# Morphological Study of Liver in Patients of Chronic Hepatitis C treated with Interferon

Pages with reference to book, From 325 To 328

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**Abstract**

The effect of interferon therapy on liver morphology was assessed in ten patients with serologically proven chronic hepatitis C. All these patients received 3 million units of alpha interferon three times a week. Six patients received therapy for 6 months, two patients for 12 months, one patient each for 3 and 9 months. All patients underwent a second liver biopsy 1 to 6 months after cessation of therapy. Alanine aminotransferase levels were determined before, during and after therapy. Each biopsy was assessed histologically by revised classification of chronic hepatitis proposed by Desmet et al and Kondell histological activity index was determined. Four patients showed significant reduction in the necroinflammatory activity with decrease in the HA! and normalisation of ALT level. Three patients showed partial reduction in the necroinflanunatory activity with partial reduction of ALT levels. Two patients did not show any change in the grade of disease while one patient showed worsening of necroinflammatory activity with rising ALT levels. One patient showed a significant reduction in fibrosis with conversion of early developing cirrhosis into bridging fibrosis, A second liver biopsy is extremely useful for assessing the response of interferon treatment, however, it must be done at a suitable time after cessation of therapy (JPMA 48:325,1998).

## Introduction

The beneficial effects of interferon (IFN) in NANB hepatitis were first reported by Hoofnagle in 1986[1]. Since the discoveiy of hepatitis C virus in 1989[2], interferon is the most widely used therapeutic agent for the treatment of chronic hepatitis C[3]. There are various ways to monitor interferon treatment in these patients which include alanine aminotransferase (ALT) levels[4], polymerase chain reaction (PCR)[5] and histological changes in post treatment liverbiopsy specimens[6-8]. This study analyzed histological, changes in liver biopsy specimens often patients of serologically proven chronic hepatitis C treated with interferon.

## Patients and Methods

A study carried out at Armed Forces Institute of Pathology, Rawalpindi from September, 1995 to December, 1996 included those cases who had serologically proven chronic hepatitis C. A needle biopsy of liver was obtained from all these patients alongwith ALT levels. They received three million units of alpha interferon three times a week for three to twelve months. A second liver biopsy was done 1-6 months after cessation of therapy and ALT levels were repeated. The specimens comprised 0.5 - 2 cm pretreatment and post-treatment needle biopsies of liver. They were received in 10% formal saline. All thebiopsies after gross examination were embedded as such. The sections were fixed in 10% fonual saline for 4-6 hours and were processed for paraffin embedding in an automatic tissue processor (Model RH-13 Sakura - Japan) for 17 hours. Haematoxylin Eosin stained sections were assessed histologically by revised classification of chronic hepatitis and Knodell histological activity.

**Results**

Ten cases of serologically proven chronic hepatitis C who received Interferon therapy were included in this study. Their clinical andbiochemical data are summarized inTable I.

Table I. Clinical and biochemical data of patients (n=10).

| S.No. | Age in years | Sex | Body. wt in Kg | Profession | Pretreatment ALT levels u/l | Duration of Interferon therapy | History of blood blood transfusion and parentral medication |
|---|---|---|---|---|---|---|---|
| 1. | 36 | F | 52 | House wife | 89 | 12 months | No |
| 2. | 48 | M | 70 | Business man | 113 | 9 months | No |
| 3. | 61 | M | 73 | Business man | 121 | 6 months | Yes |
| 4. | 49 | M | 68 | Office worker | 97 | 6 months | Yes |
| 5. | 43 | M | 62 | Office worker | 86 | 6 months | No |
| 6. | 37 | M | 59 | Business man | 94 | 3 months | Yes |
| 7. | 55 | M | 78 | Business man | 130 | 6 months | No |
| 8. | 57 | F | 82 | House wife | 160 | 6 months | No |
| 9. | 48 | M | 69 | Office worker | 110 | 6 months | Yes |
| 10. | 34 | F | 55 | Paramedic | 78 | 12 months | Yes |

There were seven males and three females. Their ages ranged between 34 to 61 years. Five cases gave history of blood transfusion and one patient was a paramedic.

Six patients received interferon treatment for six months, two for twelve months, one for nine months and one patient for three months. Four patients showed normalisation of ALT levels after cessation of therapy while in five patients ALT levels though reduced but were not nonnalised. One patient showed rising ALT levels after interferon treatment.

Four patients underwent second liver biopsy one month after cessation of treatment, three after two months, two after three months and one patient six months after completion of therapy. The following post treatment changes were observed:

Portal inflammation: Portal inflammation was significantly reducçd in fourpatients, in three cases the degree of portal inflammation remained unchanged, one patient showed complete disappearance of portal inflammation after IFN treatment while two patients showed worsening of portal inflammation.

Piecemeal necrosis: Six patients showed significant reduction in the piecemeal necrosis, three showed worsening, while in one patient piecemeal necrosis disappeared after treatment.

Intralobular inflammation: Post treatment liver biopsy showed significant reduction in the degree of intralobular inflanunation in four patients. In three patients there was no change, two cases showed increase and one patient showed complete disappearance of portal inflammation after interferon treatment.

Grade of Disease: Seven patients showed improvement in the grade of the disease, two cases showed worsening and onecase showedno change. Outof sevenpatients who showed improvement in the grade of disease, four patients exhibited conversion of moderately active disease to mild activity, one showed conversion of severely active disease to mild activity, one patient showed conversion of mildly active disease to minimal activity; while in one patient very mild disease showed complete absence of activity after interferon treatment.

Stage of the Disease: Three cases had fully developed cirrhosis prior to IFN treatment and there was no change in the stage of disease in these cases after LFN treatment. In three cases bridging fibrosis was found in pm-treatment which remained unchanged in two cases after treatment while one of these cases

showed worsening of the stage of disease with conversion of bridging fibrosis to early cirrhosis. Portal fibrous expansion were found in three cases prior to treatment which also remained unchanged after IFN treatment. In one case early developing cirrhosis was determined on pre-treatment liver biopsy. Post treatment liver biopsy of this case showed marked reduction in the extent of fibrosis and early developing cirrhosis was converted into bridging fibrosis. Histological features of pretreatment and post-treatment liverbiopsies are compared in Table II.

Table II. Comparison of pre treatment and post treatment histological findings.

| S.No. | Portal inflammation | | Piecemeal necrosis | | Intralobular inflammation | | Grade of disease | | Stage of disease | | Kondell HAI | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Pre treatment | Post treatment | Pre treatment | Post treatment | Pre treatment | Post treatment | Pre treatment | Post treatment | Pre treatment | Post treatment | Pre treatment | Post treatment |
| 1. | ++ | + | ++ | + | ++ | + | Mild | Minimal | Portal fibrous expansion | Portal fibrous expansion | 5/18<br>6/22 | 3/18<br>4/22 |
| 2. | ++ | ++ | +++ | + | ++ | ++ | Moderate | Mild | Cirrhosis | Cirrhosis | 8/18<br>12/22 | 5/18<br>9/22 |
| 3. | + | ++ | + | ++ | + | ++ | Mild | Moderate | Bridging fibrosis | Bridging fibrosis | 5/18<br>8/22 | 8/18<br>11/22 |
| 4. | + | ++ | + | ++ | + | ++ | Mild | Moderate | Bridging fibrosis | Bridging fibrosis | 3/18<br>6/22 | 6/18<br>9/22 |
| 5. | ++ | + | +++ | + | ++ | + | Moderate | Mild | Portal fibrous expansion | Portal fibrous exansion | 6/18<br>7/22 | 3/18<br>4/22 |
| 6. | ++ | + | +++ | + | ++ | + | Moderate | Mild | Early developng cirrhosis | Bridging fibrosis | 7/18<br>11/22 | 5/18<br>8/22 |
| 7. | ++ | ++ | +++ | ++++ | +++ | +++ | Severe | Severe | Cirrhosis | Cirrhosis | 12/18<br>16/22 | 12/18<br>16/22 |
| 8. | +++ | + | ++++ | ++ | +++ | + | Severe | Mild | Bridging fibrosis | Early developing cirrhosis | 12/18<br>15/22 | 5/18<br>9/28 |
| 9. | ++ | ++ | +++ | ++ | ++ | ++ | Moderate | Mild | Cirrhosis | Cirrhosis | 7/18<br>11/22 | 5/18<br>9/22 |
| 10. | + | - | + | - | + | - | Very mild | No activity | Portal fibrous expansion | Portal fibrous expansion | 3/18<br>4/22 | 0/18<br>1/22 |

+ = Minimal
++= Mild
+++= Moderate
++++= Severe
- = Absent
HAI =Histological activity index

## Discussion

After interferon therapy, improvement of liver histolog takes a longer time than amelioration of ALT levels. Significant differences in liver histology were noted when biopsies were performed at the end of follow up[9] in contrast to biopsies performed just after completion of treatment[10,11]. In this study there was a considerable variation (1-6 months) in the time interval between the first and the second biopsy. The ideal would have been a liver biopsy at the end of one year follow up. It is therefore likely that patients showing partial or no improvement in histology would have shown a significant histological improvement if biopsies are performed at the end ofoneyearfollow up.

Interferon suppresses viral replication in the liver resulting in improvement of liver histology[12]. A histological response had also been observed in patients who did not show normalization of transaminase levels[13]. Histological features which are influenced by interferon treatment include portal inflammation, periportal piecemeal necrosis and intralobular inflammation[7,13,14]7,13,14 Seven out of ten. cases in this series showed histological improvement. Five out of these seven cases showed significant decrease in the portal inflammation, piecemeal necrosis and intralobular inflammation; while two cases showed improvement only in the degree of piecemeal necrosis and lobular

inflammation. Out of seven cases showing histological improvement transaminase levels were normalized only in four cases. Similar observation was made by Arif et al[15]. In this study 10 out of 68 patients who did not show biochemical response demonstrated histological improvement.

A correlation has been documented between histological response and transaminase level. Patients showing normalisation of transaminase levels show significant decrease in portal inflammation, piecemeal necrosis and lobular inflammation while patients showing no biochemical response show only improvement in piecemeal necrosis and lobular inflammation[7,13,14].

In four out of seven cases in this study who showed normalisation of ALT levels, there was significant decrease in portal inflammation, piecemeal necrosis and lobular inflammation while in remaining three cases who did not show a biochemical response demonstrated a reduction in the piecemeal necrosis and lobular inflammation only.

Grade of the disease in the pretreatment liver biopsy provides an important clue to the histological response to be produced by interferon treatment. In a study carried out by Yamada et al[5], 84% of the patients with mild or moderately active disease and only 16% with severe disease showed histological response. Six out of seven cases in the present study showing histological response had mild or moderate disease and one case had severe disease as prior to interferon treatment has also been observed by Yaniada et al[5].

Initially it was reported that IFN does not effect the stage of disease and extent of fibrosis remains unchanged[6,17] but Naoki et al documented that treatment with JFN also alleviates fibrosis in addition to necroinflainmatory activity[17]. In this study one case showed a significant improvement in the stage of the disease and early developing cirrhosis in the pretreatment biopsy was converted into bridging fibrosis.

Co-infection with hepatitis B and C viruses lead to a severe liverdisease and responds poorly to interferon[18]. In this study one of the patients who had co-infection with hepatitis B and C viruses had severe active chronic hepatitis with fully developed cirrhosis prior to interferon treatment. Interferon treatment in this patient neither produced a histological impmvement nor normalised his ALT levels.

Kashara et al[19] studied the effects of prolonged interfemn treatment in patients going into relapse after cessation of therapy. They observed that prolonged interferon treatment in such casçs suppresses the relapse[19]. One patient in this series achieved a short term response after six months of treatment which was manifested by improved histology and ALT levels but three months later she had a relapse. Further interferon treatment for six months resulted in a response shown by normalized ALT levels and improved liver histology.

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