IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 23, Issue 5 Ser. 2 (May. 2024), PP 01-07
www.iosrjournals.org

Management Of Psychiatric Disorders Iatrogenic To Interferon-Alpha In Hcv-Positive Patients

Sonia Sehim , Hassen Mahiou , Mohamed Nedjari
department Of Medicine, Specialty / Psychiatry, Benyoucef Benkhedda University, Algiers 1, Algeria
Department Of Medicine, Specialty / Hepato-Gastroenterology, Benyoucef Benkhedda University, Algiers 1

Abstract:
Background*: Chronic hepatitis C virus (HCV) infection is a major public health problem. Psychiatric side effects induced by antiviral treatment (interferon alpha) of this condition are frequent (20-30%). These are mainly mood disorders, which interfere with the management of the disease. Psychiatric evaluation and follow-up are necessary to treat any associated psychiatric disorders, and thus enable better management of patients with hepatitis c virus.*
The aim of the study was to *identify and diagnose interferon-alpha-induced psychiatric disorders, and to assess their impact on compliance with antiviral treatment, through a bi-disciplinary approach involving a hepato-gastroenterologist and a psychiatrist.*
Materials and methods: *this is a prospective descriptive study, which was carried out over a period of 24 months, included 102 HCV (hepatitis c virus) seropositive patients managed in the hepato-gastroenterology department of an Algerian hospital. Patients were treated with a combination of 180 µg IFN subcutaneously once a week and 10.6 mg/kg/d Ribavirin per-os for 6 to 12 months, depending on viral genotype. Patients were monitored by a gastroenterologist every 15 days for the first month, then every month for 3 months. Patients who experienced psychiatric side-effects of IFN-α treatment were referred to and managed by a psychiatrist in conjunction with the gastroenterologist. A full psychiatric evaluation using dsm-5 diagnostic criteria and validation of cases by standardized instruments specific to each disorder and in particular depressive disorders using the Beck Depression Inventory (BDI) and Suicidal Intent Scale, which yielded a positive result before the start of antidepressant treatment, and also at 1 month, 3 months, 6 months and 12 months of treatment.*
Results: *Our sample consisted of 50 women with an average age of 47.6 years and 52 men with an average age of 44 years, with a sex ratio of 1.04. No psychiatric history, toxic intake or psychiatric comorbidities were noted. No psychiatric antecedents, toxic intake or psychiatric comorbidities were noted. The mode of contamination was known in 11 patients and unknown in 91. Half the patients had cytolysis, the remainder had normal transaminase levels. Two-thirds of patients had a high viral load (over 8000.00 IU/ml). 68% of patients had hepatitis c virus genotype 1B, 24% had mixed genotype 2A/2C and 8% had genotype 1A. In our series, only 4 cases had cirrhosis of the liver, i.e. almost 4% of cases. Among the 102 patients, 41% had presented psychiatric manifestations of various intensities iatrogenic to interferon, which appeared between 3^e and 5^e days after intramuscular injection of interferon. Eleven patients experienced irritability and thirteen insomnia, which did not require psychiatric management. Disorders of varying severity appeared between 5^e and 16^e weeks of interferon-alpha treatment in 18 patients (8 women and 10 men), i.e. 17.64%. According to the BDI depression score, 2 patients (1 male and 1 female) had experienced a major depressive episode with suicide attempts (score greater than 16), which necessitated immediate discontinuation of antiviral treatment, and 16 patients had experienced disorders of moderate intensity (BDI score between 8 and 15). Two patients discontinued antiviral treatment following suicide attempts.*
Conclusion*: In our study, premature discontinuation of IFN-α therapy was noted in 2 patients following melancholic depression with suicidal impulses. The decision to discontinue antiviral treatment was taken by consensus between the gastroenterologist and psychiatrist involved. However, it was possible to reinstate interferon therapy in one of the two patients after stabilization of the psychiatric condition with antidepressants (SSRIs) and strict bi-disciplinary follow-up.*
Key Word*: Procedure. Interferon alpha. Psychiatric disorders.*

Date of Submission: 24-04-2024 Date of Acceptance: 04-05-2024

I. Introduction

Chronic hepatitis C virus (HCV) infection is a major public health problem. Psychiatric side-effects induced by the antiviral treatment (interferon alpha) of this condition are frequent (20-30%)[1] . They are underestimated and under-treated by clinicians. Indeed, the results of most studies in the literature confirm that almost 30% of patients with viral hepatitis C will develop a depressive disorder during treatment with interferon

alpha (IFN-α), and almost one in two patients will suffer from a psychiatric disorder of any kind during treatment[2-6] . These iatrogenic effects are often at the root of non-adherence to care on the part of patients, resulting in an altered quality of life[7-9] . However, the breakdown in care may also be due to the doctor's fear of the onset of a depression characterized by suicidal behaviour. A practice survey carried out in 2007 among a representative sample of 101 hepato-gastroenterologists and/or infectiologists specializing in the treatment of hepatitis C, showed that 71% of patients whose antiviral treatment was interrupted for psychiatric reasons[10] .

In general, induced disorders typically occur between the first and third month of IFN-α antiviral treatment, with a peak at the end of 3e weeks12-13[11] . However, they may also appear throughout the course of treatment and even in the months following discontinuation[12-13] . They seem to depend on both the doses used and the route of administration. Continuous intravenous administration leads to maximum toxicity[14] . As already stated, these psychiatric manifestations are most often mood disorders, which may decompensate for pre-existing psychiatric disorders, but may also develop in subjects with no previous history. Psychiatric assessment and follow-up are necessary to treat any associated psychiatric disorders, and thus enable better management of subjects with hepatitis C virus. Subjects suffering from psychiatric pathologies, previously excluded from effective HCV therapies, should be able to benefit. However, more recent recommendations call for these subjects to be treated as part of a joint psychiatric management program between the psychiatrist and the hepato-gastroenterologist, to give patients a better chance of continuing their antiviral treatment[1, 15] . The aim of this study is to identify and diagnose interferon-alpha-induced psychiatric disorders, and to assess their impact on adherence to antiviral treatment through bi-disciplinary management by a hepato-gastroenterologist and a psychiatrist

II. Material And Methods

This is a prospective descriptive study, which was carried out over a 24-month period (January 2018 to December 2019), were included 102 HCV (hepatitis c virus) seropositive adult. Patients managed in bi-disciplinary care within the hepato-gastroenterology department of the Mohamed Debagine University Hospital Center, Beb El Oued, Algiers and outpatient follow-up by psychiatric physicians from the DRID Hocine psychiatric specialty hospital, Kouba ALGER. Age ranged from 18 to 50 and over, both sexes. Patients were treated with a combination of IFN-α 180 µg subcutaneously once a week and 10.6 mg/kg/d Ribavirin orally for 6 to 12 months, depending on viral genotype.

All patients suffering from decompensating psychiatric disorders, substance-induced disorders or general medical conditions other than hepatitis were excluded from the study. These patients were followed by a gastroenterologist every 15 days for the first month, then every month for 3 months. Patients who developed psychiatric side effects to IFN-α treatment were referred to and managed by a psychiatrist in conjunction with the gastroenterologist. A full psychiatric evaluation using the Diagnostic Statistical Manual of Mental Disorders 5e version (dsm-5) (Tab.1)[16] and assessment of symptomatology severity using standardized depression-specific instruments such as the Beck Depression Inventory (BDI) and the Suicidal Intent Scale, which yielded a positive result before the start of antidepressant treatment, and also at 1, 3, 6 and 12 months of treatment.

All patients were assessed after being informed of the study objectives and the need for multidisciplinary management. Patients were recruited for the study only after informed consent had been obtained. Data collection was carried out with respect for the anonymity and confidentiality of all information, and in particular that of the patients.

The data collection procedure was carried out by administering the research study questionnaire to all patients, assessing socio-demographic characteristics, psychiatric history, clinical history of liver pathology, clinical history of antiviral-induced psychiatric disorders and disease progression. The data were collected respectively by the two specialists (gastroenterologist and psychiatrist)

Statistical analysis

Data entry and statistical analysis were carried out using SPSS version 26 software. Qualitative variables were expressed as percentages or effectives. Quantitative variables were expressed by their means, standard deviations and extremes. Qualitative variables were compared using Pearson's chi-square test. Comparisons between qualitative and quantitative variables were made using Student's T-test. The significance level was set at 5% ($p \leq 0.05$).

Table 1 : diagnostic criteria for depression according to DSM-5 [16]

Reminder of DSM-5 diagnostic criteria A and B for depression
A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. **Note: Do not include symptoms that are clearly attributable to another medical condition.**
(1) Depressed most of the day, nearly every day as indicated by subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful)
(2) Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by subjective account or observation)
(3) Significant weight loss when not dieting or weight gain (e.g., change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day
(4) Insomnia or hypersomnia nearly every day
(5) Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
(6) Fatigue or loss of energy nearly every day
(7) Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
(8) Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)
(9) Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide
B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

III. Results

Socio-demographic characteristics:

Our sample comprised one hundred and two patients, fifty women with an average age of 47.6 years and fifty-two men with an average age of 44 years. The sex ratio was 1.04. There was no psychiatric history, no notion of psychoactive substance use, and no other psychiatric comorbidity. Over half (58.2%) of our sample were single. The majority of patients had a level of education between high school and university (67.2%). Two-thirds were gainfully employed.

Characteristics of hepatitis C:

The mode of contamination was known in eleven patients and unknown in ninety-one. Half the patients had cytolysis, the rest had normal transaminase levels. 2/3 of patients had a high viral load (greater than 8000.00IU/ml).

Concerning genotype, 68% of patients had hepatitis C virus genotype 1B, 24% had a mixed genotype 2A/2C and 8% had genotype 1A. (Figure 1). In our series, only four cases had cirrhosis of the liver, i.e. almost 4% of cases.

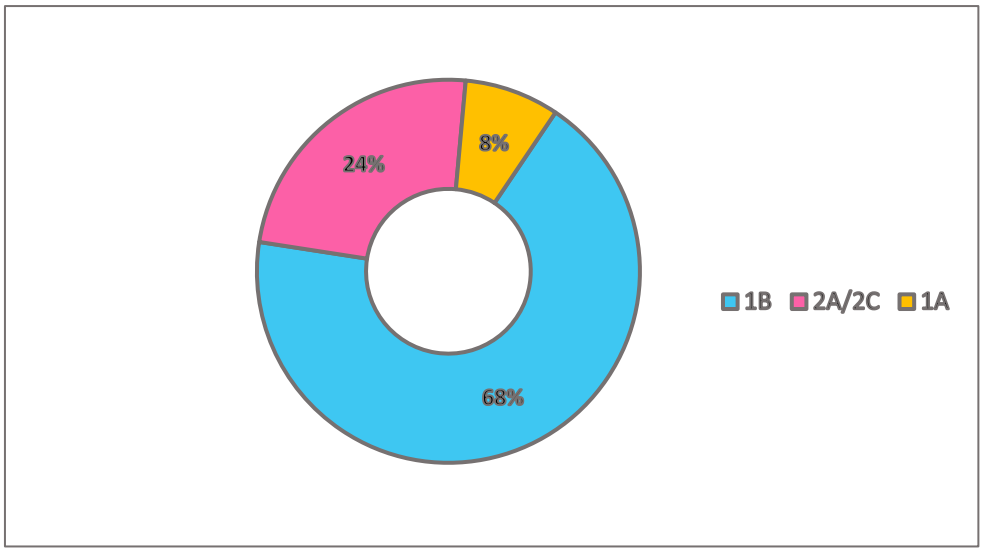

Figure 1: Distribution of patients by hepatitis virus genotype

c) Psychiatric manifestations:
Among the 102 patients, 41% had experienced psychiatric manifestations of various intensities iatrogenic to interferon:

1. Isolated and minor disorders: appeared between 3^{e} and 5^{e} days after intramuscular injection of interferon: eleven patients showed irritability and thirteen insomnia, which did not require psychiatric treatment. Interferon alpha had induced minor disturbances by 4^{e} days, and severe disturbances more than 30 days (Figure 2).

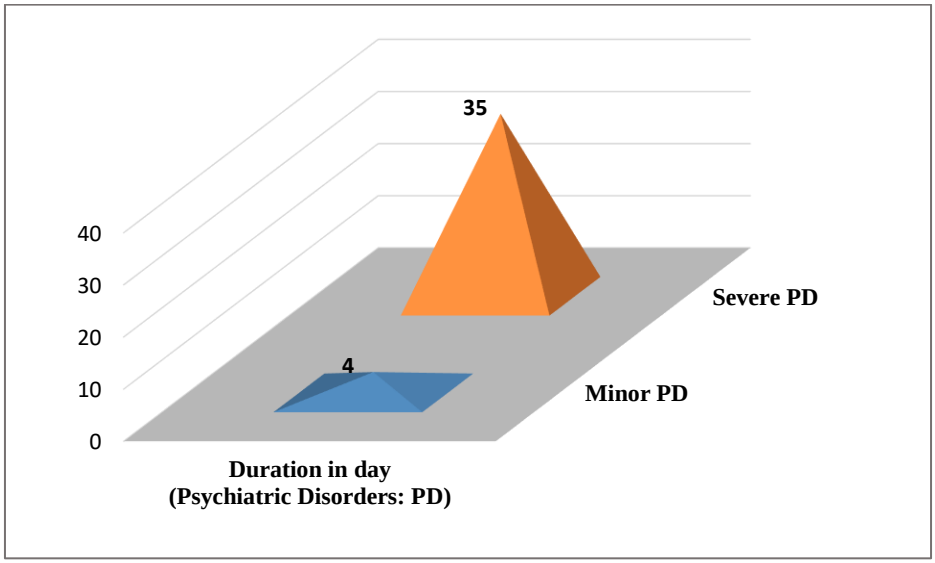

Figure 2: Distribution of psychiatric disorders according to duration of onset under IFN-α

Sixty patients had no side effects from interferon. Sixteen patients presented with major depression, thirteen with treatment-resistant insomnia, eleven with irritability and only two with suicide attempts (Fig. 3).

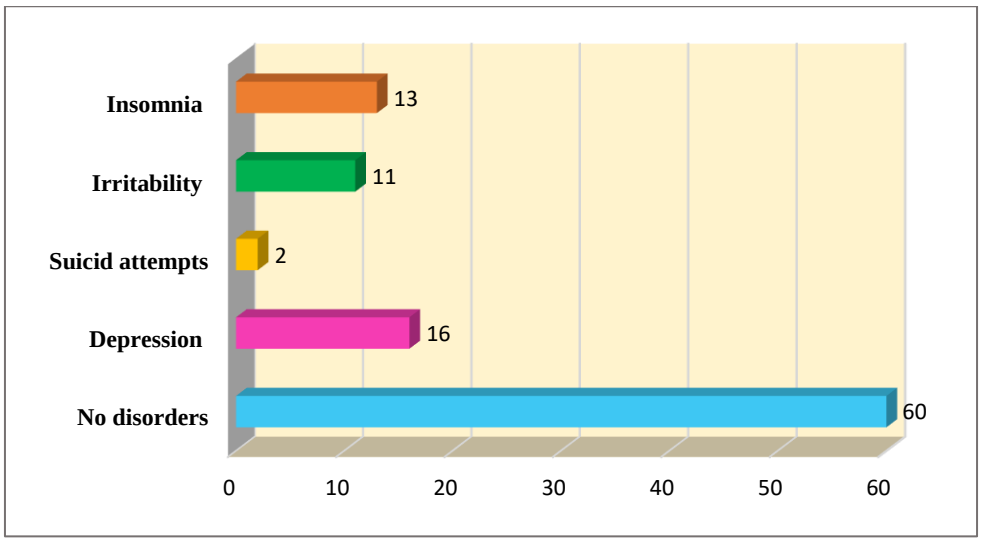

Figure 3: Distribution of patients according to IFN-α-induced psychiatric disorders

2. More or less severe disorders: appeared between 5^{e} and 16^{e} weeks of interferon-alpha treatment in 18 patients (8 women and 10 men), i.e. 18% (Figure 4).

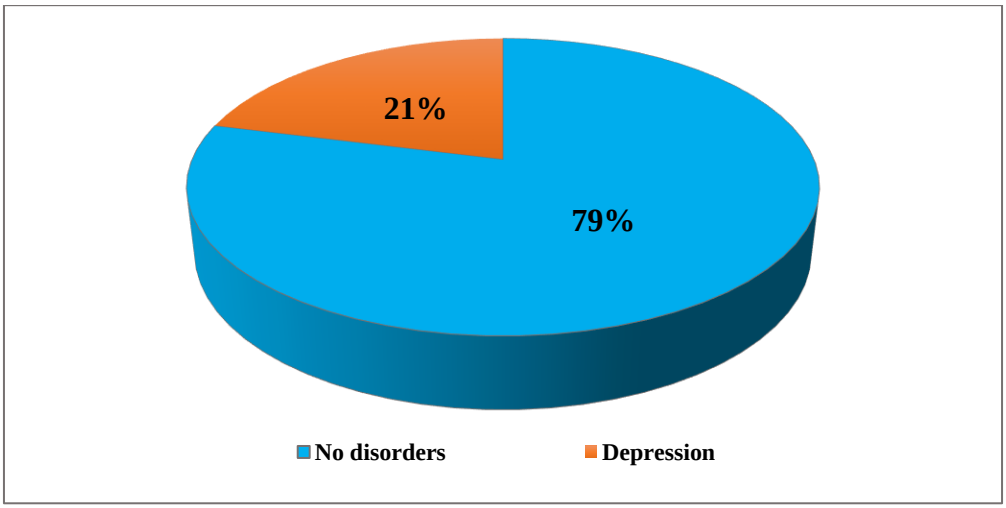

Figure 4: Distribution of patients according to prevalence of IFN-induced depression

According to the BDI depression score, 2 patients (1 male and 1 female) had experienced a major depressive episode with suicide attempts (score over 16), requiring immediate discontinuation of antiviral treatment, and 16 patients had experienced disorders of moderate intensity (BDI score between 8 and 15) (Figure 5). Discontinuation of antiviral treatment in two patients following suicide attempts.

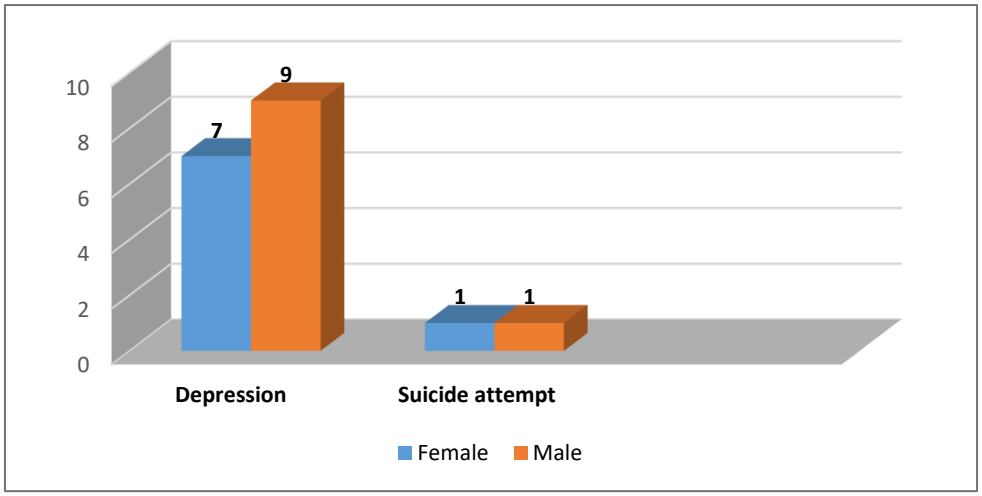

Figure 5: Distribution of IFN-α-induced mental disorders by gender

IV. Discussion

In our study, the nature of the psychiatric disorders induced by interferon alpha (IFN-α) covered a wide spectrum, ranging from isolated, minor symptoms with no mood disturbance occurring during the first week of treatment, such as irritability and insomnia, to true syndromic entities, which nevertheless remained dominated by the depressive syndrome with suicidal acts. Indeed, in our study, we noted sixteen cases of moderate depression and two cases of severe depression with suicide attempts confirmed by Beck's clinical depression severity scale, which appeared at 5^{e} and 16^{e} weeks of treatment. In fact, our results showed a prevalence of depression induced by interferon alpha during the course of treatment (1 to 3 months) of 17.64%, which is in line with the results of the literature reporting that the prevalence of depressive disorders during treatment ranges from 16 to 31% [17] .

Indeed, the French prospective multi-center study conducted between 2003 and 2006, designed to assess compliance factors in patients infected with viral hepatitis C, showed that 403 patients out of 1,860 followed-up, i.e. 22%, suffered from psychiatric disorders on initiation of antiviral treatment, with 11% suffering from depressive disorders[3,6] .

As for the duration of onset of induced psychiatric disorders in our patients, this is in line with the findings of the literature[5,18] , which observed a peak incidence in the first 4 to 8 weeks. Nevertheless, many major depressive episodes are observed after 3 or 4 months of treatment. Even in the case of good prior tolerance, the prevalence continues to increase in the first six months, and the risk persists until at least 6 months after treatment has been stopped[1, 5, 19-20] .

Hence the growing interest in prolonged multidisciplinary follow-up by psychiatrists and hepto-gastroenterologists. It is important to point out that in some studies, the use of Ribavirin in combination does not seem to worsen the psychiatric manifestations of IFN-α, in particular the incidence of depression [21] which is in line with the results of our study. However, other studies have observed an increase in the incidence of depressive episodes following the addition of Ribaverine[22-23] .

Similarly, the prevalence of suicidal acts in the literature is reported to be around 1.5%[9] which is in line with our results, since 1.9% of patients have attempted suicide. It should be noted that suicidal risk exists after cessation of treatment, and cases of attempted and successful suicides up to six months after the end of antiviral treatment have been reported [24] , with a greater risk, however, in the first four weeks of cessation[1] . Statistical analysis revealed no correlation between the variables studied - age, sex, psychiatric history, genotype and viral load - and the onset of psychiatric disorders.

The sixteen depressed patients in our study were able to complete their antiviral treatment thanks to the concomitant introduction of an antidepressant of the serotonin reuptake inhibitor (SSRI) family. Furthermore, premature discontinuation of antiviral treatment due to psychiatric side effects has been noted in several studies in the literature. Castéra et al. noted the discontinuation of antiviral treatment in four of 98 hepatitis c patients treated with IFN-α, the cause being psychiatric disorders in three patients and hyperthyroidism in one case[25] . On the other hand, in a study of 176 HCV-positive patients treated with INF-α and Ribavirin, some authors reported that only one patient discontinued treatment because of severe depression[26] .

In our study, premature discontinuation of INF-α treatment was noted in two patients following melancholic depression with suicidal impulses. The decision to discontinue antiviral treatment was taken by consensus between the gastroenterologist and psychiatrist involved. However, interferon treatment was reinstated in one of the two patientsafter mood stabilization with serotonin reuptake inhibitor antidepressants and strict bi-disciplinary follow-up.

The etiological mechanisms of these neuropsychiatric disorders have yet to be determined. Several hypotheses have been put forward regarding the induction of mood disorders, notably depression, by the antiviral IFN-α. The first hypothesis is that this antiviral, once introduced into the body, will lead to a cascade activation of the production of other endogenous cytokines capable of causing central activation, or production of a hepatic enzyme involved in the metabolism of serotonin, a major neuromediator in the monoaminergic theory of depression. Furthermore, selective serotonin transporter inhibitor antidepressants are active in treating or preventing the onset of depression under IIFNα[27-28] . Finally, other hypotheses have been put forward, notably neuroendocrine and noradrenergic[29] .

Although no specific studies have been carried out, it is now recommended that these patients be carefully monitored from a psychiatric point of view during their antiviral treatment[8, 10]. It is therefore possible to prevent or treat thymic disorders on the basis of these factors: lowering dosage, therapeutic windows, prescription of SSRIs. The general recommendations to be followed by clinicians before starting IFN-α antiviral therapy in patients with viral hepatitis C are shown in the table below (Tab.2).

Table 2: general recommendations before starting IFN-α

	Recommendations
1.	Assessment of the subject's current psychiatric clinical status before initiating antiviral treatment, even in cases of moderate symptomatology;
2.	Be careful with patients on antidepressants, who seem to be at greater risk of decompensation;
3.	Elderly patients and women, particularly those with a history of depressive disorders, appear to be more sensitive to the adverse effects of IFN-α ;
4.	If you have a personal psychiatric history of depression, bipolar disorder or suicide, your doctor must be very attentive to the risk of recurrence of mental disorders under antiviral treatment;
5.	The existence of a family history of depression, bipolar disorder or suicide should make the physician more attentive, even if the subject does not present an acute psychic disorder.

V. Conclusion

Interferon-induced psychiatric disorders have been described in numerous studies. These disorders are likely to worsen during the course of antiviral treatment, jeopardizing compliance and thus the patient's vital prognosis. Regular psychiatric follow-up enables early detection and appropriate management of these disorders, particularly depression during interferon therapy for viral hepatitis C, and optimizes treatment adherence and virological response. Close collaboration between gastroenterologists and psychiatrists is essential before, during and after initiation of antiviral treatment.

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