Adverse Effect Profile of Patients Receiving Anti Viral Treatment for Chronic Hepatitis C Virus Infection

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Chronic hepatitis C virus infection is present in 3 – 10 % of Pakistani population and genotype 3 is the most prevalent subtype in our patients. In a suitable candidate interferon along with Ribavirin is the main stay of treatment for these patients. These drugs have short as well as long term safety problem. Morbidity and frequency of discontinuation of therapy correlate directly with the frequency of adverse events while on treatment. **Objectives:** This observational study has been conducted to find out the adverse effect profile of anti viral treatment for our Chronic HCV patients. **Material and method:** From 1st March 2005 to 30th March 2005, 100 consecutive patients suffering from chronic HCV infection receiving standard interferon alpha 2 b and ribavirin were included. All of them were inquired on a questionnaire about the adverse events and then analyzed. **Results and discussion:** In as many as 65 % of the patients receiving anti viral treatment complained of an adverse event. The events were in the form of Flu like symptoms, abdominal pain, sleep disturbance, lack of appetite, dry cough and breathlessness, Depression, persistent fever, anemia, thrombocytopenia, neutropenia and skin rash. **Conclusion:** A high number of pts receiving anti viral treatment for ch. HCV infection suffer from adverse events.
Key words: Interferone, Hepatitis C, Ribavarine

Chronic HCV infection is present in 3-10% of our general population and in a suitable candidate anti viral treatment in the form of Interferon and Ribavirin are the main management options[1]. In genotype 3, the most prevalent subtype, this combination gives an end of treatment success rate of 80-87% and sustained viral response of 65-80 %[2]. These medicines are toxic and have short as well as long term adverse effects on the health of the patients. In various studies, 10-25% of the patients have to discontinue the treatment because of the adverse events. The list of the adverse events is generally long and can be divided in to clinical events related to one of the two components of treatment, either fatal, or potentially life threatening, or significantly or permanently disabling, or requiring inpatient hospitalization or minor events not requiring any dose adjustment or with drawl. These adverse events can occur in one, or combination of two, three, four and more in a given case. The ratio of discontinuation of therapy relates directly to the occurrence and nature of these adverse events[3]. If the adverse events are minor and predictable, then an explanation and or minor pharmacological intervention can keep the person compliant to the treatment and if the nature of the adverse event is serious or major, then as a treating physician it is important to either modify the treatment or withdraw the treatment depending upon the nature of the event. A better understanding of the adverse events and toxicities of these drugs in our population can help us in better management of these events and early with drawl of these medicines in case of fatal or potentially serious adverse events. The combined treatment of interferon and ribavirin is lengthy and 6-12 months therapy is recommended for the patients suffering from genotype 3 HCV infection[4]. There is long list of adverse events that can occur with interferon and Ribavirin (Table 1) and their occurrence is independent of the subtype and stage of the disease as long as the patient is not already suffering from liver cirrhosis. Co existing medical conditions do increase the risk of development of these events. Majority of the associated events are minor, predictable and manageable with the minor interventions, some require dose modification of the two drugs, some need drug with drawl and occasionally these events are serious requiring hospitalization of the patient.

Objectives: In this observational study it was intended to chart the adverse event profile of our patients receiving interferon alpha 2 b along with ribavirin for the management of HCV infection.

Material and method:

100 consecutive patients receiving Injection Interferon alpha 2 b (3 million units subcutaneously, thrice weekly) and Ribavirin (15mg/kg) for chronic HCV related hepatitis in the absence of any clinical evidence of cirrhosis at various stages of the treatment were examined on a questionnaire Performa for any on going or previously occurred adverse event. Number of hospital admissions and dose adjustments were recorded. The study was conducted in an out patient clinic and all patients presenting from 1st march 2005 to 31st march 2005 were included.

Results:

51 % of these 100 patients were males while 49% of them were females. The patients ranged in age from 13–66 years with a mean age of 35.5 years. They were all anti HCV antibody positive with raised ALT, positive HCV RNA on PCR and genotype 3 with no clinical, biochemical and imaging evidence of liver cirrhosis. 54% of these patients belonged to Gujranwala division, 33% belonged to Lahore division and rest were scattered from various regions of province Punjab ranging from Attock to Rahim Yar khan. Majority of the patients complained of one adverse event, while 35% complained of a combination of two, 24% complained a combination of three, 10% complained a

combination of four adverse events while 2% complained a combination of five or more adverse events. None of the patients examined in this series required hospital admission for these adverse events, 6% necessitated withdraw of Ribavirin, 15% needed a dose adjustment of Ribavirin, while 20 % needed an additional drug for the control of the adverse profile and 2% needed discontinuation of the therapy. The list of observed adverse events are given along with its graphical comparative representation (fig. 1).

Table 1: Side effects of interferon-alpha

Side-effect	Frequency of cases/1000	Comment
Fever Lethargy Insomnia Diarrhoea	Common early side-effects in most patients treated	Resolve partially by administration of paracetamol or non-steroidal anti-inflammatory drug
Depressive symptoms	Worse later in treatment	May need antidepressant Risk of suicide attempt if severe 5/6 severe thrombocytopenia
Serious haematological side-effects	0.52	
Mortality	0.44	4 deaths from liver failure, 1 from sepsis
Thyroiditis	0.7	Incidence of thyroid dysfunction of 0.6%; this should be monitored
Hypothyroid ism	2.57	
Hyperthyroidism	3.0	
Impotence	0.44	
Rheumatoid arthritis	0.26	
Henoch-Schonlein purpura	0.08	
Sjogren's syndrome	0.08	
Lichen planus	0.8	
Psoriasis	0.26	
Vitiligo	0.16	
Diabetes	0.88	
Cardiovascular	0.62	
Psychosis	0.88	
Seizures	0.35	
Peripheral neuropathy	0.26 0.16	
Haemolytic anaemia		

Table – 2 :Side effects of interferon-a and ribavirin in hepatitis C.

Side effects of interferon-a and ribavirin
Leukopenia
Neutropenia
Thrombocytopenia
Hemolytic anemia
Fatigue
Depression and other psychiatric symptoms
Flu-like symptoms: fever, myalgias
Gastrointestinal symptoms: nausea, anorexia
Respiratory symptoms: dyspnea, cough
Diabetes management: irregular glucose control
Thyroid dysfunction: hyperthyroidism, hypothyroidism
Dermatologic symptoms: rash, alopecia

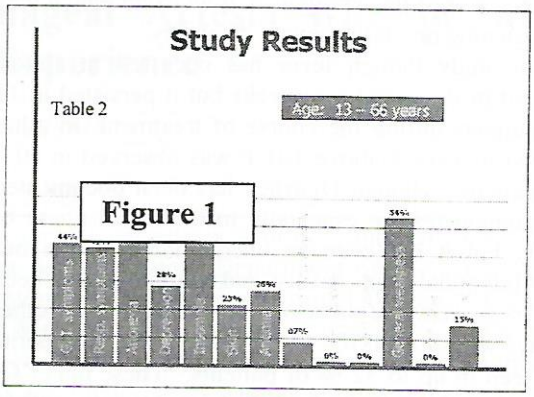

Fig: 1

Discussion:

HCV infection is associated with a high chronicity rate and is highly prevalent in our society. Because of silent nature of the disease, unawareness, poor health infrastructure, lack of financial resources, and fear of short as well as long term drug toxicity, very few patients seek the curative treatment for this infection.[5] The available treatment for Hepatitis C virus infection is far from ideal and standard interferon and ribavirin is associated with viral eradication rates of 35-54% in genotype 1 while 75 - 100% for genotype 2 and 3. The treatment has to be given for 6 months to one year for achieving and maintenance of remission from HCV infection. Few studies have shown the efficacy of 12 weeks therapy as well in genotype 2 and 3 patients but these studies are yet to be reproduced. This lengthy treatment is associated with a long list of adverse events and various studies have shown various proportions of the patients having adverse events because of the combination of interferon and Ribavirin. These adverse events are broadly classified in to upper respiratory flu like symptoms, hematological abnormalities, and neuropsychiatric manifestations. People who have been counseled properly tend to tolerate the adverse events better and similarly a strong family support or patient support groups help in better tolerance of the adverse events. 10-14 % of all the patients appear to drop out of the studies because of intolerance to the combination of interferon and Ribavirin.[3] There are certain adverse events which can be managed with simple pharmacological interventions e.g. addition of Paracetamol before giving interferon injection or a sleep tablet for insomnia, or person may be managed with explanation and motivation e.g. asthenia and lack of appetite. But at times a major intervention is required for the management of certain adverse events e.g. anemia in which either a dose reduction of Ribavirin or addition of recombinant erythropoietin is required to correct the hematological values.[6] This combination therapy has to be stopped by the patient because of intolerance or inability to suffer any more from the events mentioned in Table 3 or by the treating

physician because of the emergence of an event which may be life threatening or having severe disability.

In our study though fever has occurred in almost every patient in the initial few weeks but it persisted in 11 % of all patients during the course of treatment. In other studies persistent fever above 101 F was observed in 10 – 25 % of patients. Though Diarrhea has been documented to be a common feature especially in the initial phase of the therapy but it has been an uncommon event in our patients. Abdominal pain, nausea and vomiting have been observed in as many as 44% of our patients while other studies have a figure of 10- 14 % only. Lack of appetite has been seen in up to 52 % of patients.[3] These upper GI symptoms have been though disturbing for our patient population but they were managing them through with the hope that they shall be able to clear the virus towards the end of the day. Flu like symptoms e.g. nasal stuffiness, dry cough, hoarseness and throat irritation was seen in 63 % of patients. These symptoms have been fluctuant and of mild to moderate severity, and the patients managed themselves through the treatment with the help of menthol tablets, cough suppressants and placebos. The upper respiratory Flu like symptoms has been observed in more than 80 % of patients especially in the early weeks of the therapy. Breathlessness, asthenia and lack of stamina has been a common complaint (54%) in our patients. Other studies have described these symptoms in different ways, few have classed them as asthenia, others have labeled as cardiorespiratory symptoms and has occurred in as many as 55 – 70 % of patients.[7] Depression has been seen in 28% of the study population which is comparable to the other studies showing an incidence of 25-30%.[9-3] These patients were managed with addition of SSRI for the rest of the period of treatment. Insomnia has been a common complaint and was a problem in as many as 51 % of total number of patients. This problem was managed by reassurance, explanation and addition of benzodiazepines like Alprazolam, Bromazepam and other agents of the same group. Other studies have mentioned sleep disturbance under the neuropsychiatric disturbances but a separate mention of insomnia could not be found. Hematological abnormalities were noticed in the form of anemia (Hb. <10 Gms/dl) in 27%, Thrombocytopenia (Plt count < 50000cmm) in 7 % and neutropenia (neutrophil count < 500cmm) in 0 % of the study population. These patients were managed with addition of recombinant erythropoietin for anemia and reduction of dosage of interferon for thrombocytopenia. The incidence of thrombocytopenia and neutropenia is less in our study population as compared to the other studies conducted in the past. Clinical autoimmunity, neuropathy, and vasculopathy at times occur but it was not observed in this series of patients. Other studies have reported them to occur in 3-5% of their patients.[8] 2 patients developed severe skin reaction necessitating discontinuation of the therapy. Except for these two patients all other were able to complete the course of treatment (2%). This discontinuation rate is much less as compared to the other published studies having a discontinuation rate of 10-14%. The rate of withdrawal from treatment is known only from clinical trials in which an unusually high level of commitment is typical. In these settings, the withdrawal rate increases with both the duration of treatment and the use of combination therapy. For example, therapy was stopped in 13% to 14% of patients treated with interferon monotherapy for 48 weeks compared with 19% to 21% of patients receiving combination therapy for the same duration. The withdrawal rate for combination therapy was lower when therapy was administered for only 24 weeks (8%)[10].

Conclusion:

Although adverse events occur in majority of the patients receiving anti viral treatment making this lengthy course of treatment uncomfortable but majority of patients can complete the course of treatment required to achieve viral eradication. Asthenia, insomnia, depression and anemia are particularly common in our patients. Diarrhea and leucopenia are uncommon complaints in our patients and majority of our patients are able to complete the course of treatment. The severity of adverse events can be reduced by addition of pharmacologic agents specific for the alleviation of the symptom.

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