

HCV in HIV: Challenges and Opportunities

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HEPATITIS C VIRUS (HCV) IS ONE OF THE most important causes of chronic liver disease in the United States. Overall, there may be 300,000 persons coinfecting with HCV and HIV, representing one-third of the one million Americans infected with HIV. As discussed in this review of Dr. Douglas Dieterich's November 2000 PRN lecture, HIV coinfection is a significant factor in HCV disease progression. Coinfection with HIV is associated with higher HCV-RNA levels and more rapid progression of cirrhosis, decompensated liver disease, hepatocellular carcinoma, and death. In this way, HCV acts as an opportunistic infection—the United States Public Health Service added progressive chronic HCV infection to its list of AIDS-defining events in 1999—in that both the incidence and the severity of HCV-related hepatitis are increased. And with the continued success of HAART, it is likely that HCV will become an increasingly significant cause of morbidity and mortality in HIV-infected patients.

HIV, HCV, and Mortality in the Era of HAART

TO PROVIDE A GLIMPSE INTO MODERN-DAY morbidity and mortality trends, Dr. Dieterich drew upon some optimistic data from the CHORUS (Collaborations in HIV Outcomes Research—United States) multicenter observational database. As of November 2000, the database contained the medical histories of 4,524 HIV-infected patients residing in New York, Nashville, San Francisco, and Los Angeles. Upon sharing the data with actuaries, Dr. Dieterich and his colleagues determined that the projected survival for the average 39-year-old HIV-positive patient with greater than 200 CD4+ cells was approximately 32 years (10 years for patients with fewer than 200 CD4+ cells/mm³).

Yet, behind the CHORUS homage to HAART are a few sinister details. According to Dr.

Dieterich, 135 (2.9%) patients have died since the database was started in August 1997. Approximately half of the deaths were directly related to typical AIDS-related manifestations such as MAC, PCP, or CMV. "This, in itself, certainly suggests that AIDS hasn't gone away," Dr. Dieterich added. "But what really concerns us is the underlying cause of death in the other half of our patients. Ninety percent of the non-AIDS deaths were related to liver disease, usually due to chronic HCV infection."

Prognostic Factors for Fibrosis Progression

THERE HAVE BEEN A HANDFUL OF STUDIES FOCUSING ON host factors and fibrosis progression in HCV-infected patients, including those coinfecting with HIV. In one recent analysis, Dr. Yves Benhamou and his colleagues with the Groupe Hôpitalier Pitié-Salpêtrière in Paris analyzed progression factors in a cohort of 122 coinfecting patients, along with a matched control group consisting of 122 HCV-monoinfected patients. All patients had a biopsy sample compatible with chronic HCV infection as determined by the METAVIR scoring system, which grades the stage of fibrosis on a five-point scale (F0 = no fibrosis; F4 = cirrhosis) and necroinflammatory (histologic) activity on a four-point scale (A0 = no activity; A3 = severe activity). No patient had received anti-HCV treatment before the liver biopsy sample was obtained.

The prevalence of extensive liver fibrosis—a METAVIR score of F2, F3, or F4—and moderate or severe necroinflammatory activity—a score of A2 or A3—were higher in coinfecting patients (60% and 54% respectively) than in control patients (47% and 30%, respectively). The median fibrosis progression rate in coinfecting patients was 0.18 fibrosis units per year, compared to a rate of 0.13 fibrosis units per year in the control group. In real time, Dr. Benhamou's team estimated that the average

time to cirrhosis in coinfecting patients was 26 years, compared to an average of 34 years in patients only infected with HCV.

The factors associated with fibrosis progression in all HCV-positive patients evaluated included HIV coinfection, alcohol consumption (more than 50 g/day), age at HCV infection (less than 25 years old), and advanced immunosuppression (CD4 count <200 cells/mm³). Among coinfecting patients, alcohol consumption, advanced immunosuppression, and age at HCV infection were also associated with a higher fibrosis progression rate. "We still don't know what effect HAART has on fibrosis progression," Dr. Dieterich said. "This study included only a small number of patients receiving HAART. Theoretically, HAART should promote the recovery of immune function needed to help keep HCV replication in check and delay fibrosis." In other words, coinfecting patients who are able to maintain an undetectable viral load and a healthy CD4+ cell count may not necessarily have a higher fibrosis progression rate than HIV-uninfected patients with chronic HCV (see sidebar on page 18).

HAART and Hepatotoxicity in Coinfecting Patients

AS HAS BEEN DISCUSSED IN TWO PREVIOUS ISSUES OF *The PRN Notebook* (September 1999 and June 2000), HIV-specific antiretroviral compounds have little, if any, effect on HCV replication. While it is possible that HAART can promote and maintain the immune response needed to help slow chronic HCV disease progression, the very real risk of hepatotoxicity in coinfecting patients may preclude those patients from achieving durable virologic and immunologic responses.

It is not altogether clear why the risk of hepatotoxicity is increased in coinfecting patients receiving antiretroviral therapy. A number of possible mechanisms have been described, some directly related to the

drugs themselves and some to the underlying hcv infection.

The first mechanism discussed by Dr. Dieterich relates to mitochondrial damage. Hepatocytes, like most other cells in the body, contain mitochondria, the energy powerhouses needed to help carry out oxidative phosphorylation—the process of forming high-energy bonds, primarily ATP, that can be broken down and used by cells to generate energy. As discussed in the June 2000 issue of *The PRN Notebook* (“Mitochondrial Toxicities of Nucleoside Reverse Transcriptase Inhibitors,” Volume V, Number 3), certain NRTIs—because they are DNA-chain terminators—can do irreparable harm to mitochondrial DNA and, as a result, render mitochondria ineffective.

A common clinical manifestation of mitochondrial toxicity, lactic acidosis, has been reported by several research teams, particularly among patients receiving stavudine (Zerit). “One of the problems we see in patients with lactic acidosis and mitochondrial toxicity is microvesicular hepatic steatosis,” Dr. Dieterich commented. “This is definitely a situation to watch for, especially in our coinfecting patients.”

hcv, itself, can also damage mitochondria. According to a report published by Dr. Giuseppe Barbaro and his colleagues at the University La Sapienza in Rome, the increased lipoperoxidation seen in chronic hcv infection can lead to mitochondrial dysfunction and decreased mitochondrial DNA (Barbaro, 1999). Upon conducting liver biopsies on several chronically infected patients and analyzing the samples using an electron microscope, alterations of mitochondria were found in 23/25 (92%) patients infected with hcv genotype 1b, 15/25 (60%) patients with hcv genotype 2, and 7/25 (28%) patients with genotype 3. In patients with genotype 1b, there was also significant depletion of H-SH, lymphocytic GSH, and mitochondrial DNA. In response to these data, Dr. Dieterich concluded that, “when you consider this finding, along with what we know about the potential for NRTIs to cause mitochondrial toxicity, it’s entirely possible that hcv exacerbates the problem and increases the risk of hepatotoxicity.”


Given their effect on the cytochrome p450 isoenzyme system—a metabolic pathway situated mainly in the liver—protease inhibitors are ripe with hepatotoxic potential. However, there is not much in the way of clinical data to suggest that coinfecting pa-

DOES HAART SLOW HCV DISEASE PROGRESSION?

FEW EXPERTS WOULD CHALLENGE THE data-driven conclusion that HIV infection accelerates HCV progression, including the time to fibrosis, cirrhosis, hepatic carcinoma, liver failure, and death. What’s more, there is little argument that antiretroviral drugs are associated with increased hepatotoxicity in HIV/HCV-coinfecting patients. But it’s not all gloom and doom: a study presented at the 8th Conference on Retroviruses and Opportunistic Infections, held in Chicago in early February, showed that HAART can slow HCV-disease progression, at least to a rate that is on a par with HCV-monoinfecting patients.

The report, presented by a team of Catalunan researchers, evaluated the severity of HCV in 114 coinfecting patients receiving HAART, compared to a cohort of 57 HCV-monoinfecting patients (Tor, 2001). All coinfecting patients had asymptomatic HIV disease at baseline and 102/114 (89.4%) were receiving HAART. All patients underwent a hepatic biopsy and were classified in terms of degree of inflammation (0 to 18) and fibrosis (0 to 4).

Liver biopsies showed different degrees of inflammation in virtually all

patients studied. Cirrhosis was demonstrated in 13/170 (7.6%) evaluable patients. However, the frequency of chronic hepatitis and cirrhosis was similar in coinfecting and HCV-monoinfecting patients. In the monoinfecting patients, the mean inflammation and fibrosis scores were 5.4 and 1.5, respectively, whereas in the coinfecting patients, the mean inflammation score was 4.86 and the mean fibrosis score was 1.4. Among the coinfecting patients, high ALT and AST levels or high HCV-RNA levels and nonuse of HAART were related to hepatic inflammation at the time of biopsy, whereas the risk factors for HIV, HCV genotype, alcohol intake, previous and baseline CD4+ cell counts and HIV-RNA levels were not. In other words, coinfecting patients undergoing HAART at biopsy time showed hepatic damage similar to that of age-matched subjects with HCV-monoinfection. 

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tients are, in fact, at a much higher risk than patients infected only with HIV.

Early last year, a research team headed by Dr. Mark Sulkowski of Johns Hopkins University School of Medicine published a paper in the *Journal of the American Medical Association (JAMA)* detailing the incidence of HAART-related hepatotoxicity in the context of viral hepatitis coinfection (Sulkowski, 2000). Studied were 298 patients enrolled in a prospective cohort study at Johns Hopkins University, all of whom were prescribed new antiretroviral therapies between January 1996 and January 1998. Of patients followed, 184 (52%) had chronic hcv infection; eight (2.7%) had chronic HBV infection.

Dr. Sulkowski’s team reported that hepatotoxicity (any grade) was seen in 83 (54%) of the 154 cohort subjects infected with hcv; among non-coinfecting patients, the incidence of hepatotoxicity was re-

ported to be 39%, a statistically significant difference. Interestingly, the incidence of severe hepatotoxicity among coinfecting patients receiving ritonavir was no higher than in non-coinfecting patients (30% in each group). As for coinfecting patients receiving either a dual-nucleoside analogue combination or a regimen containing a protease inhibitor other than ritonavir, the overall incidence of severe hepatotoxicity was 9.4%, compared with 2.7% among noncoinfecting patients.

With respect to non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens, Dr. Ron Palmon, Dr. Dieterich, and several of their New York-based colleagues have analyzed data involving 272 patients with a history of NNRTI use participating in CHORUS (Palmon, 2000).

The incidence of hepatotoxicity associated with all three currently approved NNRTIs—delavirdine (Rescriptor), nevirapine (Vira-

immune), and efavirenz (Sustiva)—is reported in Figure 1. According to Dr. Dieterich, the mean time to development of severe hepatotoxicity, if it occurred, was 160 days after initiating therapy with any of the NNRTIs. With respect to the incidence of hepatotoxicity by hepatitis status, patients coinfecting with either HBV or HCV were somewhat more likely to experience grade 1 or 2 laboratory abnormalities than patients infected only with HIV. “However,” Dr. Dieterich pointed out, “this difference was not statistically significant. With the exception of delavirdine, which raised bilirubin levels more than nevirapine or efavirenz, we concluded that this class of antiretroviral drugs is relatively safe on the liver. This doesn’t match up with reports of hepatotoxicity coming out of the larger nevirapine studies, but I don’t think their use in coinfecting patients should put us on high alert.”

Therapeutic Insights and Advances

THE FACT THAT HCV CAN EXACERBATE the hepatotoxic effects of HAART provides a compelling rationale for aggressive treatment of HCV in HIV-infected patients. As with patients infected only with HCV, the primary goal of HCV treatment in coinfecting patients is to eradicate the infection. Short of that, the secondary—and most attainable—goals include reducing HCV-RNA levels in peripheral blood, reducing hepatic inflammation and necrosis, slowing disease progression, and reducing the risk of hepatocellular carcinoma.

Standard of Care: Interferon and Ribavirin

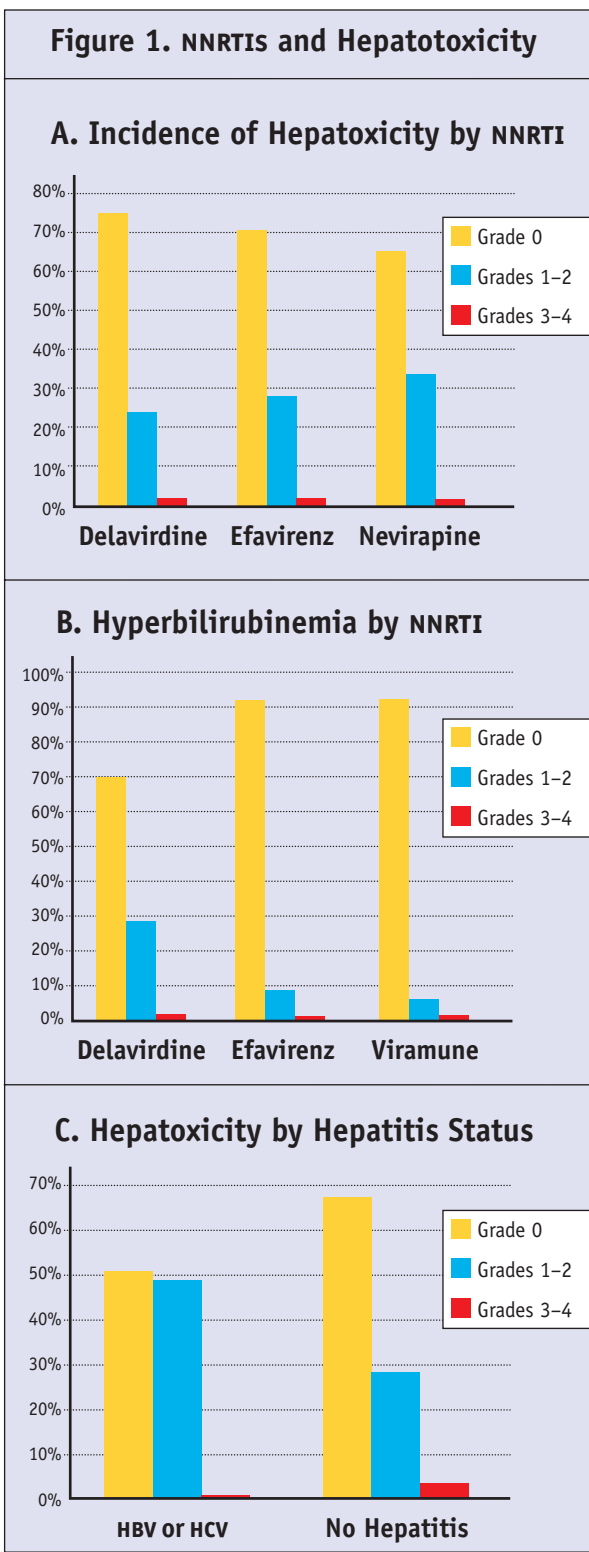
SINCE 1992, SEVERAL SMALL INTERFERON- α treatment studies in coinfecting subjects have been performed (e.g., Boyer, 1992; Soriano, 1996; Mauss, 1998). Sustained responses, defined as continuing normalization of liver enzymes and suppression of detectable HCV-RNA at least six months after termination of therapy, have been reported in as few as 8% of patients studied to as many as 44% of patients enrolled in clinical trials,

largely depending on the dose of IFN- α used and the duration of treatment. These results are roughly comparable with study results in HIV-negative study populations and were much more favorable among patients with higher CD4+ cell counts and an HCV genotype other than 1a or 1b.

Adding ribavirin to IFN- α (Rebetron) has resulted in significantly more people achieving the primary goal of therapy and, for those falling short of eradication, more durable biochemical and histologic benefits. Yet, with the added benefit of ribavirin comes the increased risk of hemolytic anemia.

As explained by Dr. Dieterich, ribavirin enters erythrocytes where it is phosphorylated. However, erythrocytes lack the enzymes needed to hydrolyze ribavirin and to transport it back out of the cell. This leads to a steady accumulation of ribavirin, eventually causing oxidative membrane damage and premature removal of the cells from the blood. Under normal circumstances, a decrease in erythrocytes would be met with an increase in erythrocyte production by the bone marrow. “But when you consider that interferon suppresses bone marrow activity,” Dr. Dieterich said, “we don’t get the reticulocyte response we need.”

According to data presented by Dr. John McHutchison and his colleagues at the 51st Annual Meeting of the American Association for the Study of Liver Diseases (AASLD) last year in Dallas, reducing the daily dose of ribavirin to prevent or reverse anemia is a double-edged sword in that it can also significantly reduce response rates. In the reported study, approximately 24% of patients receiving less than 10.6 mg/kg/daily ribavirin had a sustained virologic response, compared to 42% of those who took more than 10.6 mg/kg/daily ribavirin. “The 10.6 mg/kg dose translates into an average 800 mg a day for the typical HCV patient,” Dr. Dieterich commented. “That’s roughly 80% of the standard dose. In other words, we need to keep the dose at 800 mg a day or higher. The higher the dose, the better the response. So it behooves us to give as much ribavirin as we can.”



GRAPHS A AND B: The incidence of hepatotoxicity and hyperbilirubinemia associated with all three currently approved NNRTIs—delavirdine (Rescriptor), nevirapine (Viramune), and efavirenz (Sustiva). The mean time to development of severe hepatotoxicity, if it occurred, was 160 days after initiating therapy with any of the NNRTIs. **GRAPH C:** Patients coinfecting with either HBV or HCV were somewhat more likely to experience grade 1 or 2 laboratory abnormalities than patients infected only with HIV.

Source: Palmon, 2000; Adapted and published with permission.

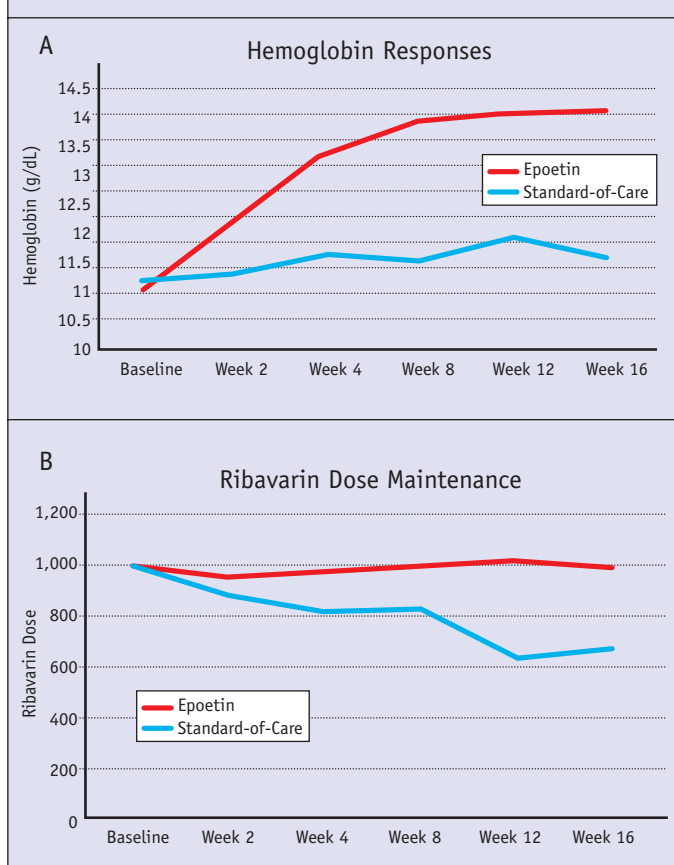
Because ribavirin dose reduction is a less than ideal approach to managing hemolytic anemia, adjunctive therapy with recombinant erythropoietin (epoetin alfa; Procrit) has gained considerable notoriety. At the 51st AASLD, preliminary results from a randomized trial comparing adjunctive erythropoietin therapy to standard ribavirin dose reductions in patients receiving combination therapy for hcv was reported (Wasserman, 2000). As shown in Figure 2, patients treated with erythropoietin experienced a significant increase in hemoglobin after 16 weeks of therapy—approximately 3 grams—compared to those who simply reduced their ribavirin dose. In fact, patients receiving erythropoietin were much more likely to maintain a standard ribavirin dose (986 mg/day vs. 682 mg/day, respectively).

With respect to efficacy in coinfecting patients, Dr. Dieterich presented data from an open-label study evaluating IFN- α (3 MU TW) in combination with ribavirin (800 to 1200 mg/day) in 20 patients being treated at Liberty Medical Group in New York. Seventeen of the 20 (85%) patients were receiving HAART, and 15/20 (75%) had undetectable HIV-RNA levels prior to receiving treatment for their hcv. The median baseline HCV-RNA was 5.3 million copies/mL, and the mean liver biopsy fibrosis score was 2.15. Fifty percent of the patients enrolled had hcv genotype 1a or 1b; an additional 30% had genotype 2a or 2b, and the remaining 20% were infected with hcv genotype 3a.

After three months, 8/20 (40%) of patients had sustained virologic responses, defined as a negative HCV-RNA PCR three and six months after stopping therapy. Among the nonresponders, hcv viral load decreased by a median 450,000 copies/mL. However, once therapy was halted, nonresponders saw their HCV-RNA increase to approximately 8 million copies/mL.

In terms of HIV surrogate markers, most patients receiving HAART maintained an undetectable viral load (<400 copies/mL); one patient receiving HAART with an un-

Figure 2. Epoetin Alfa for Hemolytic Anemia



GRAPH A: Patients with ribavirin-induced hemolytic anemia who were treated with erythropoietin experienced a significant increase in hemoglobin after 16 weeks of therapy—approximately 3 grams—compared to those who simply reduced their ribavirin dose. **GRAPH B:** Patients receiving erythropoietin were much more likely to maintain a standard ribavirin dose (986 mg/day vs. 682 mg/day, respectively).

Source: Wasserman, 2000; Adapted and published with permission.

detectable baseline viral load experienced a rebound in HIV-RNA while receiving therapy for hcv. There was also a median CD4+ count decline from 430 cells/mm³ to 270 cells/mm³. However, CD4+ cell counts returned to their baseline levels in all patients within one month after stopping IFN- α /ribavirin.

Predictably, the main ribavirin-related adverse event was anemia (hemoglobin <11 g/dL), occurring in 35% of all patients studied.

A Few Words On Pegylated Interferon

NEW TO THE HCV-TREATMENT ARENA ARE the much hyped pegylated interferons, formulations of IFN- α that have been cova-

lently bonded to polyethylene glycol (PEG). This modification allows for a slower release of IFN- α and the possibility of maintaining sustained plasma levels of the drug with more effective viral suppression. Schering Plough's 12 kDa branched-pegylated IFN- α -2b (Peg-Intron) was approved in January, and a New Drug Application (NDA) in support of Hoffmann-La Roche's 40 kDa branched-pegylated IFN- α -2a (Pegasys) is now under review.

Preliminary data from three pivotal trials involving Roche's Pegasys have been reported over the past 18 months. In one phase II study reported at the 1999 Digestive Disease Week (DDW) meeting in Orlando, Dr. Mitchell Shiffman and his colleagues determined that the most effective dose of Pegasys was 180 mcg administered once a week. Approximately 36% of patients randomized to receive the 180 microgram dose were sustained responders—defined as a negative HCV-RNA PCR six months after stopping therapy—compared to 29% of patients receiving the higher dose studied (270 micrograms every week) and 30% of patients receiving a lower dose (90 mcg every week) (Shiffman, 1999).

Data from a phase II/III study comparing two doses of Pegasys with standard IFN- α therapy in patients with chronic hcv infection and compensated cirrhosis were published last year in the *New England Journal of Medicine* (Heathcote, 2000). Approximately 270 patients were enrolled in the study and treated for 48 weeks. In an intent-to-treat analysis, HCV-RNA was undetectable at week 72 in 30% of patients treated with the 180 mcg qw Pegasys dose—perhaps the best response rate ever seen in patients with compensated cirrhosis. Sustained virologic response rates were 8% among patients receiving standard IFN- α and 15% among patients receiving the lower (90 mcg qw) dose of Pegasys. Unfortunately, virologic response rates among patients with hcv genotype 1a or 1b were significantly lower than those with non-1 genotypes (10% vs. 55%, respectively).


Positive biochemical and histologic responses were also specified in the *NEJM* report. At week 72, aminotransferase levels had normalized in 15% of patients receiving standard interferon, 20% of patients receiving the low dose of Pegasys, and 34% of patients receiving the high Pegasys dose. In a subgroup of 184 patients with paired liver-biopsy specimens, the rates of histologic response at week 72 were 31%, 44%, and 54%, respectively.

A phase III study involving European patients with less advanced chronic HCV disease was recently reported at the 35th Annual Meeting of the European Association for the Study of the Liver (EASL) in Rotterdam (Zeuzem, 2000). Approximately 530 patients—only 13% of whom had decompensated cirrhosis—were randomized to receive either Pegasys (180 mcg qw) or standard IFN- α 6 MU QD for 12 weeks, followed by 3 MU QD for an additional 36 weeks. The sustained virologic response among patients receiving Pegasys was 39%, compared to 19% among patients receiving standard IFN- α . It is also important to note that 28% of patients with HCV genotype 1a or 1b experienced a sustained virologic response to Pegasys, compared to 7% of genotype 1a or 1b patients receiving standard IFN- α .

Six-month follow-up data from a small 20-person study combining Pegasys (180 mcg qw) with standard doses of ribavirin (1000-1200 mg/daily) were recently reported by Dr. Sulkowski and his colleagues at the 2000 DDW meeting (Sulkowski, 2000a). With respect to sustained virologic responses, approximately 50% of all patients remained HCV-RNA negative six months after stopping 48 weeks of therapy; 38% of patients with HCV genotype 1 were sustained virologic responders, and a whopping 100% of patients with HCV genotype 2 were reported to be sustained responders.

With respect to Schering-Plough's newly approved pegylated interferon formulation (Peg-Intron), results from a large phase II/III Study were presented at the 35th EASL (Trepo, 2000). The study randomized 1,219 chronically infected HCV patients—only 9% of whom had histologic signs of cirrhosis—to receive one of three doses of Peg-Intron (.5 mcg/kg, 1.0 mcg/kg, or 1.5 mcg/kg qw) or standard IFN- α (3 MU TID) for 48 weeks. Approximately 25% of those randomized to receive the 1.0 mcg/kg dose were sustained virologic responders, compared to 18% of patients re-

ceiving the .5 mcg/kg dose, 23% of patients receiving the 1.5 mcg/kg dose, and 12% of patients receiving standard IFN. There were no statistically significant differences among the three Peg-Intron arms; the 1.0 mcg/kg dose is likely to be used in clinical practice once the drug is approved.

As for Peg-Intron's efficacy in patients with different HCV genotypes, data produced thus far are similar to those seen in studies involving Pegasys. According to data from the phase II/III study presented at the 35th EASL, 49% of patients with a non-1 HCV genotype who received the highest dose of Peg-Intron were sustained virologic responders, compared to 14% of patients with genotypes 1a or 1b (Trepo, 2000). Similar differences in response rates were seen in all study arms included. 

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