Interferon-α2b Induction Treatment with or Without Ribavirin in Chronic Hepatitis C
A Multicenter, Randomized, Controlled Trial

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We aimed to compare the efficacy of interferon-α2b (IFN) induction treatment in combination with ribavirin to IFN induction alone in chronic hepatitis C. In total, 125 patients (66 male, 59 female, mean age: 48 ± 9, range: 21–70) were enrolled and randomized into two arms: In the first, patients received 5 MU/day of IFN for 4 weeks followed by 3 MU/day for the next 4 weeks. Treatment was continued with 3 MU three times a week IFN for an additional 40 weeks. Ribavirin was administered 1000–1200 mg/day according to the body weight for the entire 48-week period. In the second arm, patients received placebo in addition to IFN. Fifty-nine patients were placed in the ribavirin arm and 66 in placebo arm. All patients were genotype 1. At week 48, 24/66 (36%) from the placebo and 31/59 (52%) from the ribavirin group responded (P > 0.05). However, during the 24-week untreated follow-up period, 13/24 (54%) from the placebo, and 8/31 (26%) from the ribavirin group relapsed (P = 0.002), resulting in a sustained virologic response (SVR) rate of 17% in the placebo and 39% in the ribavirin group (P = 0.005). In conclusion, IFN induction treatment in combination with ribavirin is superior to IFN induction treatment alone in genotype 1 patients, and the SVR rate of 39% is encouraging.

KEY WORDS: chronic hepatitis C; therapy; combination drug; interferon; ribavirin.

The long-term outcome of chronic hepatitis C patients who achieve sustained clearance of HCV with interferon-α (IFN) treatment is satisfactory (1). However, it is achieved in only a minority of patients infected with genotype 1 treated with standard thrice-a-week IFN schedules (2, 3). Studies of the viral kinetics of chronic hepatitis C infection showed that virologic response to interferon-α in two phases determines the sustained outcome: first in the initial 24 hr and second in the first two weeks (4–7). While the first decline is the result of suppression of viral production, the second is due to the death of infected hepatocytes. In reference to thrice-a-week interferon-α schedules, for the patients who achieve a decline, if it occurs, less than 70% of initial viral load within 24 hr of the first dose, and who are HCV-RNA positive by PCR at day 14, the chance of sustained virologic response is weak (6, 7). The viral decline is slower in genotype 1 infections (4). In an earlier Japanese randomized controlled trial (RCT), induction treatment with daily administration of IFN was shown to be more effective than standard thrice-a-week treatment for 24 weeks, especially in genotype 1 patients (8).
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However, four RCTs reported no benefit of daily induction over standard thrice-a-week treatment (7, 9–11). Ribavirin in combination with IFN-α was shown to increase the response rate, especially in genotype 1 patients (2, 3). However, ribavirin in combination did not accelerate viral clearance (12). A previous study showed that IFN combined with ribavirin was more effective than high doses of IFN in thrice-a-week schedules in reference to sustained response (13). A Norwegian study showed that high-dose daily induction improves the outcome in non-genotype 1 patients (14). A recent study with a similar design to ours on previous thrice-a-week schedule, IFN-treatment failures reported nearly reached significant benefit in induction-IFN + ribavirin group in comparison to induction alone (15). To our knowledge, this study is the first to examine the efficacy of induction treatment with IFN-α with or without ribavirin in the management of genotype 1 treatment-naive chronic hepatitis C patients with histological control.

MATERIALS AND METHODS

The local ethics committees of the four participating university hospitals and ethics committee of the health ministry approved this study. Throughout the study, Helsinki protocol was strictly adhered to. One hundred twenty-five patients from four centers were enrolled in the study. An informed consent was obtained form each participating subject.

The inclusion criteria were: anti-HCV positive by third-generation ELISA, HCV-RNA positive by RT-PCR (Roche, Amplicor, Basel, Switzerland), a serum ALT of at least 1.5× the upper limit of normal, and liver biopsy findings of chronic hepatitis. Exclusion criteria were: age <18 or >65 years, previous treatment with IFN-α or ribavirin or both, drug or alcohol addiction, clinical findings of decompensated liver disease, presence of autoimmune hepatitis, positivity for HBsAg, pregnancy, or reluctance to use contraceptive measures.

Patients were centrally randomized with a computer-generated system into two groups: The patients received daily administration of 5 MU IFN-α (IFN, Intuniv-A, Schering-Plough, Kenilworth, New Jersey, USA) for the initial 4 weeks and 3 MU IFN for the following 4 weeks. They received 3 MU of IFN for the next 40 weeks, completing 48 weeks of treatment. In addition while the patients in the first group (ribavirin group) received 1000–1200 mg/day of ribavirin according to their body weight (<75 kg: 1000 mg; others: 1200 mg), the patients in the second group (placebo group) received placebo (placebo group). The study design is depicted in Figure 1. Ribavirin and placebo tablets were supplied by Schering Plough as bottles containing 180 tablets. Bottles were distributed from the organization center according to a code, and neither the organization center nor the attending physician was aware of the content of the bottles. Throughout the 48-week treatment period the codes were not broken except if was found necessary by the coordinator of the study (H.S.). Patients were screened weekly in the first 4 weeks, biweekly in the second 4 weeks, every 4 weeks for the next 40 weeks, and every 8 weeks in the untreated follow-up period. In case of an unusual event, they paid an unscheduled visit. Serum was obtained for storage at the beginning and at 12, 48, and 72 weeks for further analysis. While genotypic determination and quantitation of HCV-RNA were done from basal sera, HCV-RNA was screened by PCR in all others. Quantitation of HCV-RNA was done by b-DNA (Quantiplex HCV RNA, Chiron Corporation). For genotyping, HCV RNA was extracted by the acid–guanidium–phenol–chloroform method (16). A genotyping method of HCV, based on restriction fragment length patterns (RFLP) of the amplified 5′ noncoding region of the HCV genome was used as described previously (17). Direct sequencing of PCR products was also done in 34 patients to confirm the RFLP patterns. Liver biopsies were intended to be repeated at 48 weeks. Histological evaluation was done according to Knodell scoring (18) and a decrease in score of 2 or more at 48 weeks was defined as histological improvement. At the end of treatment, codes were broken and the investigators were informed about the contents of the bottles, leaving the decision for informing non responsive subjects at the discretion of the involved center. The same strategy was applied for the patients who were confirmed to relapse virologically as well as biochemically at least in two examinations one month apart. Fifty-nine patients were placed in the ribavirin and 66 in the placebo arm. Pre treatment characteristics of the patients are summarized in Table 1. The variables were comparable between groups.

In statistical analyses, variables were compared using the Mann-Whitney U test, the χ2 test, or Fisher’s exact test (two tailed) where appropriate. For correlation, the Spearman correlation coefficient was used. Univariate and multivariate analyses were performed using logistic regression. All analyses were performed using a SPSS 6.1 software (SPSS Inc., Chicago, Illinois, USA).

RESULTS

Eleven of 125 patients discontinued treatment. Two patients from the ribavirin group discontinued treatment within the first 12 weeks, 9 (2 from the placebo and 7 from the ribavirin group), did so after completion of 12 weeks. Treatment was discontinued in two patients from ribavirin group because of toxic effects of treatment (one because of extreme fatigue with anemia and one because of toxicoderma, both after completion of the three-month period). Two patients were withdrawn because of poor compliance with the treatment, and the remaining 7 were either reluctant to stay in the protocol or did not show up at further visits. Biochemical response rates were significantly higher in