Therapeutic Implications of Acute Hepatitis C Infection

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The hepatitis C virus's greatest weapon might very well be its silence. It is an infection that is initially asymptomatic and often goes unrecognized, anywhere from several years to more than two decades after the infection has established itself in the liver. Because of this, countless individuals in this country and elsewhere are not aware that they are, in fact, chronically infected with the virus.

This is also true during the acute stage of infection. While symptoms such as fatigue, lethargy, myalgia, low-grade fever, nausea and vomiting do occur in patients with acute HCV infection, they are virtually indistinguishable from more common and benign viral infections and, as a result, usually go unchecked. Even one of HCV's hallmark features—jaundice—develops in fewer than half of all individuals during acute infection, even though HCV-RNA and liver enzyme levels are usually at their highest.

The clinical silence of HCV during the earliest weeks of infection is frustrating, as there is now reason to believe that the identification, diagnosis, and treatment of acute HCV may be associated with truly remarkable results. Without more telltale signs of infection—especially when a patient's risk of infection is not entirely known or appreciated by his or her clinician—it is likely that few patients will benefit from what has come to be recognized as a breakthrough in the treatment of hepatitis C: the use of interferon to reduce the likelihood of acute HCV infection progressing into a life-long and life-threatening disease.

Treatment of Acute HCV Infection: The Rationale

ACUTE HCV INFECTION IS CONSIDERED BY MANY experts to be positively ripe with therapeutic potential. At the heart of this belief are virologic and immunologic characteristics unique to acute HCV infection—most notably virus-specific cell-mediated responses—that are believed to play a significant role in determining whether an infection will be self-limited or progress to chronic hepatitis C. In a nutshell, if these immune responses are able to control viral replication early on in the course of infection, the disease will be self-limited and the virus effectively cleared from the body. If the immune system fails to contain viral dissemination during the acute stages of infection, the price is high—HCV takes up permanent residence in hepatocytes and virus-specific immune responses are permanently lost to apoptosis or rendered anergic.

In murine models of lymphocytic choriomeningitis virus (LCMV) infection—a noncytopathic RNA virus associated with high levels of replication, much like HCV—early control of viral load allows for the host immune response to clear the virus and effectively prevent the development of chronic infection: virus-specific CD4+ and CD8+ cells remain, whereas the virus does not (Moskophidis, 1993; Oxenius, 1998). Conversely, mice maintaining high concentrations of LCMV generally experience depletion in their virus-specific CD4+ and CD8+ cell responses, leading to chronic infection in the vast majority of cases. "If viral replication is not controlled," Dr. Jaeckel explained, "the initial immune response simply becomes overwhelmed and virus-specific CD4+ cell responses are either deleted or are rendered anergic."

Even more relevant, perhaps, is the recent experience with treating acute HIV infection. As has been reviewed in several past issues of *The PRN Notebook*—most recently in a special edition of the *Notebook* focusing specifically on the diagnosis and treatment of primary HIV infection, published in February 2002—data coming out of studies conducted at Massachusetts General Hospital and other groups indicate that early treatment may be associated with the long-term control of HIV replication (Rosenberg, 2000). These groups have shown that, if antiretroviral therapy is initiated during the acute stage of HIV infection, virus-specific CD4+ cell responses are permitted to proliferate and to continue orchestrating the much-needed activity of cytotoxic T-lymphocytes. "Using antiretroviral therapy appropriately during acute HIV infection appears to be the key in maintaining these necessary responses," Dr. Jaeckel said. "We don't see the same proliferation of virus-specific immune responses in patients treated with antiretroviral therapy during the chronic stage of infection.

With respect to the treatment of acute HCV infection, there have actually been a number of studies conducted over the past ten years evaluating the safety and effectiveness of early intervention strategies. During his lecture, Dr. Jaeckel made reference to 14 clinical trials that have evaluated interferon therapy during acute HCV infection, the majority of which demonstrated a benefit associated with the treatment. Only one study, conducted at the Amedeo di Savoia Hospital in Torino, Italy, failed to show a statistically significant difference in the incidence of chronic HCV infection among acutely infected patients receiving interferon or placebo (Calleri, 1998). Among

the studies that did associate interferon with a beneficial effect, Dr. Jaeckel suggested that they were either too small, too brief in duration, or did not use HCV-RNA levels as an endpoint. Some studies also used interferon-beta—including the failed Torino study—a compound that has been shown to be less effective in the treatment of hepatitis C than interferon-alpha.

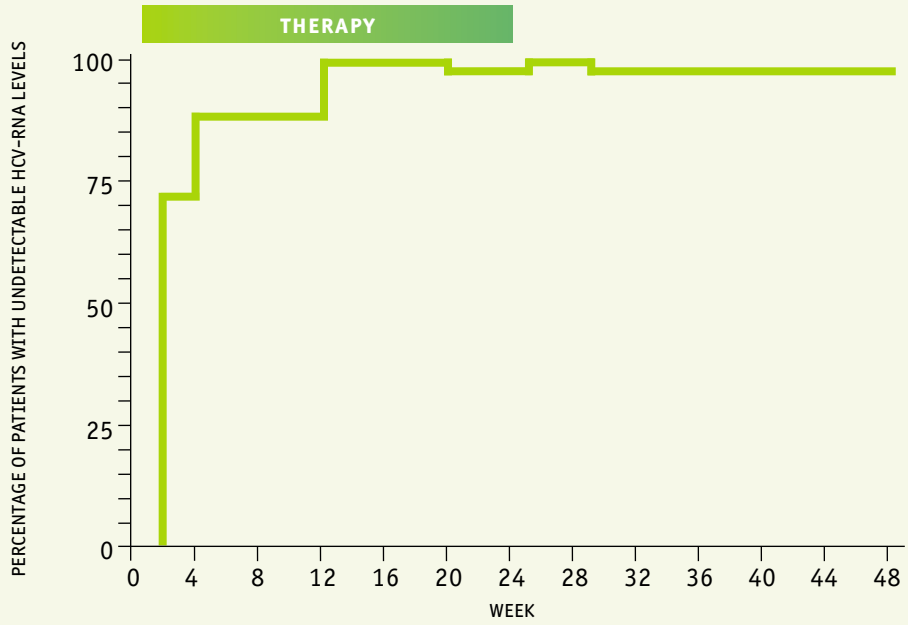
The German Prospective Treatment Trial

TO FURTHER EXPLORE THE DISEASE-LIMITING benefits of treating acute HCV infection, Dr. Jaeckel and his colleagues began enrolling patients into a nationwide clinical trial in Germany, with the support of the German Association for the Study of the Liver (Jaeckel, 2001). Patients 18 years of age or older were eligible, provided that they were positive for HCV-RNA on a PCR assay, had elevated alanine aminotransferase (ALT) levels, and were determined to be in the acute stage of HCV infection. To differentiate between acute and chronic stages of HCV infection, the following criteria were considered: known or suspected exposure to HCV within four months prior to being screened for the study; documented negative-to-positive seroconversion for HCV antibodies; or a serum ALT level higher than 350 U/l, with a documented normal level during the year prior to the infection. Patients were excluded from the trial if they had decompensated liver, kidney, or thyroid disease; liver diseases unrelated to HCV infection (e.g., chemical hepatitis, hemochromatosis, Wilson's disease, etc.); anemia; leukopenia; thrombocytopenia; coinfection with either HIV or hepatitis B virus (HBV); psychiatric conditions such as severe depression; a history of seizures; poorly controlled autoimmune diseases; a history of organ transplantation; or ongoing abuse of intravenous drugs or alcohol.

Interferon alpha-2b (Intron A) was the interferon formulation of choice. To be on the safe side, all patients received daily interferon (5 million U) injections for the first four weeks of the study, as opposed to three-times-weekly injections employed by many clinicians in the management of chronic hepatitis C. Reiterating the findings of a study published in a 1997 issue of *Hepatology*, Dr. Jaeckel pointed out that HCV-RNA levels begin to rebound in as little as 24 hours after a single dose of interferon-alpha is administered to acutely infected patients (Lam, 1997). "We wanted consistent suppressions of HCV viral load," he said. "In turn, we treated all of the patients with daily interferon for a month and then switched them to injections three times a week for an additional 20 weeks. That's 24 weeks in total."

The primary endpoint of the study was a sustained virologic response, defined as an undetectable HCV-RNA result, six months after completing interferon therapy. There were also two secondary endpoints: the absence of detectable HCV-RNA in blood samples after 24 weeks of treatment and normalization of ALT levels.

Figure 1. Cumulative Incidence Of Undetectable Serum Levels of HCV-RNA During Treatment and Follow-Up.



All 44 patients were evaluated before therapy (week 0); at weeks 2, 4, 12, and 24 of therapy; and 24 weeks after the end of therapy. Serum HCV-RNA levels were measured by a reverse-transcription-polymerase-chain-reaction assay for which the lower limit of detection is 600 copies of HCV-RNA per milliliter.

Source: Jaeckel, 2001. Reprinted with permission of the *New England Journal of Medicine* and the Massachusetts Medical Society.

Results

AFTER AN EXTENSIVE RECRUITMENT CAMPAIGN involving the distribution of approximately 7,000 printed announcements to clinical-care centers throughout Germany, 44 patients were found to meet the inclusion/exclusion criteria and were subsequently enrolled into the study. A total of 24 centers were involved in the study, which was open from March 1998 through March 2001.

Of the 44 patients, 30 (68%) either knew or suspected that they had been exposed to HCV within four months prior to entering the study. Of these, 17 had a documented negative-to-positive HCV antibody seroconversion. Six of the 44 (14%) patients also had a documented seroconversion but could not pinpoint their exposure. However, four of these patients had HCV-positive partners. Eight of the 44 (18%) patients had elevated ALT levels—ranging from 635 to 1500 U/l—with no prior signs of liver disease.

Needle-stick injuries were the most common sources of HCV infection, occurring in 32% of patients enrolled. Sexual contact also accounted for a sizeable number of exposures, occurring in 23%. Intravenous drug use and infection stemming from a surgical procedure accounted for 20% and 16%, respectively. Dr. Jaeckel also pointed out that treatment was initiated in most patients within three months after infection was established (mean 89 days).

At baseline, the median HCV-RNA level among all patients was 422,000 copies/mL. More than half of the study participants

Table 1. Baseline Comparisons: Treated Patients in the National Prospective Treatment Trial and Untreated Patients in Bari, Italy

	German Cohort (Treated)	Bari Cohort (Untreated)	p-value
Inclusion period	1998–2000	1995–2000	
Number of patients	44	40	
Mean age (years)	36	40	
Icteric	30 (68%)	20 (50%)	0.252
Female	25 (57%)	17 (42%)	0.190
Mode of infection			
IVDU	9 (20%)	7 (18%)	0.769
Needle-stick injury	14 (32%)	3 (8%)	0.006
Medical procedure	7 (16%)	24 (60%)	0.00003
Partner (sexual)	10 (23%)	3 (8%)	0.054
Unclear	4 (9%)	3 (8%)	0.792
Health-care	21 (48%)	27 (68%)	0.067
Mean viral load (HCV-RNA copies/mL)	418,954	879,057	0.057
ALT (IU/L)	885	1563	0.00006
HCV Genotypes			
I	27 (61%)	21 (53%)	0.412
II or III	12 (27%)	14 (35%)	0.444
IV	0	2 (5%)	0.133
Unclear	4 (9%)	3 (8%)	0.792

Source: Elmar Jaeckel, MD.

(57%) were female and 68% of the patients enrolled had icteric disease. As for HCV genotype distribution, 27/44 (61%) patients were infected with type 1, 27% had types 2 or 3, and 9% had genotypes that could not be accurately determined.

Forty-three of the 44 patients completed the 24-week course of treatment. Therapy was well tolerated, with the exception of the one patient who stopped therapy after 12 weeks because of mild to moderate side effects (hair loss and flu-like symptoms). As further explained by Dr. Jaeckel, "there were not any serious adverse effects seen in the patients receiving interferon, either during the first four weeks of daily treatment or during the less intensive three-times-weekly phase that followed. Side effects in our study were similar to those seen in other studies using interferon as monotherapy." Varying degrees of thrombocytopenia and leukopenia were seen during the initial four weeks of therapy. However, they were all reversible and did not result in any treatment modifications.

As for the effectiveness of interferon therapy, HCV viral load became undetectable (<600 HCV-RNA copies/mL) in all patients, usually within 3.2 weeks after beginning treatment. Twenty-four weeks after completing interferon therapy, 43/44 (98%) patients had undetectable levels of HCV-RNA—the highest sustained virologic response rate reported to date among all of the acute HCV infection studies (see Figure 1). The one patient who stopped treatment after 12 weeks was among these 43 apparent successes. At week 20, eight weeks after stopping therapy, the patient experienced a self-limited flare of hepatitis resulting in an HCV-RNA rebound. However, the patient then went on to see his HCV-RNA return to an undetectable level, which was maintained at the 24-week follow-up time point.

ALT levels normalized in most (80%) patients, usually during the first three months of interferon treatment. Of the remaining 20%, ALT levels fell precipitously, with levels no higher than twice the upper limit of the normal range by the time therapy was concluded. By the end of the study, 24 weeks after therapy had been completed, 42/44 patients had normal liver function tests.

Making Comparisons

AS IMPRESSIVE AS THESE DATA SEEM, THE TRUE test of the trial's success is in its analysis. For starters, it's always possible that some of the patients would have experienced self-limited acute infections and cleared the virus without the use of treatment. "We see self-limited disease in as many as 30% of people infected with the virus," Dr. Jaeckel pointed out. "But in this study, we halted the progression to chronic infection in 98% of our acutely infected patients. It's safe to say that we wouldn't have seen this in an untreated population."

Considering that no placebo group was included in the study, head-to-head comparisons between treated and untreated patients are not possible. For the sake of a more in-depth analysis, Dr. Jaeckel's team compared their study data with those of a cohort of patients followed at the University of Bari in Italy (Santantonio, 1999). This cohort consisted of 40 individuals with acute HCV infection, none of whom received treatment. As shown in Table 1, there were only a few significant differences between the two groups at baseline—patients participating in the German study were more likely to have been infected through a needle-stick injury (32% vs. 8%), whereas patients in the Italian cohort were more likely to have been infected as a result of a medical procedure (60% vs. 16%). Median baseline ALT levels were also significantly higher in the Italian cohort than in the German study participants (1653 U/l vs. 885 U/l).

As illustrated in Figure 2, patients treated with interferon were much more likely to have normal virologic and biochemical parameters after 48 weeks of follow-up. "Seventy percent of the patients enrolled in

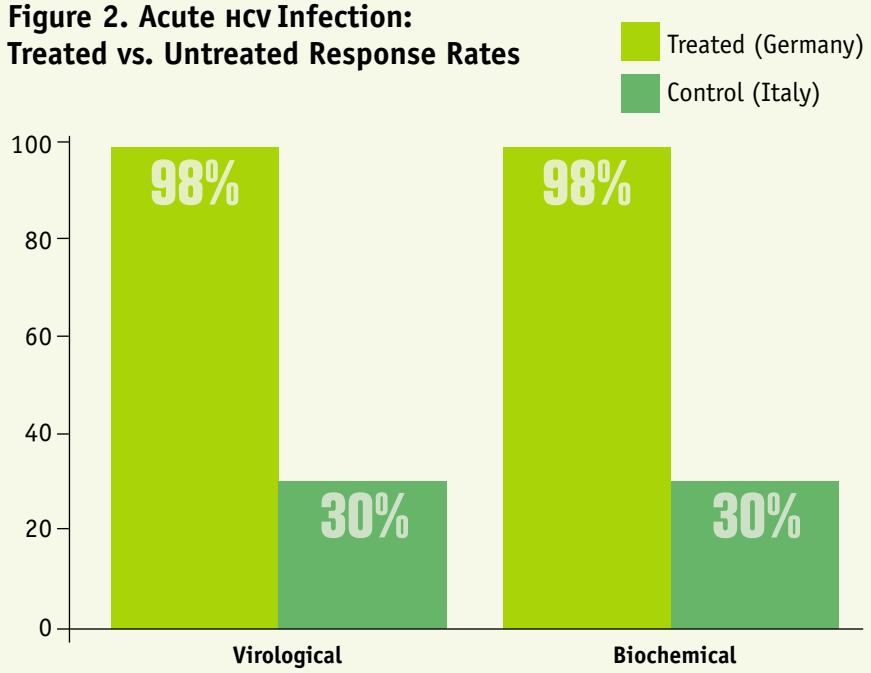
the University of Bari cohort progressed to chronic hepatitis C," Dr. Jaeckel said. "This is more or less the same rate we've seen in other cohorts involving acutely infected patients."

Dr. Jaeckel also pointed out that the success of treatment among patients who do, in fact, go on to experience chronic hepatitis C is less than stellar. "Even with pegylated interferon in combination with ribavirin, the sustained response rate—clearance of the virus—is around 54%," he explained. "There is still a sizeable population of patients who will not respond to therapy if they begin treatment during chronic disease. Treating HCV during the acute stage of infection appears to afford substantial protection, before combination therapy is needed, requiring a shorter treatment time."

As encouraging as these findings are, Dr. Jaeckel will be the first to admit that vital questions remain. For example, it is still not known how to distinguish between individuals who will experience self-limited acute infection and those who will go on to develop chronic disease. "Obviously, we don't want to treat acutely infected patients who don't need treatment, which is actually a considerable number," he said. There are also questions regarding the short- and long-term effects of treating acute HCV infection: How long after infection is the therapeutic window of opportunity open? Is virus clearance stable? Which are the best drugs to employ for the treatment of acute HCV infection (e.g. standard interferon-alpha vs. pegylated interferon, either with or without ribavirin)? Is an induction/maintenance treatment protocol appropriate? Is 24 weeks the optimal length of therapy?

Perhaps most pressing, Dr. Jaeckel reckons, is the need to identify more patients with acute HCV infection in the real world of clinical care. "Many more general practitioners and advocacy groups need to be aware of the signs and symptoms of acute HCV infection," he said. "Treatment may have a great deal to offer individuals who are in the initial stages of HCV infection, which can also reduce the possibility of spreading the virus on to others." In turn, it is imperative that people at known risk through needle-stick injuries or injection drug use be thoroughly screened. It might also serve clinicians well to consider people in discordant relationships with HCV-positive individuals to be at risk, contrary to current beliefs that HCV is not a sexually transmitted disease. "If we are to see treatment benefits," concluded Dr. Jaeckel, "this will require identifying patients early enough to begin treatment or to enroll them in clinical trials, which may be our biggest challenge yet." prn

Figure 2. Acute HCV Infection: Treated vs. Untreated Response Rates



Source: Elmar Jaeckel, MD.

References

Calleri G, Colombatto P, Gozzelino M, et al. **Natural beta interferon in acute type-C hepatitis patients: a randomized controlled trial.** *Ital J Gastroenterol Hepatol* 30:181-4, 1998.

Jaeckel E, Cornberg M, Wedemeyer H, et al. **Treatment of acute hepatitis C with interferon alfa-2b.** *N Engl J Med* 345:1452-7, 2001.

Lam NP, Neumann AU, Gretch DR, et al. **Dose-dependent acute clearance of hepatitis C genotype 1 virus with interferon alfa.** *Hepatology* 26:226-31, 1997.

Moskophidis D, Lechner F, Pircher H, et al. **Virus persistence in acutely infected immunocompetent mice by exhaustion of antiviral cytotoxic effector T cells.** *Nature* 362:758-61, 1993.

Oxenius A, Zinkernagel RM, Hengartner H. **Comparison of activation versus induction of unresponsiveness of virus-specific CD4+ and CD8+ T cells upon acute versus persistent viral infection.** *Immunity* 9:449-57, 1998.

Rosenberg ES, Altfeld M, Poon SH, et al. **Immune control of HIV-1 after early treatment of acute infection.** *Nature* 407:523-6, 2000.

Santantonio T, Mazzola M, Guastadisegni A, et al. **A cohort study of acute hepatitis C virus (HVC) infection: natural course and outcome.** *Hepatology* 30(Suppl A):205A, 1999.