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I SIDE EFFECTS AND COMPLICATIONS

A. France – trends in fat wasting

Potent combination therapy for HIV infection, commonly called ART (antiretroviral therapy) or HAART (highly active antiretroviral therapy), has saved and extended the lives of countless HIV-positive people. However, like all therapies, ART can have side effects. Some drugs used in ART, particularly older drugs, are less well tolerated and can cause certain side effects. In this issue of *TreatmentUpdate* we focus on one of these side effects—lipoatrophy.

First reported in the late 1990s, the loss of the fatty layer just under the skin (subcutaneous fat) is a process called lipoatrophy. This is deeply disturbing for HIV-positive people and has been linked to the use of the following drugs, which are called thymidine analogues:

- d4T (stavudine, Zerit)
- AZT (zidovudine, Retrovir; and in Combivir and Trizivir)

In general, d4T's impact on lipoatrophy can be more severe in the short-term than that of AZT.

By avoiding the use of these drugs, doctors can spare their patients future problems with lipoatrophy. Because the use of d4T is largely shunned in Canada and other high-income countries, new cases of HIV-related facial lipoatrophy are now uncommon.

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In place of thymidine analogues, the nucleos(t)ide analogues commonly used today are generally as follows:

- abacavir + 3TC (coformulated into one pill called Kivexa)
- tenofovir + FTC (coformulated into one pill called Truvada)

These nukes have **not** been linked to fat wasting. Still, long-term monitoring of HIV-positive people taking these and other medicines is important in case new complications develop.

Researchers in Paris have been monitoring the health of more than 2,000 HIV-positive people taking anti-HIV drugs. They have found that the loss of subcutaneous fat in the face is still being reported by some doctors and their patients even when thymidine analogues have not been used. However, the researchers did not use objective assessments of lipoatrophy, such as ultrasound or MRI scans. Rather, they relied on visual inspection by doctors and patients. This could have led to inadvertent bias when assessing facial fat.

Study details

In the Preface study, researchers surveyed 2,131 HIV-positive people and their doctors from 122 clinics in France who had been either taking (patients) or prescribing (doctors) anti-HIV drugs for up to 10 years.

A sub-analysis from 1,065 participants was released based on the following:

- 490 people who took ART for between one and five years
- 575 people who took ART for between five and 10 years

The average profile of participants in the sub-study was as follows:

- 30% females, 70% males
- age – 46 years
- length of time HIV positive – 13 years
- length of time on anti-HIV therapy – 10 years
- proportion currently taking AZT – 20%
- proportion currently taking d4T – 1%
- CD4+ count – 585 cells
- proportion with a viral load less than 50 copies – 87%
- HCV co-infection – 17%
- HBV co-infection – 8%

Results—Overall

Lipoatrophy affecting the face occurred in 22% of people who took ART for between one and 10 years. None of these people were exposed to thymidine analogues, so the finding is puzzling.

Results—Severity of lipoatrophy

In general, people with the least exposure to ART had the least severe lipoatrophy. People who had 10 or more years of exposure to ART tended to have the most severe lipoatrophy.

Caution needed

The results of the present study, while interesting, require cautious interpretation for at least the following reasons:

- Objective assessment missing
In the past five years, most studies of lipoatrophy conducted in high-income countries have used objective measures of assessment, such as ultrasound or MRI scans. In the present French study, mere visual inspection was used. Relying on visual inspection is fraught with the possibility of misclassifying or misunderstanding changes.
- Design issues
The study was cross-sectional, that is, apparently only one assessment of lipoatrophy was done. There was no control or comparison. Therefore, while the researchers may have found suggestions of lipoatrophy, they cannot prove that lipoatrophy did indeed occur. Nor can they firmly link the development of lipoatrophy to exposure to any particular drug, no matter the size of their study.

Still, the finding that about 20% of participants apparently developed lipoatrophy despite never having been exposed to d4T or AZT is intriguing. This needs to be explored in a study of a more robust design to confirm or refute the initial findings of Preface.

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B. Vitamin D linked to survival in HIV

Although vitamin D is classified as a vitamin, it behaves as a hormone within the body. Using sunlight and cholesterol, the body makes vitamin D in the skin. Vitamin D is then transported to the liver, where it is converted into vitamin D₂, and then the kidneys, where it is converted into its active form called vitamin D₃ (1,25-dihydroxy vitamin D₃).

The precise roles(s) of vitamin D in the body are unclear. Certainly it helps the body absorb calcium from food and helps in bone formation. But many cells of the body, particularly those of the immune system, have receptors for vitamin D, so some scientists suspect that this substance may play a role in several health conditions.

Some European researchers consider the following vitamin D levels in the blood to be something that requires medical attention:

- less than 30 ng/ml (75 nmol/l) – low
- less than 10 ng/ml (25 nmol/l) – deficient

Observational studies in HIV-*negative* people suggest that less-than-normal levels of vitamin D in the blood may be linked to thin bones, increased risk for cancer, tuberculosis, cardiovascular disease, kidney dysfunction, type 2 diabetes and death.

Observational studies in HIV-positive people have found that vitamin D deficiency is common, particularly among people with dark skin living in temperate countries such as Canada and even among those in tropical countries where sunny days are common. Some researchers have found that the problems linked to vitamin D deficiency among HIV-negative people are strikingly similar to the co-morbidities (thinning bones, type 2 diabetes, kidney dysfunction, cardiovascular disease, and so on) that are increasingly being recognized in some HIV-positive people.

Researchers affiliated with the EuroSIDA database have been collecting health-related information for many years from HIV-positive people and decided to investigate vitamin D deficiency and factors associated with it. Out of 5,000 people, they chose about 2,000 whose vitamin D levels were available from assessments done by one laboratory at Hôpital Necker in Paris, France.

Results

The study team focused on 1,985 people whose samples were associated with other data in its database.

In general, there was no association between vitamin D and these factors:

- CD4+ count
- viral load
- use or not of ART

However, the research team noticed that White participants tended to have higher levels of vitamin D in their blood than people of colour. Also, injection drug users (IDUs) tended to have lower levels of vitamin D than non-IDUs.

For every 10-year increase in the age of a person in the study, there was an increase of 12% relative risk for having a vitamin D deficiency.

Results—Survival

There were a total of 188 deaths among the study participants. Death rates differed by vitamin D levels as follows:

- severe vitamin D deficiency (12 ng/ml or lower) – 11% of participants died
- moderate levels of vitamin D deficiency (between 12 and 20 ng/ml) – 7% of participants died
- mild deficiency (more than 20 ng/ml) – 6% of participants died

The differences between deaths among participants with severe vitamin D deficiency compared to deaths that occurred in participants with more moderate or mild vitamin D deficiency were statistically significant.

Results—AIDS-related infections and complications

In general, the greater the deficiency of vitamin D, the more likely participants were to develop AIDS-related complications:

- severe vitamin D deficiency (12 ng/ml or lower) – 10% of participants developed AIDS
- moderate levels of vitamin D deficiency (between 12 and 20 ng/ml) – 6% of participants developed AIDS
- mild deficiency (more than 20 ng/ml) – 5% of participants developed AIDS

The differences between AIDS-related infections and complications among participants with severe

vitamin D deficiency compared to the number that occurred in participants with more moderate or mild vitamin D deficiency were statistically significant.

There was a similar trend in the distribution of non-AIDS-related events but this did not achieve statistical significance.

Why were these associations found?

Vitamin D levels have historically been linked to poverty, so the EuroSIDA group may indeed have correctly linked vitamin D deficiency to poor survival. However, it is possible that the real cause of death may have nothing directly to do with vitamin D levels but instead be linked to other associated factors. For instance, income has previously been linked to reduced survival among HIV-positive people. It is possible that low vitamin D levels could be a surrogate marker for poverty, at least in some cases.

Depending on the severity of their addiction, IDUs may prioritize getting and using substances over habits linked to healthy living. Therefore, IDUs may have vitamin D deficiency (along with other nutrient deficiencies) though the cause(s) of their death may have nothing to do with vitamin D (such as violence, suicide, drug overdose, bacterial infections, cardiac dysfunction).

The relationship between body weight and height (body mass index, or BMI) was not apparently taken into account in the present EuroSIDA analysis. This may be important because vitamin D is stored in fat and other studies have found that overweight and obese people tend to have less-than-normal levels of vitamin D in the blood. It is possible that some of the deaths that occurred in the present study were due to being overweight or obese rather than vitamin D deficient.

Preliminary ongoing analyses from the EuroSIDA cohort suggest that people who take protease inhibitor-based ART tend to have higher vitamin D levels. However, more research needs to be done to see if this finding is linked to better health and longer survival.

Why the uncertainty?

Because this was an observational study, confounding or channeling bias can inadvertently occur when interpreting the results, so the results must be taken with a degree of caution. Moreover, the study was based on just one measurement of vitamin D, so altogether, firmly linking cause and effect in this analysis is fraught with difficulty.

Larger observational studies have found that vitamin D deficiency has been linked to an increased risk of death among HIV-negative people, particularly from cardiovascular disease, so perhaps the EuroSIDA group has found something important. However, the large size of the EuroSIDA dataset suggests the possibility that low levels of vitamin D may be linked to poorer health in some HIV-positive people.

Clarity ahead

Data analysis from a randomized controlled trial, is now underway to assess stored blood samples for vitamin D levels and to try to understand the effect(s) of different ART regimens on this vitamin. Also, EuroSIDA researchers are conducting an intervention study where vitamin D supplements are given to some HIV-positive people and monitoring is being done to observe any benefit(s).

For now, vitamin D remains an intriguing subject for research. Until firm conclusions can be drawn from robustly designed studies, it is best to guide the intake of vitamin D based on laboratory testing of vitamin D levels in the blood.

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II ANTI-HCV AGENTS

A. Hepatitis C virus — infection, prevention and treatment

In high-income countries today, hepatitis C virus (HCV) is most commonly spread through sharing equipment for substance use, such as needles and straws. Exposure to unsterilized tattooing needles can be another source of infection. HCV can also be transmitted among HIV-positive men who have unprotected anal sex. Presumably this can also occur among HIV-positive women who have unprotected anal sex.

HCV infects the liver and may initially cause mild flu-like symptoms, so people infected with HCV may not be aware that they have it. If HCV infection persists, the liver slowly degrades over many years. Among people co-infected with HIV and HCV, accelerated liver damage can occur.

If left untreated, HCV infection can cause severe liver damage, eventually leading to painful complications and liver failure. In some cases, liver cancer and death are also consequences of prolonged HCV infection. Therefore, testing for HCV infection, consistently practicing safer sex, not sharing equipment for drug use and getting psychosocial support for recovering from addiction and other mental health issues are steps that can lead to better overall health.

The standard therapy for HCV infection is a combination of long-lasting peginterferon (peginterferon) taken once weekly and another drug called ribavirin, which is taken twice daily. People with acute (very recent) HCV infection can sometimes benefit from relatively short courses of HCV therapy (24 weeks) and clear HCV. But for people who have been HCV positive for longer or who are co-infected, treatment with peginterferon and ribavirin usually lasts for 48 weeks.

HCV can be divided into subtypes, or strains, called genotypes. Infection with genotypes 1 and 4 are more difficult to treat than genotypes 2 and 3. In high-income countries, genotype 1 is commonly found.

In cases of HCV mono-infection, treatment can result in about 50% of people clearing HCV. However, among people with both HIV and HCV, recovery rates are not as high.

Peginterferon can cause temporary side effects with symptoms such as those related to having the flu. Other side effects that can also occur while people are undergoing treatment with peginterferon include reduced numbers of red blood cells, irritability and depression. Therefore, new, safer and more effective therapies are needed.

New anti-HCV drugs are being tested in several phases in many clinical trials. In this issue of *TreatmentUpdate*, we present information on some of these promising compounds.

B. Some emerging HCV therapies

Underlying some of the research with new anti-HCV agents is the hope that peginterferon, and eventually ribavirin, can eventually be replaced with more tolerable agents. This may not be possible in the immediate future, but some researchers hope that over the next five years perhaps less time spent taking peginterferon and ribavirin may be a possibility for future HCV treatment regimens.

Anti-HCV drugs under development can be divided into several groups, or classes, depending on how they work.

Protease inhibitors

HCV needs enzymes called NS3/4A proteases that help HCV-infected cells produce new copies of HCV. These enzymes also appear to suppress the ability of infected cells to alert other cells about attack by HCV. So HCV protease inhibitors could have several benefits.

Drug companies often seek to get their drugs first approved by regulatory authorities in the United States, followed by the European Union and then Canada, Australia, Japan and other high-income countries. This is because the U.S. and the EU have large, relatively wealthy populations and present opportunities for sales and profit for drug companies. Also, it is likely that new therapies for

HCV will first be approved for use in HCV mono-infection because there are more cases of mono-infection than co-infection and new therapies were initially developed for treating HCV mono-infection.

The two new anti-HCV drugs that are most likely to be approved in the U.S. are the protease inhibitors telaprevir (made by Vertex Pharmaceuticals) and boceprevir (made by Merck).

Both of these drugs have shown powerful anti-HCV activity in clinical trials of HCV mono-infection when taken as part of regimens that contain peginterferon and ribavirin. These protease inhibitors are also useful in people who have previously been treated with standard HCV therapy (peginterferon and ribavirin) but who did not respond.

Boceprevir and telaprevir are expected to be approved in the United States in 2011, with approval in the EU probably occurring in the same year. These drugs are expected to be approved in Canada in 2012.

Both of these protease inhibitors must be taken three times daily and can have side effects such as anemia. Therefore, interest in other HCV protease inhibitors under development—such as TMC 435350 (made by Tibotec) and GS 9256 (made by Gilead Sciences)—as well as other drugs by other companies is intense.

Polymerase inhibitors

These drugs represent another class of anti-HCV agents and interfere with an enzyme called polymerase (hence their name). Examples of polymerase inhibitors include RG7128 and RG1628 (being developed by Hoffmann-La Roche), ABT 072 and ABT 333 (being developed by Abbott) and GS 9190 (being developed by Gilead Sciences).

Cyclophillin inhibitors

Cyclophillins are receptors for the compound cyclosporine and are found inside of cells. The role of cyclophillins in cells is not fully understood, but these receptors may play a role in infections with viruses such as HIV and HCV. By impairing the activity of these receptors, HCV cyclophillin inhibitors can reduce the ability of HCV-infected cells to produce new viruses. Alisporivir (being developed by Novartis) is an example of a cyclophillin inhibitor.

There are other classes of anti-HCV drugs under development but they are not as far advanced as those previously mentioned.

Future approaches to therapy

In the treatment of HIV infection, using a combination of drugs from several classes is now the norm. Combining classes reduces the risk of HIV developing resistance to therapy. The same principle will likely apply to HCV.

Five years from now there should be a full suite of anti-HCV drugs available from different classes. When that happens, combination therapy for HCV might then include drugs from different classes and peginterferon-free regimens might finally be possible.

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C. Emerging HCV therapies – possible interactions with HIV drugs

As liver damage is accelerated in people co-infected with HIV, doctors and their co-infected patients will be interested in using new drugs while at the same time being concerned about the possibility of interactions. Such interactions could have any number of potential effects, such as:

- weakening the activity of anti-HCV treatment
- weakening the activity of anti-HIV treatment
- causing or intensifying pre-existing side effects

Clinical trials with new anti-HCV therapies are underway. However, it will be several years before all common drug interactions and side effects are known with these new drugs. Over the next several years, HCV therapy will likely consist of peginterferon and ribavirin with one or two new anti-HCV drugs added.

Compare and contrast

For the treatment of HCV infection, a new class of drugs has emerged: HCV protease inhibitors. These drugs work by targeting enzymes containing the amino acid serine. By interfering with these serine-containing enzymes, production of HCV falls.

For the treatment of HIV infection, sometimes a class of drugs called HIV protease inhibitors is used as part of combination therapy. These drugs work by targeting enzymes containing the amino acid aspartic acid (aspartate). By interfering with

aspartate-containing enzymes, these drugs are able to decrease production of HIV.

Because each of these different classes of drugs (HCV protease inhibitors and HIV protease inhibitors) attacks different protease enzymes, using HCV protease inhibitors will not lead to drug resistance when HIV protease inhibitors are used, and vice versa. However, there may be other potential problems.

In lab experiments with human liver cells, the HIV protease inhibitor ritonavir (Norvir, and in Kaletra) impairs the breakdown of the HCV protease inhibitors telaprevir and boceprevir. Experiments with rats suggest that telaprevir and boceprevir are broken down by the liver enzyme CYP3A4.

HIV protease inhibitors such as ritonavir and lopinavir (in Kaletra) and darunavir (Prezista) inhibit the activity of CYP3A4. Therefore, taking telaprevir or boceprevir with either of these HIV protease inhibitors may affect the levels of HCV protease inhibitors in the blood. The opposite effect is also possible—taking HCV protease inhibitors may interfere with HIV protease inhibitors (and other drugs also processed by this enzyme). This may mean that if one person uses both HIV and HCV protease inhibitors, the doses of one or more of their drugs will have to be adjusted. It also raises the possibility that if telaprevir or boceprevir is taken with a small dose of ritonavir, twice-daily use of telaprevir or boceprevir might be an issue worth exploring in clinical trials. This is an important possibility because currently both telaprevir and boceprevir must be taken three times daily.

Non-nukes

HIV non-nukes commonly used in the years ahead will likely be the following:

- efavirenz (Sustiva and in Atripla)
- nevirapine (Viramune)
- etravirine (Intelence)
- rilpivirine

All of these drugs increase the activity of the enzyme CYP3A4 and have the potential for accelerating the breakdown of HCV protease inhibitors. So clinical trials may be necessary to understand how both classes of drugs affect each other.

Polymerase inhibitors

At the molecular level, HCV polymerase inhibitors are similar in shape to some HIV nukes, and so both classes of drugs have the ability to interfere

with each other. For instance, the HCV drug R7128 is based on the cytidine molecule. So are the following anti-HIV drugs:

- 3TC (lamivudine, and in Combivir, Kivexa and Trizivir)
- FTC (emtricitabine/Emtriva, and in Truvada and Atripla)

This similarity in shape or structure may weaken the antiviral activities of both groups of drugs when drugs such as R7128 are used for HCV treatment in co-infected people who are also taking 3TC or FTC nukes for HIV treatment.

A similar effect is seen among HIV treatments, so guidelines discourage the simultaneous use of 3TC and FTC, as well as AZT (zidovudine/Retrovir, and in Combivir and Trizivir) and d4T (stavudine, Zerit).

Enhanced side effects

Temporary anemia is relatively common among people who have received telaprevir or boceprevir. The anti-HIV drug AZT can also have a similar effect. So it is possible that the use of either telaprevir or boceprevir and AZT will be discouraged.

Another drug under development for HCV treatment is the cyclophilin inhibitor alisporivir. This drug is associated with yellowing of the skin and whites of the eyes, caused by a buildup of the waste product bilirubin. This effect is called hyperbilirubinemia and can also occur in people taking the anti-HIV drug atazanavir (Reyataz). Taking both of these drugs may intensify the skin and eye discoloration.

As all of the emerging anti-HCV drugs have been tested only in a modest number of volunteers in clinical trials (relative to the number of people with HCV infection in the community), their full range of side effects will not be known for several years.

Many HCV-positive people who were infected with this virus through sharing needles or other equipment for substance use will also likely be taking methadone or buprenorphine to help manage their addiction. Interactions between methadone or buprenorphine and emerging therapies for HCV infection will also need to be investigated.

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D. Telaprevir – the Advance study, phase III results

The purpose of the Advance study was to assess the effectiveness and safety of different courses of telaprevir when combined with and compared to standard therapy—a long-lasting form of interferon called peginterferon and the nuke ribavirin. Results from this trial of telaprevir suggest that when combined with peginterferon and ribavirin, telaprevir results in very high cure rates in HCV mono-infected people. Further research with telaprevir is ongoing to try to simplify the dosing of this drug, as telaprevir currently needs to be taken every eight hours.

Study details

Researchers enrolled nearly 1,000 HCV mono-infected volunteers and randomly assigned them to one of three groups. To summarize the plan for this trial, participants were treated for either 24 or 48 weeks; at the end of that time, they were monitored for an additional 48 or 24 weeks to find out if they were cured.

Participants were assigned to one of the following three treatment groups:

- **Group 1: telaprevir for 12 weeks (T12)**
telaprevir + peginterferon + ribavirin, all three drugs taken for 12 consecutive weeks, followed by peginterferon + ribavirin for 12 additional weeks, for a total of 24 weeks of treatment. At the end of week 24, if participants had an early virologic response (EVR)—that is, if HCV viral load became undetectable or fell at least 100-fold compared to baseline—they were not given any further therapy and they were monitored for 48 more weeks to see if they achieved a sustained virologic response (SVR) or cure. If they did not achieve an EVR at the end of week 24, then participants were given a further 24 weeks of peginterferon + ribavirin (for a total of 48 weeks of treatment), followed by 24 weeks of monitoring to see if they achieved an SVR or cure.
- **Group 2: telaprevir for 8 weeks (T8)**
telaprevir + peginterferon + ribavirin, all three drugs taken for 8 consecutive weeks, followed by peginterferon + ribavirin for 16 additional weeks, for a total of 24 consecutive weeks of treatment. At the end of week 24, those participants with an EVR were then monitored for 48 more weeks. People who did not have

an EVR at week 24 received a further 24 weeks of peginterferon + ribavirin (for a total of 48 weeks of treatment). This was then followed by 24 additional weeks of monitoring to assess if they achieved an SVR or cure.

- **Group 3: peginterferon + ribavirin (PR) only**
Participants received standard therapy with peginterferon + ribavirin for 48 consecutive weeks, followed by 24 weeks of monitoring to assess the durability of their SVR or cure.

Drugs and placebo

Telaprevir was given at a dose of 750 mg every eight hours; ribavirin at a dose between 1,000 and 1,200 mg (depending on body weight) taken in two divided doses each day; and peginterferon-alpha-2a was used at a dose of 180 mcg injected once weekly. For part of the beginning of the study, some participants in groups 1 and 2 received placebo instead of telaprevir.

HCV testing

The assay used to detect HCV was the Roche Taqman version 2. This test has a lower limit of quantification of 25 international units (IU)/ml. That is, it can accurately report copies of HCV as low as 25 IU/ml of blood.

There were about 360 participants assigned to each of the study's groups. The average profile of participants when they entered the study (baseline) was as follows:

- 40% females, 60% males
- main ethno-racial groups were as follows:
90% White, 8% Black
- age – 50 years
- proportion with a high baseline HCV viral load (800,000 IU/ml or greater) – 77%
- proportion of volunteers with severe liver damage (cirrhosis) – 15%

Common HCV sub-types were as follows:

- sub type 1a – 59%
- sub type 1b – 40%

Results—Dropouts

Volunteers withdraw or drop out of a study for many reasons—including severe side effects and lack of effectiveness of therapy—and these withdrawals can affect the results of the study. Overall, the proportions of participants who

dropped out from the study groups were as follows:

- T12: 26% withdrew
- T8: 29% withdrew
- PR: 44% withdrew

Among the people who dropped out of the study, people who received telaprevir were less likely to leave because of treatment failure. Here are the discontinuations in each group due to virologic failure:

- T12 – 10% (38 participants)
- T8 – 11% (40 participants)
- PR – 33% (116 participants)

Among telaprevir users, 10% left because of side effects, while 7% of people who received peginterferon + ribavirin alone left because side effects.

Sustained virologic response (SVR) or cure

The term SVR refers to people who have cleared HCV for 24 consecutive weeks since they last received therapy. Traditionally, this is the period after 48 weeks of consecutive therapy when HCV virus levels are monitored in clinical trials. In general, 72 weeks after entering a clinical trial (24 weeks after therapy has ended), if HCV remains below the level of quantification, a person is considered cured. SVR rates in each group were as follows:

- T12 – 75% cured
- T8 – 69% cured
- PR – 44% cured

These differences in SVR rates between telaprevir-containing regimens and standard therapy were statistically significant; that is, they were not likely due to chance alone.

Due to their genes, some people of African descent may not have as good a response to HCV therapy as people of other ethno-racial groups. However, in the Advance study, high rates of SVR were seen in Black people who received telaprevir.

Results—Rapid clearance of HCV

A rapid virologic response (RVR) occurs when HCV becomes undetectable after four weeks of therapy. People who develop an RVR are highly likely to experience an SVR with continued therapy. However, not getting an RVR does not predict the future failure of therapy.

In the Advance study, participants who received telaprevir were more likely to have an RVR. Participants who had an RVR in this study were distributed as follows:

- T12 – 68%
- T8 – 66%
- PR – 9%

Another phrase sometimes used is early virologic response (EVR). This occurs when HCV levels are either undetectable at week 12 or have decreased at least 100-fold from baseline at week 12. When an EVR does not occur in HCV-infected people who are on treatment and who have HCV subtypes 1 or 4, continued therapy is unlikely to cure HCV infection. Rates of EVR were as follows:

- T12 – 58%
- T8 – 57%
- PR – 8%

These findings attest to the powerful antiviral activity of telaprevir-containing regimens.

Results—Relapse

Suppression of HCV might occur early in the course of treatment only to later rebound; this is called relapse. Rates of relapse were very low among participants who received telaprevir compared to standard therapy:

- T12 – 6%
- T8 – 8%
- PR – 27%

Liver damage

In general, among people in Advance, the less pre-existing liver damage they had, the better their response to therapy, though even in people with a moderate degree of liver damage from HCV, response rates were still generally good.

Results—Side effects

Here is the distribution of common side effects:

Fatigue

- T12 – 57%
- T8 – 58%
- PR – 57%

Itchy skin

- T12 – 50%
- T8 – 45%
- PR – 36%

Nausea

- T12 – 43%
- T8 – 40%
- PR – 31%

Anemia

- T12 – 37%
- T8 – 39%
- PR – 19%

Problems falling asleep or staying asleep

- T12 – 32%
- T8 – 32%
- PR – 3%

Diarrhea

- T12 – 28%
- T8 – 32%
- PR – 22%

Side effects—Focus on the skin

Itch and rash were relatively common side effects in the Advance study. Here is the distribution of rash:

Any severity of rash (ranging from mild to life-threatening)

- T12 – 56%
- T8 – 53%
- PR – 37%

Severe rash

- T12 – 6%
- T8 – 3%
- PR – 1%

Rash so uncomfortable that people had to quit the trial

- T12 – 7%
- T8 – 5%
- PR – 1%

Focus on anemia

Less-than-normal levels of hemoglobin were more common in telaprevir users.

- T12 – 36%
- T8 – 40%
- PR – 14%

Anemia related to telaprevir use resolved over time, as this drug was only used for between eight and 12 weeks.

Summary

Overall, telaprevir-based regimens were associated with higher rates of recovery from HCV infection compared to standard therapy. These rates of recovery were unaffected by race or ethnicity.

Taking telaprevir for 12 weeks was associated with better results than taking it for eight weeks. Common side effects included itchy skin, rash, nausea, anemia and diarrhea. Telaprevir is likely to be approved in 2011 in the U.S. and in 2012 in Canada. As telaprevir needs to be taken every eight hours, research with this compound is still ongoing as the developer, Vertex, tries to find ways of simplifying the number of required daily doses.

REFERENCE:

Jacobson IA, McHutchison JG, Dusheiko GM, et al. Telaprevir in combination with peginterferon alfa-2a and ribavirin in genotype 1 HCV treatment-naïve patients: Final results of phase 3 Advance study. In: Program and abstracts of the *61st Annual Meeting of the American Association for the Study of Liver Diseases*, 29 October–2 November 2010, Boston, MA. Abstract 211.

E. Disappearing resistance with telaprevir – the Extend study

In the Extend study, researchers enrolled volunteers from several previous studies of telaprevir into a multinational three-year study to evaluate the following issues:

- the durability of a sustained virologic response (SVR)
- changes in HCV resistance to telaprevir among people who did not achieve an SVR
- complications

In previous trials researchers detected HCV that was resistant to telaprevir in participants who did not achieve an SVR, specifically in the HCV NS3 protease gene. So research on HCV drug resistance is important in helping researchers understand how best to use telaprevir and other emerging therapies.

Participants in Extend were assessed at the start of the study (baseline) and six months later, and thereafter, once yearly for up to three years in some cases. For the interim analysis reported here, researchers focused on 123 participants who achieved an SVR and 79 others who did not.

Results—SVR

After an average of two years in Extend, researchers found that SVRs were durable, with 122 out of 123 people (99.2%) continuing to have undetectable HCV. The lower limit of quantification of the assay used was 25 IU/ml.

Among participants with an SVR, no major clinical events occurred.

Results—No SVR

Among 79 participants who did not have an SVR, 56 had blood samples available for analysis. Here are some of the complications that ensued among participants without an SVR:

- two people developed severe liver complications – liver cancer in one person with severe pre-existing liver damage and the other person developed HCV-related buildup of waste materials in his blood, which severely affected his brain (HCV encephalopathy).

Initially, various mutations in the HCV protease gene (NS3) were detected in 7% to 45% of people (depending on the mutation). However, after about two years of monitoring, resistant virus could not be found in about 90% of participants.

REFERENCE:

Zeuzem S, Sulkowski MS, Zoulim F, et al. Long-term follow-up of patients with chronic hepatitis C treated with telaprevir in combination with peginterferon Alfa-2a and ribavirin: interim Analysis of the Extend study. In: Program and abstracts of the *61st Annual Meeting of the American Association for the Study of Liver Diseases*, 29 October–2 November 2010, Boston, MA. Abstract 227.

F. Boceprevir – the Sprint study, phase III results

Boceprevir, previously called SCH503034, has demonstrated antiviral activity against HCV in smaller studies. The purpose of the Sprint study was to assess two different ways of using boceprevir when added to standard therapy (peginterferon + ribavirin) and also to compare boceprevir-containing regimens to standard therapy in large number of people.

Study details

None of the participants had been previously treated for HCV. Once enrolled, they were randomly assigned to one of the following groups:

- Group 1 (control): 4 weeks of therapy with peginterferon + ribavirin, followed by 44 weeks of peginterferon + ribavirin + placebo, for a total of 48 weeks of therapy. After this, participants were monitored for an additional 24 weeks. At the end of 24 weeks of monitoring they were then assessed for HCV viral load.
- Group 2 (boceprevir + standard therapy): 4 weeks peginterferon + ribavirin, followed by 44 weeks of boceprevir + peginterferon + ribavirin,

for a total of 48 weeks of therapy. After this, participants were monitored for 24 more weeks. At the end of this period, they were then assessed for HCV viral load.

- Group 3 (boceprevir response-guided therapy): 4 weeks of peginterferon + ribavirin, followed by 24 weeks of boceprevir + peginterferon + ribavirin, for a total of 28 weeks of therapy. At the end of 28 weeks, if HCV viral load was undetectable, therapy was discontinued and participants were monitored for 48 weeks. If at the end of 28 weeks HCV viral load was still detectable, participants received an additional 20 weeks of peginterferon + ribavirin. At the end of 20 weeks, therapy was stopped and participants were monitored for 24 more weeks and then assessed for HCV viral load.

The average profile of 1,098 study participants at the start of the study was as follows:

- 40% females, 60% males
- age – 50 years
- more than 90% of volunteers had HCV viral loads greater than 400,000 IU/ml at baseline
- major ethno-racial groups: researchers classified 939 participants as “non-Black” and 159 others as “Black”

Common HCV sub types were as follows:

- genotype 1a – 60%
- genotype 1b – 36%

Results—Recovery from HCV infection

Due to genetic factors, people of African ancestry tend to have a poorer response to HCV therapy than people of other ethno-racial groups, so the study team analysed the results of this study based on race and ethnicity.

Sustained virologic response (SVR) among non-Black people:

- Group 1 (peginterferon + ribavirin) – 42% SVR
- Group 2 (boceprevir + 48 weeks peginterferon + ribavirin) – 71% SVR
- Group 3 (boceprevir response-guided therapy) – 70% SVR

SVR among Black people:

- Group 1 (peginterferon + ribavirin) – 23% SVR
- Group 2 (boceprevir + 48 weeks peginterferon + ribavirin) – 53% SVR
- Group 3 (boceprevir response-guided therapy) – 42% SVR

SVRs were even greater among non-Black people whose HCV viral load fell by at least one log at week 4 compared to baseline:

- Group 1 (peginterferon + ribavirin) – 52% SVR
- Group 2 (boceprevir + 48 weeks peginterferon + ribavirin) – 82% SVR
- Group 3 (boceprevir response-guided therapy) – 82% SVR

Results—Week 8 seems to be a critical time

Here are the proportions of participants who subsequently achieved SVR among those whose HCV viral load at week 8 was undetectable or detectable:

- Group 1 (peginterferon + ribavirin) – 86% SVR when viral load was undetectable
- Group 1 (peginterferon + ribavirin) – 31% SVR when viral load was detectable
- Group 2 (boceprevir + 48 weeks peginterferon + ribavirin) – 91% SVR when viral load was undetectable
- Group 2 (boceprevir + 48 weeks peginterferon + ribavirin) – 43% SVR when viral load was detectable
- Group 3 (boceprevir response-guided therapy) – 89% SVR when viral load was undetectable
- Group 3 (boceprevir response-guided therapy) – 43% SVR when viral load was detectable

Results—SVR

Very high rates of SVR subsequently occurred among boceprevir users whose HCV was undetectable during weeks 8 to 24, as follows:

- boceprevir + peginterferon + ribavirin – 96% SVR
- boceprevir response-guided therapy – 97% SVR

Safety

There were six deaths during the study, distributed as follows:

- Group 1 (peginterferon + ribavirin) – four deaths
- Group 2 (boceprevir + peginterferon + ribavirin) – one death
- Group 3 (boceprevir response-guided therapy) – one death

The overall proportion of participants who stopped taking therapy in each group during the study was as follows:

- Group 1 (peginterferon + ribavirin) – 16%
- Group 2 (boceprevir + peginterferon + ribavirin) – 16%
- Group 3 (boceprevir response-guided therapy) – 12%

The proportion of participants who left the study because of anemia was as follows:

- Group 1 (peginterferon + ribavirin) – 1%
- Group 2 (boceprevir + peginterferon + ribavirin) – 2%
- Group 3 (boceprevir response-guided therapy) – 2%

The proportion of participants whose hemoglobin levels fell between 10 and 8.5 g/dL in each group was as follows:

- Group 1 (peginterferon + ribavirin) – 26%
- Group 2 (boceprevir + peginterferon + ribavirin) – 41%
- Group 3 (boceprevir response-guided therapy) – 45%

Most side effects were roughly evenly distributed among all three study groups, except for these two, which were more common in boceprevir users:

- anemia
- altered sense of taste

Summary

Twenty-four weeks of boceprevir-based response-guided therapy was as effective as 44 weeks of boceprevir + peginterferon + ribavirin. High rates of SVR from HCV infection were subsequently observed in boceprevir users (between 78% and 89%) who had an undetectable HCV viral load by week 8. These high rates of SVR demonstrate the potency of boceprevir.

The response to the first four weeks of peginterferon + ribavirin therapy allows for the prediction of SVR based on early response to this therapy.

Boceprevir needs to be taken at a dose of 800 mg three times daily and is associated with an increased risk for temporary side effects such as anemia and altered sense of taste.

Boceprevir is likely to be approved in 2011 in the U.S. and in 2012 in Canada. As it needs to be taken three times daily (about every 8 hours), research with this compound is still ongoing as the developer, Merck, tries to find ways of simplifying the number of required daily doses.

REFERENCE:

Poordad F, McCone J, Bacon BR, et al. Boceprevir (BOC) combined with peginterferon alfa-2b/ribavirin (P/R) for treatment-naïve patients with hepatitis C virus (HCV) genotype (G) 1: Sprint-2 final results. In: Program and abstracts of the *61st Annual Meeting of the American Association for the Study of Liver Diseases*, 29 October–2 November 2010, Boston, MA. Abstract LB-4.

G. Boceprevir – effective in previous non-responders

In the past, some HCV-positive people may have undergone treatment with standard therapy but did not recover from this infection. Researchers refer to such people as “non-responders.” People with HCV genotype 1 are traditionally the least responsive to therapy.

In the Respond 2 study, researchers compared two strategies for trying to increase recovery from HCV infection. Participants were divided into the following three groups:

- **Group 1 (control):** 4 weeks of therapy with peginterferon + ribavirin, followed by 44 weeks of peginterferon + ribavirin + placebo, for a total of 48 weeks of therapy. After this, participants were monitored for an additional 24 weeks. At the end of 24 weeks of monitoring, they were then assessed for HCV viral load.
- **Group 2 (boceprevir + standard therapy):** 4 weeks of therapy with peginterferon + ribavirin, followed by 44 weeks of boceprevir + peginterferon + ribavirin, for a total of 48 weeks of therapy. After this, participants were monitored for an additional 24 weeks. At the end of this period, they were then assessed for HCV viral load.
- **Group 3 (boceprevir response-guided therapy):** 4 weeks of peginterferon + ribavirin, followed by 32 weeks of boceprevir + peginterferon + ribavirin, for a total of 36 weeks of therapy. At the end of 36 weeks, if HCV viral load was undetectable, therapy was discontinued and participants were monitored

for a 36 more weeks. If at the end of the initial 36 weeks of therapy HCV viral load was still detectable, participants received a 12 more weeks of peginterferon + ribavirin. At the end of this time, therapy was stopped and participants were monitored for 24 more weeks and then assessed for HCV viral load.

The average profile of participants who entered the Respond 2 study was as follows:

- age – 43 years
- 35% females, 65% males
- HCV genotypes 1a and 1b were common
- 90% of participants had an HCV viral load greater than 800,000 IUs/ml
- 35% of participants were described as non-responders to prior HCV therapy and the remaining 65% had relapsed under previous therapy

Boceprevir was taken at a dose of 800 mg three times daily.

Results—Sustained virologic response (SVR)

Overall, SVRs were distributed among the three treatment groups as follows:

- Group 1 (control; peginterferon + ribavirin) – 21% achieved an SVR while 32% relapsed
- Group 2 (boceprevir + standard therapy) – 66% achieved an SVR while 12% relapsed
- Group 3 (boceprevir response-guided therapy) – 59% achieved an SVR while 15% relapsed

Results—SVR according to the HCV detectability at week 8

- Group 1 (control; peginterferon + ribavirin) – 100% of participants whose viral load was undetectable achieved an SVR, while 12% of participants whose viral load was detectable achieved an SVR
- Group 2 (boceprevir + standard therapy) – 88% of participants whose viral load was undetectable achieved an SVR, while 40% of participants whose viral load was detectable achieved an SVR
- Group 3 (boceprevir response-guided therapy) – 88% of participants whose viral load was undetectable achieved an SVR, while 43% of participants whose viral load was detectable achieved an SVR

Overall, boceprevir increased the chances of participants achieving an SVR.

Results—According to response to prior therapy

Among non-responders to previous peginterferon + ribavirin, here is the proportion who achieved an SVR in the present study:

- Group 1 (control) – 7%
- Group 2 (boceprevir + peginterferon + ribavirin) – 52%
- Group 3 (boceprevir response-guided therapy) – 40%

Among people who relapsed when previously treated with peginterferon + ribavirin, here is the proportion who achieved an SVR in the present study:

- Group 1 (control) – 29%
- Group 2 (boceprevir + peginterferon + ribavirin) – 75%
- Group 3 (boceprevir response-guided therapy) – 69%

Results—According to changes in HCV viral load at week 4

In boceprevir studies, including the present one, for the first four weeks of therapy participants received peginterferon + ribavirin. The purpose of this lead-in phase of peginterferon is to assess participants' ability to respond to peginterferon and assess any changes in HCV viral load. Among participants in the present study whose HCV viral loads fell by at least one log after the first four weeks of therapy (in other words, who had a significant response to peginterferon), SVRs were as follows:

- Group 1 (control; peginterferon + ribavirin) – 25%
- Group 2 (boceprevir + peginterferon + ribavirin) – 79%
- Group 3 (boceprevir response-guided therapy) – 73%

Results—Safety

One death occurred during the Respond 2 study in a person who received boceprevir.

Most side effects were evenly distributed across all three groups, except for these which were more common among boceprevir users:

- anemia
- altered sense of taste

Anemia occurred as follows:

- Group 1 (control; peginterferon + ribavirin) – 20%
- Group 2 (boceprevir + peginterferon + ribavirin) – 46%
- Group 3 (boceprevir response-guided therapy) – 43%

Altered sense of taste occurred in the following proportion of participants:

- Group 1 (control; peginterferon + ribavirin) – 11%
- Group 2 (boceprevir + peginterferon + ribavirin) – 43%
- Group 3 (boceprevir response-guided therapy) – 45%

Summary

The use of boceprevir significantly increased the changes of SVR even in participants who had not previously responded to peginterferon therapy. Both strategies of boceprevir use (reponse-guided and taking it for 44 weeks) seemed equally effective in people whose previous treatment with peginterferon + ribavirin had failed.

As in other studies, boceprevir was associated with an increased risk of anemia and altered sense of taste in the present study.

REFERENCE:

Bacon BR, Gordon SC, Lawitz E, et al. HCV Respond-2 Final Results: High sustained virologic response among genotype 1 previous non-responders and relapsers to peginterferon/ribavirin when re-treated with boceprevir plus Pegintron (peginterferon alfa-2b)/ribavirin. In: Program and abstracts of the *61st Annual Meeting of the American Association for the Study of Liver Diseases*, 29 October–2 November, 2010, Boston, MA.

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