DOES MILD HEPATITIS ON LIVER BIOPSY WARRANT IMMEDIATE COMBINATION ANTI VIRAL THERAPY IN CHRONIC HEPATITIS C PATIENTS?

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Background: Not all patients with histologically mild chronic hepatitis C progress to cirrhosis. Many patients being treated on the basis of raised ALT and positive PCR alone may not be actually requiring it. Methods: All adult patients suffering from chronic Hepatitis C, qualifying for combination interferon ribavirin therapy, under went liver biopsies. Tissue samples were sent to Armed Forces Institute of Pathology (AFIP) Rawalpindi for histopathology. Reporting was done according to modified Ishaq score. Results: Total number of patients was 147. Out of these, 75 (51%) were female and 72 (49%) were male. Mean age of females and males were 35.1±8.12 and 36.31±8.56 year respectively. Out of these, 19 (12.9%) were stage zero, 61 (41.5%) at stage 1, and 31 (21.1%) at stage 2 of modified Ishaq fibrotic score. In all, 111 (75.5%) of the patients were ≤2 of modified Ishaq fibrotic score in either sex or 80 (54.4%) ≤1 of modified Ishaq fibrotic stage. The necroinflammatory score has been divided into minimal (0–3), mild (4–8), moderate (9–13), and severe (14–18). About the same number of our patients (74%) had minimal to mild inflammation. Conclusion: Since the majority of the patients have fibrotic score less than 3, so it will be cost effective to individualise their treatment on liver histopathology. Patients with low fibrotic score and minimal to mild inflammation may not be treated, but only monitored with serial ALT and liver biopsy every 4–5 years. Treatment may be started if there is increase in fibrosis on surveillance biopsy. However, there is a need to conduct prospective studies in similar group of patients to evaluate the natural course of disease in untreated patients.

Keywords: liver biopsy, chronic liver disease, HAI score, HCV

INTRODUCTION
Not all patients with histologically mild chronic hepatitis C progress to cirrhosis. The bulk of chronic hepatitis C patients is enormous in our country (6%)\(^1\) and the cost of its treatment is mind boggling. As per American Association for Study of Liver Diseases (AASLD) recommendation chronic hepatitis C patients with mild hepatitis on histopathology (modified fibrotic score <3) may wait; a repeat biopsy can be performed after 4–5 years, and if fibrosis has increased treatment may be started. If no progression is witnessed on repeat biopsy it may be repeated after another 4–5 years. We planned this study to see cost effectiveness of antiviral therapy versus natural history of chronic liver disease due to hepatitis C, based on liver histopathology from printed data; as a guide to hold treatment in mild chronic hepatitis C patients.

MATERIAL AND METHODS
All adult chronic hepatitis C patients reporting to medical out patient department of combined military hospital Sialkot, qualifying for interferon therapy were included in the study. Patients with decompensated cirrhosis, co-morbid conditions like diabetes mellitus, co-infections like HBV and HIV were excluded.

Patients qualifying for combination anti viral therapy for chronic hepatitis C underwent liver biopsy with 18# Surecut\(^a\) needle under local anaesthesia. Tissue samples were sent to Armed Forces Institute of Pathology (AFIP) Rawalpindi for histopathology. Reporting was done according to modified Ishaq score.

RESULTS
A total of 147 adult patients underwent liver biopsy prior to treatment. Out of these, 75 (51%) were female and 72 (49%) were male. Mean age of females was 35.1±8.12 year, (Range: 22–65 years). Mean age of males was 36.31±8.56 year, (Range 18–50 years). Out of these, 19 (12.9%) were stage zero, 61 (41.5%) at stage 1, and 31 (21.1%) at stage 2 of modified fibrotic Ishaq score. In all, 111 (75.5%) patients were ≤2 of modified Ishaq fibrotic score in either sex, and 80 (54.4%) were ≤1 of modified Ishaq fibrotic stage. There were no significant gender differences (Table-1).

The necroinflammatory score has been divided into minimal (0–3), mild (4–8), moderate (9–13), and severe (14–18). About 74% of our patients had minimal to mild inflammation (Table-2).
DISCUSSION

Acute Hepatitis C Virus (HCV) infected patients do not always lead to chronic infection; 60–80 percent of infected cases develop chronic hepatitis (anti-HCV antibody positive and raised ALT for more than 6 months). Chronic HCV infection is usually slowly progressive; it may not result in clinically apparent liver disease in many patients if the infection is acquired later in life. Over a follow-up period of 10–20 years cirrhosis developed in 50% of chronically infected patients.5,4

The natural history of chronic liver disease due to HCV, followed for more than 10 years without treatment and serial liver biopsies, 49% showed no change in fibrosis, 24% showed regression, and only 27% showed progression. Baseline ALT levels correlated with histologic outcomes.5,6

The best clinical predictors of disease progression in chronic HCV infection are the amount of inflammation and fibrosis on liver biopsy.4 Patients with mild inflammation (portal inflammation alone or with only focal periportal extension) and no fibrosis had only a 1.2% annual risk of progressing to cirrhosis. However the extent of liver fibrosis is an independent predictor of treatment response. These patients generally respond more favourably to treatment than do patients with more advanced fibrosis (bridging fibrosis or cirrhosis).7,8 The need for treatment in such patients is lower than it is for those with advanced fibrosis. Patients with moderate chronic hepatitis (periportal inflammation usually involving more than 30% of the limiting plate) had a 4.6% annual risk of developing cirrhosis; more than 90% developed cirrhosis within 20 years of the time of the biopsy (which was not the onset of infection). Nearly all patients with severe inflammation or bridging fibrosis developed cirrhosis within 10 years.

The cost-effectiveness of treating patients with no liver fibrosis has been questioned, since the prognosis even without therapy is excellent.9 The average cost of 24 week treatment in Pakistan ranges between Rs. 48,000 to 75,000; it doubles and may reach 150,000 in case of genotype-1, which not many people can readily afford. Genotype has no effect on disease progression but only response to treatment.

The cost of Surecut® needle is about Rs. 1,200. It has been proven to be a safe outdoor procedure, thus cost of hospitalisation is further reduced. Specimen processing and reporting costs Rs. 600–1,150. Few of the studies in Pakistan have evaluated safety, adequacy and cost of liver biopsy using spinal needle.10-12 This procedure is cheaper and safe. With the present statistics if we plan to treat the 6% of our population suffering from chronic hepatitis C, we need an enormous amount of money (Rs. 420 billion) just for the medicine. This huge amount of expenditure can be safely reduced to 50% if the patients with fibrotic score 0–1 and minimal to mild inflammatory score are kept in the 4–5 year follow-up, and even up to 70% if those with a fibrotic score of 2 are also put in this category. Patients with fibrotic score of 2 but inflammation of moderate to severe degree may be treated.

The follow-up of these patients will not only allow treatment of those whose fibrotic score has increased, but after a few years, provide us with enough data to change/continue this policy. With the current inflation and meagre health care facilities it is again desperately needed to devise a cost effective consensus statement for chronic hepatitis C treatment.

The AASLD practice guidelines also recommend considering the cost, efficacy (clearing virus in only about one half of those treated), and adverse events. There are likely many individuals in whom therapy can be safely deferred.

The other important factor predictive of more rapid disease progression is acquisition of HCV infection after the age of 40 years.5,13 The average age of patients in our study was 35 years for females and 36 years for males. The age of disease acquisition must be earlier than this.

Another very important aspect of deferring treatment is the patient psyche. Patient may remain under stress of a dreadful disease lurking inside him which he may pass over to his dear ones. But if he is
properly counselled regarding disease transmission, progression and the response rate and side-effects of combination therapy and the reassurance that the disease is being monitored, his anxiety can be allayed quite a bit.

CONCLUSION

Since the majority of the patients have fibrotic score less than 3, it will be cost effective to individualise their treatment on liver histopathology. Patients with low fibrotic score and minimal to mild inflammation may not be treated but only monitored with serial ALT and liver biopsy every 4–5 years. Treatment may be started if there is increase in fibrosis on surveillance biopsy. There is a need to conduct prospective studies in similar group of patients to evaluate the natural course of disease in untreated patients.

REFERENCES


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