

Randomized controlled trial of consensus interferon with or without zinc for chronic hepatitis C patients with genotype 2

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Abstract

AIM: The beneficial effect of zinc supplementation on the efficacy of interferon as a treatment for chronic hepatitis C had been demonstrated in hepatitis virus genotype 1b of high viral load. This study focused on patients with genotype 2, which is more sensitive to interferon than genotype 1b, and used consensus interferon (CIFN) with or without zinc.

METHODS: We randomized 83 patients with chronic hepatitis C to CIFN at 18 MIU six times/wk for 4 wk, followed by CIFN at 18 MIU six times/wk for another 20 wk, in combination with polaprezinc 300 mg (regimen A, $n=41$) or as monotherapy (regimen B, $n=42$). Thirty-one patients in regimen A and 33 patients in regimen B completed the clinical trial; the remaining patients withdrew because of side effects or a transfer to another hospital.

RESULTS: Sustained biochemical response, defined as a normal aminotransferase level at the end of the 6-mo post-treatment observation, was 68% and 69%, and sustained virological response, defined as undetectable HCV-RNA at the end of the 6-mo post-treatment observation, was 54% and 67% for regimens A and B, respectively.

CONCLUSION: CIFN treatment combined with zinc did not enhance the effect of CIFN as shown by biochemical, virological criteria. No side effects related to polaprezinc were noted.

INTRODUCTION

Interferon (IFN) is an effective treatment for chronic hepatitis C and is the only method of treatment that eliminates hepatitis C virus (HCV)^[1,2]. The incidence of hepatocellular carcinoma (HCC) decreases if liver function improves, even if the virus is not eradicated after IFN treatment^[3-6], or if HCV RNA becomes undetectable during IFN treatment^[7]. IFN treatment for chronic hepatitis C plays a pivotal role in the prevention of HCC.

HCV-RNA clearance rates are reported to be approximately 30-40% in patients treated with IFN alone^[8-10]. However, better results have been reported when IFN- α is used in combination with ribavirin in both naïve patients^[11,12] and in those who failed to respond to, or relapsed after, IFN- α monotherapy^[13,14]. However, IFN plus ribavirin treatment for 24 wk causes more frequent side effects leading to dose reduction or discontinuation of treatment in 28% of cases compared that in 21% of cases in IFN alone treatment^[11]. Furthermore, in Japan, the use of ribavirin is restricted to naïve patients with chronic hepatitis C who have high viral loads greater than 100 KIU/mL.

Consensus IFN (CIFN) is a genetically engineered novel type I IFN molecule derived from commonly observed amino acids of several natural IFN subtypes^[15]. CIFN has demonstrated higher *in vitro* antiviral effects on an equal mass basis, than IFN- 2 α or 2 β ^[16,17]. In Japan, 9-18 MIU CIFN treatment for 6 mo is reported to be well tolerated and 18 MIU CIFN is considered to be the maximum tolerable dose in patients with chronic hepatitis C and is superior in efficacy, without additional toxicity, to 9 MIU CIFN in high-titer chronic hepatitis C patients^[18].

Serum zinc levels are low in patients with chronic liver disease because of a trace element metabolism disorder^[19]. Previously, we have demonstrated that zinc supplementa-

tion in chronic hepatitis C patients with genotype 1b of high viral load enhanced the response to IFN- α monotherapy^[20]. Although zinc has diverse biological properties including antiviral, anti-inflammatory, and antioxidant functions^[21-24], the mechanism responsible for the beneficial effect of zinc during treatment with IFN remains to be elucidated. Treatment efficacy depends on the genotype, HCV load, and staging; HCV genotypes 2a and 2b are more sensitive to IFN than genotype 1a or 1b^[1,25,26].

We planned a randomized controlled study for the treatment of genotypes 2a and 2b hepatitis C to determine whether zinc supplementation could also enhance the efficacy of IFN in chronic hepatitis C patients as well as genotype 1b. We used CIFN instead of IFN plus ribavirin for the following reasons. (1) Naïve chronic hepatitis C patients with low viral load could not be treated by the standard treatment, IFN- α 2b plus ribavirin or pegylated-IFN plus ribavirin, under the current health insurance regulations in Japan, due to high sensitivity of HCV with low viral load to IFN. (2) Even with high viral loads, HCV genotype 2a/2b can be expected to be relatively sensitive to IFN monotherapy without ribavirin. (3) CIFN has fewer restrictions or contraindications, and is less expensive than the combination of IFN- α 2b and ribavirin.

MATERIALS AND METHODS

Patient selection criteria

Patients with chronic HCV infection who had never received IFN therapy were eligible for this study. The patients were continuously positive for HCV-RNA genotype 2 using the amplicor HCV monitor assay and were diagnosed with chronic active hepatitis from a liver biopsy. The eligibility criteria included histological evidence of chronic hepatitis, as judged on a liver biopsy performed no longer than 6 mo prior to enrolment, and confirmation of HCV infection by polymerase chain reaction (PCR) analysis. Liver-biopsy specimens were assessed independently by two pathologists who were blinded to the patients' clinical details. Pathological diagnosis was made using the classification established by Desmet *et al*^[27]. The exclusion criteria included: age lower than 18 years or older than 65 years, pregnancy or lack of appropriate contraceptive measures in women of child bearing age, previous treatment with antiviral or immunosuppressive drugs, current or previous drug addiction, alcoholism, positive HbsAg or HIV test, histological evidence of liver cirrhosis, concomitant metabolic, autoimmune or neoplastic liver diseases, severe concomitant diseases other than liver disease, history of depression or psychiatric diseases.

Study design

This was a randomized, open-label, controlled study conducted between December 2001 and December 2003. The study was approved by the Ethical Committee of Gunma University. Eighty-three patients gave written informed consent and were randomly assigned to two groups: patients in regimen A received CIFN with polaprezinc and patients in regimen B received CIFN alone. All patients were given CIFN subcutaneously every day for 4 wk and then thrice a wk for 20 wk at a dose of

18 mega units (MU). Forty-one patients in regimen A were given 75 mg of oral polaprezinc twice daily (Plomac; Zeria Pharmaceutical Co., Tokyo, Japan) with CIFN for 24 wk, and zinc administration was discontinued simultaneously with discontinuation of CIFN, for a total of 24 wk. Forty-three patients in regimen B were given CIFN according to the protocol for 24 wk. Serum HCV-RNA was measured before treatment and every mo for one year during and after CIFN therapy. Patient adherence to the protocol and compliance with treatment were encouraged by regular hospital visits.

Endpoints and definitions

Two endpoints were selected for comparing the efficacy of regimen A with the standard regimen B. The first endpoint involved serum HCV-RNA levels. 'Sustained virological response (SVR)' was defined as undetectable HCV-RNA at the end of the 6-mo post-treatment observation. 'End-of treatment virological response (EVR)' was defined as undetectable HCV-RNA at the end of the treatment. 'Non virological response (NVR)' was defined as detectable HCV-RNA at the end of the 6-mo post-treatment observation. The second endpoint was serum alanine aminotransferase (ALT) levels. Normalization of serum ALT at the end of treatment and at the end of the 6-mo post-treatment observation was defined as 'end-of treatment biochemical response (EBR)' and 'sustained biochemical response (SBR)', respectively. 'Non biochemical response (NBR)' was defined as elevation of serum ALT at the end of the 6-mo post-treatment observation.

Assessment of safety

We evaluated all adverse events, subjective and objective symptoms, and laboratory test results for safety. All adverse events were checked by the patients using questionnaires, double-checked, and recorded by the investigators. All adverse events were graded for severity based on the World Health Organization (WHO) criteria and the guideline to grading severity of adverse events determined by the Japanese Ministry of Health and Welfare. Global safety assessments were made at the end of post-treatment observation using the following classifications: no abnormality, abnormality requiring no symptomatic treatments, abnormality requiring symptomatic treatments, abnormality requiring study withdrawal, and non-evaluative.

Statistical analysis

Results were expressed as mean \pm SD of the mean on an intention to treat or per-protocol basis. Statistically significant differences in outcomes between the two regimens were assessed using both parametric and non-parametric tests including the Student's *t*-test for paired and unpaired observations, and Fisher's exact test as appropriate.

A logistic multiple regression model was used to examine the relationship between baseline clinical characteristics and the binary outcome of response to CIFN therapy. Each variable was transformed into categorical data consisting of two simple ordinal numbers for the logistic multiple regression model. Variable selection was an important step in characterizing prognostic relations and identifying variables most strongly related to

Table 1 Characteristics of participating patients

	Regimen A IFN + zinc	Regimen B (CIFN)	P
Number of entry	41	42	
Male/Female	28/13	21/21	NS
Age (yr)	60±8.5	55±21	NS
Body mass index	23±2.4	24±3.7	NS
Pre-treatment zinc concentration (µg/dl)	77.8±13.6	82.5±16.4	NS
Pre-treatment ALT (IU/l)	113±75	101±96	NS
Pre-treatment leukocyte counts (×10 ³ mm ⁻³)	5.1±1.3	5.0±1.4	NS
Pre-treatment platelet counts (×10 ³ mm ⁻³)	19±5	17±5	NS
Pre-treatment HCV-RNA genotype (2A/2B)	31/10	31/11	NS
Pre-treatment HCV-RNA titer (KIU/mL)	484±1075	304±318	NS
0<pretreatment HCV-RNA<100	11	16	NS
100≤pretreatment HCV-RNA<400	15	14	NS
400≤pretreatment HCV-RNA<700	6	2	NS
700≤pretreatment HCV-RNA	9	9	NS
Histological findings (staging)	1.8±1	1.3±0.8	NS
Histological findings (grading)	1.6±0.7	1.3±0.9	NS

Mean±SD; NS: not significant

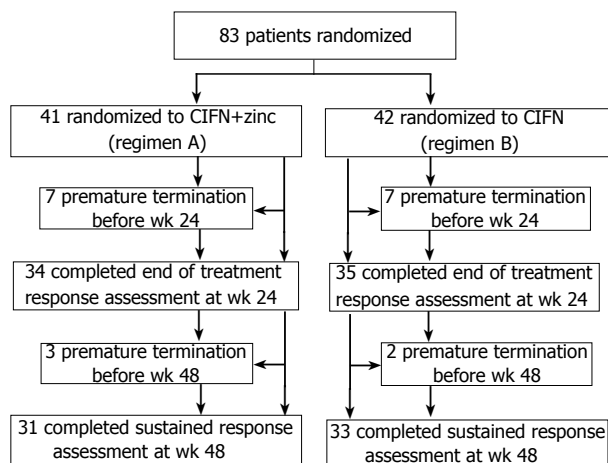


Figure 1 Trial profile.

the outcome. We selected, as candidate predictors of SVR, age, sex, weight, body mass index (BMI), pretreatment platelet counts, pretreatment ALT, pretreatment γ GTP levels, liver histology (staging and grading), pretreatment HCV-RNA viral load, wk of HCV-RNA clearance (less than 1, 4, 8, and 12 wk) and zinc supplementation. Thus, variables ($P < 0.2$) on univariate analysis, that is, zinc supplementation, BMI, staging, pretreatment HCV-RNA viral load (less than 400 KIU/mL), wk of HCV-RNA clearance (less than 8 wk) and pretreatment ALT were included in a logistic multiple regression model. Differences with a $P < 0.05$ were considered significant.

RESULTS

Eighty-three patients were enrolled into the trial; 41 were randomized to regimen A and 42 to regimen B. The pretreatment clinical characteristics of the patients assigned to the two regimens were similar (Table 1).

Table 2 Effect on viremia and serum transaminases

	Regimen A (CIFN + zinc)	Regimen B (CIFN)	P
ALT (U/l):			
Wk 0	113±75	101±96	NS
Wk 24	46±51	40±30	NS
Wk 48	26±17	22±12	NS
Biochemical response (by intention to treat):			
Wk 24 (EBR)	46%	50%	NS
Wk 48 (SBR)	68%	69%	NS
Virological response (by intention to treat):			
Wk 24 (EVR)	68%	76%	NS
Wk 48 (SVR)	54%	67%	NS

Mean±SD; EBR: End-of treatment biochemical response; SBR: Sustained biochemical response; EVR: End-of treatment virological response; SVR: Sustained virological response; NS: not significant

Follow-up and protocol compliance

The progression of randomized patients through the trial is summarized in Figure 1. Seven patients in regimen A withdrew prematurely from the study before wk 24 due to intolerance to IFN in five patients, and personal problems or low compliance in the other two patients. Seven patients in regimen B also withdrew prematurely from the study before wk 24 due to intolerance to IFN in six patients, and low compliance in the other patient. Three more patients, all in regimen A, withdrew prematurely from the study before wk 48 because of job transfer or personal problems. Two patients in regimen B withdrew prematurely due to personal problems.

Effect of treatment on viremia and serum transaminase

There were 28/41 (68%) end-of treatment virological responders for regimen A and 32/42 (76%) for regimen B when analyzed on an intention to treat basis; the corresponding values were 28/31 (90%) and 32/33 (97%), respectively, when analyzed on a per-protocol basis (Table 2). There were 22/41 (54%) sustained virological responders for regimen A and 28/42 (67%) responders for regimen B when analyzed on an intention to treat basis; the corresponding values were 22/31 (71%) and 28/33 (85%), respectively, when analyzed on a per-protocol basis. There were 19/41 (46%) end-of treatment biochemical responders for regimen A and 21/42 (50%) responders for regimen B when analyzed on an intention to treat basis; the corresponding values were 19/31 (61%) and 21/33 (64%), respectively, when analyzed on a per-protocol basis. There were 28/41 (68%) sustained biochemical responders for regimen A and 29/42 (69%) responders for regimen B when analyzed on an intention to treat basis; the corresponding values were 28/31 (90%) and 29/33 (88%), respectively, when analyzed on a per-protocol basis. There were no significant differences between the two regimens in these four responses.

Factors contributing to sustained virological response

Variables that correlated with sustained virological response were analyzed by both univariate and multivariate analyses. In univariate analysis, the sustained virological response

Table 3 Logistic regression model of predictors of response to CIFN treatment

Variables	Odds ratio (95% Confidence Interval)	
Zinc supplementation (regimen B vs. A)	0.254 (0.033-1.948)	0.1873
BMI (<23.4 vs. ≥23.4)	1.245 (0.162-9.579)	0.8330
Staging (0-1 vs. 2-3)	0.213 (0.024-1.877)	0.1635
pretreatment HCV-RNA (<400 vs. ≥400)	0.104 (0.011-0.951)	0.0450
Week of HCV-RNA clearance (<8 vs. ≥8)	0.106(0.005-2.399)	0.1584
pretreatment ALT (<107 vs. ≥107)	13.709 (0.960-195.749)	0.1873

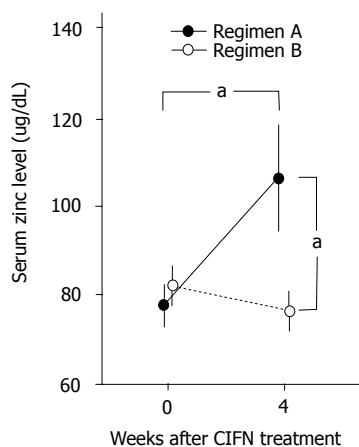


Figure 2 Serum zinc concentrations (mean±SD) at wk 0 (baseline) and after 4 wk of CIFN treatment in patients with regimen A (closed circles) and regimen B (open circles). Serum zinc levels at wk 4 were significantly higher in regimen A patients than those in regimen B patients (^a*P*<0.05). Serum zinc levels at wk 4 were significantly higher than those recorded at wk 0 (baseline) in regimen A patients (^a*P*<0.05).

correlated significantly with liver histology (staging) and pretreatment HCV-RNA viral load. In multivariate analysis, only pretreatment HCV-RNA less than 400 KIU/mL was associated with a sustained virological response (Table 3). The other factors, including zinc supplementation, BMI, staging, wk of HCV-RNA clearance, and pretreatment ALT level, did not influence sustained virological response.

Serum zinc concentrations

Serum zinc concentrations at 4 wk after the commencement of polaprezinc treatment were elevated and significantly higher than pretreatment levels in regimen A patients (Figure 2). Serum zinc concentrations in patients of regimen A were significantly higher than those of regimen B patients at 4 wk after the start of administration of polaprezinc (Figure 2).

Adverse effects

Each of the serious adverse events including depression, thrombocytopenia, leukopenia, and severe elevations in γ GTP was observed in one patient in regimen A. In addition, regimen B was also associated with serious adverse events such as depression in one patient, and severe leukopenia in two patients. Frequent adverse events and laboratory abnormalities recorded during the study are

Table 4 Incidence of selected adverse events (>10% frequency)

Adverse event	Regimen A (CIFN + zinc)	Regimen B (CIFN)
<i>n</i>	41	42
Fever	41 (100%)	42 (100%)
Headache	17 (41.5%)	16 (38.1%)
Malaise	15 (36.6%)	12 (28.6%)
Anorexia	14 (34.1%)	19 (45.2%)
Arthralgia	14 (34.1%)	13 (31.0%)
Insomnia	11 (26.8%)	11 (26.2%)
Stomach discomfort	7 (17.1%)	5 (11.9%)
Alopecia	6 (14.6%)	6 (14.3%)
depression	6 (14.6%)	5 (11.9%)
Nausea	6 (14.6%)	5 (11.9%)
Myalgia	5 (12.2%)	6 (14.3%)
Rash	5 (12.2%)	4 (9.5%)

Table 5 Incidence of selected laboratory abnormalities (>10% frequency)

Laboratory abnormality	Regimen A (CIFN + zinc)	Regimen B (CIFN)
<i>n</i>	41	42
Thrombocytopenia	31 (78%)	29 (69%)
Leucopenia	24 (59%)	30(71%)
Increase in AST	20 (49%)	18 (43%)
Increase in ALT	18 (44%)	16 (38%)
Increase in γ -GTP	12 (29%)	12 (29%)
Decrease in hemoglobin	7 (17%)	9 (21%)
Increase in ZTT	7 (17%)	7 (17%)

summarized in Tables 4 and 5. The type and frequency of the adverse events, and laboratory abnormalities were similar in both regimens. Five (12.2%) patients and six (14.3%) patients dropped out of the study due to the adverse events before wk 24 in regimen A and regimen B, respectively. There were no significant differences of grading severity of adverse effects as well as incidence of them in the global safety assessment of the two regimens (data not shown).

DISCUSSION

The metabolism of trace elements is impaired in chronic liver disease^[19]. Zinc deficiency in chronic hepatitis C is improved by IFN treatment^[28]. Zinc supplementation enhances the response to IFN- α treatment in patients with genotype 1b chronic hepatitis C^[20]. Conversely, zinc supplementation did not enhance the response to CIFN treatment in patients with chronic hepatitis C with genotype 2 in this trial. The reasons for the lack of synergy between zinc and IFN are unclear, however, there are several possible reasons that are worthy of consideration. The viral genotype 2 in both regimens may account for the virological response, differing from the previous study that involved patients with genotype 1b. It is also possible

that the relatively higher response rate achieved with CIFN in both regimens in this trial compared with the previous study with IFN- α could have masked any differences in efficacy. In addition, individual differences in serum zinc concentration increases, as a result of zinc administration, may alter the virological response because the extent of the increases in serum zinc concentration varied in regimen A. Furthermore, differences in the type of IFN may affect the virological response, given that natural IFN- α was used in the previous study.

The overall therapeutic efficacy (60% SVR) of CIFN in our study was similar to that (50% SVR) of low-titer or genotype 2 group in a previous report from Japan^[18]. Recent reports showed that pegylated-IFN plus ribavirin^[29] had excellent treatment efficacy (100% SVR) in chronic hepatitis C patients with genotype 2^[30]. SVR rates of IFN- α 2b plus ribavirin for chronic hepatitis C patients with genotypes except 1^[11] or CIFN plus ribavirin for chronic hepatitis C patients with genotypes 2/3 were reported to be from 60% to 70%^[31]. Given the overall 60% SVR in our study, CIFN without ribavirin can be considered as a good candidate for patients in whom ribavirin is contraindicated.

Interestingly, the cases of undetectable HCV-RNA titer at 1 wk, but not 4 or 12 wk after the start of treatment, showed 95% and 100% of sustained virological response rate in regimens A and B, respectively. Although only a pretreatment HCV-RNA less than 400 KIU/mL was considered to be a predictive factor for sustained virological response, based on a logistic multiple regression model in our trial, earlier responses at 1 wk after the start of treatment may also be a good predictor of sustained virological response.

The type and frequency of adverse events, and laboratory abnormalities were similar in both regimens. Overall, adverse events and laboratory abnormalities were similar to those in previous reports in Japan^[18]. Although 18 MIU CIFN was relatively well tolerated in our trial, there were a few cases of serious adverse events. Twelve MIU and nine MIU CIFN, which are now available in Japan, may allow us to reduce the incidence of serious adverse events.

In conclusion, our study does not support the use of zinc as an adjunct to CIFN for the treatment of chronic hepatitis C with genotype 2, because combination treatment was not superior to CIFN monotherapy in achieving a sustained virological response. High viral loads of over 400 KIU/mL may indicate a low probability of sustained virological response for CIFN treatment, regardless of zinc supplementation.

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