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I ANTI-HCV DRUGS

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I ANTI-HCV DRUGS

A. The looming arrival of Epclusa – sofosbuvir + velpatasvir

The pharmaceutical company Gilead Sciences has been developing combinations of anti-hepatitis C virus (HCV) drugs. One combination consists of the following two drugs:

- sofosbuvir 400 mg
- velpatasvir (formerly called GS-5816) 100 mg

Both of these drugs are co-formulated (in one pill) that is taken once daily and sold under the brand name Epclusa.

In clinical trials the combination of sofosbuvir + velpatasvir was highly effective in treating adults with chronic HCV infection, with cure rates generally exceeding 90%. This combination was effective against a broad range of strains, or genotypes, of HCV, specifically genotypes 1 through 6.

Epclusa was approved in Canada in July 2016 and has also been approved in the United States and the European Union.

In this issue of *TreatmentUpdate*, we report on the effectiveness of Epclusa in cases of HCV retreatment and in cases with HIV-HCV co-infection. Additionally, we provide information on some drug interactions between Epclusa and other medicines.

For further information about Epclusa see the following:

- Hepatitis C treatment Epclusa approved in Canada—key information (*CATIE News*, July 20, 2016)
- The debut of velpatasvir for hepatitis C (*CATIE News*, November 23, 2015)
- Sofosbuvir and velpatasvir for cirrhosis in hepatitis C (*CATIE News*, November 30, 2015)
- Sofosbuvir + velpatasvir for hepatitis C genotypes 2 and 3 (*CATIE News*, December 7, 2015)

B. DAAs found highly tolerable (and effective) in people with mental health conditions

Researchers at the University of Maryland and the U.S. National Institutes of Health (NIH) have found a relatively high rate of mental health conditions among some people who sought treatment for chronic hepatitis C virus (HCV) infection. Drugs that have been historically used to treat HCV—interferon and ribavirin—can significantly affect mental health in some people. As more new potent anti-HCV drugs (called direct acting antivirals, or DAAs) become available in Canada and other high-income countries, it will be important to formally assess their impact on mental health. To sum up the present study's findings, the DAAs assessed did not cause depression, anxiety or any other mental health issues, unlike the older HCV drug interferon. What's more, rates of depression fell after participants were cured.

Study details

As part of a sub-study of three important clinical trials, researchers reviewed data from a small sub-group of 45 participants (who were part of a larger group of participants in the three clinical trials). Below are the numbers of participants who were in the mental health sub-study:

- Spare – sofosbuvir + ribavirin; 23 participants
- Synergy-A – sofosbuvir + ledipasvir; 7 participants
- Eradicate – sofosbuvir + ledipasvir; 15 participants

On average, most participants were in their mid-50s; 60% were men and 40% were women.

Participants were screened for mental health issues before, during and after the study.

Below is the overall distribution of mental health conditions at the start of the study (prior to starting DAAs). The proportion of people with a particular diagnosis was different in each study, so what appears below is the range between all three studies:

- depression – between 53% and 61% of participants
- anxiety – between 7% and 43% of participants

- bipolar disorder – between 17% and 43% of participants
- post-traumatic stress disorder – between 7% and 20% of participants

One participant had schizophrenia.

Effectiveness of DAAs

According to the research team, in all three clinical trials rates of cure did not differ significantly between people who had mental health conditions and people who did not. In Synergy-A, which had only one DAA (sofosbuvir), cure rates were between 61% and 68%. However, in the other two trials, which had two DAAs (sofosbuvir + ledipasvir), cure rates were between 97% and 100%.

Assessment of depression

Researchers found that, on average, the intensity of depression decreased while participants were in the study and taking DAAs. Once DAA therapy was completed, participants were less depressed than before they started this therapy. This should not be interpreted as DAAs having an antidepressant-like effect. Rather, it is likely that participants experienced improved mental (and physical) health because they were being treated with potent anti-HCV drugs, and as a result, in the majority of cases, they became cured. Chronic HCV infection causes inflammation. In some cases, elevated levels of proteins associated with inflammation could, in theory, increase the risk of depression in some people with HCV who may be susceptible to depression and/or anxiety. Another study reported later in this issue of *TreatmentUpdate* found improvements in physical and mental health among people who were cured with DAAs.

For comparison, researchers also examined previously collected data from participants who were treated with interferon. They found that rates of depression were greater while participants took interferon and even when they ceased taking interferon compared to participants who used DAAs.

Other assessments

Researchers also checked other measures that might have been impacted by mental health, including the following:

- the ability to visit the study clinic as required
- the concentration of DAAs in participants' blood samples

Researchers found that the mental health status of patients did not affect these issues.

Key point

Bear in mind that the researchers' analysis was a sub-study of three larger studies. Furthermore, the main purpose of the three larger clinical trials was to investigate the ability of DAAs to cure people. These two limitations mean that the sub-study's analysis about DAAs and depression are not definitive. However, the findings from the mental health sub-study are still important and suggest that DAAs do not cause depression and may even indirectly decrease feelings of depression because they cure HCV, a chronic viral infection.

REFERENCES:

1. Tang L, Masur J, Sims Z, et al. High tolerability and sustained virologic response with sofosbuvir-based therapy among patients with mental health disease. *The International Liver Congress*, 13-17 April 2017, Barcelona, Spain. Abstract SAT-203.

2. Curry MP, Moczynski NP, Liu L, et al. The effect of sustained virologic response on cerebral metabolism and neurocognition in patients with chronic genotype 1 HCV infection. *The International Liver Congress*, 13-17 April 2017, Barcelona, Spain. Abstract SAT-215.

3. Golabi P, Elshekh E, Karrar A, et al. The levels of monoamine neurotransmitters in HCV patients treated with ledipasvir/sofosbuvir. *The International Liver Congress*, 13-17 April 2017, Barcelona, Spain. Abstract SAT-201.

C. One Vancouver clinic finds low rates of HCV reinfection after cure

People who share equipment for substance use are at increased risk for infection with germs, including hepatitis C virus (HCV) and HIV. In the past five years, powerful treatments called DAAs (direct acting antivirals) for HCV infection have

become available and, as a result, more people are being cured. However, if the drivers of substance use are not addressed—addiction, mental health issues and so on—then it is possible that in some cases reinfection could occur.

To investigate the issue of reinfection, researchers at the Vancouver Infectious Disease Clinic reviewed the medical records of several hundred people who had been treated and cured of HCV. They found that cases of reinfection were very low. This low rate of reinfection is likely underpinned by the clinic's multidisciplinary approach toward HCV infection and substance use.

Study details

Researchers focused on 340 participants, all of whom had previously injected street drugs (most commonly cocaine and heroin). The average profile of participants while being treated was as follows:

- age – 53 years
- 75% were men and 25% were women
- co-infection with HIV and HCV – 52%
- about 36% of participants were taking opioid substitution while they were treated for HCV

Participants who were cured returned to the clinic every six months to receive clinical and laboratory monitoring, including tests for HCV's genetic material. This latter test reveals if active HCV infection is present. If routine laboratory monitoring detected elevated liver enzyme levels in the blood or if the patient had symptoms suggestive of HCV infection, then clinic staff would request more frequent screening for HCV's genetic material.

Results

Out of 340 participants, 306 (90%) were cured of HCV. Of those who were cured, about 38% continued to inject street drugs.

After an average monitoring period of two and a half years, researchers found that four out of 306 participants (about 1%) became reinfected with HCV.

Focus on the four cases

Here is a brief profile of the four cases:

- all were men
- they were aged between 47 and 60 years
- all used amphetamines and three of the four also used heroin
- two of the men attended support group meetings
- three of the men had been diagnosed with mental health conditions, including depression, bipolar illness and schizophrenia

The Vancouver researchers noted that the rate of HCV reinfection was very low. They also stated that the risk of reinfection among people who use substances and who receive psychological support is likely to be low. Intensified multidisciplinary approaches for the care and support of people who are recovering from HCV infection and addiction will likely continue to help minimize reinfection rates.

REFERENCE:

Hakobyan S. HCV re-infection in high-risk people who inject drugs. *The International Liver Congress*, 13-17 April 2017, Barcelona, Spain. Abstract SAT-272.

D. Acid-reducing agents and HCV treatment

Some direct acting antivirals (DAAs) used for the treatment of hepatitis C virus (HCV), including ledipasvir (in Harvoni), require an acidic environment in the stomach for maximal absorption. However, in general, many people, including some with HCV, routinely take acid-reducing agents such as the following:

- pills or liquids that contain calcium and/or magnesium
- a class of drugs called H2 blockers – commonly used examples include cimetidine (Tagamet) and ranitidine (Zantac)
- PPIs (proton pump inhibitors) – esomeprazole (Nexium, Vimovo), omeprazole (Losec, Prilosec) and pantoprazole (Pantoloc)

It is possible that acid-reducing agents could reduce the absorption of ledipasvir and, therefore, its ability

to help cure HCV infection. An observational study called Target has reported an association between the use of acid-reducing agents and decreased effectiveness of Harvoni (sofosbuvir-ledipasvir). In Target, participants who used PPIs had a cure rate of 93% vs. a cure rate of 98% in people who did not use PPIs.

Associations are just that; they are not conclusive. As a result of Target's findings, researchers at the Ottawa Hospital sought to analyse their database of patients who received interferon-free regimens of DAAs. The researchers also assessed their patients' use of acid-reducing agents, specifically H2 blockers and PPIs. A total of 168 people took part in this study.

Prior to initiating DAA therapy, 24% of participants in the Ottawa Hospital study took PPIs and 2% took H2 blockers. The researchers found that among 168 participants, those with severe scarring of the liver (cirrhosis) were most likely to use H2 blockers or PPIs. In total, among the participants who were taking PPIs prior to initiating therapy with DAAs, 93% continued to take PPIs (once daily) while on DAA therapy. There was no difference in cure rates between people who took PPIs and those who did not take these or other acid-reducing agents.

Study details

The average profile of the 168 participants in the Ottawa Hospital study was as follows:

- age – 56 years
- 63% men, 37% women
- common strains of HCV – genotypes 1a and 1b
- doctors had diagnosed cirrhosis in 45% of participants

During the course of the study, the following regimens were used:

- sofosbuvir + ledipasvir (with or without ribavirin) – 51%
- sofosbuvir + ribavirin – 15%
- sofosbuvir + simeprevir (with or without ribavirin) – 31%
- other (unspecified) regimens – 3%

Results

Cure rates were generally high in this group of participants—greater than 90%. There was no statistically significant impact of acid-reducing agents on the cure rate of DAA-based regimens. When subgroups of participants were assessed—such as those with the difficult-to-treat genotype 1a or those who had cirrhosis or those who only received sofosbuvir + ledipasvir—there was also no significant impact on cure rates caused by acid-reducing agents.

For the future

To minimize any possible risk that acid-reducing agents might have on cure rates, the Ottawa researchers suggest that the dosing of these medicines be limited to once daily. Furthermore, they encourage doctors who care for people with HCV to reassess their patients' need for acid-reducing agents.

REFERENCE:

DeVreese L, Giguère P, Cooper C. Influence of proton pump inhibitors and H2 receptor antagonists on direct-acting antiviral HCV sustained virologic response. *The International Liver Congress*, 13-17 April 2017, Barcelona, Spain. Abstract SAT-200.

E. Caution needed about claims of increased risk of liver cancer recurrence with use of DAAs

Hepatitis C virus (HCV) infects the liver, causing inflammation. If left untreated, it also results in a gradual loss of healthy tissue and its replacement with useless scar tissue in a process called fibrosis. As more of the liver becomes scarred, it increasingly becomes dysfunctional. This leads to complications, serious infections and, ultimately, liver failure. As scar tissue accumulates, the risk for developing liver cancer also increases.

The arrival of potent all-oral anti-HCV therapy—called direct acting antivirals (DAAs)—has greatly increased the chances of people being cured from HCV infection. In clinical trials, cure rates with modern DAAs are generally around 95% or greater.

Results from observational studies in the United States (see U.S. study looks at long-term

durability of cure, risk of relapse and liver cancer – *TreatmentUpdate* 215) and France suggest that after a person is cured of HCV there is a small and temporary residual risk for developing symptoms associated with cirrhosis, and in some cases there is also a small and temporary risk for developing liver cancer. These risks seem greatest for people who have cirrhosis. However, the risk for such serious complications declines after one has been cured and data so far suggest that it is extremely low two years after being cured.

Recently, reports have appeared at conferences and in journal articles suggesting that there is an unexpected increase in rates of recurrence of liver cancer. These reports have emerged from clinics in Barcelona and Vienna but may also appear from clinics in other cities in the future.

How should this news be interpreted? We urge our readers to treat these reports with caution. There are several reasons that could explain why such cancers have recurred and these are discussed later in this issue of *TreatmentUpdate*. The reports generally contain a dataset that is relatively small compared to clinical trials. Such small datasets are not likely to be broadly representative of people at high risk for liver cancer. For this and other reasons, the link that some researchers attempt to make between the use of DAAs and the onset of liver cancer recurrence is not robust and may even be due to chance.

Bear in mind that tumours do not usually appear suddenly. Cells generally slowly transform into an abnormal state, and even then, only some of those abnormal cells become cancers; some form benign tumours. Thus, liver cells that have been transformed into cancers take time to grow and form large tumours that can be detected with scans. Although ultrasound scans performed every six months are considered part of the basis of screening for liver tumours, such scans are imperfect and do not always detect tumours. Indeed no scanning technology that seeks to detect tumours in the liver is perfect. As a result, some people in the reports that we will present may have had cancer but it was not detected until much later. This could have confused some of the doctors when they attempted to link the development or recurrence of such cancers with exposure to DAAs. Also, liver cancer does not generally cause symptoms until it has become advanced, so some patients and their doctors may not be aware that cancer has formed and is growing.

It is also possible that reports from the smaller datasets in Barcelona and Vienna were inadvertently over-represented with people at very high risk for the recurrence of liver cancer. This elevated risk may stem from one's medical history, the type of liver tumour(s) that they had previously been diagnosed with and, possibly, the type of anti-cancer therapy that they had received.

Collectively, all of the factors mentioned here weaken the association between the use of DAAs and risk for the recurrence of liver cancer.

Whatever the cause(s) of the apparent increased risk for the recurrence of liver cancer, there is no evidence that DAAs cause liver cancer or increase the risk for its recurrence. Though the reports from Barcelona and Vienna are interesting, they are based on relatively small numbers of patients and are not definitive. Doctors who have reviewed the reports from Barcelona and Vienna strongly suggest that people who are cured of HCV and who are at high risk for liver cancer because of cirrhosis or having had such cancer in the past undergo regular screening for liver cancer.

F. Looking back at liver cancer rates among people who received interferon therapy

Historically, treatment for chronic hepatitis C virus (HCV) infection consisted of weekly injections of interferon accompanied by daily oral doses of the broad-spectrum antiviral drug ribavirin. Both drugs would need to be taken for 48 weeks. At best, the side effects from this therapy were highly unpleasant and the combination was not highly effective.

Today in Canada and other high-income countries, more effective and safer interferon-free regimens called direct acting antivirals (DAAs) are available. Over the next year more combinations of potent DAAs will become licensed.

Reviewing the impact of interferon

Researchers at the University of Toronto conducted an intensive review (called a systematic review

and meta-analysis) of 37 published studies in which interferon was used as treatment for HCV infection. These studies included data from 22,858 participants. The overall rate of cure (also known as a sustained virological response, or SVR) was 48%. Among participants who were cured, 3% subsequently developed liver cancer. Among participants who were not cured, rates for the subsequent development of liver cancer were 12%.

In detail

Most of the studies reviewed were retrospective in design. That is, such studies reviewed data that had already been collected for one purpose in the past and re-analysed the data for another purpose. Only some of the studies reviewed collected data on factors such as the presence of type 2 diabetes and alcohol intake. Therefore, the effect of these factors on the subsequent risk of liver cancer could not be assessed by the Toronto team. However, data from large numbers of patients were assessed as part of the review and this provides a very good idea of the risk of liver cancer among people who were treated with interferon.

According to the Toronto team, the risk for subsequently developing liver cancer among participants who received interferon therapy and who were cured decreased by 76%.

The analysis by the Toronto researchers is timely and helpful. It can be used as a reference with which to compare liver cancer rates among people who use modern-day DAAs.

REFERENCE:

Hosni A, Hansen T, Sampalis J, et al. The development of hepatocellular carcinoma in patients who have obtained a sustained virologic response (SVR) vs. no SVR after antiviral therapy for hepatitis C: a systematic review and meta-analysis. *American Society of Clinical Oncology Annual Meeting*, Chicago, 3-7 June 2016. Abstract 1551.

G. Barcelona: Reports of unexpected cases of liver cancer in people undergoing treatment with DAAs

Doctors in Barcelona recently reported an unexpected increase in liver cancer recurrence in people who had been or who are being treated for chronic hepatitis C virus (HCV) infection with new potent all-oral medicines called direct acting antivirals (DAAs). All participants had previously been treated for liver cancer. They had been treated successfully with different combinations of DAAs. In their report, the Barcelona doctors focused on patients treated for HCV between October 2014 and December 2015.

We urge our readers to treat this report from Barcelona with caution. The possible association between exposure to DAAs and liver cancer recurrence may be an association that has arisen by chance. Large numbers (tens of thousands) of people in North America and Western Europe have been treated with DAAs and there have not been reports of multiple cases of recurrent liver cancer in such patients by major clinics. The analysis from Barcelona may have been inadvertently biased by its small size and because the researchers included people at very high risk for recurrence of liver cancer.

Study details

As all participants had undergone treatment for liver cancer, they subsequently were considered cured and were under routine clinical and laboratory surveillance for the return of liver cancer. For instance, many participants underwent regular CT, MRI (magnetic resonance imaging) and ultrasound scans of their liver every six months.

The Barcelona doctors focused on 58 participants whose average profile was as follows:

- age – 66 years
- 69% men, 31% women
- 95% had cirrhosis
- 94% were infected with HCV genotype 1b
- the distribution of commonly used anti-HCV regimens included the following: Harvoni (sofosbuvir + ledipasvir) – 36%; the 3D regimen (Holkira Pak – dasabuvir + ombitasvir + paritaprevir boosted with ritonavir) – 26%; sofosbuvir + simeprevir – 26%; sofosbuvir + daclatasvir – 10%

The distribution of therapy for the first occurrence of liver cancer was as follows:

- surgery – 35%
- radiation – 55%
- injection of chemotherapy into the tumour – 10%

Results

At the time the Barcelona doctors submitted their report, they noted that 40 participants have been monitored for 12 consecutive weeks after the cessation of DAA therapy. Of these 40 people, 39 (98%) have been cured from HCV.

Here is the situation among the remaining 18 participants:

- three have not yet completed their course of DAAs
- 11 completed their course of DAAs but virological results are not yet available
- three others who completed their course of DAAs have promising preliminary virological results
- one person died due to liver failure

Focus on liver cancer after DAA therapy

Overall, the entire group of 58 participants has been monitored for nearly six months and their current status is as follows:

- 55 participants are alive
- three participants have died

Among the three participants who died, their deaths occurred 12, 10 and five months after DAAs had been initiated.

A total of 15 cases of liver cancer recurrence have been found through CT or MRI scans.

A high rate and a theory

The Barcelona doctors claim that the recurrence rate for liver cancer in their report is relatively high, approaching 28%. They do not think that these results are due to tumours being detected very early because of "more intense screening [for liver cancer]." Furthermore, these doctors do not think that DAAs directly caused cancer, as they did not find any evidence for this. Rather, they proposed a complex idea whose key elements are as follows:

- Billions of copies of HCV are produced every day by infected liver cells.
- Once DAA regimens are initiated, HCV levels in the blood quickly become undetectable, sometimes in days or weeks.
- This massive and relatively sudden fall in HCV levels results in the decrease of proteins associated with inflammation also circulating in the blood and immune system. The sudden absence of HCV and inflammatory-associated proteins may somehow impair the immune system's ability to keep liver tumours under monitoring and control.

Readers should note that this idea, though immunologically interesting, has not been proven.

Counterpoint

The Barcelona doctors note that reviews of clinical trials of interferon-based therapy for chronic HCV infection have not found any signal of increased risk for liver cancer. That is true, but a meta-analysis of interferon treatment for HCV infection done by researchers at the University of Toronto, reported earlier in this issue of *TreatmentUpdate*, has found that even among people who were cured there was still a small risk for the subsequent development of liver cancer. Furthermore, a report from Vienna, also in this issue of *TreatmentUpdate*, notes that cases of liver cancer have occurred among people who were treated with interferon and not DAAs. In that report, about 11% of participants treated with interferon later developed liver cancer.

Some researchers at the University of Palermo in Italy have reviewed the report from Barcelona. They issued this caution: "A definitive estimate of the likelihood of [liver cancer] recurrence is difficult." This difficulty arises because of many factors (that are beyond the scope of our article).

The Barcelona doctors calculated that they found a 28% rate of liver cancer recurrence and they say that this was greater than what they expected. Yet, according to the Italian researchers who reviewed the Barcelona data and then recalculated the estimated risk of liver cancer, the risk of recurrence should have been between 7% and 13%. The Italian researchers therefore see no need for alarm. Note that the numbers of patients upon which both teams used to base their calculations is small and much caution is needed, as these estimates are not robust.

It is possible that the report from Barcelona contains a major flaw: It was inadvertently over-represented with patients who were at very high

risk for the recurrence of liver cancer. This could have biased their conclusions.

Whatever the ultimate reason for the apparently increased rate of liver cancer recurrence noted by the Barcelona doctors, their report has ignited disagreement and controversy. To seek clarity on this issue, many people in the liver field will now look to large databases that have data on hundreds, and in some cases thousands, of patients.

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5. Bruix J, Sherman M; American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma. *Hepatology*. 2011 Mar;53(3):1020-2.

6. Meniconi RL, Komatsu S, Perdigao F, et al. Recurrent hepatocellular carcinoma: a Western strategy that emphasizes the impact of pathologic profile of the first resection. *Surgery*. 2015 Mar;157(3):454-62.

7. Kim DJ, Clark PJ, Heimbach J, et al. Recurrence of hepatocellular carcinoma: importance of mRECIST response to chemoembolization and tumor size. *American Journal of Transplantation*. 2014 Jun;14(6):1383-90.

H. Vienna doctors urge caution when assessing possible associations between liver cancer recurrence and use of DAAs

Doctors in Vienna, Austria, recently reported a group of cases of liver cancer in 19 participants whose hepatitis C virus (HCV) was treated with direct acting antivirals (DAAs). Three of these participants had previously been diagnosed with liver cancer. Nearly all had been infected with HCV for many years and had what the doctors called "advanced liver disease."

The Austrian doctors cautioned people who read their report to bear in mind the following:

- As their patients had advanced liver disease, they were already at high risk for liver cancer (and its recurrence in people who previously had this cancer).
- Since they were already at high risk for liver cancer, the development of such tumours in relation to the timing of DAA therapy could have occurred by "chance."
- Although regular ultrasound scans, and in some cases CT or MRI scans, are recommended as part of liver cancer screening, they note: "Even the best imaging methods cannot exclude a small [liver tumour with 100% certainty]."

The doctors concluded that an apparently increased risk for liver cancer in some patients who have been treated with DAAs might be due to the following factor:

- older age – this represents a surrogate or stand-in indicating prolonged chronic HCV infection. Long-term HCV infection would have allowed more time for scarring of the liver to have occurred and therefore an increased risk for liver cancer.

The Austrian doctors also found it "difficult to develop" a highly robust estimate of the risk for liver cancer in their clinic's population. However, their interim data suggest that among patients who were cured of HCV with DAAs the subsequent risk for developing liver cancer is about 5%.

They also stated that among 94 other patients in their clinic who were cured of HCV with a combination of interferon and ribavirin, 10 developed liver cancer after nearly eight years of monitoring. Thus, about 11% of these 94 interferon-treated patients developed liver cancer. This is another piece of evidence underscoring that interferon-based therapy does not provide 100% protection from the risk of developing liver cancer.

The Austrian doctors stated that their findings have several implications, including the following:

- Patients with cirrhosis should undergo regular screening for liver cancer even after they have been cured of HCV.

- Treating HCV-infected patients who do not have cirrhosis as early as possible may help to reduce their future risk for developing liver cancer.

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I. Bologna researchers find no link between DAAs and liver cancer

Spurred by reports from other cities, doctors in Bologna, Italy, have reviewed their database to assess possible risk factors for liver cancer development and recurrence in 344 participants who were treated for hepatitis C virus (HCV) infection with direct-acting antivirals (DAAs) in 2015. All participants had extensive scarring of the liver (cirrhosis) prior to DAA treatment and were therefore at heightened risk for developing liver cancer.

As a result of treatment with DAAs, 91% of participants were cured. Readers should note that despite participants being cured cirrhosis does not immediately resolve. Such severe scarring of the liver takes years to develop and it will take years for the liver to repair and regenerate. During the time when the liver is repairing itself, because there is still scarred tissue, liver cancer can still arise.

After successful treatment with DAAs, participants were monitored for 24 weeks. Subsequently, technicians detected liver cancer in 26 out of 344 participants (8%). The cases of liver cancer were distributed as follows:

- 17 out of 59 participants (29%) with a history of liver cancer
- nine out of 285 participants (3%) without a history of liver cancer

Liver cancer recurrence in context

The Bologna doctors stated that in their experience liver cancer recurrence after treatment for liver cancer is "not uncommon." Indeed they found it useful to put the present reports of liver cancer in context. They did this by referring to a major study that monitored participants who were treated for liver cancer (and who did not receive modern-day DAAs). One year after liver cancer treatment, 20% of participants had a recurrence of this disease. The Bologna researchers stated, "Therefore, our finding of a [29%] recurrence rate in patients…was not unexpected."

The researchers concluded by stating that in patients with HCV-related cirrhosis, cure with DAAs "does not seem to reduce the occurrence of liver cancer in the short-term."

In light of their findings, the Bologna doctors recommend that all patients with cirrhosis undergo the following:

- close monitoring during and after DAA therapy
- regular screening for liver cancer even if they are cured of HCV

As liver cancer risk is influenced by the presence of cirrhosis, the Bologna doctors recommend: "When possible, [DAA] treatment should be started early, before the development of cirrhosis."

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Conti F, Buonfiglioli F, Scuteri A, et al. Early occurrence and recurrence of hepatocellular carcinoma in HCV-related cirrhosis treated with direct acting antivirals. *Journal of Hepatology*. 2016; *in press*.

J. Large review from three French studies finds no link between use of DAAs and recurrence of liver cancer

As mentioned earlier in this issue of *TreatmentUpdate*, reports from Barcelona and Vienna have emerged suggesting that exposure to direct acting antivirals (DAAs) in a small number of patients may somehow be associated with an increased risk for the recurrence or development of liver cancer. However, analyses of small databases can sometimes inadvertently produce biased conclusions.

To cast clarity on the possible association between the use of DAAs and the risk for the development or recurrence of liver cancer, researchers in France who were interested in assessing risks for liver cancer conducted a large review of three prospective studies. Each of these studies, for different reasons, collected data on more than 6,000 people who had been treated with these drugs. An analysis of such a large number of people is very powerful. Such large analyses help to reduce the risk of inadvertent bias that could occur when analyzing much smaller numbers of people.

The researchers found that rates of liver cancer recurrence were relatively low and that there was no increased risk for liver cancer or its recurrence among people who were treated with DAAs.

Study details and results

ANRS CO22 HEPATHER
By the end of 2015, this study had recruited more than 14,000 people with past or active HCV infection. A total of 5,458 people initiated treatment with DAAs. Researchers focused on 267 participants who had chronic active HCV and who had previously been treated for liver cancer. Researchers divided these 267 people into two groups as follows: 189 were subsequently treated with DAAs and 78 were not. The research team found three statistically significant differences between these two groups of people. Specifically, DAA users were more likely to have the following features:

- they were slightly younger (62 vs. 66 years)
- they were more likely to be men (78% vs. 73%)
- they were more likely to have scarring of their liver (78% vs. 63%)

However, the rate of recurrence of liver cancer was not significantly different between the two groups of participants.

The researchers also noted that there were five cases of liver cancer recurrence in people who received a combination of sofosbuvir + interferon + ribavirin. They stated that this undercuts support for the argument that interferon provides some sort of protection from the subsequent development of liver cancer.

ANRS CO12 CIRVIR
This study, which enrolled 1,822 people with cirrhosis (severe scarring of the liver), was focused on studying people with complications from cirrhosis. The French research team reviewed data collected on 1,354 participants who had cirrhosis caused by HCV infection. It is important to note that because participants had cirrhosis their risk for developing liver cancer was elevated.

The research team found 77 people who were in remission from liver cancer. Thirteen of these people subsequently received DAAs. One of these 13 (8%) had a recurrence of liver cancer three years later. In contrast, among the 66 remaining participants who did not receive DAAs, 31 recurrences (41%) occurred.

ANRS CO23 CUPILT
Participants in this study were enrolled so that doctors could monitor the impact of liver transplantation on their health. Researchers focused on 314 people who underwent liver transplantation and who subsequently received DAAs. A recurrence of liver cancer occurred in seven participants (2%). Five of these seven people died within five years of receiving the transplant. Researchers found that in five of these seven cases, based on analysis of the tumours from the first bout of liver cancer, it was likely that liver cancer would recur.

Key points

After searching through medical records and analysing data from three studies, which included participants with and without cirrhosis and some of whom had liver transplants, researchers found no evidence of an increased risk for the recurrence of liver cancer in patients who had been treated with DAAs.

This finding should reassure patients, doctors, nurses and pharmacists about the safety of DAAs. Furthermore, these findings are aligned with those from larger studies reported in *TreatmentUpdate* 215 (U.S. study looks at long-term durability of cure, risk of relapse and liver cancer).

REFERENCES:

1 Pol S. Lack of evidence of an effect of direct acting antivirals on the recurrence of hepatocellular carcinoma: The ANRS collaborative study group on hepatocellular carcinoma (ANRS CO22 HEPATHER, CO12 CIRVIR and CO23 CUPILT cohorts). *Journal of Hepatology*. 2016; *in press*.

2. Lawitz E, Ruane P, Stedman C, et al. Long-term follow-up of patients with chronic HCV infection following treatment with direct-acting antiviral regimens: maintenance of SVR, persistence of resistance mutations and clinical outcomes. *The International Liver Congress*, 13-17 April 2016, Barcelona. Abstract 166.

K Background – Getting to know your HCV drugs and classes

In *TreatmentUpdate* 215 we published a short guide about some classes of treatment for hepatitis C virus (HCV). Before reading the rest of the reports in this issue, it may be useful to review that guide (Know your drugs and classes) now.

L. Sofosbuvir + velpatasvir (Epclusa) + ribavirin for retreatment

The hepatitis C virus (HCV) protein NS5A plays an important role in the creation of new copies of HCV. As a result, pharmaceutical companies have developed (and continue to develop) drugs that disable this protein.

Currently approved drugs that target NS5A include the following:

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

Inhibitors of NS5A are generally considered to be the most powerful of anti-HCV drugs. Therefore, regimens that contain the above-listed drugs are powerful and rates of cure with such regimens in clinical trials are usually at least 95%. However, a small proportion of people may not be cured despite the use of powerful regimens. The reasons for this can vary and are discussed in *TreatmentUpdate* 215 (When HCV treatment failure occurs).

It is possible that in people whose regimens fail, HCV may change, or mutate, and develop the ability to resist inhibitors of NS5A. If that happens, new regimens containing more powerful NS5A inhibitors will be needed.

Enter Epclusa

Velpatasvir is an anti-HCV drug that will be co-formulated (put in one pill) with another anti-HCV drug called sofosbuvir (Sovaldi). These two drugs in one pill will be sold as Epclusa. Velpatasvir is a powerful inhibitor of NS5A.

In a clinical trial where Epclusa was used along with the broad-spectrum antiviral drug ribavirin, the combination was able to cure 91% of participants who needed retreatment after their previous regimen had failed. Bear in mind that in this study 24 consecutive weeks of retreatment were necessary to effect such a high rate of cure.

Study details

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

- 77% men, 23% women
- age – 57 years
- 26% had cirrhosis (but participants did not have symptoms of cirrhosis)
- HCV viral load – more than 3 million IU/mL

- common strains of HCV were as follows: genotype 1a – 37 people; genotype 1b – 32 people; genotype 2 – 14 people; genotype 3 – 18 people

For 99% of participants, their previous experimental treatment was initially able to suppress HCV levels in the blood. However, once that course of treatment ceased, HCV levels resurged. Participants in this study either had been in previous phase I/II studies sponsored by Gilead Sciences that used very short durations of treatment or in studies where they may have received less-than-ideal doses of drug (as such studies were exploring different doses of medicines).

The dose of ribavirin used varied depending on a person's weight.

Results—distribution of cure rates

Overall, 91% (59 out of 65 participants) were cured.

Cure rates by genotype were as follows:

- genotype 1 – 97% of participants (33 out of 34) were cured; one person relapsed
- genotype 2 – 91% of participants (13 out of 14) were cured; one person relapsed
- genotype 3 – 76% of participants (13 out of 17) were cured; two people relapsed, another did not respond to treatment and one person prematurely left the study for unknown reasons

In cases of genotype 1 and 2 infections where mutations to NS5A were detected prior to retreatment, all participants were cured with sofosbuvir + velpatasvir + ribavirin. In cases of genotype 3 infection, 13 out of 16 people had mutations to NS5A detected at the start of the study. The cure rate in genotype 3 patients who were retreated was 77% (10 out of 13 people). Bear in mind that, in general, genotype 3 infection does not respond as well to DAAs as other genotypes do.

Side effects

Common side effects were as follows:

- lack of energy/unexpected tiredness – 32%
- nausea – 22%
- headache – 17%
- sleeping problems – 16%
- rash – 16%
- itchy skin – 14%
- irritability – 13%

Bear in mind that some of these side effects were likely due to exposure to ribavirin.

Researchers graded most of these side effects as mild to moderate. However, three people experienced severe side effects (details were not provided).

One participant left the study because of severe irritability.

No one died in the study.

Lab tests—focus on anemia

Red blood cells help bring oxygen to tissues and remove the waste product carbon dioxide. Ribavirin can cause some red blood cells to prematurely die. As a result, people who use this drug can be at elevated risk for (temporarily) reduced levels of red blood cells—anemia. They may also feel unexpectedly tired, have skin rash and can experience irritability and depression. Despite the effects of ribavirin, only four participants developed anemia in the study.

Key points

Overall, among people who were retreated with a combination of sofosbuvir + velpatasvir + ribavirin, cure rates were greater than 90%.

There was no impact of mutations associated with the HCV protein NS5A in people with HCV genotypes 1 or 2. However, such mutations in people with genotype 3 resulted in lower rates of cure.

A higher rate of effectiveness across all genotypes may be found with the following combination:

- sofosbuvir + velpatasvir + GS-9857

This combination has entered phase III clinical trials. Other combinations of potent anti-HCV drugs are also being tested and these may be candidates for some people who seek retreatment.

REFERENCE:

Gane EJ, Shiffman ML, Etzkorn K, et al. Sofosbuvir + velpatasvir in combination with ribavirin for 24 weeks is effective retreatment for patients who failed prior NS5A-containing DAA regimens: results of the retreatment study. *The International Liver Congress*, 13-17 April 2017, Barcelona, Spain. Abstract PS024.

M. Sofosbuvir + velpatasvir in HIV co-infection

In a study sponsored by Gilead Sciences called Astral-5, researchers in the United States tested the fixed-dose combination of sofosbuvir + velpatasvir (sold as Epclusa) in 106 people who were co-infected with hepatitis C virus (HCV) and HIV. Overall, 95% of participants (99 out of 104) were cured. The combination of sofosbuvir + velpatasvir was effective against genotypes present in the study (genotypes 1 through 4). Side effects were mostly of mild-to-moderate intensity.

Study details

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

- age – 54 years
- 91% men, 8% women
- 18% had severe scarring of the liver (cirrhosis) but no symptoms of this
- 29% had unsuccessfully attempted treatment in the past
- HCV viral load – 2 million IU/mL
- CD4+ cell count – 600 cells/mm^3
- all participants were taking anti-HIV medicines and their HIV viral loads were less than 50 copies/mL
- no participant was taking efavirenz (Sustiva, Stocrin and in Atripla), as this anti-HIV drug significantly reduces the amount of velpatasvir in the blood

The distribution of genotypes was as follows:

- genotype 1a – 66 people
- genotype 1b – 12 people
- genotype 2 – 11 people
- genotype 3 – 12 people
- genotype 4 – five people

Cure rates

Overall, so far 95% of participants (99 out of 104) were cured (final data from two participants are pending).

Cure rates distributed by genotype are as follows:

- genotype 1a – 95% (62 out of 65) cured; two participants relapsed
- genotype 1b – 92% (11 out of 12) cured; one person stopped visiting the study clinic
- genotype 2 – 100% (11 out of 11) cured
- genotype 3 – 92% (11 out of 12) cured; one participant prematurely left the study
- genotype 4 – 100% (four out of four) cured

All participants who had cirrhosis were cured.

HCV resistance testing

At the start of the study before participants began taking sofosbuvir + velpatasvir, Gilead tested blood samples from 101 participants for the presence of HCV that could, in theory, have the ability to resist the effects of treatment. Technicians found that a total of 12 participants (12%) had HCV that could resist an inhibitor of NS5A. However, all 12 of these people were cured.

Side effects

Although 71% of participants reported side effects, the vast majority of these were graded mild to moderate by researchers. However, 8% of participants experienced more intense side effects.

Common side effects included the following:

- lack of energy/unexpected tiredness – 25%
- headache – 13%
- bone/joint pain – 8%
- diarrhea – 8%
- problems sleeping – 7%
- nausea – 7%

No one died during the study.

Nineteen people developed highly abnormal lab test results. This was most commonly elevated levels of the waste product bilirubin in the blood, which occurred in participants who were taking the anti-HIV medicines atazanavir (Reyataz) and ritonavir (Norvir).

Participants who were taking the anti-HIV drug tenofovir (Viread and in Truvada) together with a protease inhibitor or the boosting agent cobicistat experienced a modest decrease in the functioning of their kidneys. This was assessed with eGFR (estimated glomerular filtration rate).

Key points

Treatment with 12 consecutive weeks of sofosbuvir + velpatasvir resulted in a high rate of cure: 100% of participants with cirrhosis and 97% of participants whose past therapy failed were cured.

Sofosbuvir + velpatasvir was generally safe.

REFERENCE:

Wyles D, Brau N, Kottilil S, et al. Sofosbuvir and velpatasvir for 12 weeks in patients co-infected with HCV and HIV-1: the Astral-5 study. *The International Liver Congress*, 13-17 April 2017, Barcelona, Spain. Abstract PS-104.

N. Sofosbuvir + velpatasvir – interactions with other medicines

The fixed-dose combination of sofosbuvir + velpatasvir (sold as Epclusa) has activity against all major strains, or genotypes, of hepatitis C virus (HCV). The combination of these drugs has been evaluated for possible and potential interactions with other drugs.

Results

Here are recommendations from Epclusa manufacturer Gilead Sciences:

In people co-infected with HIV and HCV, the following drugs can be used:

Nukes (nucleoside and nucleotide analogues)
- FTC (emtricitabine)
- TAF (tenofovir alafenamide)
- TDF (tenofovir DF; the original formulation of tenofovir)

Non-nukes
- rilpivirine (Intelence and in Complera)

Integrase inhibitors
- dolutegravir (Tivicay and in Triumeq)
- elvitegravir (in Genvoya and Stribild)
- raltegravir (Isentress)

Protease inhibitors
- atazanavir (Reyataz)
- darunavir (Prezista and in Prezcobix)
- lopinavir (in Kaletra)

Boosters
- ritonavir (Norvir and in Kaletra)
- cobicistat (in Genvoya and Stribild)

What is clear from the drug interaction studies with Epclusa is that the anti-HIV drug efavirenz (Sustiva, Stocrin and in Atripla) must not be used because it can reduce absorption of velpatasvir by about 50%.

Hormonal contraceptives ("the pill")
No loss of efficacy with oral contraceptives containing norgestimate/thinly estradiol should occur.

Transplant drugs
Sofosbuvir-velpatasvir does not appear to have significant interactions with cyclosporine (Neoral, Sandimmune) or tacrolimus (Advagraf, Prograf).

Complete details about drug interactions between sofosbuvir-velpatasvir and other medicines will be released in the future by Gilead.

REFERENCE:

Mogalian E, McNally J, Shen G, et al. Drug-drug interaction profile of sofosbuvir-velpatasvir fixed-dose combination. *The International Liver Congress*, 13-17 April 2017, Barcelona, Spain. Abstract FRI-168.

O. Sofosbuvir + velpatasvir – improvements in quality of life, energy and emotional and mental health

Researchers conducted a double-blind placebo-controlled study of the combination of sofosbuvir + velpatasvir (Epclusa) in participants with hepatitis C virus (HCV) infection. The term *double-blind* means that neither the researchers directly involved with the study nor the participants knew who received Epclusa or fake Epclusa (placebo). As part of this study, called Astral-1 sponsored by

Gilead Sciences, participants completed surveys on a regular basis about such issues as physical functioning, pain, general health and vitality, emotional and mental health and fatigue. In total, 624 participants received sofosbuvir + velpatasvir and 116 received placebo for 12 consecutive weeks. After treatment cessation, participants were monitored for 24 additional weeks. Astral-1 took place in Canada, Belgium, France, Germany, Italy, the UK and the U.S.

Researchers found that among participants who received sofosbuvir + velpatasvir, aspects of mental health assessed began to improve significantly by the 4th week of the study. Among participants who received placebo, the only area of improvement was a decreased sense of worry. However, participants who received sofosbuvir + velpatasvir had a much greater decrease in their sense of worry than people who received placebo.

Improvement in quality of life, emotional and mental health and other assessments were sustained and statistically significant for participants who received sofosbuvir-velpatasvir. Furthermore, these improvements continued to be statistically significant for 12 and 24 weeks after treatment was initiated. In contrast, among placebo users scores of the same assessments generally declined significantly.

A major strength of the study was that it was placebo-controlled, which allowed researchers to draw firm conclusions about the trends in scores measured.

Researchers are not certain precisely why people treated with sofosbuvir + velpatasvir would feel better. However the research team that undertook the quality of life assessments advanced the following ideas:

HCV infection results in inflammation and activation of the immune system. Treatment that cures HCV reduces this inflammation and activation and may indirectly improve overall health and feelings of well-being.

HCV-infected cells of the immune system can travel to the brain and alter the functioning of this vital organ. Successful HCV treatment quickly reduces the amount of HCV in the blood and likely the brain, improving health and quality of life.

REFERENCE:

Younossi ZM, Stepanova M, Feld J, et al. Sofosbuvir-velpatasvir improves patient-reported outcomes in HCV patients: results from Astral-1 placebo-controlled trial. *Journal of Hepatology*. 2016 Jul;65(1):33-9.

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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