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Original Article

Depression in Patients on Interferon Therapy for Chronic Hepatitis C

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Abstract

Background: To determine the frequency and severity of depression in patients on Interferon therapy for chronic hepatitis C

Methods: Total 97 diagnosed patients of chronic hepatitis C were enrolled. They were on IFN therapy, either conventional or Peg- IFN for at least last three months. Proforma comprising of Zung Self Rating Depression Scale was administered to assess the frequency and severity of depression.

Results: Out of 97 patients, 46% were male and 54% were female. Conventional interferon was given to 79% patients whereas 21% patients received Peg IFN. Depression was found in 58% patients.

Conclusion: Interferon treatment causes depression in a considerable numbers of patients.

Key Words: Depression, interferon, hepatitis C

Introduction

The hepatitis C virus is a major public health problem and is becoming the leading cause of liver failure requiring transplantation.[1] According to WHO 3% of the world's population, are infected with HCV and are at risk of developing liver cirrhosis and/or liver cancer.[2]Hepatitis C virus (HCV), which was first characterized in the late 1980s, is an RNA flavivirus with 6 major genotypes and more than 50 subtypes. Genotype 1 is predominant in Canada, accounting for over 60% of cases, followed by type 2, Genotype 5 HCV is common in southern Africa and distinctly rare elsewhere. Genotype 6 is generally limited to Southeast Asia. It is estimated that 123–170 million people worldwide are living with HCV infection.[3] There have been major antiviral treatment advances in recent years. No vaccine is available, although vaccine research is underway. The goal to reduce the number of people living with hepatitis C and its complications cannot be achieved without the contributions of public health, specialty care and primary care clinicians. Interferon (IFN) in combination with ribavirin, a synthetic nucleoside analogue, has been the mainstay of treatment for chronic hepatitis C.[4] Since the success rate of the anti viral treatment of hepatitis C is increasing, the knowledge of side effects due to this therapy must also improve. Interferon accounts for most of the side effects and some are attributed to ribavirin. Neuropsychiatric symptoms that frequently occur during or shortly after interferon therapy for chronic viral hepatitis include lethargy, somnolence, fatigue, drowsiness, disorientation, impaired concentration, irritability, emotional liability, social withdrawal, depression, hopelessness, psychosis, suicidal ideation and successful suicides.[5] The incidence of IFN induced depression in patients who have hepatitis C reportedly ranges from 3% to 44 % and among those who develop it, 39% develop the major depressive disorder.[6] Most patients who develop depression will do so in the first three months of the therapy.[7] Combined with fatigue, these symptoms represent a primary cause of poor compliance and/or treatment discontinuation. Only a limited number of studies have been devoted to the problem of depression until now. Keeping in view the seminal importance of adherence in achieving viral clearance, increasing attention is now being paid to IFN–induced neuropsychiatric side effects as potentially manageable impediments to achieving sustained viral response during hepatitis C virus (HCV) treatment.

The mechanisms of IFN-a-induced depression remain poorly understood. Among the different hypotheses, the impact of IFN on glucocorticoid receptors (GR) and on serotonin 1A (5-HT) receptors seems to be important. These receptors are known to be implicated in mechanisms leading to depression. IFN

administration significantly increases plasma ACTH, cortisol and interleukin-6 concentrations in patients who will develop depression. Also the reduction in serum 5-hydroxytryptophan (5-HTP) and serotonin levels is highly correlated to the degree of depression during IFN treatment. From a mechanistic point of view, these data are in favor of the use of SSRI in the treatment of IFN-a-induced depression as well as in their prophylactic use. Moreover, in vitro data reinforce this point of view by demonstrating that IFN down-regulated GR and 5-HTR1A levels in lymphoid and hepatic cell lines. It has also been suggested that SSRIs could be prescribed preemptively in all HCV patients before starting antiviral therapy. This attitude has been proposed in view of the elevated incidence of depression and other neuro-psychiatric symptoms induced by antiviral treatment in HCV patients with or without pre-existing neuro-psychiatric symptoms. This point of view must be investigated in the context of clinical trials to avoid potentially unnecessary exposure of patients to SSRI.

Patients and Methods

This descriptive study was conducted at District Headquarter Hospital Rawalpindi. The duration of study was six months, i.e., from March to October 2013.

Table 1: Key to scoring the Zung self rating depression scale

Make Check Marks( )In appropriate Column	A little of the time	Some of the time	Good part of the time	Most of the time
1.I feel down hearted and blue	1	2	3	4
2.Morning is when I feel the best	4	3	2	1
3.I have crying spells r feel like it.	1	2	3	4
4.I have trouble sleeping at night	1	2	3	4
5.I eat as much as I used to	4	3	2	1
6.I still enjoy sex	4	3	2	1
7.I notice that I am loosing weight	1	2	3	4
8.I have trouble with constipation	1	2	3	4
9.My heart beats faster then usual	1	2	3	4
10.I get tired for no reason	1	2	3	4
11.My mind is as clear as it used to be	4	3	2	1
12.I find it easy to do the things I used to	4	3	2	1
13.I am restless and can't keep still	1	2	3	4
14.I feel hopeful about the future	4	3	2	1
15.I am more irritable then usual	1	2	3	4
16.I find it easy to make decisions	4	3	2	1
17.I feel that I am useful and needed	4	3	2	1
18.My life is pretty full	4	3	2	1
19.I feel that others would be better off if I were dead	1	2	3	4
20.I still enjoy the things I used to	4	3	2	1

Key for the value (1-4) that correlates the patient's responses to each statement. Add up the numbers for a total score

Total 97 diagnosed patients of chronic hepatitis C were enrolled. They were on Interferon (IFN) therapy, either conventional or Pegylated (PEG)- IFN for at least last three months who presented in out patients departments (OPD) of District Headquarter Hospital Rawalpindi. Proforma comprising of Zung Self Rating Depression Scale (Table 1) was administered to assess the Frequency and severity of depression. Symptoms of depression were assessed using the 20item Self Rating depression Scale (SDS) (Table 1). Each item was rated 1 to 4, with higher scores representing greater symptom severity (or less severity for negatively phrased questions). Following standard procedure for the SDS , frequency and severity of depression assessed, in which < 50 = normal mood (no Depression), 50 to 59 = mild depression, 60 to 69 = moderate to marked depression, and ≥ 70 = severe depression

Results

Out of these 97 patients, 45 (46%) were male and 52 (54%) were female.

Table 2: Frequency of Education Level in Study Population

Education Level	Gender of Patients		Total
	Male	Female	
Illiterate	8(22.9%)	27(77.1%)	35(100.0%)
Primary	7(28.0%)	18(72.0%)	25(100.0%)
Middle	12(80.0%)	3(20.0%)	15(100.0%)
Matric	11(73.3%)	4(26.7%)	15(100.0%)

Graduation	6(100.0%)	0(.0%)	6(100.0%)
Post Graduation	1(100.0%)	0(.0%)	1(100.0%)
Total	45(46.4%)	52(53.6%)	97(100.0%)

Table 3: Comparison of Education Level with Depression

Education Level	Depression		Total
	Yes	No	
Illiterate	21(60.0%)	14(40.0%)	35(100.0%)
Primary	13(52.0%)	12(48.0%)	25(100.0%)
Middle	11(73.3%)	4(26.7%)	15(100.0%)
Matric	5(33.3%)	10(66.7%)	15(100.0%)
Graduation	5(83.3%)	1(16.7%)	6(100.0%)
Post Graduation	1(100.0%)	0(.0%)	1(100.0%)
Total	56(57.7%)	41(42.3%)	97(100.0%)

Table 4: Comparison of Type of Interferon with Severity of Depression

Severity of Depression	Type of Interferon		Total
	Conventional	PEG IFN	
No Depression	35(85.4%)	6(14.6%)	41(100.0%)
Mild	24(77.4%)	7(22.6%)	31(100.0%)
Moderate	9(56.3%)	7(43.8%)	16(100.0%)
Severe	9(100.0%)	0(.0%)	9(100.0%)
Total	77(79.4%)	20(20.6%)	97(100.0%)

Minimum age of the patients was 17 years and maximum age of the patients was 65 years with mean age 38±12.67 .In our study population 36% patients were illiterate.(Table 2) Conventional interferon was given to 79% patients whereas 21% patients received Peg IFN. Depression was found in 58% patients and was absent in 42% patients in our study. Score of self rating depression scale (SDS) was less than 50 in 42% cases, 50—59 in 31% cases, 60—69 in 18% cases and more than 70 in 9 (09%) cases(Table 3&4). Depression was found in 64% male and 52% female patients**.** In 77 patients who received conventional therapy, depression was found in 54% patients where as in 20 patients who received PEG Interferon, depression was found in 70% patients **.** Among 77 patients who received conventional therapy, 31% had mild depression, 11% patients had moderate depression, 11% patients had severe depression and 45% patients did not have any depression. In contrast to that, among 20 patients who received PEG IFN, 35% patients had mild depression, 35% patients had moderate depression and 30% patients did not have any depression (Table 4).

Discussion

Interferon has become available for therapeutic indications by recombinant DNA techniques since the eighties. Interferon is used in the treatment of hepatitis C, multiple sclerosis, and various malignancies because of its immunomodulatory and antitumor effects. Shortly after the introduction of interferon therapy, severe psychiatric side-effects were reported.[9] In particular depression fulfilling Diagnostic Statistical Manual (DSM) criteria was frequently observed. Such psychiatric side-effects are responsible for a significant number of failures of the interferon therapy. [8,9] .

IFN is a potent inducer of proinflammatory cytokines. Cytokines cause a variety of changes in the brain that lead to symptoms similar to major depression (anhedonia, reduced activity, listlessness, hyperalgesia, altered sleep, altered appetite, and poor memory).[10] IFN-induced major depressive disorder (MDD) is classified as a substance-induced MDD by current diagnostic standards. [11]

Female patients were slightly predominant (54%) in our study as compared to male population. Whereas in study conducted at Showa university hospital, Japan, male were predominant (63%).[11] In our study depression was found in more than half (58%) of the patients which is much higher prevalence of depression. Depression was found in 31% of the patients with hepatitis and on interferon therapy in study conducted in Tokyo.[11] Other prospective controlled trials showed the frequency of interferon induced depression in patients with hepatitis C occurred in 19.2% to 45% of the treated patients.[12,13] In contrast to this high prevalence of depression, there are certain studies that showed very low frequency of depression ranging from 5.2% to 9.5%.[14,15] Prospective clinical trials of IFN (in HCV or cancer patients) reported that approximately one-fourth (9%–40%) of

IFN-treated patients experienced mood symptoms (not isolated depression), a much higher rate than the low rates reported in retrospective studies (0.9%–2.2% of HCV or melanoma patients). [16-22]

Most of the study population was illiterate (36%) followed by primary pass, middle and matric, and only one patient was post graduate. Literacy level can also be held responsible for increased prevalence of hepatitis in our population and increased frequency of depression in our setup. Hepatitis C per se is also associated with depression and other psychiatric disorders. [12].

Mild-to-moderate depression symptoms occur in 20%–40% of IFN-treated patients, whereas severe IFNinduced depression occurs in fewer than 10%. Depression symptoms at the time of treatment initiation increase the likelihood of developing depression during IFN treatment but the depressive symptoms that develop during IFN treatment appear to be treatable with antidepressant medication. Neuropsychiatric symptoms associated with IFN-α therapy include cognitive, behavioral and affective components, which can affect both mental and physical functioning of the patient and these symptoms not only decrease the response of the treatment but are particularly distressing as they may interfere with work and interpersonal relationships. The mechanism of IFN induced depression is described in many ways by different hypothesis and studies.[23] INF alpha activates some cytokines which are good candidates for induction of psycho behavioural disorders. IFN alpha modulates the peripheral activity of indolamine-dioxygenase, a regulating enzyme of serotonin metabolism. An immune-induced vagal mechanism is also postulated..IFN alpha treatment is reported to produce decrease in tryptophan availability for serotonin synthesis, decrease in the 5-HIAA level and modification of the central serotoninergic receptors

Conclusion

1. Interferon treatment causes depression in a considerable numbers of patients. Depressive symptoms are observed in the patients treated with conventional interferon therapy as well as with PEG interferon therapy.
2. Proper identification and management in this cohort of patients is likely to produce better outcomes.
3. Preemptive prescription of serotonin selective receptors inhibitors (SSRIs) should be considered as a viable option.

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