCV and HIV. In the latest report from the centre, a team of healthcare workers reviewed data collected from 148 people who had been using substances for many years. All participants had received treatment with direct-acting antivirals (DAAs) between June 2015 and May 2017 and had been cured.

At the centre, participants received multidisciplinary care to address the following list of issues compiled by the healthcare workers:

- general medical care
- psychiatric care
- addiction-related care
- social needs

This care was provided before, during and after treatment with DAAs. All participants were substance users.

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

- 79% men, 21% women
- age – 69 years
- 66% used heroin and 44% used cocaine (some people used both substances); researchers provided ongoing urine screening to monitor substances used
- the most common type of HCV infection was genotype 1a, infecting 63% of participants
- 23% had extensive scarring of the liver
- 10% were co-infected with HIV

Commonly used DAAs during the study were as follows:

- Epclusa
- Harvoni
- Holkira Pak
- Zepatier

Results

After an average of 66 weeks of monitoring, no one became re-infected.

The Vancouver team stated that providing relevant health and social services to patients before, during and after HCV treatment helped to decrease the risk of HCV re-infection.

The study was done in an era when overdoses among people who inject drugs have increased in Vancouver (and other parts of North America). These overdoses are increasingly caused by exposure to fentanyl and its analogues. However, no one in the study experienced a fatal overdose. Thus, it is possible that the multidisciplinary care and services provided by the clinic not only helped to prevent re-infection with HCV but also helped to prevent fatal overdoses.

REFERENCE:

Alimohammadi A, Thiam A, Holseka J, et al. Recurrent viremia after successful hepatitis C virus therapy with direct-acting antiviral therapy in a cohort of people who use drugs. *International Liver Congress*, 11-15 April 2018, Paris, France. Poster FRI-405.

D. Germany—experience with Maviret after licensure

Maviret is the brand name of a pill containing two anti-HCV drugs—glecaprevir and pibrentasvir. Maviret has been approved in Canada, the U.S. and the European Union for the treatment of hepatitis C virus (HCV) infection. For further information about how Maviret is used, see the CATIE factsheet on this drug.

Clinical trials tend to enroll relatively healthy people, so it is important to test newly licensed drugs in the people who attend clinics to get a better idea of the effects of the drug in a wider population.

Researchers in Germany collaborated in a large study with adults who had chronic HCV infection who either had not previously received HCV treatment or whose past treatment with interferon or the combination of sofosbuvir and ribavirin had failed. Data were collected between July 2017 and February 2018. In total, 321 people have completed treatment in this analysis and viral load information is still being collected. However, researchers confirmed that 96 people have been cured and 225 are currently being monitored.

The average profile of participants was as follows:

- 68% male, 32% female
- age – 47 years
- HCV viral load – 1.5 million IU/mL
- 90% had not previously been treated
- 71% had another co-existing health condition (such as cardiovascular disease)

The distribution of genotypes was as follows:

- GT 1a – 34%
- GT 1b – 17%
- GT 2 – 7%
- GT 3 – 35%
- GT 4 – 5%
- GT 5 or 6 – less than 1%

Most (98%) participants were treated with an eight-week regimen and the remaining 2% with a 12-week regimen.

Results

Three participants left the study prematurely, in two cases because of diarrhea or nausea. One participant stopped visiting the clinic. None of these people had serious symptoms of liver injury.

Among the remaining 93 patients who were cured and whose data were complete, common adverse events reported in the study were as follows:

- lack of energy – 9%
- headache – 8%

Such symptoms are commonly seen in people who have been treated with direct-acting antivirals (DAAs), regardless of the DAAs used, and resolve after a course of treatment has finished.

Severely abnormal blood test results were rare and occurred in three people. In two cases this was because of elevated liver enzymes, and in the third it was due to elevated levels of the waste product bilirubin. These abnormal blood test results were temporary.

The results from this observational study in Germany are very similar to the results seen with Maviret in clinical trials.

REFERENCE:

Berg T, Stoehr A, Pangerl A, et al. First real-world data on safety and effectiveness of glecaprevir/pibrentasvir for the treatment of patients with chronic hepatitis C virus infection: data from the German Hepatitis C registry. *International Liver Congress*, 11-15 April 2018, Paris, France. Presentation GS-007

E. Experience with Maviret in northern Italy

Researchers in the Lombardy region in northwest Italy collected data from 30 clinics in the area where people with chronic hepatitis C virus (HCV) used Maviret between October 2017 and January 2018. Participants took Maviret for the following durations:

- eight weeks – 639 people
- 12 or 16 weeks – 84 people

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

- age – 58 years
- HCV genotypes 1 to 4 were the most common
- viral load – 1 million IU/mL
- most (83%) had a modest degree of liver injury, graded as F0 to F2
- 50 people had both HCV and HIV
- 71% had other co-existing conditions, including cardiovascular disease, mental health issues and chronic kidney disease
- 26% were on methadone or buprenorphine

Results

Not all the data have been fully analysed; most participants have completed their course of treatment and are being monitored until their final blood test. Preliminary results from the fourth week after cessation of treatment suggests that as many as 97% of participants have been cured.

Here is the distribution of cure rates that are available (12 weeks after the cessation of treatment):

- 8-week regimen – 98% cured (43 of 44 people)
- 12- or 16-week regimen – 100% cured (five of five people)

One person relapsed, as HCV became detectable four weeks after cessation of therapy. This person was 51 years old and had not previously been treated. He had minimal liver injury and was infected with genotype 3a with a pre-study viral load of about 200,000 IU/mL. His adherence to Maviret was considered good. Researchers are unsure why relapse occurred.

Adverse events

Side effects were not common and were distributed as follows:

Lack of energy
- 8-week regimen – 2%
- 12-week regimen – 0%

Nausea
- 8-week regimen – 1%
- 12-week regimen – 2%

Itchy skin
- 8-week regimen – 1%
- 12-week regimen – 7%

Adverse events leading to premature cessation of treatment were uncommon and distributed as follows:

- 8-week regimen – one person
- 12-week regimen – three people

The adverse events that were linked to the premature cessation of treatment were as follows:

- nausea – two people
- itchy skin – one person
- yellowing of skin – one person

Deaths

Three people died while in the study, one on the 8-week regimen and two on the 12-week regimen. Investigation revealed that none of the deaths were due to Maviret but rather to the following causes:

- disseminated blood clots
- stroke
- a severe inflammatory response to bacterial infection

Bear in mind

The interim results from the Lombardy region show high rates of cure and low rates of side effects with Maviret. These results are similar to what was observed in phase III clinical trials.

REFERENCE:

D'Ambrosio R, Colli A, Colombo A, et al. Real-life effectiveness and safety of glecaprevir/pibrentasvir among 723 Italian patients with chronic hepatitis C: The Navigator-II study. *International Liver Congress*, 11-15 April 2018, Paris, France. Presentation GS-013.

F. Maviret for people with HCV and chronic kidney disease

In a study called Expedition-5, researchers enrolled 110 participants who had moderate to severe kidney injury and chronic HCV infection. Participants were assigned to receive one of the following regimens:

- 8 weeks of Maviret – 84 people
- 12 weeks of Maviret – 13 people
- 16 weeks of Maviret – four people

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

- age – 60 years
- most participants had HCV genotypes 1 to 4
- viral load – 1 million IU/mL
- most participants had a moderate degree of liver injury
- no participant was co-infected with hepatitis B virus

Staging of kidney disease

The researchers used the estimated glomerular filtration rate (eGFR) to assess participants' degree of kidney injury. Participants fell into the following categories based on eGFR results:

- stage three – an eGFR between 30 and 44
- stage four – an eGFR between 15 and 29
- stage five – an eGFR less than 15 or being dependent on dialysis (about 60% of participants required dialysis)

Results

Results were made available for 101 (of 110) participants, as the remainder were still being monitored to assess if they were cured from HCV.

Of the 84 people who were taking the 8-week regimen, 81 were cured. Two participants left the study prematurely because of itchy skin, and in one case, intestinal obstruction. The third person stopped attending the study clinic.

Among the 13 people who took the 12-week regimen, all were cured.

Among four people who took the 16-week regimen, all were cured.

Adverse events

The most common adverse event was itchy skin, reported in 6% of participants.

Lab tests did not detect any serious abnormalities.

Most participants with stage 3 or 4 chronic kidney disease did not have their eGFRs change after being cured. However, two participants had their eGFR improve after being cured and two others had their eGFR decline after being cured.

Bear in mind

- All participants who completed treatment were cured.
- Maviret was generally well tolerated, with the most common side effect being itchy skin in a minority of participants.
- Maviret did not affect the health of the kidneys.

REFERENCE:

Persico M, Aglitti A, Bruchfeld A, et al. Efficacy and safety of glecaprevir/pibrentasvir in renally-impaired patients with chronic hepatitis C virus genotype 1-6 infection. *International Liver Congress*, 11-15 April 2018, Paris, France. Poster THU-363.

G. About treatments for HCV in Canada

TreatmentUpdate has always reported on the experimental use of treatments for HCV and other conditions. For information about how major HCV treatments are used in Canada, please see CATIE's HCV drug chart as well as the factsheets below:

- Epclusa (sofosbuvir + velpatasvir)
- Harvoni (sofosbuvir + ledipasvir)
- Maviret (glecaprevir + pibrentasvir)
- Vosevi (sofosbuvir velpatasvir + voxilaprevir
- Zepatier (elbasvir and grazoprevir)

Disclaimer

Decisions about particular medical treatments should always be made in consultation with a qualified medical practitioner knowledgeable about HIV- and hepatitis C-related illness and the treatments in question.

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