COMPARATIVE EFFECTIVENESS AND ADVERSE EFFECTS OF INTERFERON ALPHA-2b PLUS RIBAVIRIN THERAPY IN HEPATITIS 'C' FOR 26 WEEKS

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Background: Hepatitis C is major emerging challenge for pathologists and treating physicians all over the world. Already 10 million Pakistani population has become anti-HCV positive. It is not only affecting hepatobiliary system but with passage of time research is revealing that Hepatitis C is going to involve almost every organ of the body. With timely diagnosis and treatment, millions of patients can be saved from morbidity and mortality. The nation has to sacrifice initial economic allocations to avoid later millions of mortalities and greater economic losses on affected patients and to support their families. The objective of this study was to evaluate effectiveness of combine therapy of Hepatitis C in local population of Pakistan. **Methods:** This case series study was done at CMH Okara, Kohat, Abbottabad, and PAF Hospital, Shorkot from August 2000 to August 2009. All 1,000 patients from 10 to 60 years of age, confirmed anti-HCV Positive by ELISA and PCR Positive for HCV RNA, were subjected to Interferon alpha-2b and Ribavirin therapy for similar period of time. Response and adverse affects were observed by clinical examination, blood complete picture including platelet count and ALT fortnightly. PCR for HCV RNA and ultrasound abdomen (hepatobilliary system) was done quarterly during treatment and 6 monthly for 2 years after treatment to review the sustained response and relapse. **Results:** Over all cure rate after 2 years was 855 (85.5%) excluding the 50 (5%) of initial resistant to one year treatment and 95 (9.5%) re-treated relapse cases. One hundred and forty-five (14.5%) patients were found to be resistant to treatment. **Conclusion:** Hepatitis C must be treated timely after proper diagnosis. Interferon and Ribavirin combination have shown high 'cure' rate in Hepatitis C. In spite of high cure rate of 85.5% with timely and proper treatment, low socio-economic status is a major problem for poor individuals to get treatment. Preventive aspect must be strictly followed and implemented.

Keywords: HCV, Anti-HCV, PCR, ALT, ELISA, Interferon alpha-2b, Ribavirin, Adverse effects

INTRODUCTION

Is it impossible to really know the origin of Hepatitis C since there are no stored blood samples to test for the hepatitis C and other viruses that are old then (50) fifty years. However the evolution of all viruses including Hepatitis C has probably been around hundreds of thousands of years or more before evolving them to current strains.[1]

In 1987 investigators headed by Daniel W Bradly and Michael Haghton identified Hepatitis C virus from non-A non-B group and in 1989 the first ELISA was performed for detection of anti–HCV. In 1990 Blood banks started screening of blood donors for Hepatitis C. Perfect ELISA was performed in 1991 for detection of anti-HCV in human blood.[2] Accurate PCR for HCV RNA was established in 1992.[3] In 1992 blood banks with discovery of ELISA and PCR for HCV RNA started screening of blood and its products before transfusion which has decreased the risk of HCV transmission approximately to 0.1%.[1]

Up till now, 6 genotypes of Hepatitis C has been discovered and approximately 10 million (6%) population of Pakistan is suffering from HCV.[5] Isolation of HCV from blood has opened the new era of research and treatment in medicine. In 1957 scientists discovered naturally occurring substance having antiviral properties and named it as Interferon. There are three deferent types of Interferon: alpha, beta and gamma. Beta and gamma Interferon exsist in one form, while alpha interferon has multiple forms.[1]

United States Food and Drug Administration (FDA) first time approved alpha interferon for treatment of hepatitis C in 1996.[1] In 1997 FDA approved with consensus interferon to treat Hepatitis C. FDA approved Interon plus Ribavirin to treat Hepatitis C in 1997 which proved a valuable breakthrough for treatment of Hepatitis C and avoiding chronic effects.[1] In 2002 FDA approved pegylated Interferon alone and in combination with Ribavirin.[1] In 2003 FDA approved Interferon-A with combination of Ribavirin oral paediatric solution, this may by a revolution in future for treatment of paediatric Hepatitis C.[1] In 2005 scientist were first time succeeded to replicate type-1 Hepatitis C virus in test tube.[1]

Israeli scientist developed salvia based test for detection of HCV antibodies but it requires larger scale studies in future which may enable us to find the alternate route of Hepatitis C transmission.[1]

Hepatitis C leads to chronic liver disease in 10 years, cirrhosis of liver in 20 years and Hepatocellular Carcinoma in 30 years. Hepatitis C has been discovered just 2 decades ago and its treatment has been started just a decade ago. It still requires time for confirmation.[5] Hepatitis C is not only associate with hepatic disease but is also associated with multiple systemic diseases like essential mixed cryoglubinaemia[6], porphyria cutanea tarda[7], membranoproliferative glomerulonephritis[8] diffuse proliferate glomerulonephritis,[9] lymphocytic sialadenitis, Söjgren's syndrome[10], immunological disorder[11], anti-thyroid antibodies,[12] Lichen planus[13], idiopathic pulmonary fibrosis[14], corneal ulcers[15]. Effects of Hepatitis C virus and impact of its antibodies on multiple body organs systems will continue to open new areas of research and treatment in future.

The Objective of this study was to observe the therapeutic response of Interferon alpha-2b plus Ribavirin in chronic Hepatitis C patients in Pakistan.

MATERIAL AND METHODS

One thousand (1,000) patients of two thousand (2,000) on HCV positive reported in last (10) years, from August 2000 in CHM Okara, CMH Kohat, PAF Hospital Shorkot Cantt and CMH Abbottabad till August 2009 were selected for Interferon alpha-2b and Ribavirin therapy. Patients from 10 years to 60 years of age were included for treatment without considering the gender difference. Children less 10 years of age, older than 60 years of age, not willing for treatment due to economic reasons, firm believe on spiritual or *Hakims*' treatment, overt cirrhosis of liver or co-existence of moribund systemic diseases, pregnant females, and lactating mothers were not included this treatment. Lactating mother were included in treatment only when they stopped breast feeding.

All patients irrespective of age and gender were subjected to similar investigations. Anti-HCV was confirmed by ELISA and PCR was performed for HCV RNA (Qualitative). All PCR positive patients were subjected to following base line investigations prior to start of treatment:

- Liver function test
- Blood complete picture including platelet counts
- Coagulation profile
- Routine urine examination
- Blood sugar
- ECG
- X-Ray chest PA view
- Ultrasound abdomen

Liver biopsy was done in 400 patients because it was mandatory in Armed Forces personnel prior to initiation of treatment. With normal findings on ultrasound abdomen, liver biopsy makes no difference in outcome of Hepatitis C treatment, hence liver biopsy was later on abandoned as pre-request to treatment.

All patients under treatment were given similar medication for same duration according to bodyweight. All patients were given 78 Interferon injections over 26 weeks along with Capsule Ribavirin as under:

a. Inj. Interferon alpha-2b 3 million units subcutaneously thrice weekly
b. Cap. Ribavirin 800 mg to 1,200 mg daily in divided doses
c. Patients of 10–15 year age were given injection Interferon alpha-2b 50,000 Unit/Kg body weight subcutaneously thrice weekly with capsule Ribavirin 15 mg/kg body weight in divided doses.

Patients were followed for response and adverse effects fortnightly with clinical examination, complete blood picture including platelet count, liver function test especially ALT levels. PCR for HCV RNA and ultrasound abdomen were done quarterly during treatment to observe the response and hepatic status, after completion of initial treatment, PCR negative patients were followed by PCR for HCV RNA and ultrasound abdomen 6 monthly for two yeas to review the relapse and stained viral response. Patients who did not respond to initial treatment or had relapse within 2 year of treatment were given the same treatment for another 6 months. Patients who remained PCR positive after 1 year of treatment were labelled as resistant patients. Patients who remained PCR negative for two years after treatment were declared 'cured' or disease free.

RESULTS

Out of 1,000 patients, 50 (5%) remained resistant to treatment with Interferon alpha-2b and Ribavirin for 1 year. Two hundred and seventy-five (27.5%) patients had relapse within 2 years of treatment and were re-treated for another 6 months. 180 re-treated patients were declared 'cured' after further 2 year follow up and only 95 out of 275 re-treated patients remained PCR positive.

Out of one thousand patients ALT was settled in 900 (90%) in 4 weeks. PCR for HCV RNA became negative in 700 (70%) in 13 weeks (39 Injections) and 950 (95%) in 26 weeks (78 injection) 50 (5%) remained PCR positive after 78 injections (26 weeks) they were subjected to extended treatment up to one year.

Patients who underwent interferon alpha-2b and Ribavirin therapy had significant adverse effects as body aches in 550 (55%), malaise in 600 (60%), fever in 350 (35%), anaphylaxis in 20 (2%), bone

marrow suppression (Aplastic Anaemia, Hb less than 10 gm%) in 225 (22.5%), Thrombocytopenia in 150 (15%), granulocytopenia in 260 (26%). All except 30 (3%) patients responded to erythropoietin, Granulocyte Colony Stimulating factor and Blood transfusion, and treatment had to be stopped in these patients till recovery of bone marrow.

None of the patients subjected to interferon alpha-2b and Ribavirin therapy developed chronic liver disease.

DISCUSSION

Hepatitis C is a major emerging challenge all over the world especially in the third world countries but is fairly treatable if diagnosed early. Seven hundred and twenty-five (72.5%) of the 1,000 patients treated with Interferon alpha-2b and Ribavirin were found disease free (cured) after 2 years of follow up. When treatment was repeated for another 6 months in 275 (27.5%) patients who were PCR positive within 2 years, another 180 patients became PCR negative and remained negative for next 2 year follow up. On the other hand, Scotto G *et al*[16], showed only 20–25% remission, Kryczk W *et al*[17], revealed 35.4% and McHutchison *et a1*[18] reported 43% remissions in 48 weeks. Painko S study revealed 41% sustained virological remission in 48 weeks.[19] Overall comparative remission rates of current study are much better than above studies. There is no variation in adverse affects in all the studies. None of them followed their patients for 2 years.

Over all resistant rate was 14.5% and genotyping was done in resistant cases which revealed most of them were having Hepatitis C type b. Over all cure rate in the present study was 85.5% with combined Interferon alpha-2b and Ribavirin therapy which can further be improved by creating awareness in the society and timely intervention. Timely treatment and high cure rate of 85.5% will automatically help in decreasing the disease in society. This will also help in decreasing morbidity and mortality from Hepatitis C. Patients must be briefed about adverse affects, and its counter-measures for better compliance of treatment. Whenever required prompt supportive treatment like analgesics, antipyretics, anti-ulcers, anti-emetics, erythropoietin, granulocyte colony stimulating factors, and blood transfusion must be given for continuation of treatment and better results in affected patients.

All hospitals, clinicians, and other personnel involved in medical care and procedures must be strictly monitored and properly screened. Use of disposable instruments, and proper disposal of hospital refusal, absolute sterilisation of instruments, education of society to avoid unnecessary injectable medication, tattooing, and fool-proof screening of blood and its products prior to transfusion must be ensured to decrease the prevalence of Hepatitis C.

CONCLUSION

Hepatitis C must be treated timely after proper diagnosis. It will help in prevent chronic liver disease, cirrhosis of liver and HCC which will help in preventing morbidity, mortality in thousands of individuals along with economic suffering of same number of families. Hepatitis C virus and its antibodies are involving all body systems which are being discovered with passage of time.

In spite of high cure rate of 85.5% with timely and proper treatment, low socio-economic status is a major problem for poor individuals to get treatment. Government must allocate sufficient funds for suffering individuals, *Zakat* fund, and *Baitualmal* can be affectively utilised for this noble purpose. Also non-government organisations must come forward to treat and eradicate the Hepatitis C. Society must be educated about prevention, and proper treatment of Hepatitis C.

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