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# C형 만성활동성간염 환자에서 알파 인터페론의 치료효과에 관한 연구

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**강상중, 오세진, 임동현, 권수경, 윤병철, 이상욱, 한병훈**

# A Study on The Efficacy of Alpha Interferon in Chronic Active Hepatitis C

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## 국문초록

C형 만성활동성간염 환자에서 인터페론은 효과적인 치료제로 알려져 있으나 인터페론의 투여량과 투여기간에 관한 표준요법이 없는 실정이다. 본 연구의 목적은 알파 인터페론의 치료효과를 평가하고 이에 영향을 미치는 예측인자를 설정하는데 기여하고자 하였다.

57명의 환자를 대상으로 알파 인터페론 300만 Unit를 주 3회 총 24주간을 투여한 후 혈청 ALT의 변화를 관찰하였는데 대상환자의 66.7%에서 ALT의 정상화를 보였고 ALT의 평균 정상화 기간은 2.81개월이었다. 치료 종료 후 6개월의 추적기간 중에 반응군의 33.3%에서 ALT의 재 상승이 관찰되었고 평균 재발기간은 3.3개월이었다. 치료반응의 예측인자로는 발병기간, r-GTP 및 간 조직 손상정도가 관여하였다.

이상의 결과에서 알파 인터페론은 C형 만성간염에 효과적인 치료법으로 생각되며 치료 후 재발률과 이에 관여하는 인자는 보다 더 장기적인 추적이 필요할 것으로 생각된다.

**중심 단어** : C형 만성간염, 알파 인터페론, 예측인자

## INTRODUCTION

Hepatitis C is a common disease that accounts for more than 90 percent of the hepatitis that developed after transfusion.[1] Chronic hepatitis develops in at least half of the patient with acute hepatitis C ,and cirrhosis develops at least 20 percent of this group.[1,2] Several preliminary reports have suggested that alpha interferon(IFN α) may be useful in treatment of patients with chronic hepatitis C. Results are encouraging since IFN α diminish aminotransferase activities and improves histology in chronic hepatitis C cases.[3,4] But 50 percent of them experience relapse within 6 months after completion of IFN α treatment.[4-6] Many questions regarding optimal dose, frequency and duration of IFN α therapies still remain to be verified. In addition, the predictive factors of response to IFN α in chronic hepatitis C have not been clearly identified yet. The aim of this work was to assess the efficacy of IFN α among patients with chronic hepatitis C and to identify predictive factors of response to IFN α therapy.

## MATERIALS AND METHODS

### 1. Patients

Fifty-seven patients (men 33 and female 24, mean age=44 years) with elevated serum alanine aminotransferase(ALT) levels for at least 1 year, with antibodies against HCV (Anti HCV) and with liver histological findings compatible with chronic HCV hepatitis infection, were included in the study.

Patients with antibodies to the human immunodeficiency virus, as well as patients with chronic liver disease with other etiology, were excluded.

Criteria for exclusion included liver cirrhosis, evidence of other forms of liver diseases and presence of another serious medical illness. Patients treated with corticosteroids or interferon within 6 months before entry, were also excluded.

All patients were HBsAg-negative, although 34 patients had antibodies to HBs and Anti-HBc and 17 patients had anti-HBc alone. 8 patients had received blood transfusion, 12 patients had a history of operation, 5 patients had acupuncture and other patients had unknown cause for their HCV infection. The reference values were those determined the day before the first interferon injection. Their clinical characteristics are shown(Table 1).

Table 1. Clinical features of patients

| | |
|---|---|
| Age, mean years(range) | 44(26-65) |
| Sex, No of males(%) | 33(57) |
| Source of hepatitis, N(%) | |
| transfusion | 8(14) |
| operation | 12(21) |
| acupuncture | 5(8) |
| Laboratory, mean(range) | |
| Leukocyte count ($10^3/mm^3$) | 6.9(3.2-8.9) |
| Hemoglobin(g/dl) | 13.9(11.4-15.1) |
| Platelet ($10^3/mm^3$) | 257(123-365) |
| albumin(g/dl) | 4.2(3.8-4.5) |
| Globulin(g/dl) | 3.1(2.5-3.9) |
| AST(IU/liter) | 114.8(50-270) |
| ALT(IU/liter) | 147.8(45-460) |
| Histology, N(%) | |
| CAH, mild | 30(54) |
| CAH, moderate | 14(24) |
| CAH, severe | 13(22) |

## 2. Study Design

All patients were treated with 3 million units recombinant IFN α subcutaneously three times a week for an intended period of 6 months. ALT activity was measured monthly during treatment and also for 6 months after completing treatment.

The response to interferon was defined according to ALT activity at the end of treatment. If ALT activity was normal in two assays during the fifth and six months, the patients were defined as a responder, other patients without normalization of ALT were defined as non-responders. Relapse was defined as an increase in serum ALT value to 1.5 times the upper normal limit for a complete responder on at least three determinations during 6 month follow-up period after completion of therapy. Anti-HCV was analyzed with second- generation ELIZA(Abott Lab. North Chicago. IL. USA).

## 3. Candidate Predictors and Statistical Analysis

Clinical, laboratory and histologic predictors of response to interferon into a computerized database together with data on biochemical outcomes at the end of therapy and at the end of follow-up for each patient.

The selected predictors were age, sex, duration of hepatitis, AST and ALT baseline levels, leukocyte count, platelet counts, albumin, alkaline phosphatase, gamma-GTP, hepatitis B serological markers and necroinflammatory activity.

Duration of hepatitis expressed as the time(months) since first observation of an abnormal ALT level.

Univariate data comparison among groups was performed with $x^2$ tests for proportion and student t tests for means. Multivariate data comparison among groups was perfo-rmed so that we might identify characteristics of treated patients useful in predicting response after adjustment for the effect of covariates. Regression analysis performed with the PROC LOGISTIC program(SAS Institute, Inc., Cary, NC).[7] Variable significant on multivariate analysis included in the final model and used to generate prediction rules.[8] Rates of remission and that of relapse were calculated with life table method.

# RESULTS

At the end of the administration period, the numbers of the responder whose ALT level within normal range were 38 cases (66.7%) out of the 57 cases. The normalization rates of ALT level at the 1 month, 3 months and 5 months was 35.1%, 57.9% and 66.7% respectively. The average duration of ALT normalization was 2.81 months (Table 2).

Table 2. Probability of response during treatment with recombinant INF in patients with chronic hepatitis C

| month | cumulative rate of response(%) |
|---|---|
| 1 | 35.1 |
| 2 | 54.4 |
| 3 | 57.9 |
| 4 | 61.4 |
| 5 | 66.7 |
| 6 | 66.7 |
| mean(months) | 2.91 |

Only 24 cases out of 38 cases responder continuously observed after completing treatment. Among them, 8 cases relapsed. The relapse rates were 16.7% at the 1 months, 29.2% at the 3 months and 33.3% at the 4 months. The average onset of relapse was 3.3 months after completing treatment(Table 3).

Table 3. Probability of relapse after discontinuation of treatment with recombinant INF in patients with chronic hepatitis C

| month | cumulative rate of relapse(%) |
|---|---|
| 1 | 16.7 |
| 2 | 25.0 |
| 3 | 29.2 |
| 4 | 33.3 |
| 5 | 33.3 |
| 6 | 33.3 |
| Mean(months) | 3.29 |

Sixteen of the 24 patients who initially responded to treatment remained in remission throughout the follow-up period. Five of these patients had a transient rise in serum alanine aminotransferase levels after completing therapy. The elevation of serum alanine aminotransferase levels occurred in 4 to 12 weeks after the discontinuation of interferon treatment. In these 5 cases, the serum ALT levels decreased within 4 weeks to normal levels.

Univariate comparison of variables between responders and non-responders is reported in table 4. Mean age, sex, mean duration of disease, mean baseline serum AST & ALT level and ϒ GTP level, hepatitis B viral marker, and liver histology before treatment are given for all patients according to response to treatment(responders and non-responders). A high response rate was noted in cases whose disease duration was below 24 months, gamma GTP was below 60 IU/L and lower grade of histology, a difference did reach statistical significance. Female and cases that onset age was below 50 were also highly responsive but this result was not statistically significant (Table 4).

Table 4. Dermographic, clinical and laboratory features according to response to INF

| | Total | Responder N(%) | Nonresponders N(%) |
|---|---|---|---|
| Sex | | | |
| Male | 33 | 19(58%) | 14(42%)* |
| Female | 24 | 19(79%) | 5(21%) |
| Age(years) | | | |
| < 40 | 26 | 19(73%) | 7(27%)† |
| 40 - 49 | 15 | 12(80%) | 3(20%)† |
| > 50 | 16 | 7(44%) | 9(56%)† |
| Duration of Disease(months) | | | |
| < 6 | 27 | 20(74%) | 7(26%)‡ |
| 6 - 24 | 20 | 15(75%) | 5(25%)‡ |
| > 24 | 10 | 3(30%) | 7(70%)‡ |
| ALT(IU/liter) | | | |
| < 121 | 31 | 23(74%) | 8(26%) |
| > 120 | 19 | 15(58%) | 4(42%) |
| ϒ-GTP(IU/liter) | | | |
| < 60 | 19 | 17(89%) | 2(11%)§ |
| > 60 | 38 | 21(62%) | 17(38%)§ |
| HBV marker | | | |
| Anti HBs(-) Anti HBc(-) | | 6(100%) | 0(0%) |
| Anti HBs(+) Anti HBc(+) | | 21(62%) | 13(38%) |
| Anti HBs(-) Anti HBc(+) | | 11(65%) | 6(35%) |
| Histology | | | |
| CAH, mild | 30 | 23(77%) | 7(23%)∥ |
| CAH, moderate | 14 | 10(71%) | 4(29%) |
| CAH, severe | 13 | 5(38%) | 8(62%) |

Stepwise logistic regression identified 3 independent predictors of non-response : long duration of disease(>24 months), ϒ-GTP level and severe histologic activity. The odd ratio of long duration of disease (>24 months), high ϒ-GTP level and severe histologic activity were 21.45, 15.9 and 17.0 respectively(Table 5).

Table 5. Multivariate models to predict no response to IFN

| Variable | β | S.E. | p value | Odds ratio |
|---|---|---|---|---|
| Sex | −7.36 | 2.88 | 0.537 | 0.63 |
| Age(years) | | | | |
| 40 −49 | −2.36 | 1.35 | 0.8 | 0.94 |
| 〉 50 | 0.61 | 1.06 | 0.56 | 1.85 |
| Duration of Disease(months) | | | | |
| 6 −24 | 1.251 | 0 89 | 0.16 | 3 49 |
| 〉 24 | 3.1 | 1.5 | 0.03 | 21.5 |
| γ-GTP(IU/liter) | 3.25 | 1.4 | 0.02 | 25.9 |
| Histology | | | | |
| CAH, Severe | 2.84 | 1.3 | 0 03 | 17.1 |

Subjective side effects of interferon therapy were mild. Most patients experienced flu-like symptoms including myalgia, arthralgia, headache and fever after their initial injection. These symptoms were controlled by acetaminophen and improved during subsequent injection. Eight patients complained alopecia, but this symptom was corrected after completing of therapy. Pruritus and Mood depression occurred in 7% and 2%, respectively. One patient developed simple thyroid cyst at 20 weeks after initiating therapy, but it disappeared with simple aspiration. Four patients developed transient leukopenia(Table 6).

Table 6. Adverse effects of INF treatment

| | N (%) |
|---|---|
| Fever | 51(90) |
| Myalgia | 48(85) |
| Fatigue | 42(74) |
| Headache | 26(45) |
| Indigestion | 18(32) |
| Anorexia | 14(25) |
| Alopecia | 8(14) |
| Pruritus | 4(7) |
| Leukopenia | 4(7) |
| Depression | 2(3) |
| Thyroiditis | 1(2) |
| Simple thyroid cyst | 1(2) |

## DISCUSSION

Although it is known that IFN α is effective to suppressing disease activity and to inducing remission in disease in a high proportion of patients with chronic hepatitis C, the optimal dose of interferon and the optimal duration of treatment have been controversial.

One previous controlled study showed high prevalence of patients who responded clinically to IFN α but later had frequently disease relapse. In that study, 26 patients were treated according to the exact same schedule as ours, response rate was 85% and histological improvement demonstrated. Relapse within sixth month after completion of treatment occurred in 51 percent of these patients.[4]

In another study[6] involving forty swedish patients who were treated with 3million units IFN α 3 times a week for 60 weeks, response rate was 60% and 38% of responders relapse by 6 months after cessation of treatment. Viladomiu and colleague in Spain,[9] who treated similar patients with dose of 3 million units of IFN α thrice weekly for 3 months showed no beneficial effects on the clinical outcome of chronic hepatitis C. Davis et al[4] conducted a multicenter randomized control trial with similar method of our study. This considered as a standard regimen, and 38 percent of the patients with chronic hepatitis C completely responded, based on the same criteria as in the present study.

In our study, the complete response rate was observed in 66% of the treated patients. Although we cannot simply compare our results with others due to many differences

in patients characteristics and type, dose and administration route of interferon, the rate of response was slightly higher than previously published reports. This high rate of response could be the result of several factors. One could be the criteria of patients selection, (i.e., recruitment of patients with histories of blood transfusion plus others with sporadic type of disease, who have benign course.[10,11]

Another factor could be differences in the natural history of hepatitis C between western and oriental patients, which could be due to the prevalence of different viral strain that might be have different pathogenicity to the liver or sensitivity to INF.[12] Finally, what might well be the important difference between these other studies was the schedule of therapy.

Relapse following the completion of therapy was seen in 8 of 24 patients(33%) of our responders. All relapse patients were seen within first four months after cessation of treatment. The relapse rate of our study seems rather lower compared to 48% rate noted in the study by Davis et al.[4] In their definition, however relapses did included patients with transient rise in serum ALT levels after cessation of treatment. A transient rise in serum ALT levels occurred in 5 patients of our responder.

The phenomenon of transient flare of the serum ALT level after treatment has been observed previously in patients treated with INF β.[13,14] Without means of measuring the changes in viral replication during such biochemical flare, we cannot be sure of their cause or meaning. The clinical implication, however, is that a rebound elevation of serum ALT level after treatment may be transient and should not prompt the immediate reinstitution of treatment.

Finally it should be noted that in this study follow-up period after treatment has reached only 6 months to date. With further follow-up period, it is possible that some patients will have late recurrence of disease activity.

It is important to identify predictive factors for response to IFN α therapy. Virus related features, such as low level of viremia[15,16] and some HCV genotype[17] or variants,[17] seem to correlate with sensitivity to IFN α. Practical usefulness of these criteria is, however, limited by their scarceness of availability to clinician.

Several pretreatment features have been reported as useful in identifying patients with increased probability of ALT normalization under INF treatment. These include absence of cirrhosis[19-23] and less consistently, female gender,[20] young age,[20] low baseline ALT level,[20] low baseline Υ-GTP level,[22] short duration of disease,[22] low body weight[22] and low knodell scores.[24] Most of these findings originated from the analysis of single trial in which only univariate comparisons were performed. In our study, however no significant difference was seen between responders and non-responders in sex, age, duration of disease and baseline ALT level, we found that responder tended to be female, young age (<50 years), short duration of disease(<24 months) than non-responder.

A significant difference in response rate according to lower Υ-GTP(<60 IU/L) and lower necroinflammatory activity was seen in our univariate analysis. In the previous multivariate analysis of various pretreatment clinical parameters disclosed signific-

ant difference in treatment outcome, depending on the long duration of disease, ϒ-GTP level, and histologic activity.[23] It was similar result with our study. ϒ-GTP level was independently predictive of short term response to interferon treatment. The worse predictive value of ϒ-GTP was higher than 60 IU/L. This suggests that cholestasis may play a role in resistance to interferon. Cholestasis have been shown to inhibit cell mediated immunity in various model[24] and may thus interfere with antiviral and immunomodulatory activity.[25]

To obtain a more accurate prediction of INF response across the whole spectrum of patients with chronic hepatitis C, other variables could be of value. Possible candidate predictors might be the recently identified genotype of HCV[12,17] and serum concentration of HCV RNA .[15]

## CONCLUSION

This study demonstrated that a six-months course of recombinant INF $\alpha$ at a dose of 3 million units thrice weekly is generally well tolerated and induced biochemical improvement in the patients with chronic active hepatitis C. High ϒ-GTP level, long duration of disease and severe necroinflammatory activity are major worse predictive factors of short term response.

In contrast, predictive factors for relapse or long term response were not evaluated here. Whether higher doses or longer duration of treatment with interferon will increased frequency and durability of response will only be answered by future studies. Finally, the effects of interferon therapy on viral replication, infectivity, and the long-term natural history of chronic hepatitis C remain to be defined.

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