The "Hit Hard And Hit Earl" Strategy To Treat Chronic Hepatitis C

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Citation

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Abstract

Daily dosed interferon-alpha may prevent mutations of the hepatitis C virus (HCV) quasi-species and may therefore be more efficient in the treatment of chronic hepatitis C than the conventional therapy regimen given three times a week ([1,2]). The drop of viral load in the initial therapy phase has been shown to substantially influence the sustained response rates ([3,4]). In this randomised case controlled study seventy therapy-naïve patients with chronic hepatitis C were analysed before, during and after IFN treatment. Group A comprised 42 patients, 24 with genotypes 1 or 4 and 18 with genotypes 2 or 3, that received an induction monotherapy with 6 MIU interferon alfa-2a daily s.c. for 12 weeks.

After interferon dosages were tapered down to 4.5 MIU and 3 MIU daily for 4 weeks each, HCV-RNA negative patients received maintenance therapy containing 3 MIU interferon alfa-2a three times weekly plus 800 mg ribavirin p.o. daily for another seven months. Group B comprised 28 patients, 22 with genotype 1 and 6 with genotypes 2 or 3, that had been treated with 6 miu interferon alfa-2a three times weekly for 12 weeks. Then, patients with negative HCV-RNA received the same maintenance combination therapy as described above. Informed written consent was obtained from each subject before treatment. Furthermore, the study protocol was been approved by the local ethics committee.

RESULTS

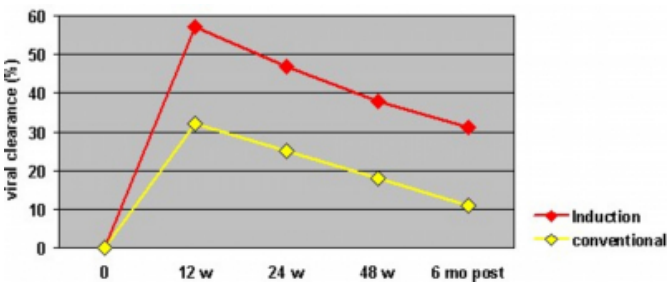
In group A, biochemical and virological responses were observed in 28 patients (57%) after 12 weeks and 16 patients (38%) at the end of treatment. Six months after therapy 13 patients (31%) showed sustained complete therapy responses defined by viral clearance and normal alanine aminotransferase (ALT) levels. In group B, nine patients (32%) had negative HCV-PCR after 12 weeks and five patients (18%) at the end-of-treatment. However, sustained complete responses were observed only in three patients (11%) from group B ($p < 0.01$).

Regarding the unfavourable genotype 1 or 4 expression 12 of 24 patients (50%) in group A and five of 22 patients (23%) in group B had negative HCV-RNA after 12 weeks and seven (29%) respectively three patients (14%) at the end of treatment. Six months later, six genotype 1 patients from group A (25%) but only 2 two patients from group B (9%) showed sustained complete responses ($p < 0.01$).

The HCV genotypes 2 or 3 were expressed from 18 patients in group A and six patients in group B. Sixteen patients of group A (89%) and three patients of group B (50%) had negative HCV-RNA after 12 weeks while nine (50%) of group A patients and two (33%) of group B patients showed an end-of-treatment response. Long-term sustained responses were observed in seven patients of group A (39%) but only one patient in group B (17%; $p < 0.01$).

Figure 1

Figure 1: Relative viral clearance rates after 0, 12, 24 and 48 weeks (0, 12w, 24w, 48w) of antiviral therapy and six months after treatment (6 mo post). Induction therapy: Interferon alfa-2a (IFN) 6 miu s.c. daily for 12 weeks, 4,5 miu daily for 4 weeks, 3 miu daily for 4 weeks followed by 3 miu three times weekly (tiw) combined with 800 mg ribavirin daily for 7 months. Conventional therapy: IFN 6 miu tiw for 12 weeks followed by 3 miu tiw plus ribavirin 800 mg daily for 9 months.



DISCUSSION

This intention-to-treat analysis of 70 therapy-naïve patients with chronic hepatitis demonstrated that patients with high dose daily interferon induction therapy (group A) showed significantly higher initial response rates than the patients who received the conventional interferon therapy three times weekly (group B). This effect was also observed when patients with genotypes 1 or 4 and patients with genotypes 2 or 3 were analysed separately ([5,6]). Similar rates of breakthroughs were observed in during the maintenance therapy with interferon-alfa plus ribavirin in both therapy arms. Therefore, it appeared that the significantly increased end-of-treatment and sustained response rates response observed in group A, were consequent to stronger viral suppression in the initial induction therapy phase ([2,7]). Although we observed more dose-related adverse effects in group A than in group B, the induction therapy regimen was well tolerated in the majority of patients and WHO grade III or IV severe adverse effects have not been observed at all.

CONCLUSION

We concluded that the high dose induction therapy with daily interferon alfa-2a significantly increased the response rates in this prospective intention-to-treat analysis. Future studies will show whether the prolongation of the initial daily dose regimen, as it might be mimicked by the pharmacokinetic characteristics of the 40kD pegylated interferon alfa-2a formulation, will decrease the relapse rates during maintenance therapy or after therapy cessation.

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