Up to date treatment of hepatitis C in adults

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Therapy of chronic hepatitis C has been subject of two consensus reports (1,2), that appeared in 1997. The recommendations, made by distinguished physicians without specific expertise in hepatitis C virus infection (HCV), are surprisingly similar in view of the widely dissimilar views of HCV-experts (3).

Treatment with alpha interferon 3 million units thrice weekly for 12 months is now considered the standard regimen. In view of the limited sustained virological response rate (about 10% in the most prevalent genotype 1), the cost and side-effects of such therapy, the indication of therapy has been limited to patients with progressive fibrosis (elevated ALT and fibrosis stage ≥ 2 on liver biopsy), but without advanced cirrhosis or immunodeficiency syndromes like HIV, dialysis or transplant recipients. Antiviral therapy will be more widely indicated when the sustained response rate increases considerably. Why does interferon therapy fail so often ? Two major pathobiological problems appear to be responsible : 1. relapse of viral replication after stopping interferon therapy ; 2. lack of "viral clearance" within the first 4 weeks of therapy (4, fig. 1).

This year it has become clear that progress has been made in both these areas, most notably by :

a) Interferon-ribavirin combination therapy to reduce relapse rates, and ;
b) Interferon induction therapy, to induce early viral clearance.

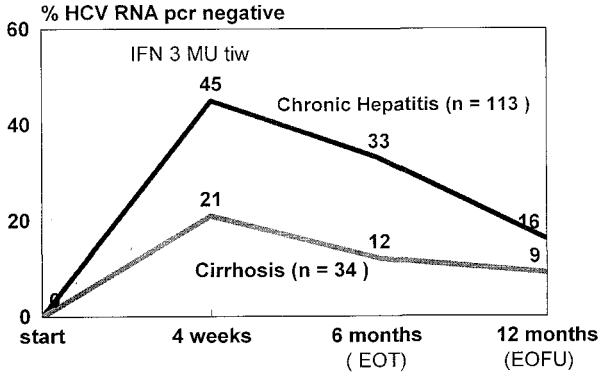

Fig. 1. — Interferon monotherapy in chronic hepatitis C. The graph illustrates the two major problems :

a. a low rate of viral clearance in the first 4 weeks of therapy, most pronounced in patients with cirrhosis, and
b. a high rate of relapse after stopping therapy (Data derived from the Benelux study 90-01, reference 4).

Interferon-ribavirin combination therapy

As part of the European Concerted Action of Viral Hepatitis (Eurohep) data from individual patients participating in randomized controlled trials including an arm with interferon-ribavirin combination therapy have been collected in one central data base. The data base containing 186 patients (more than 90% of the published experience) in 1996 (5) is still expanding to allow subgroup analysis of different genotypes and stages of chronic hepatitis C (no cirrhosis, cirrhosis, advanced cirrhosis). The data base for a recent interim-analysis contained 349 patients from 6 centers.

The sustained response rate (ALT normal and HCV RNA-PCR negative 6 months after therapy) was 50 percent for naive patients, similar to that of a recently reported trial from Sweden (6). Of particular interest is the response rate of 35 percent in patients with genotype 1. The number of patients with cirrhosis was too low to allow an estimate of response for this category. For patients that had been treated previously with interferon, the sustained response rate was 40% for those with response relapse (ALT normalization at the end of previous IFN therapy) and 15 percent for non-responders (no ALT normalization during previous IFN therapy). Response rates at the end of therapy were independent of genotype, but patients with genotype 1 had a significantly higher relapse rate than patients with genotype 2 or 3. Patients with cirrhosis had a lower response at the end of therapy but virtually no relapse, resulting in similar sustained response rates as patients without cirrhosis (fig. 2). A comparison of response rates with 6 months interferon monotherapy and those of interferon-ribavirin combination therapy showed that the effect of combination therapy was the reduction of the high relapse rate (fig. 3). Combination of interferon with ribavirin for 6 months shows — in all types of studies : pilot-studies, meta-analysis of individual patient data, and randomized controlled trials — enhanced efficacy without major toxicity (anaemia) ; in particular patients with high viral load, cirrhosis or genotype 1 will benefit from combination therapy. Registration of the combination therapy is to be expected from late 1998 onwards.

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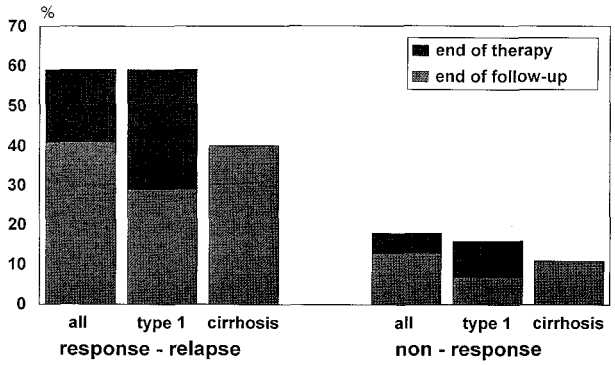

Fig. 2. — Estimated ALT & HCV RNA response rates of IFN-Riba combination therapy in chronic hepatitis C (data derived from the Eurohep Group Meta-analysis Individual Patient Data, interim analysis, in 158 patients, 1997).

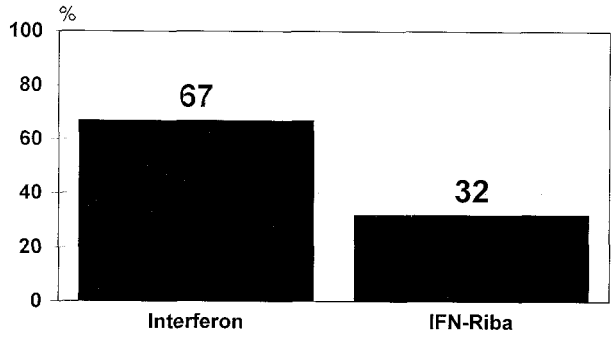

Fig. 3. — Relapse-rates in patients with an ALT-HCV RNA response at the end of therapy. The relapse rate in patients with IFN-Riba combination therapy is about half that of interferon monotherapy (data derived from the Eurohep Group MIPD).

Interferon induction therapy

Further advances in therapy may come from increased awareness of the high predicted value of early viral clearance for a sustained response. Early observations from the Benelux study (7) have been confirmed (8) that almost all sustained responders have undetectable HCV RNA (detection limit : 1000 copies per ml) at 4 weeks of therapy ; patients not achieving a HCV RNA negative state in serum after 4 weeks have a close to 100% relapse rate. In that setting, reports from Japan about the effectiveness of daily high-dose alpha-interferon therapy (9) induced renewed interest in dose-response studies (10) and in viral kinetics after daily high dose interferon (11). Ten millions units of interferon per day appears a highly effective strategy to induce HCV RNA negativity in more than 80% of patients within several weeks (9) (fig. 4). Such a regimen also induces a rapid fall in viraemia in non-responders (11), allowing calculation of the half-life of the HCV virus (about 5-7 hours) and the daily production rate (about 10^{11} copies per day). The disappearance of viraemia fits a 2-compartment

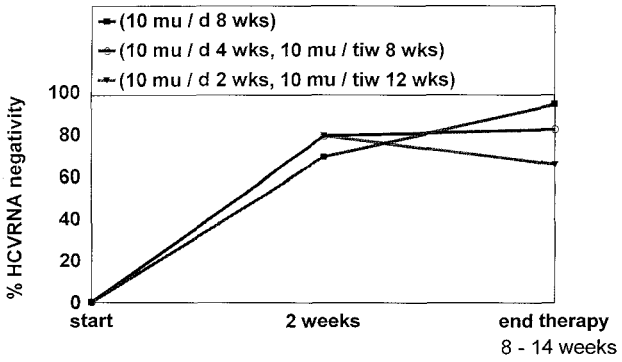

Fig. 4. — Interferon-induction therapy in naive patients without cirrhosis. More than 80% HCV RNA negativity was observed in 2 out of 3 treatment groups, all starting with daily 10 MU of interferon (data derived from reference 9).

model ; the half-life of the second phase is about 400 hours for genotype 1 under therapy of 10 million units thrice weekly (12). From the Japanese data one must assume that extending daily high dose therapy can shorten the half-life of the second phase considerably.

In summary, considerable evidence is accumulating that suggest the enhanced efficacy of interferon-ribavirin combination therapy. Furthermore, interferon induction therapy is highly effective in inducing early viral clearance ; it remains to be proved whether this event can also be translated in high sustained response rates.

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