

# New HCV Antivirals and Drug Resistance

Alan Franciscus, Editor-in-Chief  
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Researchers are investigating new antiviral medications to treat hepatitis C virus infection (HCV). Some of these drugs are referred to as *direct* antiviral medications since they specifically target HCV. However, unlike current HCV medications, direct antivirals carry the potential for drug resistance. This article will discuss the basics of HCV replication and drug resistance.

## THE BASICS

Viruses are like rabbits; what they do best is multiply. The term for this is *viral replication*. However, a virus cannot survive on its own. It can only survive inside of another living cell, known as a *host cell*. Viruses use various pieces of the host cell's genetic material in order to reproduce. Viruses survive because of their ability to adapt and change when they are under attack from the immune system. Viruses still try to reproduce even while under attack. In a hurry to escape, a virus may make a bad copy of itself, which slightly alters its genetic

make-up. The process of change actually produces a variation in the virus, known as a *mutation* or *quasi-species*.

HCV acts like this. When you are initially infected, your immune system recognizes that an uninvited intruder (HCV) is in your body. Your immune system alerts your body to destroy HCV. However, HCV hurries to escape, makes a sloppy copy of itself, which outwits your immune system. Your immune system is patrolling for the original intruder, not realizing that the virus now looks a bit different. Now HCV can multiply at a faster rate. Eventually your immune system catches on and looks for the bad copy. In a hurry, HCV mutates again. This process may cycle through many mutations.

One way to think about this is with Darwin's theory of evolution and *survival of the fittest*. In nature,

*"Drug resistance is inevitable. However, scientists are looking for way to prevent or interfere with drug resistance."*



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the strong survive. The weak die and if they die before they reproduce, their weak genetic material dies too. In this way, it is more likely that strong genetic material is passed along. Evolution applies to plants, animals *and* microorganisms.

## CURRENT THERAPIES

The current standard of care for treating hepatitis C is a combination of pegylated interferon plus ribavirin therapy. How pegylated interferon works is not completely understood. What is known is this: 1) interferon boosts the ability of the body's immune system to kill a virus, and 2) it protects non-infected cells from becoming infected. Interferon is used to treat a variety of diseases including hepatitis C.

We also do not understand ribavirin's mechanism of action against HCV, but when used with interferon, it seems to interfere with

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## ANTIVIRALS

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HCV's ability to replicate. Ribavirin alone is not effective against hepatitis C. When interferon and ribavirin are combined, there is a *synergistic effect*, which eliminates HCV in about half the people who take this combination. *Synergy* means that the combined total is greater than the sum of the separate parts.

Drug resistance does not develop with interferon and ribavirin since these drugs do not specifically target the enzymes used in the viral replication process. This means that treatment durations may vary in length and be tailored to patients' needs. Patients may also undergo multiple treatments using the same drug(s). It is also the reason why people may interrupt or stop therapy without the development of drug resistance.

### THE HCV REPLICATION PROCESS AND DIRECT ANTIVIRALS

The hepatitis C virus is a single stranded RNA virus of the *flavivirus* family with a very rapid turnover rate. HCV enters the body and targets the liver – the main replication site of HCV. The virus attaches itself to the outer coating of the liver cell or *hepatocyte*, and enters the cell. After entering the cell, HCV releases its genetic material and hijacks the cell's internal processes.

Now that HCV has taken over, it binds to various ribosome sites within the cell. A *ribosome* is like a factory with printing presses. If a master copy of a document has a mistake in it, all of the copies will have that same mistake. This is referred to as *translation*. Drugs are being developed to interfere with this process, but so far, none has been found to be effective in stopping the translation process.

The next step involves an enzyme called the *protease*. HCV genetic material uses the protease enzyme to 'cut up' the genetic material into smaller pieces before additional viral processing. If this process is interrupted, then the virus cannot make copies of itself. Protease inhibitors are exciting prospects in drug development to treat HCV. Two drugs that look the most promising are VX-950 and SCH 503034.

Other materials that viruses depend on for replication are *polymerase* enzymes. HCV cannot multiply without these enzymes. Polymerase inhibitors are drugs used to stop this process. The polymerase inhibitor that is farthest along in development in this class is NM 283.

Viral replication relies on the *helicase* enzyme to complete the process. There are no HCV helicase inhibitors currently in development. Most experts believe that it will be difficult, if not impossible, to develop helicase inhibitors.

### RESISTANCE AND DIRECT ANTIVIRALS

The new direct antivirals work by inhibiting the entry of the virus or by inhibiting the specific enzymes during one of the replication processes. The medications that look the most promising are the HCV protease and polymerase inhibitors. During the normal lifecycle of HCV, the body's immune system exerts pressure on the replicating virus. This pressure produces mutations that escape the host's immune response.

In a similar way, drugs to treat hepatitis C will exert pressure on the virus to change and mutate in order to survive. For this reason, it is believed that most of the direct antiviral medications will produce drug resistant mutations, especially if these drugs are taken for a long time. This in turn may make the

new medications ineffective in treating the new viral mutations.

Drug resistance is inevitable. However, scientists are looking for ways to prevent or interfere with drug resistance. For instance, drug resistant mutations may be identified earlier in the process, such as during the test tube development phase.

### PREVENTING AND REDUCING DRUG RESISTANCE

The reduction or prevention of drug resistance depends on a number of factors. Some of these are:

- *Eradicating HCV*: Unlike HIV and HBV, hepatitis C does not integrate into the host cell. For this reason, we have been able to eradicate HCV from the body with the use of current medications – pegylated interferon and ribavirin. In addition, HCV is an RNA virus. Since it does not integrate into the host cell's DNA it will be easier to eliminate HCV without the risk of viral mutation.

- *Combination of direct and indirect antivirals*: Direct antivirals can be given for a shorter period of time, thus reducing drug resistance. When used in combination with indirect antivirals – peginterferon and/or ribavirin, the risk of resistance drops. An example of this is extending the duration of treatment with peginterferon and/or ribavirin after stopping the direct antiviral. This may prevent drug resistance while allowing for continual viral suppression. For instance, a new clinical trial of VX-950 is underway to test the theory of taking VX-950 for 12 weeks with and without pegylated interferon, followed by additional treatment using just pegylated interferon with or without ribavirin. Hopefully, this trial will test this

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# HealthWise:

## *Healthy Living with HCV Series*

### *Part 4: Tipping the Scales towards Successful Weight Loss*



Lucinda K. Porter, RN

Last month's *Healthwise* column discussed the importance of maintaining a healthy weight, especially for those with liver disease. This month's column focuses on weight loss. We will offer some concrete suggestions for how to make small, but potentially life-saving changes. Throw the word *diet* out of your vocabulary. Skip deprivation. It is possible to lose weight and enjoy life at the same time.

Although it does not have to be torture, losing weight does take thought and commitment. You are more likely to succeed if you formulate a plan. "Failing to plan is planning to fail," notes Pamela Peeke, MD, Assistant Clinical Professor of Medicine at the University of Maryland School of Medicine. Some find it easier to maintain the commitment if there is a plan in place. Hunger and temptation are harder to resist when there is no plan in place.

The most successful weight loss plans encourage a low fat, reduced-calorie diet along with exercise and eating behavioral changes. Ask your medical provider to recommend a weight loss and exercise plan. You may have specific health issues that will need medical monitoring while you are changing your eating and activity styles.

The "trick" to weight loss is this: burn more calories than you eat. It is important to know how much to eat and how much to exercise. Some plans count calories, while others use points or other systems. It takes about 3500 calories to gain one pound of body weight. In order to lose a pound, you need to reduce the amount of calories you eat and/or burn more calories. Unless you are an elite athlete, it is hard to burn that many calories. The best way to approach this is to eat less and move more.

For instance, if it takes 2000 calories per day for you to maintain your current weight, then if you cut

back to 1500 calories daily, then in seven days you will lose one pound. In other words, 500 calories a day for seven days equals 3500 calories – the amount you ate to gain that pound. If in the same week you increase your daily exercise by 200 calories daily, then your net loss will be 700 calories per day. You will lose that pound in five days rather than seven.

Personally, I favor the slow and steady method. If I need to lose weight, I will cut back by 200 to 300 calories a day and increase my physical activity. It will not get quick results, but it works. I adapt more easily to small changes and these are more likely to become permanent ones. Some people are successful with bigger changes, so it may help to identify your style of change.

Two important components of weight loss involve *what* and *how much* you eat. For example, a fish filet sandwich at McDonald's has 410 calories per serving. A regular hamburger has 260 calories. That is a difference of 150 calories. If you dine daily at McDonald's, theoretically you could lose a pound in less than a month just by switching to the lower calorie burger. A large order of fries contains 520 calories, whereas there are 230 calories in a small. Again, if you are a McDonald's regular already, in twelve days you could knock off another pound if you ate the small order instead.

Naturally, a constant diet of McDonald's is not healthy. Fast food can be high in fat and sodium, while low in fiber. Fortunately, many fast-food restaurants offer salads and other healthy choices. The point is, know what you are eating and watch the amounts.

Another concept to keep in mind, is serving size. The label on a small frozen quiche may claim 350

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## WEIGHT MANAGEMENT

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calories. That does not seem too bad except that the label also states there are two servings per container. If you eat the entire quiche, you consume 700 calories.

*“Two important components of weight loss involve **what** and **how much** you eat.”*

Choose a food plan that you can stick to. You may have to modify a food plan to include foods that you really want to eat. If you must eat jellybeans every day, then perhaps you can limit your intake to 25 jellybeans a day. This is about 100 calories. You may skip the tablespoon of butter on your morning toast in order to allow for the jellybean calories. However, if jellybeans are a binge food and you can't eat just 25 of them, then perhaps keep them out of the house or only purchase them occasionally and in small amounts.

The National Weight Control Registry maintains a database of over 5000 people who have lost 30 or more pounds and kept it off for at least a year. Here are some of the common practices used by successful weight losers:

- Ate breakfast every day
- Consumed between 1300 and 1500 calories per day
- Weighed themselves regularly and often – either daily or weekly
- Exercised between 60 and 90 minutes of moderate-intensity on a daily basis

If you relapse into old behaviors, it is a good idea to have a good relapse strategy. Refrain from self-criticism. Remind yourself that you are a work in process. Applaud any effort you have made.

To help me meet my goals of healthy eating, I have posted this Turkish proverb at my kitchen table: “He who keeps eating after his stomach is full, digs his grave with his teeth.” I remind myself that nothing tastes as good as feeling healthy feels. A piece of cake may look good, but eaten over time it won't feel good. If I think of it in those terms, the choice between food and feeling good is an easy one to make. Furthermore, anytime I contribute to my overall health, I may be keeping ahead of hepatitis C.

### Resources

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For more information, look under the Resource sections of previous “Healthy Living with HCV Series” *Healthwise* columns, or check out our new HCSP Guide: *A Guide to Healthy Living with HCV*.

- **CaloriesPerHour** – *caloriesperhour.com* This website is a favorite. Start here and you may find everything you need to develop a good weight loss strategy.
- **Cyberdiet** – *www.cyberdiet.com* This website charges a fee for membership but also offers free information. The Nutrition Calculator is one of this site's many good features.
- **Diet Detective** – *www.dietdetective.com* This for-profit website offers excellent free information.
- **Dietwatch** – *www.dietwatch.com*

This commercial website maintains the Cyberdiet website. There is ample free information worth looking into, particularly about the emotional aspect of over-eating.

- **The National Weight Control Registry** – *www.nwcr.ws* A national database of over 5000 people who have lost 30 or more pounds and kept it off for at least one year.

- **Prevention Magazine** – *www.prevention.com* This is an excellent magazine with a helpful website if you ignore the advertising. Check out the following sections: Weight Loss, Food and Nutrition, Fitness to kick off your weight management program.

- **Overeaters Anonymous** – *www.oa.org* This non-profit program addresses the compulsive nature of overeating by using many of the tools developed by Alcoholics Anonymous.

- **ShapeUp** – *www.shapeup.org* This nonprofit organization offers excellent practical information.

- **Three Fat Chicks** – *www.3fatgirls.com* In 1997 these three sisters addressed their collective weight problems by starting this website. If you need support, this is a good place to start.

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# Genetic Variation and Hepatitis C



Liz Highleyman

In the study of viral hepatitis, HIV/AIDS, and other illnesses, an increasing amount of attention in recent years has focused on “genomics,” or how individual genetic variations affect disease pathogenesis and treatment. Several recent studies have looked at the influence of genetic variations on hepatitis C virus (HCV) infection, response to therapy, and progression of liver disease.

## GENETICS 101

The human genome contains an estimated 25,000-35,000 genes. Every individual has two copies of each gene, one inherited from the mother and one from the father. Most genes have two or more alternative forms, known as alleles; an individual may carry two copies of the same allele (homozygous) or two different alleles (heterozygous). The likelihood of having specific alleles varies across different racial/ethnic groups.

A variation at a specific position on a gene is known as a single nucleotide polymorphism, or SNP. Gene expression refers to the production of specific proteins using the instructions encoded by the gene. Some SNPs cause substitution of different amino acids (building blocks) in a protein, which can alter the protein’s biological function; other SNPs alter the regulatory mechanisms that control gene expression itself.

## HCV INFECTION

In the May 2006 issue of *Gut*, D.A. Price and colleagues reported that common variations in the apolipoprotein E gene – known as APO\*E2 and APO\*E4 – were associated with spontaneous HCV clearance and a reduced likelihood of chronic infection. None of the 420 HCV positive Northern European participants in the study carried two copies of the E2 allele. The researchers suggested that the E2 allele may prevent lipoprotein (cholesterol) particles carrying the virus from binding normally to their receptors and entering host cells.

## INTERFERON-RELATED GENES

Genetic variations may also help explain the difference in treatment response rates across racial/ethnic groups. Research has shown that African-Americans are less likely to spontaneously clear HCV and do not respond as well to interferon-based therapy compared with Caucasians. The Virahep-C trial, designed to explore the reasons for this difference, included 196 African-Americans and 205 Caucasians with genotype 1 HCV who were treated with pegylated interferon plus ribavirin for 24-48 weeks.

At the annual Digestive Disease Week (DDW) conference in May, X. Su and colleagues (abstract 2) reported that variations in genes involved in the immune system’s interferon-signaling pathways

were associated with response to treatment with interferon. During interferon-based therapy, interferon alpha and beta bind to their respective receptors; this leads to the activation of interferon-signaling pathways, transcription of interferon-stimulated genes, and induction of an antiviral response.

The researchers analyzed polymorphisms in five genes involved in the interferon-signaling pathway (STAT1, STAT2, IFN $\alpha$ 1, IFN $\alpha$ 2, and IRF9) and 12 interferon-stimulated genes (MX1, MX2, OAS1, OAS2, OAS3, OASL, IRF7, G1P2, G1P3, IFI35, PKR, and IP10). In both African-Americans and Caucasians, there was a consistent association between sustained virological response (SVR) and a SNP called rs3213545 on the OASL gene. About 30% of African-Americans and 50% of Caucasians carried the “T” allele. The SVR rate was 50.7% among “T” carriers, compared with 34.1% among subjects who carried non-“T” alleles. Other SNPs on the STAT1 and STAT2 genes were significantly associated with SVR in one race, but not in a combined analysis of both groups. Although the function of rs3213545 is not known, the researchers concluded that this interferon-induced pathway is “critical for the host-mediated antiviral effect in response to interferon-based therapy.”

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## GENES

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### ROLE OF THE MAJOR HISTOCOMPATIBILITY COMPLEX

The major histocompatibility complex (MHC) is a family of genes that enables the immune system to distinguish “self” from “non-self.” A subset of MHC genes, known as the human leukocyte antigen (HLA) genes, encode antigen-presenting proteins on cell surfaces. MHC activity is believed to play a role in immune response to HCV. Some HLA variations appear to be associated with spontaneous viral clearance, and may also affect response to interferon-based therapy.

S. Rhodes and colleagues (DDW abstract 656) looked at the association between HLA alleles and sustained response to pegylated interferon plus ribavirin in a subset of Virahep-C participants. Three alleles – known as A\*02, B\*58, and DPB\*1701 – were independently associated with SVR. HLA A\*02 was present in 27% of Caucasians and 16% of African-Americans. The other two alleles were more common among African-Americans than whites: 7% vs 0.5% for B\*58, and 8% vs 1% for DPB\*1701. The A\*02 allele was previously reported to be associated with spontaneous HCV clearance in studies of mostly white patients. Similar associations involving B\*58 and DPB\*1701 have not been reported previously, perhaps because African-Americans have been underrepresented in most prior studies.

### INTERFERON-INDUCED DEPRESSION

Another study presented at DDW looked at genetic influences on the risk of developing depression during interferon therapy. Depression is often due to altered levels of the neu-

rotransmitter serotonin; a class of antidepressants known as selective serotonin reuptake inhibitors (SSRIs) may be used to manage depression during hepatitis C treatment.

In a study of 139 patients treated with conventional or pegylated interferon with or without ribavirin, M.R. Kraus and colleagues (abstract 197) assessed the occurrence of depression during therapy and determined which subjects carried the C-1019G polymorphism on the 5-HT1A serotonin receptor gene.

The researchers found a significant association between the 5-HT1A receptor polymorphism and depression during interferon therapy. In particular, carriers of the “G” allele had both a higher incidence and a greater severity of depressive symptoms. The researchers concluded that variations in expression of the 5-HT1A gene play a significant role in the development of interferon-induced depression, and suggested that this information might be used to help predict who will develop depression during treatment.

### DEVELOPMENT OF FIBROSIS

Several studies have also explored the link between genetic variations and the development of liver fibrosis and hepatocellular carcinoma (HCC).

In a study published in the July 5, 2006 issue of *Virology*, K.A. Walters and colleagues analyzed the gene expression profiles of liver biopsy samples from 16 HIV/HCV coinfecting patients and 12 individuals with HCV alone. Overall, they found that gene expression did not differ between coinfecting and HCV mono-infected individuals. However, they did identify a subset of patients who shared a specific gene

expression pattern, dubbed EGE (for enhanced gene expression). Patients with this gene profile showed decreased expression of several genes associated with apoptosis (programmed cell death), increased expression of lymphocyte adhesion molecules (which play a role in

*“Variations in genes involved in the immune system’s interferon-signaling pathways were associated with response to treatment with interferon..”*

fibrosis), impaired interferon-mediated antiviral immune responses, and reduced activity of interferon-gamma (which reduces fibrosis). The EGE pattern is similar to that observed in patients who developed fibrosis within one year after receiving a liver transplant.

In a related study, reported in the May 2006 issue of *Gastroenterology*, H. Huang and colleagues looked at more than 24,800 genetic variations and their relationship to fibrosis. They found 1,609 SNPs that were significantly associated with advanced fibrosis; 100 of these were selected for further analysis. Individuals who carried a certain mutation on the DDX5 gene were at increased risk of developing advanced fibrosis, while those who carried a specific allele on the CPT1A gene had a decreased risk of fibrosis.

### HEPATOCELLULAR CARCINOMA

Another research team looked at gene variations associated with HCC. A polymorphism on the MDM2 gene, known as SNP 309, was recently linked to tumor

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## ANTIVIRALS

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theory and more importantly, find out if taking this new antiviral results in a durable sustained virological response.

- **Potent direct antivirals:** The development of potent direct antivirals that quickly distribute throughout the body and reach high blood concentrations in a short time period will exert enough pressure on the virus before it has a chance to mutate. If the drugs are not potent enough, the escaped viral mutations may become the dominant virus, rendering the antiviral medication ineffective.

- **Combination direct antivirals:** The use of direct antivirals that inhibit several different protease and/or polymerase enzymes simultaneously, will reduce the ability of the virus to mutate.

- **Adherence:** Current HCV medications require adherence to prescribed doses and durations to be more effective in treating HCV. The new direct antivirals will require strict adherence. Doses that are skipped or forgotten could lead to viral mutations and drug resistance.

HCV research has benefited from what we know about HIV and HBV drug resistance and hopefully will be able to contribute to this body of knowledge. As we begin this era of new HCV medications, now is the right time to develop strategies to make HCV therapy more effective. Now is the time to reduce the chances of the emergence of drug resistance that could potentially negate some of the benefits of new therapies. The best strategy for moving forward depends on using knowledge from the past in order to discover the future.



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formation in people with various types of cancers; this SNP appears to down-regulate expression of the p53 tumor suppressor protein. N. Dharel and colleagues (DDW abstract S1052) assessed whether SNP 309 was associated with development of liver cancer in 435 Japanese patients with chronic hepatitis C and 48 healthy volunteers. They found that 51% of participants carried the "T/G" allele of SNP 309, 27% carried the "G/G" allele, and 22% had the "T/T" allele (among Caucasians, the respective proportions are about 40%, 12%, and 48%). Among the hepatitis C patients, significantly more individuals with HCC had the "G/G" variation compared with non-HCC patients (33% vs 23%). The researchers concluded that SNP 309 is associated with development of HCC in this population, and suggested that the "G/G" allele might serve as a marker to predict who is likely to develop liver cancer.

Finally, in a study published in the June 2006 issue of *Gastroenterology*, Y. Zhai and colleagues found that certain polymorphisms in the estrogen receptor gene ESR1 appeared to increase the risk of developing HCC in Chinese patients with chronic hepatitis B.

### HOPE FOR THE FUTURE

Together, these studies expand our knowledge of how genetic variation contributes to viral hepatitis pathogenesis and response to therapy, and add to the evidence that genetic testing may soon play an increasing role in predicting or managing various aspects of hepatitis C and its treatment.



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# DDW 2006: Conference Highlights – Part 2



Alan Franciscus, Editor-in-Chief

This report will focus on the information about Pegasys and Peg-Intron combination therapy presented at the Digestive Disease Week (DDW) 2006 Conference

## **COST-EFFECTIVENESS OF PEGASYS/RIBAVIRIN**

One of the concerns about treating people with mild hepatitis C (little or no disease progression) is whether the cost of therapy outweighs the cost of future dollars spent on the complications of HCV disease progression.

H.B. El-Serag and colleagues put the cost effectiveness of combination therapy of Pegasys plus ribavirin to the test in an abstract titled “Cost-effectiveness of first-line peginterferon alfa-2a (40KD) (PEGASYS) plus ribavirin (COPEGUS) in patients with mild chronic hepatitis C (CHC) in the US” (abstract T1805).

Information from two multinational randomized phase III studies of 328 HCV genotype 1 patients were analyzed. Of the 328 genotype 1 patients, 241 were found to have no fibrosis or no portal fibrosis according to the Knodell scoring system and staged as F0, F1 or F2 according to the METAVIR scoring system. All patients were treated with peginterferon alfa-2a (40KD) 180 µg/week plus ribavirin at 1000/1200 mg/day for 48 weeks. The SVR rate in this group of genotype 1 patients was 56%.

The Markov model of the natu-

ral history of chronic hepatitis C was used to assess cost-effectiveness of Pegasys/ribavirin treatment compared to no treatment for those HCV genotype 1 patients with mild chronic hepatitis C. According to this complex model it was found that the incremental cost per quality-adjusted life-years (QALYs) is \$3396.

The authors concluded that “compared with no treatment, peginterferon alfa-2a (40KD) (PEGASYS) plus ribavirin (COPEGUS) is a cost-effective treatment strategy in adults with mild chronic hepatitis C and genotype 1 infection in the US setting.” The authors also speculated that the cost savings are most likely a “result of a reduction in the incidence of future complications, including cirrhosis, hepatocellular carcinoma and liver transplantation, and an increase in the life expectancy and quality of life.” Finally, it was suggested that the practice of treating only moderate to severe liver damage should be re-evaluated.

## **PEGASYS IN JAPANESE PATIENTS**

“High response rates with peginterferon alfa-2a (40kd) (PEGASYS) plus ribavirin (COPEGUS) in treatment-naïve Japanese chronic hepatitis C patients: a randomized, double-blind, multicenter, phase III trial” by T. Sakai and colleagues (abstract T1811). This study of HCV-infected genotype 1 patients was presented in a poster.

In this study, 200 treatment naïve HCV genotype 1b patients from 43 centers in Japan were assigned to receive either pegylated interferon alfa-2a (PEGASYS) (40KD) 180 µg/week with ribavirin at 600-1000 mg/day or pegylated interferon alfa-2a (PEGASYS) (40KD) 180 µg/week plus placebo for 48 weeks. Patient characteristics were similar between the two arms – 62% male, 50.6-52 mean age. Age was higher and weight was lower in this study population compared to the U.S. population with hepatitis C.

The authors found that in the Pegasys/ribavirin arm the SVR was 61% compared to 26% in the monotherapy arm. The side effects were generally mild and typical of what would be reported in previous studies. The usual standard for predicting SVR in those who have an early virological response (EVR-undetectable or two log drop of HCV RNA) was different in the Japanese population compared to previous studies. Of the 24 patients who did not achieve an EVR, 4 patients (17%) achieved an SVR. As a result the authors recommend that stopping treatment in Japanese patients should not be considered before week 24.

In another Japanese study, “High response rates with peginterferon alfa-2a (40KD) (PEGASYS) plus ribavirin (COPEGUS) in Japanese non-responders or relapsers to

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conventional interferon” (abstract T1824), N. Izumi and colleagues reported on the SVR rates in this difficult to treat patient population.

Previously-treated adults (non-responders (40%) and relapsers (60%)) with chronic hepatitis C were treated with peginterferon alfa-2a (40KD) 180 µg/week plus ribavirin 600–1000 mg/day for 48 weeks. Non-responders were defined as previously treated patients who did not become HCV RNA negative during treatment and relapsers were defined as patients who became HCV RNA (viral load) negative, but reverted to HCV RNA (viral load) positive. The mean age was 52, 74% males; mean body weight was 67 kg. Eighty-four percent were genotype 1b and 16% were non-genotype 1b.

The SVR rate for the non-responder group was 48% and 58% for the relapser group. The side effects were generally mild and typical with what you would expect from therapy. Sixteen percent of patients withdrew from therapy due to adverse events or laboratory abnormalities. The only factor that increased the likelihood of achieving an SVR was younger age.

The authors concluded that “Peginterferon alfa-2a (40KD) (PEGASYS) plus ribavirin (COPEGUS) is associated with a relatively high response rate in Japanese chronic hepatitis C patients who failed to respond to or relapsed after conventional interferon monotherapy.” Given the high response rates of treatment in naïve, non-responder and relapsing Japanese patients, it would be interesting to study why Japanese HCV patients have a much higher treatment response

than patients in other countries.

### DRUG USERS AND TREATMENT

Another poster from DDW reviewed records of 9414 HCV patients from more than 500 centers in Germany to assess the treatment of patients with Peginterferon alfa-2a (40KD) (PEGASYS) plus ribavirin (COPEGUS) in drug users vs. non-drug users. “Treatment of chronic hepatitis C with peginterferon alfa-2a (40KD) and ribavirin in patients with or without drug use” (abstract T1815) by E. Zehnter and colleagues included 635 or 28.6% out of 2217 patients with drug or alcohol abuse (DU), and 3366 or 46.7% out of 7197 without drug or alcohol abuse (NDU) in the analysis. Breaking it down by patients treated with Pegasys/ribavirin – 142 alcohol abusers, 551 drug abusers, and 176 opioid maintenance therapy patients. The mean or average age was 36.1 yo (DU) vs. 42.8 yo (NDU), Males, 75.7% (DU) vs. 59.2% (NDU), mean duration of infection was 8.4 years (DU) vs. 12.0 years (NDU). Most of the patients were treatment naïve – 89.6% (DU) vs. 84.1% (NDU). Genotype distribution was: genotype 1, 49.6% of DUs vs. 61.5% of NDUs; genotypes 2/3, 47.1% of DUs and 35.1% of NDU patients; genotypes 4, 5 and 6, 3.3% of DUs and 3.4% NDUs.

Of the available data, 153 of 208 DUs (73.6%) and 645 of 967 NDUs

(66.7%) achieved an SVR. Unfortunately, opioid maintenance therapy and drug users were lumped together so it is not possible to tease out the numbers between the two subgroups. It was cautioned that the higher SVR in DUs could be attributed the DU characteristics – younger age, lower BMI and a higher percentage of genotype 2 and 3. Discontinuance rates were higher in the DU group compared to the NDU for all reasons, including dropping out for virological nonresponse, poor tolerability, lack of compliance, lost to follow-up, and for personal reasons, which the authors acknowledged as a special problem that should be closely monitored with psychological care during therapy.

### PEG-INTRON

At AASLD 2006 results from the **WIN-R** (Weight-Based Dosing of PEG-INTRON and REBETOL) was presented that found that weight-based ribavirin in combination therapy with peginterferon alfa-2b (Peg-Intron) achieved higher SVR rates and lower rates of relapse when compared to using Peg-Intron combination therapy with a flat dose of ribavirin. The study also showed that in patients with HCV genotype 2 or 3 that 24 weeks of treatment was as effective as 48 weeks of therapy.

More information on the trial was released from the WIN-R data

### Distribution of Fibrosis Score

Fibrosis Stage	Number of Patients
0	654
1	1460
2	1324
3	975
4	500

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**ARIZONA ORGAN DONOR REGISTRY**

One of the many myths about organ transplantation is that wealthy individuals can purchase organs, either openly or via the black market. The sale of organs is illegal in the United States. Stories circulate on the Internet about healthy people being maimed or killed for their organs. Not one of these stories has been substantiated. The United States uses a system that distributes organs in various regions. Although the distribution system is not perfect, it is fair. Wealthy people cannot skip to the head of the list just because they may have more resources available to them.

Residents of Arizona wishing to donate organs upon death may indicate their wishes at the Arizona Donor Registry [www.donatelifeeaz.org](http://www.donatelifeeaz.org). Alternatively, prospective donors may sign a donor card and inform their family or other medical decision makers about their wishes.

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## DDW – PART 2

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including the affect of fibrosis and HCV RNA (viral load) on treatment outcome.

Fibrosis and cirrhosis are known to negatively affect treatment outcome. A subset analysis, “The effect of liver fibrosis and cirrhosis on SVR in 4913 patients with hepatitis C: Results from the Win-R trial (Abstract 655), by N. Afdhal and colleagues was presented. This study included 4913 patients receiving Peg-Intron in combination with either weight-based or fixed-dose ribavirin. Fibrosis stage was obtained on biopsies within 3 years of randomization using the METAVIR scoring system by local pathologists. Only patients with weight > 65kg were included in the analysis – 4223 patients. The effect of each individual fibrosis stage on SVR was determined by logistic regression for all patients (4913 patients) regardless of treatment group.

It was found that there was no difference in the SVR rates between weight-based dose and fixed-dose in patients with stage 0-2 fibrosis. There **was** found to be a significant increase in SVR rates in fibrosis stage 3-4 between the weight-based group (43% SVR) compared to the fixed-dose group (37% SVR). In the entire population of patients, logistic regression showed no statistically significant difference in SVR rates between stage 0 (44%), stage 1 (46%), stage 2 (44%) and stage 3 (44%) except in fibrosis stage 4 which only achieved an SVR of 34%.

The authors commented that it is important to use weight-based dosing to increase the SVR in the patients with more advanced liver disease and concluded that “overall

only cirrhosis is a negative predictor of SVR when individual fibrosis stage and SVR is evaluated.”

Now turning to the analysis of viral load on treatment outcome, a poster titled “Stratification of viral load in patients with genotype 1 HCV: Impact on sustained virologic response in the WIN-R trial” (T1806) by I.M. Jacobson and colleagues was released.

In this analysis, a total of 2706 out of 3018 patients with genotype 1 were included – no data was available for 312 patients so they excluded these from analysis. The mean age was 46 years and mean weight was 84.3 kg. Patients were treated with Peg-Intron in combination with either weight-based dosing (800-1400mg/day) or fixed dose (800 mg/day). High viral load was defined by HCV RNA > 2,000,000 copies and low viral load was defined as < 2,000,000 copies.

As expected, higher SVR rates were observed in the weight-based dosing of genotype 1 patients compared to the fixed dose (34% vs. 29%). Breaking it down by viral load – *High viral load*; SVR for weight-based dosing was 32% vs. 27% for fixed base dosing; *Low viral load*; 39% in the weight-based group compared to 34% in the fixed-dose group. Surprisingly, the study did not find that incremental increases in viral load necessarily correlated with lower response rates in patients with viral load over 2,000,000 copies.

The authors concluded that in genotype 1 high viral load patients, the SVR rates were significantly higher in the weight-based dosing group. In addition, authors recommended additional research to more clearly define the cut-off between high and low viral loads.

There is data on the effect of cigarette smoking and HCV disease progression showing more inflam-

mation and fibrosis in people with HCV who smoke cigarettes. But there has not been any research to find out if cigarette smoking affects treatment outcome.

“The influence of cigarette smoking on response to treatment with pegylated interferon alfa-2b and ribavirin in patients with chronic hepatitis C,” by M.P. Pauly and colleagues, was presented as another sub-analysis of the WIN-R study. During the enrollment of WIN-R it was noted in the charts if a patient was a smoker (S) or non-smoker (NS). Smoking data was available on 2865 out of 4223 patients (67.8%). The patient characteristics were similar between the two groups except that patients with F3-F4 were more likely to be smokers than non-smokers (34% vs. 14%). In the smoking group, there was no data available on the number of cigarettes smoked daily. The analysis found that there was no difference in treatment outcomes between smokers or non-smokers in patients with genotype 1 regardless of dose. However, there was significant difference found in patients with genotype 2/3 – Fixed dose (62% (NS) vs 51% (S)); Weight-based (66% (NS) vs. 57% (S)).

*Part three of DDW conference coverage will be on information about herbal therapies and more interesting information on HCV treatment response, side-effect management and epidemiological data.*



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