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ARTICLE

The Effect Of Long Term and High Dose Interferon Treatment In Chronic Hepatitis C

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The results of 43 interferon treatments of 35 patients (23 male, 12 female) are reported. The duration of the treatment was 6-18 months, the dose of interferon was 3x3-5 MU weekly. Complete response (HCV RNA became negative) was found in 11, relapse was observed in 3 patients. Partial response (transaminase levels became normal, or less than twice normal value, but patients remained HCV RNA positive) occurred in 23 cases, relapse was obeserved in 16. The therapy had no effect in 9 cases. The higher dose and longer term interferon therapy resulted in a higher rate of response to the treatment and a reduction in the number of relapses. (Pathology Oncology Research Vol 2, No1–2, 59–62, 1996)

Key words: chronic hepatitis C, interferon treatment

Introduction

Chronic infection by HCV is a common cause of chronic hepatitis, liver cirrhosis and hepatocellular carcinoma. The prevalence of HCV infection is 0.2-2% in blood donors, 60-80% in hemophiliacs, 5-58% in patients on hemodialysis, 20-30% in acute post-transfusion hepatitis, 70-90% in chronic post-transfusion hepatitis, 27-57% in chronic liver diseases and 40-67% in hepatocellular carcinoma.[10,18,19,23,24] Since the long-term consequences of a chronic HCV infection may be serious, with progression to liver cirrhosis and hepatocellular carcinoma, it is highly desirable to find an effective antiviral treatment. Although many drugs have been tested, today IFN is the only established treatment for chronic HCV infection. Normalization of serum transaminase levels is seen in approximately 50% of patients treated for 6-9 months, of whom some 50% will relapse after treatment cessation.[7,17,25] A parallel decrease in transaminase and HCV RNA levels in serum during IFN treatment has been found among most responders.[26] The optimal duration of the therapy and the optimal dose of IFN has, however, not yet been established. Recent studies have suggested possible improved long-term results with prolonged treatment, whereas the results with increased doses were controversial.[1,2,4,5,9,11,12,15,20,21,22,26] The purpose of this study was to determine whether a longer term and higher dose treatment with IFN could increase the response rate and improve the long term results over shorter treatment courses with lower dosages. The data for completed IFN treatments in our department between Jan 1, 1991 and July 31, 1995 were analysed retrospectively.

Patients and methods

43 IFN treatment courses of 35 patients (23 male, 12 female; age: 30-65 years, with mean: 43.4 year) were studied. The histological diagnosis was chronic hepatitis C in every case with a Knodell index of 3 or higher.[6,8,13,14] Histological signs of progression to cirrhosis from chronic hepatitis C were also found in 3 cases, but no one had decompensated cirrhosis. Every patient was HCV RNA seropositive with elevated levels of serum transaminases (more than two times higher than the upper limit of the normal value) for at least 6 months. There were no patients with antibodies to HIV or with other precursors of chronic

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Abbreviations: IFN: interferon; HCV: hepatitis C virus.

liver diseases – such as hepatitis B, autoimmune hepatitis, primary biliary cirrhosis, alcohol use, drug use, haemochromatosis, alpha-1-antitripsin deficiency or Wilson disease – in the tested group.

IFN treatment was given once to 27 and twice to 8 patients. The time between the repeated treatments was 6-12 months. Recombinant alpha 2b IFN (Intron-A, Schering Plough) was given thrice weekly. The dose of IFN was 3 MU in 34 treatment periods (6 months in 25 cases and 12 months in 9 cases), and 5 MU in 9 treatment periods (9 month in two, 12 months in six and 18 months in one case). The follow-up period was 6-34 months. Hematological and biochemical tests were performed before treatment and in every month during therapy and the follow-up period. HCV RNA was measured before treatment and in every third month during therapy and the follow-up period. Control liver biopsy was performed in 3 cases.

Complete response was defined if HCV RNA became negative and transaminase levels became normal. Partial response was defined if transaminase levels became normal, or decreased below twice the normal value, but HCV RNA remained detectable. Sustained remission was defined if no relapse occurred in the follow-up period.

Statistical analysis was performed using the chi-square test.

Results

The therapy has been effective in 34 of 43 cases *(Table 1)*. Complete response was observed in 11 cases and relapse occurred in 3 of them. Partial response was observed in 23 cases, but 16 relapsed. The therapy had no effect in 9 patients.

Table 1. **The results of 43 IFN treatment courses of 35 patients**

	n	*relapse*
Complete response	11	3
Partial response	23	16
Non-responder	9	–
All	43	19

Eight patients were given repeated IFN treatment. The duration of IFN treatment in the first period was 6 months in 5 cases and 12 month in 3 cases. The dose was 3 MU in every case. Complete response was observed in 1 and partial response in 7 cases. The complete response was observed in a patient with a 6 month treatment period *(Table 2)*.

Table 2. **The results of repeated IFN treatment of the 8 patients**

	1. treatment		*2. treatment*	
		relapses		*relapses*
Complete response	1	1	5	1
Partial response	7	7	3	3

IFN treatment was restarted when relapse occurred. A second IFN therapy was administered for 12 months in 6 cases and for 9 and 18 months in 1 case each. Six patients were given 5 MU IFN, two patients 3 MU IFN (both of them were treated for 12 months). The second IFN treatment resulted in complete response in 5 and partial response again in 3 cases. All 3 patients with partial response relapsed again, but whereas only 1 did so from the 5 patients with complete response. This patient has been treated for 9 months *(Table 3)*.

Table 3. **The results of the second IFN treatment of the 8 patients**

	3 MU IFN		*5 MU IFN*	
		relapses		*relapses*
Complete response	1*	0	4	1**
Partial response	1*	1	2	2
No response	0	–	0	–

* the duration of the treatment was 12 months
** the duration of the treatment was 9 months

Detailed results are shown in *Table 4*. The number of responders was 18 out of 25 in the cases of shorter (6 months) in contrast to 16 responders from 18 cases given longer (9-18 months) IFN therapy. The rate of complete response was 4/25 in the former and 7/18 in the latter group. Sustained remission was observed in 2 out of 4, and in 6 out of 7 cases, respectively. 18 patients were treated for longer (9-18 months) periods, either with higher dose (5 MU) or with lower dose (3 MU) of IFN. All patients in the former group responded to the treatment (5 with complete response; but one of them relapsed after cessation of a 9 month therapy), while only 7 did so out of 9 patients treated with lower dose (with two complete response, without relapse).

There were no non-responders among the 9 cases treated with the higher dose of IFN, while the therapy had no effect in 9 of 34 cases treated with 3 MU IFN. The response rate of the two groups, treated with 3 MU IFN for 6 or 12 months was similar (18/25 versus 7/9). The occurrence of complete response was similar too (4/25 and 2/9), but relapse occurred in 2 out of 4 cases in the group with shorter treatment period, while relapse was not noticed in the two patients with complete response treated for 12 months. Comparing the effect of therapy with higher dose and longer term to that of lower dose and shorter treatment period of IFN, the response rate of the latter group was 18/25, while no non-responder was found in the former group. These differences, however, are not statistically significant. Complete response was observed in 4 of 25

Table 4. **The effect of the IFN treatment in cases with different doses and lengths of therapy**

	3 MU IFN		*5 MU IFN*	
	treatment for 6 monts	*treatment for 12 monts*	*treatment for 12 monts**	
		relapse	*relapse*	*relapse*
Complete response	4/25[a] 2/4[b]	2/9 0/2	5/9[a]	1/5**[b]
Partial response	14/25 8/14	5/9 5/5	4/9	3/4
Non-responder	7/25	2/9	0/9	

* the length of the treatment was 9 months in two and 18 months in one case
** the treatment period was 9 months in this case
[a] $p<0.05$
[b] $p<0.05$ (sustained response rate: 2/25 versus 4/9)

cases with shorter term and lower dose treatment, but this rate was 5/9 in the other group. This difference is statistically significant ($p<0.05$ – *Table 4:* [a]), as is the difference of the rates of sustained remission in the two groups. Sustained remission was registered in 4 of the 9 cases with higher dose and longer term therapy, but it was detected only in 2 of 25 cases with lower dose and shorter term treatment ($p<0.05$ – *Table 4:* [b]).

Control liver biopsy was performed in 3 cases. The improvement in clinical performance was reflected in the histology in 2 cases (Knodell index changed from 3 to 2 and from 8 to 4). In the third case the inefficiency of therapy was accompanied by unchanged histological picture.

There was no greater number of serious side effects among patients treated for a longer time and/or with higher dose IFN.

Discussion

The overall response rate was 79% (34/43) in our study. Complete response was observed in 27.5% (11/43) and sustained remission in 19% (8/11). These results are similar to other data.[3,7,9,17,21,25,27] Nine patients did not respond to treatment. The reason of the treatment failure is unknown. Short duration of HCV infection before treatment, absence of cirrhosis, sex, low viral load and specific HCV genotypes have all been suggested to be predictive factors of response.[16,17,27,28,29] We found no difference in the response rate of patients with or without cirrhosis, however none of our patients had decompensated cirrhosis. In most cases, the duration of the HCV infection was unknown, so the correlation between the response to the therapy and the period of the HCV infection could not be studied. HCV strains were not separated in different genotypes, although in Hungary – based on only one former study – the majority of patients with chronic hepatitis C are infected by genotype HCV 1.[17]

The efficacy of repeated treatments in relapsing cases suggests that better long term effect of the IFN treatment on patients reacting to the therapy depends almost entirely on the correct choice of regimen for treatment.

The number of responders and the complete response rate was higher among cases on prolonged IFN therapy. Besides, in complete responses sustained remission occured in 6 of 7 cases with the longer, while in 2 of 4 cases with the shorter interferon treatment. Relapse occcurred only among the patients with shorter term IFN therapy. The advantage of prolonged treatment courses have been also reported by others.[3,4,20,21] The better long term results of prolonged, high dose IFN therapy are much more evident when the data of the longer term with higher dose was compared to the shorter term with lower dose IFN treatment. The complete response rate and the number of cases with sustained remission are notably higher in the former group, and differences are statistically significant ($p<0.05$).

Control liver biopsy was performed only in three cases due to the lack of approval of the majority of patients. The control histological examinations correlated well with the clinical findings.

The importance of adequate IFN therapy in chronic HCV infection is emphasized not only for the prevention of progression towards cirrhosis and development of hepatocellular carcinoma. These patients are also potentially infectious, endangering those around them. Furthermore, the cost of treatment may be increased due to repeated treatment periods resulting from relapses following inadequate IFN therapy. After correct selection of patients with chronic HCV infection, to increase the efficacy of therapy, we prefer the following treatment regimen: 5 MU IFN thrice weekly for at least 12 months.

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