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I ANTI-HIV AGENTS

A. Integrase inhibitors

The first integrase inhibitor for HIV treatment, raltegravir (Isentress), has been used for different purposes—from part of an initial regimen to more complex regimens for treatment-experienced people. For some patients, raltegravir's twice-daily dosing requirement may be considered a disadvantage in an era when there are several options offering an entire regimen in a single tablet. Still, raltegravir is noteworthy for having few interactions with other drugs and is relatively well tolerated.

The second integrase inhibitor, elvitegravir, is available as part of an entire regimen in one pill (Stribild). In addition to elvitegravir, Stribild contains the anti-HIV drugs tenofovir (Viread) and FTC (emtricitabine, Emtriva). Stribild also contains a novel drug called cobicistat, which is a boosting agent (also known as a pharmacoenhancer). The purpose of cobicistat is to raise and maintain levels of elvitegravir in the blood so that Stribild can be taken once daily. Stribild is roughly equivalent in strength to other commonly used combinations for HIV treatment. It must be taken with food and the presence of cobicistat results in the potential for interactions between many other commonly used medications.

Enter dolutegravir

Dolutegravir is a second-generation experimental integrase inhibitor. Dolutegravir (sold under the brand name Tivicay) has been licensed for use in the U.S. Approval in Canada and the European Union is likely in the coming months. In one

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clinical trial, when taken as part of combination therapy, dolutegravir was considered statistically superior to a regimen called Atripla—a single pill taken once daily containing efavirenz (Sustiva, Stocrin) + tenofovir + FTC—in participants new to HIV therapy. In the same population, dolutegravir-based regimens were considered roughly equivalent to raltegravir-containing regimens.

In Sailing, the latest clinical trial with dolutegravir, the drug was compared to raltegravir in treatment-experienced participants who had never previously used an integrase inhibitor. Researchers found that, in general, once-daily dolutegravir-based regimens were more potent than raltegravir-containing regimens. Further details about this particular clinical trial appear later in this issue of *TreatmentUpdate*.

Dolutegravir likely has at least these advantages:

- It can be taken once daily (50 mg) without the need for also taking a booster.
- It does not need to be taken with food.
- It is generally well tolerated.
- In some cases it can be used against HIV that has developed resistance to elvitegravir or raltegravir.

Note that when dolutegravir is taken by people who have HIV that is somewhat resistant to integrase inhibitors, it will likely have to be taken twice daily. Prior to prescribing dolutegravir, and particularly in the case of treatment-experienced patients, doctors will have their patients' blood analysed for the degree of resistance to this drug. Also, each patient's treatment history needs to be taken into account.

REFERENCE:

Karmon SL, Markowitz M. Next generation integrase inhibitors: Where to go after raltegravir? *Drugs*. 2013 Mar;73(3):213-28.

B. Dolutegravir in treatment-experienced people who have not previously used an integrase inhibitor

Researchers in Australia, Latin America, North America, Europe, South Africa and Taiwan recruited 715 HIV-positive people for a double-blind, placebo-controlled study comparing

regimens containing dolutegravir to regimens containing raltegravir. All participants had previously used anti-HIV therapy (commonly called ART or HAART) and nearly half of participants had a history of AIDS. Moreover, according to researchers, nearly half of participants had HIV that was resistant to “at least one drug in each of three or more [classes of drugs].”

After one year, researchers found that, in general, a dolutegravir-containing regimen was statistically superior to a raltegravir-containing regimen. This finding was driven by virologic results with fewer dolutegravir users developing treatment failure.

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

- gender – 32% women, 68% men
- age – 43 years
- 70% of participants had a viral load of 50,000 copies or less
- CD4+ count – 200 cells
- history of AIDS – 46%
- 79% had HIV that was significantly resistant to protease inhibitors **or** did not use the powerful protease inhibitor darunavir (Prezista)
- HIV resistant to three or more classes of drugs – nearly 50%
- duration of previous HIV therapy – 6 years
- co-infection with hepatitis B virus (HBV) – 5%
- co-infection with hepatitis C virus (HCV) – 11%
- co-infection with both HBV and HCV – 1%

Researchers referred to the drugs used in addition to dolutegravir or raltegravir as the “background” regimens. Drugs commonly used as background regimens in this study were as follows:

- darunavir (Prezista) + ritonavir (Norvir) + tenofovir (Viread)
- lopinavir-ritonavir (Kaletra) + tenofovir
- darunavir + ritonavir + etravirine (Intelence)
- lopinavir-ritonavir
- atazanavir (Reyataz) + ritonavir + tenofovir
- darunavir + ritonavir + maraviroc (Celsentri)

Participants were randomly assigned to receive dolutegravir or raltegravir, so that their regimens were as follows:

- dolutegravir + background regimen + placebo
- raltegravir + background regimen + placebo

The double-blind, placebo-controlled part of the study lasted for 48 weeks. After this, participants who received dolutegravir and who completed the first 48 weeks of the study were told which drug they received. They were also offered continued treatment with dolutegravir and will be monitored every 12 weeks.

Results—Changes in viral load

In both study groups the proportion of participants with a viral load less than 50 copies/ml rose sharply during the first four weeks, then less so over the subsequent four weeks. After the eighth week of the study, the proportion of participants with a low viral load (less than 50 copies/ml) remained relatively stable. The swiftness of the initial decline in viral load is something that is associated with integrase inhibitors.

The proportion of participants with a viral load less than 50 copies/ml at the 48th week of the study was distributed as follows:

- dolutegravir-based regimens – 71%
- raltegravir-based regimens – 64%

Researchers performed calculations and concluded that dolutegravir’s anti-HIV effect was “statistically superior” to that of raltegravir.

Why the difference?

Both dolutegravir and raltegravir are good drugs when used as part of combination therapy. However, the finding of statistical superiority favouring dolutegravir arose according to the researchers because virologic failure “occurred earlier and more frequently in [participants who took raltegravir (12%) compared to participants who took dolutegravir (6%)].”

Furthermore, 42% of 45 participants who took raltegravir and who developed virologic failure were termed “non-responders” by researchers. Essentially, non-responders did not have a major decrease in viral load and were not able to have their viral load fall below the 400-copies/ml mark. This contrasts with only 10% of 21 participants who took dolutegravir *and* who developed virologic failure and who were also virologic non-responders.

Darunavir plays a role

Darunavir is a powerful protease inhibitor. When taken with a small dose of ritonavir, darunavir can be taken once daily. When researchers analysed the data from Sailing among participants who took darunavir-ritonavir with dolutegravir or raltegravir, dolutegravir’s anti-HIV effect was found to be roughly equivalent in potency to raltegravir. However, bear in mind that the majority of participants did not use darunavir.

Complications and side effects

Rates of side effects were similar whether participants were taking dolutegravir or raltegravir. There are at least two possible reasons for this. First, as a class, integrase inhibitors are generally well tolerated. Secondly, the background regimens for nearly all participants were combinations of protease inhibitors. These drugs can cause a range of side effects, mostly affecting the gastrointestinal tract (nausea, vomiting, diarrhea). Such side effects may have dwarfed any, more minor side effects that may have occurred with exposure to integrase inhibitors. Researchers noted that, in general, side effects were mostly of mild-to-moderate intensity.

No deaths occurred among participants who received dolutegravir. Although there were three deaths among raltegravir users, investigators found that none were caused by raltegravir (two cases of unrelated cancer and one case of multi-organ failure).

Some commonly reported side effects appear below. Bear in mind that many participants were taking complex regimens, so it is difficult to connect exposure to the study drugs with specific side effects.

Diarrhea

- dolutegravir – 20%
- raltegravir – 18%

Lung/throat infections

- dolutegravir – 11%
- raltegravir – 8%

Headache

- dolutegravir – 9%
- raltegravir – 9%

Vomiting

- dolutegravir – 6%
- raltegravir – 6%

Fatigue

- dolutegravir – 4%
- raltegravir – 7%

Rash

- dolutegravir – 5%
- raltegravir – 5%

Joint pain

- dolutegravir – 3%
- raltegravir – 5%

Severely abnormal lab test results

ALT (alanine aminotransferase – a liver enzyme)

- Elevated levels of liver enzymes in the blood are suggestive of inflammation and injury to the liver. A similar proportion of participants receiving dolutegravir (3%) and raltegravir (2%) developed markedly increased levels of ALT (at least five times the upper limit of normal). These cases were reviewed by an independent panel of doctors and they judged the severe increases in liver enzymes to be related to HBV or HCV co-infection. Specifically, these rises in ALT levels likely occurred because upon entering the Sailing study and receiving a potent drug (integrase inhibitor), the immune systems of participants subsequently partially recovered. As a result, their immune systems were able to sense and attack liver cells infected with HBV or HCV. The ensuing attack by the immune system was responsible for the rise in liver enzyme levels. Another reason for elevated liver enzymes was the inadvertent removal of participants' anti-HBV therapy just prior to entering the study, as physicians focused on optimizing their anti-HIV regimens.

Cholesterol

- dolutegravir – 2%
- raltegravir – 4%

Creatinine

- Measuring levels of the waste product creatinine in the blood is one way to assess general kidney health. Higher-than-normal levels of creatinine are suggestive of kidney injury. In the present study, severe or serious elevations of creatinine in the blood were rare—occurring in less than 1% of participants who received dolutegravir or raltegravir. Upon investigation, most of these cases were

related to pre-existing conditions that can affect kidney health, such as higher-than-normal blood pressure, diabetes or infections (other than HIV).

- However, as a group, dolutegravir users had slightly elevated levels of creatinine in the blood that persisted throughout the study. This effect was apparently not harmful and has also been seen in clinical trials where participants received the drug cobicistat, one of the drugs found in the pill called Stribild. In the case of Stribild users, the elevation in creatinine levels is also apparently not harmful.

Higher-than-normal blood sugar

- dolutegravir – 1%
- raltegravir – 2%

Elevated levels of creatine phosphokinase (CPK)

- CPK is one of several enzymes (specifically called CPK-3) whose levels in the blood increase in cases of muscle inflammation and injury. In rare cases, muscle inflammation can occur with raltegravir and likely other integrase inhibitors. In the present study, elevated levels of CPK were distributed as follows:
 - dolutegravir – 2%
 - raltegravir – 1%

For the future

Dolutegravir is expected to be approved as part of combination therapy for HIV-positive people in the U.S. by September and in Canada later this year.

A future issue of *TreatmentUpdate* will explore the issue of kidney health and dolutegravir.

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Cahn P, Pozniak A, Mingrone, et al. Dolutegravir is superior to raltegravir in ART-experienced, integrase-naïve subjects: week 48 results from Sailing (ING111762). In: Program and abstracts of the 7th IAS Conference on Pathogenesis, Treatment and Prevention, 30 June to 3 July, 2013, Kuala Lumpur, Malaysia. Abstract WELBB03.

II HEPATITIS C VIRUS

A. The changing role of SVR₁₂ in clinical trials of HCV drugs

In clinical trials of therapy for hepatitis C virus (HCV) infection, the standard to assess the effectiveness of treatment has been the decline of HCV RNA (viral load) during therapy such that it becomes very low followed by undetectable viral load for 24 consecutive weeks after therapy has ended. Such a response in the 24 weeks after the cessation of therapy is called a sustained virologic response, written as SVR₂₄.

The previous regimen

Over much of the past decade in high-income countries such as Canada, Australia and the U.S. and in regions such as Western Europe, standard therapy for HCV has been a combination of long-lasting interferon called peginterferon, injected once weekly, combined with twice-daily doses of the drug ribavirin. Interferon activates genes that help control viral infections and ribavirin is a broad-spectrum antiviral agent. Both drugs have indirect effects on HCV-infected cells.

Designer drugs

In the past several years, researchers have developed drugs specifically designed to target key proteins of HCV. Due to the highly specific way that they work, these drugs are called DAAs—direct-acting antivirals. Two currently licensed DAAs are boceprevir (Victrelis) and telaprevir (Incivek, Incivo). These two drugs are used in combination with peginterferon and ribavirin for the treatment of HCV genotype 1. Expect additional DAAs to be licensed over the next several years. Most of these additional DAAs will be multi-genotypic, meaning that they will have anti-HCV activity against different genotypes, or strains, of HCV.

An FDA review

Researchers at the U.S. Food and Drug Administration (FDA) have reviewed results from clinical trials of HCV treatment in nearly 13,600 adult participants. Some of these studies have included the use of boceprevir and telaprevir. In doing the review, the FDA researchers found that 51.8% of participants had an undetectable viral load 12 weeks after cessation of therapy; this is

written as SVR₁₂. Overall, 50.6% of participants also had the same result at week 24 after cessation of therapy—SVR₂₄. This means that the vast majority (more than 98%) of participants who had SVR₁₂ also had SVR₂₄. This suggests that SVR₁₂ may be a very important result or end-point in HCV clinical trials. Expect more pharmaceutical companies to focus on SVR₁₂ in the future.

Missing data

Overall, there were 388 participants who achieved SVR₁₂ but who did not achieve SVR₂₄. The majority of these participants did not return to the study clinic for assessment at week 24, so blood could not be drawn to measure their viral load. Researchers, in making a strict interpretation of the dataset, decided that these missing values would be considered to be detectable.

Genotypes

Most participants in the FDA dataset had the genotype of HCV that is commonly found in North America and Western Europe—genotype 1, written as GT 1.

Results by genotypes

The close relationship between SVR₁₂ and SVR₂₄ was also seen for participants who had genotypes 1, 2 and 3. Specifically, people with these three genotypes who achieved SVR₁₂ were extremely likely to also develop SVR₂₄.

Not recovering

The most common reasons for having a detectable viral load at the 24th week after treatment cessation were listed by the FDA researchers as follows:

- relapse
- reinfection
- other (undisclosed) reasons

New therapies and subgroups

When the analysis was restricted to clinical trials with boceprevir and telaprevir, the association between having SVR₁₂ and subsequently SVR₂₄ was similar to the other analyses.

Not a major factor

Furthermore, when the researchers analysed people with the following characteristics, trends between SVR₁₂ and SVR₂₄ were similar:

- race
- gender
- having been treated more than once
- GT 1a vs. GT 1b
- severe liver damage

Using these analyses

Based on the findings of a close link between SVR₁₂ and SVR₂₄, the FDA has instructed pharmaceutical companies that they can use SVR₁₂ as a primary endpoint, or goal, in clinical trials. This will speed up clinical trial development—an important effect, as there are many drugs and combinations of drugs that require testing in the race to find the perfect combination.

For interferon-free regimens of DAAs, the FDA requires that companies continue to collect both SVR₁₂ and SVR₂₄ data so that the relationship between these two time points can be confirmed. The equivalent to the FDA in Europe—the European Medicines Agency (EMA)—also agrees with the FDA analysis and has given similar guidance to companies.

Even shorter

Previous mathematical analyses have suggested that with regimens containing peginterferon + ribavirin, 70% of relapses are forecast to occur within the first four weeks of treatment cessation. Furthermore, the same mathematical analyses have predicted that 95% of relapses of HCV treatment should occur within the first 12 weeks of treatment cessation.

In analyzing the SVR₄ data (the fourth week after treatment cessation to observe an undetectable viral load), the FDA researchers in the present study found that 65% of participants who did not have SVR₂₄ also did not have SVR₄. In the future, SVR₄ may be an endpoint worth observing, if only for its ability to predict future trends.

Bear in mind

The present FDA analysis was based upon previously collected data from clinical trials and this data was subjected to a reanalysis. Such analyses that look back upon previously collected data can find associations and trends but cannot produce definitive results. That is why the FDA is requiring the developers of interferon-free regimens to collect SVR₂₄ outcomes in the early phase clinical trials (such as phase I/II or phase II). Results from these studies can be used to guide the design of phase III clinical trials with DAAs and their choice of endpoints (SVR₁₂ or SVR₂₄).

When it comes to outcomes of HCV-positive people who have initiated treatment, the FDA warns that doctors should exercise “caution” in using its analysis at the individual level. The agency encourages doctors to follow clinical guidelines. In such guidelines SVR₂₄ is the goal of therapy.

REFERENCE:

Chen J, Florian J, Carter W, et al. Earlier sustained virologic response end points for regulatory approval and dose selection of hepatitis C therapies. *Gastroenterology*. 2013 Jun;144(7):1450-1455.

B. Getting to know HCV proteins and drugs

HCV infects mainly liver cells but it can also infect some cells of the immune system such as macrophages. HCV does not integrate its genetic information into a cell’s DNA. As a result, HCV infections are relatively easier to cure than viral infections, such as HIV, that do integrate themselves into a cell’s DNA or genome.

High value targets

There are many steps involved from the moment of first contact between HCV and its target cell—through that cell becoming a mini virus factory to the cell releasing its first copy of HCV. In theory, each of these steps can serve as a target for the development of drugs that can interfere with HCV infection and the production of new copies of this virus.

An array of enzymes

Once inside a cell, HCV can begin the process of producing proteins—many of which are enzymes—necessary to transform the cell into a mini virus factory. The genes carried by HCV carry information for making two groups of proteins as follows:

- structural proteins
- non-structural proteins

Structural proteins are used to make a natural container for the virus. Examples of these proteins include the following:

- C
- E1
- E2

Non-structural proteins are the many enzymes and co-factors that help incite and assist the manufacture of new copies of HCV. Examples of non-structural proteins include the following:

- NS1
- NS2
- NS3
- NS4A
- NS4B
- NS5A
- NS5B

Protease inhibitors

The first drugs designed and licensed to attack specific HCV proteins were the following:

- boceprevir (Victrelis)
- telaprevir (Incivek, Incivo)

These work by attacking the proteins NS3 and NS4A.

When either of these protease inhibitors (PIs) is used in combination with peginterferon + ribavirin they can be effective against cases of infection with HCV genotype 1, with cure rates generally reaching between 68% and 75%.

In general, protease inhibitors can have a low-to-moderate genetic barrier to resistance. This means that HCV only needs to develop just a few changes (mutations) in its genes to overcome the effect of these drugs. The ability of HCV to develop resistance to the first-generation protease inhibitors varies by genotype and subtypes. For

instance, in genotype 1 there are mainly subtypes 1a and 1b. Resistance to telaprevir can occur more easily with GT 1a than 1b.

Second-wave protease inhibitors

Emerging protease inhibitors that should begin to be licensed by regulatory authorities over the next 18 months are called second-wave PIs rather than second-generation PIs by researchers. This is because these emerging therapies are somewhat similar to the first generation of PIs but have several advantages, including the following:

- once-daily dosing
- better tolerability
- somewhat increased effectiveness

Examples of these second-wave PIs include the following:

- ABT-450
- asunaprevir
- faldaprevir (BI 201335)
- simeprevir (TMC 435)

Polymerase inhibitors

This is the name given to drugs that interfere with HCV NS5B. This protein is an enzyme called polymerase. Polymerase inhibitors can be further sub-divided into two groups as follows:

- nucleoside or nucleotide analogues (nukes)
- non-nucleotide inhibitors (non-nukes)

Nucleoside or nucleotide analogues

Nukes mimic the shape of naturally occurring molecules that HCV uses to make the polymerase enzyme. When HCV-infected cells use nukes to try to build polymerase, the enzyme becomes dysfunctional, which impairs the manufacture of new copies of HCV.

The basic shape of polymerase is similar across HCV genotypes so, in theory, polymerase inhibitors should work against different genotypes of HCV. Furthermore, it appears difficult for HCV to develop resistance to nukes when they are used as part of combination therapy in clinical trials. An example of an HCV nuke is sofosbuvir (GS-7977).

Non-nucleoside polymerase inhibitors

These drugs attack the polymerase enzyme, causing it to change its shape and impair its activity. Examples of non-nukes include the following:

- GS-9669
- ABT-333
- ABT-072
- deleobuvir (207127)

Some of the drugs mentioned in this report are discussed further in this issue of *TreatmentUpdate*.

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1. Clark VC, Peter JA, Nelson DR. New therapeutic strategies in HCV: second-generation protease inhibitors. *Liver International*. 2013 Feb;33 Suppl 1:80-4.
2. Asselah T, Marcellin P. Interferon free therapy with direct acting antivirals for HCV. *Liver International*. 2013 Feb;33 Suppl 1:93-104.

C. What to expect over the next two years in HCV drug development

The first wave of direct-acting antiviral drugs (DAAs) for HCV treatment was comprised of telaprevir or boceprevir.

The second wave of drugs that will be licensed in Canada, Australia, the U.S., the European Union and other high-income countries and regions over the following 18 months will likely be drugs such as these:

- simeprevir
- faldaprevir

Both of these drugs will be licensed for use with peginterferon + ribavirin.

Also expected to be approved in that time period is sofosbuvir. This will likely be approved for use together with ribavirin in certain situations and/or peginterferon + ribavirin in others.

In 2015, likely the ABT-trio of drugs mentioned toward the end of this report will likely be licensed. There are also other drugs likely to be approved in 2015, such as the combination of daclatasvir + asunaprevir. Another combination that should be licensed by that time is that of sofosbuvir + ledipasvir. This combination may be very useful when a third DAA is added, forming yet another option for interferon-free treatment of HCV.

It is also possible that there are also drugs that we have not mentioned that may become licensed over the next two years.

Limits to knowledge

At present, only limited information about the full potential uses of DAAs is available. However, once these drugs are licensed by regulatory authorities, doctors may decide to conduct clinical trials with different combinations of DAAs, as they strive to find the perfect interferon-free regimen. Further information about side effects and complications associated with the new drugs will also become available upon licensure.

In this issue of *TreatmentUpdate*, we bring you selected highlights of clinical trial results of leading DAAs.

D. Using daclatasvir and sofosbuvir when prior therapy fails

Daclatasvir is a direct-acting antiviral (DAA) that works by interfering with the HCV protein called NS5A. In laboratory experiments with HCV-infected cells, it inhibits the production of HCV genotypes 1 through 6. It is generally well tolerated, with few drug-drug interactions. It has been tested in more than 2,000 HCV-positive people in different combinations and found to be generally safe. Preliminary research has found that when daclatasvir is combined with another DAA—sofosbuvir—both drugs have intensified anti-HCV effects.

The current standard of care for genotype 1 (GT 1) HCV is a combination of either boceprevir or telaprevir with peginterferon + ribavirin. Such combinations can clear HCV in around 70% of patients. However, some people who use boceprevir or telaprevir can develop HCV that is resistant to those drugs and their regimen can fail.

Researchers designed a study to compare the effects of two regimens for people who have previously been treated with boceprevir- or telaprevir-containing regimens that have failed.

- 21 participants received a combination of daclatasvir 60 mg once daily and sofosbuvir 400 mg once daily, both drugs for 24 weeks.

- 20 other participants received daclatasvir 60 mg + sofosbuvir 400 mg, both drugs once daily, and ribavirin, 400 mg twice daily. These participants took all drugs for 24 weeks.

All 41 participants had genotype 1a or 1b and none had severe liver damage (cirrhosis). Their average profile at the start of the study was as follows:

- age – 58 years
- gender – 61% male, 39% women
- 80% had genotype 1a
- 95% had genes that are associated with a good response to peginterferon
- nearly 50% of participants had HCV that was resistant to boceprevir or telaprevir

Results

The initial response to treatment was similar regardless of the presence of virus resistant to boceprevir or telaprevir.

The proportion of participants with SVR₁₂ was 100% for those on daclatasvir + sofosbuvir and 95% for those on triple-drug therapy. This lower figure for triple-drug therapy was due to the incompleteness of data from the final participant.

Focus on complications and side effects

- no cases of anemia occurred
- one participant who received triple therapy developed less-than-normal levels of potassium in his blood, but this was temporary
- no participants developed higher-than-normal levels of the waste product bilirubin in their blood

Here is the distribution of common complaints:

Fatigue

- dual therapy – 29%
- triple therapy – 45%

Headache

- dual therapy – 33%
- triple therapy – 30%

Temporary hair loss

- dual therapy – 10%
- triple therapy – 15%

Joint or bone pain

- dual therapy – 14%
- triple therapy – 10%

Constipation

- dual therapy – 5%
- triple therapy – 20%

Diarrhea

- dual therapy – 5%
- triple therapy – 20%

The results of this trial demonstrate that daclatasvir + sofosbuvir have potent anti-HCV activity when both drugs are used. The combinations were generally well tolerated without serious side effects such as anemia and depression. This combination underscores the potential for a simple interferon- and possibly ribavirin-free regimen in a larger study.

REFERENCE:

Sulkowski MS, Gardiner DF, Rodriguez-Torres M, et al. Sustained virological response with daclatasvir plus sofosbuvir ± ribavirin in chronic HCV genotype 1-infected patients who previously failed telaprevir or boceprevir. In: Program and abstracts of the 48th Annual Meeting of the European Association for the Study of the Liver, 24-28 April 2013, Amsterdam, Netherlands. Abstract 1417.

E. Daclatasvir + peginterferon + ribavirin

Though the anti-HCV drug daclatasvir works well against genotypes 1 and 4 when combined with peginterferon and ribavirin for 24 weeks, researchers are exploring shorter courses of therapy. However, as other articles in this issue of *TreatmentUpdate* note, there are several other genotypes of HCV that also require treatment.

In the study featured in this report, researchers combined daclatasvir (60 mg once daily) and ribavirin (400 mg twice daily) with a standard dose of peginterferon given once weekly for people who had genotypes 2 or 3. Participants were assigned to one of the following regimens:

- daclatasvir + peginterferon + ribavirin; planned for 12 weeks (50 people)
- daclatasvir + peginterferon + ribavirin; planned for 16 weeks (50 people)
- placebo + peginterferon + ribavirin; planned for 24 weeks (50 people)

In the two daclatasvir-containing regimens, if participants' viral loads at the 4th week of therapy were less than 25 IU/ml **and** undetectable at the 10th week of therapy, they ceased all HCV

treatment at weeks 12 or 16. If these viral load changes were not met, at the 12th week of the study they received placebo + peginterferon + ribavirin for 12 weeks, for a total of 24 weeks of therapy.

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

- age – between 20 and 67 years
- gender – 65% men, 35% women
- viral load – 4 million copies
- 28% had cirrhosis
- participants had either genotype 2 or 3

Results

Here are the results distributed by the genotype of participants:

Genotype 2 – proportion with SVR₂₄

- 12 weeks of daclatasvir + peginterferon + ribavirin – 83%
- 16 weeks of daclatasvir + peginterferon + ribavirin – 83%
- 24 weeks of placebo + peginterferon + ribavirin – 63%

Genotype 3 – proportion with SVR₂₄

- 12 weeks of daclatasvir + peginterferon + ribavirin – 69%
- 16 weeks of daclatasvir + peginterferon + ribavirin – 67%
- 24 weeks of placebo + peginterferon + ribavirin – 59%

Complications and side effects

Rash

- 12 weeks of daclatasvir + peginterferon + ribavirin – 26%
- 16 weeks of daclatasvir + peginterferon + ribavirin – 24%
- 24 weeks of placebo + peginterferon + ribavirin – 24%

Itchy skin

- 12 weeks of daclatasvir + peginterferon + ribavirin – 28%
- 16 weeks of daclatasvir + peginterferon + ribavirin – 26%
- 24 weeks of placebo + peginterferon + ribavirin – 28%

Anemia

- 12 weeks of daclatasvir + peginterferon + ribavirin – 8%
- 16 weeks of daclatasvir + peginterferon + ribavirin – 6%
- 24 weeks of placebo + peginterferon + ribavirin – 10%

Severely low levels of neutrophils (a type of white blood cells)

- 12 weeks of daclatasvir + peginterferon + ribavirin – 20%
- 16 weeks of daclatasvir + peginterferon + ribavirin – 24%
- 24 weeks of placebo + peginterferon + ribavirin – 34%

Key points

Overall, the combination of daclatasvir + peginterferon + ribavirin for 12 or 16 weeks cured a relatively high rate of people with genotypes 2 and 3 compared to interferon + ribavirin. Treatment was more effective for genotype 2 than 3. This is something that has been seen in some other studies of new anti-HCV agents and may suggest the possibility that either more complex therapies and/or longer periods of therapy may be needed for genotype 3.

REFERENCE:

Dore GJ, Lawitz E, Hézode C, et al. Daclatasvir combined with peginterferon alfa-2a and ribavirin for 12 or 16 weeks in patients with HCV genotype 2 or 3 infection: Command GT2/3 Study. In: Program and abstracts of the *48th Annual Meeting of the European Association for the Study of the Liver*, 24-28 April 2013, Amsterdam, Netherlands. Abstract 1418.

F. Faldaprevir + peginterferon + ribavirin

Faldaprevir (formerly BI 201335) is an HCV protease inhibitor and impairs the activity of the HCV proteins NS3/4A. Laboratory experiments with cells suggest that faldaprevir has activity against HCV genotypes 1, 2, 4, 5 and 6. This drug can be taken once daily.

In a complex study design that enrolled 666 HCV-positive participants from Europe and Japan, researchers randomly assigned them to receive one of the following regimens:

- faldaprevir at a dose of 120 mg or 240 mg + peginterferon + ribavirin for 12 or 24 weeks, followed by peginterferon + ribavirin for 12 or 24 weeks
- placebo + peginterferon + ribavirin for 24 weeks, followed by a further 24 weeks of peginterferon + ribavirin

No participant had hepatitis B virus (HBV) or HIV and the average profile of participants at the start of the study was as follows:

- age – 52 years
- 66% had genotype 1b
- 34% had genotype 1a
- viral load – 2.5 million IU/ml
- 40% had a genetic background suggestive of a good response to therapy with peginterferon

Overall results

- faldaprevir 240 mg: SVR₁₂ – 80%
- faldaprevir 120 mg: SVR₁₂ – 79%
- peginterferon + ribavirin: 52%

At this time SVR₂₄ results are not available.

In this study, researchers examined the response to therapy at different points in time. In particular, they focused on what they called “early treatment success” (ETS), which they defined in this way:

- HCV viral load less than 25 IU/ml at the 4th and 8th week of therapy

All participants who received faldaprevir and who had ETS could stop treatment at the 24th week of the study. In total, 88% of faldaprevir users had ETS.

Among participants with ETS here are the SVR₁₂ results after a total of 24 weeks of therapy:

- faldaprevir 240 mg – 89% achieved SVR₁₂
- faldaprevir 120 mg – 86% achieved SVR₁₂

Here are the distributions of SVR₁₂ according to genotype:

Faldaprevir 240 mg

- GT 1a – 76% achieved SVR₁₂
- GT 1b – 83% achieved SVR₁₂

Faldaprevir 120 mg

- GT 1a – 69% achieved SVR₁₂
- GT 1b – 84% achieved SVR₁₂

Specific genes and responses

Researchers use this shorthand for the set of genes (or genotype) that are associated with a favourable response to interferon-containing therapies: CC. The shorthand version for indicating the genotype with an intermediate response to interferon is: CT. The shorthand version for indicating the genotype with a poor response to interferon is: TT.

Here is the distribution of SVR₁₂ responses sorted by genes associated with a response to interferon:

CC genotype

- faldaprevir 240 mg – 95% achieved SVR₁₂
- faldaprevir 120 mg – 90% achieved SVR₁₂
- interferon + ribavirin – 63% achieved SVR₁₂

CT genotype

- faldaprevir 240 mg – 69% achieved SVR₁₂
- faldaprevir 120 mg – 70% achieved SVR₁₂
- interferon + ribavirin – 51% achieved SVR₁₂

TT genotype

- faldaprevir 240 mg – 79% achieved SVR₁₂
- faldaprevir 120 mg – 76% achieved SVR₁₂
- interferon + ribavirin – 28% achieved SVR₁₂

This type of genetic screening will be important for doctors and patients who are considering the use of faldaprevir.

Side effects

Side effects were relatively common in this study. Here are how some key side effects were distributed:

Rash

- faldaprevir 240 mg – 9%
- faldaprevir 120 mg – 8%
- interferon + ribavirin – 6%

Sensitivity to sunlight

- faldaprevir 240 mg – 0%
- faldaprevir 120 mg – 0%
- interferon + ribavirin – 1%

Gastrointestinal problems (nausea, vomiting, diarrhea)

- faldaprevir 240 mg – 12%
- faldaprevir 120 mg – 7%
- interferon + ribavirin – 3%

Anemia

- faldaprevir 240 mg – 12%
- faldaprevir 120 mg – 13%
- interferon + ribavirin – 11%

Yellowing of the skin and whites of the eyes (jaundice)

- faldaprevir 240 mg – 3%
- faldaprevir 120 mg – 2%
- interferon + ribavirin – 0%

Less-than-normal levels of neutrophils

- faldaprevir 240 mg – 12%
- faldaprevir 120 mg – 20%
- interferon + ribavirin – 18%

Less-than-normal levels of lymphocytes

- faldaprevir 240 mg – 18%
- faldaprevir 120 mg – 19%
- interferon + ribavirin – 11%

Elevated bilirubin

- faldaprevir 240 mg – 53%
- faldaprevir 120 mg – 12%
- interferon + ribavirin – 1%

Although elevated levels of the waste product bilirubin occurred shortly after initiation of faldaprevir-based therapy, they fell after the 12th week of therapy. By the 18th week of therapy, bilirubin levels were similar to those seen in participants who were not taking faldaprevir.

Key points

Overall, triple therapy with faldaprevir can be highly effective against HCV GT 1 in people of European and Japanese ancestry. Clinical trials in people from other ethno-racial groups are ongoing.

Nearly 90% of participants given faldaprevir were able to cease therapy after 24 weeks.

The 120-mg/day dose was generally as effective as the 240 mg/day dose and had less toxicity.

Elevated levels of bilirubin in the blood were temporary and not linked to any symptoms of toxicity.

The dose of faldaprevir to be used in everyday treatment will be 120 mg (in combination with interferon + ribavirin). Clinical trials are also planned for testing faldaprevir in people co-infected with HIV.

REFERENCE:

Ferenci P, Asselah T, Foster GR, et al. Faldaprevir plus pegylated interferon alfa-2a and ribavirin I chronic HCV genotype-1 treatment-naïve patients: final results from Startverso 1, a randomized, double-blind, placebo-controlled phase III trial. In: Program and abstracts of the *48th Annual Meeting of the European Association for the Study of the Liver*, 24-28 April 2013, Amsterdam, Netherlands. Abstract 1416.

G. Simeprevir + peginterferon + ribavirin

Simeprevir (formerly TMC435) is taken orally once daily. It is active against the HCV proteins called NS3 and NS4 and belongs to the class of drugs called HCV protease inhibitors. These proteins are used by HCV-infected cells to make new copies of HCV. By interfering with NS3 and NS4, simeprevir—together with interferon and ribavirin—is able to significantly reduce production of HCV and effect a cure in a relatively high percentage of HCV-positive people.

Laboratory experiments with HCV suggest that simeprevir has activity against a broad range of HCV genotypes including: 1, 2, 4, 5 and 6.

Simeprevir is being tested or being considered for testing in many clinical trials, such as the following:

- a long-term (three years) observational study to assess the safety of past exposure to simeprevir
- treatment of HCV genotype 4 in a study called Restore
- comparison of simeprevir vs. telaprevir where both drugs are taken with peginterferon + ribavirin
- comparisons of simeprevir + sofosbuvir, with or without ribavirin
- simeprevir + the emerging therapy TMC647055 + another emerging therapy called IDX719, with or without ribavirin in people who have never previously been treated
- simeprevir + TMC647055 with or without ribavirin
- simeprevir + daclatasvir with or without ribavirin
- simeprevir + the emerging therapy VX-135, with or without ribavirin

One of the phase III trials of simeprevir is called Quest 2. In this study, participants were randomly assigned to receive simeprevir or placebo,

both drugs accompanied by a combination of peginterferon + ribavirin.

In Quest 2, participants received simeprevir 150 mg + peginterferon + ribavirin for 12 consecutive weeks. After this, their therapy was simplified to peginterferon + ribavirin for a further 12 weeks. At the end of this period, if HCV viral load was undetectable, participants stopped therapy and their viral load was analysed again. If HCV levels were detectable, they received 24 additional weeks of peginterferon + ribavirin. If it was undetectable, no further therapy was necessary.

Participants initially assigned to placebo received the combination of peginterferon + ribavirin for a total of 48 weeks. At the end of this time they were monitored for a further 24 weeks to assess HCV viral load.

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

- 55% men, 45% women
- age – 46 years
- 30% had genes that suggested a favourable response to interferon-based therapy
- HCV viral load – 3 million IU/ml
- 41% had genotype 1a
- 59% had genotype 1b

Results

The proportion of participants who achieved a suppressed viral load 12 weeks after the start of therapy and maintained this to 12 weeks after the cessation of therapy (SVR₁₂) was as follows:

- simeprevir – 81%
- peginterferon + ribavirin – 50%

This difference was statistically significant.

Overall, 91% (235 of 257) of participants were virologically suppressed with 12 weeks of triple therapy followed by 12 weeks of interferon + ribavirin. Of these 235 patients, 86% subsequently achieved SVR₁₂.

Among the remaining 22 participants who had received simeprevir and whose viral load was not suppressed, seven of the 22 (-32%) subsequently cleared the virus after an additional 24 weeks of interferon + ribavirin.

In general, participants who had a set of genes (called genotypes) that suggested a favourable

response to interferon-based therapies had greater rates of recovery from HCV. The genotypes are represented as follows:

- CC – the set of genes associated with the most favourable response to interferon
- CT – the set of genes associated with an intermediate response to interferon
- TT – the set of genes associated with the least favourable response to interferon

Among participants with the different genotypes, here are the responses:

CC genotype

- simeprevir + interferon + ribavirin – 96% had SVR₁₂
- interferon + ribavirin – 81% had SVR₁₂

CT

- simeprevir + interferon + ribavirin – 80% had SVR₁₂
- interferon + ribavirin – 41% had SVR₁₂

TT

- simeprevir + interferon + ribavirin – 58% had SVR₁₂
- interferon + ribavirin – 19% had SVR₁₂

Response by genotype of HCV:

Genotype 1a

- simeprevir + interferon + ribavirin – 80% had SVR₁₂
- interferon + ribavirin – 46% had SVR₁₂

Genotype 1b

- simeprevir + interferon + ribavirin – 82% had SVR₁₂
- interferon + ribavirin – 53% had SVR₁₂

REFERENCE:

Manns M, Marcellin P, Poordad FPF, et al. Simeprevir (TMC435) with peginterferon/ribavirin for treatment of chronic HCV genotype 1 infection in treatment-naïve patients: results from Quest-2, a phase III trial. In: Program and abstracts of the *48th Annual Meeting of the European Association for the Study of the Liver*, 24-28 April 2013, Amsterdam, Netherlands. Abstract 1413.

H. Sofosbuvir + peginterferon + ribavirin

Sofosbuvir is an emerging therapy for HCV and works by interfering with an HCV protein called NS5B. It is being tested in combination with many drugs, including peginterferon + ribavirin. In laboratory experiments it has activity against several strains, or subtypes, of HCV called genotypes. In one clinical trial, researchers enrolled 327 HCV-positive people with genotypes 1, 4, 5 and 6 and gave them 12 weeks of the following combinations of drugs:

- sofosbuvir 400 mg once daily, taken orally
- peginterferon – one injection once weekly
- ribavirin – between 1,000 and 1,200 mg, depending on body weight, taken in divided doses twice daily

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

- age – 52 years
- gender – 64% male, 36% women
- Genotypes (GT): GT 1 – 89%; GT 2 – 11%
- HCV viral load – 3.2 million IU/ml
- severe liver damage (cirrhosis) – 17%

Results—Recovery and relapse

Twelve weeks after treatment had ceased, the overall proportion of participants with an undetectable viral load (SVR₁₂) was 90%.

SVR₁₂ results were broadly similar by genotype, as follows:

- GT 1 – 89% (261 of 292 people) had SVR₁₂
- GT 4 – 96% (27 of 28 people) had SVR₁₂
- GT 5 and 6 – 100% (seven people) had SVR₁₂

These results were not affected by factors such as a person's gender, race or having genes associated with a favourable response to interferon.

Among 54 participants with cirrhosis, 80% achieved SVR₁₂.

Relapse occurred in 28 participants and one other person who prematurely discontinued therapy (due to side effects). In all cases, researchers could not detect HCV that was resistant to sofosbuvir.

Results – Side effects

Overall, 95% of participants reported side effects. This is not surprising, as interferon is associated with many side effects (the vast majority of which are similar to symptoms resembling a flu. However, interferon can also cause anxiety, fatigue, difficulty sleeping and depression). Only 15% of participants developed severe symptoms of side effects. Common side effects reported included the following:

- fatigue – 59%
- headache – 36%
- nausea – 34%
- difficulty falling asleep – 25%
- rash – 18%
- decreased appetite – 18%
- fever – 18%
- chills – 17%

Nearly 50% of participants developed abnormal laboratory blood test results. However, these returned to normal after the trial ended. A few examples of abnormal laboratory test results during the study included the following:

- anemia – 23%
- less-than-normal levels of a type of immune system cell called neutrophils – 20%

As this study did not enroll participants who were given a different regimen, it is difficult to separate side effects of sofosbuvir from those caused by interferon and ribavirin.

Further studies with sofosbuvir are underway or planned with many combinations of drugs. Hopefully these will reveal more about sofosbuvir's possible side effects and extend its application with different genotypes of HCV.

REFERENCE:

Lawitz E, Wyles D, Davis M, et al. Sofosbuvir + peginterferon + ribavirin for 12 weeks achieves 90% SVR₁₂ in genotype 1,4,5 or 6 HCV-infected patients: the Neutrino study. In: Program and abstracts of the *48th Annual Meeting of the European Association for the Study of the Liver*, 24-28 April 2013, Amsterdam, Netherlands. Abstract 1411.

I. Sofosbuvir + ledipasvir or GS-9669

In a small clinical trial with participants who had a poor response to prior therapy (so called null responders) only about 10% recovered when re-treated with a combination of sofosbuvir and

ribavirin. This suggests the possibility that adding another potent anti-HCV drug to a regimen for prior null responders may be more effective in curing them.

Enter ledipasvir

Ledipasvir is an emerging anti-HCV drug that works by interfering with an HCV protein called NS5A needed to help produce new copies of HCV.

In studies of ledipasvir monotherapy, when it has been taken once daily at doses between 10 and 90 mg, this drug can reduce HCV levels by slightly more than 3 logs in people who have HCV genotypes 1a and 1b. The dose used in the clinical trial that we later describe is 90 mg/day.

GS-9669

This drug is designed to attack another HCV protein called NS5B. Taken at a dose of 500 mg once daily in monotherapy, it can also reduce HCV viral load by at least 3 logs. GS-9669 does not interact with sofosbuvir.

Researchers conducted several 12-week studies of direct-acting antiviral drugs (DAAs) with ribavirin, as follows:

- sofosbuvir + ledipasvir + ribavirin in people who had not previously been treated
- sofosbuvir + ledipasvir + ribavirin in people who were classed as null responders
- sofosbuvir + GS-9669 + ribavirin in people who had not previously been treated
- sofosbuvir + GS-9669 + ribavirin in people who were classed as null responders

In this study, prior treatment would have been with interferon and ribavirin.

The average profile of participants in these studies was as follows:

- age – mid-to-late 40s
- gender – 60% men, 40% women
- at least 80% had the difficult-to-treat GT 1a
- HCV viral load – at least 1 million copies/IU

No participant had severe liver damage (cirrhosis).

Results

The virologic results or the proportion of participants with an undetectable viral load 12 weeks after the cessation of therapy were as follows:

- sofosbuvir + ledipasvir + ribavirin: 25 people who had no prior treatment; SVR₁₂ = 100%
- sofosbuvir + ledipasvir + ribavirin: 10 null responders to prior treatment; SVR₁₂ = 100%
- sofosbuvir + GS-9669 + ribavirin: 25 people who had no prior treatment; SVR₁₂ = 92%
- sofosbuvir + GS-9669 + ribavirin: 10 null responders to prior treatment; SVR₁₂ = 3/3 people

Note that not all participants for this last course of treatment have completed the study.

Side effects

As with all HCV clinical trials, temporary side effects occurred. Based on the design of the study and the relatively small number of participants, it is difficult to draw firm conclusions about the side effects caused by each drug.

Rates of anemia were relatively low, occurring in up to 20% of participants who received sofosbuvir + ledipasvir + ribavirin. In contrast, anemia occurred in up to 8% of participants who received GS-9669-containing regimens.

Fatigue was reported in as many as 22% of participants who received sofosbuvir + ledipasvir + ribavirin. This side effect was not reported in participants who received GS-9669-containing regimens.

The combinations of drugs used in this study were highly effective and relatively safe. Larger studies are needed to confirm these results and find out more about potential side effects.

REFERENCE:

Gane EJ, Stedman CA, Hyland RH, et al. All-oral sofosbuvir-based 12-week regimens for the treatment of chronic HCV infection: the Electron study. In: Program and abstracts of the 48th Annual Meeting of the European Association for the Study of the Liver, 24-28 April 2013, Amsterdam, Netherlands. Abstract 14.

J. Interferon-free: sofosbuvir in HCV genotypes 2 or 3

A large fraction of HCV-positive patients cannot tolerate interferon because of its many impacts, including mental-health-related side effects such as anxiety, irritability, difficulty falling asleep and depression. Also, people who have conditions caused by the immune system attacking the body—called autoimmunity—may not be able to tolerate interferon because this drug can intensify underlying immunological dysfunction.

Researchers recruited participants for a 12-week study called Positron. In this study, participants had HCV genotype 2 or 3.

Overall, 278 volunteers were screened and then randomized as follows:

- sofosbuvir (400 mg once daily) + ribavirin (1,000 to 1,200 mg per day, taken in two divided doses)
- placebo (these participants were offered sofosbuvir + ribavirin after completion of the study)

These interventions were taken for 12 weeks.

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

- age – 52 years
- gender – 57% men, 43% women
- most participants (53%) had genotype 2
- HCV viral load – 2 million IU/ml
- severe liver damage (cirrhosis) – 15%
- interferon status: unwilling to take interferon 49%; medically ineligible for interferon 43%; intolerant of interferon 8%.

Results

Overall, 78% (161 of 207 participants) on sofosbuvir + ribavirin achieved SVR₁₂. The figure for placebo was zero.

When researchers analysed SVR₁₂ status by genotype, results were as follows:

- GT 2 (101 of 109 participants) – 93% achieved SVR₁₂
- GT 3 (60 of 98 participants) – 61% achieved SVR₁₂

When results were analysed by cirrhosis status and genotype, the results were as follows:

- GT 2 no cirrhosis – 92% achieved SVR₁₂
- GT 2 with cirrhosis – 94% achieved SVR₁₂
- GT 3 no cirrhosis – 68% achieved SVR₁₂
- GT 3 with cirrhosis – 21% achieved SVR₁₂

Although most participants achieved an initial response to therapy, overall only 78% were cured. This rate seems relatively low for a combination with sofosbuvir. Relapse, not resistance, was the main cause of treatment failure. This means that re-treatment with a sofosbuvir-containing regimen is a possibility for some participants.

Side effects

Overall, rates of side effects were greater in participants who received sofosbuvir + ribavirin (89%) than placebo (78%). Also, the rate of serious side effects was greater in participants who received sofosbuvir + ribavirin (8%) than placebo (1%).

Anemia occurred in 7% of participants exposed to sofosbuvir + ribavirin and no cases of this problem appeared in placebo users.

Here is the distribution of other side effects, most of which were of mild-to-moderate intensity:

Fatigue

- sofosbuvir + ribavirin – 44%
- placebo – 24%

Nausea

- sofosbuvir + ribavirin – 22%
- placebo – 18%

Difficulty falling asleep

- sofosbuvir + ribavirin – 19%
- placebo – 4%

Itchy skin

- sofosbuvir + ribavirin – 11%
- placebo – 9%

Decreased appetite

- sofosbuvir + ribavirin – 3%
- placebo – 10%

The question of genotype

In this study, 12 weeks of therapy with sofosbuvir + ribavirin was highly effective for participants with GT 2 but less so for those with GT 3. This is an issue not only for sofosbuvir but other direct-acting antivirals (DAAs). Future studies need to

be designed to deal with the difficulty of treating GT 3. Such studies might employ longer courses of therapy—perhaps 16 or 24 weeks—or become more complex, using three or four therapies instead of two.

REFERENCE:

Jacobson I, Yoshida EM, Sulkowski M, et al. Treatment with sofosbuvir + ribavirin for 12 weeks achieves SVR₁₂ of 78% in GT2/3 interferon-ineligible, -intolerant, or -unwilling patients: results of the phase 3 Positron trial. In: Program and abstracts of the *48th Annual Meeting of the European Association for the Study of the Liver*, 24-28 April 2013, Amsterdam, Netherlands. Abstract 61.

K. Aviator: a large interferon-free combo

Abbvie (formerly Abbott) is developing a regimen of the following HCV drugs:

- ABT-450 interferes with the HCV proteins NS3/4A and it is taken once daily with a small dose (100 mg) of another drug called ritonavir (Norvir). The purpose of the small dose of ritonavir is to boost and maintain levels of ABT-450 in the blood. Ritonavir does not have activity against HCV and has only minimal activity against HIV at such a low dose.
- ABT-267 interferes with the HCV protein NS5A and is taken once daily.
- ABT-333 interferes with the HCV protein NS5B and is taken twice daily.

Preliminary results with this combination of drugs have found that it is very effective for HCV genotype 1, with SVR₁₂ rates of 98% occurring in people who have not been previously treated and SVR₁₂ rates of 93% in people who were poor responders to prior therapy with interferon + ribavirin.

In study M11-652 (dubbed “Aviator” by Abbvie), researchers recruited 571 participants with HCV and assigned them to receive one of nine different combinations and durations of therapy. In many cases, the broad-spectrum antiviral drug ribavirin was part of their combination therapy.

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

- age – 50 years
- gender – 60% men, 40% women

- viral load – 4 million IU/ml
- 67% had the difficult-to-treat genotype 1a

Results – SVR₂₄ with initial treatment

- ABT-450 + ABT-267 + ABT-333 + ritonavir: 80 people were treated for 8 weeks; 88% achieved SVR₂₄
- ABT-450 + ABT-333 + ribavirin + ritonavir: 41 people were treated for 12 weeks; 83% achieved SVR₂₄
- ABT-450 + ABT-267 + ribavirin + ritonavir: 79 people were treated for 12 weeks; 89% achieved SVR₂₄
- ABT-450 + ABT-267 + ABT-333 + ritonavir: 79 people were treated for 12 weeks; 87% achieved SVR₂₄
- ABT-450 + ABT-267 + ABT-333 + ribavirin + ritonavir: 79 people were treated for 12 weeks; 96% achieved SVR₂₄
- ABT-450 + ABT-267 + ABT-333 + ribavirin + ritonavir: 80 people were treated for 24 weeks; 90% achieved SVR₂₄

Results – SVR₂₄ in people with a previous poor response to interferon + ribavirin

- ABT-450 + ABT-267 + ribavirin + ritonavir: 45 people treated for 12 weeks; 89% achieved SVR₂₄
- ABT-450 + ABT-267 + ABT-333 + ribavirin + ritonavir: 45 people treated for 12 weeks; 93% achieved SVR₂₄
- ABT-450 + ABT-267 + ABT-333 + ribavirin + ritonavir: 43 people treated for 24 weeks; 95% achieved SVR₂₄

When treatment failure did occur, in the majority of cases it seemed to be caused by relapse rather than treatment failure. There were cases of treatment failure in participants on therapy, but these will require further virological analyses of stored blood samples so that researchers can determine the cause of treatment failure and any cases of resistance that may have occurred.

The following factors had no impact on the response to therapy:

- race, gender, HCV subtype (1a or 1b), having genes that suggest a favourable response to interferon-based therapy, having an initial high or low viral load, the degree of liver damage

Results – Side effects

According to investigators, a total of four participants left the study prematurely due to apparent side effects of therapy, including the following:

- “feeling jittery”
- “[thoughts of committing murder]”
- kidney dysfunction
- elevated levels of liver enzymes in the blood

Four participants experienced joint pain, possibly caused by their medicines.

There were six cases where levels of the waste product bilirubin were temporarily elevated in the blood.

The most common side effects were as follows:

- headache – 31%
- fatigue – 30%
- nausea – 23%
- difficulty falling asleep – 20%
- diarrhea – 15%

In general, seriously abnormal blood test results were rare. No cases of anemia occurred and no side effect was life threatening.

Overall, the results from Aviator suggest that the combination of drugs used in this study can be taken for 12 weeks with high rates of SVR₂₄ and likely cure. Phase III trials of the main combinations seen in Aviator are underway. Abbvie will also be conducting trials of these drugs in people co-infected with HIV. However, it must first assess potential drug-drug interactions between these drugs used for HCV and drugs used for HIV.

REFERENCE:

Kowdley KV, Lawitz E, Poordad F, et al. Safety and efficacy of interferon-free regimens of ABT-450/r, ABT-267, ABT-333 ± ribavirin in patients with chronic GT1 infection: Results from the Aviator study. In: Program and abstracts of the *48th Annual Meeting of the European Association for the Study of the Liver*, 24-28 April 2013, Amsterdam, Netherlands. Abstract 3.

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CATIE, Canada's source for HIV and hepatitis C information, is committed to improving the health and quality of life of all people living with HIV/AIDS in Canada. CATIE serves people living with HIV/AIDS, and the people and organizations that support them, by providing accessible, accurate, unbiased and timely treatment information. CATIE provides such information through a comprehensive Web site, a bilingual toll-free phone service, electronic and print publications, a national reference library and workshops and exhibits at conferences across Canada.

CATIE Publications

TreatmentUpdate

CATIE's flagship treatment digest on cutting-edge developments in HIV/AIDS research and treatment. Subscribe to TreatmentUpdate and automatically receive an email notifying you the moment a new issue is available on-line or contact us at 1.800.263.1638 to receive a print subscription.

A Practical Guide to HIV Drug Treatment

The latest on what is known about the various aspects of treatment, including a description of the virus and the immune system, the stages of HIV disease, the tests used to assess health status, and anti-HIV medications.

A Practical Guide to HIV Drug Side Effects

The latest on what is known about various side effects related to treatment, from appetite loss to sexual difficulties, and tips for countering or preventing them.

The Practical Guide series also includes:

- A Practical Guide to Nutrition
- A Practical Guide to Complementary Therapies
- A Practical Guide to Herbal Therapies

The Positive Side magazine

Holistic health information and views for PHAs.

Fact Sheets

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

pre*fix

A harm reduction booklet for HIV+ drug users.

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