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I HEPATITIS C VIRUS

A. New treatments for hepatitis C virus (HCV) to get approved in Canada later this year

In 2017, pharmaceutical companies expect to see two new treatments for hepatitis C virus approved. These new treatments will be fixed-dose combinations of two or three drugs, as follows:

- sofosbuvir + velpatasvir + voxilaprevir (made by Gilead Sciences)
- glecaprevir + pibrentasvir (made by Abbvie)

These drugs have powerful activity against a broad range of different strains (or genotypes) of HCV and will likely be effective against many strains of HCV that have some degree of resistance to currently licensed treatments. This effect against drug-resistant viruses should be particularly useful for patients whose initial therapy for HCV failed.

Both sets of new treatments are likely to be licensed in late summer or early autumn 2017 by Health Canada and a similar time frame is expected by regulatory agencies in the United States and European Union.

Once a drug is approved by Health Canada, it undergoes further reviews and analyses. After these have been completed, pharmaceutical companies then engage in negotiations with Canada's provinces and territories to find a mutually agreeable price. Only after those negotiations are concluded do new drugs get listed on provincial and territorial formularies. These processes mean that it could take at least six months after a new drug is licensed before subsidized use becomes possible on a large scale in Canada. Even people with private insurance coverage for medicines usually have to wait several months after a treatment (for HCV or any other condition) is approved by Health Canada before it makes it onto a list of drugs covered by insurance companies.

In this issue of *TreatmentUpdate* we present data on these upcoming treatments for hepatitis C virus.

B. Improvements in mood and energy after successful HCV treatments

Untreated, unrecognized or poorly managed mental health issues can be a driver of substance use and can make some people vulnerable to infections such as hepatitis C virus (HCV) and HIV. Once these infections become established, having a chronic viral infection can lead to persistent activation and inflammation of the immune system, which can affect the health of the brain. This effect on the brain occurs because cells of the immune system become activated and inflamed due to the chronic viral infection (in this case HCV) and travel to the brain where they release chemical signals that can trigger inflammation in that organ.

Treatment for HCV and mood

Modern treatments for HCV are called direct-acting antivirals (DAAs). Treatment with DAAs is generally highly effective, with currently approved treatments achieving cure rates greater than 90% in clinics.

Researchers at a medical centre in the German city of Homburg conducted a study to assess the impact of DAAs on issues such as mood and factors affected by mood, such as physical activity and fatigue. Additionally, the researchers also assessed changes in the blood of the chemical messenger serotonin, a compound that can affect mood.

About serotonin

To manufacture serotonin, the body's cells start with the amino acid tryptophan, found in many protein-rich foods, and put it through a series of processes. This amino acid is converted by cells into another molecule called 5-HTP (5-hydroxytryptophan), which is then converted into serotonin. Cells, particularly those in the brain, use serotonin and similar molecules to communicate with each other. Some treatments for depression and anxiety are thought to work by affecting serotonin levels.

Study details

Researchers recruited 29 participants with chronic HCV infection—24 received treatment and the remaining five were used for the purposes of comparison. Participants were assessed before, during and after DAA treatment. Researchers took

blood samples, surveyed patients with validated health questionnaires and gave them devices to track physical activity.

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

- 14 men, 15 women
- age – mid-50s
- most participants had a moderate degree of liver injury
- the most common strain of HCV was genotype 1, followed by genotypes 3 and 2

Commonly used combinations of DAAs were as follows:

- sofosbuvir + ledipasvir (Harvoni)
- sofosbuvir + ribavirin
- paritaprevir + ritonavir + ombitasvir + dasabuvir (Holkira Pak)

Results—Changes in fatigue

Over the course of therapy, researchers found that the degree of fatigue fell significantly in the 24 participants who received DAAs. Furthermore, by the end of treatment, 70% of treated participants reported a lack of fatigue. In contrast, no changes in fatigue occurred among the control group.

Symptoms of depression also improved significantly in treated people but did not change in the control group.

Analyses of blood samples found that levels of the serotonin precursor 5-HTP rose significantly in the blood of DAA-treated participants. An increase in 5-HTP is likely to lead to an increase in serotonin levels.

Overall, the results of this analysis suggest that DAAs have a positive, persistent and likely indirect effect on fatigue and mood. This may come about because DAAs quickly reduce production of HCV and then help eliminate this virus from the body.

REFERENCE:

Hahn D, Stokes CS, Kaiser R, et al. Effects of direct-acting antiviral agents for the treatment of chronic hepatitis c virus infection on serotonin metabolism, depression scores and fatigue. In: Program and abstracts of the *International Liver Congress*, 19-23 April 2017, Amsterdam, the Netherlands. Poster 253.

C. Better blood sugar control in people with diabetes after HCV has been cured

Many people who have been living with chronic hepatitis C virus (HCV) also have other health issues, such as type 2 diabetes. In 2015, researchers at the University of Turin, Italy, sought to assess the impact on type 2 diabetes once HCV was cured with modern all-oral HCV treatment, otherwise known as direct-acting antivirals, or DAAs.

Researchers recruited 122 people, most of whom (101) subsequently became cured of HCV. The researchers found that people who were cured underwent "significant improvement" in blood sugar levels. As a result of the decrease in blood sugar levels, in many cases participants' doctors were able to reduce the dose of medicines used to help control blood sugar.

Study details

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

- 70% men, 30% women
- age – 61 years
- smokers – 22%
- higher-than-normal blood pressure (hypertension) – 40%
- previous diagnosis of liver cancer – 6%
- all participants had extensive scarring of their liver (cirrhosis)

Participants were monitored for between 24 and 36 weeks (before, during and after treatment cessation).

Results

Researchers divided participants into two groups, as follows:

- 101 people who were cured
- 21 people who were not cured—nine of whom were not cured despite the use of DAAs and 12 others who were not offered treatment during the study

Researchers found that, on average, blood sugar levels (taken when participants had fasted overnight) fell significantly after cure was achieved.

Furthermore, 37% of cured people were able to reduce their dose of diabetes medicine after cure was achieved. In contrast, among people who were not cured, only 5% were subsequently able to reduce their dose of diabetes medicine.

On average, after being cured, people gained about 3 kilograms in weight. Among those who were not cured, their weight did not change significantly during the study.

Although this was not a randomized clinical trial, the overall results suggest an additional aspect of improved health—better control of blood sugar—among some people who were cured of HCV.

REFERENCE:

Ciancio A, Bosio R, Bo S, et al. Marked improvement of glycaemic control in diabetic patients with chronic hepatitis C achieving sustained virological response after direct-acting antiviral therapy: results of a prospective controlled study. In: Program and abstracts of the *International Liver Congress*, 19-23 April 2017, Amsterdam, the Netherlands. Poster 221.

D. Services for people with HCV who use homeless shelters

Researchers in Brighton, England, have found that some homeless people are at increased risk for liver disease. Unfortunately, in the experience of the researchers, this vulnerable population may be reluctant to engage with hospital-based services, where monitoring and care of liver diseases usually take place.

To help remedy this problem, the Brighton researchers established a liver monitoring and care service located in the community that focused on people 40 years and older. Specifically, in late 2015, the researchers, together with doctors and nurses, established a liver care service at two major hostels that catered to homeless people aged 40 and up. At these mini-clinics each participant was asked to do the following:

- a brief survey about their use of alcohol and street drugs
- screening for blood-borne viruses
- specialized ultrasound scans of the liver (Fibroscans)

If participants were found to have chronic hepatitis C virus (HCV) infection and/or significant liver injury arising from HCV infection, they were offered treatment.

So far researchers have enrolled 84 people whose key features at the time of enrollment in the liver care service were as follows:

- 79% men, 21% women
- average age – 51 years
- underlying drivers of liver injury were excessive intake of alcohol, chronic HCV infection or both. About 45% of participants disclosed that they had become addicted to alcohol.
- 68% of participants disclosed that they had mental health issues
- 77% of participants disclosed that they had used or currently used street drugs

HCV and liver assessments

- 36 participants (43%) had HCV infection
- 27% of participants had what the researchers termed "clinically significant" levels of liver injury
- 18% had severely injured livers

Putting it all together

The present study of the liver care service should be considered preliminary. However, it shows that a high proportion of people (97%) who use homeless shelters in Brighton are willing to engage in liver care when services are located in the community for their use.

The researchers used Fibroscans to reveal the extent of liver injury in participants. The researchers found that these machines were "perceived [by participants] to be a powerful tool that facilitated patient engagement."

The researchers encouraged health authorities in other regions to "replicate" their model of providing services to older and vulnerable homeless adults.

At present, only a small proportion of people have started HCV therapy. The researchers will provide an update on the safety and effectiveness of treatment in the future.

Some people with relatively uncomplicated mental health issues are also looked after by clinicians affiliated with the study. However, people with complex mental health conditions and substance

use issues are referred to other clinics that specialize in such care.

REFERENCE:

Hashim A, Worthley T, Macken L, et al. Enhancing detection and treatment of chronic hepatitis C related liver disease in vulnerable adults through a dedicated homeless hostel-based liver service: Vulnerable Adults Liver Disease Study. In: Program and abstracts of the *International Liver Congress*, 19-23 April 2017, Amsterdam, the Netherlands. Poster 179.

E. Depression and anxiety not barriers to HCV treatment success

Researchers have found that some people with chronic hepatitis C virus (HCV) in high-income countries also have mental health and substance use issues. At least two studies have found that people with HCV are more likely to have illnesses such as schizophrenia and bipolar disorder than the average person without HCV. It is possible that some people with HCV who also have undiagnosed, untreated or poorly managed mental health conditions may not be able to fully engage with their overall care and their treatment of HCV unless they get adequate support.

To investigate the intersection of mental health, substance use and HCV treatment, researchers at several community health centres in San Diego undertook a study.

The researchers reviewed the clinics' healthcare records and found the following:

- 3,233 people had HCV infection
- 369 people had already been treated for HCV
- 65 people were currently taking HCV treatment

Among all 3,233 people with HCV, researchers stated that nearly 78% had a "mental health and/or substance abuse diagnosis." The specific diagnoses were distributed as follows:

- 28% had "only a substance abuse diagnosis"
- 12% had "only mental health disorder"
- 38% had "both diagnoses"

Among the 434 people who had taken or were currently taking HCV treatment, researchers found that 78% had "either a substance abuse, a mental health diagnosis or both."

Specific diagnoses

Among all 3,233 people diagnosed with HCV infection, common additional diagnoses were as follows:

- major depression – 17%
- anxiety disorders – 11%
- psychotic disorders – 5%
- alcohol dependence – 6%
- stimulant dependence – 6% (mostly to amphetamines)

Among the people who had taken or who were currently taking HCV treatment, the most common additional diagnoses were as follows:

- major depression – 32%
- anxiety disorders – 17%
- "drug dependence in remission" – 13%
- "alcohol dependence in remission" – 10%

Moving forward

According to the San Diego researchers, here were some key points from their study:

> "Mental health and substance abuse issues are common in our urban, underserved, primary care–based HCV treatment program."

The researchers said that having both "mental health and substance diagnoses" was not a barrier to successful HCV treatment.

The study team encouraged other care providers to identify these co-morbidities before HCV treatment is initiated or during HCV treatment. Once identified, the diagnosis of these co-morbidities could serve as an opportunity to offer services such as "case management, behavioural therapy, rehabilitation services and group therapy." Such interventions could help improve success rates with HCV treatment and the overall health and quality of life of people struggling with mental health and addiction issues.

REFERENCE:

Nateras A, Wallace D, Moreau M, et al. High prevalence of concomitant substance abuse and mental health disorders in an urban underserved FQHC-based HCV treatment program. In: Program and abstracts of the *International Liver Congress*, 19-23 April 2017, Amsterdam, the Netherlands. Poster 200.

F. Know your drugs and classes of HCV treatment

In this issue of *TreatmentUpdate* we discuss several emerging treatments for hepatitis C virus (HCV). Here is a brief guide to some drugs and the classes to which they belong.

Know your drugs and classes

Treatments for 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 to 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 target multiple proteins and enzymes makes for a more effective regimen than one 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.

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 (Sunvepra)
- grazoprevir (in Zepatier)
- paritaprevir (in Holkira Pak)
- simeprevir (Galexos)
- glecaprevir (formerly ABT-493)
- voxilaprevir (formerly GS-9857)

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. NS5B inhibitors are divided into subclasses such as nukes (sofosbuvir) and non-nukes (dasabuvir, in Holkira Pak).

NS5A

Researchers are not certain about the exact 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)
- velpatasvir (in Epclusa)
- pibrentasvir (formerly ABT-530)

REFERENCE:

Gotte M, Feld JJ. Direct-acting antiviral agents for hepatitis C: structural and mechanistic insights. *Nature Reviews. Gastroenterology & Hepatology*. 2016 Jun;13(6):338-51.

G. Glecaprevir + pibrentasvir in HCV genotype 1 or 4 with previous treatment failure

There are limited treatment options for patients whose previous direct-acting antivirals (DAAs) have failed to cure them of chronic hepatitis C virus (HCV) infection. A combination that is in development for the treatment of many strains of HCV, including drug-resistant ones, consists of the following two drugs:

- glecaprevir (formerly ABT-493) is a pan-genotypic inhibitor of the HCV proteins NS3/4A
- pibrentasvir (formerly ABT-530) is active against the NS5A protein

Both of the above drugs work against a broad array of strains, or genotypes, of HCV and are co-formulated into one pill. The dose used in clinical trials is three pills once daily taken with food. This combination of drugs is a complete regimen. Results from phase I and II clinical trials show that these drugs are generally very safe and highly effective. Results from phase III studies have confirmed these trends.

In this report we will shorten the names of the drugs to G (glecaprevir) and P (pibrentasvir).

In a study called Magellan-1 part 2, researchers tested the combination of G+P for 12 or 16 weeks in participants with one of the following genotypes whose previous regimens had failed:

- genotypes 1, 4, 5 or 6

Researchers randomly assigned participants as follows:

- G+P for 12 consecutive weeks – 44 participants
- G+P for 16 consecutive weeks – 47 participants

All participants were monitored for a total of 28 weeks after completing therapy.

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

- 70% men, 30% women
- age – 57 years
- body mass index (BMI; a relative indicator of fatness) – 29
- HCV viral load – 6 million IU/mL
- the proportion of participants with cirrhosis was 30%; no participants had symptoms of cirrhosis

Key resistance to certain classes of HCV treatments were distributed as follows:

- none – 30%
- NS3 only – 7%
- NS5A only – 54%
- NS3 + NS5A – 10%

Results

The distribution of people cured by each regimen was as follows:

- 12-week regimen – 89% cured
- 16-week regimen – 91% cured

Participants who had not previously used an NS5A inhibitor had cure rates of 100% with either 12 or 16 weeks of G+P.

Patients with prior failure to NS5A inhibitors and who had never previously received protease inhibitors had a 94% cure rate with 16 weeks of G+P.

REFERENCE:

Poordad F, Pol S, Asatryan A, et al. Magellan-1, Part 2: glecaprevir/pibrentasvir for 12 or 16 weeks in patients with chronic HCV genotypes 1 or 4 and prior direct-acting antiviral treatment failure. In: program and abstracts of the *International Liver Conference*, 13-22 April 2017. Amsterdam, the Netherlands.

H. Safety and efficacy of glecaprevir + pibrentasvir in cases of liver or kidney transplant with chronic HCV infection

People with organ transplants and hepatitis C virus (HCV) are difficult to treat because of the potential for drug-drug interactions. An advantage of glecaprevir (G) and pibrentasvir (P) is that they have limited interactions with most transplant drugs.

In a clinical trial called Magellan-2, participants—all of whom had a liver or kidney transplant—received 12 weeks of G+P.

The average profile of 100 participants upon entering the study was as follows:

- 75% male, 25% female
- age – 60
- body mass index (BMI; a relative indicator of fatness) – 26
- HCV viral load – 6.5 million IU/mL
- most participants (80%) had minimal or low levels of liver fibrosis (F0 to F1)
- 34% of participants had previously been treated for HCV, mostly with interferon

The main distribution of genotypes was as follows:

- GT 1a – 57%
- GT 2 – 13%
- GT 3 – 24%
- GT 4 – 4%
- GT 6 – 2%

The distribution of transplanted organs was as follows:

- liver – 80%
- kidneys – 20%

The transplantation drugs used were as follows:

- tacrolimus
- mycophenolate mofetil
- cyclosporine
- prednisone/prednisolone
- everolimus
- azathioprine
- sirolimus

A majority of participants did not have any HCV drug resistance, though there were some people with resistance against HCV drugs that attacked the NS5A protein.

Results

- 99% of participants were cured after 12 weeks
- one participant with the sub-genotype 3a relapsed four weeks after the cessation of treatment
- one other participant stopped making clinic visits

Adverse reactions

Two participants developed problems that could plausibly have been related to the use of G+P:

- one participant developed a sinus inflammation
- another participant developed temporary elevation of liver enzyme levels after treatment cessation

Common side effects reported were as follows:

- headache – 22%
- fatigue – 22%
- nausea – 12%
- itchy skin – 12%
- diarrhea – 10%

Overall, most of these adverse effects are similar to those seen with other modern direct-acting antivirals (DAAs) and even in placebo-controlled trials among people who received placebo (such as in Polaris-1, with the combination of sofosbuvir + velpatasvir + voxilaprevir, reported later in this issue of *TreatmentUpdate*).

No participants died during the study.

Seriously abnormal blood test results were rare and, if they occurred, temporary in duration. Again, this is similar to reports of other DAAs in phase III clinical trials.

The combination of G+P is expected to be licensed in Canada by the end of the summer of 2017.

REFERENCE:

Reau N, Kwo PY, Rhee S, et al. Magellan-2: Safety and efficacy of glecaprevir/pibrentasvir in liver or renal transplant adults with chronic hepatitis c genotype 1-6 infection. In: Program and abstracts of the *International Liver Conference*. 13-22 April 2017, Amsterdam, The Netherlands.

I. Glecaprevir + pibrentasvir—highly effective against genotype 3

Hepatitis C virus (HCV) genotype 3 does not usually respond well to therapy with previously licensed direct-acting antivirals (DAAs). Therapy for this strain of HCV has to be given for up to 24 weeks to ensure a high rate of cure. A highly effective therapy that could be given for shorter duration would therefore fulfill an unmet need, as this could enhance adherence and the willingness of patients to receive treatment.

Glecaprevir + pibrentasvir (G+P) is highly active in vitro against genotype 3 (GT 3) and was tested in a clinical trial called Endurance against a combination of sofosbuvir + daclatasvir in a 12-week course of therapy. An additional arm of this study had an eight-week course of G+P.

Participants were distributed as follows:

- G+P for 12 weeks – 233 people
- sofosbuvir + daclatasvir for 12 weeks – 115 people
- G+P for 8 weeks – 157 people

The average profile of participants who entered the study was as follows:

- 55% men, 45% women
- age – 48 years
- HCV viral load – 6 million IU/mL
- 64% had a history of injecting street drugs
- 80% had minimal or no liver fibrosis
- 99% had genotype 3a

Results

Both 12-week regimens were highly effective with cure rates as follows:

- G+P – 95%
- sofosbuvir + daclatasvir – 97%

These differences were not statistically significant and showed that G+P was non-inferior to the other regimen. In other words, G+P was roughly equivalent in effectiveness to the other regimen.

The results for the shortened duration of G +P were remarkable (considering that the duration of therapy was shortened from 12 weeks to eight weeks):

- 95% cured

This result was statistically non-inferior to the 12-week duration of G+P. In other words, a shorter duration of G+P is more or less equivalent in effectiveness to the longer 12-week course of the same medicines.

In all three regimens the most common reason for virological failure was relapse. That is, the drugs were initially able to suppress levels of HCV in the blood to an undetectable level. However, after the cessation of treatment, virus levels surged.

Adverse events

Serious adverse events were rare in this study, occurring in 2% of participants in each study arm.

Common side effects in all three arms were as follows:

- headache – 20%
- nausea – 15%
- fatigue – 13%

These results are similar to those reported in other clinical trials of emerging therapies for HCV.

Seriously abnormal blood test results were rare, occurring in less than 1% of participants receiving any treatment.

This study shows that the combination of G+P can be very useful for people with HCV genotype 3.

The combination of G+P is expected to be licensed in Canada by the end of the summer of 2017.

REFERENCE:

Foster G, Gane E, Asatryan A, et al. Endurance-3: Safety and efficacy of glecaprevir/pibrentasvir compared to sofosbuvir plus daclatasvir in treatment-naïve HCV genotype-3-infected patients without cirrhosis. In: Programs and abstracts of the *International Liver Conference*. 13-22 April 2017, Amsterdam, The Netherlands.

J. Sofosbuvir + velpatasvir + voxilaprevir for HCV re-treatment

Most people with chronic hepatitis C virus (HCV) infection will likely be cured when they take modern all-oral treatments (otherwise known as direct-acting antivirals, or DAAs) for their infection. Combination therapy with DAAs usually results in cure rates ranging between 90% and 95%. However, the remaining proportion of patients who are not cured will require re-treatment. The best combination for re-treatment is not clear.

DAAs work by impairing the activity of proteins and/or enzymes needed by HCV-infected cells to make more copies of this virus. One HCV protein that is impaired by DAAs is called NS5A. In cases where treatment has failed, a person's HCV can develop resistance to NS5A inhibitors. Examples of drugs that are inhibitors of NS5A include the following:

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

Pharmaceutical companies are developing combinations of drugs that may be suitable for re-treating people whose initial DAA regimen failed. One experimental combination is made by Gilead Sciences and consists of the following drugs in one pill:

- sofosbuvir – 400 mg
- velpatasvir – 100 mg
- voxilaprevir (formerly GS-9857) – 100 mg

As the brand name for this trio is not yet available, we will shorten the combination to sof-vel-vox.

Results from well-designed clinical trials of people with HCV whose previous regimens had failed suggest that when this trio of drugs is taken once daily for 12 consecutive weeks, it is effective against a broad range of genotypes, with cure rates ranging between 96% and 98%. Commonly reported adverse effects included headache, fatigue, diarrhea and nausea.

This trio of drugs is expected to be licensed in Canada by the end of the summer of 2017.

Study details

Researchers in Canada, Western Europe, New Zealand, Australia and the U.S. recruited participants for a trial called Polaris-1. In this study, participants were randomly assigned to receive one of the following taken daily:

- sof-vel-vox – 263 participants
- placebo – 152 participants

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

- 80% men, 20% women
- age – late 50s
- participants with severe scarring of the liver – 40%
- HCV viral load – 2 million IU/mL
- genotypes – the most common was genotype 1 (60%), followed by genotype 3 (30%). There were smaller proportions of participants with genotypes 2, 4, 5 and 6.
- 67% of participants had undergone one course of treatment in the past with other drugs
- about 50% of participants had previously used an NS5A inhibitor combined with an NS5B inhibitor
- most treated participants (80%) had experienced a relapse of HCV on their previous regimen

Participants underwent extensive laboratory and clinical assessments before, during and after the cessation of treatment.

Results—Overall

Twelve weeks after the cessation of pill taking, the proportions of participants cured were distributed as follows:

- sof-vel-vox – 96% cured
- placebo – 0% cured

Most of the people cured with sof-vel-vox (253 of 263 participants) returned 24 weeks after they stopped taking the medication and blood tests continued to show that they were cured.

Results—Focus on subgroups

Genotype 1 can be subdivided into different strains, or genotypes, such as 1a and 1b. Of these two strains, subtype 1a generally does not respond as well to treatment. Rates of cure distributed by genotype were as follows:

- 1a – 96% cured
- 1b – 100% cured

Results—Focus on cirrhosis

In past clinical trials of earlier DAAs with people with extensive scarring of the liver, treatment failure occurred in some patients. In Polaris-1 there were participants with cirrhosis, however, none of them had the severe symptoms that can accompany cirrhosis. The distribution of cure rates in the present study were as follows:

- no cirrhosis – 99% cured
- cirrhosis – 93% cured

Results—Focus on pre-existing resistance

In Polaris-1, researchers had viral resistance data on 248 participants who received sof-vel-vox. Of these people, researchers found that 205 (83%) had a strain of HCV at the start of the study that was resistant to previously used inhibitors of NS3 or NS5A. Most of these participants (97%) were cured after they completed their course of sof-vel-vox. This compares to a cure rate of 98% among people who entered the study without such resistant viruses.

Results—Safety issues

In general, the combination of sof-vel-vox was well tolerated by participants.

The term *adverse events* is used by researchers to describe unfortunate events that can occur during a clinical trial. These events can include issues and symptoms that arise from exposure to treatment (side effects) and/or the underlying disease process or from factors that have nothing to do with the clinical trial, such as accidents, injuries and other trauma.

The overall distribution of adverse effects reported by participants was as follows:

- sof-vel-vox – 78%
- placebo – 70%

The most common adverse events reported by participants who received sof-vel-vox were as follows:

- headache – 25%
- fatigue – 21%
- diarrhea – 18%
- nausea – 14%

The most common adverse events reported by placebo users was as follows:

- fatigue – 20%
- headache – 17%
- diarrhea – 12%
- dizziness – 9%

Based on this reporting, it is likely that some adverse events were related to the underlying disease process but some were also caused by the drugs. For instance, it is likely that some of the following symptoms were related to exposure to study medicines:

- headache
- fatigue
- diarrhea

Similar side effects have been seen with other combinations of HCV treatments. Usually the side effects are temporary and fade after several weeks or, at worst, after the course of treatment ends.

Adverse events graded as serious occurred in only seven people (2%) who took sof-vel-vox. Serious adverse events also occurred in seven people who took placebo.

Lab test results

Very unusual lab tests results were not common during the study, affecting a total of 7% of participants who received sof-vel-vox. Note that a total of 14% of participants who took placebo had similarly abnormal lab tests. The grading and distribution of abnormal or very abnormal blood tests affected the following substances measured:

- creatine kinase (elevated levels of this enzyme are possibly suggestive of muscle injury)
- blood sugar (consistently elevated levels can indicate the development of pre-diabetes or worsening of pre-existing diabetes)
- lipase (elevated levels of this enzyme are possibly suggestive of an inflamed pancreas gland)

Despite these lab test results, no participants developed symptoms of any of the issues associated with these tests.

Bear in mind

Overall, the results from Polaris-1 show that the combination of sof-vel-vox is highly effective at curing people of chronic HCV whose prior regimen failed. In this and other clinical trials, sof-vel-vox was effective against a range of genotypes.

There were several shortcomings to the study, as follows:

Only a small proportion of participants had been treated with the latest DAAs, such as Zepatier (a fixed-dose combination of elbasvir and grazoprevir) or Epclusa (a fixed-dose combination of sofosbuvir and velpatasvir). So, the effectiveness of sof-vel-vox against strains of HCV that are resistant to these drugs is not clear.

Certain populations were excluded from the study, including people co-infected with HIV or hepatitis B virus and people who had symptoms of cirrhosis. As such, it is not clear how effective sof-vel-vox will be in these populations.

REFERENCE:

Bourlière M, Gordon SC, Flamm SL, et al. Sofosbuvir, velpatasvir, and voxilaprevir for previously treated HCV infection. *New England Journal of Medicine*. 2017; *in press*.

K. Sofosbuvir + velpatasvir + voxilaprevir for people with genotypes 1, 2 or 3 whose previous treatment failed

In a study called Polaris-4, researchers enrolled participants whose previous regimen(s) of direct-acting antivirals (DAAs) had failed to cure them. Researchers randomly assigned participants to receive one of the following regimens taken for 12 consecutive weeks:

- sof-vel-vox (sofosbuvir + velpatasvir + voxilaprevir) – 182 people
- sofosbuvir + velpatasvir (Epclusa) – 151 people

Participants had the following strains, or genotypes, of HCV: 1, 2, 3 or 4. Overall results were as follows:

- sof-vel-vox – 98% were cured
- sofosbuvir + velpatasvir – 90% were cured

Commonly reported adverse effects in this study included headache, fatigue, diarrhea and nausea.

Study details

Researchers recruited participants whose average profile upon entering the study was as follows:

- 77% men; 23% women
- age – 57 years
- common HCV genotypes – 1, 2 and 3
- 46% had extensive scarring of the liver
- HCV viral load – 2 million IU/mL
- most participants (73%) had been previously treated with an NS5B inhibitor. A majority of participants (60%) had been treated once prior to entering Polaris-4. The most common reason for previous treatment failure was relapse.

Participants received 12 consecutive weeks of either study regimen. Before, during and after the cessation of treatment, participants underwent extensive lab tests and other monitoring.

Results—Overall

Among participants who had been previously treated with DAAs (people who had used an NS5A inhibitor were excluded from this study), overall rates of cure were as follows:

- sof-vel-vox – 98% were cured
- sofosbuvir + velpatasvir – 90% were cured

As with the related clinical trial called Polaris-1, the vast majority of participants returned for additional blood testing 24 weeks after pill taking ceased and remained cured.

The most common reason for the failure of treatment to cure people was relapse. This was most common in people who had genotype 3a.

Results—Focus on cirrhosis

In past clinical trials of earlier DAAs with people with extensive scarring of the liver, treatment failure occurred in some patients. There were participants with cirrhosis in Polaris-4, however, none of them had the severe symptoms that can accompany cirrhosis. The distribution of cure rates in the present study were as follows:

No cirrhosis
- sof-vel-vox – 98%
- sofosbuvir + velpatasvir – 94%

Cirrhosis
- sof-vel-vox – 98%
- sofosbuvir + velpatasvir – 86%

Results—Pre-existing resistance

At the start of Polaris-4, nearly 50% of participants had strains of HCV that had mutated and, due to previous treatment failure, had become resistant to inhibitors of NS3 or NS5A. Researchers presented data on the response to current treatment distributed according to previous past treatment, as follows:

No pre-existing resistance
- sof-vel-vox – 100% cured
- sofosbuvir + velpatasvir – 90% cured

Having pre-existing resistance
- sof-vel-vox – 99% cured
- sofosbuvir + velpatasvir – 89% cured

Results—Safety issues

In general, the combinations of drugs used in Polaris-4 were well tolerated by participants.

The term *adverse events* is used by researchers to describe unfortunate events that can occur during a clinical trial. These events can include issues and symptoms that arise from exposure to treatment (side effects) and/or the underlying disease process or from factors that have nothing to do with the clinical trial, such as accidents, injuries and other trauma.

The overall distribution of adverse effects reported by participants was as follows:

- sof-vel-vox – 77%
- sofosbuvir + velpatasvir – 74%

Common adverse events reported by participants who used sof-vel-vox were as follows:

- headache – 27%
- fatigue – 24%
- diarrhea – 10%

Common adverse events reported by participants who used sofosbuvir + velpatasvir were as follows:

- headache – 28%
- fatigue – 28%
- diarrhea – 8%

According to the researchers, "the majority of cases of diarrhea were mild in severity." There were no severe cases of diarrhea.

Lab test results

Most participants in Polaris-4 did not have severe abnormalities in their blood tests results, as follows:

- sof-vel-vox –7% of participants
- sofosbuvir + velpatasvir – 7% of participants

The grading and distribution of abnormal or very abnormal blood tests only affected the following substances measured:

- creatine kinase (elevated levels of this enzyme are possibly suggestive of muscle injury)
- blood sugar (consistently elevated levels can indicate the develop of pre-diabetes or worsening of pre-existing diabetes)
- lipase (elevated levels of this enzyme are possibly suggestive of an inflamed pancreas gland)

Despite these abnormal lab test results, no participants developed symptoms of any of the issues associated with these tests.

Bear in mind

Overall, the results from Polaris-4 show that the combination of sof-vel-vox and, to a lesser extent, sofosbuvir + velpatasvir, is highly effective in curing people of chronic HCV whose prior regimen failed. Sof-vel-vox was effective in the vast majority of people who received this drug combination, which were people whose previous regimen had failed and who had HCV genotypes 1, 2 or 3.

There were several shortcomings to the study, as follows:

Only a small proportion of participants had been treated with the latest DAAs, such as Zepatier (a fixed-dose combination of elbasvir and grazoprevir) or Epclusa (a fixed-dose combination of sofosbuvir and velpatasvir). So, the effectiveness of sof-vel-vox against strains of HCV that are resistant to these drugs is not clear.

Certain populations were excluded from the study, including people co-infected with HIV or hepatitis B virus and people who had symptoms of cirrhosis. As such, it is not clear how effective this combination will be in these populations based on the data in Polaris-4.

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II HIV

A. Isentress HD—a new once-daily formulation of raltegravir approved in Canada

In late June 2017, Health Canada licensed the sale and use of a new formulation of the anti-HIV drug raltegravir (Isentress) as part of the treatment of HIV. The new formulation is called Isentress HD (high dose). The formulation can be taken once daily with or without food.

Raltegravir belongs to a family of drugs called integrase inhibitors. As part of combination therapy, integrase inhibitors can usually quickly reduce and suppress the amount of HIV in the blood to very low levels that are commonly called undetectable. In general, Isentress HD does not affect the level of many other drugs in the body and vice versa.

Raltegravir was the first HIV integrase inhibitor, introduced to Canada and other high-income countries in 2007. It has a decade of generally good safety and antiviral activity.

Isentress HD should not be confused with the earlier formulation, which needs to be taken twice daily.

Isentress HD is meant for adults who either have never previously taken HIV treatment or who are currently taken a regimen based on the older formulation of raltegravir and whose viral load is undetectable.

The approval of Isentress HD was based on a clinical trial of that formulation that was conducted over two years. In this issue of *TreatmentUpdate* we report on the first year of that study. The final two-year results will be released at a biomedical conference later this year.

Isentress HD will not become available in Canada until later this year, perhaps in the Autumn.

B. Isentress HD in clinical trials

In a two-year trial called Oncemrk, researchers in Canada and other countries compared a regimen containing the older formulation of raltegravir (Isentress) to a regimen containing the new formulation of raltegravir (Isentress HD). Analysing the data after one year, researchers found that Isentress HD was roughly equivalent in effectiveness and safety to the older formulation.

Study details

Researchers randomly assigned HIV-positive adults who had never previously been treated, in a 2:1 ratio, to one of the following regimens:

- Isentress HD 1,200 mg (taken once daily) + Truvada (tenofovir + FTC) – 533 people
- Isentress 400 mg (taken twice daily) + Truvada – 269 people

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

- 85% men, 15% women
- age – 34 years
- history of AIDS – 12%
- co-infected with hepatitis B or C viruses – 3%
- HIV viral load – 36,000 copies/mL; 28% of participants had a viral load greater than 100,000 copies/mL
- CD4+ count – 390 cells/mm^3

Results—Changes to viral loads and CD4+ cell counts

Both regimens were highly effective and viral loads fell rapidly in the study regardless of which formulation of raltegravir was used. For instance, by the fourth week of the study the following proportions of participants had a viral load less than 40 copies/mL:

- Isentress HD-based regimen – 54%
- a regimen based on the older formulation of raltegravir – 52%

By the 24th week of the study the figures were as follows:

- Isentress HD-based regimen – 87%
- a regimen based on the older formulation of raltegravir – 87%

By the 48th week of the study the figures were as follows:

- Isentress HD-based regimen – 89%
- a regimen based on the older formulation of raltegravir – 88%

Among participants who entered the study with a viral load greater than 100,000 copies/mL, the figures at week 48 were as follows:

- Isentress HD-based regimen – 87%
- a regimen based on the older formulation of raltegravir – 84%

Increases in CD4+ cell counts

Overall, CD4+ cell counts increased by an additional 230 cells/mm^3 at the end of the study. This meant that on average a person's cell count had moved from almost 400 cells at the start of the study to about 600 cells/mm^3 at week 48.

Based on these results, the new formulation of raltegravir is roughly equivalent to the older formulation. The technical term for this is *non-inferior*.

Sub-analyses of the study found that both study regimens were similarly effective in men, women and people of different ethno-cultural groups.

Adverse events

Side effects are common during the first few days or weeks of a new regimen. Integrase inhibitor–based regimens are generally well tolerated and adverse effects tend to fade over time.

Overall, the distribution of drug-related adverse effects were as follows:

- Isentress HD-based regimen – 25%
- a regimen based on the older formulation of raltegravir – 26%

The most common side effects associated with Isentress HD are as follows:

- difficulty falling asleep
- headache
- dizziness
- nausea
- fatigue

However, in general, these side effects were less common in people who used Isentress HD compared to the older formulation of raltegravir.

More detailed information on Isentress HD, including uncommon side effects, will appear in a CATIE factsheet that is being developed on this drug.

There were three deaths in the study, none of which appeared to be related to the use of the study medicines. Instead, the deaths were likely related to underlying disease processes (immunological dysfunction and deficiency) caused by HIV. The deaths were distributed as follows:

- Isentress HD-based regimen – lymphoma (diagnosed on the 36th day of the study); tuberculosis (diagnosed on the 7th day of the study)
- a regimen based on the older formulation of raltegravir – multiple life-threatening infections occurring on the 17th day of the study

Summary

Regimens based on the new or old formulation of raltegravir appear to be equally effective in people who have not previously taken HIV treatment. Both regimens were generally safe.

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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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