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Research Article

PSYCHIATRIC DISORDERS INDUCED BY INTERFERON THERAPY OF CHRONIC HEPATITIS C PATIENTS: LONGITUDINAL STUDY

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ABSTRACT

Background: The hepatitis C treatment is based on a combination of pegylated interferon alpha (IFN Peg) and Ribavirin. However, this treatment causes many side effects including psychiatric disorders. The aim of study is to evaluate the depressive symptoms, anxiety and risk factors for psychiatric symptoms in patients with chronic hepatitis C (CHC) treated with combined pegylated interferon alpha and Ribavirin (PEG-IFN- α + RBV) in a Moroccan patient sample. **Methods:** This prospective, descriptive and analytical study followed 30 patients with chronic hepatitis C (CHC) treated with combination therapy with pegylated interferon alpha with Ribavirin (PEG-IFN-α + RBV) for one year. All but one of the patients were infected through blood transfusion. Our patients were evaluated by a standardized interview and psychological instruments in the first, third, sixth and twelfth months of treatment. **Results**: The average age of patients was 57.03 years old, with a slight female predominance. Depressive symptoms were found in 36.6%, with a maximum rate found in the first month of treatment. The incidence of anxiety peaked at three months and generalized anxiety was diagnosed in 15% of the patients. Major depressive disorder with suicidal ideation resulted in arresting the interferon therapy in 2 patients. Regression analysis failed to identify any risk factors of psychiatric disorders induced by IFN.
Conclusion: The clinical psychiatric symptoms occurring in with PEG-IFN-α treatment are atypical and the time course varies per disorder. These findings support the recommendation that complete care of HCV patients treated with IFN requires a multidisciplinary collaboration.

Keywords: chronic hepatitis C, interferon-alpha, depression, anxiety.

INTRODUCTION

The hepatitis C virus (HCV) is a public health problem in Morocco since its prevalence is estimated to be between 0.9 to 1.2%[1]. Optimal treatment of HCV is based on a combined therapy of the pegylated interferon alpha (IFN Peg) and Ribavirine (RBV). This allows obtaining satisfying results in more than 50 % of patients[2, 3]. However, this treatment can cause various negative side-effects including psychiatric effects. These psychiatric symptoms are mostly mood disorders such as depression and a complication of pre-existent depressive disorders. Depressive signs can also occur in patients without depressive history. The prevalence of depressive disorders is estimated between 20 and 40%, with a general consensus of a rate of 30%.[4, 5, 6] Frequently, other psychiatric clinical signs are also evident including anxiety, sleeping disorders, mood lability and irritability. Patients manifesting suicidal behavior, psychotic disorder, and manic or mixed episodes have also been reported [2, 7, 8, 9]. These severe psychiatric reactions can result in decreasing the treatment dose or a complete arrest of the treatment, which would compromise the chance of successful HCV treatment.[10]

Researchers have attempted to ascertain the variables that predict which patients will develop psychiatric disturbance while on the combination therapy. The gender has not been identified as risk factor of depression during the HCV treatment by the IFN in most studies[11,12] despite well-known predominance of females in depression. Recent literature reviews, including one containing only the prospective studies, concluded that the main risk factors for a major depressive episode are the female gender, history of major depression and other psychiatric disorders, and low education[13]. Not all have found that pre-treatment psychiatric history predicts IFN-related depression. Some have shown that pre-treatment psychiatric history was not a risk factor of depression while undergoing IFN treatment[14]; while others have identified it as a risk factor[8, 15]. Likewise, a recent study showed that lifetime history of mania was predictive of depression during the IFN treatment[16]. Poor sleep quality before the IFN treatment and intravenous drug use have also been identified as risk factors for depression[8, 17]. Finally, the literature has focused predominantly on depression prevalence, while the anxiety is rarely reported. Lieb and colleagues, however, have demonstrated a rate of 8.6% for anxiety disorders in HCV positive patients treated with IFN[14]. To our knowledge, no one has tracked anxiety symptoms to assess both the time course and predictors of this symptom in HCV patients receiving antiviral treatment with IFN Peg.

The goal of our study was to prospectively assess the prevalence of the psychiatric disorders and symptoms induced by IFN Peg treatment of the HCV patients. We also sought to further clarify the risk factors for both depressive symptoms and anxiety. According to the 1999 WHO classification system[1], in Morocco where the prevalence of HCV is average relative to other countries, but the time course and predictors of psychiatric symptoms have not been studied.

METHODS

Subjects. Thirty patients were recruited between March 2007 to April 2010. All patients were treated at the gastroenterology and hepatology department of the University Hospital of Fez, Morocco. The HCV patients were receiving treatment for the first time IFN Peg treatment. The chronic HCV was diagnosed basing on biological criteria such the presence of the ARN HCV and positive anti-HCV antibody in the blood. Their HCV treatment consisted of IFN Peg (Pegasys® 180 µg or Viraferon® 1.5 µg/kg/week through subcutaneous path once a week) or standard IFN Peg and the Ribavirine (Rebetol®, Copegus®). Both protocols were administrated during 6 and 12 months depending of the diagnosed genotype of the HCV. All included HCV patients were candidate for an antiviral treatment. HCV patients with hepatitis B virus or HIV co-infection were excluded. Patients with history of hepatic, renal and cardiac deficiency were also excluded. Each patient was closely followed by both a hepatologist and a psychiatrist.

Psychiatric procedures. All patients received clear and detailed explanation of the protocol, and they gave written consent before being included in the study. The protocol was approved by the Ethical Review Board at Fez University. A full psychiatric evaluation was completed on each patient before starting any HCV treatment. This consisted of a clinical interview using the MINI Neuropsychiatric International Interview (MINI), the Beck Depression Inventory (BDI), and the Hamilton's Anxiety Scale (HAS). Additional assessments using BDI and HAS were collected by the end of the first, third, sixth and the twelfth month of the treatment protocol. Diagnoses were determined by consensus after review of the clinical assessment and testing by two psychiatrists (authors IR and CA).

Statistical analysis.

The statistical analysis was done using the EPI-Info package (EPI-Info, version 5.0). The significance of the results was fixed for p-value less than 0.05.

RESULTS

Demographics. The patient's age ranged from 42 to 70 years old, with an average age of 57.03 years old (SD = 11, 3). A total of 14 males and 16 females participated in the study. Pre-treatment psychiatric history was evident in 4 patients (13.3%) including 2 with depression (6.6%), one with history of bipolar disorder (3.3%) and one with paranoid schizophrenia (3.3%). Twelve patients demonstrated a medical history of diabetes, high blood pressure and hypothyroidism. While most (96.7%) of our patients did not disclose a history of illicit drug use.

Disease profile. The mode of transmission is known by only 1 patient (3, 3%), the mode contamination for other patients is unknown. Seventeen patients showed a cytolyse and 3 patients demonstrated a normal rate of transaminases. The viral load assessment indicated that 25 patients (83.3%) had a strong viral load (>800,000UI/ml), while 5 patients (16.6%) had a low viral load. Twenty-one patients (70%) were contaminated with HCV of genotype 1B, 2 patients (7%) showed a genotype 1A, and 7 patients (23%) patients demonstrated a mixed genotype 2A/2C or 2A/5. It is important to note that 11 patients (55%) underwent a hepatic biopsy puncture revealing that 9 patients had moderated necrotic inflammation activity (stage Metavir A2) and 2 patients have had a severe necrotic inflammation activity (Metavir A3). Fibrosis was found 11 patients: Metavir F2 in 5 patients, Metavir F3 in 5 patients and Metavir F4 in a single patient. The remaining patients (45%) did undergo any hepatic biopsy puncture. Only 5 patients (16.7%) of our sample demonstrated cirrhosis of the liver. Histological examination supported the diagnosis for one patient, and the diagnosis was based on clinical, ultrasound and endoscopic data in 2 cases. Twenty-eight patients were treated with double-agent pegylated therapy, one patient was treated with mono-therapy pegylated IFNα-2b and one patient was treated with standard IFNα and Ribavirine. Twenty-six patients (85%) underwent a full protocol of the antiviral treatment but 3 patients required a reduced dose of the antiviral treatment because of the hematological side effects such as leucopenia, thrombopenia, and anemia.

Psychiatric diagnoses & symptom time course: Three patients (10%) were diagnosed with a major depressive episode, two patients (5%) with hypomania episode. The psychotic disorders were found in two patients (5%). Eleven patients (36.7 %) did not reveal any depression affect before the start of the interferon treatment. The BDI assessment showed a mild depressive affect scores (4 - 7 points) in 9 patients (30%), a moderate depressive affect score (8 - 15 points) in 7 patients (23.3%), and severe depressive affect score (> 16 points) in three patients (10%). The incidence of depressive symptoms was 36.6%. The depressive affect peaked in the 1st month of the interferon treatment within the moderate and severe depressive affect range.

Three patients (15%) were diagnosed with generalized anxiety disorder and minor anxiety was seen in 27 patients (90%). The HAM scores were moderate in two patients and elevated in one patient. The HAM scores peaked in the 3rd month of the treatment. One patient presented with a worsened bipolar disorder with major depression and suicidal ideation by the 8th week of the antiviral treatment. Two patients stopped their treatment because of an intolerable anemia, a hyperthyroid and a severe asthenia with mental confusion. The last patient died before the end of the study.

The logistic regression to predict of the occurrence of depression during the antiviral treatment found that older age (>60 y/o) and the female gender were marginal independent factors for the occurrence of the depression during the treatment (p = 0.06). No other variable predicted the occurrence of depression during the antiviral treatment. In addition, logistic regression to determine the risk factors of anxiety during the antiviral treatment did not reveal any significant predictors (Table 1).

DISCUSSION

In this study we demonstrate that depressive affect is common (36.6%) and peaks around the first month of antiviral treatment. Approximately 10% of our patients qualified for a diagnosis of depression. We further show that anxiety occurs in the majority of patients, though the rate of psychiatric diagnosis of anxiety is about one third lower than that of depression. Anxiety peaked 2 months later than deperssion in the time course of treatment. Regression models for each diagnosis indicated that only marginal effects were seen with female gender and age (> 60 years old). In contrast, none of the variables assessed here predicted an increased risk of anxiety. In this study adverse events leading to the discontinuation of IFN Peg therapy was infrequent and made in each case after consensual consultation of both involved

therapists namely the hepatologist and the psychiatrist. One patient demonstrated a worsening of maniac-depressive psychosis with suicidal ideation by the 8th week; the 2nd case due to worsened by depression with cognitive impairment by the 40th week of the treatment (this patient died 2nd months after stopping the IFN treatment); and the 3rd case was discontinued from the treatment because of a hyperthyroid.

The prevalence of depressive affect in our study (36.6%) is extends the existing literature obtained from other studies within the U.S. and Europe. The prevalence of depressive affect shown in other prospective studies has ranged from a low of 11%[18] to high of 48%[19]. The same is true for the prevalence of pre-treatment depression. Our rate of 13.3% is within the range found by other studies. For example, Leutscher and colleagues found that 6% of their patients had suffered of major depression disorder at the start of their treatment[20]. Michel found that 22 % patients have had manifested pre-existent psychiatric disorders including anxious and depressive disorders[21]. In contrast, our finding that mild anxiety is common (90%) and diagnoses of generalized anxiety elevated (15%) was inconsistent with other reports. For example, Stewart's team studied 395 HCV patients and showed a prevalence of 41% for anxiety[22]. Likewise, our study did not support previous findings showing that gender predicts depressive affect in this context. Our findings are consistent with the general lack of an association with age. A single study was reported in the literature and showed that advanced age is a depression risk factor during the treatment HCV by the IFN[11]; while most reported studies revealed that a young age is a predictive factor of depression[22, 23]. Regarding the biological markers, our work confirmed results of previous studies by showing that the cirrhosis presence before the antiviral treatment, the genotype, the viral load and the degree of fibrosis were not predictive factors of depression during treatment[24, 25].

To our knowledge, there are no other published studies examining the predictive factors of anxiety in HCV patients treated by the IFN alpha. In our study, there were no correlations between studied variables such as age, gender, psychiatric histories, genotypes, viral load and the level of fibrosis. The variation between our studies and others regarding gender and depression could be due to cultural differences, methodological biases and/or a lack of consensus on evaluation tools to be used and criteria to be retained. Unexamined co-factors for mental illness could also account for some of the variability. For example, sleep disorders were also reported in 60% of HCV patients, which could account for differences in psychiatric co-morbidity[26]. One patient in our series presented a new onset of insomnia without a depressive disorder. Finally, in our study there was a single case presenting a history of manic-depressive psychosis but it was not possible to assess the link between the previous mania and the depression appearance during the IFN treatment.

The predictors of these psychiatric symptoms remain unclear. Table 2 illustrates a comparison of depression prevalence with INF and Ribavirine treatment in reported studies[11, 12, 14, 15, 18, 19, 24, 25, 27, 28, 29,30, 31]. Studies have suggested that the use of Ribavirine does not seem to worsen the psychiatric symptoms of patients treated by IFN alpha including depression incidence[32]. However, some have observed an increase of the rate of depressive episodes while using antiviral treatment during the year of initiating Ribavirine[33] and more a randomized trial showed that the patients receiving a stronger dose of Ribavirine developed more depressive episodes[6]. Other factors such as drug or alcohol use are important factors that impact the risk of both depression and anxiety. Addictive behaviors are also frequent at HCV patients in western countries where 30 to 60% of diagnosed hepatitis is connected to substance abuse. The prevalence of HCV in addictive patients and constitutes 50 to 80%[34].

In our study, however, the presence of drug use was not predictive of either depression or anxiety and the only recognized mode of infection in our sample was the blood transfusion.

This study is limited by a small sample size and the lack of a control group. Due to this, we were unable to compare those who received IFN-Peg mono-therapy (n = 1), standard IFNα and Ribavirine (n = 1) and the majority who received double-agent pegylated therapy (n = 28). This distinction may be important as treatment course depends on viral genotype[3] and psychiatric symptom profiles have their own time course, as demonstrated here. These psychiatric manifestations might appear at any time including acute or chronic phases the disease, in the first few weeks after the initiation of antiviral treatment, or even up until six months after stopping the treatment. In our series the peak depressive affect was recorded in the 1st month of treatment with moderate and severe depression, while anxiety peaked two months later (3rd month). It has been suggested that the timing of symptom change such as prior to IFN initiation[31] or during the 1st

week is predictive of later increase of depression. Indeed, some have proposed that prospective tracking of depressive affect symptom change induced by IFN treatment could be useful predictive factor of the capacity to tolerate the treatment[35]. However this conclusion remains preliminary as others suggested that the depression appearance during the antiviral treatment favorably predicts virological outcomes[24] and premature termination may have negative viral load[36] and psychiatric consequences[37,38].

Finally, caution in interpreting this and other published data is warranted due to a lack of consistency in psychological instruments across studies (See Table 2). Indeed the depression prevalence is lower when basing on DSM-IV diagnostic criteria, while it is higher when using other evaluation scales[2]. Similarly, not all scales are free of bias due to symptom overlap. For example, even in the absence of any depressive symptoms, IFN Peg treatment alone leads to weight loss, sleeping disorders and asthenia, all of which are three of five symptoms required to formulate the major depressive episode diagnosis. The IFN Peg treatment can also lead to irritability, memory and concentration problems, and algetic (pain) complaints which are characteristic of a depressive profile. The most commonly used depression scales contain many of these somatic items and their scores could be inflated by the presence of the neurovegetative or somatic symptoms contained in these measures. Indeed, a depressive mood associated with the flu syndrome occurring in the first 48 hours following the injection of INF alpha treatment is frequent[5].

CONCLUSION

The occurrence of psychiatric disorders, particularly depression, in HCV patients using IFN treatment has critical bio-psychosocial consequences that could further accelerate the evolution of the disease, deteriorate treatment adherence, and significantly reduce the patient's quality of life[19]. In this study we demonstrate that the time course differs for depressive affect and anxiety. Furthermore, the best predictors of who will present these symptoms are, as yet, unclear. Our sample is unique in that nearly all of the patient's HCV infection (29/30) was due to a single known mode of infection (transfusion). In this situation, none of our proposed predictors were supported. Further research might benefit from the use of psychological tools free of symptom overlap or bias towards somatic symptoms and the consideration of other co-factors such as sleep disruption, symptom change metrics (sequence, direction, or cycling), or diet. Yet, our work highlights the high prevalence of anxio-depressive mood disorders in HCV-positive patients treated with IFN Peg. These disorders limit the utility of IFN-based antiviral treatment or may contribute to irregularity of good therapeutic adherence to IFN treatment, therefore negatively affecting the vital prognosis of patients. These complex patients require a close collaboration between hepatologists and psychiatrists based on the latest consensus treatment recommendations. The psychiatrist's role remains critical and their specialized assessment should include a systematic evaluation before initiating any antiviral treatment.

Table 1: Psychiatric disorders in HCV patients according to various parameters

	Depression (by the first month)	Anxiety (by the third month)
Age 40- 50 years-old 50-60 years-old Sup to 60 years-old	33.3% 20% **50%** **p : 0.06**	33.3% 10% 28%
Gender Male Female	21.4% **50%** **p : 0.06**	21.4% 25 p : 0.41
Psychiatric history Yes No	38.5% 25% p : 0.33	23.1% 25% p : 0.45
Illicit drug use history Yes No	37.9% 0% p : 0.31	24.1% 0% p : 0.38
Comorbidity Yes No	33.3% 50% p : 0.24	33.3% 20% p : 0.27
Viral load Strong Low	40% 20% p : 0.23	28% 0% p : 0.11
Genotype 1B Others	40% 30% p : 0.31	25% 20% p : 0.39

Table 2: Depression prevalence in HCV patients treated IFN and Ribavirine reported in previously reported prospective studies

	Year of publication	Type of study	Evaluation scale(s)	Depression prevalence (%)	Sample size
Miyoaka et al. [1812]	1999	Prospective	DSM III R/HDRS	43.9	66
Scalori et al. [1918]	2000	Prospective	MMPI	11.2	67
Malaguamera et al. [2027]	2001	Prospective	DSM-III-R/HDRS	15.6	96
Lang et al. [2115]	2002	Prospective	DSM-IV	52	50
Horikawa et al. [2211]	2003	Prospective	DSM-IV/HDRS	23.4	99
Loftis et al. [2324]	2004	Prospective	BDI/SCID	33	39
Raison et al. [2425]	2005	Prospective	SDS	39	162
Lieb et al. [2514]	2006	Prospective	HADS/BDI/SCL-90-R	20	44
Fontana et al. [2628]	2008	Prospective	BDI	42	201
Santos et al. [2729]	2008	Prospective	SCID/BDI/PHQ	35	176
Castellvi P [2830]	2009	Prospective	SCID/TCI-R/HADS	42%	180
Pavlovicet al. [2931]	2011	Prospective	HADS/ZSRDS	20	74
Baranyiet al. [3019]	2012	Prospective	BDI/HADS	48%	25
Our study	2008	Prospective	BDI	**36.6**	**30**

NOTE: HADS: Hospital Anxiety and Depression Scale, BDI: Beck Depression Inventory, SCL-90-R: Symptom Checklist-90-Revised, SCID: Structured Clinical Interview for DSM-IV Axis I Disorders, PHQ: Physicians Health Questionnaire (PHQ-9), TCI-R: Temperament and Character Inventory-Revised (TCI-R), ZSRDS: Zung Self-Rating Depression Scale.

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