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Roche Dramatically Reduces Cost of Hepatitis C Combination Therapy

By Alan Franciscus
Editor-in-Chief

On January 13th 2003, Roche announced that Copegus™ (Roche's ribavirin in tablet form), the drug studied by Roche in combination with Pegasys® (peg interferon alfa-2a) for the treatment of chronic hepatitis C, is being introduced into the U.S. market with a list price or wholesale acquisition cost that is 43 percent less per milligram than the other available brand of ribavirin (Rebetol, licensed to Schering Plough by ICN).

Copegus will be available in U.S. pharmacies beginning the week of January 13. The list price or wholesale acquisition cost for Copegus is \$5.06 per 200mg tablet which is equivalent to the cost of ribavirin in 1998. In August 1998, branded ribavirin (Rebetol) was only available in combination with Intron A, packaged as Rebetrone. To extrapolate the August 1998 price of branded ribavirin, the following calculation was performed on a comparable 1200mg pack: 1998 Rebetrone price (\$1,200 for 4 weeks of treatment with 1200mg daily ribavirin and Intron A 3 times per week) minus the 1998 Intron A price (\$349.30 for 4 weeks of treatment with Intron A 3 times per week) = \$850.70 for 4 weeks of treatment with 1200mg per day of branded ribavirin. Pricing is based on published wholesale acquisition costs by First Data Bank in August 1998. The current price of Rebetol was obtained from First Data Bank on January 6, 2003. For patients prescribed 1200mg of ribavirin per day, there is a list price or wholesale acquisition cost savings with Copegus of approximately \$7,600 for 48 weeks of therapy. Copegus is available as a 200mg tablet, and is administered orally two times a

day as a split dose.

Roche has thrown down the gauntlet to Schering-Plough by pricing Copegus (ribavirin) at 57% of the US price of branded capsule ribavirin (Rebetol), but is this enough to start a price war between the two pegylated interferon and ribavirin manufacturers, Roche and Schering Plough? There are pros and cons to such a price war; although it will have the potential to drive the cost of hepatitis C therapy down considerably, it also has the potential to devalue the combination pegylated interferon franchise to a point where neither company will have a large enough revenue stream to reinvest back into a disease marketplace that is fundamentally being ignored by the government. It is the hope of the HCV community that the strategy initiated by Roche in their progressive pricing of Copegus will only be beneficial for people challenged everyday by hepatitis C, and that this initiative will be appropriately responded to by Schering Plough, resulting in hepatitis C treatment being more financially accessible to all.

The Copegus pricing move by Roche follows last October's US approval of Roche's Pegasys (peg interferon alfa-2a) for hepatitis C monotherapy, when the company said it would provide, free of

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A Child's Perspective on *My Mom Has Hepatitis C*, by Hedy Weinberg and Shira Shump

Part II of this book review is written by a ten-year-old child who, like so many children, has felt the impact of someone close to them having chronic hepatitis C. The review includes the perceptions that they had of hepatitis C prior to reading the book My Mom Has Hepatitis C as well as those they had after reading the book.

The Hepatitis C Support Project asked me to read this book and tell them how it helped me to better understand hepatitis C. Before I read the book I knew quite a lot about the disease as my mommy's best friend has hepatitis C. Hepatitis C is a virus that hurts the liver and because the liver removes the poisons from our body when our liver is sick the poisons stay in the body and make people with hepatitis C feel very tired, nauseous and sometimes cranky. My mom's best friend spends a lot of time in bed and can't do fun things with us often as he does not have the energy. I know my Mom worries a lot about him. I worry mostly that he will die and my mom won't have a best friend anymore. My mommy is a bit happier at the moment as he is going to go on medicine. I've been told that the medicine is injections that will make him even sicker for a while and that he will have to take the injections for a year. Mommy has told me that even if the hepatitis C doesn't go away the medicine will help his liver be better. I really hope that the medicine works as he can make my mommy laugh and he is so much fun when he isn't sick and tired.

After I had read the book *My Mom Has Hepatitis C* I had so many questions that I wanted to ask. I thought it was rude before to ask how he got hepatitis C but the mom in the book explained it and so now I wanted to know. I used to worry that my mommy would catch hepatitis C and be very sick too but I now understand that mommy or I can only get hepatitis C if our blood touches the blood of someone who has hepatitis C. We will be careful to put a Band-Aid on mommy's friend's cuts. I also learned that there is a test that can be done to see how much the hepatitis C virus has hurt the liver. It is called a liver biopsy and what the doctor does is he takes a little bit of the liver and looks at it under a microscope to see how healthy it is and if the virus has

caused damage. In the book the mommy gets rid of the virus with the injection medicine that my mommy's friend is going to take for a year. There was another person in the book whose liver was so sick from hepatitis C that they gave him another person's liver who died and this helped him get much better. I know this is now called a liver transplant and that the liver is one of the organs in our body that can be transplanted to another person.

I am happy that I got to read this book because I now understand much more about hepatitis C and so I don't feel so scared.

Pegasys *Continued from page 1*

charge, three months of Pegasys therapy for the first 15,000 patients. Despite this free-product launch, Roche was the target of scrutiny and disappointment from the HCV and HIV communities. The communities had been falsely led to believe that Roche would price Pegasys at a considerable discount to Peg-Intron (peg interferon alfa-2b), which they felt was very overpriced, and not at an equivalent price, as Roche ultimately did. For this reason, Roche's free drug launch was far from altruistic in the community's eyes but rather a tactic to divert attention from the fact that they were introducing a product into the disease market at a price that the market could not bear, ignoring the advice of a community they had courted for support for years.

Pegasys in combination with Copegus was approved in the US on December 3, 2002. From the recent launch of free drugs and now a drastic discount in the pricing of Copegus it appears that Roche is not only trying to overcome the fact that Pegasys is entering the US market two years behind Schering-Plough's competing hepatitis C product, Peg Intron, but also that they have responded to the pleas of the HCV and HIV communities who both recognize the importance of access to care for the hepatitis C epidemic and the need for more reasonable pricing to help make that a possibility.

What Did We Learn From AASLD ?

Part 3

By Alan Franciscus
Editor-in-Chief

Part three focuses on what we learned about future therapies for the treatment of hepatitis C at the 2002 AASLD conference. This is an important area because in the past few years we have experienced the introduction of pegylated interferons in combination with ribavirin, but many patients with this combination will still not eradicate virus. The published data to date has shown that there is still going to be approximately 35% of the naïve HCV population (those who have never been treated with interferon) who will not clear the virus with the pegylated interferon plus ribavirin combination (and this percentage rises to about 50% in the patients that have genotype 1 hepatitis C—the most common genotype in the United States). There is minimal data on the use of pegylated interferon and ribavirin in the treatment of hepatitis C in relapsers and non-responders (these are patients who either initially cleared the virus on therapy but in whom the virus returned when the therapy was discontinued or patients whose viral load did not decline at all while on treatment), and the data available is not that impressive, with SVR's in the range of 10-25% and outcomes obviously going to be less favorable for genotype 1, advanced liver disease, high viral load, etc.

Targets for Future HCV Drug Development

At AASLD 2002 Keeney and colleagues talked about a judicious plan for drug development to customize therapies for HCV infection. In their analysis, they identified the enzyme NS3 helicase as a future prospective site of drug development. This enzyme is a bi-functional protein possessing an N-terminal protease activity and a C-terminal NTP-dependent helicase activity that unwind nucleic acid complexes in a reaction energized by the hydrolysis of nucleoside triphosphates. During HCV replication, the HCV helicase unwinds the duplex RNA to produce the positive-sense single-stranded DNA, in order to expose part of the nucleic acid binding site. In this analysis the investigators hypothesized that two strictly conserved phenylalanines (F438 and F444) may perhaps help transmit conformational changes that take place upon ATP hydrolysis to allow the helicase

to translocate along the DNA template. When both H438 and F444 are mutated to alanine, the protein has no evident activity and replication does not occur. This work certainly shows the advances recently made in the drug development of potential future therapies for hepatitis C.

Next Generation Ribavirin

One of the most common side effects of ribavirin is the occurrence of hemolytic anemia that results in such symptoms as fatigue, irritability, angina, and even myocardial infarction. Ribavirin, once absorbed, is transported into red blood cells and phosphorylated, where it accrues over time. This accrual leads to the development of hemolytic anemia which then requires dose reduction or discontinuation in as many as 30% of treated patients.

Researchers are studying new forms of ribavirin that may be more effective and less toxic in the body. One of these, viramidine, is a prodrug of ribavirin that must be processed within the body to become active, and the other is Levovirin, an L-isomer of ribavirin.

At AASLD 2002, Yeh and colleagues presented a study which compared the red blood cell concentrations of viramidine with standard interferon in healthy volunteers. Initial studies have shown that viramidine cannot enter the human red blood cell until it is converted to ribavirin. This study found that a dose of viramidine similar to that of standard ribavirin resulted in 2.4 times less total ribavirin accruing in red blood cells. This finding suggests that viramidine may result in a lesser degree of hemolytic anemia than does standard ribavirin. Viramidine potentially would allow for greater serum ribavirin concentrations with fewer side effects, leading to improved sustained response rates and greater patient adherence to therapy.

In another study presented at AASLD 2002, Lau and associates reported on the safety and pharmacokinetic profiles of viramidine in patients with hepatitis C. These investigators determined that viramidine at doses up to 800mg given twice daily for four weeks is safe and well tolerated. No significant changes in the hemoglobin levels were seen in the viramidine group.

The data presented at AASLD 2002 confirms that viramidine-derived ribavirin has a much lower probability for inducing hemolytic anemia than standard

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Questions to Ask Your Medical Provider

Part 2 of a Three-Part Series on Health Self-Advocacy

By Lucinda K. Porter, RN, CCRC

Last month's HealthWise column explored some ways to enhance your effectiveness while communicating with your physician and health care team. This month's column offers a list of questions you might want to add to your own list of issues. You can prepare for your medical appointment by prioritizing and writing down your questions.

Before you start with your list, ask your practitioner how much time she has for questions. Respect the time constraints that the practitioner has and you will benefit in the long run. Some of these questions can be answered over the phone by the office staff, thus saving precious face-to-face time.

1. Is your insurance accepted? If so, be certain you understand any co-pays, deductibles, or other out-of-pocket costs for which you may be responsible. Does the office bill your insurance or will you need to pay the fee directly and manage the insurance reimbursement yourself?

2. If you are seeing a nurse practitioner or physician assistant, then who is the physician overseeing his/her practice?

3. Which hospitals is the physician affiliated with?

4. How can the physician be contacted for emergencies?

5. What are the physician's feelings about second opinions?

6. Are there certain diseases that you are more susceptible to because of your ethnic background or health history? Does the doctor need to test for these?

7. If your doctor makes a treatment suggestion and it is not one that you are prepared to follow, ask about the alternatives.

8. If medication is prescribed, what are the side effects, and how should the medication be taken?

9. If one of the pegylated interferons with ribavirin is prescribed for treatment of chronic hepatitis C virus (HCV) infection, ask why this particular medication was recommended rather than that of a different manufacturer.

10. Ask how the practitioner manages some of the side effects of HCV therapy, particularly depression, insomnia, neutropenia, and anemia.

11. Discuss the follow-up plan – If you are scheduled to have diagnostic tests, ask the doctor when you can expect the results and how these results are conveyed to you. If the results are going to be disclosed at your next appointment and if there is going to be a long interval between appointments, ask how you can obtain earlier results. Additionally, ask the physician what the best way is to contact his office should a need arise that may not require an office visit.

12. If you run out of time and still have more questions on your list, ask how you might be able to get the answers to your questions without disrupting the physician's schedule. Ask the physician if there are resources he would recommend.

Coming next month: Preparing for HCV Treatment

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HealthWise

HCV Advocate

Alan Franciscus.....Founder/Editor-in-Chief
e-mail: sfhepcat@msn.com
C.D. Mazoff, PhD..Webmaster/Managing Editor
e-mail: cdmazoff@hcvadvocate.org
Liz Highleyman.....Contributing Editor
Janya H. Maxwell..Contributing Editor

Back To Life A group dedicated to providing patient education and support.
Orange County.....Carol Craig 949-654-4250

You may contact us at:

P.O. Box 427037

San Francisco, CA 94142-7037

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Hepatitis C Support Project - A Tides Center Project

Hepatitis C and Smoking

By Ian Campsall, MA

We all know that smoking is bad for us. Between the recent disclosures by tobacco industry insiders revealing the deliberate increases in nicotine levels, and numerous studies tracking the health of long-term smokers, there is little room left for debate about the consequences of the habit. It is true that science is not able to predict the probable effects on a single individual. However, sufficient studies have been conducted, and sufficient information has been gathered to arrive at an undeniable mean average—smoking is harmful. If you smoke, or if you expose yourself to second-hand smoke, you are impairing your body's ability to function properly.

At a conference held in Seattle in June of this year by the International Agency for Research on Cancer, a branch of the World Health Organization, a panel of experts concluded that tobacco smoke causes cancer in many more parts of the body than was previously believed. While smoking has been established as a leading cause of cancer, it is only now, when researchers have been able to track more than one generation of smokers, that they have been able to arrive at a complete understanding of the dangers of tobacco.

The study conducted by the IARC is the first major examination of the accumulated research on tobacco smoke and cancer since 1986. The researchers combined the results of more than 3000 studies involving millions of people, which allowed them to draw conclusions that were not possible in previous smaller studies. The twenty-nine experts representing twelve countries stated their new findings indicated that tobacco plays a much more prominent role in types of cancer already linked to smoking than was previously thought. Dr Paul Kleihues, director of the UN Cancer Research Agency, said: "For example, for tumors of the bladder and the renal pelvis, previously we thought the elevated risk was maybe three to four times that of a non-smoker. Today, it looks like the risk is elevated five to six times."

Cancers of the breast and endometrium, or lining of the womb, which scientists had believed to be connected to smoking, were found to be unrelated. Prostate cancer has not been studied, but the group did not believe it is caused by tobacco. However, *cancers of the stomach, liver, cervix, uterus, kidney, nasal sinus, and myeloid leukemia were found to be directly linked to smoking.* Cancers already identified as being caused

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ribavirin. This lower probability is due to the reduced interaction of viramidine with red blood cells. The pharmacokinetic effects of taking viramidine with food or on an empty stomach did not appear to be clinically important. To date it appears that viramidine has all the benefits of ribavirin but with a much more desirable side effect profile.

Ribozymes

Heptazyme is a nuclease-stabilized ribozyme that targets the 5' UTR (untranslated region) of the hepatitis C RNA genome. In preliminary cell culture studies it has shown antiviral activity against hepatitis C alone or in combination with interferon.

At AASLD 2002 a primary study was presented on the use of Heptazyme alone in doses of either 50 mg/m² twice daily or 100 mg/m² twice daily in patients with chronic hepatitis C. This primary study showed that treatment with the 50-mg/m² twice-daily dose was safe, without any associated serious adverse events. There were, however, no significant reductions in HCV-RNA seen in this group. Among patients receiving the higher dose of the nuclease-stabilized ribozyme, 9% had a greater than 0.5-log reduction in HCV-RNA levels, with the maximum being a 1.7-log reduction. There were no patients in this study in whom HCV-RNA became undetectable.

Due to a combination of findings from the chronic monkey toxicology study and the clinical results of this trial presented at AASLD 2002, this nuclease-stabilized ribozyme will no longer be tested in trials for the treatment of hepatitis C.

HCV Enzyme Inhibitors

The ideal targets for new drug therapies are viral enzymes which are crucial for HCV replication. If these enzymes are inhibited and their action stopped, HCV cannot multiply and infect new cells. This approach has been quite successful in HIV treatment, which serves as a reasonable disease model for hepatitis C drug development. Unfortunately, HIV protease is aspartase based, while HCV protease is serine based; therefore, HIV type protease inhibitors have no effect on HCV replication. As with HIV, the use of HCV viral enzyme inhibitors would likely promote the development of drug-resistant HCV, especially if used as monotherapy.

HCV has three likely target enzymes: protease, helicase, and polymerase. Each is necessary for a crucial step in virus replication. The crystal structure of the

HCV NS3 protease enzyme was first written about in 1996; however, an effective HCV protease inhibitor has not yet been developed. Other HCV proteases, NS4A and NS43, are also possible drug targets. HCV polymerase inhibitors will be the first HCV enzyme inhibitor drugs tested in humans. A number of research teams have described the three-dimensional structure of these enzymes and have developed various inhibitors, which have been studied in animals.

BILN 2061 is a small, selective, and potent inhibitor of the NS3 serine protease. It is intended that blockage of this site will stop hepatitis C viral replication. BILN 2061 possesses C-terminal carboxylic acid activity functionality that provides selectivity of action. Overall, BILN 2061 was found to have potent activity in vitro towards the NS3 serine proteases of hepatitis C genotypes 1a and 1b. Based on this information and an adequate safety profile in animal models, BILN 2061 was selected for clinical evaluation in patients with hepatitis C.

At AASLD 2002 there were a couple of reports on the use of BILN 2061 taken orally. The first was in patients infected with HCV genotype 1 who had minimal fibrosis on liver biopsy. Preliminary results in 8 patients given BILN 2061, 200 mg twice daily for 2 days (a total of 4 doses), revealed a greater than 2-log drop in viral load in 7 of the 8 treated patients.

In a second study, 31 patients were treated with 25 mg, 200 mg, or 500 mg of BILN 2061 twice daily for 2 days in an open, placebo-controlled comparison. The primary end point was measurement of reduction in HCV viral load. Fourteen of the patients evaluated were treatment-naive; the remainder had received previous therapy for chronic hepatitis C infection. No safety issues were identified in the 25 patients exposed to BILN 2061. A greater than 1-log drop in viral load was noted in all treated patients. All patients treated with either the 200-mg or 500-mg regimens had at least a 2-log drop in viral load. One patient had a 3-log drop in viral titer during the 2 days of therapy. There was no difference in response seen between treatment-naive and previously treated patients. No decrease in viral load was seen in the placebo group. After cessation of therapy, viral load returned to baseline in 1-7 days. The second study presented is important because it shows dramatic decreases in viral load with only 48 hours of therapy using a novel oral compound. Additional studies with BILN 2061 as monotherapy and in combination with interferon are warranted.

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by the consumption of tobacco include those of the lungs, oral cavity, gullet, larynx, pharynx, pancreas, and the bladder.

For the person living with hepatitis C, the situation is much more complicated. As we all know, the liver's function is to process the chemicals that are introduced into the body, including alcohol and tobacco. Under normal circumstances the cytochrome P450 enzyme system converts toxic substances into nontoxic ones; however, when a hepatotoxic substance is present the reverse happens. In this situation a nonhepatotoxic substance is broken down into hepatotoxic by-products that cause liver damage as they accumulate. This means that substances such as Tylenol can, over time, begin to accelerate the degeneration of the liver. Furthermore, as different chemicals build up, treatment may become ineffective as the therapeutic drugs are broken down or their effect is nullified by the presence of other chemicals. As the toxins accumulate, they begin to circulate causing damage throughout the body. Now, in addition to having to treat the hepatitis, the doctors must take into consideration the fact that the body contains numerous unknown free radicals which may cause unexpected reactions and side-effects with medications or treatment.

Previous studies of the effects of alcohol on hepatitis C did not take into account the fact that many of the subjects were smokers as well as drinkers, and it may well be that many of the hepatotoxic effects ascribed to alcohol were actually being caused by smoking. A study published in the *Journal of Hepatology* in 2001 found that alcohol was only statistically related to liver fibrosis when smoking was NOT included as a factor in the analysis, and that this relation was independent of the other factors known to affect the course of hepatitis C, such as age, gender, and alcohol intake.

In two separate studies smoking was found to be independently related to the risk of alcoholic cirrhosis, and to the occurrence of cirrhosis in chronic HBsAg carriers. In another recent study of 122 patients with alcoholic cirrhosis smoking was linked to increased five-year mortality rates. Furthermore, tobacco consumption has been associated with an increased risk of hepatocellular carcinoma in patients with viral hepatitis.

While science has contributed greatly to the demonization of smoking, it has also recognized that nicotine is one of the most difficult addictions to kick—even

more so than heroin. This can be problematic for persons in recovery because smoking is often the only habit they can keep without returning to their previous lifestyle. However, science has also developed many effective smoking cessation programs that can help ease the symptoms of withdrawal. Furthermore, as smoking has become a prominent social issue, awareness of the difficulties involved in quitting has increased and resources to offer emotional support have been established. Now the only question that remains is whether or not you choose to make a health-positive decision, or whether you will ignore the inevitable until it can be ignored no longer.

Help with Quitting Smoking

Smoking is one of the most difficult addictions to give up. Usually people make 2 to 3 tries, or more, before finally being able to quit, but each time they try to quit, they develop new skills and strategies to prevent relapse. The success of quitting smoking depends on many factors but the most important factor is how much someone really wants to stop smoking.

Methods for Quitting

- * You can use the nicotine patch, gum or other aids
- * You can get support from family and friends
- * You can learn how to handle the urges that make you want to smoke
- * You can join a smoking cessation support group

Some Helpful Online Resources:

<http://cis.nci.nih.gov/resources/smoking.html>
<http://www.surgeongeneral.gov/tobacco/>
http://www.lungusa.org/tobacco/replacement_factsheet99.html
<http://www.quitnet.com/Library/Guides/NRT/bupropion.jhtml>

Additional Resources:

American Heart Association - 800-242-8721
 American Cancer Society - 404-320-3333
 American Lung Association - 212-315-8700

HBV/HIV Coinfection

By Liz Highleyman

A great deal of attention has focused recently on coinfection with hepatitis C virus (HCV) and HIV. But coinfection with hepatitis B virus (HBV) and HIV is also an important public health issue.

Coinfection refers to infection with more than one disease-causing organism. HIV, HBV, and HCV are spread in similar ways, and many people are infected with two or even all three of these viruses. All may be transmitted through blood-to-blood contact (for example, sharing used needles), but HIV and HBV are more likely than HCV to be transmitted through sex or from mother to child during pregnancy or birth. Studies show that sexual and perinatal HBV transmission are more likely if a person also has HIV. Experts increasingly recommend that people with HIV should be screened for both HBV and HCV.

Like HCV, HBV can cause serious liver disease—including cirrhosis and liver cancer—usually after many years. Most people with healthy immune systems are able to clear HBV. Only about 5% of HBV-infected adults develop chronic hepatitis B; the rate is higher—about 90%—among those infected as infants. People coinfecting with HIV, however, are 3–6 times more likely to develop chronic hepatitis than those with HBV alone. In addition, HBV genetic material remains in human cells and the virus may reactivate as immune function deteriorates.

Much remains unknown about HBV/HIV coinfection, and study results are sometimes conflicting. Studies have shown that liver damage is more common and more severe and hepatitis B disease progression is more rapid in HBV/HIV-coinfecting people than in those with HBV alone. Some researchers have shown that the risk of death due to liver complications is increased in HBV/HIV-coinfecting people, although others have not found this to be the case. On the other hand, most research indicates that HBV does not appear to adversely affect HIV disease progression. For example, Dr. Andrea de Luca and colleagues reported in the October 14, 2002 issue of the *Archives of Internal Medicine* that coinfection with HBV did not increase the risk of AIDS-defining illnesses or death. In one

small study presented at a recent medical conference, HBV coinfection was actually associated with reduced HIV replication.

Many people with chronic hepatitis B do not need treatment. Most doctors recommend against treatment for people who have low HBV viral loads, normal ALT levels, and minimal liver damage as determined by liver biopsy. HIV coinfection should not be regarded as a contraindication to HBV therapy. People with active, replicating HBV—including those with HIV—should be considered for treatment. Three drugs are currently approved to treat hepatitis B: standard interferon, 3TC (lamivudine or Epivir), and adefovir (Hepsera, just approved this past September); pegylated interferon and tenofovir (Viread) are under study, and results so far look promising.

Unlike HCV drugs, some medications used to treat HBV—notably 3TC, adefovir, and tenofovir—are also active against HIV. Coinfecting people who take 3TC as part of their HIV treatment regimen typically have lower HBV viral loads. However, use of 3TC usually leads to the development of drug-resistant HBV. Adefovir was originally developed as an HIV treatment (under the brand name Preveon), but was never approved because it caused kidney toxicity; Hepsera for HBV is used in lower doses (about one-tenth as much) and is safe. Tenofovir is already approved to treat HIV.

Several studies presented at recent conferences have shown that adefovir and tenofovir are effective treatments for people with HBV/HIV coinfection. The drugs appear active against both wild-type (non-mutated) and 3TC-resistant HBV. For example, at the 2002 International AIDS Conference, Dr. Yves Benhamou and colleagues presented data showing that HBV viral load decreased in HBV/HIV-coinfecting people after they added adefovir to their existing HIV drug regimens; about one-quarter (9 out of 35) achieved an undetectable HBV viral load and 3 out of 35 became negative for HBe antigen. ALT levels also decreased, and among those who had repeat liver biopsies over half showed reduced liver tissue damage. Even more promising, Mark Nelson and colleagues reported at a conference last

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Molecular Approaches

Antisense oligonucleotides – Antisense drugs block the synthesis of disease-causing proteins by binding with and preventing translation of RNA. In the case of HCV, an antisense oligodeoxynucleotide directed against a specific HCV genetic sequence effectively inhibits viral gene expression. This agent concentrates in the liver when given by intravenous infusion. ISIS 14803 is such a molecule. A number of people with HCV have received this antisense oligonucleotide infusion in a Phase I/II trial, which demonstrated safety and tolerability. The compound is currently in a Phase II trial to determine its efficacy.

Early studies with this compound have been promising and report a 1- to 2-log reduction in plasma HCV RNA levels in about 30% of patients treated with this intravenous therapy given thrice weekly.

There was a report at AASLD by Gordon and colleagues on the use of a 12-week course of ISIS 14803 in patients with chronic hepatitis C infection and abnormal liver biopsies. The study had 2 treatment arms: (1) Group 1 received ISIS 14803 as a 2-hour infusion of 2.5 mg/kg thrice weekly for 2 weeks followed by intravenous injections of ISIS 14803 at a dose of 4 mg/kg once weekly for 10 weeks; (2) Group 2 received ISIS 14803 as a 2-hour infusion of 2.5 mg/kg thrice weekly for 2 weeks followed by intravenous injections of ISIS 14803 at a dose of 4 mg/kg twice weekly for 10 weeks.

The results reported in this study are preliminary. To date, this compound appears to be well tolerated, with minimal adverse effects. The most frequent side effects were headache, nausea, fever, rigors, arthralgias (joint pain), and myalgia (muscle pain). One patient developed cryoglobulemic glomerulonephritis. Transitory drops in HCV-RNA viral load greater than 1 log were observed in 2 patients. Three patients had transitory increases in their alanine aminotransferase levels of up to 5 times normal, which resolved with continual therapy. Although it has been found that the antisense oligonucleotide is well tolerated, the limited reduction in viral load is very disappointing. Additional studies of this compound at higher doses to determine overall efficacy are needed and underway.

There is a lot of excitement in the HCV community as a result of the reports released at AASLD 2002 on the newer agents that are being developed and tested for the treatment of hepatitis C. In summary, Virmidine, an oral ribavirin prodrug appears to offer advantages over

standard ribavirin by a reduction in hemolytic anemia which will allow for flexibility in higher dosing. BILN 2061, an oral inhibitor of NS3 serine-protease appears to be the most promising drug on the horizon for hepatitis C, with small studies signifying considerable declines in HCV RNA viral load within just 48 hours of initiation of therapy.

HBV/HIV *Continued from page 8*

September that over half of the 18 HBV/HIV-coinfected people in their study achieved undetectable HBV viral loads when tenofovir was added to their HIV drug regimens. Both adefovir and tenofovir appear to be well tolerated, with few people discontinuing treatment due to side effects.

Coinfection with HBV can complicate HIV treatment. Many HIV drugs are metabolized by the liver, and people with existing liver damage due to chronic hepatitis are more likely to develop drug-related hepatotoxicity (liver toxicity, indicated by elevated liver enzyme levels). For example, Dr. Mark Sulkowski and colleagues reported in the January 2002 issue of *Hepatology* that over two-thirds of the cases of severe liver toxicity due to HIV drugs in their study were seen in people coinfecting with HBV or HCV. Among the HIV drugs, nevirapine (Viramune) and ritonavir (Norvir) are most often associated with liver toxicity. In addition, some HIV drugs can cause side effects similar to those of HBV drugs; for example, both interferon and AZT can cause low white blood cell counts. When these drugs are used together, worse side effects can result. Finally, much of the liver damage associated with hepatitis B is due to the immune system's response to the virus, rather than the activity of HBV itself. Starting HIV treatment can sometimes cause liver enzyme "flares" in people with HBV as the HIV drugs promote immune recovery.

Whenever possible, the care of people with HBV/HIV coinfection should be managed by a doctor who has experience with both diseases, or a team that includes both a hepatologist (liver disease specialist) and an infectious disease expert. Given the promising results of recent drug trials, use of 3TC together with adefovir or tenofovir should lead to less drug-resistant HBV and better treatment outcomes for HBV/HIV-coinfected people. With careful monitoring, most people with hepatitis B and HIV can be successfully treated for both diseases.

Clinical Trials

National Trials

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Northern California

University of California, Davis
Dr. Rossaro (916) 734-8696
University of San Francisco Medical Center
Stephanie Straley, PA (415) 353-2328
VA Hospital-UCSF
(415) 750-2105
California Pacific Medical Center
(415) 600-1100 or (415) 600-1106
San Francisco General Hospital
Athiana (415) 206-3725
San Francisco
Dr. Cazen (415) 565-6288
Stanford University Hospital
Stanford Liver Research Clinic (650) 724-7057

Quest Medical Research (HIV/HCV Coinfection)
Dr. Lalezari (415) 353-0800
East Bay Liver Clinic
Oakland, CA - Grant Young (510) 208-1777
Dr. John J. Jolley - San Rafael
Contact: Lynn Jolley
(415) 257-3030

Southern California

USC Hepatitis Research Clinic
Dr. Karen Lindsay, Susan Milstein, RN
(323) 442-5550
UC Irvine Medical Center
Dr. John Hoefs, Barbara Walker, RN
(714) 456-7821
VA Medical Center - Long Beach
Dr. Timothy Morgan, Julia Sanborn, RN
(562) 494-5933
Santa Barbara/Ventura Counties
Dr. Kip Lyche (805) 641-6525

HCSP

P.O. Box 427037

San Francisco, CA

94142-7037