RESPONSE RATES TO STANDARD INTERFERON TREATMENT IN HCV GENOTYPE 3A

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Background: Chronic Hepatitis C infection infects almost 130 to 170 million or approximately 2.2–3% of world's population. HCV is one of the main causes of chronic liver disease leading to progressive liver injury, fibrosis, cirrhosis and liver cancer. It is also one of the leading indications for liver transplantation worldwide. The objective of the study was to determine the response of treatment with standard Interferon and Ribazole in treatment naïve Hepatitis C infected patients. **Methods:** This quasi-experimental study was carried out at the Department of Medicine, KRL General Hospital Islamabad, from January 2003 to January 2005. A total of 250 patients were enrolled in this descriptive study. All patients were anti HCV positive, PCR positive for HCV RNA and had 3a genotype. A non-probability purposive sampling technique was applied to collect data. After taking a written and informed consent; specially designed performa containing the patient profile, family transmission, and baseline laboratory values was filled. Patients were treated with a set protocol of Interferon plus Ribavarin therapy (IFN alpha 2a, 3 mIU thrice weekly for 24 weeks plus Ribavarin 1,000 to 1,200 mg/day) for six months. Chi-Square tests were used to analyse the data. Primary end point was a sustained virological response (SVR) that is response assessed after six months of completion of treatment. **Results:** Response rates to standard Interferon plus Ribazole therapy were studied over two years period. Out of the total of 250 patients, 60 patients were excluded; as 30 patients did not meet inclusion criteria, 23 patients were lost to follow. Seven patients declined treatment. Out of the190 patients, 155 (81.6%) achieved End of Treatment Complete Response (EOTCR) whereas 35 (18.4%) were non-responders (NR). These 155 patients, who showed complete response were followed for six months after the treatment to assess sustained viral response, which was seen in 112 (72.25%) patients whereas 43 (27.7%) were relapsers. Response rates were co-related with gender, baseline ALT and necro-inflammatory stage assessed by liver biopsy, probable risk factors and family history. **Conclusion:** Management of Hepatitis C with genotype 3a, with standard Interferon and Ribazole for six months showed lower SVR compared to that reported in previous international and local data.

Keywords: HCV, Interferon, Response Rates, SVR.

INTRODUCTION

Chronic Hepatitis C infection infects almost 130 to 170 million or approximately 2.2–3% of world's population.[1] HCV is one of the main causes of chronic liver disease leading to progressive liver injury, fibrosis, cirrhosis and liver cancer.[2] It is also one of the leading indications for liver transplantation worldwide.[1]

It is estimated that there are approximately 10 million people infected with HCV in Pakistan with an average prevalence rate of 6%.[3] Multiple studies confirm that type 3 is the prominent genotype in Pakistan with the prevalence of between 75–90%.[4] Treatment of Hepatitis C virus has shown response rates of up to 80% in the easy to treat group as observed in western[5–13] and local studies[14–16]. However, we observed recently that the SVR appears to be lower in contrast to previously published data. Recent international studies using Pegylated Interferon also suggest that previous response rates were due to falsely assuming similar response rates in geno 2 and 3, with lower rates for geno 3. We know from studies in other infectious diseases that both bacterial and viral resistance factors and mutagencity causes shift in response rates.

In this study we attempted to identify the magnitude of this problem in a closed population and assessed the efficacy of the current regimen to achieve associated potential long-term benefits. This study was done to assess patterns of response in HCV infected patients with a standard treatment protocol and to see whether the current response rates are similar to those available in both international and local studies.

PATIENTS AND METHODS

Eligible patients were previously untreated adults who had HCV RNA detectable in serum by PCR with genotype 3a; All patients had liver biopsy done before the start of treatment to assess the degree of necro-inflammatory response to HCV, which was further sub grouped by HAI scoring system into mild, moderate & severe.

Patients included in the study had ALT values ranging from normal (>19 IU/L for men and 30 IU/L for

women) to 4 times the normal, with the minimum haematological and biochemical values of haemoglobin 10 g/dl for women and 13 g/dl for men; white blood count 3×10^9/L; platelet counts not less than 100,000/mm^3; and bilirubin, albumin, prothrombin time and creatinine within normal limits. Patients were excluded if they had decompensated cirrhosis; other causes of liver disease, seizure disorders, cardiovascular disease, haemoglobinopathies, thyroid disease, haemophilia, poorly controlled diabetes, autoimmune disease, previous organ transplant or if they were unable to use contraception.

This quasi-experimental study was carried out at the Medical Department of KRL General Hospital Islamabad from January 2003 to September 2005. All patients provided written informed consent. Instead of wait and see approach we treated all the patients with the same standard treatment to identify response in patients with different grades of liver injury and fibrosis.

All patients fulfilling the inclusion criteria were treated with Interferon 2b alpha 3 mIU subcutaneously three times per week, plus Ribazole 1,000–1,200 mg/day. The dose of Ribavarin was adjusted according to the body weight (1,000 mg for weight below 75 kg and 1,200 mg for weight 75 kg or more). It was given in two divided doses per day. Both drugs were started at the same time. Study treatments were administered for 24 weeks; with a subsequent 24-week follow up period. During treatment patients were assessed as outpatients at weeks 2, 4, 6, 8, 12 and 24 weeks after the end of the therapy. Qualitative PCR for HCV RNA was done before, at the end of the treatment and 24 weeks after the end of the treatment. At each visit, blood cell counts, platelet counts and ALT were measured and recorded. Side effects were also recorded at each visit and were graded as mild, moderate, severe and life threatening. Other adverse events were treated symptomatically.

The primary measure of efficacy was the sustained virological response (SVR), defined as undetectable HCV RNA in serum at the end of follow-up, i.e., 6 months after the treatment. Analyses were done on the whole treated population, i.e., all the patients who received at least one dose of study medication.

The distribution of individual characteristics was evaluated by simple descriptive statistics. To compare the overall distribution of response, end of treatment complete response, non-responder, relapse, sustained response and its association with different variables 2df Chi-Square test was used.

SPSS 11 software was used for statistical analysis and $p<0.05$ defined the statistical significance.

Enrolment began in January 2003 and was completed by 2004. A total of 250 patients were screened. Out of this group, 30 patients did not meet the inclusion criteria due to presence of decompensated chronic liver disease, confirmed by deranged synthetic functions of liver, episode of upper GI bleed or ultrasonographic evidence of cirrhotic liver, spleenomegaly and ascites. Twenty-tree patients were lost to follow up, 7 patients declined treatment.

RESULTS

All patients had a genotype 3a with almost equal number of males (4, 49.5%) and females (96, 50.5%), with different grades of liver injury. Demographic results are given in Table-1.

Table-1: Demographic results

Parameter	Mean±SD	Median	Range
Age (yr)	39.79±8.13	40	20–65
Weight (kg)	66±9.5	68	45–96
Alanine AminoTransferase (IU/L)	98±68.8	80	14–496
Hb gm/dl	13.3±1.89	13.6	9–17
Platelets mm^3	199,677±59,068	198,000	48,000–331,000
Family History (%)			
Positive			80.5
Negative			19.5
Risk Factors (%)			
Transfusion			17
Surgical			40
Dental			30
Injections			6
Sporadic/unknown			7

An EOTCR was seen in 155 (81%) out of 190 patients, whereas 33 (17.4%) patients did not respond to treatment and were non-responders. At EOT the results are in complete conformity with the western and local studies with approximately 81% of the patients showing EOTCR (Table-2).

Table-2: Outcome at EOT stage at 24 weeks (n=190)

	Number	%
End of treatment complete response	155	81.6
Non response	35	18.4

Patients showing EOTCR were followed for another 6 months to assess Sustained Viral Response. The SVR was calculated in the evaluable cohort of 155 patients. Out of these, 112 (72.25%) patients showed sustained response. Relapse was seen in 43 (27.7%) patients (Table-3).

Table-3: Outcome at SVR stage (48 weeks)

	n=155	%
Sustained virological response	112	72.3
Relapse	43	27.7

The influence of potentially important prognostic factors on SVR (HCV genotype, cirrhosis, age, gender, and baseline weight, activity at liver biopsy and probable risk factors) were examined individually.

Response rates were almost the same in both genders and the effect of gender on the outcome of response was not found to be statistically significant.

The maximum number of patients (62) who showed SVR were seen in the older age group (45–65 year) compared with the younger age group of 20–44 yrs. However this was not statistically significant (p=0.55). Non-responders and relapsers were almost equal in both the groups.

A positive family history was seen in 19.5% of patients. Out of these, 1/3rd of the patients were spouses of patients with previously known HCV infections, and the rest were siblings or offsprings of parents with HCV infection. There was no history of exposure to probable risk factors associated with HCV transmission in 34% of patients. Most of these patients were first diagnosed as anti HCV positive at the time of blood donations or before a surgical procedure or routine investigations. A history of surgical procedures was seen in 40% with 20.8% of the patients giving a history of dental procedure and 17% patients of having received blood transfusions. A history of receiving frequent injections from local GPs and clinics was seen in 8% of the patients while 3 patients (paramedical staff) had become infected following needle stick injury.

In this group of the patients the association of weight with the final response was found to be statistically significant (p=0.04). Most of our patients who showed SVR had an average weight of 55 to 70 kg as compared to relapsers and non-responders, who were overweight (>70 kg).

Most of the patients with SVR had ALT levels between 2 to 4 times normal but so did the non-responders and relapsers showing that the baseline ALT did not have a significant effect on the outcome of the treatment (p=0.468). ALT value of more than four times the baseline was only seen in 14 patients. No significant increase in ALT was observed in any patient during the study.

Out of the 112 patients who showed SVR, 49 patients had mild, 53 patients had moderate activity at liver biopsy whereas only 10 patients, who had marked activity, showed SVR. Most of the non-responders and relapsers had moderate to marked activity however this relationship between the sustained response and activity of liver disease was not found to be statistically significant (p=0.27).

Mild to marked degree of steatosis was seen in almost all patients. Favourable response was also significantly associated with degree of steatosis. Fifty-nine percent of the sustained responders had mild to moderate degree of steatosis. Most of the non-responders and relapsers had marked degree of steatosis, which was found to be statistically significant (p=0.015).

The side effect profile is given in Table-4. The most common side effects seen were influenza like symptoms with fever occurring in >80%, fatigue in >24% of our patients. Nausea was felt by >45% patients and vomiting was seen in >18% cases. Insomnia was seen in about 36% patients. Other side effects with combined Interferon and Ribazole therapy were seen in different percentages and were almost the same as reported in both local studies[14–16] and international studies.[12,17] The side effects were reasonably well tolerated and treated accordingly.

Table-4: Side Effects Profile (n=190)

Adverse Events	Number	%
Influenza like Symptoms		
Fever	153	80.5
Malaise	46	24.2
Myalgias	63	33.2
Gastrointestinal Symptoms		
Nausea	86	45.3
Anorexia	74	38.9
Vomiting	36	18.9
Psychiatric Symptoms		
Depression	25	13.1
Insomnia	68	35.8
Irritability	27	14.2
Haematological Symptoms		
Anaemia	63	33.2
Thrombocytopenia	38	20.0
Neutropenia	93	48.9
Dermatological Symptoms		
Rash	11	5.8
Pruritis	36	18.9
Redness at Injection Site	25	13.2

DISCUSSION

The current standard of care for patients with chronic HCV infection with genotype 2 and 3 is Interferon alpha 2a/2b in combination with Ribazole for six months. Response rates of up to 80% have been reported with similar treatment protocols in international[5–13] and local studies[14–16]. More recent international studies however have shown response rates, which are lower as compared to earlier landmark studies, i.e., 66% with pegylated interferon in genotype 3[10–13] with somewhat higher results in genotype 2[13]. Review of Pakistani studies has also shown non-consistent results with SVR ranging from 46%[14,] 78%[15] to 76%[16].

Latest data appears to confirm that response rates of up to 80% for genotype 3 are erroneous and were due to assuming similar response rates of genotype 2 and 3. However we cannot rule out shift in resistance of hepatitis C virus secondary to mutation in NS 5 region or decreased efficacy of interferon in hot climates. Our study has shown sustained response rates of 72% with standard treatment and relapse rates of 29%. However if non-responders are included in the relapser group; a non-responder rate 59% is seen.

This cohort of patients was remarkable as compared to other local population studies, in that the

patients had been on strict observed follow-up for at least twice monthly for the entire period of treatment, up to the SVR stage and beyond. Majority of this group has been in the easy to treat category, with mild to moderate disease, and minimal or up to stage 2 fibrosis. The mean age has been 40 years, which lies in the relative easy to treat group.

The study included almost equal numbers of either gender. As observed in the published data there is an increase prevalence of HCV infection and low response rates in males as compared to female.[17] In our study no statistically significant regarding the prevalence of disease was found (p=0.35).

Weight of the patients has also been an important factor in response to treatment. A low baseline body weight is a predictor of sustained viral response.[6] The association of weight with the final response was found to be statistically significant (p=0.04). The patients who were relapsers and non-responders were overweight. Although BMI is a more reliable predictor than weight some landmark papers studying the response rates with combined therapy has only considered body weight as compared to BMI.[10]

Elevated serum ALT levels indicate active liver disease however normal levels can be seen in up to 25% of patients with Chronic Hepatitis C.[19,20] Individuals with HCV may have normal ALT values. Some studies have also shown that patients with HCV and normal ALT are more likely to be women. This was also seen in our cohort of patients with ALT values of more than 4 times normal was seen in males (p=0.03).

In our patients, baseline ALT did not affect the SVR and was the same in those with normal versus raised ALT levels indicating that ALT is not a reliable indicator of either the presence and severity of the disease, as has been seen in studies by western authors in other genotypes.[20,21]

Liver biopsy is considered the gold standard for assessing hepatic histology in chronic hepatitis C. In our study, liver biopsy was performed in all patients. Biopsies were scored by the HAI Knodell index, for the degree of necroinflammatory changes and stage of fibrosis. In our data most of the patients showing a complete response had mild to moderate activity, while an increased rate of sustained virological responses was seen in patients who had moderate activity at liver biopsy. This group of patients is the most important group as successful treatment is likely to have the greatest impact by preventing progression to cirrhosis and its complications. Out of the 112 patients who showed SVR 49 patients had mild, 53 patients had moderate activity at liver biopsy whereas only 10 patients, who had marked activity, showed SVR. Most of the non-responders and relapsers had moderate to marked activity however this relationship between the sustained response and activity of liver disease was not found to be statistically significant (p=0.27).

Steatosis as part of histological feature of chronic hepatitis C has been described. Steatosis has been reported to be more common in patients with genotype 3 infections and its severity is directly related to degree of necroinflammatory change. Epidemiologic studies have shown that HCV related steatosis correlates with both patient factors, such as obesity as well as viral genotype.[22,23] The degree of steatosis has also been linked to the extent of hepatic fibrosis and patients with genotype 3 with steatosis were found to be at risk of accelerated fibrosis.[23,24] Patients with steatosis in particularly due to obesity or diabetes generally respond less frequently than patients without steatosis.[23] Mild to marked degree of steatosis was seen in almost all patients. Favourable responses were significantly associated with degree of steatosis, with 59% of the sustained responders having mild to moderate degree of steatosis compared to the non-responders and relapsers who had marked degree of steatosis. This difference was found to be statistically significant (p=0.015). Dietary counselling, good glycaemic control and weight reduction prior to initiation of therapy may improve therapeutic response.

Frequent use of injections for medical purpose or drug abuse is important routes of transmission of the virus. Those at risk include persons who have a history of repeated blood transfusions, surgical and dental procedures. In our study a history of surgical and dental procedures was seen in 45%. A small percent of our patients (up to 3%) had a positive family member or spouse infected with HCV. However in a large number of patients no risk factor was found.

The SVR in this study especially if we include the non responder group is lower as compared with other published data and needs to be evaluated. This becomes even more important in the context of shifts in the viral mutagencity, which is an integral property of the Hepatitis C virus. Other explanation like interferon resistance arising again as a result of above mentioned factors remain the likely probability. This can only be assessed with follow-ups of patients with viral sequencing with special reference to sub types and analysis of NS-5 region of viral genome.

CONCLUSIONS

The sustained viral response is lower in this study as compared to international and national data. The emergence of resistance, its clinical consequences, monitoring drug efficacy and finally managing resistance needs to be tackled on emergent basis. Refining our approach to management of patient with Hepatitis C genotype 3 has become imperative and attention to predictors of response and then tailoring duration of therapy, on the basis of responses at 4 or 12

weeks as is now being done for the more resistant genotypes, may lead to better outcomes.

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