INTRODUCTION

Hepatitis C virus (HCV) chronically infects approximately 180 million people worldwide\(^1\) and is a frequent cause of liver disease, including liver failure and hepatocellular carcinoma.\(^2\) Hepatitis C virus is a major cause of chronic liver disease worldwide.\(^3\) HCV is an RNA virus belonging to the family Flaviviridae, with an approximate diameter of 40-50 nm. The HCV genome is a single-stranded RNA molecule of 9500 kilo Daltons.\(^4,5\) HCV is a tremendous health problem not only in Pakistan but also throughout the world. About 200 million people are infected with HCV worldwide, which covers about 3.3% of the world’s population.\(^6,7\) In Pakistan more than 10 million individuals are living with HCV with high morbidity and mortality.\(^8\) Despite the employment of modern laboratory apparatus for the screening of blood, blood transfusion remains the main mode of transmission of HCV infection, since unscreened blood and blood products are still used in many developing countries. As a result, HCV is one of the most common blood-borne infections.\(^9\)

National Institute of Health (NIH) has recommended interferon (INF) as the standard therapy for chronic hepatitis C.\(^10\) It is given subcutaneously at doses of three million units three times a week for 24 weeks.\(^11\) Exogenous INF is a group of cytokines that exhibit antiviral effects via immunomodulation and ribavirin is a guanosine analogue.\(^12\) The duration of therapy depends on the genotype and level of viremia. In patients with genotype 2 or 3, the duration is 24 weeks, while patients with genotype 1 need 48 weeks of treatment.\(^11,13\)

The ability to accurately predict the response of patients to antiviral therapy is of great interest. In general, predictors may be clinical, biochemical or histological. They can be assessed before therapy is started (pre-treatment predictors) or during therapy (on-treatment predictors). Preferably the on-treatment predictors should be available early in the treatment course so that patients who are unlikely to respond can have their treatment stopped and those who are likely to respond can be encouraged to complete therapy. This drug regimen is very expensive and in Pakistan 10 million individuals have difficulty in affording this therapy.

ABSTRACT

Objective: To determine the efficacy of interferon-ribavirin therapy for chronic viral Hepatitis C (HCV) patients.

Study Design: A quasi-experimental study.

Place and Duration of Study: Medical Unit-III, Ward-7, Jinnah Postgraduate Medical Centre, Karachi, from August 2006 to December 2007.

Methodology: Adult patients who had not received any prior anti-HCV therapy and had been infected with positive anti-HCV antibodies and detectable HCV RNA were enrolled in the study. Patients were excluded from the study if there was evidence of decompensated cirrhosis, coexistent HIV, or HBV infection, previous organ transplantation, psychiatric disease, seizure disorder, serious cardiovascular disease and other co-morbid diseases like uncontrolled Diabetes. Patients were given Interferon-alfa-2b 3 million international units three times a week sub-cutaneously and oral ribavirin at 1000-1200 mg in two to three divided doses a day for a 6-month period. At the end of treatment over all efficacy as depicted by non-detectable HCV RNA by PCR and its relation with factors of like age, gender, and serum ALT were assessed.

Results: A total of 404 patients with mean age of 36.03±9.30 years, ranging from 13 to 60 years, were offered combination therapy that satisfied the inclusion criteria. Among these, females were 243 (61.1%) and males were 161 (39.9%), age range 13-60 years with mean of 36.03 years. Out of 404, 336 (83.2%) showed response to combined interferon and ribavirin therapy depicted by HCV RNA by PCR at the end of 24 weeks treatment. Age under 40 years (p < 0.001) was significantly associated with favourable response.

Conclusion: Combination therapy of interferon and ribavirin in chronic hepatitis C patients has still better response rate in our set-up. Younger age and female gender were the favourable predictors.

Key words: Interferon. Ribavirin. Chronic hepatitis C. Age.
Therefore, early discontinuation of treatment in non-responders could avoid the expense and inconvenience of continuing unnecessary treatment.

The aim of this study was to investigate overall response of conventional interferon and ribavirin therapy and also to identify the factors that influence response to antiviral therapy.

**METHODOLOGY**

This quasi-experimental study was conducted in the setting of Prime Minister’s Program for prevention and control of Hepatitis at Medical Unit III, Jinnah Postgraduate Medical Centre, Karachi, from August 2006 to December 2007. Adult native patients of either gender and all ages infected with hepatitis C virus (HCV) were enrolled in the study. All patients had anti-HCV antibodies detectable levels of HCV RNA in the serum by polymerase-chain-reaction (PCR). HCV genotyping and viral load were not performed because of technical and financial constraints.

Patients were excluded from the study if there was evidence of decompensated cirrhosis, patients with co-infection of either HIV or HBV infection, previous organ transplantation and patients with absolute or relative contraindication to interferon ribavirin therapy like psychiatric disease, seizure disorder, serious cardiovascular disease or other co-morbid diseases like uncontrolled diabetes or ongoing substance abuse and when the patients were unable to use contraception. Decompensated cirrhosis assessed clinically and in suspected cases abdominal ultrasound, upper GI endoscopy and liver biopsy parameters were used if needed.

The blood values (haemoglobin > 12 gm/dL; white blood cells count > 4,000/mm, platelets > 110,000/mm) and biochemical values of normal bilirubin, albumin and creatinine levels were considered as strict inclusion criteria. All patients were evaluated clinically for autoimmune hepatitis and in suspected cases the presence of antinuclear antibodies (ANA) carried out. After informed consent the interferon-alfa-2b 3 million international units three times a week subcutaneously and oral ribavirin at 1000 mg (< 75 kg body weight) or 1,200 mg (> 75 kg body weight) in two to three divided doses a day were given to patients for a 6-month period. HCV RNA by PCR qualitative has been done before and after treatment. All patients were followed-up in the outpatient clinics every month until treatment was completed. Haematological and biochemical assessment carried out on each follow-up visit. At the end of treatment over all efficacy of combined therapy as depicted by non-detectable HCV RNA by PCR and effects of host related factors like age, gender, and serum ALT were assessed and analyzed by applying chi-square test and using SPSS 15.0 statistical program. Significance was kept at p-value of less than 0.05

The measure of efficacy was the end treatment response (ETR). In accordance with the NIH consensus statement, the end of treatment response (ETR) was defined as when a patient achieved undetectable serum HCV RNA levels at the end of therapy. Patients for whom HCV RNA levels remained detectable at the end of treatment were considered Non-responders (NR).

**RESULTS**

A total of 512 patients were assessed for eligibility out of whom 428 patients were enrolled in the study. Four hundred and four patients completed combination therapy and came back with ETR reports (Figure 1). Among those 243 (61.1%) were females and 161 (39.9%) were males. The mean age of patients was 36.03±9.30 years, ranging from 13 to 60 years. Out of 404, 336 (83.2%) responded to combined interferon and ribavirin therapy depicted by negative HCV RNA by PCR at the end of 24 weeks treatment. Over all 336 (83.2%) patients turned out to be responders to combination therapy while on the basis of age, younger patients of age ≤ 40 years showed significant response of (88.54%) as compared to older patients aged > 40 years (69.83%) (p=0.0001, Table I).

On the basis of gender, female patients showed the response rate of 84.8% vs. male patients 30.7% which was statistically not significant (p=0.289). Regarding baseline ALT levels; 120 patients (29.7%) had normal ALT levels of less than or equal to 40 IU/L, 158 (39.11%) patients had 41-80 IU/L, 62 (15.35%) cases had 81-120 IU/L and 64 (15.84%) patients presented with ALT...
Analysis of baseline characteristics of responders and non-responders

Table I: Base line characteristics of responders and non-responders patients.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Responders</th>
<th>Non-responders</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td>Total</td>
<td>336 (83.2%)</td>
<td>68 (16.8%)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>≤ 40</td>
<td>288</td>
<td>33 (11.46%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>&gt; 40</td>
<td>116</td>
<td>35 (30.17%)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>243</td>
<td>37 (15.2%)</td>
<td>0.289</td>
</tr>
<tr>
<td>Male</td>
<td>161</td>
<td>31 (19.3%)</td>
<td></td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 40</td>
<td>120</td>
<td>18 (15%)</td>
<td>0.047</td>
</tr>
<tr>
<td>&gt; 40</td>
<td>128</td>
<td>41 (33.33%)</td>
<td></td>
</tr>
<tr>
<td>Haemoglobin (gm/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 12</td>
<td>149</td>
<td>24 (16.1%)</td>
<td>0.766</td>
</tr>
<tr>
<td>&gt; 12</td>
<td>255</td>
<td>44 (17.26%)</td>
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<tr>
<td>Platelets (count/µL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 150000</td>
<td>62</td>
<td>14 (22.58%)</td>
<td>0.188</td>
</tr>
<tr>
<td>&gt; 150000</td>
<td>342</td>
<td>54 (15.79%)</td>
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</tr>
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levels of ≥ 121 IU/L. The patients who had normal to moderately elevated ALT levels showed significantly better response vs. markedly elevated ALT levels group (p=0.047).

Base line haematological parameters like haemoglobin level and platelet count did not have significant effect on efficacy of combination therapy.

DISCUSSION

An optimal way to manage antiviral therapy in patients with chronic hepatitis C would be to treat only those patients who will become responders and also because of considerable side effects and treatment costs, it is highly desirable to identify virologic non-responders as early as possible. Keeping this in mind a wide range of pretreatment factors, both viral-related and patient-related are evaluated to determine to predict successful outcome before initiating IFN therapy. However, the use of these does not accurately predict response in all patients. Also, deciding not to initiate treatment should not be based on the presence or absence of one pre-treatment factor.

Combination therapy with interferon-alpha and ribavirin has resulted in two to three folds improvement in virological response to the disease. Response rates have been found to be favourable in 80-85% of chronic hepatitis C patients with genotypes 2 and 3 which are pre-dominant in Pakistan. In genotypes 1 and 4 as is prevalent in America and Europe, response rates have been found to be 60-70% with INF and ribavirin and may require 48 weeks treatment. Pegylated interferon has now replaced standard interferon alpha for chronic hepatitis C patients. Because of the pre-dominance of genotypes 2 and 3 in Pakistan, the response rate to combination therapy with interferon plus ribavirin is close to the result achieved with pegylated interferon. It is, therefore, recommended to use pegylated interferon not routinely but only for non-responders.

In the present study, 336 out of 404 (83.2%) patients of chronic hepatitis C showed favourable response to combined interferon and ribavirin therapy depicted by negative HCV RNA by PCR at the end of 24 weeks of treatment. This supports a number of earlier studies showing that, combination therapy is significantly effective in patients of chronic hepatitis C in our part of the world probably because of prevalence of genotypes 2 and 3. The genotype and age of patients are the only two independents factors influencing efficacy of treatment either as an end treatment or sustained response. Although the definite evidence is not available as genotyping was not done in this study because of financial constraints. But regarding age, these findings are also reported in other studies.

In this study younger patients had shown significant better response rate than the older ones probably due to their better immunological response and adhesion to therapy. Older patients are less likely to response to treatment and are less likely to have sustained responses regardless of genotype and other baseline characteristics. Immunological suppression, chronic disease and other medication use in the elderly age group can significantly impair the drug response.

This study also demonstrated that female gender had a favourable response to standard interferon and ribavirin combination therapy vs. male gender, the reason might be hormonal, but it did not show statistical significance.

Base line ALT level of studied patients had significant effect on response rate that normal to moderate elevation of ALT had better response than the markedly elevation. This might be due to the depth of hepatic damage as the serum ALT reflects the liver cells damage, but this hypothesis should be tested through additional research on a larger scale.

The present data suggest a need for additional research to test the hypothesis that host and virologic factors like age, gender, weight, ALT levels on a larger scale that can predict the response of standard interferon and ribavirin combination therapy before and/or during therapy.

CONCLUSION

This study re-confirmed that combination therapy of interferon and ribavirin in chronic hepatitis C patients has better response rate in our set up, furthermore the host related factors like younger age and elevated ALT level are significant reliable predictors of combination therapy while gender has no significant effect on response to combination therapy.
REFERENCES


