Original Article

NEUROPSYCHIATRIC ADVERSE EFFECTS OF HVC TREATMENT AND THEIR IMPACT ON THE TREATMENT RESPONSE

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Objective: Hepatitis C (HC) is an infectious disease of the liver and is associated with multiple complications. It has been reported that the medicines, which are being used to treat HC, cause neuropsychiatric adverse effects like depression, sleep disturbances, insomnia and irritability. Moreover, hepatitis C virus (HCV) infection itself is also strongly associated to psychiatric disorders. This study was conducted to check the impact of these neuropsychiatric adverse effects on treatment outcome.

Method: A prospective study was designed to look for the neuropsychiatric adverse effects in HCV genotype 3a infected patients, as HCV 3a is on the top to causeHCV infection in South East Asian population, when treated with Interferon alpha and ribavirin (INF + RV) or pegylated interferon alpha and ribavirin (Peg INF + RV) and their effects on treatment outcome.

Results: This study was conducted in two different public hospitals of Lahore. It was found that these patients had depression, anxiety, emotional lability, irritability and insomnia. It was also observed that the patients who were treated with INF + RV had higher frequency of neuropsychiatric adverse effects. Moreover, when we compared the occurrence of these adverse effects with other populations our study group had much lower frequency.

Conclusion: It was concluded that a multidisciplinary tam approach with timely strategies could improve the treatment outcome of HC patients.

Key words: hepatitis C, Hepatitis C virus, neuropsychiatric adverse effects, treatment outcome

INTRODUCTION:

Even though HC infection is the one, being on the top of virus-induced liver diseases in many parts of the world, and has acquired endemic proportions in our population[1] but unlike other, chronic infectious diseases people infected with HC can be cured of the virus. It is also true that when liver fails to eradicate the virus, the infected individuals become chronic carriers. Patients with chronic infections can behave in different manner, ranging from mild (minimal inflammation of the liver) to severe illness leading to tissue fibrosis, cirrhosis resulting in hepatocellular carcinoma (HCC) or/ andfinally death[2]. There are seven major genotypes of HCV, which differ by about 30 per cent in their nucleotide sequence, and are known as genotypes one to seven[3]. Statistically there is no difference in HCV genotypes in terms of age and sex of the patients in Pakistan, in contrast to reports from developed countries like USA and Southeast Asia, where lifestyles among young adults affect the molecular epidemiology[3].

The hepatitis C (HC) treatmenttargets to eradicate HCV infection.Complete eradication of HCV reduces the risk of progression to HCV-related liver complications. Sustained virologic response (SVR) correlates strongly with a permanent clearance of the virus and successful cure[4-5]. European Association for the study of liver (EASL) has recommended that while treating HC patients the treatment safety can be monitored by assessing the

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patient for the clinical adverse effects at each visit. Flu like symptoms caused as a side effect of therapy usually subsides after 4-6 weeks of therapy[6]. There are different factors which can alter treatment response, which include genotype of the infecting HCV, the race to which the patient belongs and proper and timely treatment,being on the top.HCV itself is also profoundly connected to psychiatric disorders[7-8]. The patients of HC are preferably treated with IFN-alpha or Peg INF-alpha in our population. It is responsible to induce a variety of neuropsychiatric adverse effects such as acute anxiety, irritability, insomnia, depression, and agitated manic episode[9]. The treatment outcome is mainly dependent upon the compliance of the patient to the medicines[6]. Most of the time the treatment is to be discontinued or the dose of the drugs is to be reduced due to these adverse effects, whichin turn can affect the treatment outcome. So, a study was designed to evaluate the neuropsychiatric adverse effects and their impact on treatment outcome in patients with HCV genotype 3a infection in our local population.

METHODOLOGY:

Total 84 patients infected with HCV 3a genotype were included in the study after an informed written consent. Patients with neuropsychiatric disorders, anemia (hemoglobin concentration, less than 12g/dl in women and less than 13g/dl in men), pregnant women, men whose female partner is pregnant, not willing to take contraceptive measures and patients with human immunodeficiency virus infection were excluded from the study. A structured data collection form was designed to record all findings. Our study group was divided into two main groups. Group 1 included the patients, who were infected with HCV Genotype 3a and were treated with INF + RV. Group 2 included the patients who were infected with HCV Genotype 3a and were treated with Peg INF + RV.

To record the adverse effects, patients were followed every month as per EASL (European Association of the Study of the Liver) recommendations for the treatment of hepatitis C, 2014. The European Expert Consensus Statement has developed a guideline to manage the mental health disturbances concomitant with IFN treatment[10]. According to these guidelines, a comprehensive psychiatric historywas taken before starting the antiviral treatment, and patient was informed about the psychiatric adverse effects. Once the antiviral treatmentwas started, the patient was assessed for the psychiatric disturbances on every follow-up visit, which was scheduled after every four weeks during the initial three months of treatment and then at least every 12 weeks after wards. Those who developed neuropsychiatric adverse effectswere referred to psychiatrist, where they were managed withcounseling and pharmacotherapy.

STATISTICAL ANALYSIS:

Data are presented as frequencies, average, standard deviations and ranges where possible. An independent samples t-test was used to compare the means of a neuropsychiatric adverse effect for Peg INF + RV and INF + RV.

RESULTS AND DISCUSSION:

Out of 84 patients 31 were males and 53 were females and their age was 45-51 years of age on average. Their body mass index (BMI) was 27.68 with a SD of ±4.1. 24 patients had Hep C positive family history (See Table 1).

Table 1: Patient's characteristics

Characteristics	Number (84)
Age (in yrs.)	45.91 ± 6.72
Gender	
Male	31
Female	53
BMI	27.68 ± 4.1

Family History of Hep C	
Positive	24
Negative	60

Hep C = Hepatitis C

Table 2: Comparison of treatment related adverse effects

Neuropsychiatric Adverse effects	**Treatment Regimen**		**p-value**
	Peg INF + RV	**INF + RV**	
	Number of patients (n)	**Number of patients (n)**	
Anxiety	2	2	*0.006*
Impaired Concentration	1	6	*0.137*
Depression	13	13	*0.619*
Emotional Lability	7	26	*0.000**
Insomnia	4	19	*0.000**
Irritability	0	0	-

**Statistically significant (2-tailed), if p-value is less than 0.005*
INF +RV= interferon + ribavirin
Peg INF + RV= Pegylayted interferon + ribavirin

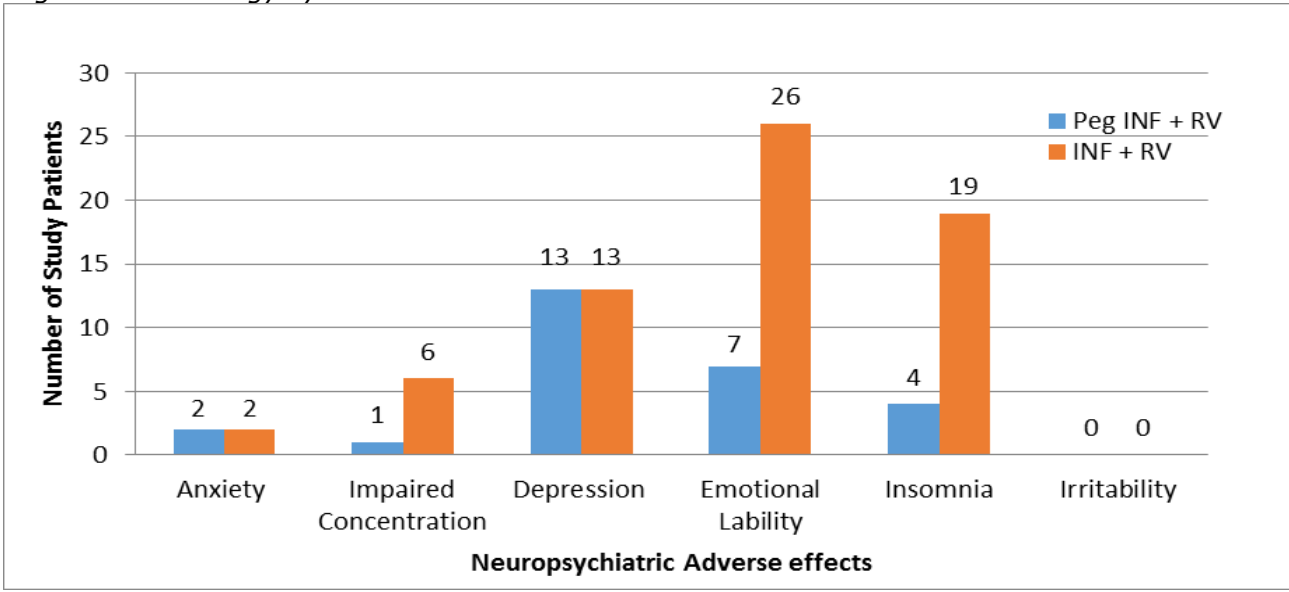

Fig1: Neuropsychiatric Adverse effects of two treatment regimens

INF +RV= interferon + ribavirin
Peg INF + RV= Pegylayted interferon + ribavirin

Among the neuropsychiatric symptoms, the emotional lability, insomnia and depression were most commonly seen with INF + RV therapy, while only 'depression' was higher with Peg INF + RV. Furthermore, the frequency of anxiety and depression in both

regimens were found equal (See Table 2& Fig 1). The results indicate that there is a statistically significant difference between the mean neuropsychiatric adverse effects of emotional lability and insomniafor both treatments (t = 4.047, p = 0.000; t = 4.255, p = 0.000 respectively). Occurrence of neuropsychiatric symptomslike anxiety, impaired concentration and depression is not statistically different between two groups of treatment.

In this study group 32.5% of the patients on Peg INF + RVhad depression while 29.54% of the patients had depression when were treated with INF + RV. In one of the studies conducted on other populations, 70% of the patients, who were being treated for HC with INF alpha developed depression[8].The frequency of sleep disturbances like insomnia was 27.38% (23 out of 84). When compared in two treatment regimens, it was found to be higher when patients were treated with INF + RV (See Table 2). The studies addressing sleep disorders in other populations showed occurrence of sleep disruption, insomnia and restlessness in almost 60% of the patients[11]. This study reveals that sleep disturbances in our population do occur but in lower frequency. Moreover, emotional lability and irritability was also observed in 39.28% of the patients, which was also lesserwhen compared with other studies conducted on other populationsexhibiting irritability in 75% of the patients with HCV[12].

The patients with depression, anxiety, and cognitive complaints responded well to serotonergic antidepressants. Patients having sleep problems were treated with sleep-promoting agents such as antihistamines, probenzodiazepines, and sedative antidepressants for insomnia and for anxiety with anxiolytics like alprazolam. Other studies also reported the same results[11, 13]. There was no need of dose reduction or discontinuation of treatment but only increased the cost of therapy, hence did not alter the treatment outcome.

Coping with stress, depression and anxiety is inconstant in different individuals and exhibits the individual's cognitive and behavioural response to alleged stress. In a study conducted on group of 100 individuals infected with HCV, different coping styles like problem-solving behaviour, distraction and self-revalorization, religiousness and search for meaning, cognitive avoidance and dissimulation were used. It was observed that the highest levels of problem-solving behaviour are associated with the lowest levels of depression[14]. Some other studies have demonstrated that if coping strategies are used inappropriately theymay affect negatively to the management of psychiatric disorders[15-17]. So, lower percentages of all neuropsychiatric adverse effects in our population can be explained on the basis of these coping strategies where religion is the main difference. Moreover, genetic factors may also play important role so a further study should be designed to look for the genetic differences in different populations with HCV infection.

CONCLUSION:

Depression, insomnia and emotional lability are the major neuropsychiatric side effects with HCV treatment in this study. However, they can be reduced by acquiring amultidisciplinary team approach and can result inbetter treatment outcome of patients. Furthermore, to attain SVR,timely management of these adverse effects by specialized healthcare professionalhelps to lower the incidence of recurrent interventions including drug dose and frequency adjustment.

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