SIDE EFFECTS OF COMBINATION OF INTERFERON PLUS RIBAVIRIN THERAPY IN PATIENTS WITH CHRONIC HEPATITIS C; AN EXPERIENCE WITH 400 PATIENTS

Khalid Mahmood, Noor Muhammad

Department of Medicine,
Postgraduate Medical Institute, Lady Reading Hospital Peshawar and
DHQ Hospital Daggar Buner – Pakistan

ABSTRACT

Objective: *To assess the side effects of combination therapy of interferon plus ribavirin in chronic hepatitis C patients.*

Material and Methods: *This prospective observational study was conducted in Medical unit DHQ hospital Daggar and a private clinic of consultant physician in Peshawar from January 2001 to June 2004. A total of 400 patients of chronic hepatitis C with positive Anti HCV (hepatitis C virus) antibodies and HCV RNA by polymerase chain reaction (PCR) were enrolled in the study. These patients received combination therapy of interferon plus ribavirin for six months. During each visit these patients were assessed for various unwanted effects related to the treatment. These side effects were graded as mild, moderate and severe.*

Result: *The most common side effects observed in our patients were haematological in 92.5% (n=370), flu like symptoms in 91% (n=364)., gastro intestinal in 88.5% (n=354), dermatological in 81.5% (n=326), neuropsychiatric in 71.25%(n=285), respiratory symptoms in 14% (n=57), thyroid function abnormalities in 4% (n=16), major depression in 1% (n=4) and suicide attempt in 0.5% (n=2). Most of the side effects were mild to moderate. The severe adverse effects that led to reduction in dose or withdrawal of treatment were noted in 50 (12.5%) patients.*

Conclusion: *Treatment of hepatitis C with combination therapy is not without harmful effects. Most of the side effects are attributed to interferon and some to ribavirin.*

Key words: *Chronic hepatitis C, Combination therapy, Side effects.*

INTRODUCTION

Hepatitis C virus (HCV) infection is evolving public health problem globally. The virus [1] infect approximately 3% of the world population, placing approximately 170 millions people at risk for developing HCV related chronic liver disease. [2] The natural history of HCV infection is characterized by acute asymptomatic or mildly symptomatic phase. More than half of these patients then become chronically infected with the virus. [3,4] Hepatitis C virus infection is an important etiological agent for chronic hepatitis, hepatic cirrhosis and hepatocellular carcinoma. [5] In Pakistan, although hepatitis B virus (HBV) is an important cause of chronic liver disease, HCV is emerging rapidly as an infection warranting attention. [6, 7]

Therapy for chronic hepatitis C infection has evolved substantially over the past decade. An effective treatment is now available in the form of combination therapy with interferon and ribavirin which has led to marked improvement in response rates. [8,9] This type of treatment is cost effective but produce wide range of side effects, which becomes troublesome for some of the patients. One of the barriers to adherence in combination therapy for chronic hepatitis C is that treatment associated side effects that can lead to dose reduction or sometime premature discontinuation. [10] It is therefore essential to monitor the patients at regular interval during treatment to detect the undesirable effects timely and to manage them properly. This study was designed to assess the spectrum of the side effects of combination therapy (interferon and ribavirin) in patients having chronic hepatitis C.

MILD TO MODERATE SIDE EFFECTS

Side Effects		Frequency (n = 400)	%age
Haematological side effects		**370**	**92**
	Mild to moderate anaemia (Hb>8.5g/dl	280	70
	Mild to moderate leukopenia	256	64
	Asymptomatic thrombocytopenia (platelet count>50000)	244	61
Flu like symptoms		**364**	**91**
	Fever	280	70
	Fatigue	268	67
	Headache	248	62
	Myalgia	216	54
	Rigors	160	40
	Arthralgia	136	34
Gastrointestinal side effects		**354**	**88.5**
	Nausea	220	55
	Loss of appetite	140	35
	Dyspepsia	64	16
	Constipation	20	05
Dermatological side effects		**326**	**81.4**
	Photosensitivity	96	24
	Loss of hair	152	38
	Pruiritis	60	15
	Skin rashes	32	08
Neuropsychiatric side effects		**285**	**71.4**
	Insomnia	140	35
	Irritability	112	28
	Depression	80	20
	Anxiety	48	12
	Emotional instability	40	10
	Suicide ideas	4	0.5
Local reaction at the site of injection		**84**	**21**
	Erythema at the site of injection	80	20
	Injection abscesses	4	01
Respiratory problems		**57**	**14.5**
	Rhinitis	40	10
	Pharyngitis	32	8
	Tightness in chest	16	4
Thyroid function abnormalities		**16**	**4**
Retinopathy		**2**	**8**

Table 1

MATERIAL AND METHODS

This prospective observational study was conducted in a private clinic of consultant physician in Peshawar and DHQ hospital Daggar from January 2001 to June 2004. A total of 442 patients were initially enlisted in the study, there age ranging from 20-60 years (means 39.5+ 10). Out of these 442 patients, 400 completed follow up. There were 201 male and 199 female patients. The remaining 42 patients were either lost (22), or did not come for regular follow up (20). They were excluded from the final analysis. Inclusion criteria was that all Patients with chronic hepatitis C, raised Alanin Aminotransferase (ALT), positive HCV antibodies by 3rd generation Elisa and positive HCV RNA by polymerase chain reaction (PCR) were included in the study. Exclusion

SEVERE SIDE EFFECTS OF THERAPY

Sever Side Effects		Frequency (n=400)	%age
Haematological side effects		**42**	**10.5%**
	Severe anaemia	34	8.5%
	Severe neutropenia	12	3%
	Severe thrombocytopenia	4	1%
Neuropsychiatric side effects		**6**	**1.5%**
	Major depression	4	1%
	Suicide ideation	2	0.5%
Severe thyrotoxicosis		**2**	**0.5%**

Table 2

AGE AND SEX DISTRIBUTION OF STUDY PATIENTS

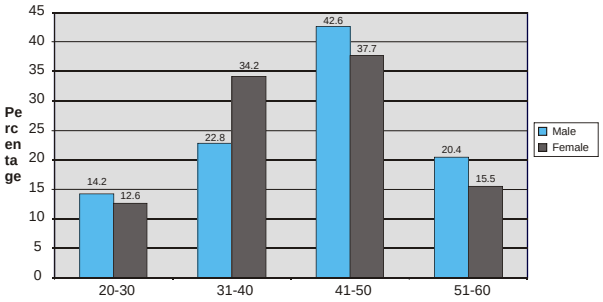

Figure 1

criteria was that patients with evidence of decompensated liver disease; serious underlying medical illness and patients who had other contraindication to combination therapy.

After verbal consent and base line investigations, the patients were given injection Interferon 3 MIU subcutaneously thrice weekly & ribavirin 800 to 1200 mg/day, as per their body weight i.e. those less than 50 kg received 800 mg/day, 50-75 kg received 1000mg/day and more than 75 kg received 1200 mg/day. These patients were evaluated at week 1, 4, 8, 12, 16, 20 & 24 for various side effects. Patients were also encouraged to report any unwanted effects anytime during the course of treatment. These unwanted effects were graded as mild (not requiring consultation and not affecting quality of life), moderate (requiring consultation, reassurance and symptomatic treatment) and severe (requiring reduction or discontinuation of treatment). Finally data was analyzed to analyse side effects of combination therapy of interferon plus ribavirin in chronic hepatitis C patients.

RESULTS

Four hundred chronic hepatitis C patients who received the combination treatment were included in the study. Otherwise they in (male = 201, female = 199). Their ages ranged between 20-60 years with mean age of 39.5 + 10 years (figure 1). There were a number of side effects observed during the treatment. The frequency of mild to moderate side effects, which improved with explanation, reassurance and simple medication, is given in table 1. *Flu like symptoms* were observed in 91% (n=364) cases. These included fever (70 %), headache (62%), fatigue (67%), myalgia (54%), rigors (40%) and arthralgia (34%). *Haematological side effects* were noted in 92% (n=370) cases. Mild to moderate anaemia (Hb>8.5g/dl) was noted in (70%) patients, mild to moderate leukopenia in 64 % patients The leucocytes counts decreased during therapy with a mean value 3200 + 850 per cubic millimetre. The lowest leucocytes count experienced was 2100 per cubic millimeters. Asymptomatic thrombocytopenia was seen (platelet count>50000) in 61% patients. *Neuropsychiatric side effects* were noted in 71.4% (n=285) of patients and included insomnia (35%), irritability (28%), anxiety (12%), emotional liability (10%), depression (20%) and suicidal tenderly ideation (0.5%). *Gastrointestinal symptoms* were noted in 88.5% (n=354) patients. The symptoms were loss of appetite (35%), *nausea (55%), dyspepsia (16%) and constipation (05%). Dermatological side effects* were noted in 81.4% (n=326) patients and included photosensitivity (24%), loss of hair (38%), pruiritis (15%), and skin rashes (08%). *Local reaction* at the site of injection included erythema at the site of injection (20%) and *injection abscesses* (01%). *Respiratory* problems were noted in 14.5% (n=57) patients. They were rhinitis (10%), pharyngitis (8%) and tightness in chest (4%). *Thyroid function abnormalities* were noted in 4% (n=16) of the patients. *Retinopathy* was found in two cases. One had cotton wool exudates and the other had retinal haemorrhages. Both the patients were diabetic. The *severe adverse effects* which led to reduction in dose or withdrawal of treatment were noted in 50 (12.5%) patients (Table 2). They were haematological; Severe anaemia (Hb <8.5gms/dl) in 8.5%, severe neutropenia (absolute count 500 mm^3) was noted in 3% of patients and severe thrombocytopenia (platelet count <30000) in 1% only. Erythropoietin was used in two patients with

improvement in anaemia. Only two patients had evidence of infection due to neutropenia. Bleeding attributed to low platelet count was not noted. The major Neuropsychiatric side effects included major depression in 4 patients out of 400, depression with suicide attempts in 2 patients. Severe thyrotoxicosis was seen in 2 patients only.

DISCUSSION

Treatment of hepatitis C with combination therapy is not without unwanted effects. Most of these side effects are attributed to interferon and some to ribavirin. The adverse effects noted in this study were generally mild to moderate except in few patients in whom treatment had to be withdrawn due to serious side effects. Influenza like symptoms occurred in most of the patients (91%) during the first month of treatment. They were usually alleviated by explanation and simple analgesics like paracetamol. Giuseppe B et al [11] have reported influenza like symptoms in 77.7% of the patients with combination therapy and 65% of the patients with Interferon alone. Haematologic adverse event were the commonest laboratory abnormalities leading to dose modification or stoppage of therapy. Mild to modest anaemia was noted in 70 % of the patients. The mean drop in the haemoglobin concentration in the first month of the treatment was 3.5 g/dl. The haemoglobin level ranged between 8.5 g/dl and 12 g/dl in majority of these patients (70%). The dose of ribavirin was decreased in over 8 % of the patients in whom the haemoglobin fell below 10g/dl. A reduction in the dose resulted in an increase in haemoglobin concentration and it remained stable through out treatment. The haemoglobin concentration returned to base line within four to eight weeks after the completion of treatment. Discontinuation of ribavirin was necessary in 8.5% patients, in whom the haemoglobin fell below 8.5 gm/dl. Anaemia is caused both by interferon due to myelosupression and ribivirin causing haemolysis. [12,13] The leucocytes counts decreased in 64% patient during therapy with a mean value 3200 + 850 per cubic millimetre. The lowest leucocytes count experienced was 2100/Ul. Neutropenia is one of the expected side effects of combination therapy but the risk of serious infection is very low even with severe neutropenia as was the case in our study. [14] Neutrophil count rapidly returned to baseline after treatment is discontinued. Asymptomatic thrombocytopenia (platelet count>50000) was seen in 61% patients and severe thrombocytopenia (platelet count <30000) in 1% only. Clinically, thrombocytopenia does not pose significant problem unless the patient is having pre-existing thrombocytopenia. [10] The neuropsychiatric side effects were noted in 71% patients. They are mostly attributed to interferon. The exact mechanism is unknown. These effects include fatigue, asthenia, drowsiness, confusion, depression and apathy. Severe depression was observed in six patients and two had suicide ideation with suicide attempt. Depression has been reported to be as high as 30% in patient receiving combination therapy for chronic hepatitis C. [15] Dieprink E et al [16] have reported a suicide in patients with out a previous psychiatric history. These neuropsychiatric side effects respond to selective serotonin reuptake inhibitor and regress after discontinuing therapy, albeit after some weeks. None of our patient had seizure reported in 1.3 % of patients in literature. [17] Dermatological side effects were noted in 81 % patients and ranged from photosensitivity, dry skin, pruiritis, itching and alopecia. Respiratory symptoms were noted in 14% of patients. Thyroid function abnormalities were noted in 4% (n=16) of the patients. Hyperthyroidism occurred in two patients in whom there was diffuse enlargement of the thyroid gland with increase in T3 and T4 and suppression of TSH. The mechanism seems to be related to immuno-modulatory properties of interferon, which induces non-organ specific antibodies causing autoimmune thyroiditis. Thyroid disorders have been reported in 2.5 to 20 % of patients. Both hypothyroidism and hyperthyroidism can occur [18-20] Retinopathy was found in two cases. One had cotton wool exudates and the other had retinal haemorrhages. Both the patients were diabetic. Retinopathy is well-documented side effect of interferon and ribavirin therapy. [21] The side effect profile of our patients is comparable with that of Khan AQ et al [22], who reported fever in 68.9 %, myalgia 49.3 %, headache 39.4 %, fatigue 35.5 %, arthralgia 36.9 % and erythema at injection site 9.9%. In another study conducted in Peshawar by Khan PM et al [23] reported flu like symptoms in 80 %, gastrointestinal in 50 % and depression in 20 %. [23] Part of the discrepancy in some of the side effects is due to the non-specific nature of these complaint, being common in the population at large. Also chronic hepatitis C patients not on treatment do have these constitutional symptoms and therapy could not be the sole reason for these side effects.

CONCLUSION

Combination therapy is not without harmful effects. Most of the unwanted effects are well tolerated by the patients. Some patient had serious untoward effect.

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Address for Correspondence:
Khalid Mahmood
Assistant professor of Medicine,
Medical "C" unit, Post Graduate Medical Institute,
Lady Reading Hospital, Peshawar – Pakistan.