Active Disease in Chronic Hepatitis C Patients with Normal Alanine Aminotransferase

Ambreen Arif1, Waquaruddin Ahmed1, Syed Ejaz Alam1 and Huma Qureshi2

ABSTRACT

Objective: To quantify liver damage using Metavir score, in chronic hepatitis C patients having normal alanine aminotransferase (ALT) to determine active disease requiring treatment.

Study Design: An analytical study.

Place and Duration of Study: Pakistan Medical Research Centre, JPMC, Karachi, from January 2007 - December 2010.

Methodology: Patients suffering from hepatitis C with positive PCR, having persistently normal ALT on 3 separate occasions over a 6 months period and also having normal platelets and albumin were included in the study. After written consent, all patients underwent a liver biopsy and the degree of damage was assessed using Metavir scoring system.

Results: A total of 99 patients suffering from chronic HCV were included in the study. A majority of the patients (55.6%) were females. Using Metavir score, minimal fibrosis of ≤ 1 was seen in majority (78.8%) of the patients. Only 21.2% patients had fibrosis score ≥ 2, with 16 (47.1%) of these also having inflammatory score ≥ 2 (p < 0.001). The age of patients (mean 38.1 ± 10.2 years) had a significant association with the severity of liver damage (p < 0.001) as compared to younger age group (mean 33.1 ± 9.8 years).

Conclusion: A large proportion of patients with normal ALT have insignificant fibrosis indicating non active disease and thus questions the blanket use of interferon in all HCV RNA cases. It is strongly recommended that a liver biopsy should be done in all cases with normal ALT before deciding antiviral therapy.

Key words: Chronic hepatitis C. Alanine amino-transferase. HCV RNA. Liver biopsy.

INTRODUCTION

Chronic hepatitis C virus is a global health problem with a worldwide prevalence of ≈ 3% (approximately 170 million people).1 Hepatitis C virus infection without specific HCV treatment will clear in 20-50% cases,2 while 50- 80% will develop chronic infection, which is generally asymptomatic. Even asymptomatic disease may progress to chronic liver disease, cirrhosis and hepatocellular carcinoma over 10 - 30 years, hence making it an important public health issue.

Though most cases with active disease have elevated ALT levels but approximately 30-40% patients may have an active disease with normal ALT levels.3 Previously terms like 'healthy' or 'asymptomatic' have been used for this particular group, but majority of these patients had some degree of liver damage,4,5 documented on histology. This quiescent phase of the disease may go unnoticed for many years and might be noticed in an advanced stage where patient is not fit to receive the recommended treatment.

World Health Organization (WHO) defines chronic hepatitis C as a high burden of disease for Pakistan, with an intermediate prevalence of 4.9%6 which is quite alarming, with some districts of Sindh and Punjab having much higher prevalence.

Interferon combination therapy is an effective treatment modality for patients having chronic hepatitis C, who fulfill the criteria for chronic liver disease (i.e. raised ALT value more than twice the upper limit of normal for 6 months along with sero-positivity for anti-HCV and a positive HCV RNA). Recommendations for treatment of patients having normal ALT still remains a matter of debate. Many liver associations except American Association for the Study of Liver Diseases (AASLD) still defer interferon treatment in patients with normal ALT and recommend regular follow-up of these patients. Keeping in mind the local economic situation and the fact that treatment cost in most cases is beared by the patients, there is a dire need to review patients who should be treated and who should be followed.

To resolve this issue and to develop our own strategy according to the local perspective, the present study was conducted on liver biopsy grading of disease in patients having chronic hepatitis C with positive HCV RNA and normal ALT levels and thus decide how many have active liver disease and are candidates for treatment.

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METHODOLOGY

It was an analytical study done from January 2007 to December 2010. It was done on chronic hepatitis C patients (positive anti-HCV on ELISA), who had normal ALT levels and detectable HCV RNA. These patients came for the treatment of their liver disease to the outpatients department of Pakistan Medical Research Centre, Jinnah Postgraduate Medical Centre. All patients had normal ALT (male = 40 IU/L, female = 30 IU/L as the limit of normal values) on three separate occasions 6 months apart. An informed written consent was taken from all the patients who agreed to be included in the study and strict confidentiality was maintained. Blood samples were taken for haematology (CBC), biochemistry (liver function tests, serum proteins and albumin) and prothrombin times. Ultrasound of abdomen was also obtained. Alfa-fetoprotein was done when required.

Patients with raised ALT, albumin less than 3 grams, prolonged prothrombin time (more than or equal to one and half time normal), platelets less than 50,000, and any sign of liver decompensation or cirrhosis and those patients who had received antiviral therapy in the past were excluded from the study. Chronic hepatitis C was defined as a patient with normal ALT, reactive anti-HCV antibodies test on ELISA, detected HCV RNA and normal alanine aminotransferase at least on three occasions 2 months apart over a period of 6 months.7

A liver biopsy was performed under strict aseptic measures with a Surecut biopsy needle and the specimen collected in formalin was sent for histopathology to Ziauddin Medical University. Trichome stain was used for evaluation of fibrosis. The biopsies were scored by a single pathologist (who was blinded to clinical data of the patient) according to the Metavir index and scoring for inflammatory activity was done on a 4-point scale from 0-4 and fibrosis score on a 4-point scale from 0-4.8 All demographic, clinical, biochemical and virological parameters were documented.

Data was analyzed using statistical software SPSS (Statistical Package of Social Sciences) 11.0. In the results, mean ± S.D was reported for quantitative variables and number and percentage for qualitative variables. Differences between groups were compared using Student's t-test for quantitative variables and Chi-square test/Fisher's exact test for qualitative variables. A p-value < 0.05 was considered significant.

RESULTS

A total of 99 patients suffering from chronic HCV and fulfilling the inclusion criteria were enrolled in the study. There were 44 males (44.4%) and 55 females (55.6%) with age range of 15-60 years; mean age was 34.1 ± 10.1 years. None of the patients were diabetic. HCV genotype 2 and 3 were detected in 73 patients (73.7%) and rest (26.3%) were other genotypes.

Using Metavir scoring, insignificant fibrosis of < 1 was seen in majority 78 of the patients (78.8%). Only 21 patients (21.2%) had fibrosis score of ≥2, and 16 (47.1%) out of these 21 patients also had significant inflammation score ≥2 (p < 0.001, Table I).

Table I: Characteristics of patients related to liver fibrosis.

| Characteristics | Overall (n=99) | Insignificant (Stage 0 - 1) (n=78) | Significant (Stage 2 and above) (n=21) | p-value  
|-----------------|---------------|-----------------------------------|--------------------------------------|----------
| Gender          |               |                                   |                                      |          
| Male            | 44 (44.4)     | 34 (43.6)                         | 10 (47.6)                           | 0.741    
| Female          | 55 (55.6)     | 44 (56.4)                         | 11 (52.4)                           |          
| Age in years    |               |                                   |                                      |          
| 15 - 29         | 33 (33.3)     | 30 (38.5)                         | 3 (14.3)                            | 0.110    
| 30 - 39         | 39 (33.3)     | 28 (35.9)                         | 11 (52.4)                           |          
| 40 and above    | 27 (27.3)     | 20 (25.6)                         | 7 (33.3)                            |          
| Severity of inflammation | | | |          
| Insignificant (Grade 0 - 1) | 65 (65.6) | 60 (76.9) | 5 (23.8) | < 0.001*  
| Significant (Grade ≥ 2 ) | 34 (34.3) | 18 (23.1) | 16 (76.2) |          

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<tr>
<th>Characteristic</th>
<th>Mean ± S.D</th>
<th>p-value</th>
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<tr>
<td>Age in years</td>
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<tr>
<td>34.1 ± 10.1</td>
<td>33.1 ± 9.8</td>
<td>0.042*</td>
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<tr>
<td>Haemoglobin (g/dl)</td>
<td>12.8 ± 1.82</td>
<td>12.7 ± 1.72</td>
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<tr>
<td>WBC</td>
<td>6752 ± 2368</td>
<td>6784 ± 2447</td>
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<td>ALT (IU/L)</td>
<td>36.1 ± 18.1</td>
<td>35.3 ± 18.5</td>
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<tr>
<td>Platelet (thousand)</td>
<td>237 ± 81</td>
<td>242 ± 85</td>
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<tr>
<td>Protein</td>
<td>7.5 ± 0.75</td>
<td>7.6 ± 0.80</td>
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<tr>
<td>Albumin</td>
<td>4.11 ± 0.46</td>
<td>4.11 ± 0.48</td>
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* Statistically significant p < 0.05
The age of patients (mean = 38.1±10.2 years) had a significant association with the severity of liver damage (p < 0.001) as compared to younger age group (mean = 33.1 ± 9.8 years).

Mean alanine aminotransferase (ALT) levels were slightly lower in patients having insignificant inflammation and fibrosis but this difference along with other parameters like haemoglobin, platelets, WBC count, gender and genotype were not statistically significant.

**DISCUSSION**

In the present study, 78.8% cases who had a positive PCR but a normal ALT had insignificant fibrosis (< 1) indicating no requirement to start interferon therapy. Case series and natural history studies have shown that patients with normal ALT levels usually have mild disease on histology (fibrosis stage 0 or 1) but yet some of them can progress to advanced fibrosis / cirrhosis.\(^9\),\(^10\)

Lauer and Walker reported a longitudinal study in which patients were followed after acute hepatitis C infection. They showed that following acute infection 20% recover spontaneously, 80% develop chronic liver disease, out of these chronic cases, 80% remains stable for life and only 20% progress to develop cirrhosis.\(^11\),\(^12\)

Decompensated liver disease occurs in 20% cases and hepatocellular carcinoma in 1 - 4%/year but remaining 75% develop complications very slowly and all these processes take almost 20 - 30 years.\(^11\),\(^12\)

The prevalence of hepatitis C in the general population of Pakistan is 4.9% with approximately 8.3 million people exposed to this virus, thereby creating a huge pool of patients who might require treatment.\(^6\) Some of these cases might just be exposed, while others might be carrying the disease with a detectable HCV RNA (some with raised ALT and some with normal ALT). Keeping in mind the quantum of disease and cost of treatment, it is important to define who should be treated and whether cases with normal ALT should be treated or not.

Using EASL (European Association for the Study of Liver) practice guideline 2011,\(^13\) where Metavir score F2-F4 signifies significant disease that requires to be treated, these results showed that only 21 patients (21.2%) were eligible candidates whereas 78 patients (78.8%) had insignificant fibrosis (< 1) and therefore, treatment may be deferred. These findings are also similar to the unpublished data of Umar et al. in which 85.4% patients had normal ALT and fibrosis ≤ 1 on liver biopsy and similar figures were reported by others.\(^14\)
Using older APASL guidelines,\textsuperscript{15} which had recommended treatment to all cases with Metavir score F1 and above (irrespective of inflammation), in our group of patients only 7 patients (7.1\%) had insignificant fibrosis and thus did not fall in the treatment category.

Another local study, however, is discordant to our results probably due to a higher fibrosis scale.\textsuperscript{16} Other possible reason for this disparity could be the stringent inclusion criteria followed in the present study where patients with signs of decompensation like splenomegaly, thrombocytopenia, reversed albumin/globulin ratio and cirrhosis documented on ultrasound, endoscopy or on clinical ground were excluded. In this study majority of patients were females as reported by others.\textsuperscript{17,18}

International guidelines like EASL (European Association for the Study of Liver), AASLD (American Association Society for Liver Disease)\textsuperscript{19} and local guidelines (Pakistan Society of Gastroenterology and GI Endoscopy,\textsuperscript{20} Pakistan Society of Hepatology) recommend that individuals with normal ALT values and mild to moderate hepatic fibrosis (bridging fibrosis or early cirrhosis), should be considered for treatment provided that liver biopsy shows fibrosis. Patients with normal ALT may experience a milder or non-progressive liver disease. In past alanine aminotransferase (ALT) levels have been used as a surrogate marker for chronic HCV infection but when it was found that some patients with normal ALT may also have active liver disease with visible fibrosis or cirrhosis, the use of ALT levels alone was discarded as an indicator of disease severity or marker for treatment initiation.

**CONCLUSION**

The present study shows that if HCV RNA is detected and ALT is not raised, then these cases should undergo liver biopsy before deciding antiviral therapy. Only those cases having fibrosis score of more than 2 should be considered for treatment while rest should be followed.

**REFERENCES**


