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I ANTI-HCV AGENTS

A. Zepatier for hepatitis C approved in Canada

Zepatier is a fixed-dose pill containing the following two anti-HCV drugs:

- elbasvir – 50 mg
- grazoprevir – 100 mg

Zepatier is taken once daily with or without food.

This story first appeared in *CATIE News* and we include it here as part of a package on Zepatier-related information. It is important to note that this story contains a summary of key information about Zepatier and in which patient populations it can be used.

<http://www.catie.ca/en/catieneews/2016-01-29/zepatier-hepatitis-c-approved-canada>

B. Zepatier in hepatitis C virus genotype 1a

There are several strains, or genotypes, of hepatitis C virus (HCV) as follows—genotypes 1 through 6. These genotypes can be further divided into subgroups, such as genotype 1a, 1b and so on.

In Canada, Australia, the U.S., UK, Brazil and Scandinavia, genotype 1 is common, and genotype 1a is more common than genotype 1b. Furthermore, genotype 1a tends to respond less to therapy than 1b.

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Canada's source for
HIV and hepatitis C
information

555 Richmond Street West, Suite 505
Box 1104
Toronto, Ontario M5V 3B1 Canada
phone: 416.203.7122
toll-free: 1.800.263.1638
fax: 416.203.8284
www.catie.ca
charitable registration number: 13225 8740 RR

Researchers in several countries, along with the pharmaceutical company Merck (known as MSD outside of North America), pooled data from phase II and phase III trials of Zepatier (a fixed-dose combination of elbasvir and grazoprevir) taken with or without the broad-spectrum antiviral drug ribavirin in people with HCV genotype 1a. They then reviewed this data.

Key findings from the review were as follows:

When taken once daily for 12 consecutive weeks, Zepatier is highly effective among patients with genotype 1a who have not been previously treated or who were previously treated and experienced relapse.

Zepatier + ribavirin taken for 16 to 18 weeks is highly effective in patients with genotype 1a who have experienced virological failure with previous treatment.

The effectiveness of Zepatier was similar in participants whether or not they had cirrhosis (extensive scarring of the liver).

Study details

Researchers analysed data from 893 participants distributed as follows:

- no previous HCV treatment – 550 people
- previously treated but subsequently relapsed – 343 people

The average profile of participants at the start of the study was as follows:

- 70% men, 30% women
- 92% were younger than 65 years
- main ethno-racial groups – 75% white, 20% black
- most (70%) participants did not have cirrhosis
- most (80%) participants had an HCV viral load of 6 million IU/mL or less

Among treatment-experienced participants, 76% had previously experienced virological failure, while the remaining 24% had relapsed.

Results

The effectiveness of Zepatier was high, ranging between 90% and 100% cure rates. Cure can also be expressed as a sustained virological response (SVR) 12 or 24 weeks after a course of treatment has ended, written as SVR₁₂ or SVR₂₄.

Here are the rates of cure for different groups of participants:

No previous treatment

- Zepatier for 12 weeks – 95% of participants were cured (402 out of 426 people)
- Zepatier + ribavirin for 12 weeks – 95% of participants were cured (71 out of 77 people)
- Zepatier for 16 to 18 weeks – 91% of participants were cured (21 out of 23 people)
- Zepatier + ribavirin for 16 to 18 weeks – 100% of participants were cured (23 out of 23 people)

Prior relapse

People in this group had previously been treated (with interferon and/or ribavirin). Although this prior treatment was able to greatly reduce the amount of HCV in their blood, once their course of treatment ended, HCV levels surged in their blood. Here is the distribution of cures in this group of participants by regimen:

- Zepatier for 12 weeks – 100% cured (22 out of 22 people)
- Zepatier + ribavirin for 12 weeks – 96% cured (25 out of 26 people)
- Zepatier for 16 to 18 weeks – 92% cured (12 out of 13 people)
- Zepatier + ribavirin for 16 to 18 weeks – 100% cured (21 out of 21 people)

Previous treatment failures

In this category, people had been previously treated but the amount of HCV in their blood was not significantly reduced. The proportions of participants achieving cure by regimen were as follows:

- Zepatier for 12 weeks – 90% cured (62 out of 69 people)
- Zepatier + ribavirin for 12 weeks – 94% cured (75 out of 80 people)
- Zepatier for 16 to 18 weeks – 94% cured (49 out of 52 people)
- Zepatier + ribavirin for 16 to 18 weeks – 100% cured (54 out of 54 people)

Cirrhosis

People who have extensive liver injury due to HCV do not generally respond as well to treatment as people without cirrhosis.

Overall, here are the results of Zepatier treatment for 12 weeks (with or without ribavirin), depending on cirrhosis status, in participants who either had not been previously treated or had been previously treated and experienced relapse:

- no cirrhosis – 95% cured (345 out of 362 people)
- cirrhosis – 98% cured (79 out of 81 people)

Here are the results among participants whose previous HCV therapy failed and who received Zepatier with or without ribavirin for 16 to 18 weeks:

- no cirrhosis – 100% cured (31 out of 31 people)
- cirrhosis – 100% cured (23 out of 23 people)

Resistance

Some participants had HCV that was somewhat resistant to the study drugs. Resistance could develop because HCV-infected cells produce a great deal of virus, and occasionally some of these viruses have changes (or mutations) that occur by chance. Some of these mutations could help HCV to partially or wholly resist the effect of treatment. Resistance also could have developed if some participants had been treated with therapies in the past that were similar in structure or shape to the medicines in Zepatier and such past therapy failed.

Resistance and past treatment relapse

In analyzing the blood samples of a sub-set of participants, here is how mutations associated with resistance to treatment were distributed and the result of Zepatier therapy:

- no resistance mutations present – 98% cured (284 out of 289 people)
- resistance mutations present – 91% cured (136 out of 150 people)

Resistance and past treatment failure

Among participants who experienced relapse when previously treated and who received Zepatier + ribavirin for 16 to 18 weeks, here are the rates of cure distributed by the presence of resistance mutations at the start of the study:

- no resistance mutations – 100% cured (38 out of 38 people)
- resistance mutations present – 100% cured (14 out of 14 people)

Note well

The present analysis found that, overall, 12 weeks of Zepatier with or without ribavirin is highly effective among treatment-naïve participants with the difficult-to-treat strain of HCV called genotype 1a.

Longer regimens—16 weeks—have been approved by regulatory authorities in Canada and the U.S. for use by patients with genotype 1 who have previously experienced virological failure on other regimens.

Safety analyses of Zepatier appear in other reports in this issue of *TreatmentUpdate*.

REFERENCE:

Thompson A, Zeuzem S, Rockstroh J, et al. The combination of elbasvir and grazoprevir is highly effective for the treatment of genotype 1a-infected patients. *American Association for the Study of Liver Diseases*, 13-17 November 2015. Abstract 703.

C. Zepatier in cirrhosis

Zepatier is a fixed-dose pill containing the following two anti-HCV drugs:

- elbasvir – 50 mg
- grazoprevir – 100 mg

Zepatier is taken once daily with or without food.

Researchers reviewed information from six clinical trials on Zepatier to better understand its safety and effectiveness. For this review, researchers relied on data from 402 participants, focusing on extensive scarring of the liver (cirrhosis).

The presence of cirrhosis was confirmed with one of the following assessments (in most participants):

- liver biopsy (29% of participants)
- a specialized ultrasound scan called Fibroscan (64% of participants); a result greater than 12.5 kilopascals indicates cirrhosis
- blood tests (7%) such as the ratio of the liver enzyme AST to the number of platelets; results greater than 2.0 are highly suggestive of cirrhosis. This test is called the AST to platelet ratio. Participants who had this test also had another blood test called Fibrotest (which measures six different proteins) to confirm the presence of cirrhosis.

Note that all participants enrolled in this study had cirrhosis without serious associated symptoms (this is called compensated cirrhosis). Their doctors classified them as Child-Pugh A—this is a scoring system that grades their chances of survival over the next two years if they do not receive treatment. In the case of Child-Pugh A, HCV-positive patients have a predicted 100% chance of surviving the next 12 months and an 85% chance of surviving for 24 months.

The average profile of participants upon entering clinical trials of Zepatier was as follows:

- age – 56 years
- 66% men, 34% women
- HCV genotypes (GT) and subtypes: GT1a – 55%; GT1b – 38%; GT4 – 6%; GT6 – 1%
- HIV co-infection – 10%
- no previous HCV treatment – 42%

Results

Cure rates can differ depending on the sub-group studied. In this section, we look at cure rates based on factors such as treatment history, genotype and method of assessing cirrhosis.

The duration of therapy is 12 weeks unless stated otherwise.

The proportions of participants with an undetectable HCV viral load 12 weeks after the cessation of a course of Zepatier-based therapy (this milestone is referred to as a sustained virological response, written as SVR₁₂, and participants who achieved it are considered cured) were as follows:

No previous HCV treatment

- Zepatier – 98% cured (135 out of 138 participants)
- Zepatier + ribavirin – 90% cured (28 out of 31 participants)

A history of HCV treatment

- Zepatier + ribavirin for 16 to 18 weeks – 100% cured (49 out of 49 people)

Although we will not go into details, Zepatier alone for 16 to 18 weeks was less effective in treatment-experienced patients than Zepatier + ribavirin taken for the same period.

By genotype

The proportions of participants who were cured were distributed as follows:

- Zepatier – GT1a – 96% cured (73 out of 76 people)
- Zepatier – GT1b – 100% cured (56 out of 56 people)
- Zepatier – GT4 – 100% cured (6 out of 6 people)

By method used to assess cirrhosis

- Zepatier – biopsy – 100% cured (38 out of 38 people)
- Zepatier – blood tests – 100% cured (8 out of 8 people)
- Zepatier – Fibroscan – 98% cured (89 out of 91 people)

Focus on safety

For the safety analysis, additional data from more participants were used. The participants were distributed among the following regimens:

- Zepatier – 264 participants
- Zepatier + ribavirin – 193 participants
- placebo – 22 participants

Drug-related adverse events were distributed as follows:

- Zepatier – 42% reported side effects
- Zepatier + ribavirin – 73% reported side effects
- placebo – 41% reported side effects

Serious drug-related side effects were distributed as follows:

- Zepatier – 0.4%
- Zepatier + ribavirin – 0%
- placebo – 0%

Deaths were distributed as follows:

- Zepatier – one death due to cardiovascular disease
- Zepatier + ribavirin – one death due to a vehicular accident
- placebo – no deaths

Common side effects were distributed as follows:

Unexpected tiredness or lack of energy

- Zepatier – 15%
- Zepatier + ribavirin – 31%
- placebo – 18%

Headache

- Zepatier – 17%
- Zepatier + ribavirin – 21%
- placebo – 14%

Nausea

- Zepatier – 4%
- Zepatier + ribavirin – 14%
- placebo – 14%

Summary

Zepatier was generally well tolerated. Common side effects were unexpected tiredness/lack of energy, headache and nausea. Side effects were usually mild or moderate in severity.

Zepatier was highly effective in participants with compensated cirrhosis, with cure rates between 97% and 100%.

REFERENCE:

Jacobson I, Lawitz E, Kwo P, et al. An integrated analysis of 402 compensated cirrhotic patients with HCV genotype 1, 4 or 6 infection treated with elbasvir and grazoprevir. *American Association for the Study of Liver Disease*, 13-17 November 2015. Abstract 42.

D. Zepatier in HCV and HIV co-infection

Due to shared routes of infection, some people are infected with two viruses—HIV and HCV. This state is called co-infection. Researchers in North America, Western Europe, Australia and Israel recruited 218 participants who were co-infected with HIV and HCV to participate in a 12-week trial of Zepatier. Results showed that Zepatier had high rates of cure in co-infected people with HCV genotypes 1a, 1b, and 4.

Study details

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

- age – 49 years
- 84% men, 16% women
- the distribution of the main HCV genotypes was as follows: GT1a – 66%; GT1b – 20%; GT4 – 13%
- cirrhosis was present in 16% of participants
- CD4+ count – 568 cells/mm³
- 97% of participants were taking potent combination anti-HIV therapy (commonly called ART)

Results

In an analysis that excluded participants who were cured with Zepatier but then became reinfected or who left the study for reasons unrelated to treatment, researchers found that, overall, 98% of participants were cured. That is, 203 out of 208 participants had an undetectable level of HCV both at 12 and 24 weeks after the cessation of Zepatier.

By genotype

Here are the rates of cure distributed by genotype:

- GT1a – 97% (135 out of 139 people) were cured
- GT1b – 100% (42 out of 42 people) were cured
- GT4 – 96% (26 out of 27 people) were cured

Relapse and reinfection

A total of five participants relapsed; none of these participants had cirrhosis. Four of them had GT1a and one had GT4.

Four of the five participants who relapsed were taking ART, so their relapse is not likely due to a weakened immune system as a result of HIV infection.

Two participants were re-infected. The first entered the study having GT1a and after this was cured technicians detected a new strain—GT3.

The second participant was initially infected with GT1b and after this was cured technicians found that he was reinfected with GT3.

Resistance in HCV

If left untreated, HCV-infected cells produce many copies of the virus and a small proportion of these copies can have naturally occurring changes, or mutations, that may help them to at least partially resist the effect of treatment. At the start of the study, technicians assessed blood samples from many participants who were infected with GT1a, because this was the most common strain of the virus. In 63% of these cases (91 out of 141 participants), there were no cases of HCV with the ability to resist treatment. Furthermore, in these 91 participants, 98% were cured.

However, technicians found that the remaining 53 participants had HCV with the capacity to resist treatment with Zepatier. Yet when treated with this drug, 94% (50 out of 53 participants) were cured.

So, at least in this study, Zepatier may be sufficiently strong to overcome naturally occurring mutations in HCV that can confer some degree of resistance to therapy.

Adverse events

“Adverse events” is a term used in clinical trials that refers to a broad array of unfortunate events that can occur during a trial. Some adverse events may be related to exposure to the study medicines and are called side effects. Other adverse events may be unrelated to the study medicines.

Here are some common side effects that occurred:

- lack of energy and/or unexpected tiredness – 13%
- headache – 12%
- nausea – 9%

No participants left the study due to side effects. During the study, one person developed a seizure and another person was diagnosed with pneumonia. It is not clear if either of these were related to exposure to Zepatier.

No one died while in the study.

HIV-related assessments

During the study, two participants developed elevated levels of HIV in their blood despite their use of ART. When nurses intervened and interviewed the participants, they determined that these participants were not taking all of their HIV medicines exactly as directed. The nurses provided education reinforcing the importance of adherence. The HIV viral loads in these two participants subsequently became undetectable.

Overall, CD4+ cell counts did not significantly change during the study.

Key points

The present study found that Zepatier was effective and well tolerated in patients with GT1 and GT4. Rates of cure were high, usually greater than 90%.

REFERENCE:

Rockstroh JK, Nelson M, Katlama C, et al. C-Edge co-infected: final results from phase III study of elbasvir and grazoprevir in patients with HCV and HIV. *American Association for the Study of the Liver Disease*, 13-17 November 2015. Abstract 210.

E. Zepatier in people grappling with drug addiction

In Canada and other high-income countries the main way that HCV infection generally spreads today is through sharing equipment for substance use.

Researchers in Canada, Australia, Europe, Israel, Taiwan and the U.S. collaborated in a study called Co-Star that sought to treat HCV in people who use street drugs.

Co-Star was a placebo-controlled trial wherein 301 participants were randomly assigned to receive either Zepatier or fake Zepatier (placebo) for 12

consecutive weeks. After the end of this period, participants who had received placebo were offered treatment with Zepatier.

For at least three months prior to entering the study, participants would have been receiving care and treatment for addiction and taking therapies associated with addiction treatment, including the following:

- buprenorphine (Suboxone)
- methadone
- naloxone
- naltrexone

In that time period, participants were supposed to have kept 80% of their scheduled drug treatment appointments.

The average profile of participants at the start of the study was as follows:

- age – 48 years
- 76% men, 24% women
- most (55%) participants had an HCV viral load greater than 2 million IU/mL
- common genotypes of HCV were: GT1a (76%); GT1b (15%); GT4 (6%) and GT6 (3%)
- 21% of participants had extensive scarring of the liver (cirrhosis)
- 7% of participants were co-infected with HCV and HIV
- among those taking potent combination anti-HIV therapy (ART), commonly used drugs included raltegravir (Isentress), dolutegravir (Tivicay and in Triumeq) and rilpivirine (Edurant and in Complera)

On the first day of the study, urine testing for opiates revealed that 58% of participants were still using street drugs.

Results

In an analysis that excluded participants who left the study for reasons unrelated to treatment, 96% of participants were cured. Rates of cure were not generally different among the different genotypes of HCV, with one exception: Only three of five participants with genotype 6 infection were cured in this study. It is important to note that regulatory authorities have not approved Zepatier for the treatment of genotype 6 infection.

There were seven cases of relapse.

Five other participants were initially cured of HCV but subsequently developed elevated HCV viral loads. Technicians testing blood samples from these five found that they had been re-infected with a different strain of HCV.

Screening for street drugs

Participants had their urine screened for the presence of the following classes of street drugs:

- amphetamines
- barbiturates
- benzodiazepines
- cannabinoids
- cocaine
- opiates
- phencyclidine
- propoxyphene

Substance use was steady during the study, with about 60% of participants testing positive for the above-mentioned classes of drugs.

According to the researchers, adherence to the study medications was high, averaging between 97% and 100%. Researchers did not provide details as to how adherence was assessed.

Adverse events

Common side effects were distributed as follows:

Unexpected tiredness or lack of energy

- Zepatier – 16%
- placebo – 20%

Headache

- Zepatier – 13%
- placebo – 14%

Nausea

- Zepatier – 11%
- placebo – 9%

Diarrhea

- Zepatier – 10%
- placebo – 9%

Two people taking Zepatier and another taking placebo left the study prematurely because of perceived side effects.

One person who received placebo died from an undisclosed cause.

Key points

Zepatier was highly effective in participants who were taking opioid substitution therapy. Zepatier was generally safe. Substance use was stable throughout the study and adherence was good. The Co-Star study was important because it showed that HCV-positive people who use street drugs and who are being treated for addiction can successfully take modern anti-HCV treatment and be cured.

REFERENCE:

Dore GJ, Altice F, Litwin AH. Co-Star—efficacy of grazoprevir and elbasvir fixed-dose combination for 12 weeks in HCV-infected persons who inject drugs on opioid agonist therapy. *American Association for the Study of the Liver Disease*, 13-17 November 2015. Abstract 40.

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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Credits

Writer
Editor

Sean Hosein
RonniLyn Pustil

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Contact CATIE

By e-mail: info@catie.ca

On the Web: www.catie.ca

By telephone: 416.203.7122
1.800.263.1638 (toll-free)

By fax: 416.203.8284

By social media: www.facebook.com/CATIEInfo;
www.twitter.com/CATIEInfo

By post: 505-555 Richmond Street W
Box 1104
Toronto, Ontario
M5V 3B1
Canada