DEPRESSION AND INTERFERON THERAPY IN CHRONIC HEPATITIS C PATIENTS: EPIDEMIOLOGY, PREDICTIVE FACTORS AND PROPOSED ETIOPATHOGENIC MODELS

António Cruz Neves*, Christopher Dickens** and Miguel Xavier***

Abstract

Objective: Neuropsychiatric symptoms are commonly associated with chronic hepatitis C virus infection and its treatment. In particular, interferon, a primary component of treatment for chronic hepatitis C, has been strongly associated with depressive symptoms. The aim of this review of the literature was to evaluate the incidence of depression and related predictive factors in patients with hepatitis C on interferon alpha therapy and the proposed etiopathogenic models.

Method: A review of the literature was undertaken.

Results: An increase in depression or in psychiatric disturbance in general during therapy with IFN alpha was found - reported rates of interferon alpha-induced Major Depressive Disorder have ranged from 10% to 44% across studies. It appears that the development of depression in chronic hepatitis C patients treated with IFN alpha may be dependent on both duration of treatment and dosage of IFN alpha. Regarding the ascertainment of predictive factors for depression, the findings are not conclusive and sometimes contradictory.

Conclusions: More studies are needed in order to clarify the possible links and associations between INF use and depression. Furthermore, research is needed so that patients with psychiatric problems are not excluded from effective treatments for this growing medical problem.

***Key-words**: Hepatitis C; Interferon-alpha therapy; Depression*

* Assistente de Psiquiatria e Saúde Mental. Clínica Universitária de Psiquiatria e Saúde Mental – Faculdade Ciências Médicas - Universidade Nova de Lisboa

** Senior Lecturer in Psychological Medicine. Department of Psychiatry – University of Manchester, Manchester Royal Infirmary.

*** Professor de Psiquiatria e Saúde Mental. Clínica Universitária de Psiquiatria e Saúde Mental. Faculdade de Ciências Médicas. Universidade Nova de Lisboa.

I. INTRODUCTION

Chronic hepatitis C is a major public health problem. According to World Health Organization (WHO) 1999 estimates, 3% of the world's population, or

approximately 170 million people, are infected with hepatitis C virus (HCV)[1], which in the United States is estimated to affect approximately 3-4 million, that means 1.8% of the general population[2].

The mode of acquisition is often unclear, but typical ways of infection are intravenous drug use (IVDU) and blood transfusions[2]. When the disease is detected, approximately 20% of patients with chronic hepatitis C already have liver cirrhosis[2]. Hepatocellular carcinoma occurs in 1% to 4% of patients per year during the first 5 years after cirrhosis has been established. The risk has been estimated to be approximately 7% after 5 years of cirrhosis and 14% at 10 years; it is higher in men and in older patients [3]. Chronic hepatitis C is now the leading indication for orthotopic liver transplantation in the United States and other western countries[4].

Ribavirin plus interferon combination therapy is presently considered the optimal treatment of patients with chronic hepatitis C[5]. However, interferon (IFN) causes significant neuropsychiatric side effects[6]; among the most prominent are symptoms of depression, anxiety and cognitive impairment (that include impaired concentration, decreased alertness, deficits in verbal memory, and mental slowing)[7].

Based on the DSM-IV[8] criteria, a depressive syndrome that occurs during IFN therapy is considered a substance-induced mood disorder[8]. These side effects are a frequent reason for stopping the therapy[5].

II. REVIEW OF THE LITERATURE

The aim of this review of the literature was to evaluate the incidence of reported depression in patients with hepatitis C on interferon alpha therapy. The papers included in this review were selected from studies identified using different search strategies and sources:

- Electronic literature searches were performed on different databases. On Medline the complete search strategy devised by the Cochrane Collaboration Review Group for Depression, Anxiety and Neurosis was used covering depression, depressive disorders, dysthymia, adjustment disorder, mood disorder and affective disorder, and also the keyword 'interferon alpha' and 'all interferon' subheadings. This was then run against a keyword search on 'hepatitis' and 'all hepatitis viruses' sub-headings. Similar search strategies were used on Psychinfo, Embase and Cinahl.
- Relevant references from the bibliographies of identified papers.
- References from previous reviews.

Quality criteria were used in the selection of relevant papers. Only studies with identified and robust measures were included, and all the patients had chronic hepatitis C.

The papers were reviewed and divided into four major categories: 1. Studies using self rated measures; 2. Studies using observer based rating scales; 3. Studies using observer based rating scales and standardised criteria according to DSM; 4. Studies using standardised interviews.

1. Studies using self rated measures

Malguarnera *et al.*[9] studied the effects on depression of IFN alpha. Ninety-six patients were included and compared with a control group of untreated hepatitis C patients. All patients were randomly assigned to four different treatment groups (recombinant INF alpha 2a – group A; recombinant INF alpha 2b – group B; lymphoblastoid INF alpha – group C; leucocyte IFN alpha – group D) which were similar in number of patients (24), age, sex, grading and duration of the disease, and in the dose administrated (3 MU, three times a week, 6 months). The Zung Self-Rating Depression Scale (SDS) was used for the assessment of depression, and the patients were evaluated before the beginning, at the 1st, 3rd and 6th month of treatment.

In all patients treated with INF alpha, the mean SDS values increased from mild to moderate depression, but never attained severe depression. This increase was significant compared with to the non--treated patients. Elevated values were observed in the first month of treatment, with a progressive decrease in the following end points. The SDS scores reverted to pretreatment values after suspension of the treatment. No statistical correlation between duration of treatment and grade of depression was observed during the 6-month treatment, except in the lymphoblastoid group at the 3-month end point.

Dieperink *et al.*[10] in their study describe the neuropsychiatric side effects of treatment with IFN-α-2b and ribavirin in patients with chronic hepatitis C. Fifty-five patients were divided in 4 groups: group 1 – Receiving psychiatric treatment before beginning INF/Ribavirin; group 2 – Antidepressant treatment recommended during INF therapy; group 3 – No treatment for neuropsychiatric side effects required during INF therapy; and group 4 – Untreated control group. The protocol was IFN-α 3 MU 3 times weekly and ribavirin (1,000-1,200 mg/d). Several instruments were used for the assessment (at baseline, 4, 8, 12 and 24 weeks): the Hamilton Depression Rating Scale, the Zung Self-Rating Depression Scale (SDS), the Medical outcomes Study 36-item Short-Form Health Survey Quality of Life Scale (SF 36), the Beck Depression Inventory (BDI), the Inventory to Diagnose Depression, the Positive and Negative Affect Scale, the Profile of Mood States, and the Multidimensional Fatigue Inventory.

According to BDI data, and regarding the 31 patients not in psychiatric care at baseline, 48% required treatment for neuropsychiatric symptoms and 23% had Major Depressive Disorder (MDD). The untreated control group had baseline BDI scores similar to those of the subjects receiving psychiatric treatment at baseline but significantly higher scores than patients not in psychiatric care at baseline and 38% met criteria for major depression at baseline. Scores in all measures in this group decreased over the course of the study.

They found that a family history predict a seven fold increase in likelihood of requiring psychiatric intervention, and a prior history of two or more psychiatric diagnosis was also predictive of the need of psychiatric treatment. The only predictor of developing major depression was an elevated baseline BDI score (p=0.003).

Kraus *et al.*[11] tried to assess prospectively the incidence, spectrum and extent

of psychiatric symptoms of patients receiving interferon alpha therapy as compared with an untreated reference group. One hundred and four patients were divided into two nonrandomized groups. Patients in whom therapy with interferon alpha was indicated and that gave written consent to receive this therapy and participate in the study before enrolment formed the treatment group. The reference group was formed by patients not treated for chronic hepatitis C due to nonpsychiatric comorbidities, refusal of interferon alpha therapy or previous interferon alpha therapy unsuccessful. The treatment protocol was changed during the investigation: 44 patients received IFN-α-2b, 5 MU, administered three times a week and the other 40 IFN-α-2b, 3 to 5 MU, administered three times a week plus ribavirin 1000-1200 mg/day. The Hospital Anxiety and Depression Scale (HADS) and the Symptom Checklist-90 Revisited (SCL-90) were used for the assessment. The treatment group patients were evaluated before therapy (T1), after 4 weeks (T2), 3 to 4 months (T3), 6 to 8 months (T4) of interferon therapy, as well as 4 weeks (T5) and 6 months (T6) after termination of interferon therapy. The reference group was assessed after corresponding time intervals (T10-T50), T50 was set to 12 months after T10 and no evaluation was made at T6. They found a significant increase of depression scores in the treatment group during interferon alpha therapy ($p < 0.001$). Using a HAD cut off ≥ 9 the depression rate at T1 was 15.5% and at T4 was 35%. The depression scores decreased to pre-treatment levels after the therapy was stopped (T5 and T6). No significant association between incidence or extent of psychiatric symptoms during interferon alpha therapy and socio-demographic features (age, gender), histological grade of disease, or mode of acquisition was found.

The depression scores of the reference group were considerably higher (probably due to a significantly older age or to the psychological reaction to the fact that no treatment was available) than the pre-treatment scores of the interferon group but remained stable.

Koskinas *et al.* [12] evaluated the degree of depression in patients with chronic viral hepatitis before and during INF therapy. The study population was divided in 3 groups; the first group had 38 patients with chronic HCV infection, the second group had 36 patients with chronic HBV infection. The control group consisted of 58 patients who had undergone cholecystectomy. The treatment protocols were: INF-α-2b, 3 MU, administered three times a week, 52 weeks, and ribavirin 800-1000 mg/day for hepatitis C and INF-α-2b, 3 MU, administered three times a week, 52 weeks, for hepatitis B. The Zung Self-Rating Depression Scale (SDS) was used for the assessment of depression, before treatment, 3 months after the beginning of the treatment and 3-6 months after stopping the treatment.

At baseline the SDS index was not significantly different between patients with viral hepatitis and the control group [although it was more increased in the HBV group, $p=0.001$)]. Treatment was associated with a statistically significant increase in the SDS index, both in HBV and HCV related hepatitis ($p<0.001$), but more in patients with hepatitis C (mean SDS=60, $p=0.001$) than in hepatitis B patients

(mean SDS=47.5, p=0.001). Severe depression was found in 21% of the patients treated for HCV and in 2.8% of the HBV cases. The SDS index was significantly more increased in females.

Hunt *et al.* [13] examined the impact of INF-α therapy in patients with chronic hepatitis C on the perception of health status and the incidence of depressive symptoms during the treatment. They evaluated 38 patients using the SF-36 subscale, the Hospital Anxiety and Depression Scale (HADS) and the Beck Depression Inventory (BDI). The patients received IFN-α-2b, 3 MU, administered three times a week.

They found a significant increase of depression during the first six months of treatment. Prior to INF-α therapy, possible depression was detected in 7% of patients and definitive depression in 4% of them. The HADS depression scores did not change significantly during INF-α therapy, but definitive depression was detected in 8% of patients at six months of treatment. The BDI revealed a 30% prevalence of mild depression in the included patients prior to the treatment. During the six-month treatment the BDI scores increased significantly (p=0.05), with 20% of patients exhibiting mild depression, 8% moderate depression and 4% with severe depression. No significant changes in health related quality of life before, during or after the treatment were reported.

Hauser *et al.*[14] tried to assess the incidence of INF-induced Major Depression Disorder (MDD) in HCV patients, the average length of time on IFN therapy until the development of MDD, and the efficacy of the SSRI citalopram in treating IFN-induced MDD. Fifty-three patients were evaluated with the Structured Clinical Interview for DSM-IV Axis I disorders, Version 2.0 (SCID-I/P) to determinate presence of psychiatric illness. In addition present depressive symptoms were assessed by the Beck Depression Inventory (BDI) prior to the starting of the IFN therapy (IFN alpha-2b, 3 MU, administered three times a week in association with ribavirin 600 mg/day, for 6-12 months). BDI were administered weekly over the course of treatment. If at any point in the study a patient showed a BDI score ≥ 18, the SCID-I/P was used again to determinate criteria for MDD. Thirty--nine patients completed at least 2 months of IFN therapy.

They found that 33.3% (13/39) of these patients met criteria for IFN-induced MDD. The proportion of Caucasians was significantly higher in the MDD group (p=0.005) but no significant differences were found between the MDD and non-MDD groups regarding age, proportion of patients with a past history of MDD or substance abuse. In the MDD group, the mean time from baseline to the development of a diagnosis of MDD was 12.1 weeks, with a mean increase in the BDI score of 20.0±6, and most of these patients were diagnosed as having MDD between 6 and 22 weeks from baseline. The BDI scores at baseline were significantly higher, suggesting that patients with more symptoms of depression prior to the therapy may be at a grater risk of developing IFN-induced MDD.

Mulder *et al.*[15] also studied prospectively the psychiatric side effects of INF-α in patients with hepatitis C. Sixty-three patients were included in the trial, and re-

ceived IFN-α_1, 3 MU, administered three times a week, during 6 months. In the baseline psychiatric assessment was used the Hopkins Symptom Checklist (SCL-90). The monthly follow up assessment was made with the SCL-90. Of the 63 patients included, 59 completed the treatment but only 49 completed the SCL-90 forms. While there was a trend for non-completers to be male and have a diagnosis of antisocial personality disorder, there were no significant differences between the completer and the non-completer groups. Both groups have high rates of psychopathology, particularly alcohol and polysubstance dependence (approximately 75% of the sample had used intravenous drugs).

They found no significant change in total SCL-90 scores or in any of the subscale scores. Patients on INF-α therapy did not suffer a drop in mood or an increase in anxiety or irritability. The subgroup with past depression also did not suffer an increase in depressive symptoms, and therefore a lifetime history, according to this study, did not predict the onset or worsening of mood symptoms. Nevertheless these patients had higher mean depression scores throughout their treatment.

2. Studies using observer based rating scales

Gohier *et al.*[16] tried to estimate the incidence of depressive disorders during and after a treatment by IFN-α in patients with chronic hepatitis C and to determinate related predictive factors. Seventy-one patients were included and they received INF-α, 3-6 MU, administered three times a week, 12 months, alone or in association with ribavirin 1000 mg/day, and were assessed before the treatment (M0), at during (M4) and at the end of treatment (M12), and 6 months later (M18), using the Hamilton-Anxiety Scale and Montgomery and Äsberg Depression Rating Scale (MADRS).

The authors found 28% of patients with depressive symptoms (3% with suicidal ideation). The overall treatment withdrawal rate was 10% and most of these patients were depressed and/or with suicidal ideation. They also found that the independent factors that can be used to predict depression during the treatment were female gender ($p<0.05$) and the MADRS score at M4 (>15) ($p<0.001$), and that an increase in the scores on Hamilton Anxiety Scale between M0 and M4 ($p<0.05$) and sleep disorders ($p<0.05$) can be used to predict suicidal behaviour. Many patients presented depression or anxiety after the treatment (8%), in spite of discontinued treatment. Prior antidepressant treatment and the MADRS score at M4 were significant predictive factors of anxiety or mood disorders after the end of the treatment.

Castera *et al.*[17] also reported in a letter an evaluation of the incidence of depression and factors predictive of depressive symptoms in hepatitis C patients receiving interferon therapy. Thirty-three patients were assessed before and 12 weeks after the treatment using the Montgomery-Äsberg Depression Rating Scale (MADRS) and the Schedule for Affective Disorders and Schizophrenia, Lifetime Version, an observer based semi-structured mental state examination providing a psychiatric diagnosis according to DSM-III-R criteria.

The patients were treated with IFN-α, 3 MU, thrice weekly for 3 to 12 months.

The authors found that 12% of the patients developed Major Depressive Disorder, according to the DSM-III-R criteria. A significant increase in the average MADRS score was observed after 12 weeks of treatment ($p<0.01$). None of the patients with a normal baseline MADRS score (<3) developed depressive symptoms, whereas 42% of the patients with a high baseline MADRS score (>15) developed depressive symptoms ($p<0.04$).

Bonaccorso *et al.*[18] evaluated the incidence of depressed mood and major depression in 37 patients, who were treated with IFN-α, 3 MU, administered three times a week. The subjects were evaluated before therapy (baseline) and after 3 months of treatment (end-point) with the Montgomery Asberg Depression Rating Scale (MADRS). Two psychiatrists made the diagnosis of major depression disorder (MDD), according to the DSM-IV criteria. At end-point, 40.7% of the patients suffered from MDD (comparing to 0% at baseline). The total MADRS score and the MADRS items are significantly higher at end-point ($p=0.0008$) and no significant gender-related differences were seen.

3. Studies using observer based rating scales and standardized criteria according to DSM

Miyaoka *et al.*[19] report in a letter the incidence and risk factors for depression among sixty-six hepatitis C patients receiving interferon therapy. The interferon protocol consisted of recombinant interferon-alpha-2b was administered to 33, natural lymphoblastic interferon-alpha to 29, and other forms of interferon to four of these patients. Ten million units of recombinant interferon-alpha-2b or 6 MU of natural lymphoblastic interferon--alpha, every day for the first 2 weeks and then three times a week for the next 22 weeks. The psychiatric assessments were performed four times by a psychiatrist using the DSM-III-R criteria and the Hamilton Rating Scale for Depression.

Criteria for major depressive episode, according to the DSM-III-R, was found in 3 of 66 (4.5%), 14 of 64 (21.9%), 23 of 60 (38.3%), and 16 of 59 (27.1%) at 0, 4, 12, and 24 weeks, respectively. The cumulative depression rate throughout the 6-month treatment period (depression related with IFN therapy) was 44%. The mean maximum Hamilton Rating Scale for Depression score among the four assessments in these patients was 20.5 (SD=5.7) and at week 0 was significantly higher in the depressed patients ($p<0.05$). There were no significant differences in socio-demographic factors (age and gender) between the depressive and non-depressive groups.

Horikawa *et al*[20] performed a study to investigate the incidence, clinical course and risk factors for depression in patients with chronic hepatitis C during the treatment period with interferon alpha. Ninety nine patients received six or 10 MU of natural IFN-alpha or recombinant IFN-α-2b, once a day for the first 4 weeks and three times per week for the following 20 weeks.

Psychiatric interviews were performed by two psychiatrists for the diagnosis of major depressive episode, according to the DSM-IV criteria, together with the Hamilton Rating Scale for Depression.

The evaluations were made before the start of interferon therapy, and once every 4 weeks during both the 24-week treatment period and 12 weeks after the end of therapy.

Patients diagnosed as having major depression before the therapy were also assessed with the Zung Self-Rating Depression Scale (SDS) and the Taylor Manifest Anxiety Scale (MAS). No patients were diagnosed as having major depression disorder (MDD) before the start of INF therapy, although 8.1% showed depressive mood/anhedonia. During the treatment 23.2% of patients met criteria for MDD and 73.9% of those patients developed depression during the first 8 weeks. The only risk factor for depression was advanced age.

4. Studies using standardised interviews

Schaefer *et al.*[21] evaluated compliance with treatment, side effects, response rates, and dropout rates during treatment of chronic hepatitis C in eighty-one patients with current or preexisting psychiatric disorders, former drug addiction, or ongoing methadone substitution compared with controls without a psychiatric history or drug addiction (the patients were stratified into four groups). All patients received IFN-α-2a, 3 MU 3 times weekly and ribavirin 1,000-1,200 mg/ /day. Hepatologists and psychiatrists saw all patients biweekly during the first 8 weeks of treatment and then monthly on an outpatient basis. Psychiatric history and diagnosis was assessed by a structured clinical interview. A present psychiatric illness and the development of depression during treatment were diagnosed by using a semi structured diagnostic interview according to the DSM-IV criteria. At each visit, patients were screened for number and severity of depressive symptoms, suicidal thoughts, irritability, sleeping disturbances, lack of concentration, and craving for drugs or alcohol.

A total of 16% developed a new depression during treatment with INF. No significant differences between groups were detected with respect to IFN related development of depression during treatment. Suicidal thoughts were observed in 4 to 6% patients. Depression before or during treatment had no significant influence on therapeutic outcome (sustained response) or dropout rate. No increased risk for IFN induced mental side effects and dropouts in psychiatric patients if interdisciplinary care and antidepressant treatment are available. Sustained virologic response (overall, 37%) did not differ significantly between subgroups.

III. DISCUSSION

Methodological issues

One potential methodological problem of this review is the quality criteria to determinate which studies were reviewed. Studies capable of determining the nature of the casual association between depression and interferon alpha therapy would need to be either prospective cohort studies, or double-blind, randomised-controlled trials in which one variable is changed and the effect on the other variable is assessed. In studies of either design, observer-rated measures of depression would be required. In this re-

view only 3 studies were found which met these criteria (Malguarnera *et al.*, 1998; Dieperink *et al.*, 2003; Kraus *et al.*, 2003). As a result of the paucity of studies of high quality, it was decided to not restrict the studies reviewed according to strict quality criteria.

The literature about the psychiatric effects of IFN therapy has provided insight on the strength and quality of these relations. Regardless, several limitations are worthnoting. Primarily, these include differences in the operational definition of depression, type of sample and design of the study, unclear identification of the aetiology of the outcomes, and difficulty identifying risk factors for the development of depression.

Secondarily, measures of depression range from those that have diagnostic properties (e.g., Diagnostic Interview Schedule and Structured Clinical Interview for Diagnostic and Statistical Manual IV) to those that are reliable and valid measurements of depressed mood (e.g., Hospital Anxiety and Depression Scale, Beck Depression Inventory, and Brief Symptom Inventory) but that are not diagnostic in nature. It should be noted that caution needs to be exercised when using some of these measures with medically ill individuals (e.g., Beck Depression Inventory) because there is a tendency within the measure to increase depression scores because of the endorsement of somatic items. The potential result is a spurious increase in depression solely because of somatic items.

The issue of selection bias – specialist/ /tertiary care naturally attracts the more severe end of the spectrum, and any study based entirely in tertiary care will inevitably report more associations between the exposure in question and the clinical outcome. Another limitation comes from the small sample sizes included in most studies. In some studies, the measures used for the ascertainment of depression were self reported and the question of response bias may have been present.

Proposed etiopathogenic models

The mechanisms of IFN alpha induced depression are not fully understood, but it is most likely to be multifactorial, involving various neurotransmitters, cytokine production, and endocrine regulation.

In a dose-dependent fashion, IFN alpha has been shown to reduce serotonin (5-HT) in the midbrain, frontal cortex, and striatum of the rat brain[22]. In addition, IFN alpha may deplete synaptic concentrations of 5-HT by augmenting its reuptake through the increased production of 5-HT transporter mRNA[23]. Therefore, IFN can modulate the expression of serotonin transporter mRNA in the brain[23]. IFN alpha can also alter the metabolism of tryptophan by activating indolamine 2,3-deoxygenase and tryptophan deoxygenase, both enzymes that catalyse the destruction of tryptophan[24] and there is some suggestion that IFN alpha may indirectly decrease tryptophan levels by stimulating various pro-inflammatory cytokines[25].

Other studies suggest that IFN alpha modulates neuroendocrine functions and this fact can be related with a partial explanation for the development of depression. The hypothalamic-pituitary-adrenal (HPA) axis is known to be overactive in depression[26]. IFN alpha induces the re-

lease of corticotrophin releasing factor (CRF) and arginine vasopressin (AVP) from the hypothalamus[27]. IFN alpha may indirectly stimulate the HPA axis by causing the activation of endogenous cytokines, especially interleukin (IL)-6[28]. It has been demonstrated that IL-6 stimulates the release of corticotropin releasing factor (CRF), leading to increased activity of the HPA axis[28]. IFN alpha may have effects on the hypothalamic-pituitary- thyroid (HPT) axis that also contribute to the development of depression. Thyroid dysfunction, either hypothyroidism or hyperthyroidism, has been reported in approximately 5%-20% of HCV patients undergoing treatment with IFN alpha[29,30]. Thus, thyroid dysfunction represents the most common autoimmune condition observed with IFN alpha treatment[30].

A unifying theory postulates the induction of sickness behaviour by IFN alpha, as a parallel depressive behaviour in humans to the innate part of the behavioural repertoire (a so-called motivational state), which is activated by infection and inflammation and thought to have evolutionary value and could be induced in laboratory animals [31].

IV. CONCLUSIONS

From the literature on depression and IFN alpha in HCV patients we can summarise the following points:

The studies

Taken together, all studies but one, regardless of their methods of ascertainment, find an increase in depression or in psychiatric disturbance in general during therapy with IFN alpha compared to baseline (and to a control group in four studies). Reported rates of interferon alpha--induced Major Depressive Disorder have ranged from 10% to 44% across studies.

Features associated with the relationship between depression and IFN

It appears that the development of depression in chronic hepatitis C patients treated with IFN alpha may be dependent on both duration of treatment and dosage of IFN alpha:

- With a dosage of 3 MU, the MDD scores vary between 12% and 28%, and in two studies using 10 MU of IFN the observed MDD rates were between 23.2% and 44%.
- In four studies most patients developed depression during the first 12 weeks, but in one study the self-rating scores increased significantly only at 6 months.
- In one study was found that 8% of patients presented depression after the treatment, in spite of discontinued treatment.

Regarding the ascertainment of predictive factors for depression, no significant association between psychiatric symptoms during interferon alpha therapy and histological grade of disease or mode of acquisition was found.

The findings about sociodemographic factors (age, gender) were contradictory. Most studies found no association, but in two studies depression was significantly associated with female gender and one study found a significant association with advanced age.

No significant association between in-

terferon alpha induced depression and lifetime history of depression was seen in three studies, but in one study family history and a prior history of two or more psychiatric diagnosis could be predictive of the need of psychiatric treatment. Elevated depression scores at baseline (in two studies) and at the fourth month (in one study) were predictive of depression but in other study current psychiatric history was not related with the development of depressive side effects during treatment. Depression seemed to have no significant influence on therapeutic compliance or outcome (sustained virologic response).

Given these sometimes contradictory results, further studies are needed in order to clarify the possible links and associations between INF use and depression.

Resumo

Diversos sintomas neuropsiquiátricos estão habitualmente associados à infecção crónica pelo vírus da hepatite C e ao seu tratamento. Em particular, a terapêutica com Interferão alfa tem sido fortemente relacionada com o aparecimento de sintomatologia depressiva. Foi realizada uma revisão da literatura com o objectivo de avaliar a incidência da depressão nos pacientes com hepatite C, bem como os seus factores preditivos e os modelos etiopatogénicos propostos. Verificou-se um aumento da incidência de depressão durante a terapêutica com Interferão alfa, relativamente às taxas de depressão existentes na comunidade – as taxas de depressão encontradas variam entre os 10% e os 44% ao longo dos estudos. Os dados disponíveis na literatura parecem apontar para a existência de uma correlação entre o desenvolvimento de depressão nos doentes com hepatite C tratados com Interferão alfa e variáveis tais como a duração do tratamento e a dosagem de Interferão. No que respeita à avaliação dos factores preditivos para a depressão os resultados encontrados não são conclusivos, o que na perspectiva dos autores justifica a necessidade de efectuar mais estudos, a fim de esclarecer a natureza da eventual associação entre o uso de Interferão e o aparecimento de um síndrome depressivo.

***Palavras-chave**: Hepatite C; Interferão alfa; Depressão.*

REFERENCES

1. World Health Organization. Global surveillance and control of hepatitis C. *J Viral Hepatitis* 1999; 6: 35-47
2. Alter M, Kruszon-Moran D, Nainan O, et al. The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. *N Engl J Med* 1999; 341: 556-62.
3. NIH Consensus Program. National Institutes of Health consensus development conference panel statement: management of hepatitis C. *Hepatology* 1997; 26: 2S-10S.
4. Hoofnagle JH. *Chronic Viral Hepatitis C: Clinical*. Chicago, III: Association for the Study of Liver Diseases; 1998
5. Kjaergard LL, Krogsgaard K, Gluud C. Ribavirin with or without alpha interferon for chronic hepatitis C (Cochrane Review). In: *The Cochrane Library*, Issue 2, 2004. Chichester, UK: John Wiley & Sons, Ltd.
6. Lerner DM, Stoudemire A, Rosenstein DL. Neuropsychiatric toxicity associated with cytokine therapies. *Psychosomatics* 1999; 49: 428--435.
7. Dieperink E, Willenbring M, Ho S. Neuropsychiatric Symptoms Associated With Hepatitis C and Interferon Alpha: A Review. *Am J Psychiatry* 2000; 157(6): 867-876.
8. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV, 4th edn*. APA: Washington, DC, 1994
9. Malaguarnera M, Di Fazio I, Restuccia S, Pistone G, Ferlito L, Rampello L. Interferon alpha-induced depression in chronic hepatitis C patients: comparison between different types of interferon alpha. *Neuropsychobiology* 1998; 37(2): 93-7.
10. Dieperink E, Ho SB, Thuras P, Willenbring ML. A prospective study of neuropsychiatric symptoms associated with interferon-α-2b and Ribavirin Therapy for patients with Chronic Hepatitis C. *Psychosomatics* 2003; 44(2): 104-112.
11. Kraus MR, Schafer A, Faller H, Csef H, Scheurlen M. Psychiatric symptoms in patients with chronic hepatitis C receiving interferon alfa-2b therapy. *Journal of Clinical Psychiatry* 2003; 64(6): 708-14.
12. Koskinas J, Merkouraki P, Manesis E, Hadziyannis S. Assessment of depression in patients with chronic hepatitis: effect of interferon treatment. *Digestive Diseases* 2002; 20(3-4): 284-8.

13. Hunt CM, Dominitz JA, Bute BP, Waters B, Blasi U, Williams DM. Effect of interferon-alpha treatment of chronic hepatitis C on health-related quality of life. *Digestive Diseases & Sciences* 1997; 42(12): 2482-6.
14. Hauser P, Khosla J, Aurora H et al. A prospective study of the incidence and open-label treatment of interferon-induced major depressive disorder in patients with hepatitis C. *Molecular Psychiatry* 2002; 7: 942-947.
15. Mulder RT, Ang M, Chapman B, Ross A, Stevens IF, Edgar C. Interferon treatment is not associated with a worsening of psychiatric symptoms in patients with hepatitis C. *Journal of Gastroenterology & Hepatology* 2000; 15(3): 300-3.
16. Gohier B, Goeb JL, Rannou-Dubas K, Fouchard I, Cales P, Garre JB. Hepatitis C, alpha interferon, anxiety and depression disorders: a prospective study of 71 patients. *World Journal of Biological Psychiatry* 2003; 4(3): 115-8.
17. Castera L, Zigante F, Bastie A, Buffet C, Dhumeaux D, Hardy P. Incidence of interferon alfa-induced depression in patients with chronic hepatitis C. *Hepatology* 2002; 35(4): 978-9.
18. Bonaccorso S, Marino V, Biondi M, Grimaldi F, Ippoliti F, Maes M. Depression induced by treatment with interferon-alpha in patients affected by hepatitis C virus. *Journal of Affective Disorders* 2002; 72(3): 237-41.
19. Miyaoka H, Otsubo T, Kamijima K, Ishii M, Onuki M, Mitamura K. Depression from interferon therapy in patients with hepatitis C. *American Journal of Psychiatry* 1999; 156(7): 1120.
20. Horikawa N, Yamazaki T, Izumi N, Uchihara M. Incidence and clinical course of major depression in patients with chronic hepatitis type C undergoing interferon-alpha therapy: a prospective study. *General Hospital Psychiatry* 2003; 25(1): 34-38.
21. Schaefer M, Schmidt F, Folwaczny C et al. Adherence and Mental Side Effects During Hepatitis C Treatment With Interferon Alfa and Ribavirin in Psychiatric Risk Groups. *Hepatology* 2003; 37(2): 443-451.
22. Kamata M, Higuchi H, Yoshimoto M, et al. Effect of single intracerebroventricular injection of alpha-interferon on monoamine concentration in the rat brain. *Eur Neuropsychopharmacol* 2000; 10: 129-132.
23. Morikawa O, Sakai N, Obara H, et al. Effects of interferonalpha, interferon-gamma and cAMP on the transcriptional regulation of the serotonin transporter. *Eur J Pharmacol* 1998; 349: 317-324.
24. Widner B, Ledochowski M, Fuchs D. Interferon-gammainduced tryptophan degradation: Neuropsychiatric and immunological consequences. *Cur Drug Met* 2000; 1: 193-204.
25. Song C, Lin A, Bonaccorso S, et al. The inflammatory response system and the availability of plasma tryptophan in patients with primary sleep disorders and major depression. *J Affect Disord* 1998; 49: 211-219.
26. Dinan T. Glucocorticoids and the genesis of depressive illness: A psychobiological model. *Br J Psychiatry* 1994; 164: 365-371.
27. Shimizu H, Ohtani K, Sato N. Increase in serum interleukin- 6, plasma ACTH and serum cortisol levels after systemic interferon-alpha administration. *Endocrine Journal* 1995; 42: 551-556.
28. Dafny N, Prieto-Gomez B, Dong WQ, Reyes-Vazquez C. Interferon modulates neuronal activity recorded from the hypothalamus, thalamus, hippocampus, amygdala and the somatosensory cortex. *Brain Res* 1996; 734: 269-274.
29. Lisker-Melman M, Di Bisceglie A, Usala S, et al. Development of thyroid disease during therapy of chronic viral hepatitis with interferon alfa. *Gastroenterol* 1992; 102: 2155-2160.
30. Marcellin P, Pouteau M, Benhamou J. Hepatitis C virus infection, alpha interferon therapy and thyroid dysfunction. *J Hepatol* 1995; 22: 364-369.
31. Dantzer R, Bluthe R, Laye S, et al. Cytokines and sickness behavior. *Ann N Y Acad Sci* 1998; 840: 586-590.