Long-term efficacy of combination therapy with Interferon alpha and ribavirin for chronic hepatitis C in Korea

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ABSTRACT

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The prevalence of chronic hepatitis C virus (HCV) infection in Korea is approximately 1-1.8%.

Combination therapy with interferon alpha (IFN-α) and ribavirin for 24 or 48 weeks according to HCV genotype has improved the overall sustained virological response (SVR) rates to approximately 40%. However, data on the long-term efficacy of combination therapy in Korean patients with chronic hepatitis C

is limited.

Between 1995 and 2002, all 138 patients with chronic hepatitis C were enrolled and analyzed. All patients were treated with IFN-α 3-6MU TIW in combination with 900-1200mg/day of ribavirin for 24 weeks. In this study, overall SVR rate was 41.3 %. There were no significant differences between naïve and retreatment patients (42.5% vs 39% respectively) except nonresponders to previous combination therapy. Based on data in naïve and retreatment patients, it was possible to estimate SVR rate of additional 24 weeks combination therapy. Estimated SVR rate by additional 24 weeks combination therapy, which was initial combination therapy for 24 weeks and then additional 24 weeks therapy to relapsers, was about 53.1%. It was comparable to SVR rate of initial treatment for 48 weeks according to major trial's data in 2001 (The overall SVR rate was 47%).

In this study, patients were followed up during 12 to 105 months (mean 39 months) after completion of therapy. Out of all SVR patients, no one progressed to decompensated liver disease or hepatocellular carcinoma (HCC) during follow-up. However, 5 patients among 81 non-SVR patients (6.2%) progressed to decompensated liver disease or HCC during follow-up.

In conclusion, combination therapy with IFN-α and ribavirin has a good long-term efficacy in patients with chronic hepatitis C. Furthermore, initial combination therapy for 24 weeks and then additional 24 weeks therapy to relapsers only may be more cost effective in Korean naïve patients than combination therapy for 48 weeks.

Key words: Hepatitis C, chronic; Interferon-alpha; Ribavirin; Retreatment; Combination drug therapy

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I. INTRODUCTION

Chronic hepatitis represents a series of liver disorders of varying causes and severity in which hepatic inflammation and necrosis continue for at least 6 months. The major cause of chronic hepatitis is chronic viral hepatitis, especially hepatitis B virus (HBV) and C virus (HCV) infection.

Chronic hepatitis C infection affects nearly 170 million people worldwide and commonest indication for liver transplantation.[1-5]

20-30% of these individuals will eventually develop cirrhosis and its sequelae.[1-5] Unfortunately, even in developed countries, death due to hepatitis C is increasing because of inadequate detection and treatment.[6-10] In a high endemic area of HBV infection, chronic hepatitis C may be overlooked until progressed status. In Korea, one of the high endemic areas of HBV infection, about 50-90 thousand people are chronically infected by HCV, and at least 10-17% of hepatocellular carcinoma (HCC) is probably attributable to HCV infection.[11]

The treatment for patients infected with HCV consists of combined treatment with interferon and ribavirin, which leads to the elimination of HCV-RNA and the long-term remission of the liver disease in approximately 40% of the patients.[12] There are some studies which addressed the long-term clinical outcomes of interferon-based treatments.[13-20] These reports suggested that

treatment with standard interferon-based therapy produced a moderate decrease in the risk for HCC.[13-20] However, data on the long-term efficacy of combination therapy in Korea is limited.

Therefore, the aim of this study was to investigate long-term efficacy of combination therapy with interferon alpha and ribavirin in Korea.

II. MATERIALS AND METHODS

1. Patients

This study included 138 chronic hepatitis C patients, who were serum anti-HCV positive by a third-generation immunoenzyme assay and HCV RNA positive by the reverse transcriptase-polymerase chain reaction (PCR). Criteria for exclusion were: (i) evidence of any cause of liver disease other than chronic hepatitis C; (ii) decompensated liver disease; hypoalbuminemia (albumin < 3.0g/dl), jaundice (total bilirubin > 2.0mg/dl), prothrombin time (PT) prolongation (PT > 3 seconds), hepatic encephalopathy or ascites; (iii) severe other systemic disease; and (iv) pregnancy.

Patients were treated at the outpatient clinics of Severance Hospital in Seoul, Korea from January 1995 to December 2002. The total of 138 patients was allocated to two groups (naïve

group, retreatment group). Naïve group consisted of 94 naïve patients, and retreatment group consisted of 44 retreatment patients who had previous interferon (IFN) monotherapy or previous IFN plus ribavirin combination therapy. This study reviewed data of patients retrospectively and patients were followed over 24 weeks after treatment.

All patients were treated for 24 weeks with recombinant interferon alpha (Intermax-α; LG chemical Ltd, Korea: Intron - A; Schering-Plough, Kenilworth, NJ, USA) plus ribavirin (Rebetol; Schering-Plough, Kenilworth, NJ, USA). Interferon alpha was administered subcutaneously three times weekly (3-6 million units (MU)) and ribavirin was given 900mg-1200mg/day orally. All patients were evaluated for safety, tolerance and efficacy by interview, biochemical and hematological testing every 4 week during treatment and 24 weeks after treatment. Thereafter,

patients were assessed every 12 week. Serum HCV-RNA concentrations were measured before treatment every 12 week during follow-up period. Serum HCV RNA by PCR was tested using a commercial assay with a lower limit of detection of 50 IU/ml (Cobas Amplicor HCV Monitor; Roche Diagnostics, Hoffman-Laroche, Basel, Switzerland).

The interferon or ribavirin dose could be modified if an important adverse event occurred or in the case of important abnormalities in laboratory values, including serious alterations of kidney function, hematological toxicity as manifested by hemoglobin levels of less than 9.0 g/dl, white cell count of less than 2000 per cubic millimeter, granulocyte count of less than 1000 per cubic millimeter, and platelet count of less than 50,000 per cubic millimeter. All patients provided written informed consent before initiation of treatment.

2. Assessment of efficacy

In accordance with NIH consensus statement,[22] end of treatment response (ETR) was defined as undetectable serum HCV RNA levels at the end of therapy. And sustained virological response (SVR) was defined as persistent serum HCV RNA clearance for 24 weeks after completion of therapy. A patient was considered to have relapsed when HCV RNA became undetectable on treatment but was detected again after discontinuation of treatment. Persons in whom HCV RNA levels remained detectable at end of treatment were considered nonresponders (NR).

3. Analysis of data

The Chi square and the Fisher's exact test were employed when necessary for the comparison of categorical variables, and

the Student's t-test, for the comparison of continuous variables. Univariate and multivariate logistic regression analysis was carried out in order to study the influence of different variables in the achievement of a SVR. Differences were considered as significant, when the p-value was < 0.05. Calculations were performed using the SPSS statistical package (SPSS Inc., Chicago, IL).

III. RESULTS

1. Patients' characteristics

Of the 138 patients included in the study, 94 underwent interferon alpha plus ribavirin combination therapy as initial therapy (naïve group) and 44 as retreatment therapy (retreatment group). The patient characteristics of the two groups are shown in Table 1.

There were no significant differences in age, gender and baseline laboratory findings between the two groups.

Table 1. Base-line characteristics of the patients.

	Naïve group (N=94, means±SD)	Retreatment group (N=44, means±SD)
Age (years)	49.8 ± 11.8	47.0 ± 11.4
Gender(male:female)	54 : 40	29 : 15
ALT (IU/L)	149 ± 96	151 ± 111
T.bilirubin (mg/dl)	0.7 ± 0.3	0.8 ± 0.3
Albumin (g/dl)	4.2 ± 0.3	4.3 ± 0.4
Prothrombin time(%)	98 ± 5	98 ± 3
Hemoglobin (g/dl)	13.9 ± 1.4	13.9 ± 1.4
White cell count(/ul)	5,367 ± 1,648	5,368 ± 1,226
Platelet ($x10^3$/ul)	157 ± 58	168 ± 59

ALT = alanine aminotransferase

p: NS between two groups

2. Efficacy of combination therapy

A. Virological response in naïve and retreatment patients

The proportion of patients according to efficacies in both treatment groups is reported in Table 2. In all enrolled patients, a SVR was observed in 57 of 138 patients (41.3%). There were no

significant differences between naïve and retreatment group in SVR (42.5% vs 39% respectively). In retreatment group, 20 patients were treated by previous interferon (IFN) monotherapy and 24 patients were by previous IFN plus ribavirin combination therapy. The proportion of patients according to efficacies in retreatment groups divided by previous treatment responses is reported in Table 3. None of NR to previous combination therapy had SVR by retreatment. However, the others had similar SVR in comparison with naïve group.

Table 2. Response rates after treatment by end of treatment response (ETR), sustained virological response (SVR), relapse or no response (NR).

	Total (N=138)	Naïve (N=94)	Retreatment (N=44)
NR(%)	43 (31.2)	30 (32)	13 (30)
ETR(%)	95 (68.8)	64 (68)	31 (70)
SVR(%)	57 (41.3)	40 (42.5)	17 (39)
Relapse(%)	38 (27.5)	24 (25.5)	14 (31)

p : NS between two groups

Table 3. Treatment responses by end of treatment response (ETR), sustained virological response (SVR), relapse or no response (NR) in retreatment group.

	Previous interferon Monotherapy (N=20*)		Previous combination therapy (N=24†)	
	Relapse(N=9)	NR(N=8)	Relapse(N=15)	NR(N=7)
NR(%)	2 (22.3)	1 (12)	4 (27)	5 (71)
ETR(%)	7 (77.7)	7 (88)	11 (73)	2 (29)
SVR(%)	3 (33.3)	5 (63)	6 (40)	0 (0)
Relapse(%)	4 (44.4)	2 (25)	5 (33)	2 (29)

* : Previous response unknown in 3 patients (SVR = 2/3)

† : Previous response unknown in 2 patients (SVR = 1/2)

B. Estimated sustained virological response (SVR) by additional 24-week combination therapy to relapsers

In this study, it was possible to estimate SVR rate of additional 24-week combination therapy. In the additional 24-week combination therapy hereof, naïve patients, regardless of genotype, received the initial combination therapy for 24 weeks

and then the retreatment combination therapy for 24 weeks. The SVR rate of initial 24-week combination therapy in naïve patients was 42.5% (Table 2). Among naïve patients, 24 patients have relapsed after combination therapy. Furthermore relapsers with previous combination therapy could achieve SVR of 40% (Table 3). Therefore, about 10 patients (24 times 0.4) among naïve patients (94 patients) could have possibility for SVR. In addition, the SVR rate of 24-week retreatment in relapsers was 10.6 % (10 over 94 times 100). Therefore, estimated SVR rate of additional 24-week combination therapy was about 53.1% (42.5% plus 10.6%).

C. Long-term clinical outcomes of combination therapy

In this study, patients were treated at the outpatient clinics from January 1995 to December 2002. They were followed up during 12 to 105 months after completion of therapy (mean 39

months).

In all of SVR patients (57 patients), SVR was conserved persistently during following-up period (13-87 months, mean 34 months). No one progressed to decompensated liver disease or HCC during following-up period.

However, 2 (2.5%) patients of decompensated liver disease and 3 (3.7%) patients of HCC occurred in non-SVR patients (81 patients) during following-up period (12-105 months, mean 44 months). The 2 patients who progressed to decompensated liver disease consisted of NR to combination therapy. 3 patients who progressed to HCC consisted of relapsers (2 patients) and nonresponder (1 patient) to combination therapy (Table 4).

Table 4. The characteristics of non-sustained virological response (non-SVR) patients who progressed to decompensated liver disease or hepatocellular carcinoma (HCC).

Patients	Long-term outcomes	Responses of therapy	Following-up months*
1	Decompensated	NR	42
2	Decompensated	NR	42
3	HCC	Relapse	33
4	HCC	Relapse	90
5	HCC	NR	21

Decompensated = decompensated liver disease

NR = no response

*: Following-up months mean the duration after 24 weeks from completion of combination therapy subject to patients.

D. Variables associated with SVR; pre-treatment and on-treatment predictors

The SVR was unrelated to gender, age, baseline ALT and biopsy stage before treatment.

In this study, the on-treatment predictors for response rates are analyzed as follows: out of 88 patients with ALT normalization at 4 weeks after initiation of therapy, 44 (32%) patients achieved SVR. Out of 50 patients with abnormal ALT at 4 weeks, about 13 (9%) patients achieved SVR, with marked differences among them (p = 0.014, Table 5.A). In a multivariate logistic model, ALT normalization at 4 weeks after initiation of therapy was significantly associated with a SVR (p = 0.018) (Table 5.B).

Among 83 patients with evaluation of HCV-RNA by PCR, 37 (45%) patients who were negative to HCV-RNA at 12 weeks after initiation of therapy could have SVR. Therefore, the predictability of the SVR based on the early virologic response (EVR) could be confirmed.

Table 5. A. Univariate analysis of on-treatment factors associated with sustained virological response (SVR) B. Multivariate analysis of on-treatment factors associated with SVR

A.

	N (%)	SVR rate (%)	*P*
ALT at 4weeks	138		0.014
Normal	88 (64)	44 (32)	
Abnormal*	50 (36)	13 (9)	
HCV RNA at 12weeks	83		0.000
Negative	58 (70)	37 (45)	
Positive	25 (30)	2 (2)	

B.

	Odds ratio (95%CI)	*P*
ALT at 4 weeks	4.17 (3.57-4.78)	0.018
HCV RNA at 12 weeks	20.38 (19.58-21.18)	0.000

ALT = alanine aminotransferase

* : ALT>46 IU/L

E. Tolerability and adverse events

There was no one who quitted combination therapy because of side effects. There were no differences between the naïve and retreatment groups in the rates of dose modification. However, the side effect profiles were higher in naïve group than retreatment group (Table 6). In hematologic side effects which can be fatal, there were no significant differences between two groups. The most common non-hematologic side effect was general weakness (13 patients, 21%).

Table 6. Rates of adverse events or dose reduction

	Naïve group N=94 (%)	Retreatment group N=44 (%)	*P*
Side Effects	49 (52)	12 (27)	0.006
Hematologic	16 (17)	2 (5)	
Others	33 (35)	10 (22)	
Dose reduction	26 (28)	5 (11)	0.343

IV. DISCUSSION

Combination therapy with IFN-α and ribavirin for 24 or 48 weeks has improved the overall SVR rates which have been reported in major trials as 31% to 47%.[1, 13, 21] In some studies, late virological relapse which was defined as the appearance of detectable HCV RNA more than 24 weeks after treatment with 24-week combination therapy,[22] occurred in less than 1% of SVR patients.[22-24] However, the effect of interferon-based therapies on the incidence of long-term clinical outcomes, such as decompensated liver disease or HCC, remains uncertain.[13] There are some studies which addressed the long-term clinical outcomes of interferon-based treatments.[13-20] Although limited by the lack of randomized controlled trials and substantial heterogeneity among the retrospective and prospective cohort studies, the evidence generally was consistent in suggesting that

treatment with standard interferon-based therapy produced a moderate decreased in the risk for HCC in complete response and relapsers.[13-20] Therefore, this study intended to investigate long-term clinical outcomes of responders and non-responders for interferon-based combination therapy. Given lack of long-term follow-up data in Korea, this study can be more meaningful.

According to this study, none of 57 SVR patients achieved late virological relapse including decompensated liver disease and HCC did not occur in them. However, 5 patients among 81 non-SVR patients (6.2%) progressed to decompensated liver disease or HCC during follow-up period. Among 5 patients, 3 patients (60%) were nonresponders and 2 patients (40%) were relapsers with combination therapy. This fact raised the possibility that standard interferon-based combination therapy produced decrease in the risk of decompensated liver disease or HCC in

SVR. However, regarding the impact of standard interferon-based combination therapy on long-term outcomes in treated patients in comparison with untreated patients, more studies should be conducted.[13-20]

There are some studies about optimal treatment duration.[25-27] Those studies recommended that patients with genotype 1 need combination treatment with extended duration to 48 weeks. This study examined efficacy of additional 24-week retreatment therapy to relapsers compared with initial 48-week combination therapy. Based on data in naïve and retreatment patients, estimated SVR rate of additional 24-week retreatment therapy to relapsers was about 53.1%. According to major trial's data in 2001,[25] overall SVR rate of initial combination treatment for 48 weeks was 47%, in which the proportion of genotype 1 was 68%, similar to Korean data (60 to 70%).[28-29] In Korea, genotype Ib has

been known as the predominant genotype. Although it was impossible to analyze genotype due to retrospective selection of patients, given our hospital data, that genotype 1b was predominant as being about 62%. In this study, it can be inferred that genotype 1b is the predominant genotype as about 60 to 70%, and accordingly the estimated SVR of additional 24-week retreatment therapy to relapsers was comparable to SVR of initial 48-week combination therapy to all patients in major's data.

There is a report that initial 48-week combination therapy had more side effects than 24-week combination treatment.[21] Furthermore, in this study, retreatment patients had more tolerability than naïve patients. Therefore, initial 24-week combination therapy followed by additional 24-week combination therapy to relapsers can reduce unnecessary over-treatment.

This study can have significant meanings, as follows;

First, this study is the almost first report to investigate efficacy and long-term clinical outcomes of interferon alpha plus ribavirin combination therapy in Korea.

Second, this study intended to decide optimal duration of combination therapy. It concluded that initial 24-week combination therapy followed by additional 24-week combination therapy to relapsers could give comparable SVR rate and tolerability with initial 48-week combination therapy.

However, it has been reported that pegylated interferon (PEG-IFN) plus ribavirin is more effective than standard interferon-ribarivin combination or PEG-IFN alone.[25,30,31] Therefore, recently, the treatment of choice for chronic hepatitis C has been PEG-IFN plus ribavirin. It is required to investigate whether better results of long-term clinical outcomes for HCV-infected patients can be achieved with a combination therapy consisting of PEG-IFN and ribavirin.

V. CONCLUSION

Combination therapy with IFN-α and ribavirin has a good long-term efficacy in patients with chronic hepatitis C, which could decrease the risk of decompensated liver disease or HCC in responders.

As initial combination therapy for 24 weeks and then additional 24 weeks therapy to relapsers only may be more cost effective in naïve patients than combination therapy for 48 weeks, randomized prospective study will be needed in the near future.

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Abstract (in Korean)

만성 C형 간염 치료와 관련하여 한국에서의 인터페론과 리바비린 병합요법의 장기적 치료 효과

<지도교수 한광협>

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김지현

한국에서의 만성 C형 간염의 유병률은 대략 1-1.8%이다. 만성 C형 간염의 치료로서 24주 또는 48주 동안의 인터페론과 리바비린 병합요법은 지속적 혈청학적 반응을 약 40%까지 향상 시켰다. 그러나, 국내에서는 치료성적의 충분한 대상과 기간으로 한 보고는 드문 실정이다. 따라서, 본 연구는 1995년부터 2002년까지 만성 C형 간염으로 진단 받고 병합치료를 시행 받은 138명을 분석하고 추적 관찰하였다.

모든 환자는 24주 동안 인터페론 300만-600만 단위를 1주일에 3번, 리바비린은 900-1200mg을 매일 투여 받았다. 본 연구에서 지속적 혈청학적 반응(sustained virological response)은 41.3%로 측정되었다. 이전의 병합치료에 대한 무반응군을 제외하고 초치료군과 재치료군 모두에서 이와 비슷한 결과를 나타내었다 (초치료군과 재치료군 각각 42.5%, 39%). 초치료군과 재치료군의 치료 결과에 근거하여 24주 병합요법 시행 후 재발 환자에 대해 24주 추가 병합요법을 시행하였을 때의 지속적 혈청학적 반응을 예측할 수 있다. 본 연구에서의 24주 추가 병합요법의 지속적 혈청학적 반응은 대략 53.1% 측정되었으며 이는 2001년도 기존에 보고된 48주 병합요법의 치료 반응 (지속적 혈청학적 반응 47%)과 견줄만한 결과이다.

이번 연구에서 환자들은 치료 후 12개월에서 105개월까지 추적 관찰되었다 (평균 41 개월). 병합치료 후 57명의 지속적 혈청학적 반응 환자들은 추적 관찰 기간 동안 비대상성 간질환이나 간암이

발생하지 않았으나, 81명의 비지속적 혈청학적 반응 환자들 중 5명(6.2%)에서는 비대상성 간질환이나 간암이 발생하였다.

결론적으로 인터페론과 리바비린의 병합요법은 만성 C형 간염 환자의 장기 치료 효과를 향상 시킬 수 있다. 또한 24주 병합치료 후에 재발군에 대해 24주 병합치료 추가는 48주 동안 연장하여 병합치료 한 것과 비슷한 정도의 지속적 혈청학적 반응을 기대할 수 있었다.

핵심되는 말: 만성 C형 간염, 인터페론, 리바비린, 재치료, 병합요법