

## Sustained virological response after treatment in patients with chronic hepatitis C infection - a five year follow up

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### Abstract

Peginterferon  $\alpha$ -2a and ribavirin combination therapy achieves a sustained virological response (SVR) in patients with chronic hepatitis C. Little is known about long-term durability of hepatitis C virus – Ribonucleic acid (HCV-RNA) negativity in patient treated with pegylated interferon and ribavirin therapy. Aim of this study was to evaluate the durability of virologic response in patients with SVR to anti-viral therapy treated at our centre. A total of 52 patients with chronic hepatitis C virus infection who had obtained SVR after Peginterferon  $\alpha$ -2a and ribavirin combination therapy were followed up to 5 years with annual HCV-RNA testing. During this follow up period, 4 of 52 patients with initial SVR developed late relapse of hepatitis C virus infection. Relapse was more common in patients who has cirrhosis (3/6 [50%]) vs (1/46 [2.17%]) without cirrhosis. In conclusion, SVR is durable in most patients, but some patients do have late relapse; long term follow up may be particularly important in a subset of patients with hepatitis C virus infection who have liver cirrhosis.

### Introduction

Hepatitis C virus (HCV) is a major causative agent for chronic liver disease<sup>1,2</sup>. The infection with HCV tends to persist in majority of infected individuals and perhaps as many as 70-90% of the infected individuals fail to clear the virus once acquired. The infection has a significant role in causing chronic hepatitis, cirrhosis and hepatocellular carcinoma<sup>3,4</sup>. The goal of treatment is to prevent complications of HCV infection.

Currently, pegylated interferon (Peg-IFN) alfa 2a/2b with ribavirin is the standard treatment for chronic HCV infection. Absence of serum HCV RNA 6 months after discontinuation of therapy i.e., sustained virological response (SVR) is generally taken as cure of HCV infection. Sustained virological response rates with Peg-IFN and ribavirin treatment are 42-52% of those with genotype 1 HCV infection and 80% in those with genotype 2 or 3 HCV infection<sup>1</sup>. Successful eradication of HCV is associated with regression of fibrosis and clinical improvement<sup>2,3</sup>.

However, despite treatment, HCV may persist in liver tissue and extrahepatic locations like peripheral blood mononuclear cells (PBMCs) leading to late relapse, defined as reappearance of viremia after SVR has been achieved<sup>4</sup>.

Although the near-term benefit of a sustained virologic response (SVR) after treatment of chronic

hepatitis C infection is well-established<sup>1,2</sup>, knowledge is still incomplete regarding the long-term clinical, virologic, biochemical, and histologic outcomes after SVR<sup>3-8</sup>. In particular, the risk of late virologic relapse and late sequelae of HCV infection including hepatocellular carcinoma (HCC) and decompensated liver disease are not known. Although previous studies have demonstrated improvement by histologic evaluation more than 1 year after end of treatment (EOT)<sup>3,5,9-11</sup> the long-term histologic benefit of SVR has not been studied in large patient populations. This outcome is of critical importance, because the ultimate goal of anti-HCV therapy is prevention of cirrhosis and death from liver disease.

Since, no data are available on long-term clinical outcomes and virological relapse in Bangladeshi patients with HCV infection who achieve SVR<sup>5,6</sup>, we undertook a prospective, long-term follow up study assessing of such patients.

### Materials and Methods

Patients with chronic hepatitis C who had achieved SVR with Peginterferon  $\alpha$ -2a and ribavirin treatment between July 2004 and July 2006 who agreed for follow up using annual HCV RNA testing, were enrolled in the study. All patients provided written informed consent. The period of study was from July'2006 to July' 2011 and place

of study was department of Gastroenterology, Bangabandhu Sheikh Mujib Medical University (BSMMU).

Chronic hepatitis C was defined as presence of anti-HCV antibodies, detectable serum HCV RNA and elevated (twice the upper limit of normal) serum alanine aminotransferase (ALT) levels. Sustained virological response was defined as undetectable serum HCV RNA levels 6 months after stopping therapy.

The patients of chronic hepatitis c were treated with peginterferon  $\alpha$ -2a and ribavirin combination therapy. Therapy was given for 24 weeks in genotypes 2 and 3 and for 48 weeks in genotypes 1 and 4 infections.

A total of 52 patients were selected for this study. Out of 52, 32 patients had genotypes 2 and 3 infections and 20 patients had genotypes 1,4, mixed (3 and 4) infections. Peginterferon  $\alpha$ -2a (Inj. Pegasys, Roche Bangladesh Limited) was given at a dose of 180 $\mu$ gm subcutaneously per week and ribavirin (Cap Rivarin 200 mg) was given at a dose of 800 mg for genotypes 2 and 3 infections and 1000-1200 mg for 1 and 4 infections according to body weight daily.

The patients underwent a clinical follow up every 3-6 months for 1 year and yearly thereafter. At each visit, physical examinations, hemogram, liver function tests and prothrombin time were done. Patients with ultrasound (US) evidence of cirrhosis were screened for HCC by alpha – fetoprotein measurement every 6 months and ultrasound every year. HCV RNA was tested every year.

## Results

Between July 2004 to July 2006, 72 patients received anti- HCV treatment. Of these, 8 patients did not complete the treatment due to adverse effects (n=2), decompensation of disease (n=4) or financial reasons (n=2). Of the 64 patients who completed treatment, 52 achieved SVR and were followed up. The baseline demographic, clinical, virologic, histologic characteristics and treatment of these 52 patients are shown in table I.

All the study patients were negative for HBsAg and anti-HIV. None had decompensated cirrhosis at enrollment, or evidence suggesting HCC on US or serum AFP levels. Six patients had US evidence of cirrhosis.

Duration of follow up was 06 to 60 months. The number of patients completing 1<sup>st</sup> to 5<sup>th</sup> year of follow up was 52,48,46,40 & 30 respectively. Four of 52 patients had virological relapse (7.69%) during follow up, including two each during the

first and the second year of follow up, and none subsequently.

Clinical, virologic and treatment details of these patients are shown in table II. Relapse occurred more often in patients with liver cirrhosis (3/6-50%) than in those without cirrhosis (1/46-2.17%).

**Table I:** Baseline characteristics of study subjects

Characteristics	Value
Age (mean [SD]) (year)	41.4[11.0]
Gender (M:F)	78:22
BMI(mean [SD])	26.3[4.3]
Cirrhosis	6
Alcohol intake	2
Diabetes	4
Genotype	
3(a,b)	28
2b	4
1(a,b)	8
3 and 4 mixed	8
4	4

**Table II:** Characteristics of patients who had a relapse following sustained virological response

Sl. No	Age	Sex	BMI (kg/m <sup>2</sup> )	Alcohol	Genotype	Cirrhosis	Time to relapse(year)
1	48	M	32.1	N	3	Y	1 <sup>st</sup>
2	45	M	30.4	N	3	Y	1 <sup>st</sup>
3	52	M	23.7	Y	3	N	2 <sup>nd</sup>
4	45	M	33.6	N	1	Y	2 <sup>nd</sup>

## Discussion

Infection with hepatitis C virus is a leading cause of liver disease worldwide<sup>1,2</sup>. Progression to chronic hepatitis C occurs in most people acutely infected with HCV and persistent infection is an important cause of cirrhosis, end stage liver disease and hepatocellular carcinoma. Thus, early detection and treatment is of great importance. The goal of treatment is to prevent complications of HCV infection<sup>3,4</sup>.

There have been substantial improvements in the success of HCV treatment and there are currently several treatment regimens approved by the FDA. In randomized clinical trials, the highest overall SVR rates have been achieved with the combination of weekly subcutaneous injection of long acting peginterferon  $\alpha$ -2a and daily oral ribavirin, which represents the current standard of care<sup>12-14</sup>.

Nevertheless, little is known on the outcome of patients treated with PEG-IFN/ribavirin combination therapy. Recently, swain et al. evaluated the durability of SVR after the treatment with peginterferon  $\alpha$ -2a  $\pm$  ribavirin in 845 patients, who had participated in pivotal trials<sup>15</sup> and achieved SVR. Only in seven patients (<1%), HCV-RNA was detected (after 391-1076 days of treatment). All these data indicate that the late relapse after SVR in chronic hepatitis C patients following an IFN-based anti-viral therapy is rare<sup>16-19</sup>.

This is the first study from Bangladesh on long-term outcomes of anti-viral therapy for chronic HCV infection. Our study shows that SVR is durable in a majority of patients but late relapses do occur. These relapses occur more commonly in patients with cirrhosis. Our study revealed late relapses in 7.69% over 5 year follow up. One reason for high late relapse in our study could be due to presence of poor baseline predictors of response: obesity i.e., BMI>30 (n=3), alcohol intake (n=1) and cirrhosis (n=3). In addition, on retrospective analysis we found that mean dose of ribavirin and peginterferon used in these patients was suboptimal as dose reductions were required more frequently due to severe adverse effects. A theoretical explanation for late relapse could be persistence of undetected occult hepatitis C virus in hepatocytes, PBMCs, lymphocytes or macrophages.

There are several limitations of the study. Liver biopsy was not done. So histological relapse could not be seen. Similarly, retesting of genotype/sequencing was not done and possibility of re-infection cannot be ruled out.

SVR once achieved is sustained in majority of patients. The treating hepatologist need to be aware of occurrence of late relapses in patients with chronic HCV infection with cirrhosis.

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