

Long Term Follow Up of Chronic Hepatitis C Patients: Will Sustained Virological Response be Enough to Prevent Cirrhosis in The Long Term?

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Conflict-of-interest statement: The authors declare that there is no conflict of interest regarding the publication of this paper.

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Received: January 7, 2018

Revised: April 5, 2018

Accepted: April 8, 2018

Published online: April 21, 2018

ABSTRACT

AIMS: In the present study, we aimed to evaluate the impact of sustained virological response (SVR) and some other predictive factors on development of cirrhosis secondary to chronic hepatitis C (CHC).

MATERIALS AND METHODS: 100 patients with CHC, who were followed at least 1 year between 2000-2015 in Uludag University, School of Medicine Hospital were reviewed and cirrhosis development was investigated.

RESULTS: The median follow-up period was 5.9 (1-14.4) years.

The 10 year cumulative incidence of cirrhosis was significantly lower in the treated group compared to untreated group (19.5% and 44.4%, $p = 0.025$). In treated group; cirrhosis wasn't observed in the cases with SVR ($p < 0.001$). Univariate analysis revealed that female gender ($p = 0.041$), age ≤ 40 ($p = 0.05$), platelet count > 150.000 ($p < 0.001$), low AST/ALT score ($p = 0.003$), low Fibrosis-4 score ($p < 0.001$), low AST/Platelet ratio index score ($p < 0.001$), SVR ($p < 0.001$) resulted in statistically significant less cirrhosis. In cox regression analysis; SVR was found to be the only independent factor affecting development of cirrhosis (Hazard ratio, HR = 0.279; $p = 0.04$).

CONCLUSION: Although there are useful parameters in predicting the development of cirrhosis in CHC patients, SVR is the only independent factor to prevent cirrhosis. Elimination of cirrhosis with higher SVR rates with currently used new direct-acting antiviral agents will be probably shown in the future long term studies.

Key words: Chronic Hepatitis C (CHC); Cirrhosis; Sustained virological response (SVR); Interferon (IFN)

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Demirtas CO, Pekgoz M, Gurel S. Long Term Follow Up of Chronic Hepatitis C Patients: Will Sustained Virological Response be Enough to Prevent Cirrhosis in The Long Term? *Journal of Gastroenterology and Hepatology Research* 2018; 7(2): 2569-2573 Available from: URL: <http://www.ghrnet.org/index.php/joghr/article/view/2243>

INTRODUCTION

Hepatitis C virus (HCV) infection is a common, serious health problem all over the world. According to the World Health Organization (WHO) there are about 130-150 million HCV infected patients^[1]. Of all HCV-infected individuals, 80-85% develop chronic infection and 15-30% of patients with chronic HCV infection develop cirrhosis. Hepatocellular carcinoma (HCC) can develop in 1-4% of these cases^[2]. It is known that age, gender, alcohol consumption, diabetes mellitus, genotype, viral load, presence and extent of liver fibrosis are both effective in disease progression and sustained virological response (SVR)^[3].

Initiation of interferon (IFN) -based HCV treatments in the early 2000s, was predicted to reduce the risk of cirrhosis development. For a long time, the combination of peg-IFN and ribavirin (RBV) was the standard treatment. Approximately 40-50% of the genotype 1 cases in our country was able to achieve SVR with this combination therapy^[4]. With the addition of a third agent, such as telaprevir or boceprevir, SVR rates increased to 63-75% in naive genotype 1 patients^[5]. Development of cirrhosis is an important stage in the natural history of CHC, because it heralds significant morbidity and mortality and higher health care costs related to complications of end-stage liver disease. Treatment response has been proven to be a determinant factor for the development of cirrhosis. It has also been shown that disease progression can be predicted by AST / ALT, Fibrosis-4 (FIB-4) score and AST/Platelet ratio index (APRI) scores^[6,7]. Nowadays, the use of triple therapy containing telaprevir and boceprevir has now been superseded by combinations of direct acting antivirals (DAA) which achieve higher SVR rates.

These parameters are well studied and defined, thus the current study was designed to provide useful information about our population with genotype 1b dominance and compare their effectiveness. Many studies have been conducted to determine the risk of cirrhosis due to CHC, but there are few long-term follow up studies evaluating the predictive parameters and responses to antiviral agents all together. Fibroscan or liver biopsy can be used to show the fibrosis stage, but liver biopsy is an invasive procedure and fibroscan is not always an easily accessible device globally. We aimed to emphasize the impact of sustained virological response (SVR) and some other predictive factors on development of cirrhosis secondary to chronic hepatitis C (CHC). Therefore, with these results we can foresee the long term follow-up results of direct acting antiviral agents.

METHODS

Patients

We retrospectively reviewed 183 patients tested positive for both anti-HCV and HCV-RNA, who admitted to Uludag University Gastroenterology polyclinic between 2000-2015. 83 cases were excluded because of the following criterias: acute hepatitis C ($n = 1$), HBV or HIV co-infection ($n = 9$), story of chronic alcohol consumption ($n = 4$), autoimmune liver disease ($n = 1$), Wilson's disease ($n = 3$), cirrhosis-HCC within 12 months after diagnosis ($n = 17$), insufficient data and follow-up less than 1 year ($n = 148$). Consequently, 100 patients were enrolled for analysis. Of the enrolled patients, 82 received antiviral treatment for at least 12 weeks and 18 were followed without treatment due to reasons such as comorbid conditions, presence of contraindications and the patient's rejection. Treatment regimens were consisted of; IFN monotherapy ($n = 5$), double combination with peg-IFN+RBV ($n = 43$) and triple combination with peg-IFN + RBV + telaprevir ($n = 34$)

Follow-Up and End Point Assessment

The starting points of follow-up was considered the first examination for untreated group and initiation of antiviral treatment for treated group. All patients were followed up every 3-6 months for at least 1 year. Biochemical tests, alcohol consumption history and identity informations were recorded from hospital database. AST / ALT ratio, APRI [AST (IU/L) / Platelet] and FIB-4 [Age(year) \times AST(IU/L)] / [Platelet \times (sqr (ALT) (IU/L))] scores were calculated from laboratory results exactly as described. FIB-4 score were grouped as normal (<1.45), indeterminate (1.45-3.25), very high (> 3.25). Follow-up

periods were calculated based on the starting point and latest visit. Diabetes mellitus was diagnosed if fasting serum glucose levels exceeded 126 mg/dl or if there was a need for insulin or an oral hyperglycemic drug to control glucose levels. A patient with SVR was defined as aviremia 24 weeks after completion of therapy. Other patients were classified as non-responders.

First, all patients were divided into 2 groups as treated and untreated, and all parameters were compared in these groups. Then, treated patients were divided into 2 groups according to SVR. Annual rates and the cumulative incidences of cirrhosis for 3-5-10 years were estimated. All patients (including untreated patients) were analyzed for cirrhosis development and possible predictive factors.

Cirrhosis, HCC and death were defined as endpoints. The diagnosis of cirrhosis was based on either histology or the presence of at least 2 following factors: surface nodularity of liver, documented varices, splenomegaly, or platelet counts $< 120 \times 10^3 / \mu\text{l}$. HCC was diagnosed by histological evaluation or clinically according to guidelines of the European Association for the Study of the Liver.

A chemiluminescence immunoassay was used to determine anti-HCV activity. The HCV genotype was amplified by PCR using the core region of the HCV cDNA after which the DNA was sequenced. PCR using an Abbott m2000rt instrument was used to quantitatively measure the serum HCV RNA level (detection limit < 50 IU/ml).

Statistical analysis

Statistical analysis package program SPSS (Statistical Package for Social Sciences) version 22.0 was used for statistical analysis. Whether the data have normal distribution was tested by the Shapiro-Wilk test. Independent sample t test was used to compare the data with normal distribution and Mann-Whitney U test was used to compare non-normal distributions between two independent groups. Data with normal distribution was expressed as mean \pm standard deviation, whereas the non-normal distribution is indicated by med (min-max) (descriptive statistics). Pearson chi-square test and Fisher's exact chi-square test was used to compare categorical data. Descriptive statistics for categorical variables are given in terms of frequency and n (%). Cox regression analysis was used as a multivariate analysis in evaluating factors affecting cirrhosis. In the Cox regression analysis, the variables were added according to significance in the model Kaplan-Meier analysis. The results were examined at 95% confidence level and $p = 0.05$ significance level.

Ethical Approval

Ethical approval was taken on 26.04.2016 from Uludag University Medicine Faculty ethical committee with the decision number of 2016-8/8.

RESULTS

The median follow-up period was 5.9 (1-14.4) years for all patients, 4.4 (1-11.7) years for untreated group and 6.1 (1-14.4) years for treated group. The mean follow-up time was longer in the treated group ($p = 0.041$). The median follow-up time was 6.9 (3.5-7.7) years for single IFN, 6.6 (1.1-14.4) years for double combination, 2.5 (1-8.1) years for treatment inexperienced triple combination and 6.7 (2.3-12.2) years for the treatment experienced triple combination group. There was no statistically significant difference between the treated and untreated groups, when baseline parameters were evaluated (Table 1).

24 patients (24%) were found to have cirrhosis and 1 patient (1%) developed HCC in follow-up period. Incidence of cirrhosis for 3-5-

10 years in all patients were 13% - 17% - 24% and the annual rate of cirrhosis was 2.4%. Cumulative cirrhosis incidences for 3-5-10 years in treated group was significantly lower than the untreated group (Treated group: 8.5%, 11%, 19.5%; Untreated group: 33.3%, 44.4%, 44.4%, respectively, $p = 0.025$) (Figure 1). In the treated group, 34 (41.5%) cases had SVR and none of them developed cirrhosis. The incidence of cirrhosis for 3-5-10 years in patients without SVR was 14.6% ($n = 7$) - 18.8% ($n = 9$) - 33.3% ($n = 16$) and annual cirrhosis development rate was 3.33% ($p < 0.001$) (Figure 2). Double combination group had 20.9% ($n = 9$) and triple combination group had 73.5% ($n = 25$) SVR rates, while there was no SVR achieved with IFN monotherapy. There was a significant difference in the rates of SVR among these groups ($p < 0.001$).

Univariate analysis revealed that female gender ($p = 0.041$), age ≤ 40 ($p = 0.05$), platelet count > 150.000 ($p < 0.001$), low AST/ALT score ($p = 0.003$), normal Fibrosis-4 score ($p < 0.001$), low AST/Platelet ratio index score ($p < 0.001$), SVR ($p < 0.001$) resulted in statistically significant less cirrhosis (Table 2). As a result of multivariate analysis; SVR was found to be the only statistically significant predictor (Hazard ratio, HR = 0.279; $p = 0.04$) for cirrhosis development independent of all other parameters (Table 3).

Table 1 Distribution of baseline parameters according to treatment status.

	Untreated	Treated	P value
Male sex (n)	12 (66.7%)	45 (54.9%)	0.360
Age (n)	58 (24-76)	54 (22-73)	0.059
Diabetes (n)	2 (11.1%)	10 (12.2%)	0.898
Genotype 1 (n)	17 (94.4%)	79 (82.3%)	0.554
AST (IU/L)	42 (17-177)	35 (6-287)	0.448
ALT (IU/L)	56 (15-312)	38 (10-304)	0.311
INR	1.08 (0.95-1.94)	1.01 (0.86-2.52)	0.074
Albumin (g/dl)	4.2 (3.6-5)	4.3 (1.9-5.3)	0.838
RBC (milion / mm^3)	4.80 (4.18-6.83)	4.61 (1.50-7.54)	0.098
MPV (fL=femtolitre)	8.15 (6.80-11.00)	8.30 (5.80-11.80)	0.896
PLT ($\times 10^3/\mu\text{l}$)	232 (151-446)	213 (124-369)	0.602
HCV-RNA >800.000 IU/ml (n)	10 (55.6%)	56 (68.3%)	0.302
AST/ALT	0.88 (0.53-1.53)	0.90 (0.40-1.81)	0.805
FIB-4 score	2.26 \pm 1.89	1.78 \pm 1.29	0.195
APRI score	0.65 \pm 0.60	0.57 \pm 0.63	0.629

Table 2 Results of univariate analysis in the development of cirrhosis.

	Cirrhosis (-)	Cirrhosis (+)	P value
AST (< 40 / ≥ 40)	43 (81.1%) / 33 (70.2%)	10 (18.9%) / 14 (29.8%)	0.202
ALT (< 56 / ≥ 56)	53 (80.3%) / 23 (67.6%)	13 (19.7%) / 11 (32.4%)	0.160
Albumin (≤ 3.5 / > 3.5)	5 (62.5%) / 71(76.9%)	3 (37.5%) / 21 (23.1%)	0.361
INR (≤ 1.1 / > 1.1)	35 (87.8%) / 41 (74.5%)	10 (22.2%) / 14 (25.5%)	0.707
RBC ($< 5.500.000$ / $\geq 5.500.000$)	73 (75.3%) / 3 (100%)	24 (24.7%) / 0 (0%)	0.323
MPV (≤ 10.4 / > 10.4)	70 (77.8%) / 6 (60%)	20 (22.2%) / 4 (40%)	0.212
Genotype (1 / others)	73 (76%) / 3 (75%)	23 (24%) / 1 (25%)	0.962
HCV RNA (< 800.000 / ≥ 800.000)	26 (76.5%) / 50 (75.8%)	8 (23.5%) / 16 (24.2%)	0.937
Platelet count (< 150.000 / ≥ 150.000)	7 (39%) / 69 (84.1%)	11 (61%) / 13 (15.9%)	<0.001
Diabetes mellitus (+ / -)	7 (58.3%) / 69 (88.4%)	5 (41.7%) / 19 (21.6%)	0.127
Gender (Female / Male)	37 (86%) / 39 (68.4%)	6 (14%) / 18 (31.6%)	0.041
SVR (+ / -)	34 (100%) / 32 (66.7%)	0 (0%) / 16 (33.3%)	<0.001
Age (≤ 40 y / > 40 y)	16 (94.1%) / 60 (73.3%)	1 (5.9%) / 23 (27.7%)	0.05
AST / ALT score	0.867 (0.409-1.739)	1.079 (0.553-1.810)	0.003
APRI score	0.32 (0.07-4.69)	0.76 (0.18-2.49)	<0.001
FIB-4 score (< 1.45 / $1.45-3.25$ / > 3.25)	45 (%95.7) / 5 (%35.7) / 26 (66.7%)	2 (4.3%) / 9 (64.3%) / 13 (33.3%)	<0.001

DISCUSSION

Global researches has shown that CHC patients has a incidence of cirrhosis about 15-20% and risk of HCC between 1-5%. 10-year incidence of cirrhosis was 24% and the incidence of HCC was

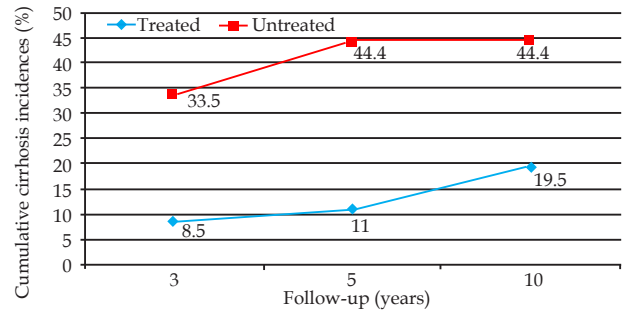


Figure 1 Cumulative cirrhosis incidence according to treatment status.

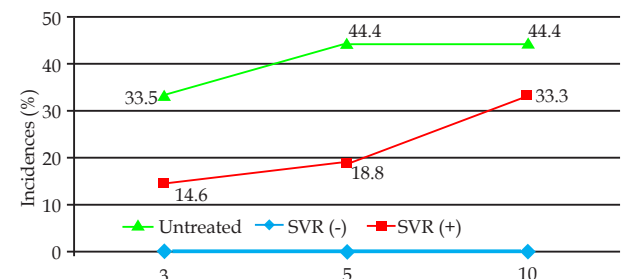


Figure 2 Cumulative cirrhosis incidence according to treatment response.

Table 3 Results of cox regression analysis in the development of cirrhosis.

	Hazard ratio (HR)	%95 Confidence interval (CI)	P value
PLT < 150.000	0.422	0.99-1.790	0.242
MPV > 10.4	1.858	0.543-6.363	0.324
FIB-4 score 1.45-3.25	4.435	0.325-60.449	0.264
FIB-4 score > 3.25	3.576	0.587-21.801	0.167
AST/ALT score > 1	2.587	0.747-8.966	0.134
APRI score > 1	1.632	0.561-4.750	0.369
SVR (+)	0.279	0.082-0.943	0.04

1% in this study. The increase in the incidence of cirrhosis may be explained by the fact that the vast majority of our patients (96%) were infected with the more aggressive genotype (genotype 1). Annual rate of cirrhosis was found to be 2.26-5% in previous studies for the untreated patients^[8,9], which was similar to our results (4.44%). The annual rate of cirrhosis (1.95%) was significantly declined in treated group.

Combination of peg-IFN + RBV provides SVR rates between %50-80 independent of genotype^[4,10], and 40-50% for genotype 1^[3]. In a study in Turkey^[11], the combination of Peg-IFN + Ribavirin + Telaprevir increased the SVR rate to 74% for genotype 1 patients. International randomized controlled studies^[12,13] has revealed SVR rates with IFN+RBV (41%, 44%) and IFN+RBV+telaprevir (61-67%, 69-75%). In a phase 3 randomized controlled trial^[9] with 663 patients who had previously received double combination therapy and did not receive a response; the rate of SVR was 24% when double combination was given again and 83-88% when triple combination was given. SVR rates obtained with double combination (20.9 %) was lower and triple combination (73.5%) was comparable with the literature in this study.

This study emphasized the importance of antiviral treatments and SVR. C. Koh *et al*^[14] and Morisco F *et al*^[15] also showed that CHC patients with SVR has a markedly reduced risk for relapse and cirrhosis (0.97%, 0.77 respectively). Lee HJ *et al*^[8] followed up 280 CHC patients for 10 years in Korea and the cumulative incidences of cirrhosis were found to be 0.6% in patients with SVR, 33.9% in patients without SVR and 44.4% in untreated group. In this study, similar results were observed as treated patients without SVR had lower cirrhosis incidence comparing to untreated patients, although it was not statistically significant. Cirrhosis incidence was slightly increased in double combination group comparing to triple combination group. Lower SVR rates in this group may explain it and increasing SVR rates in triple combination group resulted with less cirrhosis. It is expected that the increasing SVR rates with the new direct-acting antiviral therapies can eliminate HCV-dependent cirrhosis.

Amorim TG *et al*^[16] performed liver biopsy to 119 HCV RNA (+) patients and AST / ALT, FIB-4, APRI score levels were compared with metavir scores. These three parameters were associated with liver fibrosis, indicating that FIB-4 and APRI scores were better predictors of liver fibrosis than AST / ALT ratio. On the other hand, Pohl A *et al*^[17] performed liver biopsy to 211 CHC patients and results suggested that AST / ALT ratio and low platelet count may be useful in determining the degree of liver fibrosis. Shiratori Y *et al*^[18] and Bruno *et al*^[19] have examined the changes in liver histology after IFN treatment. Both studies revealed that liver histology is significantly improved in patients with SVR. However, unchanged fibrosis was observed in untreated patients and patients without SVR as a result of these two studies. Our study revealed that older age, male gender, low platelet count, high AST / ALT ratio, high FIB-4 score, high APRI score, and no SVR were found to be predictive in cirrhosis development. Diabetes mellitus, which is emphasized as a predictor in the literature, was also found more frequently in the cirrhosis patients, but it wasn't statistically significant. Our multivariate analysis has shown that patients with SVR has significantly decreased risk for cirrhosis independent of other factors (1-0.279). In a metaanalysis^[20] with 1013 CHC patients, SVR has been shown to be the only determining factor in maintaining the regression of liver fibrosis. Ferreira Sda C *et al*^[21] also supported this by showing that 174 patients with SVR with different treatment protocols had no recurrence, cirrhosis or HCC for 47 (12-156) months. In another

study^[22], different types of HCV genotypes were evaluated and it has been shown that the only parameter that provides a significant reduction in liver-related mortality is SVR.

There are several limitations in our study. Firstly, this was a retrospective study and it would have been useful to have a more accurate fibrosis/cirrhosis status of the patients at entry by fibroscan or liver biopsies, which may undermine the interpretation of the results. For ethical reasons it is difficult to perform a prospective study on effectiveness of anti-HCV therapy in preventing disease progression and perform liver biopsy to all patients. Thus most patients with cirrhosis were diagnosed using clinical criteria. Although ultrasound is inaccurate in detecting the early stages of liver cirrhosis, combination of clinical, laboratory and morphologic findings can improve accuracy over 80%^[23]. Secondly, we lack number of patients because of the intensive exclusion criterias, but age distribution and baseline parameters were well matched between groups. However with the long follow up period of well distributed groups, gives us useful information about effectiveness of predictive parameters in cirrhosis. The beneficial effect of antiviral treatment and sustained virological response has been reported before from multicenter clinical trials, but this paper delivers the experience of genotype 1b dominant patients in a single center with different treatment protocols and comparison of predictive laboratory scorings which supports literature. The use of triple therapy containing telaprevir and boceprevir has now been superseded by combinations of direct-acting antivirals which achieve higher SVR rates. This study can't be considered as local; because it encourages the need for long term follow up results comparing the SVR rates and cirrhosis/HCC development in patients treated with direct acting agents. Multicenter long term follow up of patients treated with direct acting anti-viral agents is required.

In conclusion; cirrhosis was not observed in patients with SVR, as expected, in our study. Platelet count, gender, age, AST / ALT ratio, APRI score and FIB-4 score are useful parameters for predicting fibrosis/cirrhosis and should be kept in mind at diagnosis if fibroscan or liver biopsy is not reachable. Although these factors are proven to have affect, SVR is the only independent factor to prevent cirrhosis. Currently used direct-acting antiviral agents with higher SVR rates can totally prevent cirrhosis development in the long term.

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