

Digestive Disease Week Conference: Summary of HCV Presentations

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Alan Franciscus, Editor-in-Chief

PART I

Part I of this report will focus on the treatment of hepatitis C and what was learned from the information presented at the Digestive Disease Week 2003 Conference in Orlando, Florida. Future parts of this conference summary will include data presented on the epidemiology and natural history of hepatitis C as well as side effect and toxicity issues associated with the treatment of hepatitis C.

Current and Future Considerations

While the incidence of new infections of hepatitis C has decreased in the recent years, the complications of long-term hepatitis C are increasing and the morbidity (the number of people sick in the general population) and mortality (the death rate) due to hepatitis C virus infection are expected to rise significantly over the next decade. In patients with long-term hepatitis C, cirrhosis is detected in approximately 20% of patients which puts them at further risk for hepatocellular carcinoma. Therefore, it is important to research and develop new methodologies for identification and treatment of progressive disease in patients with hepatitis C.

The recent NIH Consensus on Hepatitis C Disease Management

states that *all hepatitis C patients are potential candidates for treatment*. It has also been well documented that patients with hepatitis C have significant psychosocial issues due to the complications and stigmata of the disease. Therefore, it is very important that investigators continue to work on identifying strategies to make treatment and potential eradication of the virus an opportunity for everyone infected with hepatitis C regardless of socio-economic considerations.

The Current State of HCV Treatment

Treatment with pegylated interferon and ribavirin has increased the percentage of chronically infected hepatitis C patients who are able to achieve a sustained viral response over the previous gold standard, Rebetron.

Pegylated interferon overall sustained response rates in prospective trials are as high as 61% with pegylated interferon alpha 2a (Pegasys) and 53% with pegylated interferon alpha 2b (Peg Intron), and 46% - 51% for genotype 1 with Pegasys and 42% for Peg Intron. Additionally, Pegasys has been able to demonstrate increased efficacy over Rebetron in the most difficult to treat patients, both those with genotype 1 and high viral load (>2 million copies/ml) as well as those patients with advanced liver disease.

Unfortunately, the increased effectiveness of pegylated interferon plus



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ribavirin therapy has also resulted in increased hematological side effects, such as anemia and neutropenia. Most of these types of side effects respond to either reduced doses of one or both of the medications or to the use of growth factors, such as erythropoietin (Procrit) or Granulocyte Colony-Stimulating Factor ((G-CSF)-Neupogen).

Patients who are deemed “non-responders” (do not show a decline in HCV RNA during treatment), or “slow responders” (patients who have a very delayed decline in their HCV RNA during treatment) are still difficult to treat, but strategies presented at the Digestive Disease 2003 Conference show promise for improving these outcomes although much more research is still needed to optimize treatment in difficult to treat patient groups. It is apparent from the conference that in the near future hepatitis C therapy will consist

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Legislators Introduce Federal HCV Plan

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Liz Highleyman

On May 23, Senators Kay Bailey Hutchison (R-TX) and Edward Kennedy (D-MA) introduced the Hepatitis C Epidemic Control and Prevention Act (S 1143), a bill that would require the federal government to develop a comprehensive national treatment and prevention plan for hepatitis C—the first federal response to the HCV epidemic. The legislation would create HCV public awareness campaigns; implement screening, counseling, and surveillance programs; and fund professional training and HCV research.

The bill is supported by the National Hepatitis C Advocacy Council, a new coalition composed of nearly two dozen organizations—including the Hepatitis C Support Project—spearheading the same kind of advocacy around HCV that has successfully garnered more attention and funding for HIV/AIDS.

It is currently estimated that 4 million people in the U.S. are infected with HCV and about 15,000 die from complications related to the disease each year. Researchers estimated in the April 2003 issue of *Liver Transplantation* that while the rate of new HCV infections has decreased dramatically, the prevalence of cirrhosis and its complications will likely increase over the next 10-20 years: decompensated cirrhosis by more than 100%, liver cancer by about 80%, and liver-related deaths by 180%. If untreated, as many as one-third of people infected in the past may develop cirrhosis by the year 2020.

Please write or call your congress members and ask them to support this important legislation. A House of Representatives companion bill to S1143 is expected to be introduced within weeks. See www.senate.gov and www.house.gov for addresses and phone numbers.



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of continued efforts to individualize and maximize current therapies (pegylated interferons in combination with ribavirin) but also include the use of mycophenolate mofetil and other immunomodulators as well as ribavirin analogs (levovirin and viramidine). One physician pointed out that up until now, current treatment strategies have been very rigid—one size fits all. But now we have to “think outside the box” since one treatment strategy can not begin to address the complexities

of the hepatitis C virus. future of hepatitis C therapy will consist of continued efforts to individualize and maximize the therapies with pegylated interferons in combination with ribavirin as well as the use of mycophenolate mofetil and other immunomodulators as well as the use of ribavirin analogs (levovirin and viramidine). One physician pointed out that up until now, current treatment strategies have been very rigid—one size fits all. But now we have to “think outside the box” since one treatment strategy can not begin to address the complexities of the hepatitis C virus.

Peg Intron Dosing

Flamm and colleagues presented interim data on an ongoing prospective, randomized, controlled, multicenter trial comparing the efficacy and safety of the current approved dose of pegylated interferon alfa-2b (Peg-Intron - 1.5 mcg/kg/wk) plus ribavirin (800-1400 mg/day) with a lower dose of pegylated interferon alfa-2b (Peg-Intron - 1.0 mcg/kg/wk) and ribavirin (800-1400 mg/day).

One hundred and three patients out of 246 had completed at least 24 weeks of therapy at the time of the presentation. In the low dose group, 52% were negative for HCV RNA (viral load) at 24 weeks, as were those people receiving the higher dose. Of the patients who were negative for HCV RNA, 41% of the patients receiving the low dose of Peg Intron exhibited extensive fibrosis on liver biopsy compared to 45% of those receiving the higher dose.

The study authors concluded that viral response rates appeared equal in both treatment groups with no difference noted in drug discontinuation rates. As expected, there was a trend to fewer side effects in the group that received the lower Peg Intron dose.

What is interesting from this presentation is that earlier published monotherapy trials with pegylated interferon alpha 2b (Peg Intron) showed equal effectiveness between regimens involving pegylated interferon alfa-2b at 1.0 mcg/kg/wk and 1.5 mcg/kg/wk, but Schering Plough pursued the 1.5 mcg/kg/wk dose for their combination approval. If this combination trial data presented at DDW can show equal benefit with the lower pegylated interferon alpha 2b dose at the end of the study, it may aid in decreasing side effects associated with pegylated interferon alpha 2b therapy, without decreasing effectiveness. It does however challenge the weight based theory,

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Bone Loss and HCV

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Liz Highleyman

Bone loss (osteopenia and osteoporosis) is one of the many conditions associated with chronic hepatitis B or C, although it is not yet clear why liver damage—and viral liver disease in particular—leads to bone destruction. Researchers have reported widely varying rates of bone loss in people with liver disease, with most finding that it is worse in people with more advanced liver damage. By keeping your HCV under control through effective treatment, therefore, you may be able to reduce your risk of osteopenia and osteoporosis. In addition, there are other steps you can take—ranging from exercise to medication—to help prevent or treat bone loss.

What is Bone Loss?

Bone loss refers to loss of minerals from the bones. As the bones become more porous and brittle, they are more likely to break, or fracture. Bone mineral depletion is a “silent” condition, and usually has no symptoms. Bone loss encompasses two related conditions:

- **Osteopenia:** a more mild condition characterized by moderate loss of bone mineral density.
- **Osteoporosis:** a more serious condition in which a more substantial amount of bone is lost.

Bones are made up of cells embedded in an intracellular scaffolding, or matrix, made up largely of minerals. Bones are constantly being “recycled,” or remodeled. Cells called osteoclasts dissolve bone and allow the minerals to be re-absorbed, while cells called osteoblasts build new bone. Normally,

these two processes are in balance. But sometimes bone is destroyed faster than it can be rebuilt, causing overall bone mineral density to decrease.

What Causes Bone Loss?

Many different factors can contribute to bone mineral loss. Osteopenia and osteoporosis are most often associated with older people—particularly post-menopausal women—and, indeed, people start to lose about 0.5–1.0% of their bone tissue per year after age 35. But in addition to the demineralization that normally occurs with

Osteopenia:
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a more serious condition in which a more substantial amount of bone is lost.

aging, various diseases, dietary deficiencies, medications, and lifestyle factors can also increase the risk of bone loss.

Research has shown that progressive liver disease is associated with accelerated bone loss. For example, Sif Ormarsdottir and colleagues reported in the January 2002 issue of the *European Journal of Gastroenterology*

and Hepatology that people with higher Child-Pugh cirrhosis scores had more bone loss in their spines and hip-bones than those with lower scores, and that higher bilirubin levels were associated with greater bone loss. A study reported at the 2001 AASLD conference found that about three-quarters of people with end-stage liver disease (ESLD) had either osteopenia or osteoporosis, and that people with viral hepatitis were five times more likely to have bone loss compared with those who had liver disease due to other causes. Likewise, Elizabeth Carey and colleagues from the Mayo Clinic found that people with ESLD related to HCV had lower bone mineral density than people with alcoholic liver disease. At the 2002 EASL conference, Ingolf Schiefke and colleagues reported decreased bone mineral density even in non-cirrhotic people with hepatitis B or C, with higher rates in HCV-infected people compared with HBV-infected people.

It is not completely understood how liver dysfunction in general, or viral liver disease in particular, contributes to bone loss, but there are several theories; many researchers believe multiple factors may interact. People with chronic disease (of any sort) often have abnormal levels of hormones, immunoglobulins (antibodies), and intercellular messenger chemicals. Low levels of the sex hormones—testosterone and estrogen—are known to predispose people to bone loss, while elevated levels of certain cytokines can promote destruction of bone by the osteoclasts. In people with advanced liver disease, the damaged liver may not be able to produce enough insulin-like growth factor 1 (IGF-1), a hormone that stimulates the osteoblasts to

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Extrahepatic Manifestations of Hepatitis C

Part One: Essential Mixed Cryoglobulinemia

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Kara Wright, PA-C

There are several extrahepatic diseases (diseases of organs other than the liver) associated with chronic hepatitis C infection. Although rare, about 38% of patients with hepatitis C experience at least one extrahepatic manifestation of the virus. Most of these diseases appear to be directly related to the viral infection. In this series, we will discuss the different disorders by starting with the blood disorder, essential mixed cryoglobulinemia (EMC).

Cryoglobulinemia is a medical condition that is caused by proteins called cryoglobulins present in the blood. Cryoglobulins are abnormal proteins that precipitate (clump together to form a solid) from the blood when it is chilled and redissolve into the blood upon rewarming. These proteins can be deposited in the small and medium sized blood vessels, which restricts blood flow and leads to further problems. These cryoglobulins can af-

fect many different bodily systems, causing pain and dysfunction.

It is unclear why cryoglobulins are produced. The exact cause of essential mixed cryoglobulinemia is not known, which is why it is called “essential.” However, it is considered to be an autoimmune disorder. (Autoimmune disorders are caused when the body’s immune system, which is meant to defend the body against bacteria, viruses, and any other foreign product, malfunctions and produces antibodies against healthy tissue, cells and organs.) The hepatitis C virus has the ability to bind to certain cells called B lymphocytes, which promotes production of autoantibodies.

Several studies of patients with essential mixed cryoglobulinemia found that 95% of patients had signs of HCV infection including HCV antibodies or virus. This suggests a strong association between HCV and cryoglobulinemia. The prevalence of cryoglobulinemia is particularly high in hepatitis C (54.3 %) as compared to other forms

of viral hepatitis (hepatitis B 15 %; other liver disorders 32 %). It correlates with longer duration of disease and the presence of cirrhosis as scarring of the liver appears to be higher in patients with cryoglobulinemia. Patients with chronic HCV infection and EMC are more frequently females, cirrhotics and have a longer duration of HCV infection. Only a minority (approximately 10%) is associated with actual signs and symptoms of cryoglobulinemia disease. The other 90% have no symptoms or organ dysfunction.

The symptoms of EMC are caused by the deposition of cryoglobulins into the small blood vessels. This results in an abnormal thickness of the blood, which can lead to many problems, such as stroke or blood clots in the eyes leading to blindness. It also causes red or purple blotchy skin suggesting some form of vasculitis (inflammation of the vessels). Vasculitis of arteries can result in blockage of arteries leading to damage to the organ(s) supplied by the affected blood vessels, such as the skin, kidneys, or elsewhere. This can also lead to pain in the joints (arthralgias), enlargement of the lymph nodes, and peripheral neuropathy (numbness or weakness in feet and hands due to nerve damage from decreased blood flow). Other common symptoms are recurrent pain in the abdomen, heart attack, and bleeding in the lungs. Weight loss can occur as well as poor appetite.

EMC can cause renal disease in up to 60% of patients due to the deposition of proteins in the kidney. Symptoms of this include blood in the urine, and protein in the urine found by a simple urine test.

CRYOGLOBULINEMIA

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The diagnosis of EMC is first suspected due to the history the patient provides. Most patients first notice the characteristic blotchy skin rash. A simple blood test can be done to assess for cryoglobulins by drawing blood, then cooling it to see if precipitation occurs. Blood tests can also be done to determine the exact type of abnormal protein in the blood. A biopsy of a skin lesion can often confirm that cryoglobulins are responsible for the patient's signs and symptoms.

Treatment is indicated in patients with progressive systemic disease affecting the small blood vessels, kidneys, liver or peripheral nerves. Essential mixed cryoglobulinemia is treated with combinations of medications which reduce inflammation and suppress the immune system. Medications used include nonsteroidal anti-inflammatory drugs (ibuprofen, aspirin, and others), cortisone preparations (prednisone, prednisolone), as well as medications that suppress the immune system.

Plasmapheresis (removing plasma from the body and replacing it with a saline solution to remove the circulating cryoglobulins) in conjunction with steroids and cyclophosphamide (chemotherapy) to prevent new antibody formation is used in severe cases. This regimen may lead to a reduction in the plasma concentration in 55-87% of patients. Renal function can usually be stabilized by this regimen. The two major concerns are: possible enhancement of HCV replication due to immunosuppression and possible exacerbation of low-grade non-Hodgkin's lymphoma. Some facilities can filter the cryoglobulins out of the patient's plasma and reinfuse the patient's own plasma.

In patients with hepatitis C, as a reduction in the HCV virus in patients responding to interferon treatment occurs, cryoglobulin levels decrease and skin lesions and symptoms diminish. Recent studies have demonstrated some benefit of using interferon-alfa for those patients with evidence of hepatitis C virus. Approximately 50% of patients with hepatitis C associated cryoglobulinemia appear to respond to interferon-alfa, 3-5 MUs given three times weekly, for 12-18 months. Since decreasing the viral load leads to EMC disease improvement, pegylated interferon with ribavirin would be the best option since it has significantly improved hepatitis C viral response. If the patient has renal impairment, pegylated products are not advised. After therapy discontinuation, patients often experience a rebound of signs and symptoms of EMC. Antiviral therapy should be delayed for 2-4 months in patients with severe disease who are initially treated with plasmapheresis and immunosuppressive therapy.

The prognosis and natural history of the illness is not predictable. Kidney damage can be serious, and recent reports state that permanent failure of the kidney occurs in approximately 10% of patients. Death can occur, usually from serious heart disease, infection, or brain hemorrhage. Approximately 1/3 of patients undergo partial or complete remission, while most have a slowly progressive course that may be complicated by periodic acute exacerbations.

In conclusion, EMC associated with chronic HCV infection should no longer be referred to as "essential" but rather as hepatitis C associated cryoglobulinemia. Many patients with chronic HCV infection may have cryoglobulinemia, but most do not suffer from complications of the disease. If you have any of these symptoms, you should discuss them with your health care provider.



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The Hepatitis C Support Project



An Artificial Liver Device

A Potential Breakthrough in the Management of Acute Liver Failure

■■■■
Alan Franciscus
Editor-in-Chief, HCV Advocate

Acute liver failure is a potentially fatal condition that affects about two thousand people in the United States each year. The majority of cases of liver failure usually develop over many years and are the outcome of prolonged insult to the liver either by a virus (chronic hepatitis B or hepatitis C) or by toxin or alcohol abuse. On the contrary, acute liver failure can develop in a very short period, days or months as in the example of Tylenol (acetaminophen) overdose.

Persons diagnosed with acute liver failure have only a small chance of recovery and survival, but a new technology that has been used to develop an artificial liver may bring hope for end-stage liver disease patients whose options are otherwise limited to a liver transplant. Donor livers are in grave shortage in the United States and patients in acute liver failure may have to wait months or even years for a compatible donor organ with often a negative outcome during the wait.

The new technology is known as ELAD which stands for extracorporeal liver device. The technology has been

developed by VitaGen located in La Jolla, California. It is the first technology of its kind and actually integrates functioning human liver hepatocytes (liver cells) into the process. The human hepatocytes help assist and support the exhaustive work of the patient's damaged and failing liver. This new ELAD technology is the first liver assist system that utilizes hepatocytes from humans rather than pigs.

The ELAD device will be undergoing many clinical tests in the coming months. It is hoped that this device will serve in the future as a bridge to successful transplantation. The ELAD device is a closed system that joins to a patient through a catheter inserted into the main vein in the neck. After the blood is initially filtered, the residual plasma is funneled through cartridges in the device where hepatocytes (human liver cells) help accomplish much of the liver's critical functions, such as energy storage and regulation, bile production, blood detoxification and the production of clotting factors and many essential proteins. The filtered blood and ELAD-treated plasma are then returned to the patient.

Investigators are very optimistic of the role that the ELAD device will

play in managing acute liver failure in the future. The liver has a remarkable ability to regenerate itself so if the patient in acute liver failure can be sustained early on, it is feasible that they may not need liver transplantation and may recuperate without any substantial liver problems, including chronic liver disease.

The ELAD is not yet FDA approved in the United States but an initial phase clinical trial conducted in Great Britain and the United States showed hopeful results. In the initial trial, almost 92% of patients who had been selected at random to receive treatment with the ELAD achieved either a successful bridge to transplantation or full recovery. In the comparative control group of patients who received only current standard care, only 42% achieved the same positive outcome. In an analysis of overall results in twenty-five patients, including those not listed for transplantation, 81% improved on the device compared to only about 50% of those in the control group. VitaGen will now need to conduct a subsequent clinical trial to test ELADs with a primary objective of evaluating overall effectiveness, safety and tolerability and a secondary objective of evaluating appropriate inclusion/exclusion criteria and system performance with regard to specific endpoints. This next trial in ELADs overall development plan will be conducted in about forty patients.

Currently there are no effective therapies for patients with acute liver failure so this new technology brings hope and could potentially save many lives.



The new technology is known as ELAD which stands for extracorporeal liver device. The technology has been developed by VitaGen located in La Jolla, California. It is the first technology of its kind and actually integrates functioning human liver hepatocytes (liver cells) into the process.

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BONE LOSS

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build more bone. Thyroid and parathyroid dysfunction in people with hepatitis may also play a role in bone loss.

Several medications have been linked to bone loss. Long-term use of steroids, particularly the glucocorticoids (e.g., prednisolone, hydrocortisone) is one of the major risk factors. Drugs from this family are often given after a transplant to prevent rejection of the new organ. This is one reason why people who have received a liver transplant are at high risk for bone fractures. Some studies have shown that people taking ribavirin to treat hepatitis C are more likely to develop osteopenia and osteoporosis, but other researchers have not found an elevated risk. Likewise, in recent years there have been increasing—but conflicting—reports that anti-HIV medications (both protease inhibitors and nucleo-

side analogs) may be associated with bone mineral loss, a concern for people coinfecting with HIV and viral hepatitis. Some researchers believe that both ribavirin and the nucleoside analogs may contribute to bone loss through mitochondrial toxicity and lactic acidosis (a high level of acid in the blood), which may cause important minerals to be leached out of the bones.

Other risk factors for bone demineralization include alcohol use, tobacco smoking, lack of exercise (especially being bedridden for long periods), race (Caucasians and Asian have higher rates of bone loss, while African-Americans have lower rates), and nutritional deficiencies—notably calcium and vitamin D. People with chronic diseases may be malnourished or suffer from wasting, in which case there may not be enough nutrients to build strong bones, or minerals may be leached out of the bones to provide for the normal needs of the body. Vitamin

D deficiency in particular is very common in people with ESLD. In addition to the harm it can do to the liver, even a moderate amount of alcohol is strongly linked to osteopenia. Finally, the tendency to lose bone is genetic, and people who have stronger, denser bones when they are young are less likely to develop osteopenia and osteoporosis later on.

Preventing and Treating Bone Loss

Fortunately, there are several steps you can take to prevent or minimize bone loss. The first line of defense is a healthy lifestyle: avoid tobacco smoking and alcohol use, get adequate amounts of calcium and Vitamin D, and exercise regularly. Good calcium sources include dairy products, soy products, beans, fish with bones, and green vegetables. Some people with advanced liver disease may need supplements, but consult your doctor or a nu-

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BONE LOSS

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tritionist because excess vitamin D can be toxic to the liver. (Vitamin D can also be safely absorbed through the skin during exposure to the sun.)

Regular weight-bearing exercise—such as weight lifting, walking, and climbing stairs—is one of the best ways to maintain strong bones. But some exercises that are good for cardiovascular health (such as swimming) do not strengthen the bones.

Medications including alendronate (Fosamax) and risedronate (Actonel) help restore bone mass and are approved by the FDA for treating osteoporosis. Supplements of calcitonin, a natural chemical that helps regulate bone remodeling, have been shown in some studies to reduce the risk of bone fractures. Until recently, many postmenopausal women were routinely prescribed hormone replacement therapy (HRT) to prevent osteoporosis. But since a large study revealed in July 2002 that HRT can increase the risk of breast cancer, heart attacks, and strokes, use of hormones solely to maintain bone health is no longer recommended. However, supplemental testosterone may be used in men and women who have low hormone levels (hypogonadism).

Much remains to be learned about bone loss in people with hepatitis B or C. In the meantime, getting treated for HBV or HCV (if appropriate for you) and making certain lifestyle changes can improve your overall health while helping minimize bone damage. Until more is known, ask your doctor about getting a baseline DEXA (dual energy x-ray absorptiometry) bone density measurement and regular bone density screenings, especially if you have other risk factors for osteopenia and osteoporosis.



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which Schering claims is needed to customize Peg-Intron according to a person's weight.

HCV and Children

There are currently 250,000 children in the United States infected with hepatitis C. At one time, the major cause of HCV in children was from blood transfusions, but the majority of newer cases are from vertical transmission (mother to child). Complications from the transfusion era HCV infections in children are becoming more well-known as those children age. As in the adult population, more children are progressing on to serious disease.

Currently there are no medications approved by the Federal Drug Administration (FDA) to treat chronic hepatitis C in children. Traditional alpha interferon monotherapy has been shown to provide sustained viral response rates in 37% of children, but to date there are minimal trials involving the use of ribavirin in combination with interferon in children.

One presentation of particular interest by Schwartz at DDW involved the evaluation of Pegasys (pegylated interferon alpha-2a) monotherapy for treatment of chronic hepatitis C in children. While Pegasys monotherapy and in combination with ribavirin has been shown to be safe and effective in the treatment of adults with chronic hepatitis C infection, there is not yet any published data on the safety and efficacy of peginterferon use in the treatment of children.

The primary objective of the study presented at DDW was to evaluate the safety, efficacy and pharmacokinetics (how the drug distributes, metabolizes and is excreted from the body) of Pegasys in children with chronic hepatitis C. This is a multi-center,

open-label study of treatment-naïve children with established chronic hepatitis C.

The children received Pegasys once weekly for 48 weeks with a 24-week post-treatment follow-up. The dose was normalized for patient body surface area (BSA). Multiple blood samples were obtained to determine single-dose and multiple-dose pharmacokinetics. Adverse events (side effects) were assessed by clinical exam. HCV RNA was measured at weeks 12, 24, 48 and 72.

Fourteen children, 8 males, 6 females, aged 2-8 (median=3.5 yrs) years were enrolled; the majority (13 of 14) were Caucasian and genotype 1 (12 of 13). Hepatitis C was acquired by vertical transmission in 11 children.

At weeks 24, 48, and 72, 57% (8 of 14), 43% (6 of 14) and 38% (5 of 13) of children, respectively, were HCV RNA negative. The most frequently reported side effects were pyrexia (feverish), headache, vomiting, anorexia (loss of appetite) and abdominal pain; no serious adverse events were observed. The majority of these side effects were mild in intensity.

Four children were withdrawn from therapy (1 due to lack of viral response at week 24; 2 due to elevated transaminases; 1 due to exacerbation of baseline hypertriglyceridemia). Five children required dose reductions due to neutropenia (low white blood cells).

The investigators concluded that Pegasys (peginterferon alfa-2a) was well tolerated in children although concentrations of peginterferon alfa-2a were slightly higher than in adults following a fixed 180 microgram dose. Additionally, the effectiveness of Pegasys monotherapy in children appears higher than that reported for adults and approaches that for standard interferon in combination with ribavirin in children. These results support further study of Pegasys, with and

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without ribavirin, in children with chronic hepatitis.

Methadone and Pegylated Interferon

The majority of injection drug users (IDUs) are infected with hepatitis C virus and are often treated with methadone maintenance therapy (MTT). There has been some data in the past to suggest that methadone may suppress interferon-mediated antiviral activity so the primary objective of a study presented by Sulkowski was to evaluate the potential for pharmacokinetic (PK), pharmacodynamic (PD) and clinical

drug interactions with the concomitant use of 180 mcg pegylated interferon alpha 2a (Pegasys) and methadone in patients with chronic hepatitis C undergoing methadone maintenance therapy.

The pharmacokinetics and pharmacodynamics of Pegasys were evaluated after single and multiple weekly 180 mcg doses in 24 patients with chronic hepatitis C on methadone maintenance therapy. Pegasys' effect on methadone pharmacokinetics was assessed by the comparison of methadone's pharmacokinetics before and after multiple doses of Pegasys.

The majority of patients enrolled were male (63%), Caucasian (63%), weight-50 to 124 kg, and 34 to 57 years old. Patients received stable daily methadone doses of 30 to 150 mg. Pegasys pharmacokinetics at week 1 and week 4 were similar to Pegasys pharmacokinetics determined from historic data in chronic hepatitis C patients not receiving methadone maintenance therapy. Methadone pharmacokinetics were similar at baseline and after 4 weeks of Pegasys treatment. Twelve of 20 (60%) patients demonstrated a virological response (undetectable [<600 IU/mL] or a 2-log¹⁰ drop in HCV RNA serum concentrations) by treatment week 4.

The most frequently reported side effects included headache, myalgia, pyrexia, fatigue and anorexia; most were mild or moderate in intensity. No signs of opioid withdrawal were observed. No patient modified methadone or PEG-IFN doses during the study. One subject withdrew prematurely due to poor venous access.

The authors concluded that the use of Pegasys in patients on methadone maintenance therapy is well tolerated and that the pharmacokinetics of either Pegasys or methadone are not altered, and that the biologic response was similar to that in healthy subjects. Furthermore, the HCV RNA decline was similar to that seen in chronic hepatitis C patients not receiving methadone

maintenance therapy. This data strongly suggests that methadone maintenance does not impair the antiviral activity of Pegasys.

Retreatment

While the overall sustained response of naïve hepatitis C patients is 53-61% with the newer pegylated interferon/ribavirin combinations, the interest and need for successful treatment of non responders gained a considerable amount of attention at DDW 2003. In interferon (IFN) non-responders with chronic hepatitis C, retreatment with standard interferons combined with ribavirin showed sustained virologic response rates of 20-30%. Concerning the effectiveness of antiviral retreatment in patients not responding to a previous treatment with standard interferons combined with ribavirin, only limited data with conflicting results are available.

In one study presented at DDW by Jacobson, 321 patients who had failed or relapsed from an initial response to treatment for hepatitis C using interferon or interferon with ribavirin were treated with pegylated interferon alpha-2b (Peg Intron) plus ribavirin. The patients were assigned either of two groups:

- Group 1 - patients received either Peg Intron 1.0 mcg/kg/wk plus 1000-1200 mg/day of ribavirin
- Group 2 - patients received 1.5 mcg/kg/wk of Peg Intron plus 800 mg/day of ribavirin

Patients were treated for 48 weeks but discontinued at 24 weeks if no response was seen. There were no differences between the 2 groups of patients requiring discontinuation of therapy while 27% of group 1 patients required dose reduction compared to 34% of patients in group 2.

It was reported that dose reductions did not predispose the patients to treatment failure, as has been hypoth-

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esized by some. While the sustained viral response was lower in African Americans (15%) in this report, the study was not designed to detect differences in subgroups, so no solid conclusions should be made.

What the researchers did find was that patients who had previously responded to a combination of interferon and ribavirin therapy and relapsed were the ones most likely to respond to the Peg Intron plus ribavirin therapy (group 1 - 32% vs. group 2 - 47%). They also reported that the medication regimen of 1.5 mcg/kg/wk of Peg Intron plus 800 mg/d of ribavirin was more effective than the lower dose of Peg Intron plus 1000-1200 mg of ribavirin. Overall, patients who were initial non responders, and were genotype 1 positive, had the poorest response to retreatment (6-10%), while the group with the best overall response to retreatment were those who had been initial responders to the combination therapy but had relapsed.

In another study in an attempt to identify predictors of a non response, histological features were compared in patients who had failed initial therapy with standard interferon or interferon plus ribavirin. In a study by Hassenein, patients were randomized to receive either Peg Intron 1.5 µg/kg/wk plus 800 mg/day of ribavirin (group A) or 1.0 µg/kg/wk of Peg Intron plus 1000-1200 mg/d of ribavirin (group B). A biopsy was performed at entry into the study. In general, 5% of patients had no fibrosis upon entry to the study while 23% and 21% had mild or moderate fibrosis (respectively) and 50% exhibited severe fibrosis. The overall inflammation score was 6.07. Post treatment biopsies indicated an improved inflammation score (5 vs. 3,

$p=.031$) overall, but no improvement in fibrosis. However, if they had cleared the virus by the end of the 48-week therapy, a significant improvement was seen for both inflammation and fibrosis. Overall, 35% of patients were viral load negative and 65% were viral load positive at the end of therapy. The sustained virological response rates will be presented at a later date.

Another study presented at DDW by Tueber evaluated the efficacy and safety of a retreatment with Peg Intron (pegylated interferon alpha2b) plus ribavirin in 240 patients (162 males, 78 females, mean age 45.5 years) not responding to previous antiviral treatment with standard interferons combined with ribavirin. Patients received PEG-Intron 100 mcg/week subcutaneous (s.c.) for 8 weeks followed by 50 microgram/week (s.c.) for 40 weeks in combination with ribavirin 800 mg/d for 48 weeks. Treatment was discontinued in patients with detectable serum HCV-RNA after treatment week 24.

A virologic end-of-treatment response was achieved in 25 of 240 (10.4%) patients, while after a follow-up period of 24 weeks a sustained virologic response was observed in 15 of 240 (6.3%) patients. Patients infected with HCV genotype non-1 were more likely to respond to antiviral retreatment than patients infected with HCV genotype 1 (6.8% vs. 17%).

The authors concluded that "Antiviral retreatment with pegylated interferon-alfa-2b (Peg Intron) plus ribavirin in this flat and low dose showed only a limited therapeutic efficacy in patients with chronic hepatitis C not responding to previous treatment with standard interferons and ribavirin". In these patients, virologic response rates were disappointing and in the future new strategies for this population need to be explored which may include longer duration of therapy or alternate dosing regimens. .

Another study in this population

was presented at DDW looking at what would be the role of Peg Intron (pegylated interferon alfa-2b) and ribavirin therapy for patients with chronic hepatitis C (HCV) who have previously failed interferon-based therapies.

The objective of the current study presented by Sulkowski was to compare the safety and efficacy of continuous weight-based (adjusted throughout therapy) vs. categorical weight-based pegylated interferon alpha-2b plus ribavirin in patients who have failed to achieve sustained virologic response after previous interferon plus ribavirin treatment. This is an open-label, multicenter, randomized clinical trial.

Patients were randomized to receive 800mg ribavirin twice a day with either Continuous weight adjusted pegylated interferon alpha-2b (1.5 mcg/kg) QW (n=259) or Categorical weight adjusted pegylated interferon alfa-2b (100 mcg if <80kg, 150 mcg if >80kg) for 48 weeks. HCV RNA was evaluated at baseline (BL), week 12 for early virological response, and end of treatment. Intent-to-treat response rates were compared using Fischer's Exact Test and logistic regression.

Five hundred and seventeen patients were enrolled and took at least one dose of drug. The median age was 47 years, and the patients were 64.8% male, 76.8% Caucasian, 13.5% Black and 8.3% Asian. HCV Genotype 1, 90.5% and 2 or 3, 9.5%. Two hundred-seven patients completed 48 weeks of treatment. 278 patients withdrew before end of treatment; the primary reason for withdrawal was viral non-response.

No differences were observed in adverse events between treatment groups, including neutropenia ($p=0.7$). Early virological response and end-of-treatment response for continuous and categorical were 40.0%/24.3% and 31.0%/25.6%, respectively ($p=0.47$ and 0.64). Early virological response

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for relapsers and non-responders were 50.6%/34.9% and 23.9%/20.3%, respectively ($p < .0003$). End of treatment response was 23.8% in genotype 1 and 36.7% in genotype 2 and 3 ($p=0.046$).

The investigator concluded that continuous and categorical weight-based dosing of pegylated interferon alpha-2b plus ribavirin had similar safety and efficacy in the re-treatment of patients who failed or relapsed after original interferon-based therapy for HCV. Among non-responders to prior therapy, the end-of-treatment response was more than 20%; as expected the end-of-treatment response was higher among relapsers.

These data suggest that pegylated interferon alpha-2b plus ribavirin may be effective in persons who initially failed to respond or relapsed after previous interferon plus ribavirin treatment.

What is interesting from this presentation is that the results are somewhat contradictory to Flamm's conclusion (discussed previously) which claim that pegylated interferon alpha 2b, Peg Intron, needs to be weight-based dosed to customize and enhance effectiveness.

Retreatment of Genotype 1

While HCV treatment response rates have improved with pegylated interferon plus ribavirin therapy, rates of sustained virologic response, especially in HCV genotype 1, still remain less than desirable, with sustained virological response rates in the 29-37% range for Peg-Intron plus ribavirin and in the range of 42% to 51% for Pegasys plus ribavirin. Furthermore, sustained virologic response for genotype 1 high viral load (>2 million copies/ml) remains 30% for Peg Intron plus ribavirin and 41% to 46% for Pegasys plus ribavirin—which includes

the majority of people with HCV in this country. Response rates to that therapy are even lower in patients who previously did not respond to standard interferon plus ribavirin therapy—in the 11 to 36% range.

Several studies have shown improved sustained response rates in genotype 1 and previous nonresponders treated with consensus interferon (CIFN). In a study presented at Digestive Disease Week 2003 by Kaiser, investigators evaluated the effectiveness of different doses of consensus interferon induction therapy—either 9 microgram QD for 16 weeks or consensus interferon at 27 microgram QD for 4 weeks, followed by 12 weeks of consensus interferon at 18 microgram QD—which was followed by a CIFN plus ribavirin combination treatment in patients who were previous nonresponders to pegylated interferon and ribavirin therapy.

The study enrolled 23 patients, all of whom had elevated ALT values and were HCV viremic, 22 of whom were HCV genotype 1. Liver biopsies in these patients revealed that 7 had bridging fibrosis or cirrhosis. After the initial 16 weeks of consensus interferon monotherapy, 36% and 50% of the patients achieved undetectable serum HCV-RNA in the low and high dose consensus interferon groups, respectively. After 24 weeks of consensus interferon and ribavirin therapy, a negative HCV RNA was observed in 49% and 57% of the low dose and high dose consensus interferon and ribavirin patients, respectively. Side effects led to consensus interferon dose reduction in 2 patients and discontinuation in 1 patient.

The authors concluded, “Consensus interferon daily dosing/induction therapy together with subsequent ribavirin combination therapy thus shows response rates in about half of previous peginterferon combination therapy non-responders. If these pri-

mary response rates translate into equally strong sustained response rates, an effective treatment will be in place for this difficult-to-treat patient group.”

While the data looks encouraging the patient population in the study was too small to draw solid conclusions. Clearly larger clinical trials are needed to validate these results and to determine if this regime would be a viable option for pegylated interferon plus ribavirin non-responders. In the interim, there are many trials in place looking at alternate doses of pegylated interferons plus different durations and combinations to improve the effectiveness of pegylated interferons in difficult to treat populations.

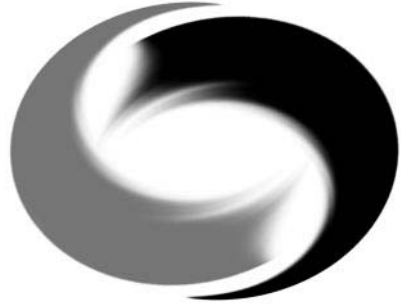


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