

## Study for frequency and aetiology of lymphadenopathy during combination therapy for chronic hepatitis C (pegylated interferon alpha plus ribavirin) at a tertiary care hospital in Hyderabad

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### Abstract

**Objectives:** To find out the frequency and etiology of lymphadenopathy at various sites distant from perihepatic region during combination therapy (pegylated interferon Alpha Plus Ribavirin) for chronic hepatitis C.

**Methods:** Retrospective case-control study conducted at Medical unit I of Liaquat University Hospital Jamshoro, Sind, Pakistan. The charts of 205 patients undergoing antiviral therapy with pegylated interferon alpha plus ribavirin for chronic hepatitis C at our ward from May 2009 to April 2010, were reviewed for those who developed lymphadenopathy at sites distant from perihepatic region.

**Results:** Out of 205 patients, 130 (63.41%) were males. Mean age of males was  $37.11 \pm 9.81$  years and of females  $42.31 \pm 8.79$  years. In total, 20 (9.75%) patients in control or 10/95 (10.52%) patients treated within clinical trials, were recorded to have lymphadenopathy during combination antiviral therapy for chronic hepatitis C. The most common site of lymphadenopathy was inguinal region in 08 (40%), followed by cervical region in 07 (35%) patients. Majority 16 (80%) of patients having lymphadenopathy were infected with HCV genotype 3a, and 17 (85%) have achieved sustained virological response. The etiology of lymphadenopathy was reactive in most 15 (75%) of our patients, followed by tuberculosis in 03 (15%). The average time for onset of lymphadenopathy during antiviral therapy for chronic hepatitis C was 21 weeks.

**Conclusion:** In conclusion, lymphadenopathy at various sites distant from perihepatic region appears to be higher than that documented in previous studies. In majority of our patients, the lymphadenopathy was reactive and resolved upon cessation of antiviral therapy.

**Keywords:** Chronic hepatitis C, frequency, lymphadenopathy, immunomodulatory effects, antiviral therapy. (JPMA 61:986; 2011).

### Introduction

Hepatitis C virus (HCV) chronic infection is the main cause of end-stage liver disease and liver cancer worldwide.<sup>1</sup> About 200 million people are infected with HCV globally, which covers about 3.3% of the world's population.<sup>2,3</sup> It has been estimated by World Health Organization (WHO) in 2004 that the annual deaths due to liver cancer caused by HCV and cirrhosis were 308,000 and 785,000 respectively.<sup>4</sup>

Pakistan is a developing country of 170 million population with low health and educational standards. In Pakistan, 10 million people are presumed to be infected with HCV.<sup>5</sup> Various studies have shown that percent prevalence of HCV in general adult population is  $4.95\% \pm 0.53$ .<sup>6-8</sup> Antiviral therapy with pegylated interferon alpha plus ribavirin remains a gold standard and can cure hepatitis C in up to 90% cases, depending on the viral genotype.<sup>9-11</sup> In addition, such treatment slows the progression of liver fibrosis,<sup>12</sup> incidence of hepato-cellular carcinoma<sup>13</sup> and finally prolongs survival.<sup>14</sup> However, side effects are numerous and include commonly fatigue, a flu-like syndrome, GI disturbances, neuropsychiatric alterations and haematologic abnormalities.

Infrequently also serious adverse events are reported, including severe depression up to suicidal attempts, hearing loss, interstitial pneumonitis and triggering of autoimmune diseases (e.g. lupus, thyroiditis, rheumatoid arthritis). The overall frequency of these side effects has been found to be higher than 20%, in a large clinical trial.<sup>10</sup> Although the mechanisms of action for interferon-alpha based therapy remain ill-defined, they have a direct antiviral and immunomodulatory effect. They usually bind to specific cell membrane receptors, the glyco-proteins which can initiate intracellular events including suppression of cell proliferation, increased phagocytic activity of macrophages and hence inhibition of viral replication in infected liver cells. As a consequence of the immunomodulatory effects of interferon, reactivation of sarcoidosis with lymphadenopathy has been described by Tahan V.<sup>15</sup>

Perihepatic lymphadenopathy is often present in patients with chronic hepatitis C and correlates with the degree of inflammation, as well as the stage of fibrosis in liver.<sup>16,17</sup> In local literature, hardly any studies have been documented on lymphadenopathy at sites distant from

perihepatic region during antiviral therapy for chronic hepatitis C. The objective of our study was to determine the frequency and etiology of lymphadenopathy during combination therapy (i.e. pegylated interferon alpha plus ribavirin) for chronic hepatitis C.

### Patients and Methods

This was a retrospective case-control study conducted at Medical Unit 1 of Liaquat University Hospital Jamshoro, Sind, Pakistan. The medical charts of 205 patients who had undergone antiviral therapy with pegylated interferon alfa-2b (Peg-Intron injection in a dose of 1.5 mcg/ kg subcutaneously every week plus Ribavirin 800-1000 mg twice per day orally) for chronic hepatitis C at our ward from May 2009 to April 2010, were reviewed for those who developed lymphadenopathy at various sites distant from perihepatic region. Special proforma were assigned to record demographics, clinical features (lymphadenopathy) and laboratory investigations. The institution's ethical committee had approved this study and all patients gave a written consent.

### Results

During the observation period of one year, 205 patients with chronic hepatitis C were treated with pegylated interferon alfa-2b plus ribavirin, 110 (53.65%) within controlled trials (Control group) and 95 (46.34%) in clinical trials (treatment group) respectively.

Out of 205 patients, 130 (63.41%) were males, while

**Table-1:- Age and Sex distribution of study subjects (n=205).**

Sex	No of patients	Age in years (Mean±SD)
Males	130(63.41%)	37.11±9.81
Females	75(36.58%)	42.31±8.79
Total	205	38.45±7.23

**Table-2:- Showing site and frequency of lymphadenopathy during combination antiviral therapy for chronic hepatitis C (n=20).**

Site of lymphadenopathy	No of patients	Percentage (%)
Inguinal region	8	40
Cervical region	7	35
Axillary region	4	20
Cervical and Axillary region	1	5

**Table-3:- Showing Histological/cytological features in patients with lymphadenopathy during antiviral therapy for Chronic hepatitis C (n=20).**

Histological/Cytological Findings	No of patients	Percentage (%)
Reactive	15	75
Tuberculosis	3	15
Non-Hodgkin's lymphoma	2	10

**Table-4: Showing specific genotype of HCV in patients with lymphadenopathy (n=20).**

Genotype	No. of patients	Percentage (%)
3a	16	80
2a	2	10
1a	2	10

75 (36.58%) females with M to F ratio of 1.73:1. The age of our patients ranged from 16- 55 years. Mean age of males was 37.11 ± 9.81 years and that of females 42.31 ± 8.79 years. This has been shown in Table-1.

In total, 20/205 (9.75%) patients in controlled trials or 10/95 (10.52%) in clinical trials, were recorded to have lymphadenopathy during combination antiviral therapy for chronic hepatitis C. Out of 20 cases, there were 13 (65%) males and 7 (35%) females with M to F ratio 1.85:1.

The age of patients with lymphadenopathy ranged from 16-53 years and mean was 32 ± 2.11 years. Amongst 20 patients who developed lymphadenopathy, 15 (75%) were investigated further by fine-needle aspiration cytology(FNAC) or surgical resection. FNAC was performed by a histo-pathologist in those cases where lymphadenopathy failed to regress after stoppage of antiviral therapy. In present study, the most common site for lymphadenopathy was inguinal region (40%), followed by cervical region (35%), axillary region (20%), and (05%) patients had simultaneous enlargement of both cervical and axillary nodes (Table-2).

The etiology of lymphadenopathy in majority 15(75%) of our patients was reactive in nature, followed by tuberculosis in 03 (15%) cases, and non-Hodgkin's lymphoma (NHL) in 02 (10%) patients respectively. This has been proven either by its clinical course with rapid resolution upon cessation of antiviral therapy and /or by cytological/histological examinations (Table-3).

The reactivation of latent tuberculosis occurred in 03 (15%) patients during antiviral therapy for chronic hepatitis C, whom exposed to primary or/post-primary infection twenty years before. These patients developed low-grade fever, cough, and marked weight loss during antiviral treatment, and cervical lymphadenopathy was noted at treatment weeks 17, 18, 19. They were carefully monitored by histological examination of lymph nodes, which revealed caseous granulomatous lymphadenitis, and culture was also positive for Mycobacterium tuberculosis. A high resolution CT-scan of chest showed mediastinal and hilar lymphadenopathy but no typical signs of active tuberculosis. The lymphadenopathy resolved within six months under anti-tuberculous therapy. Six months after antiviral combination therapy, HCV-PCR was negative and these patients were defined as sustained responders.

In our study, majority of patients 16 (80%) having

lymphadenopathy were infected with HCV genotype 3a, followed by 2a and 1a in 02 (10%) cases for each (Table-4). Only 2/20 (10%) of patients with lymphadenopathy were former intravenous drug abusers. There was no patient co-infected with HIV in the present study. Outcome of this study showed, majority 17 (85%) with lymphadenopathy were sustained responders, while only 03 (15%) relapsers. In addition, the average time for onset of lymphadenopathy during antiviral therapy for patients with chronic hepatitis C was 21 weeks. Furthermore, there was no difference in treatment response of patients with lymphadenopathy compared to those without lymphadenopathy.

### Discussion

The lymphadenopathy at sites distant from perihepatic region during combination therapy for chronic hepatitis C, is an uncommon phenomenon but it appears to be rising significantly in clinical practice. The appearance of lymphadenopathy neither depends on the dose of pegylated interferon alfa-2b plus ribavirin, nor the duration of antiviral therapy.

In our study, majority of patients who developed lymphadenopathy during antiviral therapy were young adult males. This is in contrast to the study by Welhemi M<sup>18</sup> from Switzerland, who found predominantly females (62.5%) as common victims of lymphadenopathy. The exact cause of this difference is not known but may be probable to high prevalence of HCV infection among males in our region. About 9.75% in controlled trials or 10.52% patients treated within clinical trials, were recorded to have lymphadenopathy during combination antiviral therapy for chronic hepatitis C in the present study. This is comparable with results of the study by Welhemi M,<sup>18</sup> who found 3.7% in controlled trials or 4% in clinical trials to have lymphadenopathy during antiviral therapy. The higher frequency of lymphadenopathy in our study may be related to increased prevalence of HCV infection in this region. During this study, the most common sites for lymphadenopathy during antiviral therapy were inguinal (40%) and cervical (35%) regions, which is quite similar to results of the study by Welhemi M.<sup>18</sup> The etiology of lymphadenopathy in majority (75%) of our patients was reactive in nature, which resolved usually after cessation of antiviral therapy. Welhemi M,<sup>18</sup> also observed reactive lymphadenopathy also in 75% of their patients during antiviral therapy. The reactive inflammation may be an expression of the immunomodulatory effects of pegylated interferon alfa-2b plus ribavirin due to promotion of virus-specific proliferative T-cell responses as observed by Barnes E.<sup>19</sup>

Reactivation of tuberculosis during antiviral treatment has been published in a study by Okuno H,<sup>20</sup> where interferon treatment led to aggravation of tuberculous pleurisy. Although the exact mechanism is not known, but in-vitro

interferon therapy impairs the activity of human monocytes and macrophages, which are no longer able to control the growth of Mycobacterium bovis. These results provide some evidence that interferon alpha might facilitate mycobacterial growth in patients harbouring these organisms.<sup>21</sup>

Whether the manifestations of non-Hodgkin's lymphoma (NHL) in 02 (10%) patients, was related to antiviral therapy or a co-incidence, remains unclear. Due to higher prevalence of HCV in patients with non-Hodgkin's lymphoma,<sup>22</sup> we speculate that appearance of this disease is a co-incidence rather than an effect of antiviral therapy. Hence they were referred to oncology department for further management.

### Conclusion

The present study, found that lymphadenopathy at various sites distant from perihepatic region appears to be higher (10.52%) than previous studies. In majority of the patients, it was reactive in nature and resolved upon cessation of antiviral therapy. However, it can be due to serious diseases, and therefore, warrants further laboratory investigations.

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