

Management of HIV/HCV Coinfection: An Update

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ACCORDING TO DR. RAY CHUNG, HEPATITIS C VIRUS (HCV) AND HIV COINFECTION is a tale of two viruses that can be viewed through two different prisms. To hepatologists, including Dr. Chung, the scope of the problem is typically viewed through the HCV prism, in which HIV infection is a reality for roughly one-tenth of all HCV cases in the United States. For clinicians involved in primary care, the view through the HIV prism casts a more startling picture. Among all HIV-positive individuals in this country, HCV coinfection can be documented in approximately one-third of them. "No matter which prism you're looking through, we're talking about 300,000 people coinfecting with HIV and HCV in the United States," Dr. Chung said. "Indeed, this is a substantial problem and we are all aware that HCV is a growing source of morbidity and mortality among those who are also infected with HIV."

The Virology of HCV Infection

"FROM THE STANDPOINT OF UNDERSTANDING HCV, OUR KNOWLEDGE OF the biology of HCV infection continues to grow exponentially since the virus was first discovered," Dr. Chung said. HCV is an RNA virus. But unlike HIV, another RNA virus, it encodes an RNA polymerase that does not traverse through a DNA intermediate. In other words, HCV-RNA polymerase is not a reverse transcriptase but instead copies positive RNA strands directly into negative RNA strands that in turn serve as a template for creating new positive RNA. "This cycle takes place in the cytoplasm of hepatocytes," Dr. Chung explained. "As far as we know, the nucleus is not involved in HCV replication. This is a very important point as it relates to our ability to achieve eradication of this particular infection. With no proviral form and no integrated form of the virus, cure appears to be an achievable phenomenon, something we have observed in many of our patients."

Another noteworthy fact about HCV polymerase is its lack of proof-reading function. In other words, the virus is incapable of correcting its own errors. Thus, misincorporation of nucleotides is a frequent phenomenon and, indeed, adaptive to HCV's life cycle and persistence. "This has led to an extraordinary degree of viral diversity," Dr. Chung added. "The diversity we see in HCV is even greater than the diversity seen in HIV."

There are six HCV genotypes that, genetically speaking, are even more diverse than the various clades identified in the study of HIV. "Even the most disparate HCV genotypes described worldwide have differences of 25% to 35% in their amino acid sequences," Dr. Chung said. "Really, it's almost as if we're looking at different viruses."

In the United States, HCV genotype 1 remains the most common, accounting for approximately 75% of all HCV cases; genotypes 2 and 3—with sporadic reports of genotypes 4, 5, and 6—account for the remaining 25% of all U.S. HCV cases. "Of course," Dr. Chung commented, "HCV genotype has profound implications when it comes to treatment responses. Because HCV genotypes 2 and 3 are associated with far more favorable treatment responses, genotyping patients before embarking on a course of therapy is essential."

The Pathogenesis of HCV Infection

WITH RESPECT TO THE ETIOLOGY AND PATHOGENESIS OF HCV INFECTION, there is still a great deal to be learned. For example, it still remains to be proven that HCV has direct cytopathic effects—reliable cell culture systems have proven difficult to establish. In turn, there are still no conclusive answers regarding how HCV manages to persist and replicate in hepatocytes. It is also not clear how HCV infection, either directly or indirectly, causes cellular injury. Confusing matters is the fact that the course of HCV infection varies widely in patients, along with the complexity of interactions between viral and host factors.

As suggested by Dr. Chung, the effectors of HCV-related liver disease are the host T-cell responses to chronically infected hepatocytes (Figure 1). Cytotoxic CD8+ cells recognize virus-infected hepatocytes that present peptides at the cell surface in the context of HLA class I molecules. "This results in the death of hepatocytes by apoptotic mechanisms," Dr. Chung said. "Unfortunately, this is not an efficient process and complete clearance is, generally speaking, not accomplished. This explains the marked propensity for this virus for chronicity."

Once chronic infection is established, the battle between cytotoxic T-lymphocytes (CTLs) and HCV-infected hepatocytes continues on a persistent basis. In this battle, a number of cytokines are released, in-

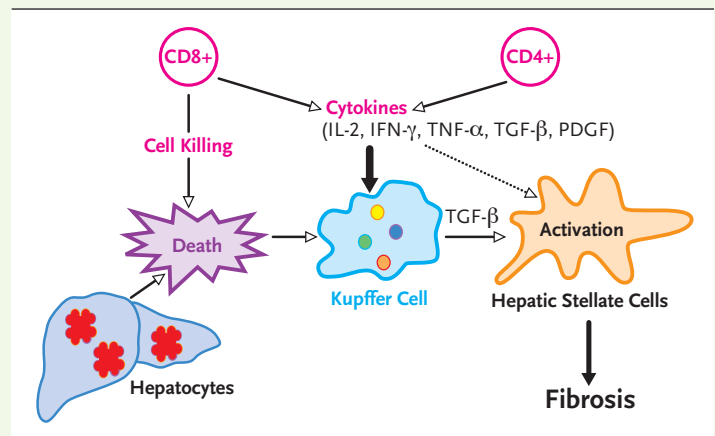


FIGURE 1. Hepatitis C Disease Pathogenesis

Once a virus has achieved entry into the cell, the cellular immune system is the dominant means of limitation of viral spread. CD4+ cells, by virtue of their capacity to produce cytokines, play a central role in the control of immune responses. Studies have been published on the pattern of CD4+ responses in those few individuals who have complete virologic recovery after HCV infection. Quantitatively, individuals who have a strong, polyclonal proliferative response to HCV antigens are able to clear HCV after acute infection and clear viremia after interferon therapy. The cytokines produced by these CD4+ cells are generally type I (IFN-γ and TNF-α), suggesting that cellular immune responses typically mediated by these cytokines are critical to resolution of infection.

Source: Ray Chung, MD

cluding interleukin-2 (IL-2), interferon-gamma (IFN- γ), tumor necrosis factor-alpha (TNF- α), transforming growth factor-beta (TGF- β), and platelet-derived growth factor. These cytokines, most notably TGF- β , expressed by Kupffer cells—the resident macrophages of the liver—lead to activation of the otherwise quiescent hepatic stellate cells. “Once the stellate cell is activated, it is transformed from a vitamin A storage depot to a collagen-producing factory,” Dr. Chung explained. “This essentially renders the phenotype of fibrosis. In other words, we see collagen deposited in the perisinusoidal space, ultimately leading to irreversible changes we know as cirrhosis. This, really, is the feared consequence of chronic liver disease of all stripes.”

Natural History of HCV Infection

AFTER ACUTE INFECTION, APPROXIMATELY 20% OF PERSONS APPEAR TO resolve their infection without sequelae, as defined by the sustained absence of HCV-RNA in serum and normalization of ALT levels. Chronic HCV infection develops in most persons (80%). Approximately 60% to 70% of individuals with chronic HCV will have persistent or fluctuating ALT elevations, indicating active liver disease. The remaining 30% to 40% will maintain normal ALT levels. However, it is important to note that some patients with histologically confirmed hepatitis may have normal ALT activity for prolonged periods of time (>12 months), which underscores the importance of direct testing for HCV in those persons at risk for HCV who present with normal ALT levels.

Generally speaking, cirrhosis develops in at least 20% of those with chronic HCV infection over a median period of 20 years. Most (75%) patients who develop cirrhosis experience slowly progressive disease. However, within five to ten years after the onset of cirrhosis, approximately 25% will go on to develop hepatocellular carcinoma and/or end-stage liver disease (ESLD).

Extrahepatic manifestations of chronic HCV infection are considered to be of immunologic origin, and include cryoglobulinemia, membranoproliferative glomerulonephritis, and porphyria cutanea tarda. Other extrahepatic conditions have been reported, but definitive associations of these conditions with HCV infection have not been established. These include seronegative arthritis, Sjögren syndrome, autoimmune thyroiditis, lichen planus, Mooren corneal ulcers, idiopathic pulmonary fibrosis (Hamman-Rich syndrome), polyarteritis nodosa, aplastic anemia, and B-cell lymphomas.

Although factors predicting severity of liver disease have not been well defined, various studies suggest that increased alcohol intake, being older than 40 years of age at the time of infection, and being male are associated with more severe liver disease. In particular, among persons with alcoholic liver disease and HCV infection, liver disease progresses more rapidly; among those with cirrhosis, a higher risk for development of HCC exists. “Alcohol consumption can fan the fire and can compress the natural history of hepatitis C disease,” Dr. Chung commented. “Instead of 20 to 25 years to progress to cirrhosis and liver failure, heavy alcohol use can shorten this to 10 to 15 years. Another factor that influences the severity of HCV disease is HIV coinfection.”

HIV Infection: Effects on HCV Progression

A LARGE NUMBER OF STUDIES—MANY OF WHICH HAVE BEEN DISCUSSED in previous issues of *The PRN Notebook*—have demonstrated that HIV accelerates the clinical course of HCV disease.

In one study reviewed by Dr. Chung, Dr. Elaine Eyster and her colleagues at Pennsylvania State University College of Medicine analyzed HCV-

RNA levels in serial samples collected from 17 HIV/HCV-coinfecting individuals, both before and after HIV seroconversion. Samples from these 17 patients were compared to those from 17 HCV-infected patients who remained HIV-seronegative throughout the study. Baseline HCV-RNA levels in the pre-HIV seroconversion group were not significantly different from the baseline levels in those who remained free of HIV. Over the entire period of study, HCV-RNA levels increased nearly threefold in those who remained uninfected with HIV. However, among those who became HIV positive, HCV-RNA levels increased 58-fold. What's more, the rate of increase in HCV-RNA levels was eightfold faster for HIV-infected subjects than for subjects who remained HIV negative. HCV-RNA levels also correlated significantly with CD4+ cell counts: the lower the CD4+ cell count, the higher the HCV-RNA level. “Not only do these data have implications for understanding the natural history of HCV infection in HIV-coinfecting patients,” Dr. Chung commented, “they also have implications for treatment.”

There have also been a handful of studies focusing on fibrosis progression in HIV/HCV-coinfecting patients. In one frequently cited 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-monoinfecting patients (Benhamou, 1999). 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 infected only 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.

Taking a look at the larger picture, studies have demonstrated that ESLD—related to chronic HCV infection in many cases—is now a leading cause of mortality among HIV-infected individuals. In one study summarized by Dr. Chung, Dr. Ioana Bica and her colleagues retrospectively examined the causes of death of HIV-infected patients admitted to Tufts-New England Medical Center in 1991, 1996, and 1998/1999 (Bica, 2001). In 1998/1999, 11/22 (50%) deaths were due to ESLD, compared with 3/26 (11.5%) deaths in 1991 and 5/36 (13.9%) deaths in 1996. In 1998/1999, 55% of patients had undetectable HIV-RNA levels and/or CD4+ counts greater than 200 cells/mm³ within the year before death. Most of the patients who died had detectable antibodies to HCV: 75% of patients who died in 1991, 57.7% who died in 1996, and 93.8% who died in 1998/1999. “These finds were certainly not unique to this study,” Dr. Chung said. “Many involved in HIV care are seeing their patients dying, not of typical AIDS-related complications, but end-stage liver disease often attributed to chronic hepatitis C.”

Why, exactly, does HIV infection have such a profound effect on the progression of hepatitis C? Dr. Chung offered a number of plausible pos-

sibilities. First, the high levels of HCV seen in some HIV-coinfected patients may have a direct cytopathic effect on hepatocytes. “Cytopathic injury, caused by the virus and not immunologic mechanisms, is possible in some coinfecting patients with very high HCV-RNA levels,” Dr. Chung suggested. “However, this only accounts for some cases at the extreme end of the spectrum. It likely doesn’t account for disease seen in the lion’s share of people with HIV and HCV coinfection.”

A more likely explanation is the cytokine derangement associated with HIV infection. “These derangements can take place in the milieu of the liver,” Dr. Chung said. “In HIV, we see increases in certain cytokines, including TGF- β and TNF- α , both of which are pro-fibrotic. There may also be antagonists of endogenous interferon action, which we believe may also be anti-fibrotic on some level. All of these may, in fact, be perturbed by HIV infection in the environment of the liver.”

Recent data also suggest that HIV itself may have direct effect on liver cells, by promoting hepatocyte apoptosis (Vlahakis, 2003). It turns out that hepatocytes may express low levels of CXCR4, one of the key coreceptors targeted by HIV, which has led to the hypothesis that envelope proteins of HIV may signal apoptosis of hepatocytes. “This is an intriguing notion that merits additional study,” Dr. Chung concluded.

HCV Infection: Effects on HIV Progression

WHILE IT IS ABUNDANTLY CLEAR THAT HIV COINFECTION CAN HAVE A PRONOUNCED effect on HCV disease progression, it is not clear if the reverse is true; that is, if there are mitigating effects of HCV coinfection on HIV disease progression. Since HAART went into widespread use approximately eight years ago, there have been at least four large studies evaluating the effects of HCV disease on HIV disease progression. Two of these studies demonstrated faster progression of HIV disease in the setting of HIV/HCV coinfection (Greub, 2000; De Luca, 2002). The other two studies did not show any influence of HCV on HIV disease progression (Sulkowski, 2002; Rancinan, 2002).

According to data from the Swiss HIV Cohort Study, HCV coinfection

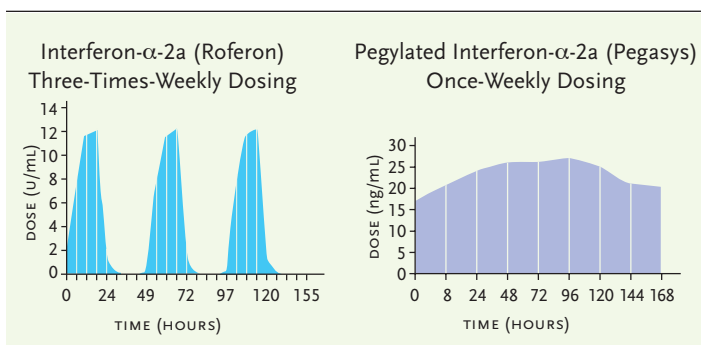


FIGURE 2. Pegylated Interferon Pharmacokinetics

Interferon- α remains a vital component of anti-HCV combination therapy. However, attention has now shifted to the pegylated interferons—formulations of alpha interferon that have been covalently bonded to polyethylene glycol (peg). This modification allows for a slower release of alpha-interferon and the possibility of maintaining sustained plasma levels of the drug with more effective viral suppression. Schering Plough’s 12 kDa branched-pegylated interferon- α -2b (Peg-Intron) was approved in January 2001 and Hoffmann-La Roche’s 40 kDa branched-pegylated interferon- α -2a (Pegasys) was approved in October 2002. Shown here are the pharmacokinetic profiles, over the course of a week, for pegylated interferon- α -2a and for standard interferon- α -2a.

Source: Ray Chung, MD; Hoffmann-La Roche.

significantly increases HIV disease progression after antiretroviral therapy is initiated (Greub, 2000). This prospective follow-up study evaluated 3,111 HIV-positive patients—1,157 of whom were coinfecting with HCV—initiating antiretroviral therapy for the first time. After three years of treatment, 80% of the HIV/HCV coinfecting patients were still alive and had not experienced any signs of clinical progression. Among HIV-monoinfected patients not using intravenous drugs, 90% were still alive and doing well on treatment. Statistically, the 10% difference between these two groups was highly significant.

The HIV/HCV-coinfecting patients had a 1.7 relative hazard of AIDS progression or death within two years, compared to HIV-monoinfected patients. Also of interest, coinfecting patients had a blunted CD4+ cell response to antiretroviral treatment and were less likely to push and keep their HIV-RNA levels undetectable.

These data are in contrast with the results of a study conducted by Dr. Mark Sulkowski and his colleagues at Johns Hopkins University (Sulkowski, 2002). This prospective study followed a cohort of 1,955 patients enrolled between 1995 and 2001. No difference was detected in the risk of acquiring an AIDS-defining illness. There were 231 (26.4%) AIDS-related events among HIV/HCV-coinfecting patients and 264 (24.4%) AIDS-related events among HIV-monoinfected patients. Similarly, mortality rates were comparable in both groups. There were 153 (17.5%) deaths among the coinfecting patients and 1,168 (15.5%) deaths among the HIV-monoinfected patients. Although an increased risk of death was detected in the subgroup of 429 HCV-infected patients with a baseline CD4+ count of 50 cells/mm³, adjusting for exposure to antiretroviral therapy and its effectiveness demonstrated that death was not independently associated with HCV infection in this subgroup. Similarly, in those receiving effective antiretroviral therapy, there was no difference in CD4+ cell count or CD4 percentage increase associated with antiretroviral therapy use between the two groups.

There are also data from a study conducted by the AIDS Clinical Trials Group (ACTG), published in *AIDS* by Dr. Chung and his colleagues (Chung, 2002). In a retrospective analysis of CD4+ responses among HIV/HCV-coinfecting and HIV-monoinfected patients receiving the same antiretroviral drug regimen, no differences in the CD4+ cell count increase were reported at either 16 weeks or 48 weeks after initiating therapy.

Therapeutic Considerations

THERE ARE A NUMBER OF POTENTIAL BENEFITS TIED TO TREATMENT OF chronic HCV infection in HIV-infected individuals. The most desired outcome of treatment—which is possible in both HCV-monoinfected and HIV/HCV-coinfecting patients—is viral eradication. Short of that, there is the possibility of delaying fibrosis progression; preventing various clinical outcomes, such as decompensation, hepatocellular carcinoma, and death; reversal of extrahepatic complications; and improved tolerability and effectiveness of antiretroviral therapy. There is also the public health component of HCV treatment: to render patients aviremic, thus reducing their chances of passing the virus on to others.

Until recently, daily or three-times-weekly injections of alpha-interferon, combined with daily oral doses of ribavirin, was considered the best option available, with sustained response rates in the 15% to 20% range in HIV/HCV-coinfecting patients. While interferon remains a vital component of anti-HCV combination therapy, attention has now shifted to the pegylated interferons—formulations of alpha interferon that have been covalently bonded to polyethylene glycol (peg). This modification allows for a slower release of alpha-interferon and the possibility of maintaining sustained plasma levels of the drug with more effective

viral suppression (Figure 2). Schering Plough's 12 kDa branched-pegylated IFN- α -2b (Peg-Intron) was approved in January 2001 and Hoffmann-La Roche's 40 kDa branched-pegylated IFN- α -2a (Pegasys) was approved in October 2002.

Both pegylated interferon brands are approved for use in combination with ribavirin, a guanosine nucleoside analogue. Schering Plough markets Rebetol-brand ribavirin and Roche markets Copegus-brand ribavirin. Doses of Peg-Intron (weight-dependent dose) and Pegasys (fixed dose) are administered, via subcutaneous injection, once a week. Ribavirin is taken orally, usually twice a day.

In HIV-negative patients, combinations of pegylated interferon and ribavirin were associated with sustained virologic response rates of up to 46% in those with genotype 1 and up to 82% in those with genotype 2/3 (see Table 1). In HIV-positive patients, a number of studies have recently been completed, with sustained virologic response data from three pivotal clinical trials being reported recently at the 11th Conference on Retroviruses and Opportunistic Infections (CROI), held in February in San Francisco. While the rates of sustained virologic responses in coinfecting patients appear to be lower than those seen in HCV-monoinfected patients, these new data clearly indicate that pegylated interferon and ribavirin is a significant improvement over regimens containing standard interferon (Table 2).

TABLE 1. Sustained Virologic Responses to Pegylated Interferon in HIV-Negative Patients with Chronic HCV

| | No. of patients | Overall response (%) | Genotype 1 (%) | Non-Genotype 1 (%) |
|--------------------------------------|-----------------|----------------------|----------------|--------------------|
| Roche (Fried, 2001) | | | | |
| Standard interferon + ribavirin | 444 | 45 | 37 | 46 |
| Pegasys + placebo | 224 | 30 | 21 | 56 |
| Pegasys + ribavirin | 453 | 56 | 46 | 76 |
| Schering-Plough (Manns, 2001) | | | | |
| Standard interferon + ribavirin | 505 | 47 | 33 | 79 |
| Peg-Intron 1.5/0.5 + ribavirin | 514 | 47 | 34 | 80 |
| Peg-Intron 1.5 + ribavirin* | 511 | 54 | 42 | 82 |

*Considering only patients who received a ribavirin dose greater than 10.6 mg/kg, the figures are 61% for the overall response rate, 48% for genotype 1 and 88% for genotypes 2/3.

ACTG A5071

AT THE 11TH CROI, HELD IN SAN FRANCISCO IN FEBRUARY, DR. CHUNG and his colleagues presented the final results from ACTG study A5071, a randomized, controlled 48-week study of pegylated interferon (Pegasys) with ribavirin vs. standard interferon with ribavirin for the treatment of chronic HCV in HIV-coinfecting individuals (Chung, 2004). One-hundred thirty three coinfecting patients were randomized in this open-label study. The 66 patients randomized to the pegylated interferon arm received 180 μ g/weekly Pegasys plus escalating doses of ribavirin, starting with 600 mg/daily and subsequently increased by 200 mg/daily every four weeks for a maximum total of 1,000 mg/day (most patients were maintained on 800 mg/day). Patients randomized to receive standard interferon began therapy with 6 million units three times weekly, with a dose reduction to 3 million units three times weekly after 12 weeks, along with dose-escalating ribavirin.

According to the intent-to-treat (ITT) analysis, favorable end-of-treatment virologic responses—defined as undetectable HCV viremia in pe-

ripheral blood—were observed in 8/67 (12%) patients receiving standard interferon/ribavirin and 27/66 (41%) receiving pegylated interferon/ribavirin. As for sustained virologic responses—defined as undetectable HCV viremia six months after discontinuing treatment—this was reported in 18/66 (27%) patients in the pegylated interferon/ribavirin group and 8/67 (12%) patients in the standard interferon/ribavirin group. The differences between the two groups, at both time points, were statistically significant.

With respect to HCV genotype and sustained virologic responses, 3/52 (6%) patients with genotype 1 who received standard interferon/ribavirin were virologic responders six months after completing therapy. As for patients with HCV genotype 1 in the pegylated interferon/ribavirin group, 7/51 (14%) were sustained virologic responders. The difference between the sustained virologic response rates among HCV genotype 1 patients was not statistically significant. Not surprisingly, patients with non-1 HCV genotypes (e.g., HCV genotypes 2 and 3) responded much more favorably. In the standard interferon/ribavirin group, 5/15 (33%) patients with non-1 HCV genotypes were sustained virologic responders, compared to 11/15 (73%) patients with non-1 HCV genotypes in the pegylated interferon/ribavirin group.

Even among patients who were considered virologic nonresponders, histologic improvements were documented in a number of cases. Approximately 36% of nonresponders in the pegylated interferon/rib-

avirin group experienced a favorable histologic response. Among responders and nonresponders combined, 62% of patients receiving standard interferon/ribavirin and 52% of patients receiving pegylated interferon/ribavirin had improved hepatitis activity index (HAI) scores, defined as a decrease by two or more points.

Also of interest were data indicating that the virologic response documented after 12 weeks of therapy has strong negative predictive value. After 12 weeks of therapy, a total of 43 (41%) patients experienced either a >2 log₁₀ copies/mL drop in HCV-RNA or an undetectable HCV-RNA viral load, compared to 63 (59%) patients who had not. Among the 43 patients who had a positive virologic response at week 12, 51% went on to be sustained virologic responders and 49% did not. Among the 63 patients who were not responding virologically after 12 weeks of therapy,

no patient was a sustained virologic responder.

Similar frequencies of flu-like symptoms, depression, and abnormality values were seen in both groups. Premature discontinuation, because of toxicities and side effects, were also similar (12% in both groups).

APRICOT

ALSO PRESENTED AT THE 11TH CROI WERE FINAL DATA FROM THE AIDS Pegasys Ribavirin International Coinfection Trial (APRICOT), by far the largest HIV/HCV-coinfection treatment trial conducted to date (Torriani, 2004). The study randomized 868 patients through clinical sites in 19 countries. Two-hundred eighty five patients were selected to receive standard interferon plus ribavirin (3 million units three times a week plus 800 mg ribavirin), 286 were randomized to receive pegylated interferon plus placebo (Pegasys 180 μ g/weekly), and 289 were allotted to receive pegylated interferon plus ribavirin (800 mg/daily). Approximately 60% of patients in all three groups had HCV genotype 1.

There were 111 (39%) treatment discontinuations in the standard in-

terferon/ribavirin group, 90 (31%) premature discontinuations in the pegylated interferon/placebo group, and 72 (25%) discontinuations in the pegylated interferon/ribavirin group. Premature discontinuations because of serious adverse events or laboratory abnormalities occurred in 44 (15%) patients receiving standard interferon/ribavirin, 47 (16%) patients receiving pegylated interferon/placebo, and 43 (15%) patients receiving pegylated interferon/ribavirin. Reports of neutropenia were higher in both the pegylated interferon/placebo and the pegylated interferon/ribavirin groups than in the standard interferon/ribavirin group (13%/11% vs <1% respectively).

As for virologic outcomes, the rates of end-of-treatment virologic responses in the ITT analysis were 14%, 33%, and 49% for the standard interferon/ribavirin, pegylated interferon/placebo, and pegylated interferon/ribavirin groups respectively. The rates of overall sustained virologic responses, again in the intent-to-treat analysis, were 12% in the standard interferon/ribavirin group, 20% in the pegylated interferon/placebo group, and 40% in the pegylated interferon/ribavirin group. Broken down by HCV genotype, the sustained virologic response rate in patients with HCV genotype 1 receiving pegylated interferon/ribavirin was 29%, compared to 14% HCV genotype 1 patients receiving pegylated

RIBAVIC

SIMILAR TO ACTG A5071 AND APRICOT, THE FRENCH RIBAVIC STUDY WAS AN open-label, randomized, controlled comparison of standard interferon/ribavirin and pegylated interferon/ribavirin. In this study, Schering-Plough's Peg-Intron formulation of pegylated interferon was used, at a dose of 1.5 µg/kg/week, along with a fixed dose of ribavirin (800 mg/day). Forty-eight and 72-week data, reflecting end-of-treatment and sustained virologic responses, were reported by Dr. Christian Perronne and his RIBAVIC study group colleagues at the 11th CROI (Perronne, 2004).

Four-hundred twelve HIV/HCV-coinfected patients were randomized to receive pegylated interferon/ribavirin or standard interferon/ribavirin. During the 48 weeks of treatment, a high number of patients—86 (42%) patients in the standard interferon/ribavirin group and 81 (39%) patients in the pegylated interferon group—discontinued therapy. Severe adverse events were common in this study, which occurred in 64 patients receiving standard interferon/ribavirin and 63 patients receiving pegylated interferon/ribavirin. Among the severe adverse events, there were six reports of symptomatic hyperlactatemia and five reports of acute pancreatitis.

In the as-treated analysis—which included all patients who completed 48 weeks of treatment—HCV viral loads were undetectable at the end of therapy in 52% of patients in the pegylated interferon group and 35% of patients in the standard interferon group. As for sustained virologic responses in the as-treated analysis, 36% of patients in the pegylated interferon/ribavirin group, compared to 28% of patients in the standard interferon/ribavirin group, maintained undetectable HCV viral loads six months after finishing therapy.

Because of the high drop-out rates, the ITT analyses paint a more somber picture. Sustained virologic responses were documented in 27% of all patients receiving pegylated interferon/ribavirin, compared to 19% of patients receiving standard interferon/ribavirin. As for the HCV genotype, the ITT analysis yielded a sustained virologic response rate of 16% of patients with genotypes 1 or 4 randomized to receive pegylated interferon/ribavirin, compared to 5% of patients with genotypes 1 or 4 receiving standard interferon/ribavirin.

It is important to note that patients participating in RIBAVIC entered the study with more advanced HCV disease than patients participating in either ACTG A5071 or APRICOT. In RIBAVIC, approximately 24% of patients had a METAVIR score of F3 (bridging fibrosis) and 16% had a METAVIR score of F4 (cirrhosis). In APRICOT, approximately 16% of patients had either bridging fibrosis or cirrhosis, and in ACTG 5071, no more than 11% of patients, in either treatment group, had cirrhosis before beginning therapy.

NR16155

NR16155, A STUDY SPONSORED BY ROCHE, ENROLLED 153 HIV/HCV-COINFECTED patients to begin 180 µg/week pegylated interferon (Pegasys) for 12 weeks (Khalili, 2003). After 12 weeks of therapy, patients responding virologically—defined as either a 2 log₁₀ IU/mL or greater drop in HCV-RNA levels or an undetectable HCV viral load—remained on pegylated interferon monotherapy. Virologic nonresponders continued pegylated

TABLE 2. Sustained Virologic Responses to Pegylated Interferon in HIV/HCV-Coinfected Patients

| | No. of patients | Overall response (%) | Genotype 1 (%) | Non-Genotype 1 (%) |
|----------------------------------|-----------------|----------------------|----------------|--------------------|
| ACTG A5071 (Chung, 2004) | | | | |
| Standard interferon + ribavirin* | 67 | 12 | 6 | 33 |
| Pegasys + ribavirin* | 66 | 27 | 14 | 73 |
| APRICOT (Torriani, 2004) | | | | |
| Standard interferon + ribavirin | 285 | 12 | 7 | 20 |
| Pegasys + placebo | 286 | 20 | 14 | 36 |
| Pegasys + ribavirin | 289 | 40 | 29 | 62 |
| RIBAVIC (Perronne, 2004) | | | | |
| Standard interferon + placebo | 207 | 19 | 5** | 41 |
| Peg-Intron + ribavirin | 205 | 27 | 15** | 44 |

* Escalating dose of ribavirin was used in ACTG 5071. Patients were started at a dose of 600 mg/daily, which was subsequently increased by 200 mg/daily every four weeks for a maximum total of 1,000 mg/day. Both APRICOT and RIBAVIC started and maintained patients on 800 mg/day ribavirin.
** Included patients with HCV genotypes 1 and 4.

interferon/placebo and 7% of genotype 1 patients receiving standard interferon/ribavirin. Sustained virologic response rates among patients with HCV genotypes 2 or 3 receiving pegylated interferon/ribavirin were 62%, compared to 36% of genotype 2/3 patients receiving pegylated interferon/placebo and 20% of genotype 2/3 patients receiving standard interferon/ribavirin.

Comparatively surveying the results of ACTG A5071 and APRICOT, it is clear that combination therapy with pegylated interferon and ribavirin was associated with higher rates of sustained virologic responses, both in the overall patient population and in those infected with HCV genotype 1, in the APRICOT trial. One possible reason for this is the lower starting dose of ribavirin used in the ACTG A5071 study. While this may have resulted in a lower discontinuation rate, it may also have contributed to lower sustained virologic responses.

interferon and were randomized to receive either ribavirin (800 mg/day) or ribavirin placebo. After a total of 24 weeks, all patients with detectable HCV-RNA levels (>50 HCV-RNA IU/mL) discontinued treatment. All patients with undetectable HCV-RNA levels after 24 weeks continued their allotted regimens for a total of 48 weeks of therapy.

After 12 weeks of pegylated interferon monotherapy, 59/153 (38%) were dubbed virologic responders, with 37 (24%) experiencing undetectable HCV-RNA levels. Among the nonresponders who continued therapy for an additional 12 weeks using ribavirin, 2 (6%) had undetectable HCV-RNA levels at 24 weeks, 3 (8%) had undetectable HCV-RNA levels at the end of treatment (48 weeks), and 1 (3%) had a sustained virologic response six months after discontinuing treatment. Among initial nonresponders who were randomized to receive ribavirin placebo, only 1 (3%) had undetectable HCV-RNA levels at the end of treatment and there were no reports of sustained virologic responses in this group six months after treatment discontinuation.

“The basic premise of this study was to see if adding ribavirin after 12 weeks of pegylated interferon would help people remain on therapy, since previous studies tended to see high discontinuation rates early in the course of treatment, given the side effects of both drugs administered together,” Dr. Chung commented. The adverse event-related dropout rate was less than 5% during the initial pegylated interferon monotherapy part of the study. But after 12 weeks, when patients either took ribavirin or continued pegylated interferon monotherapy, the dropout rate because of side effects was still greater than 10%. “So, the addition of ribavirin at week 12 certainly doesn’t make a great deal of sense in terms of a strategy to keep patients on therapy or for that matter to improve virologic response rates among initial peg nonresponders.”

Understanding Diminished Responses


“CLEARLY, WE TEND TO SEE LESS PRONOUNCED END-OF-TREATMENT AND SUSTAINED RESPONSES IN COINFECTED PATIENTS THAN WE DO IN HCV-MONOFECTED PATIENTS,” Dr. Chung said. The potential reasons for this are plentiful. First, the immune response to HCV is generally weaker in the setting of HIV infection. “A number of scientific studies have demonstrated this,” Dr. Chung added. Second, higher HCV-RNA levels are frequently seen in coinfecting patients, which may decrease the likelihood of complete viral suppression during treatment, similar to what is seen using antiretroviral therapy in patients with high HIV-RNA levels. Third, there may be more inaccessible reservoirs, such as HCV-infected peripheral blood mononuclear cells, and differences in HCV infection decay rates in the setting of HIV. Fourth, HIV infection may be associated with increased expression of various interferon antagonists, such as interleukin-8. Fifth, lower doses of ribavirin have been used in some HIV/HCV-coinfection studies—including the dose-escalation protocol employed in ACTG A5071—which may limit the effectiveness of combination therapy. “Treatment using ribavirin is quite dose-responsive,” Dr. Chung pointed out. “Higher doses of ribavirin may increase sustained virologic response rates in these patients, but possibly at the expense of increased toxicities.”

“There are still a number of questions that need to be addressed with respect to the treatment of coinfecting patients,” Dr. Chung said. “We need to look at using antiretroviral therapy to boost sustained virologic response rates, by maintaining a maximal functional immune response against the virus. We will also need to establish optimal length of therapy and to explore strategies to dose-optimize ribavirin treatment, including use of growth factors such as erythropoietin.”

Conclusion

WHILE HIV/HCV-COINFECTED PATIENTS MAY NOT RESPOND AS WELL TO pegylated interferon/ribavirin therapy as HCV-monoinfected patients, it’s clear that this drug combination can and does produce sustained virologic responses in a number of HIV/HCV-coinfecting patients—much more so than standard interferon and ribavirin—and should now be viewed as optimal antiviral therapy for HCV in coinfection. “This is tantamount to cure of this particular infection,” Dr. Chung said. “There is a great deal of genotypic discordance in coinfecting patients, with a significant prevalence of genotype 1, which will have a profound effect on the sustained response rates seen in HIV-infected patients.”

As for toxicity, Dr. Chung pointed out that it is quite common in coinfecting patients receiving both pegylated interferon and ribavirin, “but it’s still uncommon for these toxicities to result in treatment discontinuation, which is good news.”

Timing, too, is an important issue to consider when planning treatment in coinfecting patients. “I think treatment for HCV should be considered for those patients who can, in fact, defer antiretroviral therapy,” Dr. Chung said. “Fortunately, this is an increasingly large portion of HIV-positive patients. The good news is that there are a number of new drugs on the horizon, including drugs that interrupt HCV protease, helicase, and RNA polymerase, some of which are approximately three to five years away from approval. Indeed, keeping our patients going until these promises can be realized is a very important goal indeed.” 

References

- Benhamou Y, Bochet M, Di Martino V, et al. Liver fibrosis progression in human immunodeficiency virus and hepatitis C virus coinfecting patients. The MULTIVIRC Group. *Hepatology* 30(4):1054-8, 1999.
- Bica I, McGovern B, Dhar R, et al. Increasing mortality due to end-stage liver disease in patients with human immunodeficiency virus infection. *Clin Infect Dis* 32(3):492-7, 2001.
- Chung R, Andersen J, Volberding P, et al. A randomized, controlled trial of peg-interferon- α -2a plus ribavirin vs. interferon- α -2a plus ribavirin for chronic hepatitis C virus infection in HIV-coinfecting persons: follow-up results from ACTG A5071 [Abstract 110]. 11th Conference on Retroviruses and Opportunistic Infections, San Francisco, 2004.
- Chung RT, Evans SR, Yang Y, et al. Immune recovery is associated with persistent rise in hepatitis C virus RNA, infrequent liver test flares, and is not impaired by hepatitis C virus in co-infected subjects. *AIDS* 16(14):1915-23, 2002.
- De Luca A, Bugarini R, Lepri AC, et al. Coinfection with hepatitis viruses and outcome of initial antiretroviral regimens in previously naive HIV-infected subjects. *Arch Intern Med* 162:2125-32, 2002.
- Eyster ME, Fried MW, Di Bisceglie AM, et al. Increasing hepatitis C virus RNA levels in hemophiliacs: relationship to human immunodeficiency virus infection and liver disease. Multicenter Hemophilia Cohort Study. *Blood* 84(4):1020-3, 1994.
- Greub G, Ledergerber B, Battegay M, et al. Clinical progression, survival, and immune recovery during antiretroviral therapy in patients with HIV-1 and hepatitis C virus coinfection: the Swiss HIV Cohort Study. *Lancet* 356:1800-5, 2000.
- Perez-Olmeda M, Nunez M, Romero M, et al. Pegylated IFN- α 2b plus ribavirin as therapy for chronic hepatitis C in HIV-infected patients. *AIDS* 17(7):1023-8, 2003.
- Perronne C, Carrat F, Bani-Sadr F, et al. Final results of ANRS HC02-RIBAVIC: a randomized controlled trial of pegylated interferon- α -2b plus ribavirin vs interferon- α -2b plus ribavirin for the initial treatment of chronic hepatitis C in HIV coinfecting patients [Abstract 1171B]. 11th Conference on Retroviruses and Opportunistic Infections, San Francisco, 2004.
- Rancinan C, Neau D, Saves M, et al. Is hepatitis C virus co-infection associated with survival in HIV-infected patients treated by combination antiretroviral therapy? *AIDS* 16:1357-62, 2002.
- Sulkowski MS, Moore RD, Mehta SH, et al. Hepatitis C and progression of HIV disease. *JAMA* 288:199-206, 2002.
- Torriani FJ, Rockstroh J, Rodriguez-Torres, et al. Final results of APRICOT: a randomized, partially blinded, international trial evaluation peginterferon- α -2a + ribavirin vs interferon- α -2a + ribavirin in the treatment of HCV in HIV/HCV coinfection [Abstract 112]. 11th Conference on Retroviruses and Opportunistic Infections, San Francisco, 2004.
- Vlahakis SR, Villasis-Keever A, Gomez TS, et al. Human immunodeficiency virus-induced apoptosis of human hepatocytes via CXCR4. *J Infect Dis* 188(10):1455-60, 2003.