Treatment of Genotype 3a Relapsers of Chronic Hepatitis C and its duration

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Abstract

Background: To gauge the result of re-treatment in relapsers of Chronic Hepatitis C infected with genotype 3a and to determine whether a 24-week course of treatment is sufficient in them.

Methods: This prospective study was conducted in Consultant Clinics by the clinical teaching staff of Department of Medicine, Rawalpindi General Hospital and Rawalpindi Medical College from September 2006 to April 2008. Twenty-eight patients (15 males and 13 females) of Chronic Hepatitis C infected with genotype 3a who had relapsed after successful treatment with conventional interferon and ribavirin were included. They were assigned to two groups. Group A patients (12 in number) were put on pegylated interferon alfa-2b subcutaneously once a week and ribavirin 400 mg twice daily. Group B patients (16 in number) received conventional interferon 3 million units subcutaneously thrice weekly, ribavirin in the same dose as group A patients plus a hydrolytic enzymes and rutbsid preparation. Both groups received treatment for twenty-four weeks. The results were assessed.

Results: The age of patients studied ranged from 33 to 61 years. Average age of males was 43.6 years and of females 45.2 years. End treatment response was obtained in 9 out of 12 patients (75%) in Group A and 11 out of 16 patients (68.7%) in Group B. End-treatment biochemical response was 75% in both groups. However sustained virological response was documented in 50% patients of Group A and 43.8% of patients in Group B.

Conclusion: Treatment with pegylated interferon and ribavirin remains the better option for treatment of chronic hepatitis C relapsers infected with genotype 3a. A 24-week course of treatment is associated with unsatisfactory sustained virological response levels. A 48-week course, the same as recommended for non-responders of the genotype, needs to be adopted.

Key Words: Genotype 3a, Relapsers, Chronic Hepatitis C

Introduction

Approximately 3% (170 million) of the world’s population has been infected with Hepatitis C virus (HCV). The prevalence varies from 3% in western countries to over 15% in Egypt. In Pakistan, the prevalence of HCV in the general population is estimated at about 4%. This constitutes a pool of seven million individuals of which 80% can go on to develop chronic liver disease. The most common genotype in our country is type 3a which is present in about 80% of chronic hepatitis C (CHC) patients. This genotype has generally been considered the lesser evil and associated with an end treatment response (ETR) of over 80% and sustained virological response (SVR) approaching 75% with conventional (standard) interferon and ribavirin. However recent studies do not portray such an encouraging scenario. We report here 28 relapsers of CHC with genotype 3a who had previously been successfully treated with conventional interferone and ribavirin for 24 weeks. The purpose of the study was to gauge the result of re-treatment in relapsers of chronic hepatitis C infected with genotype 3a and to determine whether a 24-week course of treatment is sufficient in them.

Patients and Methods

This prospective study was conducted in Consultant Clinics by the clinical teaching staff of Department of Medicine, Rawalpindi General Hospital and Rawalpindi Medical College from September 2006 to April 2008. Twenty-eight patients (15 males and 13 females) of Chronic Hepatitis C infected with genotype 3a who had relapsed after successful treatment of the infection were included in the study. All had received conventional interferon 3 million units subcutaneously thrice weekly plus ribavirin 400
mg twice daily for a 24-week period. All had undetectable HCV RNA by the end of the stipulated period. These patients were now recommended treatment with pegylated interferon and ribavirin. Twelve patients agreed and were assigned to Group A. Sixteen patients expressed inability due to the exorbitant cost involved and were designated as Group B (Table 1).

Group A patients received pegylated interferon alfa-2b once a week in a dose of 1.5 mcg/kg body wt. subcutaneously up to a maximum of 150 mcg/week and ribavirin 400mg twice daily for a period of 24 weeks.

Group B patients received conventional interferon in a dose of 3 million units subcutaneously thrice weekly and ribavirin 400mg twice daily. To this was added a hydrolytic enzymes and rutosid preparation (phlogenzym) in a dose of two tablets thrice daily, half an hour before meals. Duration of treatment was also 24 weeks.

None of the patients included had any sign of hepatic decompensation. Patients with a major contraindication to the aforesaid drugs and those with a history of alcohol intake were excluded from the study.

Complete blood counts and serum alanine aminotransferase (ALT) levels were obtained before initiating treatment. These were repeated after two weeks and then every three weeks for the duration of treatment. HCV viral load, ultrasound abdomen and prothrombin time were obtained before the start of therapy. HCV RNA was determined at 12 weeks and at the end of twenty-four week period.

Relapsers were defined as patients who had undetectable viremia during and/or at the end of initial treatment but had detectable virus after treatment was stopped.

End treatment virological response (ETR) was indicated by undetectable HCV RNA at the end of therapy.

Sustained virological response (SVR) was documented in 6 out of 12 patients (50%) in Group A while 3 patients with ETR failed to demonstrate SVR.

In both groups, patients exhibiting SVR had a viral load ranging from 300,000 to 2.3 million IU/ml at the start of treatment. The highest pre-treatment viral load noted was 7.8 million IU/ml in a male patient of Group A who failed to achieve ETR.

Initial ALT levels in male patients showing SVR ranged from 65 u/L to 218 u/L. In female patients with SVR it ranged from 58 u/L to 188 u/L. One patient in Group A and three patients in Group B who failed to show ETR had pre-treatment ALT ranging from 46 to 78 u/l.

**Table 1: Patients in Study (n=28)**

<table>
<thead>
<tr>
<th>Patients</th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td>Male</td>
<td>6</td>
<td>9</td>
</tr>
</tbody>
</table>

| Female | 6 | 7 |

**Results**

The age of patients studied ranged from 33 to 61 years. The average age of males was 43.6 years and that of females 45.2 years, there being no significant difference among the two groups.

End treatment virological response was obtained in 9 out of 12 patients (75%) in Group A of which 5 were male and 4 female. In Group B it was seen in 11 out 16 (68.7%) patients of whom six were male and five female. (Table 2)

End treatment biochemical response was observed in the same 9 patients of Group A who exhibited end treatment virological response. In Group B, ALT levels fell to normal in 12 (75%) patients.

Sustained virological response (SVR) was documented in 6 out of 12 patients (50%) in Group A while 3 patients with ETR failed to demonstrate SVR.

In Group B, SVR was seen in 7 out of 16 patients (43.8%), with 5 patients with ETR failing to show SVR.

**Table 2: Response to Treatment**

<table>
<thead>
<tr>
<th>Response</th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virological</td>
<td>9/12 (75%)</td>
<td>11/16 (68.7%)</td>
</tr>
<tr>
<td>Biochemical</td>
<td>9/12 (75%)</td>
<td>12/16(75%)</td>
</tr>
<tr>
<td>Sustained</td>
<td>6/12 (50%)</td>
<td>7/16(43.8%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Response</th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>5/6</td>
<td>6/9</td>
</tr>
<tr>
<td>Females</td>
<td>4/6</td>
<td>5/7</td>
</tr>
<tr>
<td>Males</td>
<td>5/6</td>
<td>7/9</td>
</tr>
<tr>
<td>Females</td>
<td>4/6</td>
<td>5/7</td>
</tr>
</tbody>
</table>
Males 3/6 4/9
Females 3/6 3/7

Discussion

HCV genotype 3 is associated with a better response to the interferon-ribavirin combination compared to other genotypes except possibly genotype 25. Studies have shown that genotype 3 patients achieve a similar response with high and low-dose peg-interferon alfa 2b regimens6. Some have even found virological response to be similar in genotype 3 patients treated for 12 or 24 weeks with interferon and ribavirin7.

In Pakistan, a rather rosy picture of CHC has been painted in the past as far as the prevalent genotype is concerned. We are thought to be ‘blessed’ with genotype 3 and doubly blessed since genotype 1, the ‘black sheep’ of the family is least prevalent here. Since the response rates to treatment are so good with genotype 3, a liver biopsy is not deemed necessary before initiating treatment. Regarding re-treatment in relapsers of this genotype, a 24-week course was considered sufficient in the past.

All such concepts are rapidly changing as an increasing number of relapsers and non-responders carrying genotype 3a emerge. Researchers in one local study involving a single centre detected 58 non-responders of genotype 3a in 2005 alone8. All had received a twenty-four week treatment course of conventional interferon and ribavirin.

Genotype 3a relapsers are now increasing because of important reasons. Our first such patient (genotype was confirmed when the facility became available) received conventional interferon monotherapy in 1991-92 at Holy Family Hospital Rawalpindi, the first time it was used there. The product was not locally available then. He responded but relapsed in 1997. By this time ribavirin had also come into use, which he received in combination with conventional interferon and ribavirin.

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Pegylated interferon in combination with ribavirin is associated with a better ETR9 and 10-11% better SVR10 compared to a combination of conventional interferon and ribavirin. Hence pegylated interferon plus ribavirin is now recommended as the treatment of choice in the management of CHC non-responders and relapers10,11.

A SVR of 39% to 47% is achieved when treating genotype 2 or 3 relapsers of interferon monotherapy or interferon plus ribavirin combination therapy. Our study showed a SVR of 50% in Group A and 43.8% in Group B there by demonstrating the superiority of pegylated over conventional interferon. However the SVR after one or two years of cessation of treatment could not be assessed considering the recent duration of our study and some patients being lost to follow-up soon after attaining SVR. However it can only be expected to decline in the subsequent years. Moreover the relatively small number of patients in our two groups may not fully reflect the overall situation as a shift of even two patients would significantly alter the findings. Multi-centre studies involving larger groups of patients conducted over a longer period of time are required to resolve this issue.

The significant decline of ETR from 75% to a SVR of 50% in Group A and ETR of 68.7% to a SVR of 43.8% in Group B clearly indicates that a treatment period of 24 weeks is not sufficient when treating genotype 3a relapers of CHC. We tend to agree with those who suggest the treatment duration should be the same as that followed for non-responders of this genotype i.e 48 weeks. Some researchers in fact recommend the 48 week course even as initial treatment in genotype 3 patients with viral loads exceeding 400,000 IU/ml12. This would pose a formidable challenge in our perspective since few patients would be able to afford pegylated interferon for this time period. The practical alternative would then be conventional interferon plus ribavirin with perhaps a newer drug.

A significant percentage of our patients failed to achieve ETR and SVR even with pegylated interferon. Most had high viral loads before initiation of treatment. Unfortunately such individuals still represent an important class of CHC patients. Despite recent improvement in the efficacy of antiviral therapy, their number shows no signs of abating. Attempts to enhance the efficacy of antiviral response by other drugs given as re-treatment has produced mixed results13,14. Hopefully better agents will become available in the near future.
Biochemical response is usually achieved more frequently than virological response after treatment with conventional interferon with or without ribavirin. In our study, the biochemical response in Group B patients, the group receiving hydrolytic enzymes plus rutosid (in addition to conventional interferon and ribavirin) matched that of Group A patients (75% each). We partially attribute it to this enzyme preparation.

The role of hydrolytic enzymes plus rutosid still remains to be defined in CHC. The activity and formation of these enzymes with plant derived rutin, bromelain and trypsin have previously been used to promote the rapid breakdown of inflammatory metabolic products with rutin restoring the permeability of vascular walls there by accelerating the subsidence of swellings and haematomas. The use of this product in CHC is purportedly based on its activity as a biological response modifier where by it would exert its anti-viral effects by activation of NK-cells and macrophages which in turn would lead to increased interferon production and ETR rates as high as 40%.

Our relatively recent experience with this preparation, as yet unpublished data, suggests it is quite effective in lowering ALT levels. This effect becomes noticeable about 4 to 6 weeks after initiation of therapy. Also, most patients experience a positive change in their quality of life. Regarding efficient ETR rates we do not yet have sufficient data to comment either way.

Our results showed pre-treatment ALT levels to be minimally and mildly elevated in a significant percentage of patients of both groups who did not achieve ETR. This has also been noted by other researchers in genotype 3a non-responders. High pre-treatment ALT (>3 times normal) is associated with a good response rate.

In conclusion, there is an increasing pool of CHC genotype 3a relapsers. Treatment with pegylated interferon plus ribavirin remains the better option for them. A 24-week course of treatment is associated with unsatisfactory SVR levels. A 48-week course, the same as recommended for non-responders, needs to be adopted. The role of hydrolytic enzyme preparations needs further investigation.

References

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