

# HEPATITIS 'C': ASSOCIATION OF INTERFERON-RIBAVIRIN THERAPY WITH HEARING LOSS

ORIGINAL  
PROF-1842

**DR. MUZAFFAR MEHMOOD KHAN,  
MBBS, MCPS, FCPS**

Graded ENT Specialist,  
63medical battalion, Multan.

**DR. MUHAMMAD TAHIR, MBBS, FCPS**

Graded ENT Specialist,  
CMH, Multan

**DR. MOHSIN RAZA, MBBS, FCPS**

Graded ENT Specialist,  
HIT hospital, Taxilla.

**Dr. Muhammad Ali BHATTI, MBBS, FCPS**

Graded ENT Specialist,  
CMH Okara.

**Dr. Muhammad Riaz Khokar, MBBS**

Graded ENT Specialist,  
CMH Multan

**ABSTRACT.. Objective:** The objective of this study was to determine association of Interferon-Ribavirin therapy with hearing loss in patients suffering from Hepatitis 'C'. **Study Design:** Quasi-experimental study. **Place and Duration:** Otolaryngology Department Combined Military Hospital Rawalpindi from 09 June 2006 to 08 June 2007. Patients and **Methods:** Consenting sixty patients of Hepatitis C divided into two equal groups of 30 each, (group A receiving Interferon-Ribavirin therapy and group B, not receiving it) during the study period fitting the inclusion criteria were selected. Pure Tone Audiometry including both air and bone conduction performed as base line data at commencement of therapy and then at the end of therapy (after six months). Patients were sampled by Convenience (non-probability) technique. **Results:** The number of patients who were found to have defined hearing loss was 06 (20%) in Group A (n=30) and 05 (16.67%) in Group B (n=30). Chi Square test was applied which showed a p-value of 0.739 which is highly insignificant. **Conclusions:** Interferon-Ribavirin Therapy does not have a significant association with hearing loss in patients of Hepatitis 'C'.

**Key words:** Interferon-Ribavirin, Hepatitis 'C', Ototoxicity, Hearing Loss

## INTRODUCTION

Hepatitis C virus is now established to be one of the major causes of chronic hepatitis and cirrhosis worldwide. The population in Pakistan is having the problem at larger scale as compared to the western world<sup>1</sup>. At least 50% of infected patients go on to develop chronic liver disease. Cirrhosis develops in about 10-20% within 5-30 years and of these patients; about 15% will finally develop hepatocellular carcinoma<sup>2</sup>. First line therapy for Hepatitis 'C' virus comprises Interferon and Ribavirin for 6 or 12 months<sup>3</sup>. This is the most effect therapy currently available<sup>4</sup> but the treatment is expensive, toxic and response rate is still less than satisfactory<sup>5</sup>. Various side effects have been reported in treated patients, but their incidence and prognosis remain unknown<sup>6</sup>.

Sudden hearing loss has been reported on standard Interferon a 2b therapy<sup>7</sup>. Immunological mechanisms are thought to play an important role in the pathogenesis of some cochleo-vestibular diseases<sup>8</sup>. Auditory disability frequently develops in the later stages of treatment but

can also occur acutely during the course of therapy<sup>9,10</sup>. This study is being conducted because there is no significant regional or local data available on this subject and it may help in devising multi-centre trials for future considerations to avoid untoward effects of anti-viral therapy<sup>11,12</sup>.

## PATIENTS AND METHODS

This quasi-experimental study included 60 consenting cases of Hepatitis C divided into two equal groups of 30 each, group A receiving Interferon-Ribavirin therapy (cases) and group B, not receiving it (controls) through convenience sampling of non probability type and was completed in a period of one year (June 2006 to June 2007) in ENT department, CMH Rawalpindi.

## Inclusion Criteria

Consisted of cases and controls selected from patients of Hepatitis C already diagnosed on the basis of liver biopsy and PCR for HCV RNA ageing between 18 to 50 years. Cases were the diagnosed patients of Hepatitis 'C' receiving Interferon-a 2b-Ribavirin therapy. Controls

were selected from those comparable patients of Hepatitis C virus infection, not receiving Interferon-a 2b-Ribavirin therapy due to some contraindications for this therapy.

### Exclusion Criteria

Included patients already having hearing loss (hearing threshold in speech frequencies > 30dB) and Patients already having or developed any disease of ears during study.

Diagnosed cases of Hepatitis 'C' admitted in Medical Wards were called in ENT Department where detailed examination for presence of any ear disease was done as per exclusion criteria. Patient's particulars were noted. Informed consent obtained. PTA including both air and bone conduction performed as base line data at commencement of therapy and then at the end of therapy (after six months). Only those patients were declared to have hearing loss in which minimum loss of > 15 dB was measured in at least two consecutive frequencies.

Data obtained was analyzed using Software SPSS-10. Student t-test was applied to compare age (numerical data); Chi Square test was applied to compare gender and hearing loss (categorical data) between the two groups. p-value less than .05 was taken as significant

## RESULTS

This study included a total of 72 patients at its inception. 07 patients were dropped because they did not fulfill the inclusion criteria. 05 more patients were lost to follow up. Therefore the data of 60 patients was finally included in the study.

The subjects were divided into two equal groups of 30 patients each. Group A (n=30) consisted of patients who received Interferon-Ribavirin therapy and were labeled as Case Group. Group B (n=30) consisted of the patients who did not receive Interferon-Ribavirin therapy and were labeled as Control Group.

The mean age of Group A (n=30) was 37.73 years (SD =10.08). The mean age of Group B (n=30) was 39.47 years (SD= 8.37). Student-t test was applied which showed a p-value of 0.124 (p=0.124) which is highly

insignificant.

Out of 60 patients included in the study 48 (80%) were male and 12 (20%) were female. The male to female ratio in Group A (n=30) was 5:1 and that in Group B (n=30) was 3.3:1. Chi Square test was applied which showed a p-value of 0.519 (p=0.519) which is highly insignificant.

Pure Tone Audiometry was used for assessment of hearing loss. The number of patients who were found to have defined hearing loss was 06 (20%) in Group A (n=30) and 05(16.67%) in Group B (n=30) at the end of six month of start of therapy. Chi Square test was applied which showed a p-value of 0.739 which is highly insignificant. This is presented in Table-I.

| Treatment Groups               | Haring Loss |    | Total | Chi Square Test Sig. (2-sided) |
|--------------------------------|-------------|----|-------|--------------------------------|
|                                | Yes         | No |       |                                |
| Group A (Interferon-Ribavirin) | 06          | 24 | 30    | .739                           |
| Group B (Control)              | 05          | 25 | 30    |                                |
| Total                          | 11          | 49 | 60    |                                |

Hearing Loss present or not at the end of therapy

## DISCUSSION

This study was conducted to ascertain any association between hearing loss and Interferon-Ribavirin Therapy in patients of Hepatitis 'C'. The study did not support the hypothesis that there is a significantly increased incidence of hearing loss in patients of Hepatitis 'C' who received Interferon-Ribavirin therapy as compared with the control group. This is in agreement with the study conducted by Formann E et al<sup>7</sup> which showed that sudden hearing loss may occur in about 1% of patients on Interferon-Ribavirin combination therapy. This rate was not different to that observed in an untreated population. Possible mechanisms involved include direct ototoxicity of Interferon, autoimmunity, and hematological changes that is according to review of the FDA's Adverse Event Report System (AERS)<sup>13</sup> on

persistent hearing loss in patients treated with standard and pegylated forms of interferon. The estimated prevalence of the annual incidence of sudden sensory hearing loss ranges from 5-20 cases per 100,000 persons treated with interferon or pegylated interferon which is very low. However, authors pointed out that the true number of people with hearing loss from treatment may differ because the reporting is voluntary and often the information on the adverse event report is incomplete. Another study conducted by Kaygusuz I et al<sup>14</sup> investigated the effects of interferon-a 2b treatment on hearing in patients with chronic active hepatitis B. Twenty-six patients with chronic active hepatitis B were enrolled in the study, and pure tone audiometry was performed to determine hearing thresholds of the patients before and at the end of 6 months of interferon-a 2b treatment. There was no significant change in hearing thresholds of patients after treatment with interferon-a 2b ( $p>0.05$ ). However a prospective study conducted by Kanda Y et al<sup>15</sup> to assess the auditory function of 73 patients receiving Interferon. Therapy showed that auditory disability (tinnitus and/or hearing loss) occurred in 32 patients (43.8%) during therapy.

The results of most of these studies indicate that interferon therapy does not have any significant negative effect on hearing thresholds of patients with hepatitis C. But there is still a need for further studies involving larger numbers of patients to allow conclusions to be drawn regarding the safety of this therapy with respect to hearing. Therefore, at present, the decision whether to continue or to stop the treatment when signs of ototoxicity appear is based on the clinical judgment of the treating physician.

This study had certain limitation. Sample size of this study was 60 which is comparable to other studies in literature however a study with a larger sample size would have greater power. Gender distribution was not equal which may act as a source of bias. This was a quasi experimental study however it is recommended that a randomized controlled trial should be conducted to verify its findings.

## CONCLUSIONS

Although several mechanisms may cause hearing loss

occurring in temporal relation to treatment with interferon-Ribavirin Therapy but based on the results of this study it can be safely concluded that Interferon-Ribavirin Therapy does not have a significant association with hearing loss in patients of Hepatitis 'C'. Therefore, the decision whether to continue or to stop treatment in patients with hearing loss on Interferon-Ribavirin Therapy has to be made carefully by the clinician in concordance with the patient. If treatment is continued, a close monitoring of the auditory function is necessary. However it is recommended that based on this pilot study further larger studies should be conducted to determine the safety of Interferon when used concurrently with Ribavirin in patients of Hepatitis 'C'.

Copyright© 05 Dec, 2011.

## REFERENCES

1. Mahmood A, Karamat KA, Mubarak A, Rehman ZU. **Prevalence of hepatitis C virus antibodies in cases of chronic hepatitis and cirrhosis at PNS Shifa, Karachi.** Pak Armed Forces Med J 1999; 49:15-7.
2. Nadeem MA, Waseem T, Sheikh AM, Grumman N, Irfan K, Hasnain SS. **Hepatitis C virus: An alarmingly increasing cause of liver cirrhosis in Pakistan.** Pak J Gastroenterol 2002; 16:3-8.
3. Hoare M, Woodall T, Alexander GJ. **Bell's palsy associated with IFN-alpha and ribavirin therapy for hepatitis C virus infection.** J Interferon Cytokine Res. 2005; 25:174-6.
4. Shiffman ML, Di Bisceglie AM, Lindsay KL, Morishima C, Wright EC, Everson GT. **Hepatitis C antiviral long-term treatment against cirrhosis trial group.** Gastroenterol. 2004;126:1015-23.
5. Mohammad Z. **Beware of hepatitis C -the silent epidemic.** Med Today 2005; 3:26-9.
6. Fontana R. **Neuropsychiatric Toxicity of Antiviral treatment in chronic hepatitis C.** Digestive Diseases 2000;18:107-116.
7. Formann E, Stauber R, Denk DM, Jessner W, Zollner G, Munda SP, et al. **Sudden hearing loss in patients with chronic hepatitis C treated with pegylated interferon-ribavirin.** Am J Gastroenterol 2004; 99: 873.
8. Boulassel MR, Deggouj N, Tomasi JP, Gersdoff M. **Inner ear autoantibodies and their targets in patients with**

- autoimmune inner ear diseases. *Acta Otolaryngol* 2001;121:28-34.
9. Wong VK, Cheong LC, Ford JA, Yoshida EM. **Acute sensorineural hearing loss associated with peginterferon and ribavirin combination therapy during hepatitis C treatment: outcome after resumption of therapy.** *World J Gastroenterol.* 2005; 11:5392-3.
  10. Akyol MU, Sarac S, Akyol G, AtacA, Poyraz A, Belgin E, et al. **Investigation of the ototoxic effects of interferon-alpha 2A on the mouse cochlea.** *Otolaryngol Head Neck Surg* 2001; 124: 107-10.
  11. Butt JA, Ahmed SI, Zafar S, Chohan AR. **The role of antifibrotics in the treatment of chronic hepatitis.** *Pak J Gastroenterol* 2003; 17:33-6.
  12. Muhammad N, Jan A, Rehman N. **Outcome of combined interferon-ribavirin in the treatment of chronic hepatitis C.** *J Coll Physicians Surg Pak* 2004; 14: 651-3.
  13. **A Monthly Newsletter of the Hepatitis C Support Project.** Dec 2004,7; 12.
  14. Kaygusuz I, Kaygusuz T O, Öztürk A, Kiliç S S, Karlida T, Kele E, et al. **Effects of interferon-a 2b on hearing.** *Int J Audiology* , Sept 2004 , 43 ;438 – 441.
  15. Kanda Y, Shigeno K, Matsuo H, Yano M, Yamada N, Kumagami H. **Interferon-induced sudden hearing loss.** *Audiology.* Mar-Apr 1995; 34: 98-102.

Article received on: 08/09/2011

Accepted for Publication: 05/12/2011

Received after proof reading: 22/02/2012

**Correspondence Address:**

Maj. Dr. Muhammad Tahir  
ENT Specialist  
CMH, Multan Cantonment, Multan-Pakistan  
dr\_gopang@yahoo.com

**Article Citation:**

Khan MM, Tahir M, Raza M, Bhatti MA, Khokar MR. Hepatitis 'C'; association of interferon-ribavirin therapy with hearing loss. *Professional Med J Apr* 2012;19(2): 193-196.

## PREVIOUS RELATED STUDIES

- Dilshad Muhammad, Khalid Amin, Amin Anjum, Masood Javed. CHRONIC HEPATITIS C VIRUS INFECTION; ASSOCIATION WITH TYPE 2 DIABETES MELLITUS (Original) *Prof Med Jour* 17(4) 557-562 Oct, Nov, Dec 2010.
- Fatima Mehboob, Zafar Majeed Babar. HEPATITIS C PATIENTS; TREATMENT COMPLIANCE OF HAVING POOR SOCIO-ECONOMIC BACK GROUND (Original) *Prof Med Jour* 15(1) 61 -66 Jan, Feb, Mar, 2008.
- Faqir Muhammad Tariq, Habib Subhani, Irshad Ahmad, Irshad ul Haq. HEPATITIS C; PREVALENCE IN PARAMEDICAL STAFF OF A TEACHING HOSPITAL(Original) *Prof Med Jour* 16(2) 168-172 Apr, May, Jun, 2009.
- Muhammad Afzal, Irfan Ahmed Mughal, Naushen Afzal, Muhammad Badar Bashir, Fiyaz Ahmed Malik. CHRONIC HEPATITIS C INFECTION; CORRELATION OF GLUCOSE TOLERANCE TEST, THE LEVELS OF FASTING BLOOD SUGAR (FBS) AND HEMOGLOBIN (Original) *Prof Med Jour* 11(2) 222-227 Apr, May, Jun, 2004.
- Muhammad Naeem, Ameer Ahmad, Imran Qaisar, Fiaz Ahmad. STATUS OF HEPATITIS C VIRUS (HCV) INFECTIONS; CHILDREN ADMITTED IN PEDIATRIC WARD OF BAHAWAL VICTORIA HOSPITAL BAHAWALPUR (Original) *Prof Med Jour* 18(3) 445-449 Jul, Aug, Sep 2011.
- Nuzhat Parveen Khawaja, Uzma Hussain, Farzana Latif, Rakhshanda Reman. RISK FACTORS FOR HEPATITIS C VIRUS; OBSTETRICS PATIENTS. (Original) *Prof Med Jour* 16(3) 428-431 Jul, Aug, Sep, 2009.
- S. M. Abbas Naqvi, Qurban ali Khaskheli, Shahid Habib Ansari, Muhammad Shiraz Khan, Muhammad Saeed Talpur. HEPATITIS C VIRUS; PREVALENCE IN BLOOD DONORS IN KARACHI (Original) *Prof Med Jour* 13(4) 604-607 Oct, Nov, Dec, 2006.
- Shaukat Ali, Syed Khurram Shahzad, Atiq ur Rehman Slehria. CHRONIC HEPATITIS C; RESPONSE TO INTERFERON AND RIBAVIRIN COMBINATION (Original) *Prof Med Jour* 17(4) 563-567 Oct, Nov, Dec 2010.