LETTER TO THE EDITOR

Active Disease in Chronic Hepatitis C Patients with Normal Alanine Aminotransferase

Sir,

Arif et al.1 recently published reporting showing a large proportion of chronic hepatitis C (CHC) patients (most of them were genotype-2 and 3) with normal alanine aminotransferase (ALT) have insignificant fibrosis indicating non-active disease. Therefore, the authors recommended that a liver biopsy should be done in all cases with normal ALT before deciding antiviral therapy. This study is important but there is a paucity of cases with genotype-1, we planned a retrospective study to evaluate the proportion of fibrosis in only genotype-1 CHC patients with normal ALT.

Genotype-1 CHC patients, who had normal ALT levels (male=40 IU/L, female=30 IU/L as the limit of normal values) and detectable HCV-RNA were included in this study. Patients with raised ALT, albumin less than 3 grams, prolonged prothrombin time, platelets less than 50,000, and any sign of liver decompensation and those patients who had previously received antiviral therapy were excluded from the study. All patients had undergone a liver biopsy. Liver histology was graded according to the criteria of Ishak et al.2 The study was approved by our institutional review board and fully informed consents were obtained from all patients. The statistical analyses were performed with SPSS for Windows Release 18.0.0 (SPSS Inc., Chicago, IL, USA). Student's t-test was used to assess the significance of characteristics between groups. A p-value < 0.05 was considered significant.

A total of 44 patients fulfilling the inclusion criteria were enrolled in the study. Using Ishak scoring, insignificant fibrosis of < 3 was seen in 24 of the patients (54.5%). Twenty patients (45.5%) had fibrosis score of ≥ 3, and 13 (65%) out of these 20 patients also had significant inflammation score ≥ 9 (p < 0.001, Table I).

Many anti-HCV positive patients with normal serum ALT concentrations have an abnormal liver biopsy, although the changes are usually mild.3,4 In this study, more patients with normal ALT had significant fibrosis (≥ 3) compared with the study of Arif et al.1 One reason of this may be the high average age of our patients. As is known, the development of fibrosis usually requires several months to years of ongoing injury.

In conclusion, the data have shown that higher rates of fibrosis must be expected in genotype-1 CHC patients with normal ALT unlike the study of Arif et al.1 So, treatment may be considered in elderly genotype-1 CHC patients with normal ALT without liver biopsy.

REFERENCES


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Table I: Characteristics of patients related to liver fibrosis.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall (n=44)</th>
<th>Insignificant fibrosis (stage 0-2, n=24)</th>
<th>Significant fibrosis (stage 3-6, n=20)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years (min-max)</td>
<td>58.4 ± 8.1 (38-75)</td>
<td>57.6 ± 8.1 (43-75)</td>
<td>59.2 ± 8.3 (38-74)</td>
<td>0.516</td>
</tr>
<tr>
<td>Male, no (%)</td>
<td>21 (47.7)</td>
<td>11 (45.8)</td>
<td>10 (50)</td>
<td>0.789</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>26.8 ± 7.7</td>
<td>27.0 ± 7.0</td>
<td>26.5 ± 8.7</td>
<td>0.820</td>
</tr>
<tr>
<td>HCV-RNA (log 10 IU/ml)</td>
<td>5.7 ± 1.2</td>
<td>5.7 ± 1.1</td>
<td>5.7 ± 1.3</td>
<td>0.771</td>
</tr>
<tr>
<td>ISHAK Score, mean ± SD</td>
<td>7.8 ± 3.3</td>
<td>6.5 ± 2.0</td>
<td>9.4 ± 3.9</td>
<td>0.002</td>
</tr>
<tr>
<td>Histological activity index</td>
<td>2.6 ± 1.4</td>
<td>1.5 ± 0.7</td>
<td>3.9 ± 0.9</td>
<td>0.000**</td>
</tr>
<tr>
<td>Cirrhosis (F5-6), no (%)</td>
<td>4 (9.1)</td>
<td>0</td>
<td>4 (20)</td>
<td>0.021</td>
</tr>
<tr>
<td>Severity of inflammation, no (%)</td>
<td>29 (65.9)</td>
<td>22 (91.7)</td>
<td>7 (35)</td>
<td>0.000**</td>
</tr>
<tr>
<td>Insignificant (Grade 0-8)</td>
<td>15 (34.1)</td>
<td>2 (8.3)</td>
<td>13 (65)</td>
<td>0.000**</td>
</tr>
</tbody>
</table>

*p<0.001; **p < 0.001; ALT = Alanine aminotransferase.
Authors’ Reply

Sir,

In response to the letter from Umit et al. on our study; Active disease in chronic hepatitis C patients with normal alanine aminotransferase; Umit et al. are not disagreeing to our findings but are showing their results where they had many cases with advanced disease on histology. The major difference in their study is the genotype. Ours cases mostly had genotype 3 and theirs had genotype-1.

International literature very clearly shows that genotype-1 is a rapidly progressing, difficult to treat disease with variable ALT values (normal or raised). The genotype-1 requires 12 months of treatment and still has a high non-response and relapse rates and therefore, recently triple drug therapy has been recommended to treat these cases. Genotype-3 patients have a slow progressing, easy to treat disease with 6 months therapy. ALT levels in many of these patients are not raised for years, creating among treating physicians confusion whether to treat them or wait. A liver biopsy was, therefore, suggested by APASL almost a decade ago to assist in decision making for the treatment of genotype-3 patients with normal ALT.

As health care in Pakistan is not supported by the State, most patients spend out of pocket. Treatment is expensive; therefore, to reduce the anxiety of the patients and assist the physician in decision making we provided an evidence that many of these patients do not need treatment, who are not developing fibrosis inspite of HCV infection.

Although the ideal scenario would be to treat all anti-HCV, PCR positive patients irrespective of disease activity and their ALT levels or degree of liver fibrosis (documented on liver histology) but the rationale to treat the patient should be individualized through adoption of standard guidelines while treating patients with normal ALT especially without any fibrosis on liver biopsy.

Recent literature search also shows that treatment of hepatitis C genotype-3 is not a walk through as thought earlier. It is potentially the most difficult genotype to treat and hence an intense area of on going research for new drug development. Hence one needs to tread very carefully while treating this group of patients.

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