Hepatitis C virus (HCV) infection attacks the liver, causing inflammation of this organ. In the struggle between the immune system and HCV, the liver becomes injured as healthy tissue is gradually replaced with useless scar tissue. If HCV is left untreated, most of the liver becomes severely injured and scar tissue becomes predominant; at this stage, cirrhosis has developed. As the liver degrades and is unable to filter blood, other organs such as the kidneys and brain are affected and complications develop.

Many people who have HCV may not be aware that they carry the virus. HCV testing can help uncover hidden infection and can lead to discussion about treatment options.

As recently as six years ago, treatment of chronic HCV consisted of a long-lasting form of interferon and the antiviral drug ribavirin. Interferon activates the body’s antiviral defence system and ribavirin is an old drug with activity against different viruses. Interferon had to be injected weekly and caused side effects that at best would be considered highly unpleasant. The combination of both drugs had to be taken for 24 to 48 consecutive weeks and cure rates usually ranged between 60% and 75%.

About 12 years ago researchers created the first experimental direct-acting antiviral (DAA) called ciluprevir. However, in clinical trials HCV quickly developed resistance to this compound and it was
abandoned. Pharmaceutical companies then began developing other DAAs.

By 2011 the first generation of more effective DAAs arrived—boceprevir and telaprevir—though they had to be used in combination with interferon and ribavirin. These DAAs could also have side effects and were not highly effective, with cure rates averaging between 65% and 75%.

Spurred by the relative recent success of DAAs, companies began making more potent all-oral drugs against HCV, including the following:

- Daclatasvir (Daklinza)
- Harvoni (sofosbuvir + ledipasvir)
- Holkira Pak (dasabuvir + ombitasvir + paritaprevir + ritonavir)
- simeprevir (Galexos)
- sofosbuvir (Sovaldi and in Harvoni)
- Zepatier (elbasvir and grazoprevir)

As a group, these drugs are mainly effective against HCV genotype 1 (the most common strain of HCV), but some of these drugs or combinations of them can be used against other genotypes. However, all the leading pharmaceutical companies are now developing combinations of drugs that can treat all major HCV genotypes and can be taken once daily. Some of these regimens under development have shown to be sufficiently powerful that they can even cure some people whose previous regimens failed. More information about drugs under development for HCV appears later in this issue of TreatmentUpdate as well as in issue 216.

B. Know your drugs and classes

Treatments for hepatitis C virus (HCV) available in high-income countries today are highly effective, with rates of cure generally greater than 90%. In the years ahead, even more powerful combinations of all-oral anti-HCV drugs, called direct-acting antivirals (DAAs), will become available that can treat all major strains of HCV.

Proteins and enzymes

There are many steps that are needed within an HCV-infected cell so that copies of HCV can be made. These steps involve proteins and enzymes. A combination of drugs that targets multiple proteins and enzymes makes for a more effective regimen than a single drug alone. HCV proteins and enzymes are targets of DAAs and serve as ways to group DAAs. This grouping is also used when sorting strains of HCV that are resistant to DAAs.

Approved DAAs:

**NS3 and NS4A**
The enzyme called NS3 is part of a vital step in the production of copies of HCV. A protein called NS4A, made by HCV-infected cells, enhances the activity of NS3. Examples of drugs that work by attacking NS3 and/or NS4A include the following:

- asunaprevir
- grazoprevir (in Zepatier)
- paritaprevir (in Holkira Pak)
- simeprevir (Galexos)

All of the above listed drugs are called protease inhibitors.

**NS5B**
The enzyme NS5B is part of another vital step in the creation of copies of HCV. Approved NS5B inhibitors are divided into subclasses such as nukes (sofosbuvir) and non-nukes (dasabuvir; in Holkira Pak).

**NS5A**
Researchers are not certain about the role of this protein, but it is critical to the production of HCV. Inhibitors of NS5A include the following:

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

DAAs in development:

NS5A inhibitors are the most powerful anti-HCV agents. This is why nearly all DAA regimens in clinical trials contain an NS5A inhibitor. Below are examples of NS5A inhibitors under development:

- Velpatasvir – this drug will not be available by itself. Velpatasvir is being co-formulated (put into one pill) with another drug called sofosbuvir. The combination of both drugs is expected to be approved in North America in the summer of 2016. These drugs are made by Gilead Sciences.
• MK-8408 – this drug is being tested in combination with other drugs made by Merck in phase II and III clinical trials. If these studies demonstrate high rates of cure, MK-8408 will be made available in one pill together with other drugs from Merck.

• ABT-530 – this drug will not be available by itself but co-formulated with another experimental agent, ABT-493. Both drugs are made by Abbvie and are in phase III clinical trials.

• Odalasvir – this drug is being tested in combination with another drug code-named AL-335 (an NS5B inhibitor) and the NS3 inhibitor simeprevir in phase II clinical trials. All three drugs are made by Janssen. It is too early to know if this trio will be successful and if they will be co-formulated.

The advantages of these emerging drugs and combinations are multifold: They are very likely more powerful than existing combinations of DAAs, they can be used in some cases of treatment failure, and they will likely be effective against a broad range of strains of HCV (genotypes 1 through 6). Combinations of emerging therapies may result in shorter duration of treatment for some cases of uncomplicated HCV infection.

REFERENCE:

C. When HCV treatment failure occurs

In phase II and III clinical trials, high rates of cure (greater than 90%) have been reported with newer combinations of direct-acting antivirals (DAAs). However, as these drugs become more widely used, researchers are beginning to report occasional cases of treatment failure. In some cases treatment failure can occur because of relapse. That happens when HCV viral load first falls to an undetectable level during a course of treatment; later, once a course of treatment has ended, HCV subsequently becomes detectable. Overall, and particularly among people who have never been previously treated, cases of relapse with DAAs are uncommon.

Doctors in Madrid, Spain, have reviewed data from clinical trials as well as reports and analyses of treatment failure (due to relapse or other causes) when DAAs have been used. They noted that the following factors have been associated with treatment failure:

• the presence of symptoms linked to cirrhosis
• prior treatment failure
• very high levels of HCV in the blood
• being infected with HCV genotypes 1a or 3
• being male

Small errors in virus production

As HCV-infected cells produce millions of copies of this virus, some copies have changes, or mutations, in their genetic information that occur by chance. Some of these mutations inadvertently allow HCV the ability to resist the effect of one or more DAAs. Thus it is possible that in a small proportion of people who have never been treated there might be low levels of HCV circulating that possess the ability to resist a DAA.

An evolving field

Mutations associated with HCV drug resistance are different compared to drug resistance mutations associated with another virus—HIV. In the case of HIV, drug resistance mutations can last for many years, and the presence of just one major mutation can greatly impair the activity of an anti-HIV drug and sometimes related drugs within a class.

In the case of HCV, the situation is somewhat different. That is, some of these DAA mutations can disappear from circulation within days. This is the case with mutations to the drug sofosbuvir (Sovaldi). Mutations that affect NS3 inhibitors (protease inhibitors) can take several months to disappear from circulation. Mutations that affect another key HCV target called NS5B can persist in circulation for more than a year. Lastly, mutations that affect NS5A inhibitors persist in circulation for two years, perhaps longer.

Another aspect of HCV drug resistance mutations is the frequency with which they occur. For instance, some researchers say that in most cases unless a drug resistance mutation is found in more than 15% of circulating copies of HCV, they do not expect that this should decrease the chances of a person being cured with DAAs.
Thus, resistance testing may become an important part of HCV care, particularly in cases of treatment failure and re-treatment.

Cirrhosis
In cases of severe cirrhosis (graded as Child-Turcotte-Pugh C) rates of cure have been generally lower than in cases of less severe cirrhosis. This problem arises because in such advanced cirrhosis, blood circulation within the liver is reduced. As DAAs are transported by blood, sufficient concentrations of these drugs may not penetrate all parts of the liver that contain HCV-infected cells. Less-than-ideal levels of DAAs may allow the development of drug resistance, ultimately leading to treatment failure. In cirrhosis, the liver is also dysfunctional and may not process or break down DAAs. This could lead to cases of subtle toxicity.

After treatment failure
There is no simple path forward after HCV treatment failure because the reasons for such an outcome can differ from one patient to another. The Spanish researchers suggest that the following issues be considered by physicians in cases of possible re-treatment:

Virological challenges
• Are drug resistant mutations present?
• Was the patient’s genotype correct?
• Was the patient re-infected with a different strain of HCV?

Strategic management
• Consider adding ribavirin to a future regimen
• Think about extending the duration of a future regimen (beyond 12 weeks)

Maximize drug benefit
• Avoid drug interactions
• Prevent and manage side effects
• Ensure adherence to treatment

More powerful drugs on the way
Later in 2016 and in 2017 new combinations of DAAs that should be effective against many strains of drug-resistant HCV will likely become licensed by regulatory authorities in North America and Western Europe. Drugs in these combinations include the following:

- ABT-493 + ABT-530
- sofosbuvir + velpatasvir
- sofosbuvir + velpatasvir + GS-9857
- MK-8408 in combination with other drugs

REFERENCE:

D. Child-Turcotte-Pugh – Grading severe liver disease and the likelihood of survival
In cases of cirrhosis (severe liver injury and scarring of the liver), it is useful for doctors to know the likelihood of patient survival in the short- and medium-term so that interventions can be prioritized. Doctors have developed a scoring system called Child-Turcotte-Pugh (CTP) for this purpose. CTP takes into account cirrhosis-related symptoms and certain lab test results. The more severe the symptoms and the greater the abnormality in lab test results, the greater the CTP score. Entering these into an equation or calculator produces a score that has a relatively high predictive value.

CTP takes into account the following factors:

- HCV brain-related problems (encephalopathy)
- whether or not fluid is accumulating in the abdomen (ascites)
- analyses of lab tests focusing on the concentrations of bilirubin and albumin
- the time it takes for blood to clot

CTP scores are graded and have the following implications:

- CTP category A (5 to 6 points) – people have a 100% chance of surviving for one year and an 80% chance of surviving for a subsequent year
- CTP category B (7 to 9 points) – people have an 81% chance of surviving for one year and a 57% chance of surviving for a subsequent year
- CTP category C (10 to 15 points) – people have a 45% chance of surviving for one year and a 33% chance of surviving for a subsequent year
We will refer to CTP categories (A, B, C) later in this issue of TreatmentUpdate.

E. ABT-493 + ABT-530 – Eight-week treatment in genotypes 1 or 2 without cirrhosis

ABT-493 is the code name for a drug that attacks an HCV enzyme called NS3 and a co-factor of this enzyme called NS4A. It is being tested at a dose of 300 mg once daily.

ABT-530 is the code name for a drug that attacks an HCV protein called NS5A. It is being tested at a dose of 120 mg once daily.

Both drugs are made by Abbvie.

In lab experiments with HCV-infected cells, both of these drugs have powerful anti-HCV activity against all genotypes of HCV (genotypes 1 through 6). In phase II clinical trials, both drugs are taken together once daily and are very promising treatments. A large research program is underway with these drugs and they are in the final phase of testing. In this issue of TreatmentUpdate we present key results from phase II trials with these drugs.

In research programs called Surveyor-I and Surveyor-II, researchers conducted several studies with ABT-493 and ABT-530. In a sub-study of Surveyor-I and Surveyor-II, researchers enrolled participants with HCV genotypes 1 or 2. None of the participants had severe liver injury (cirrhosis) and none of them were co-infected with HIV or hepatitis B virus. The combination of ABT drugs was given for eight consecutive weeks to 34 participants. Researchers found that 33 out of 34 participants with genotype 1 were cured (a rate of 97%). Among the 54 participants who had genotype 2, 53 participants (98%) were cured.

Results—Genotype 1
Thirty-three out of 34 participants (97%) were cured. The remaining participant had to leave the study after four weeks of treatment because of a diagnosis of cancer; he subsequently died within a couple of months. This cancer diagnosis was unrelated to the study drugs.

Results—Genotype 2
Fifty-three out of 54 participants (98%) were cured. One participant stopped visiting the clinic and could no longer be located.

Resistance
HCV-infected cells produce millions of copies of this virus. During the virus manufacturing process, small changes, or mutations, sometimes occur in HCV’s genetic information. Some of these mutations can help HCV resist the effect of treatment. Researchers found that mutations in HCV were present in two-thirds of participants at the start of the study. However, these mutations did not affect the response to the study medications.

Adverse events
The term adverse events is used to describe symptoms and physical and laboratory-detected complications that can occur in clinical trials. Note that not all adverse events are necessarily related to the study drugs. Some adverse events may arise because of the underlying HCV infection or pre-existing HCV-related complications or even causes unrelated to the disease or study medicine.

Overall, 68% of study participants with GT-1 and 61% of participants with GT-2 developed adverse events. According to the research team, most of
these events were of mild intensity. Common adverse events occurred as follows:

- fatigue – 15%
- headache – 7%

Lab tests did not detect abnormal increases in liver enzyme levels or the waste product bilirubin. No participant developed anemia of moderate or severe intensity.

There were two adverse events that were not related to the study drugs. The first was the case of cancer previously mentioned. The second was a case of bacterial infection of the skin.

Key points
The combination of ABT-493 and ABT-530 was highly effective when taken for eight consecutive weeks in people with genotype 1 or 2 who did not have cirrhosis regardless of viral load and subtype. The drugs were well tolerated. Further studies are ongoing.

REFERENCE:

F. ABT-493 + ABT-530 in genotype 3 with cirrhosis
The strain of HCV called genotype 3 has been difficult to cure with direct-acting antivirals (DAAs). Furthermore, research suggests that genotype 3 is associated with the following:

- an increased risk for developing fatty liver
- a faster rate of scarring within the liver
- a heightened risk for developing liver cancer

Researchers in the United States and New Zealand tested the combination of ABT-493 and ABT-530 taken once daily with and without the broad-spectrum antiviral agent ribavirin in participants with cirrhosis for 12 weeks. None of the participants had previously used treatment. The combination resulted in very high rates of cure (100%) when used for 12 consecutive weeks, with or without ribavirin.

Study details
In a series of phase II clinical trials called Surveyor-2 part 2, researchers tested ABT-493 and ABT-530. The average profile of participants with genotype 3 upon entering the study was as follows:

- age – 56 years
- 65% men, 35% women
- body mass index (BMI, a relative indicator of fatness) – 27
- 96% of participants had genotype 3a
- all participants had cirrhosis (severe scarring of the liver) but none had symptoms of this condition. Seventeen percent had cirrhosis graded as Child-Turcotte-Pugh A (CTP-A), which suggested that their chances of survival over the next 12 months were very high. No participant had cirrhosis of a more severe grading.

Participants were randomly assigned to receive the following regimens:

- ABT-493 (300 mg) + ABT-530 (120 mg) – 24 participants
- ABT-493 + ABT-530 + ribavirin (800 mg) – 24 participants

All drugs were taken for 12 weeks.

Results
All participants were cured 12 weeks after cessation of study drugs. Thus, adding ribavirin to a regimen of the Abbvie drugs offers no advantage for patients with genotype 3 who have cirrhosis.

Adverse events
Reports of adverse events were distributed among the following proportion of participants:

- ABT-493 + ABT-530 – 88%
- ABT-493 + ABT-530 + ribavirin – 83%

Common adverse events were as follows:

Headache
- ABT-493 + ABT-530 – 13%
- ABT-493 + ABT-530 + ribavirin – 33%
Fatigue
• ABT-493 + ABT-530 – 8%
• ABT-493 + ABT-530 + ribavirin – 25%

Nausea
• ABT-493 + ABT-530 – 8%
• ABT-493 + ABT-530 + ribavirin – 25%

Dizziness
• ABT-493 + ABT-530 – 8%
• ABT-493 + ABT-530 + ribavirin – 17%

Diarrhea
• ABT-493 + ABT-530 – 21%
• ABT-493 + ABT-530 + ribavirin – 0%

Note that in other studies of the Abbvie drugs diarrhea was uncomman.

Serious adverse events were distributed as follows:

ABT-493 + ABT-530 – one person
One person taking this regimen developed a fracture in one of his/her leg bones 15 days after the cessation of treatment. Bear in mind that HCV infection has been associated with reduced bone density. Investigators determined that this person’s problem was not linked to the study drug.

ABT-493 + ABT-530 + ribavirin—two people
One month after starting this regimen, one person developed lower-than-normal levels of the iron-containing protein hemoglobin. This condition is called anemia. Investigators determined that this was possibly related to the use of ribavirin.

Another person developed delusions three days after treatment cessation. Investigators thought that this issue could have been related to the study medications. However, the person also disclosed the use of amphetamine and alcohol the same day, which may also have played a role.

Abnormal laboratory test results
No participant had moderate or greater elevations of liver enzyme levels in their blood.

Users of the ABT drugs without ribavirin very rarely had elevated levels of the waste product bilirubin in their blood. In contrast, about 30% of participants who took the ABT drugs plus ribavirin had elevated levels.

Resistance
The proportion of participants with strains of HCV that could resist the study drugs was between 33% and 42% (depending on the resistance mutation assessed). Despite having these mutations, participants were cured.

Key points
Twelve consecutive weeks of therapy with ABT-493 + ABT-530 was able to cure 100% of participants with genotype 3 and cirrhosis whether or not ribavirin was used. Furthermore, participants were cured despite the presence of strains of HCV that could confer resistance. Therapy was generally well tolerated.

REFERENCE:

G. ABT-493 + ABT-530 – Eight-week treatment in genotype 3 without cirrhosis

Researchers enrolled 29 participants with HCV genotype 3 and treated them with eight weeks of ABT-493 + ABT-530. Twenty-eight out of 29 participants completed the study and 28 of the 29 (97%) were cured. The remaining person quit the study after six weeks because of intolerance for study visits and drawing of blood samples.

Study details
Researchers enrolled 29 participants with the following average profile at the start of the study:

• age – 47 years
• 52% men, 48% women
• body mass index (BMI, a relative indicator of fatness) – 26
• viral load – 6.5 logs
• 86% of participants had genotype 3a (the subtype of the remaining participants was not available)
• almost 70% of participants had a minimal degree of liver injury
Overall, 13 participants had HCV that was resistant to inhibitors of NS5A or NS3 and, in one case, both classes of drugs.

**Results**

Twelve weeks after cessation of therapy, 97% (28 out of 29) of participants were cured.

Common adverse effects were as follows:
- headache – 17%
- unexpected tiredness or lack of energy – 10%
- diarrhea – 10%
- sleep problems – 10%

**Abnormal lab test results**

Once participants entered the study it was rare for them to develop abnormal lab test results that were graded worse than mild. One participant had moderately elevated levels of the waste product bilirubin.

Participants who entered the study with already elevated levels of liver enzymes had them normalize during the study.

**Key points**

- Eight consecutive weeks of therapy with ABT-493 + ABT-530 was able to cure 28 out of 29 people (97%) with HCV genotype 3 infection, none of whom had cirrhosis.
- Treatment was effective despite the presence of strains of HCV that could resist therapy.
- The combination was well tolerated.

**REFERENCE:**

**H. ABT-493 + ABT-530 in genotypes 4, 5 and 6**

In a phase II clinical trial called Surveyor-I, researchers tested the combination of ABT-493 + ABT-530 once daily in 34 people without cirrhosis who had genotypes 4, 5 or 6.

All participants were cured after 12 weeks of therapy.

**Study details**

The average profile of participants was as follows:
- age – 53 years
- 53% men, 47% women
- distribution of HCV genotypes: genotype 4 – 22 participants (mostly subtypes a, c and d); genotype 5 – 3 participants; genotype 6 – 11 participants
- viral load – 6.3 logs
- 85% of participants had never previously received treatment and the remainder had previously been treated unsuccessfully with interferon and ribavirin
- 85% of participants had a minimal or modest degree of liver injury
- no participant had cirrhosis or was co-infected with hepatitis B or HIV

**Results**

All participants were cured after 12 weeks of therapy.

Viral load declined rapidly after initiation of treatment. In the first week of therapy, viral load fell below a level at which it could accurately be counted in 50% of participants. In the second week of the study, 95% of participants had this very low level of viral load. By the fourth week of the study, all participants had achieved this milestone.

**Adverse events**

Seventy-one percent of participants (24 out of 34) developed an adverse event. According to researchers, most of these events were graded as “mild.”

Common adverse events were as follows:
- headache – 24%
- diarrhea – 15%
- unexpected tiredness and/or lack of energy – 12%

No participants had abnormalities in laboratory analyses of their blood that were graded worse than mild.
Based on these results, phase III trials of the once-daily combination of both Abbvie drugs are underway in participants with all genotypes of HCV, with or without cirrhosis.

REFERENCE:

I. ABT-493 + ABT-530 in genotype 1 with previous DAA therapy failure

In the current era of direct-acting antivirals (DAAs) for hepatitis C virus (HCV), the failure of a modern regimen is uncommon. However, because HCV-infected cells produce millions of copies of HCV, occasional errors in this process occur. These errors result in changes, or mutations, in the genes of HCV. Sometimes these mutations inadvertently provide an advantage to HCV, helping it to resist the antiviral activity of treatment. Mutations can also arise in some cases of previously unsuccessful attempts at treatment with DAAs.

Some mutations fade from circulation in days, others in weeks or months. However, mutations in the part of HCV called NS5A can persist for more than two years after the failure of an NS5A-based regimen.

Companies are developing potent regimens that may be useful for some people whose previous attempts at treatment with DAAs have failed.

The Abbvie drug combination of ABT-493 + ABT-530 has activity in lab experiments with HCV-infected cells against commonly found resistance mutations in NS3 and NS5A. In a trial code-named Magellan-1, Part 1, researchers tested the safety and effectiveness of these drugs in participants whose previous regimens, containing inhibitors of NS3 and/or NS5A, had failed. In some cases, participants' previous regimens contained the anti-HCV drug sofosbuvir (Sovvaldi and in Harvoni). Most participants in this study had genotype 1a, which is a strain of HCV that does not always respond well to treatment.

In a strict analysis where any missing participants were counted as having failed treatment, about 90% of participants were cured. However, when only documented cases of virological breakthrough or relapse were included in the analysis, more than 95% of participants were cured.

Study details

The average profile of participants was as follows:

- 86% men, 14% women
- body mass index (BMI, a relative indicator of fatness) – 28
- viral load – 6.7 logs
- 84% of participants had HCV genotype 1a
- 64% of participants had a minimal degree of liver injury

Prior treatment regimens included the following:

- Harvoni (sofosbuvir + ledipasvir)
- Simeprevir (Galexos) + sofosbuvir (Sovvaldi) with or without ribavirin
- Holkira Pak (dasabuvir + ombitasvir+ paritaprevir+ ritonavir)
- boceprevir + interferon + ribavirin
- telaprevir + interferon + ribavirin

Analyses of the blood samples of participants before they started therapy revealed that more than 80% had detectable resistance mutations that helped HCV resist inhibitors of NS3 or NS5A.

Researchers randomly assigned 44 participants to receive ABT-493 + ABT-530. Half of the participants also received the broad-spectrum drug ribavirin, 800 mg per day. All drugs were taken for 12 consecutive weeks.

Results

ABT-493 + ABT-530 – 19 out of 22 people (86%) were cured

One participant was initially able to suppress their viral load but the virus eventually became detectable. Two other people stopped returning to the study clinic after treatment cessation. Both had undetectable viral loads.
ABT-493 + ABT-530 + ribavirin – 20 out of 22 people (91%) were cured

One participant stopped returning to the study clinic after the sixth week of the study. This person’s viral load at that time was undetectable. The other person was initially able to suppress their viral load but then it resurfaced after treatment cessation.

Resistance
It is noteworthy that among participants with two or more mutations associated with drug resistance, 92% (23 out of 25) were cured.

Adverse events
None of the participants had serious adverse events or had to leave the study because of adverse events.

Most (83%) common side effects were graded as mild. Below is the distribution of side effects by regimen:

Headache
- ABT-493 + ABT-530 – 23%
- ABT-493 + ABT-530 + ribavirin – 36%

Unexpected tiredness and/or lack of energy
- ABT-493 + ABT-530 – 18%
- ABT-493 + ABT-530 + ribavirin – 36%

Nausea
- ABT-493 + ABT-530 – 14%
- ABT-493 + ABT-530 + ribavirin – 27%

Sleeping problems
- ABT-493 + ABT-530 – 0%
- ABT-493 + ABT-530 + ribavirin – 27%

Blood tests
Analyses of blood tests found that abnormal findings were uncommon. Three people who received triple drug therapy developed moderately elevated levels of the waste product bilirubin.

For the future
A trial called Magellan-1, Part 2 is evaluating a larger group of DAA-experienced participants who have genotype 1, 4, 5 or 6. Some of these participants also have severe liver injury (cirrhosis).

REFERENCE:

J. France – Events after cure of HCV
Chronic hepatitis C virus (HCV) infection increases the risk of serious liver injury. If left untreated, this can lead to serious complications, including increasing dysfunction of the liver, increased risk of bacterial infections, liver failure and liver cancer.

Direct-acting antivirals (DAAs) are relatively new in the history of HCV treatment. They are highly effective at curing HCV and the duration of treatment is relatively short, usually about 12 weeks (though longer courses of treatment may be necessary in cases of severe liver injury).

Long-term monitoring of people who have been cured with DAAs is essential to understand what happens to the health of such patients. For instance, by how much is their risk for liver-related complications, including liver cancer, reduced?

Researchers in France reviewed health-related data collected from 2,156 patients who received treatment with at least one DAA in 2013 and 2014. Prior to entering the study none of these participants had received a liver transplant or developed liver cancer.

Key results
The findings from the French observational study show that the vast majority of patients who are treated with DAAs see their health improve and this improvement is sustained. In total, 3.5% of participants developed liver cancer after they were cured. It is highly likely that these cancers were already present when they started HCV treatment. Some people with cirrhosis who are cured of HCV may become at risk for liver-related complications; therefore, close and regular monitoring may be necessary.
Study details

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

- age – 58 years
- 62% men, 38% women
- 63% of participants had cirrhosis (severe scarring of the liver)

The distribution of genotypes was as follows:

- genotype 1 – 65%
- genotype 2 – 6%
- genotype 3 – 13%
- genotype 4 – 14%
- genotype 5 or 6 – 1%

(Percentages do not total 100 due to rounding.)

Therapies used were as follows:

- sofosbuvir + ribavirin – 283 people
- sofosbuvir + peginterferon + ribavirin – 228 people
- sofosbuvir + daclatasvir with or without ribavirin – 1,048 people
- sofosbuvir + simeprevir with or without ribavirin – 597 people

Results

Participants were monitored for an average of two years after they were cured.

Liver cancer

Cases of liver cancer significantly declined over time. They were most commonly diagnosed during the first 12 months after treatment cessation and were very uncommon two years after treatment cessation. Rates of liver cancer were greater among people with cirrhosis. Here is the distribution of cases of liver cancer:

Liver cancer diagnosed within 12 months of treatment cessation
- among people with cirrhosis – 66 cases
- among people without cirrhosis – 6 cases

Liver cancer diagnosed 18 to 24 months after treatment cessation
- among people with cirrhosis – 4 cases
- among people without cirrhosis – 1 cases

The data should not be misinterpreted to imply that therapy with DAAs somehow resulted in liver cancer. Screening for liver cancer in some participants may have been irregular (details were not provided) but previous French reports suggest that within research programs such screening tends to occur every six months. Given that the majority of participants had cirrhosis, they would have been at elevated risk for liver cancer. In general, tumours tend to form slowly and usually take years to grow. Overall, there were 77 cases of liver cancer after treatment cessation. That figure is equivalent to 3.5% of participants developing liver cancer, a relatively low overall rate.

DAAs can cure HCV, but the immune system has to recover (from HCV infection) and attack the tumour. Such recovery takes time. It is reassuring that over time there were fewer cases of liver cancer. Overall, the findings from the French study underscore the need for intensive monitoring of people with cirrhosis so that any cancers that develop can be detected and treated early.

Deaths from liver-related causes

As mentioned earlier, DAAs are very effective at curing HCV. However, many underlying health problems need time to resolve as the liver slowly repairs itself once HCV has been cured. People who are very ill with liver-related health issues will need close monitoring to maximize their chances of survival after being cured.

Deaths due to liver-related complications were most common in the first 18 months after cessation of therapy. (In the final six months of the study there were no liver-related deaths.) These deaths were distributed as follows:

Liver-related deaths within the first 18 months after treatment cessation
- among people with cirrhosis – 10 people
- among people without cirrhosis – 10 people

Serious symptoms of cirrhosis

When severe scarring of the liver occurs (cirrhosis), the dysfunction of the liver increasingly affects other parts of the body, leading to further complications. This is called decompensated cirrhosis.
In the first six months after treatment cessation there were cases of decompensated cirrhosis but these quickly fell and remained low. All cases of decompensation occurred only among people with cirrhosis. Such cases of decompensated cirrhosis were distributed as follows:

The first six months after treatment cessation
- 33 cases of decompensation

During months 6 to 12 after treatment cessation
- 8 cases of decompensation

During months 12 to 18 after treatment cessation
- 6 cases of decompensation

During months 18 to 24 after treatment cessation
- 1 case of decompensation

REFERENCE:

K. U.S. study looks at long-term durability of cure, risk of relapse and liver cancer

Researchers in several countries—including France, New Zealand, the U.K. and the U.S.—reviewed the records of several thousand people who had been cured of HCV using direct-acting antivirals (DAAs) and found very high rates of cure that were sustained up to three years after cessation of therapy. That is, once cured, the vast majority of participants stayed cured. Rates of relapse, reinfection and liver cancer were very low after cure was achieved.

Study details
Participants in Gilead Sciences’ sponsored studies were encouraged to enroll in an observational study that monitored them for up to three years after cure was achieved. As part of this observational study, participants regularly visited study clinics where their blood was drawn for analysis.

There were 5,433 participants enrolled and their average profile upon entering the study was as follows:
- age – 54 years
- 63% men, 37% women
- 20% had severe liver injury (cirrhosis)
- most (99%) had been infected with genotypes 1, 2, 3 or 4

Results—Keeping track of HCV
Researchers found the following:
- 99.7% of participants maintained their cure status.
- 0.1% of participants had evidence of late relapse.
- Participants who relapsed tended to have HCV genotype 1a or 3. Historically these genotypes have tended to respond poorly to treatment.
- 0.2% of participants had evidence of HCV re-infection.
- Reinfections began to occur as early as eight months after cure was achieved.

Results—Monitoring liver cancer
Cases of liver cancer were detected after treatment cessation but were low. This is likely due to the smaller proportion of people with cirrhosis in this study compared to the previously reported French study (where more than 60% of participants had cirrhosis).

Most cases of liver cancer were distributed among people with pre-existing cirrhosis and occurred within the first year after treatment cessation.

Liver cancer diagnosed upon study entry
- among people with cirrhosis – 5 cases
- among people without cirrhosis – 3 cases

Liver cancer diagnosed 24 weeks after study entry
- among people with cirrhosis – 5 cases
- among people without cirrhosis – 1 case

Liver cancer diagnosed 48 weeks after study entry
- among people with cirrhosis – 6 cases
- among people without cirrhosis – 0 cases
Liver cancer diagnosed 72 weeks after study entry
- among people with cirrhosis – 3 cases
- among people without cirrhosis – 0 cases

After week 72, there were no further cases of liver cancer.

Other liver-related issues

A similar trend (a decrease over time) was seen with the relatively small proportion of cases of liver-related complications that were detected after treatment cessation. Complications included the following:

- build-up of fluid in the abdomen (ascites)
- internal bleeding
- brain-related issues
- yellowing of the skin and whites of the eyes (jaundice)

Over time there were fewer cases of these and by the third year of the study, there were no reports of these complications.

There was also a similar trend with analyses of blood tests with a trend to normalization over time.

Overall, the findings from this review are reassuring and show that the vast majority of people who are cured with DAAs remain cured. Rates of complications, including liver cancer, were lower than those found in another study from France (reported in this this issue of TreatmentUpdate). The lower rate of liver cancer seen in the present study likely arose because most participants were treated relatively early in the course of liver disease, before the onset of cirrhosis.

REFERENCE:

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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CATIE is Canada’s source for up-to-date, unbiased information about HIV and hepatitis C. We connect people living with HIV or hepatitis C, at-risk communities, healthcare providers and community organizations with the knowledge, resources and expertise to reduce transmission and improve quality of life. For more than 20 years, CATIE has been there to provide information that enables people to make informed choices about their health and enhances the ability of healthcare providers and other frontline organizations to respond to their clients’ needs. CATIE provides such information through a comprehensive website (www.catie.ca), electronic and print resources, webinars and other online learning, a national reference library, regional conferences, subscriptions to e-newsletters and a confidential phone inquiry service.

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A Practical Guide to HIV Drug Side Effects
The latest on what is known about various side effects related to treatment, from appetite loss to sexual difficulties, and tips for countering or preventing them.

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Concise overviews of conditions, symptoms, medications, side effects, complementary therapies, vitamins, herbs and other treatment issues.

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