Pegylated interferon alpha-2b in patients with acute hepatitis C

Kamal SM, Fouly AE, Kamel RR, Hockenjos B, Al Tawil A, Khalifa KE, He Q, Koziel MJ, El Naggar KM, Rasenack J, Afdhal NH. (Division of Gastroenterology and Liver Disease Center, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA; Department of Gastroenterology and Liver Diseases, Ain Shams University, Cairo, Egypt; Department of Gastroenterology and Hepatology, University of Freiburg, Germany.) Peginterferon alfa-2b therapy in acute hepatitis C: Impact of onset of therapy on sustained virologic response. *Gastroenterology* 2006;130:632–8.

SUMMARY
The best time to start antiviral therapy in patients with acute hepatitis has not been clearly identified. This randomized, controlled, multicentre trial was done to evaluate the efficacy of pegylated interferon α-2b (PEG-IFN α-2b) in a large cohort of patients with acute hepatitis C and identify the optimal timing of therapy.

One hundred and seventy-five patients with acute HCV infection were screened. One hundred and twenty-nine subjects whose infection did not resolve by 8 weeks were randomized to once-weekly PEG-IFN α-2b (1.5 mg/kg per week) started at either 8, 12 or 20 weeks for a total duration of 12 weeks. The primary endpoint was sustained virological response (SVR) 24 weeks after stopping therapy. By using an intention-to-treat analysis, the respective SVRs were 95%, 92% and 76% for the three groups, respectively. Initiation of therapy at 8 or 12 weeks resulted in a higher SVR than initiation at week 20. Overall, SVR was better for genotypes 2, 3 and 4 as compared with genotype 1. Subjects with SVR maintained undetectable HCV RNA at week 48 as well.

COMMENT
The management of acute hepatitis has been mired in controversy. To start with, the definition of acute hepatitis itself has been variable. In this study, the criteria used to diagnose acute hepatitis...
C infection were previously healthy individuals with elevated serum alanine aminotransferase (ALT, 5–10 times the upper limit of normal), conversion from negative to positive polymerase chain reaction (PCR) and seroconversion from negative to positive HCV antibody status (third-generation ELISA). The definition of acute hepatitis C has not been consistent in previous trials, where ALT levels more than 20 times above normal and definite exposure history were used as inclusion criteria and an ALT level of 7 times more normal was taken in another study. The initial study on IFN treatment of acute hepatitis included ALT >350 IU/L (20 times the upper limit of normal) and HCV antibody seroconversion alone. It is well known that the level of aminotransferases varies widely in chronic hepatitis C. Paradoxically, in the early phases of the infection there is a period of near normal ALT, which may last for months or years. Therefore, a normal ALT should not be excluded from the definition of acute hepatitis. The strength of the definition used in this study as opposed to those in the above three trials is the conversion of the PCR test from positive to negative and the development of anti-HCV, the so-called double seroconversion. HCV RNA may appear in the serum as early as 1–2 weeks after exposure. In this study, the mean time between infection and referral was 11 days. In day-to-day practice, it may be near impossible to detect patients before this narrow window period. Probably the best compromise is to rely on a positive HCV RNA by PCR and negative anti-HCV followed by anti-HCV seroconversion.

This study enrolled patients from 8 Egyptian, American and German centres. Though the exact number of patients recruited from each centre has not been mentioned, the equal preponderance of genotype 4, which is common in Egypt, and genotype 1, which is common in the other two regions, suggests that Egyptian patients constituted a significant proportion of enrolled patients. The commonest risk factor in this study was 'occupational exposure' as opposed to 'drug use'. Considering the short referral time, it is possible that a large proportion of patients were healthcare workers who reported HCV exposure. In the previous German trial, 22% of patients were intravenous drug abusers and the drop-out rate was significant. Intravenous drug users have low tolerance and adherence to IFN regimens, and the high incidence of psychiatric side-effects may lead to adverse psychosocial outcomes. Adherence to therapy was excellent in this study. It is important to note that host factors play an important role in the clearance of HCV and one should be prudent in extrapolating the results from one population to another.

A series of meta-analyses have documented the role of IFN in acute hepatitis C. The first meta-analysis confirmed that a short duration (12 weeks) of ordinary IFN was more effective than no treatment in achieving SVR. The second analysis showed that short term IFN (6 weeks to 6 months) was more effective than long term treatment (12 months or more). A Cochrane Database Review also confirmed that ordinary IFN was superior to no treatment in achieving SVR in transfusion-acquired hepatitis C.

The last meta-analysis addressed the issue of timing of IFN therapy and concluded that delaying therapy by 8–12 weeks after the onset of disease did not compromise the SVR rate. The key question that this study set out to answer was the optimum timing of institution of IFN therapy. Irrespective of the timing, 88.5% of patients achieved SVR after 12 weeks of therapy, which is much higher than the spontaneous clearance rate, thereby strengthening the concept that therapy is indeed beneficial. Therapy initiated at week 8 or 12 was significantly more effective in achieving SVR than when initiated at week 20. The possible explanation is the development of quasispecies and a more heterogeneous, resistant HCV virus population, or an associated blunting of the host immune response. It is important to note that 95% of spontaneous remissions in the control group occurred by 12 weeks, suggesting that this time period may be the optimum time for starting IFN therapy, allowing time for spontaneous remission to occur. Interestingly, icteric patients had higher clearance rates than asymptomatic patients, further stressing the importance of host antiviral cellular immunity.

The hepatitis C genotype plays an important role in determining the response to IFN. In this study, the highest SVR was achieved in genotype 1-infected patients in whom therapy was started at week 8. On the other hand, the SVR in genotype 2- and 3-infected patients was above 95%, irrespective of the timing of onset of therapy, and the SVR in genotype 4-infected patients was higher when started at 8 and 12 weeks than at 20 weeks. The commonest reported genotype in India is genotype 3. This study reported a 100% SVR rate at both 8- and 12-week initiation periods for patients infected with genotype 3. This suggests that treatment of acute hepatitis C also needs individualizing according to genotype. Further study is required to determine whether a longer duration of therapy than the 12 weeks prescribed in this study will provide more benefit to patients with genotype 1. More importantly, in the 48-week follow up period there was no relapse of infection in patients who had achieved SVR, suggesting that IFN therapy is effective in preventing acute hepatitis C from progressing to the chronic stage.

In conclusion, this study shows that PEG-IFN α2b treatment of acute hepatitis C leads to high SVR rates, reduces chronic hepatitis C infection and is effective when started between 8 and 12 weeks, allowing time for spontaneous resolution.

REFERENCES

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