ORIGINAL ARTICLE

Treatment Profile of Hepatitis C Patients – A Comparison of Interferon Alpha 2a and 2b Treatment Regimes

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ABSTRACT

Objective: To compare the side effects, cost, end treatment response (ETR) and Sustained viral response (SVR) with combination therapy of either interferon alpha 2a or 2b in combination with Ribavarin.

Study Design: Randomized Control Clinical Trial (RCCT).

Place and Duration of Study: The study was conducted at Sarwar Zuberi Liver Centre (SZLC), Civil Hospital Karachi (CHK), from May 2004 to July 2009.

Methodology: Patients positive for qualitative HCV ribonucleic acid (RNA) by Polymerase chain reaction (PCR) and genotype 3 were included. Patients with decompensated cirrhosis, severe depressive illness, autoimmune hepatitis, hyperthyroidism, pregnancy, heart failure, uncontrolled diabetes, obstructive pulmonary disease, children less than three years and patients who had previously received treatment were excluded.

Single blind randomization using computerized randomization list was done and patients divided into groups A and B, those requiring treatment were given injection Interferon 3 million units (MU) subcutaneously (SC) three times/week and Ribavarin 1000 mg per day (weight ≤ 75kg) and 1200 mg/day (weight > 75kg) orally with either interferon alpha 2a (group A; FDA approved products) or alpha 2b (group B; non FDA approved product). Demographics, side effects, ETR and SVR were noted. ETR was defined as absence of virus at the end of treatment and SVR was taken as absence of HCV RNA at 6 months after completion of treatment.

Results: There were a total 310 patients with mean age of 34.07 ± 9.38 years including 52.4% males, (n=162). Majority of the patients were from North Pakistan. There were 155 patients each in group A and group B respectively. The cost of treatment for interferon alpha for a single patient for 6 months was Rs 60,000, while for Interferon alpha 2b was Rs 30,000. Side effects (fever initially, followed by fatigue, headache, musculoskeletal pain, depression, alopecia, insomnia, and anorexia) were more prominent in group B when compared with group A. In group A, ETR was 83.8% (130/155) while in group B was 83.2% (129/155). While SVR available in group A was 61/70 (87.1%) and in group B was 60/72 (83.3%).

Conclusion: Response to combination therapy for HCV was 83%. ETR and SVR were similar for both interferon alpha 2a and 2b. Side effects though minor are more with alpha 2b (non FDA approved products).

Key words: *Hepatitis C. Interferon alpha 2a and 2b. ETR. SVR. Side effects. Cost.*

INTRODUCTION

WHO estimates that about 180 million, 3% of the world's population are infected with HCV and 3 to 4 million people are newly infected each year, with 130 million carriers at risk of developing liver cirrhosis and /or hepatocellular carcinoma (HCC).[1] In Pakistan the prevalence of HCV infection in the community is 6%,[2] with genotype 3 being the most prevalent.[3,4]

Patients with reactive anti HCV and presence of HCV RNA should be considered as potential candidates for anti viral therapy[5] for which initially treatment with interferon (IFN), a 6 months course of thrice weekly injections of 3 million units (MU) was approved.[6] Several landmark studies then followed that consistently demonstrated the dramatically improved responses to combination therapy (IFN + Ribavarin) especially for patients with genotypes 2 and 3.[7] Treatment guidelines recommend the use of peginterferon alfa-2b or peginterferon alfa-2a in combination with ribavirin for chronic hepatitis C virus (HCV) in genotype 1 infection. A recent study showed that the rates of sustained virologic response and tolerability did not differ significantly between the two available peginterferon-ribavirin regimens.[8] However, comparison of cost and treatment regimens of conventional interferon alpha 2a (FDA-approved products) versus interferon alpha 2b (non-FDA-approved products) are not available locally and specifically, in the treatment of chronic hepatitis C virus (HCV) genotype 3 patients. Moreover interferon alpha 2b is not FDA approved, knowledge and use is limited worldwide. Hence, this study was conducted to compare the side effects, cost, end treatment response

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(ETR) and sustained viral response (SVR) to either interferon alpha 2a or 2b in combination with Ribavarin.

METHODOLOGY

This randomized controlled clinical trial (RCCT) was conducted at Sarwar Zuberi Liver Centre (SZLC), Medical 4, and Civil Hospital Karachi (CHK), DUHS, from May 2004 to June 2009. By taking sucessful response ETR=85.14% and SVR=76.7% the required sample size on 80% power and 95% confidence interval was 277 in each group that was extended for complete follow up upto 301 in each group. A proforma containing information like patients demographic details, risk factor evaluation, past and present history was designed and filled from every patient presenting to the centre who was anti-HCV positive and further tested for qualitative HCV RNA by PCR. Those found positive were included in the study. Two groups were randomized by employing SPSS computer generated random allocation in which the patients code on the list were entered in the program and the researcher selected the either management via filter random allocation command in an equal number. Blinding technique was used while giving the agent under study i.e. alpha 2a or alpha 2b prepared by trained staff in prefilled syringes to the patient for a period of one week at SZLC following which the patient was counseled about the injection administration technique. The patient took the drug home with the knowledge of the generic (that is alpha 2a and 2b) not known to him/her. A coding was done and code number was given to the patient for further facilitation. During the period of treatment patient was getting the drug only from SZLC on a monthly basis. Group A (FDA-approved) were taken as controls and group B (non-FDA-approved) taken as cases. Two different brands of drug were used for group A and group B. HCV genotyping was done to determine duration of treatment. Only treatment naïve patients were included. Patients with decompensated cirrhosis (Child-Turcotte-Pugh score ≥ 7),[9] history of ascites, esophageal varices more than grade 2, hepatic encephalopathy, patients with history of severe, uncontrolled psychiatric disorder (e.g. severe depression), substance abuse, marked leucopenia, thrombocytopenia, anemia, cardiovascular disease and renal failure, untreated hyperthyroidism, pregnant or unwilling to comply with adequate contraception, severe hypertension, heart failure, significant coronary artery disease, poorly controlled diabetes, obstructive pulmonary disease and children three years and less, relapsers and non responders to previous interferon therapy were excluded.

Before treatment was initiated every patient had the baseline investigations including complete blood picture (CBC) to check Hemoglobin (Hb) and platelet count, liver function tests (LFT's), ultrasound Abdomen (U/S) and blood sugar. Initial one to two weeks the patients received injections at SZLC on an outpatient basis, given three times per week subcutaneously by insulin syringe preferably around the umbilical region.

During treatment period patient was counseled for cold chain maintenance of interferon, its regular subcutaneous injection thrice weekly by insulin syringe, methodology of injection and ribavarin dosage and safe disposal of syringes after which they take the injections home. Disposable needle cutters were provided to every patient for this purpose.

Patients visited SZLC at least once a month, during treatment for CBC and ALT to monitor response of therapy or earlier in case of undue side effects.[10] The drug allocated to patient (either alpha 2a or 2b) was continued till 6 months unless any severe adverse reaction like very low platelet count, allergic reaction, and severe uncontrollable depression occurred to curtail the therapy. Patients were treated with interferon alpha 2a or interferon alpha 2b. Alpha 2a (FDA-approved product) drug is more costly. ETR was defined as continued absence of virus at termination of treatment and SVR was taken as absence of HCV RNA at the end of treatment and 6 months later.

Side effects, cost, ETR and SVR in both groups (treated with IFN 2a or 2b in combination with ribavarin) was noted.

Statistical analysis was performed through SPSS-10.0. Frequencies and ranges were computed for presentation of qualitative response for variables like side effects, history of unsafe injections (intra-venous or intra-muscular), presenting complaints, genotype and lab data; Quantitative responses variables like age (years), weight (kg), height (cm) and Body mass index (BMI in kg/m^2) were presented by mean (SD). Comparison of side effects between alpha 2a and 2b was done applying Chi-Square test and p values were obtained, p values were significant when less than 0.05.

Consent from the Ethical Review Board (ERB) of DUHS was taken. A written consent was taken from every patient informing them about the use of data for medical research.

RESULTS

There were a total of 310 patients who completed treatment for six months with either interferon alpha 2a or 2b. Mean age was 34.07 ± 9.38 years ranging from 10 to 65 years. Male patients were 162 (52.3%) with majority being laborers, drivers or students, while 47.7% females were housewives with less than primary education and they were taken at time of enrollment of the individuals prior to starting the treatment. Pre treatment mean ALT levels of 72.25 ± 49.33 U/L, ranging from 15 to 231.

Commoner side effects seen during treatment within both groups (Table I) were fever initially, followed by fatigue, headache, musculoskeletal pain, depression, alopecia, insomnia, anorexia and nausea. Other complaints such as diarrhea, inflammation at site of injection and abdominal pain were less common. Overall patients treated with alpha 2b had a higher rate of side effects (Table I). On further analysis it was noted (not shown in the table) that most patients experienced these symptoms in the first 3 months. In the following months, symptoms gradually decreased in intensity. Demographic data of patients in group A and B, cultural background, previous treatment if any, genotype, lab data after treatment, HBV vaccination status, and follow up of patients is shown in Table II.

Difference between ETR (absence of HCV RNA in blood sample after 6 months of treatment) and SVR (absence of HCV RNA in blood sample after 6 months of completion of therapy) was not significant when the 2 interferon groups were compared. In those with alpha 2a, 83.8% were HCV RNA PCR negative at the end of six months (ETR) vs. 83.2% in group B. Also, 87.15% in group A vs. 83.3% in group B had a negative PCR at the end of six months of completion of treatment (SVR). The average cost of treatment in group A (interferon alpha 2a, FDA-approved) was Rs.60,000 vs. 30,000 for group B (interferon alpha 2b, non-FDA-approved).

Table I: Comparison of side effects with interferon alpha 2a (FDA-approved products) or interferon alpha 2b (non-FDA-approved products) in combination with ribavarin in HCV-RNA-PCR positive, genotype 3 patients.

Side effects	Group A (alpha 2a) N=155 n (%)	Group B (alpha 2b) N=155 n (%)	*p-value
Fever	122 (78.7)	136 (87.7)	0.06
Cough	28 (18.1)	60 (38.7)	0.001
Blisters in mouth	22 (14.2)	47 (30.3)	0.001
Fatigue	105 (67.7)	123 (79.4)	0.06
Headache	63 (40.6)	102 (65.8)	0.001
Musculoskeletal pain	61 (39.4)	100 (64.5)	0.001
Malaise	44 (28.4)	95 (61.3)	0.001
Nausea	44 (28.4)	69 (44.5)	0.009
Anorexia	50 (32.3)	88 (56.8)	0.001
Diarrhea	22 (14.2)	18 (11.6)	0.05
Abdominal pain	36 (23.2)	64 (41.3)	0.002
Dyspepsia	39 (25.2)	60 (38.7)	0.014
Vomiting	9 (5.8)	24 (15.5)	0.006
Insomnia	63 (40.6)	79 (51.0)	0.047
Depression	58 (37.4)	88 (56.8)	0.003
Irritability	58 (37.4)	87 (56.1)	0.004
Anxiety	62 (40.0)	75 (48.4)	0.122
Impaired concentration	34 (21.9)	52 (33.5)	0.033
Emotional liability	24 (15.5)	47 (18.1)	0.006
Alopecia	63 (40.6)	93 (60.0)	0.003
Rash	14 (9.0)	28 (18.1)	0.018
Pruritis	31 (20.0)	52 (33.5)	0.016
**Dry skin	68 (43.9)	72 (46.5)	0.366
Inflammation at Injection site	9 (5.8)	25 (16.1)	0.001

*Chi-square was applied to obtain p-values; *p-value is significant when less than 0.05; ** Fischer's exact was applied to obtain p-value; N= Total number of patients; n= number of patients experiencing side effects.*

Table II: Comparison of demographics, cultural background, risk factors, ALT, ETR and SVR in HCV RNA PCR positive, genotype 3, patients treated with combination therapy of interferon alpha 2a (FDA-approved products) or alpha 2b (non-FDA-approved products) with ribavarin.

Characteristics	Alpha 2a (n=155)		Alpha 2b (n=155)	
Demographic data				
Mean age (yrs) (SD)	33.65 (9.03)			34.46 (9.72)
Gender (Male) n (%)**	95 (61.3)		67 (43.2)	
Females				
Mean Weight (kg±SD)	57.8±13.44			54.10±10.43
Mean Height (cm±SD)	155.8±6.3		155.3±5.96	
Mean BMI (kg/m²±SD)	23.51±5.17			22.4±4.47
Males				
Mean Weight (kg ±SD)	61.15±11.03			60.89±8.83
Mean Height (cm±SD)	167.46±7.52		65.12±8.61	
Mean BMI (kg/m²±SD)	21.66±3.36			22.39±4.14
Cultural background	n (%)			n (%)
Urdu speaking	31 (20.3)		33 (21.5)	
Sindhi	26 (16.8)		37 (24.2)	
Pashto	36 (23.1)`		42 (26.8)	
Punjabi	42 (27.3)		21 (13.4)	
Balochi	20 (12.6)		22 (14.1)	
	†n	††n (%)	†n	††n (%)
Vaccinated for HBV**	144	58 (40.3)	152	12 (7.9)
‡Risk factors				
Dental treatment	51	23 (45.1)	89	43 (48.3)
Surgery	51	15 (29.4)	89	36 (40.4)
Blood transfusion	143	25 (17.5)	153	28 (18.3)
H\O injection**	142	115 (81)	153	137 (89.5)
H\O jaundice	142	50 (35.2)	153	49 (32.0)
Hospitalization	143	54 (37.9)	153	64 (41.8)
Investigation	Mean (SD)		Mean (SD)	
ALT (U\L)	81.88±52.27		72.59±45.89	
	†n	††n (%)	†n	*††n (%)
ETR (negative)	155	130 (83.8)	155	129 (83.2)
SVR (negative)	70	61 (87.1)	72	61 (83.3)

*†Total number; ††data out of total number; SD = Standard deviation; U\L = Unit per liter; **= p < 0.001; ‡= More than 1 risk factor was present in every patient; Alpha 2a= Interferon alpha 2a (FDA-approved product); Alpha 2b= Interferon alpha 2b (non-FDA approved product).*

DISCUSSION

This study compared an important understudied point of HCV treatment that is treatment performance of regime when interferon alpha 2b products (non-FDA-approved) is substituted for interferon alpha 2a products (FDA-approved) for cost and affordability issue.

Counseling was done with every patient and despite their low literacy rate majority understood and followed instructions for injections and had an excellent follow-up.

Since the likelihood of response to therapy in our patients with genotype 3 is high[11] and duration of therapy so much shorter,[6] therefore all the patients did not have a liver biopsy, prior to therapy. More recent studies recommend that a liver biopsy may be unnecessary in persons with genotypes 2 and 3 HCV infection,[11] since more than 80% of them achieve a SVR to standard-of-care treatment. Qualitative HCV RNA based on polymerase chain reaction (PCR) was done in majority of our patients, with lower quantitation limit of ≤ 50 IU/mL.[12]

Some of the patients who were treated but showed hepatic steatosis on histologic evaluation are still being followed. Follow-up of these patients will indicate if steatosis is a negative predictor of response to antiviral therapy, especially in patients with genotype 3 as also seen in other studies.[13]

In this study, interferon alpha 2a and 2b were both used. PEG interferon was not used in this cohort of patients at our institute and patients could not afford it. Even with the interferon alpha 2a or 2b plus ribavarin, more than 80% of our patients had qualitative PCR negative at 6 months (ETR) and 121/142 (85.2%) had a SVR.

Available SVR in group A was 60/155, 85 patients were lost to follow-up. While in group B, SVR available was 61/155 and 83 were lost to follow-up. The drawback of this study was the unavailability of SVR results as despite counseling some patients did not return after six months for SVR, they either came after one year or were lost to follow-up, even then the attrition rate in this study was around 48% which is below the normal limit of what is acceptable.[14] Hence in group A, 60/70 (87.1%) and group B, 61/72 (83.3%) had obtained an SVR. Overall SVR was 80% which is comparable to previous studies.[15]

ALT and AST testing is an important component of the diagnostic evaluation in patients with chronic hepatitis C, but elevation of ALT is not required for therapy.[6] Hence, these patients were treated with normal or raised ALT. However, very few patients with normal ALT had biopsies done prior to treatment, as majority of this cohort of patients had raised ALT prior to treatment. Response of ALT to treatment was as expected in most studies that is less than 30 around the 3rd month of therapy.[11]

Adverse effects were more severe in the initial weeks of treatment. These patients were managed with analgesics such as acetaminophen (< 0.2 grams per day), in non-hepatotoxic doses,[10] or NSAID; antidepressants such as selective serotonin reuptake inhibitors (SSRI) were given when needed after psychiatric consultation. More than 50% of the patients suffered from fever, headache initially, followed by fatigue, musculoskeletal pain, malaise, irritability, depression (diagnosed on the basis of clinical evaluation), alopecia, insomnia, anorexia and nausea.

Symptoms occurred predominantly in the first few months. Following which most of the side effects decreased in intensity. Patients were counseled to have plenty of water so that the side effects can be minimized. Frequencies of side effects were less in patients treated with interferon alpha 2a versus interferon alpha 2b. Studies have been done only on pegylated interferon alpha-2a and ribavarin versus interferon alpha 2b plus ribavarin which showed that flu like symptoms and depression occurred less frequently with PEG interferon alpha 2a compared to regular interferon alpha 2b.[16]

All patients were counseled, regarding strict contraception methods, both during treatment and for a period of six months after treatment. However, despite counseling four patients became pregnant and aborted. At least 10 patients had to discontinue treatment, due to depression.

CONCLUSION

A comparison of the two groups A and B (interferon alpha 2a and interferon alpha 2b) showed a significant difference (p value < .005) in side effects, more so with alpha 2b. However, ETR and SVR did not show a statistical significance between the two groups.

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