Interferon Treatment in Chronic Hepatitis C

Özden UZUNALİMOĞLU, Ömer DÖNDERICI, Selim KARAYALÇIN, Ali ÖZDEN, Negüz SÜMER, Nihat SİPAHİ, Abdülkadir DÖKMECİ, Necati ÖRMECİ, Kadir BAHAR,

Summary: *We studied effect of interferon alpha 2B (IFN) treatment in thirty-eight patients with chronic hepatitis C. The patients were randomly allocated into two groups: In group I (n: 19, 13 men, 6 women, mean age 51.9 years) patients were treated with IFN (Intron A), 3MU, 3 times in a week for 6 months while no treatment was given to patients in group II (n: 19, 13 men, 6 women, mean age 52.5 years) and they served as a control group.*

There were 4 (21.1%) complete, 6 (31.6%) near-complete, 4 (21.1%) partial responder and 4 (21.1%) non-responder, and 1 (5,3%) withdrawer. In group II the ALT levels remained significantly unchanged. Among the 10 good responder 6 of them (60%) relapsed after cessation therapy, in 1-2 months; but these all patients who were treated with 1 MU 3 times in a week, again responded.

Side effects were seen in many treated patients; but the treatment was generally well tolerated and only one patient refused continuation of treatment. Our results with Turkish patients were found to be comparable with Western counterparts.

Key Words: Chronic hepatitis C, Interferon treatment.

Faculty of Medicine University of Ankara

Hepatitis C is an important healthy problem, but not as much as hepatitis B in our country: According to randomly study of prevalence (0.4-0.8 %), approximately 400.000 Turks have chronic hepatitis C (CHC) (1,2,3). The patients who are chronic liver disease have a prevalence of 23% according to our specimen study which we have got. Approximately 50% of acute hepatitis C patients develop chronic hepatitis and, of these, nearly 25% develop cirrhosis. In addition, in several studies it is shown that hepatitis C is an important cause of hepatocellular cancer.

Before the usage of interferon α 2B (IFN) in the treatment of CHC, there was no satisfactory treatment for this serious disease. The treatment of chronic hepatitis B and chronic hepatitis C with IFN is currently the subject of intense research although the optimal treatment scheme for these diseases is still being investigated. At present, IFN treatment is the only one alternative choose in the treatment of hepatitis C in spite of it is not perfect.

The response rate to IFN treatment in chronic hepatitis B is different in Western and Eastern populations and a similar problem may exist in the treatment of CHC (4). In addition there are different types and mutants of hepatitis C that is capable to the countries; variants are being described, particularly from Japan, Taiwan, and United States (5). The aim of our study is to evaluate the rate of changes in serum aminotransferase (sALT) levels and liver histology in anti-HCV positive Turkish patients with IFN treatment.

Table I: The criterias of population selection criterias

A- Inclusion criteria

Age greater than 18 years,
Patients with a positive test for HCV antibody
Persistent ALT elevation (at least 1.5 times the upper limit of normal)
for a minimum period of six months
Patients with a liver biopsy picture of chronic active hepatitis (CAH)
Well compensated liver disease

B- Exclusion criteria

Anti viral or immunomodulatory therapy within six months of entry to the study
Evidence of liver disease due to alcohol or drug use
Evidence of Hepatitis B infection or Delta infection
Presence of significant other disease which might interfere with the trial
Evidence of decompansated liver dysfunction
(Ascites, bleeding oesophageal varices, encephalopathy..)

Table II: Charasteristics of two groups of patients with CHC before treatment

	Treated G	Untreated G
Cases (n)	19	19
Sex (Male/Female)	13/6	13/6
Age (years)	51.9	52.5
Range	30-73	23-64
Duration of dis. (yr)	3.7	5.4
Blood Transfusion	5	4
Surgery	12	11
IV Drug Abuse		
Homosexual		
sALT (IU/I)	141.4	137.7
sAST (IU/I)	129.3	113.7
Bilirubin (mgr/dl)	1.2	1.3
Serum albumin (g/l)	3.8	3.9
Prothrombin time (sec)	15.2	15.2
CAH	16	15
CAH+Cirrhosis	3	4

PATIENTS and METHODS

Thirty-eight patients with HCV associated who were examined in our Center during 1990 and 1992 years and who were ill at least for 6 months and histological suitable for chronic liver disease were included in this study. The criterias of population selection are shown in the table I.

The presence of antibody to hepatitis C virus was determined in all patients by the ELISA test (Abbott second generation). Blood counts and biochemical tests (BUN, creatinine, alkaline phosphatase, sALT, sAST, total bilirubin, total protein, albumin, prothrombin time) were done in our clinic, with routine automated techniques. Liver biopsies were performed routinely.

Selected 38 patients were randomly allocated into two groups, then was followed without therapy for 3 months (table II): In group I (n: 19, 13 men, 6 women, mean age 51.9, range 30-73) patients were treated with IFN (Intron A) 3 MU, subcutaneously (with tuberculin sy-

Table III: Evaluation of ALT Response

response	criteria
- complete	Normalisation of ALT
- near-compete	>50% decrease in ALT and ALT <1.5* upper limit of normal
- partial	>50% decrease in ALT

Table IV: The Evaluation of sALT Response to the Interferon Therapy at the and of 6th Months.

	Treatment G.		Control G.	
	n	%	n	%
Complete response	4	21.1		0.0
Near-complete response	6	31.6	1	5.3
Partial response	4	21.1	4	21.1
Non-response	4	21.1	14	73.7
Withdraw	1	5.3		0.0

ringe), 3 times in a week (preferably before bedtime and at the hospital for the first 15 days) for six months while no treatment was given to patients in group II (n: 19, 13 men, 6 women, mean age 52.5 years, range 23-64) and they served as a control group. These patients' some characteristics are shown in table II. The two study groups were similar to respect to the clinical features.

In both two groups, during the follow-up period biochemical and haematological tests, and urin analyses were performed weekly in the first months and then every month. Liver biopsies were performed before randomization and 3 months after discontinued therapy.

The treatment has been continued for six months in the patients which we did not see any serious toxicity and side effects. At the end of 6 months their laboratory and clinically details were evaluated. The most important thing in the evaluation of response to treatment was the changes of sALT levels. The evaluations with these changes are shown at the table III.

The treatment in the patients who gave complete or near-complete response and non-response was stopped. In partial responders we gave 3 MU Intron A 3 times in a week for second 6 months. If any patients (from Group I) show evidence of improvement during the 24 treatment weeks but relapses on follow-up, they were retreated at the 1 MU dose, (if tolerated) for an additional 24 weeks. Patients were examined each month whether the treatment was stopped or not.

RESULTS

One of patients was unable to continue the therapy because of severe headache in the second week of therapy. She had also this complain before the therapy. There were 18 patients at the and of the 6 months that was the first step of the treatment. Complete response were taken in the 4 (21.1 %) of them; near-complete response were taken in 6 (31.6 %) of them; partial response were taken in the 4 (21.1 %) of them. Four patients (21.1 %) didn't give any answer to the therapy. However one near-complete response, four partial response and 14 non-response were taken in the control group at the same time (table IV).

Early relapse was seen in the 6 patients (60.0 %) at the 10 patients which we took complete and near-complete response, after withdrawal therapy, in 1-2 months. Two of these 6 patients refused the second-step therapy. Second therapy cure was started in the remained 4 patients. This cure was made 3 times in a week 1 MU for 6 months. All of the patients gave the response again as it was at the first step; we obtained rapid remission in all. There was not seen any difference in the patients we have taken partial response at the first step therapy.

Table V: The side effects during interferon treatment

	n	%
Flu-like Syndrome	8	42.1
Fever	4	21.1
Headache	2	10.5
Myalgia/Arthralgia	4	21.1
Weakness	7	36.8
Diarrhea	2	10.5
Decreased Libido	2	10.5
Hair Loss	2	10.5
Anxiety and Depression	3	15.8
Ichting	3	15.8
Skin Eruption	1	5.3
Transient Atrial Fibrillation	1	5.3
Haemorrhagic Diatheses	2	10.5
Granulocytopenia	2	10.5

During therapy and follow-up, response to the sALT levels of the control and treatment groups is shown at the figure 1. In group II (untreated) the sALT levels remained unchanged whereas in group I (treated) the sALT levels decreased significantly, with IFN therapy. It is seen that sALT pick can not be seen at the beginning of the therapy in the patients of hepatitis B which were given IFN.

If we compare good responder (complete response and near-complete response) group's with bad responder (partial response and non-response) group's sALT levels we saw that the response to therapy was formed within four week of treatment. In the good responder groups, that is sALT levels decreased rapidly and in the 4 th week this decreasing reached at the top of values and it continued. Whereas, in the bad responder groups sALT decreasing was not clear (Figure 2).

Repeat liver biopsies, which, when compared with pretreatment biopsies, revealed mild or moderate improvement in the degree of portal and lobular inflammation, hepatocyte necrosis; in the good responder group. Histopathological stages were not seen in any of the patients.

We did not see significantly any age, sex, history, clinically and laboratory finding changes between the good response given group and the had response given group after we compared them different angles.

Side effects were seen in the most of the patients in the early period, but the treatment was generally well tolerated and as we said before, only one of them refused the therapy because of her severe headache. The others ha-

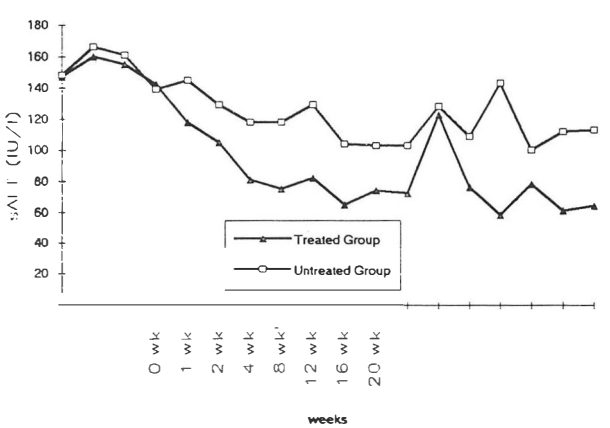

Figure 1: Changes in serum ALT activities in treated with IFN and untreated groups

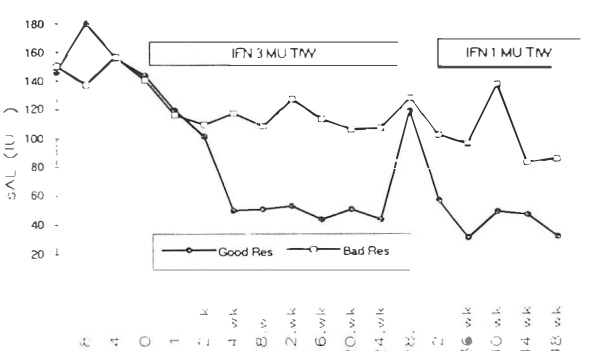

Figure 2: Changes in serum ALT activities IFN treatment in good and bad responder groups

ven't had any side effects as much important as to stop. The side effects are shown in the table V.

The complaints influenza-like syndrome was seen in the most of the patients but they were controlled quickly with paracetamol. Transient atrial fibrillation was seen in a patient who had the same complain and coronary ischaemia before. Atrial fibrillation was treated easily. Two of men complained from decreasing libido; two of women complained from hair loss. We didn't determine severe myelosuppresion except two patients who had transient granulocytopenia. Leucopoenia improved spontaneously in a short time. In two patients who had haemorrhagic diatheses, haemostasis tests were normal. An other observation was that the complaints were more in the good responder than bad responder.

DISCUSSION

CHC is clearly a significant cause of morbidity and mortality from liver disease and a disease in need of a safe and effective treatment. Early therapeutic trials in patients CHC proved that corticosteroid and acyclovir are ineffective. IFN therapy was first suggested by Hoofnagle in 1986 (6). Although, several anecdotal reports followed the initial pilot study. These firsts encouraging preliminary results led many investigators' worlds wide to start using IFN in the treatment of CHC at variable (1-5 MU) dosage and for variable periods of time.

Results of these studies have indicate that in CHC, IFN can reduce serum aminotransferase levels, improve hepatic histology, and also reduce serum HCV RNA levels (7). The PCR technique for detection of HCV RNA demonstrates that IFN therapy is associated with a decrease in serum levels of the virus, and in patients with a long-term response, HCV RNA remains undetectable despite discontinuation of treatment (8). Unfortunately, the dose and duration, patients' selections remain uncertain. Among patients treated with 3 MU of IFN 3 times in a week for 6 months, response rates have varied from 36 to 70% (median 45%) (9). After completion of 6 months' treatment with IFN for CHC, the relapse rate varies from 40 to 80% (9).

Our results (52.7 % complete or near-complete response, 60% recurrence) were confirmed by these results. Thus, our results with Turkish patients were found to be comparable with the Western counterparts.

When response to IFN occurs, it almost always does so within the first 12 weeks of IFN treatment (10,11). We saw also that the response to therapy was formed in end of the first month nearly (figure 2). Japanese workers found that 3 MU of IFN three times in a week for only 8 weeks induced biochemical and histologic improvement in more than half the patients (12). May be this finding about duration of therapy is new dimension for management. In view of this finding, it seems reasonable to give 3 MU three times in a week for 2-3 months in the first instance. If transaminase have fallen by 50%, IFN is continued for a total of 6 months and perhaps-according to answer to the therapy-one year or more.

The first condition of success in the treatment is choosing the appropriate patients. Either foreign studies or our determinations in a few events out of study protocol determine that the treatment is not favourable in the patients with cirrhosis and especially decompanseted cirrhosis.

According to our observations, early relapse was seen very much (60%) but the response can be taken again with low dose (1 MU) IFN treatment. Although, during the follow-up period, a transient rise in sALT levels (self-limited relapse) can occur in a subgroup of them. The phenomenon of transient flare of sALT level has been observed previously in

several trials (13). Because of the phenomen of transient flare of the sALT, in any case, patients should not be started on therapy immediately on relapse of disease. For this reason, patients should be followed without treatment for at least six months before restarting IFN (14).

Both our and the other countries' studies indicated that the side effects are seen very much but few of them are as important as to stop therapy. In addition, symptoms commonly attributed to IFN treatment may be relation with disease.

Summarily, IFN is not extraordinary drug but its usefulness is seen in the treatment of CHC. One of the most difficulties for IFN treatment in hepatitis C was that there were not reliable criteria for the response of the treatment. The most discussed subject was which dose and how long the interferon's using will give better results. In view of these results it is appropriate to further study efficacy of IFN in CHC.

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