

Durability of Sustained Virological Response and Long Term Follow Up To Pegylated Interferon and Ribavirin in Treated Patients with Chronic Hepatitis C

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ABSTRACT

Objective: To study the clinical, biochemical and virological long-term outcome in chronic hepatitis C patients with a Sustained Virological Response after Pegylated Interferon plus ribavirin combination therapy.

Methods: Twenty eight patients with a Sustained Virological Response after treatment with Pegylated Interferon plus ribavirin were included in a 5-year follow-up study in a single Gastroenterology & Hepatology center, based on standard clinical practice. Clinical and ultrasonic evaluation, liver function tests, alpha-fetoprotein and hepatitis C virus RNA by PCR were performed annually for a period of 5 years.

Results: The mean follow-up period of the 28 patients was 67 ± 4 months after they obtained a sustained virological response. Eleven patients (39.2%) presented with high fibrosis score (Metavir >3) before treatment. Seventeen patients (60.7%) had genotype 4, nine patients (32.1%) genotype 1, one patient genotype 2 and one patient genotype 3. One patient (3.5%) showed evidence of hepatic decompensation. One patient (3.5%) showed virological relapse after achieving sustained virological response. At the end of the 5-year follow-up there were no deaths, no elevation in liver function tests and no hepatocellular carcinoma.

Conclusion: The long-term outcome of patients with sustained virological response to Pegylated Interferon plus ribavirin was maintained in 96.5% with one patient having virological relapse, indicating that Long term recurrence rate to combination therapy was very low.

Key words: Chronic hepatitis C; Pegylated interferon; Ribavirin; Sustained virological response; viral genotype.

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Introduction

Combination therapy with Pegylated interferon and Ribavirin is the current standard of care for the naïve patients infected with hepatitis C virus, achieving a high sustained virological response (SVR) rate depending on viral genotype.⁽¹⁻³⁾

There are good number of published data that shows the long term effect of therapy for chronic hepatitis C (CHC)⁽⁴⁻⁸⁾ but most studies used IFN monotherapy or IFN combined with ribavirin, while only 5 studies used PEG-IFN plus ribavirin combination therapy.⁽⁹⁻¹³⁾

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We conducted an open-label cohort study in a single center in Jordan from 2004 to 2012, and included all patients with SVR after antiviral combination therapy with Pegylated Interferon (PEG-IFN) Alfa 2 a 180 mcg plus ribavirin between 2004 and 2007, with a mean follow-up period of 5 years. Our major aim was to assess the clinical, biochemical and virological outcomes, and the durability of the SVR.

Methods

A total number of fifty one Chronic Hepatitis C consecutive patients (18-65 years) treated with PEG-IFN Alfa 2 a 180 mcg plus ribavirin 1200 mg in 2004-2007 were included in this study. All patients attended the Gastroenterology & Hepatology Unit in Al Bashir Governmental Hospital (The biggest tertiary public hospital in Amman-Jordan) (Chart flow 1).

Patients

Eligible patients were those who achieved a SVR after PEG-IFN plus ribavirin.

Sustained Virological response was defined as of HCV-RNA negativity at the end of treatment and after 6 months of follow-up.

Criteria for exclusion were: alcohol, intravenous drug abuse; other liver diseases not related to HCV infection (autoimmune, metabolic or drugs); decompensated liver disease; coinfection with HBV or HIV; and pregnancy.

All patients received the standard of care combination therapy: PEG-IFN α -2a 180 mcg (Pegasys 180, Roche) plus ribavirin (1.2 g/d), twenty patients (39.4%) were of genotype 1, one patient (1.9%) of genotype 2, one patient (1.9%) of genotype 3 and 29 patients (56.8%) were genotype 4. Characteristics of patients are showed in Table I.

Patients with genotypes 1 and 4 were treated for 48 weeks and patients with genotypes 2 or 3 were treated for 24 weeks.⁽¹⁴⁻¹⁸⁾

Data from the 51 chronic hepatitis C treated patients with combination therapy showed SVR in 28 (59.5%), 11(21.5%) non-responders and 12 (25.5%) relapsers (Table II).

Twenty eight patients with SVR were followed up yearly after obtaining the SVR, with median follow up period of 67 ± 4 months.

Table I: Characteristics of fifty one patients with chronic hepatitis C treated with Pegylated interferon alpha 2 a 180 mcg plus ribavirin combination treatment

	No. (%)
Age (mean/ year)	49
Sex	
Female	20 (39.3)
Male	31 (60.7)
Genotypes	
1	20 (39.4)
2	1 (1.9)
3	1 (1.9)
4	29(56.8)
Stage of fibrosis (before therapy)	
F1-2	23 (45)
F3	13 (25.4)
F 4	15 (29.4)
Viral load (before therapy)	
High Viral Load	22 (43.1)
Low Viral Load	29 (56.8)

Table II: Virological response to combination therapy

Viral response	No. (%)
Sustained Viral Responders (SVR)	28 (59.5)
Non-Responders (NR)	11 (21.5)
Relapsers (R)	12 (25.5)

Laboratory Assessment

We collected data on patients sex and age, treatment, virological data (genotype, baseline HCV-RNA), biochemical data [aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), α lfa-fetoprotein (AFP)], and complete blood count.

Pre-treatment liver biopsy was recorded.

Patients were evaluated as outpatients at sequential annual clinical visits (1, 2, 3, 4, 5 years after the completion of antiviral therapy and 6 months of follow-up). Blood tests were performed at the basal visit and thereafter. Serum HCV-RNA levels (IU/mL) were determined with Cobas Taqman HCV (Roche Diagnostics), with a lower limit of detection 50 IU/mL. HCV genotyping was performed by a reverse-hybridization line probe assay (INNO-LiPA HCV).

Liver decompensation was defined if a patient showed any of clinical decompensation signs: bleeding varices, hepatic encephalopathy, jaundice, or ascites.

Virological relapse was defined as HCV RNA positivity for previously SVR individuals at any time beyond the 6 months of the end of treatment. Patients were classified pretreatment by liver biopsy, and the establishment of cirrhosis was done using the METAVIR score for fibrosis stage.

Hepatocellular carcinoma (HCC) was diagnosed if two imaging techniques shows focal lesions in the presence of an AFP level > 100 ng/mL.

Statistical Analysis

Quantitative variables are expressed as mean \pm SD. Qualitative variables are expressed as percentage with range. Statistical analyses were performed using SPSS version 15. A value of $P < 0.05$ was considered to be statistically significant.

Ethical Issues

This study has the approval of the ethical committee – Research Ethics committee (REC) of the Ministry Of Health number MOH-REC-09-0009.

Results

Among the fifty one chronic hepatitis C treated patients with combination therapy, a total number of 23 were excluded as they did not achieve a SVR (non-responders and relapsers) as shown in Table II. Those 28 patients with a SVR after treatment with a mean age of 46 years were followed up for five years. There were 17 males (60.7%) and 11 female (39.28 %). Genotypes of HCV were distributed as follows: 17 genotype 4 (60.7%), one genotype 2 (3.5%), one genotype 3 (3.5%) and 9 patients with genotype 1 (32.1%).

The baseline characteristics of patients with a SVR are shown in Table III. All patients were followed up for 5 years after SVR.

All 28 patients with SVR were alive at the end of follow up.

Of 28 sustained responders, 4 patients had cirrhosis (F4) and 7 patients had (F3) stage fibrosis before the start of the treatment, as determined by the METAVIR score. One patient with SVR and with Metavir 4 on pre-treatment biopsy and genotype 1 developed signs of liver decompensation during the follow-up period (Ascites). The patient was still negative for HCV-RNA by PCR at the time of decompensation, and

Table III: Characteristics of 153 patients with Characteristics of twenty eight patients with a sustained virological response after Pegylated interferon 180 mcg plus ribavirin combination treatment

	No. (%)
Age (mean/ year)	46
Sex	
Female	11 (39.28)
Male	17 (60.7)
Genotypes	
1	9 (32.1)
2	1 (3.5)
3	1 (3.5)
4	17(60.7)
Stage of fibrosis (before therapy)	
F1-2	17 (60.7)
F3	4 (14.2)
F 4	7 (25)

at last follow-up, HCV-RNA remained undetectable, and was referred to a liver transplant center for liver transplantation.

One patient, with cirrhosis on pre-treatment biopsy (Metavir 4) and genotype 1, showed virological relapse after achieving SVR on the second year of follow up (at 42 months of the beginning of combination therapy), he is listed for triple therapy regimen.

All 28 SVR patients had yearly biochemical evaluations after achieving the SVR. There were normalizations in ALT, AST and ALP levels between the samples collected pre-treatment and samples after the end of treatment.

All 28 SVR patients had HCV-RNA tests by PCR annually with one patient had detectable HCV-RNA in serum by RT-PCR at month 24 after SVR.

Discussion

Our study assessed the long-term clinical, biochemical and virological outcomes of 28 patients with chronic hepatitis C who achieved a SVR after combination therapy with Pegylated interferon Alfa 2 a 180 mcg plus Ribavirin.

Our study showed that a SVR is associated in most patients with permanent undetectable HCV-RNA in blood during a long-term follow-up. Only one patient genotype 1 and Metavir 4) showed late relapse after 2 years of follow up. A late relapse of at least 0.8% after 4-5 years of follow-up has been reported.^(4,5,6)

There are some studies of the long-term clinical outcome of chronic hepatitis C patients with a

SVR^(19,20) but the majority analyzed patients treated with recombinant IFN as monotherapy or in combination with ribavirin.

At present, there are 6 studies which have enrolled patients treated with PEG-IFN plus ribavirin. In one study by Veldt *et al*⁽⁹⁾ analyzed 141 patients with SVR and showed improved clinical outcomes, mainly prevention of liver failure, in patients with chronic hepatitis C and advanced fibrosis; Chavalitdhamrong *et al*⁽¹⁰⁾ studied 78 patients and showed no virological relapse, no hepatic decompensation and 3 patients with hepatocellular carcinoma; George *et al*⁽⁸⁾ published the results of a long-term study of SVR patients and showed no evidence of virological relapse, three patients with persistently elevated ALT levels and two patients with hepatocellular carcinoma; Giannini *et al*⁽¹¹⁾ included 231 patients treated with PEG-IFN plus ribavirin, and showed two patients with virological relapse; Maria Trapero-Marugan *et al.* published recently a study that included 153 SVR patients treated with Pegylated interferon and Ribavirin that showed no virological relapse, one patient with persistent elevation in ALT levels and one patient with hepatocellular carcinoma.⁽¹²⁾

Sang Bu Choi *et al.* published in a study that included 292 patients treated with combination therapy showed no virological relapse and two patients with hepatocellular carcinoma.⁽¹³⁾ More recent study published by I. Puig-del-Castillo *et al*⁽²¹⁾ showed that from 80 patients with SVR after PEG-IFN and Ribavirin therapy and follow up for five years, only one patient experienced virological recurrence and all other patients had negative HCV RNA levels, absence of liver complications and normal ALT levels.

Our study included all patients treated with Pegylated interferon plus ribavirin with a high proportion being genotype 4 (60%), the other studies Chavalitdhamrong *et al*,⁽¹⁰⁾ genotype 3 represented 62%; George *et al*,⁽⁸⁾ genotype 1 represented 47%; Giannini *et al*⁽¹¹⁾ genotype 1 represented 66.6%; I. Puig-del-Castillo *et al*⁽²¹⁾ genotype 1 represented 58.1%; and Maria Trapero-Marugan *et al.* genotype 1 represented 75.8%.⁽¹²⁾ Our study is the first one that majority of patients are of genotype 4, which showed no relapsers in this particular genotype and good clinical and chemical outcome.

Overall, our study showed that clinical events were rare in this population, indicating that SVR patients have an excellent prognosis, similar to previous studies.⁽²²⁻²⁵⁾

One patient developed decompensated liver disease that had compensated cirrhosis (Metavir F4) in the pretreatment liver biopsy. Similar data was shown by Pradat *et al*⁽²⁶⁾ who found that cirrhosis developed in 2 of 87 patients who were followed for at least 5 years after a SVR.

No patient developed liver cancer during the period of follow up, but these data must not assure us that our treated patients are protected from acquiring HCC. Japanese authors^(27,28) have reported a HCC rate of 0.02%-0.5% per year, also Maria Trapero-Marugan *et al*⁽¹²⁾ reported incidence of 0.65% of HCC, Sang Bu Choi *et al.* rated an incidence of 0.68% of HCC,⁽¹³⁾ Chavalitdhamrong *et al.* rated an incidence of 1.7% of HCC⁽¹⁰⁾ and George *et al.* had an incidence of 1.3%.⁽⁸⁾ These data raise up that the risk of late development of HCC after a SVR is a real problem, and we must continue the follow-up of these patients for a long time. Developing HCC in SVR patients does not require detectable HCV-RNA. Lot of studies explain that the possibility of liver carcinogenesis, despite null replication of HCV, by other pathways.⁽²⁹⁻³¹⁾

Our data confirms that clearing the viral replication and obtaining SVR does correlate with normalization in liver function tests, as shown in other studies,^(32,33) where 100% of our SVR patients had normal Liver tests during the whole period of follow up.

This long-term study may be criticized by the small number of patients, taking in mind that overall prevalence of hepatitis C in Jordan is low (0.56%) with majority of hepatitis C patients of genotype 4.⁽³⁴⁾

Conclusions

Our study maybe the first one that include genotype 4 as the main investigated genotype in the group of long term follow up SVR CHC patients

The study demonstrated that the long-term outcome of CHC patients who were sustained virological responders was good, and virological relapse was low. It is important that evidence of a virological relapse must be assessed for a long

time, as well as screening for hepatocellular carcinoma.

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Chart 1: Flow chart of patients

