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FDA APPROVES PEGASYS

HCV Community Stunned by Roche's Pricing Decision

By Alan Franciscus
Editor-in-Chief

Roche announced on October 16th, 2002 that the U.S. Food and Drug Administration (FDA) has approved Pegasys (peginterferon alfa-2a) monotherapy for the treatment of adults with chronic hepatitis C who have compensated liver disease and have not previously been treated with interferon alpha. Patients in whom efficacy was demonstrated included patients with compensated cirrhosis. This indication is different from Schering's Peg Intron label because it includes treating patients with compensated cirrhosis which Peg Intron does not include. This addition to the Pegasys label is due to a study that was done comparing Pegasys 180µg versus Roferon-A 3 MIU in 173 patients with cirrhosis or transition to cirrhosis, the results listed in the 'effectiveness' section. Pegasys has already been approved for use in 50 countries, including all European Union countries.

THE COST OF PEGASYS

Pegasys monotherapy is priced at \$291.00 per 180µg vial of Pegasys which is comparable to the other available pegylated interferon - Peg Intron. For 24 weeks of therapy the cost of Pegasys is \$6,984 and \$13,968 for 48 weeks of therapy. Until the approval of Roche's ribavirin (Copegus) anticipated in December 2002, patients only have two options for ribavirin, Schering's Rebetol or compounded ribavirin.

Schering's Rebetol was recently priced (4/2002) at \$7,062 (800mg) to \$10,590 (1200mg) for 24 weeks to \$14,124 to \$21,180 for 48 weeks. The community had hoped that Roche would price their Pegasys monotherapy considerably lower than Peg Intron which is perceived by the community as being exorbi-

tantly over-priced.

It is the sincere hope and expectation of the community that when Roche has an opportunity to price their combination Pegasys/Copegus at the end of 2002 they will take into consideration what the market **will bear in order** to get a handle on hepatitis C and not charge outrageous prices for ribavirin, a product which is inexpensive to manufacture, will be generic shortly and has absolutely no value outside of combination therapy for hepatitis C.

ROCHE SAMPLE PROGRAM - FREE PEGASYS

Roche will be providing physicians with samples of Pegasys for the first 12 weeks of therapy. These samples will be provided at the request of a physician for the first 15,000 patients who are started on Pegasys therapy prior to December 31, 2002. Twelve weeks was selected because at that point physicians can predict those patients who will not respond to Pegasys therapy. Samples are available to all physicians.

According to a Roche company spokesperson this sample program is designed to help physicians gain experience with Pegasys, establish Pegasys' 12 week predictability marker, and alleviate fears around supply and demand issues. Additionally, Pegasys/Copegus (Pegasys in combination with ribavirin) is

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FDA Panel Recommends Warning Label for Acetaminophen

By **Liz Highleyman**
Contributing Editor

The painkiller acetaminophen is one of the best-selling and most widely used over-the-counter medications on the market. It is sold under dozens of brand names including Tylenol, and is a component of some 200 combination medications including Anacin, Excedrin, Nyquil, and several opiate combinations available only by prescription.

Most of the millions of Americans who use acetaminophen each year believe the drug is safe, despite the fact that it has long been associated with liver damage if taken in high doses. This impression is promoted by pharmaceutical manufacturer Johnson & Johnson, which promotes Tylenol with advertising claims that “nothing’s safer.”

In September, an advisory panel of the U.S. Food and Drug Administration (FDA) recommended that acetaminophen should carry a warning about the potential for liver toxicity. Before making the decision the panel heard testimony from people affected by the drug, including a woman whose son died from liver failure after taking the painkiller.

Acetaminophen is one of the leading causes of acute liver failure in the United States. According to the FDA there are over 50,000 emergency room visits and 100 deaths each year in this country related to acetaminophen overdose, many of which are suicides.

The FDA panel’s decision came about as a result of accumulating evidence that acetaminophen—which has been available over-the-counter since 1960—can sometimes cause liver toxicity even at relatively low doses. Most cases of liver damage occur in people who have taken at least 10-15 grams of the drug—more than double the recommended dose. But some people seem to be more susceptible to acetaminophen toxicity and have experienced liver failure and even death at recommended doses. A recent FDA study of patients with liver damage linked to acetaminophen found that 20% had used less than the recommended daily dose.

Unfortunately, there is little leeway between a safe dose and one that can cause serious liver damage. According to Dr. William Lee of the University of

Texas Southwestern Medical Center, “The window between therapy and toxicity is much smaller with acetaminophen than with most other compounds.”

Acetaminophen is more likely to cause liver damage at normal doses if taken by people who drink alcohol. In fact, people who regularly drink alcohol may be more prone to liver damage even if they do not use alcohol at the same time as acetaminophen. In 1994 Johnson & Johnson lost a lawsuit and paid a multimillion dollar settlement to a man who suffered liver failure after taking the recommended dose of Tylenol with a small amount of wine. Soon thereafter the company began to include a warning on the drug package that using Tylenol with alcohol could lead to liver damage.

Still, some experts believe that acetaminophen label warnings should be strengthened and not limited to those who drink alcohol. FDA panels recommended adding a liver toxicity warning for acetaminophen in 1977 and again in 1988 and 1993. However, on none of these occasions did the full FDA formally adopt the recommendation—due, some advocates allege, to pharmaceutical lobbying efforts.

Acetaminophen-related liver toxicity is dose-related; that is, the higher the dose, the greater the likelihood of liver damage. Acetaminophen, like many drugs, is metabolized by the liver. If the normal processing pathway is overwhelmed by a high dose, a different pathway known as the cytochrome P450 enzyme system kicks in. When this occurs, a toxic metabolite called NAPQI is produced that can cause liver cell death. This metabolite is normally detoxified by glutathione. But if excessive amounts of acetaminophen are present, the glutathione system can also become overwhelmed.

Alcohol and certain other drugs affect the cytochrome P450 system, increasing the level of NAPQI and depleting glutathione stores.

Acetaminophen toxicity has three stages. During the first 12-24 hours after ingestion, a person may experience nausea and vomiting. During the second phase, from 24-48 hours, the person usually feels

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Report from 42nd ICAAC in San Diego

By Liz Highleyman
Contributing Editor

Viral hepatitis—and especially HCV/HIV coinfection—was a key topic at the 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) held Sept. 27-30, 2002 in San Diego.

Jurgen Rockstroh from Bonn, Germany, gave an overview of the state of knowledge about HCV/HIV and HBV/HIV coinfection (abstract 403). Less than 10% of HIV positive people are coinfecting with HBV, and about 30% are coinfecting with HCV. Lamivudine (3TC, Epivir) remains the best treatment option for people with chronic hepatitis B, but the nucleotide analog drugs adefovir (Hepsera, just approved in September) and tenofovir (Viread) are

promising. Pegylated interferon plus ribavirin appears to be the most effective therapy for people with HCV/HIV coinfection. While there is evidence that anti-HIV treatment slows the progression of liver disease in HCV/HIV-coinfected patients, liver toxicity due to antiretroviral drugs remains a concern.

HCV TREATMENT IN COINFECTED PATIENTS

Several presentations discussed HCV treatment in HCV/HIV-coinfected individuals. Christian Perronne and colleagues with the French RIBAVIC study (abstract 1083) presented results from a trial comparing Peg-Intron plus ribavirin to standard interferon plus ribavirin in 416 HCV/HIV-coinfected patients. After 48 weeks, 38% in the Peg-

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Acetaminophen

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better. After 48-72 hours, levels of the liver enzymes ALT and AST begin to rise. A physician can estimate the risk of liver injury based on the level of acetaminophen in the blood. In the emergency room doctors will usually pump the stomach to remove any remaining drug and administer an antidote, N-acetylcysteine, that replenishes glutathione. N-acetylcysteine is most effective if administered within 16 hours after acetaminophen ingestion.

Unfortunately, early symptoms usually are not recognized as being related to an acetaminophen overdose during this time frame. In the most severe cases a person may develop acid buildup in the blood, excessive bleeding, and coma. At this stage, only a liver transplant can prevent death.

What does the FDA panel's recommendation mean for people with chronic hepatitis? Most doctors still commonly recommend acetaminophen, including for fever and aches that occur as side effects of interferon therapy. Most people who use the drug—including those with liver disease—experience no problems. Compared to other medications on the market, acetaminophen still appears safe. In particular, aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) used as mild painkillers can also cause liver toxicity.

People with hepatitis who require a mild painkiller may continue to take acetaminophen, but should be

careful not to exceed the recommended dose. For healthy adults this is four grams or 4000 mg within a 24-hour period—12 regular-strength or eight extra-strength tablets. Even this amount may cause liver injury if taken all at once. Adults who drink more than two or three alcoholic beverages per day should not exceed half this amount (two grams or 2000 mg within 24 hours). It is usually recommended that people with decompensated cirrhosis (advanced liver damage) should not take acetaminophen or many other medications.

Keep track of how much acetaminophen you take by writing it down. Check the labels of all medications, since many drug combinations contain acetaminophen and these small doses add up. Check with your doctor about whether any other drugs you are taking may increase the risk for acetaminophen-related liver toxicity. Perhaps most important, avoid alcohol—even small amounts—when using acetaminophen.

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Healthy Habits for the Holidays

By Lucinda K. Porter, RN, CCRC

This is a challenging time of the year. Halloween kicks off a parade of fall and winter events that are associated with food. Between Thanksgiving, holiday parties, and Sunday football, Americans are at risk for adding extra pounds. Include poor weather and fewer daylight hours in this equation, and you have a formula for disaster.

Obesity has been linked to an increased risk of fibrosis in those with chronic hepatitis C virus (HCV) infection. This article focuses on strategies for avoiding weight gain, especially during the holidays.

The issues surrounding food, weight, and exercise can be complicated. There are emotional and social aspects to our relationship with food. Books have been written on these issues, so a short article can only make a few suggestions. If you struggle with weight issues, it may be helpful to seek professional advice. If you prefer the self-help approach, try to avoid fads or unproven advice.

In the meantime, here are some suggestions for you to consider.

Set a goal – Choose a goal that is realistic. For instance, the goal of “not gaining any weight in the month of December” is a more reasonable goal than that of losing 20 pounds in a month.

Make a commitment – Good intentions are more likely to become realized if they are reinforced with the power of commitment. Visualizing yourself keeping that commitment can add an extra element for success.

Formulate a plan – Be concrete. If the goal is to not gain weight over the holidays, then devise a plan to support that goal. Simply willing it is not going to make it happen. Some tips for success have been listed at the end of this article.

Implement the plan – Having a plan is worthless if it is not put into action. This is where visualizing a commitment can really boost success. If you can picture it, you can do it.

Evaluate the process – At some point it is important to evaluate your success. If you have met your goal, make sure you congratulate yourself. Making change is hard and you deserve to be told how wonderful you are. If you have not met your goal, try to determine the obstacles. Refrain from self-criticism. Remind yourself that you are a work in process. Applaud any effort you have made.

Modify the plan or goal – If you did not meet your goal, learn from the evaluation and formulate a new plan. You can also fine-tune a successful plan.

HEALTHY EATING TIPS FOR THE HOLIDAYS

* Do not attend an event overly hungry. Eat something before you go.

* Choose your food wisely. Skip the ordinary snack foods such as chips and cookies. Spend your calories on food that really satisfies you.

* Start with a large non-alcoholic, non-caloric beverage, such as mineral water. Keep your glass and

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The HCV Advocate offers information about various forms of intervention in order to serve our community. By providing information about any form of medication, treatment, therapy or diet we are neither promoting nor recommending use, but simply offering information in the belief that the best decision is an educated one.

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Healthy Habits

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stomach full.

* Keep your back to the food. Sometimes just looking at food can raise temptation.

* Suck on a mint. The minty taste can interfere with the taste of other foods.

* Load up on low calorie foods, such as vegetables, fruit, or shrimp.

* Keep portions small. Nuts are healthy, but only in small quantities.

* Savor what you choose. A handful of nuts eaten one at a time is a reasonable amount to eat, rather than eating handfuls at a time.

* Focus on socializing. Sometimes the most wonderful gifts can be exchanged in the process of talking to another person.

* Seek support. Commitments are easier to keep with the aid of friends, family or a support system.

One final tip – remember to exercise. Daily walking, dancing, yoga, gardening, swimming, biking, or whatever gives you pleasure provides wonderful balance to our lives. Exercise reduces stress, improves sleep, burns calories, and may enhance the immune system. It also feels good to move. Try to resist excuses, such as poor weather. A good antidote to resistance is to tell yourself you will only exercise for 10 minutes. Usually when one gets moving, the desire to keep going takes over. A hike on Thanksgiving can become a wonderful tradition and may

deemphasize the importance of the food. May you have ample reasons to give appreciation for this Thanksgiving.

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Lucinda K. Porter, RN is a research nurse and patient educator at Stanford in the area of hepatology. She co-facilitates a support group and is active in many aspects of hepatitis C education. In addition to being HCV positive, she has a life which include her husband and teenaged daughter.

Influenza Vaccinations Recommended

Influenza vaccinations are usually given between October and mid-November each year to prevent influenza and life-threatening complications such as pneumonia.

The CDC recommends influenza vaccinations for people 65 years of age and older that the elderly are at increased risk for influenza and its complications. The CDC also recommends that people with underlying chronic medical conditions, and people with compromised immune systems receive influenza vaccinations.

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Intron group and 24% in the standard interferon group achieved an undetectable HCV viral load using an intent-to-treat analysis. About 40% of those with genotypes 2 or 3 and about 25% of those with genotypes 1 or 4 achieved an undetectable viral load in the Peg-Intron group. The response rate in the Peg-Intron group (25%) was better than that seen in the standard interferon group (10%) for those with genotype 1 or 4, but the difference was not significant for those with genotypes 2 or 3. In both groups, patients with CD4 cell counts above 500 had better response rates. The incidence of serious side effects was high in this study—about 25% in the Peg-Intron group—and about one-third of participants discontinued treatment.

Similarly, Margaret Hoffman-Terry of Lehigh Valley Hospital and colleagues (abstract 1725) reported that after 24 weeks, 39% of 119 coinfecting people (most with HCV genotype 1) experienced at least a 2-log decrease in HCV viral load when treated with Pegasys, with or without ribavirin. Several commentators have described the RIBAVIC results as disappointing. Indeed, the response rates in this study are lower than those reported earlier this year for another trial, ACTG 5071, which found a response rate of 44% among coinfecting patients using Pegasys plus ribavirin (33% for those with genotype 1). In that study, the rate of serious side effects in the Pegasys group was just 15%. Although response rates for HCV/HIV-coinfecting people do appear to be lower than those for people with HCV alone, it is increasingly clear that pegylated interferon is superior to standard interferon for HCV patients with or without HIV. Pegylated interferon also offers promise for HCV/HIV-coinfecting people who have not responded to previous HCV therapy. Maribel Rodrigues-Torres and colleagues from the University of Puerto Rico (abstract 686) reported that after 24 weeks, 27% of coinfecting patients who did not respond to prior interferon monotherapy experienced at least a 2-log decrease in HIV RNA and 30% achieved an undetectable HCV viral load when treated with Pegasys, with or without ribavirin. These response rates were higher than

those previously seen in non-responders.

Finally, Vincent Soriano and colleagues from Madrid (abstract 684) reported that HCV/HIV-coinfecting patients are as likely as those with HCV alone to experience an early response to treatment with standard interferon plus ribavirin.

HIV TREATMENT IN HCV/HIV-COINFECTED PATIENTS

Douglas Dieterich of Mt. Sinai Medical Center and colleagues (abstract 1729) presented data showing that the anti-HIV drug nelfinavir (Viracept) is safe and effective for people with HCV/HIV coinfection. Three percent of those taking nelfinavir or ritonavir (Norvir) experienced grade 3 or 4 elevations of ALT, compared to 7% of those taking indinavir (Crixivan) or saquinavir (Fortovase). Four percent of those taking nelfinavir had grade 3 or 4 AST elevations, compared to 7% of those on indinavir, 8% of those on ritonavir, and 11% of those on saquinavir. Considering ALT and AST together, nelfinavir appears to be the safest protease inhibitor for coinfecting people, with little risk of severe liver toxicity.

But other research continues to show increased risk of liver toxicity in coinfecting patients. J. Olalla from Marbella, Spain and colleagues (abstract 1732) presented evidence that people with HCV/HIV coinfection are more likely to experience elevated liver enzyme levels when taking antiretroviral drugs than those with HIV alone. After analyzing various factors including age, sex, CD4 cell count, HIV viral load, baseline ALT and AST levels, alcohol consumption, and coinfection with HCV or HBV, the researchers found that only baseline ALT level and coinfection with HCV predicted grade 3 or 4 liver enzyme elevations.

High blood fat levels—a side effect associated with antiretroviral drugs—may be less likely to occur in people with HCV/HIV coinfection compared to those with HIV alone. Julio Collazos and colleagues from Vizcaya, Spain (abstract 1733) reported that HCV/HIV-infected patients on HAART had hyperlipidemia (high blood fat) rates similar to those of people not receiving HIV therapy. However, Jose Antonio Maradona and colleagues from Ovideo, Spain (abstract 1734) reported similar cholesterol and triglyceride levels in coinfecting patients and

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those with HIV alone; moreover, in this study lipodystrophy (body fat redistribution) was more common in coinfecting patients.

Mitochondrial toxicity is a known side effect of certain nucleoside analog drugs, and the risk is compounded when these are taken with ribavirin. The RIBAVIC study team detected evidence of mitochondrial toxicity in 22% of those taking ribavirin, ddI, and d4T; 7% of those taking ribavirin and ddI; 1% of those taking ribavirin and d4T; and 1% of those taking ribavirin with neither ddI nor d4T. These results suggest that it may be advisable for HCV/HIV-coinfecting patients to use nucleoside analogs other than ddI or d4T.

HBV TREATMENT

As is the case with hepatitis C, coinfection with HIV appears to accelerate hepatitis B disease progression. However, HBV does not appear to have a negative impact on HIV disease. Ron Palmon from New York University and colleagues (abstract 1738) presented evidence confirming that HBV coinfection does not adversely affect HIV disease progression. In fact, in this study HBV coinfection was actually associated with reduced HIV replication.

Mark Nelson and colleagues from London (abstract 1740) reported that 55% of the 18 HBV/HIV-coinfecting people in their study achieved undetectable HBV viral loads when tenofovir was added to their anti-HIV regimen. Both adefovir and tenofovir appear well tolerated, with very few participants discontinuing treatment due to side effects.

Several researchers presented promising results for experimental treatments for hepatitis B. H. Mommeja-Marin from Triangle Pharmaceuticals and colleagues (abstract 239) reported results indicating that emtricitabine (Coviracil or FTC, a nucleoside analog related to 3TC) shows activity against HBV. At the end of treatment 42% of HBV-infected patients had undetectable HBV viral load and 29% had a serological response. After two years, the rate of drug-resistant mutations was 19%, lower than the resistance rate seen with 3TC.

In contrast to the many presentations on new drugs for hepatitis B, there were none on experimental hepatitis C drug candidates.

DIAGNOSIS

While liver biopsy remains the “gold standard” for assessing liver damage, researchers are seeking non-invasive tests. Dr. Hoffman-Terry and colleagues retrospectively compared liver biopsy results to various surrogate markers of liver damage in 45 HCV/HIV-coinfecting patients. The markers were ALT and AST levels, the international normalized ratio (INR, a standardized measure of blood clotting time), platelet count, abdominal ultrasound, alpha fetoprotein level, CD4 count, and HIV viral load. The researchers found that higher AST level, lower ALT/AST ratio, higher INR, lower platelet count, and abnormal ultrasound results were all associated with greater liver damage (grade 3 or 4 biopsy results).

These results suggest that a combination of markers can potentially indicate which patients are most likely to have liver damage, potentially sparing them from biopsies. However, larger studies are needed, and for now biopsy remains the best way to assess liver damage.

NEW HCV RISK FACTORS

An estimated 20-40% of people with hepatitis C do not have a recognized risk factor. An epidemiological study by Gilles Raguin and colleagues from Paris (abstract 681) looked at possible new HCV risk factors. They interviewed 450 HCV-infected people from 57 French hospitals and 757 HCV-negative controls from the general population. Those who reported a history of injection drug use, transfusion, hemodialysis, or transplant, and those with possible sexual or occupational exposure risks were excluded. The researchers identified 13 independent risk factors for HCV: hospital stays, surgery, digestive endoscopy, diathermy, home care of skin ulcers, cocaine use, gammaglobulin injections, violent sports, use of beauty salons, abortion, varicose vein sclerosing, intravenous injections, and acupuncture. Taken together these risk factors accounted for three-quarters of HCV cases with previously unidentified transmission routes.

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Pegasys

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anticipated to be approved by completion of the program. It was also stated by the company spokesperson that no patient data would be collected for marketing purposes, a practice that has been highly scrutinized by the HCV community in the past. Physicians will be responsible for applying for the sample drug and patients will be given a unique identification number without having to divulge any personal information.

Details of Roche's patient drug assistance program as well as their patient support programs for Pegasys, including and not limited to the free sample program, the patients support program, the patient assistance program and reimbursement services, will be available through 1-877 PEGASYS. Both patients and healthcare providers may call this toll-free number.

HOW IS PEGASYS SUPPLIED?

Pegasys is expected to be available in pharmacies within two weeks. Pegasys is a premixed solution that is dosed at 180 µg for all patients regardless of body weight (except patients on hemodialysis). It is supplied in a clear glass vial providing 1.0ml containing 180µg peginterferon alfa-2a for subcutaneous injection. Pegasys needs to be stored at 36-46 degrees Fahrenheit (2-8 degrees Celsius). Pegasys vials should not be frozen or shaken. In contrast PEG-Intron needs to be reconstituted and is dosed by body weight.

EXPEDITED REVIEW - PEGASYS + RIBAVIRIN

The FDA has granted Pegasys in combination with Copegus® (Roche's ribavirin) priority review status, and a decision is expected by the end of 2002. The FDA grants priority review status to products that, if approved, are expected to offer a significant improvement over existing therapies in the safety or effectiveness of the treatment, diagnosis or prevention of a serious or life-threatening disease. It should be noted that Pegasys plus ribavirin has been widely studied in many difficult to treat patient populations such as African Americans, HIV/HCV coinfecting, transplant, end stage renal disease, cirrhotics, non-responders/relapsers as well as naïve patients. Pegasys/ribavirin is also being studied in the NIH HALT-C maintenance trial designed to study histological improvement (improved liver health) in virologic non-responding cirrhotics that at this time have no

further treatment options.

ABOUT PEGASYS

Pegasys is made when interferon alfa-2a undergoes the process of pegylation in which one or more chains of polyethylene glycol, also known as PEG, are attached to another molecule. In Pegasys, a large, branched, mobile PEG is bound to the interferon alfa-2a molecule and provides a selectively protective barrier. Pharmacokinetic behavior (the way a drug is metabolized and acts within the body) of the end product depends on the length of the PEG and the nature of the link between the PEG and the protein. The high molecular weight (40 kilodalton) branched PEG in Pegasys has been shown to provide sustained pegylated interferon alfa-2a exposure over the entire one-week dosing period with a terminal half-life after subcutaneous dosing in patients with chronic hepatitis C of 80 hours (range 50 to 140 hours) compared to 5.1 (ranged 3.7 to 8.5 hours) for Roferon-A. Maximal serum concentrations occur between 72 to 96 hours post dose and are sustained for up to 168 hours. Steady state levels are reached within 5 to 8 doses and there is no accumulation after steady state is established. The peak to trough ratio at week 48 is approximately 2.0. The peak to trough ratio is low for Pegasys which means that there is a low ratio between the highest and lowest concentration of the drug within each dosing interval. This explains the better tolerability profile and improved quality of life that has been demonstrated over standard interferon in the clinical trials, which has a much higher peak to trough ratio.

PEGASYS EFFECTIVENESS

Pegasys was granted approval based on the results of three pivotal Phase III clinical trials that demonstrated it is an effective treatment for patients with chronic hepatitis C, including patients with bridging fibrosis and compensated cirrhosis, versus treatment with Roferon-A® (interferon alfa-2a). Two of these pivotal trials were published in *The New England Journal of Medicine*. The sustained virological response rate in the Pegasys treated patients was as high as 38 percent in the overall population versus 19 percent in the interferon alfa-2a group. The sustained virological response in patients with cirrhosis treated with Pegasys was as high as 30 percent versus 8 percent in the interferon alfa-2a group. Higher sustained viro-

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Pegasys

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logical response results were also found in patients with genotype 1 (the most common genotype in the U.S. and most difficult to treat) compared to the interferon alfa-2a group. On Pegasys treatment (23 percent) versus interferon alfa-2a (6 percent) achieved a sustained virologic response – a four fold increase in genotype 1 patients. Sustained virological response was defined as undetectable serum hepatitis C RNA levels 6 months post-treatment. In the Peg Intron monotherapy package insert, the overall SVR was 25% and 14% in genotype patients.

PEGASYS SIDE EFFECTS

The most common adverse events (side effects) reported for Pegasys, observed in clinical studies to date, were headache, fatigue, myalgia (muscle ache), pyrexia (feverish), rigors (stiffness), arthralgia (joint pain), nausea, alopecia (loss of hair), injection-site reaction, neutropenia (low white blood cells), insomnia, depression, anorexia (loss of appetite), and irritability. Other less common serious adverse events include thrombocytopenia (low platelets), bone marrow toxicity, cardiovascular disorders, hypersensitivity, endocrine (glands) disorders, pulmonary disorders, colitis, pancreatitis, and ophthalmologic (eye) disorders. The Pegasys phase III monotherapy trials showed a side effect profile very similar to standard interferon with slightly less flu like symptoms and depression. The incidences listed in the package insert for Pegasys versus standard interferon are as follows: Nausea (23% versus 30%), pyrexia (36% versus 41%), rigors (32% versus 42%), myalgia (37% versus 38%), arthralgia (28% versus 29%), headache (54% versus 58%), insomnia (19% versus 23%), dizziness (16% versus 12%), depression (18% versus 19%) and irritability (13% versus 17%). The incidence of neutropenia and thrombocytopenia, however are higher with pegylated interferons, including Pegasys, than with standard interferon, neutropenia (21% versus 8%) and thrombocytopenia (5% versus 2%).

PREDICTING RESPONSE WITH PEGASYS

Clinical trials of Pegasys have shown that patients can determine at 12 weeks if they are unlikely to attain a sustained virological response with Pegasys. Pegasys investigator, Donald Jensen, MD, director of Hepatology at Rush-Presbyterian-St. Luke's Medical

Center, Chicago said, "With Pegasys, we can determine at week 12 of therapy those patients who are unlikely to achieve a sustained virological response to treatment. This reduces the cost and burden of taking therapy for patients who are unlikely to respond to therapy. This may help patients adhere to therapy that can be difficult on them, particularly during the first few months." The Pegasys monotherapy trials showed that, of patients who did not demonstrate by 12 weeks of Pegasys therapy either undetectable HCV RNA or at least a 2 log₁₀ drop in HCV RNA titer from baseline, only 2% achieved a sustained virological response. (2 log₁₀ drop is determined by taking two zeros off the end of the number. For example a 2 log₁₀ drop from a baseline HCV RNA of 6 million copies is 60 thousand copies or 6,000,000 to 60,000.) Predicting response to therapy using the 12 week model is a good tool for physicians and patients to use to help make decisions regarding whether to stay on or stop therapy. The 12 week predictability model however was established during the Pegasys mono and combination drug development program. This new marker of predictability was developed solely on data derived from naïve patients (patients who had not been previously exposed to interferon therapy). For this reason the HCV community has voiced many concerns that using this model would enable insurance companies to uniformly deny coverage for all hepatitis C patients not responding at 12 weeks of therapy. There is data to suggest that certain populations may require an extended period of interferon therapy in order to establish a virologic response. In addition there is much data to suggest that patients with more advanced liver disease can respond histologically to full or extended courses of interferon therapy even in the absence of virologic response. For this reason the community feels very strongly that as algorithms are established for treatment moving forward, the 12 week predictive model is only used as a discussion point and not as a marker to determine whether withdrawing therapy is appropriate. Another example to further support this position is patients who would benefit from therapy for reduction in symptoms even in the absence of virologic response as well as naïve patients with advanced disease who have no other options in the near future outside of interferon.

Clinical Trials **National Trials**

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