Depression and Interferon Use in Patients with Chronic Hepatitis C: Clinical and Epidemiological Correlation

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Key words:

Depression, Interferon α, Chronic Hepatitis C, Risk factors
Chronic Hepatitis C

Epidemiological data

It is a condition so common that in many countries is considered a public health issue. In Romania, the sero-prevalence of the infection with virus hepatitis C in the adult population worldwide is estimated at 3.23%.

Clinical aspects

In the chronic phase of the disease, at 20% of people viral infected, the liver damage is evidenced clinically by fatigue or malaise, while 50% are asymptomatics. HCV may be associated with a variety of extrahepatic manifestations. Several studies report depression as part of clinical manifestations of Hepatitis C, with different prevalence and intensity.

Antiviral therapy at the HCV patients

Interferon-α (IFN) is the main treatment for HCV. The initial euphoria induced by the use of IFN alone in the treatment of patients with HCV, was overshadowed by the emergence of side effects.

Psychiatric effects associated with IFN

The interest in this type of side effects finds motivation in the fact that their appearance determin a reduction of the dose or a discontinuation of the antiviral therapy with consequent decrease in the rate of SVR (sustained virological response).

In "Hepatology – a Clinical Textbook” it is presented the prevalence of psychiatric adverse effects:

- Asthenia, fatigue 70-80%
- Sleep disorders 45-65%
- Irritability 60-85%
- Cognitive disorders 45-60%
- Depressive episode 50-60%
  - Mild 20-40%
- Moderate 15-30%
- Severe 2-5%
  - Delirium, psychosis 1-6%
  - Suicide syndrome <1%

**Depression during IFN therapy**

**Epidemiological data**

Reported rate of depression associated with IFN treatment varies between very wide limits, 3-57%, with most investigators reporting between 10-40% share.

**Risk factors**

**Risk factors related to IFN α therapy**

- **Route of administration.** Data suggest that neuropsychiatric side effects are more severe in patients receiving IFNα by i.c.v. (intracerebroventricularly) or i.v. (intravenous), than in whom is sc (subcutaneously).

- **The dose and length of administration.** Some studies argue that increasing the dose and length of IFN administration, may enlarge the risk of depression.

- **The combination with ribavirin.** Discussions in connection with the combination of ribavirin lead to conflicting conclusions: some studies claim that the combination with ribavirin synergistically increase IFN capacity to induce depression, others argue that ribavirin may be a protective factor.

**Risk factors related to patient**

- **Psychiatric personal history**

  History of major depressive disorder may be a predictive factor only if, immediately before starting treatment with IFN, the patient experiences symptoms of depression. The patient's mental status immediately prior to treatment with IFN is actually the most important.
• **Gender**: prevalence is higher in women than in men.

• **Medical disorders associated** (cancer or other viral infections) can increase the risk of secondary depression IFN.

**Clinical aspects**

Depression associated with IFN treatment can take two forms, as the structure of symptoms:

• **Depressive**, is generally installed after a few weeks and includes emotional, cognitive and neurovegetative disorders

• **Neurovegetative**, with early appearance, having in the foreground fatigue, slowness psihomotory, apathy and anorexia.

Hypothesis that IFN is involved in the pathogenesis of depression are multiple and incompletely understood, following the trend of new discoveries in biological psychiatry.

**Treatment of depression associated with IFN**

**Therapeutic Options**

Regarding the pharmacological management of IFN-induced depression, the clinician has to choose between two strategies: administration of antidepressants to prevent or mitigate the development depression or close monitoring for the initiation of antidepressant when the diagnosis is certain.

**Factors which influences the choice of antidepressant**

For patients with risk of developing depression or for those who developed depression secondary to treatment with IFN, any antidepressant (AD) is better than none, those "next generation" being safe, tolerable side effects. Besides the fundamental principle of adequacy of treatment, it should be considered other factors as drug interactions, side effects and efficacy profile.

**Objectives. Methodological coordinates**

**The main objective**

• Identifying the risk factors involved in onset of depression during
antiviral therapy in patients with HCV.

Secondary objectives

- Tracking evolution of depression secondary to antiviral therapy
- Identifying of other psychiatric side effects of antiviral therapy

Methodological coordinates

This observational and prospective study was performed on a group (N = 148) of subjects selected from hospitalised with the main diagnosis of HCV during 2007-2008 in the Gastroenterology Clinic of Colentina Clinical Hospital and Institute of Diseases ”Prof. Dr. Matei Bals”, Bucharest. Patients were enrolled after obtaining informed consent, based on inclusion and exclusion criteria. Assessment tools used: MINI, HAMD, MADRS, CGI-S.

Inclusion criteria:

- patients eligible for HCV antiviral therapy or the initiation of therapy has been initiated
- men and women aged 25 to 64 years
- patients who agreed and signed informed consent.

Exclusion criteria:

- thyroid disorders manifesting
- malignancy
- VHB, VHD, HIV viral coinfection
- a history of addiction / abuse of alcohol in the last 12 months (positive response to the module J of Mini test)
- concomitant treatment with clonidine, reserpine, hydrazine, propranolol, prednisone or other drugs that can influence emotional state.

Results

Psychiatric examination

From the 148 patients included in the study - 71 (47.97%) received psychiatric consult immediately before initiation of antiviral therapy, because of
the presence of psychiatric history.

Psychiatric consult was requested for installed symptoms during antiviral therapy in 59 patients (39.87%), of which 27 (18.24% in group N) for a depressed clinical state and 32 (21.63% in group N) for sleep disturbances associated with irritability, decreased ability to concentrate the attention or asthenia, fatigue. Only 18 patients (12.16%) were sent by the attending infectionist physician at a prophylactical psychiatric consult immediately before initiation of antiviral therapy.

**Psychiatric side effects secondary to antiviral therapy**

**Major depression during antiviral therapy**

During the first 6 months of antiviral treatment, a number of 83 patients (56.08%) of 148 enrolled developed elements of depression. Only 52 met the diagnostic criteria for DSM IV-TR major depressive episode and scale scores over 7 and over 13 at HAMD / MADRS scale. This means that the share of major depression secondary to antiviral therapy (N = 148) is bigger than a third - 35.13.

Other psychiatric side effects due to antiviral therapy were: asthenia and fatigue - 89 patients (60.13%), sleep disturbances - 58 patients (39.19%), irritability - 85 patients (57.43%), anxiety - 41 patients (27.70%) and cognitive disorders - 10 (6.76%).

**Risk factors involved in onset of major depression secondary to antiviral therapy**

**Risk factors related to drug**

**Dose**

The maximal dose of ribavirin used during the study was 1200 mg/day in combination with one of the two forms of peginterferon and more than half of patients (55.40%) received this dose.

Calculation of relative risk of developing depression in patients studied
showed a high risk (OR = 3.571), statistically significant (P-value = 0.02) for those receiving peginterferon α2b 1.5 mg/kg/week and 1200 mg ribavirin/day.

**Lenght of administration of antiviral therapy**
For the 52 patients with major depression, the moment of diagnosis is situated in a fairly wide range, namely 0-20 weeks. It appears that the vast majority of patients (90.38%) were diagnosed with depression within 0-12 weeks.

**Risk factors related to patient**

**Sex**
From the gender distribution of the 52 patients diagnosed with major depression - 35 women (67.31%) and 17 men (32.09%), we can say that the ratio women / men is 2.06 / 1.

Female gender could not be incriminated as a risk factor in the onset of depression in patients receiving antiviral treatment. (OR=0.686 and p-value=0.319)

**Age**
Distribution by age shows that most belong to the age groups 35-44 and 45-54, this group fits 22 and 24 patients.

The value for OR=13.347 and a p-value<0.05 indicates that patients aged between 35 and 44 years have a statistically significant higher risk to develop depression during the antiviral therapy.

According to data obtained for the whole group, age group 35-44 years is a risk factor in onset of depression secondary to IFN therapy and also for female gender (OR of 12.750 and p-value of 0.000). Values for male patients aged 35-44 years (16.100 for OR and 0.014 for p-value) allow us to reach the same conclusion.

**Psychiatric history**
From the 52 patients, 22 (42.31%) had psychiatric history, most depression.
The values obtained for OR (0.254) allow us to say that depressive history can not be included in risk factors, even the value of 0.000 for p-value indicates that the result is statistically significant.

**The importance of psychiatric status at the start of antiviral therapy**

Depressed psychiatric status at the start of antiviral therapy is a risk factor for depression, OR = 29.647 showing a significantly higher risk (p-value=0.02).

**The onset of secondary depression antiviral therapy: clinical manifestations and intensity**

The items most frequently ranked in HAMD were work and activity, anxiety, retardation, delayed insomnia, sleep, agitation and somatic symptoms. Quantification of depression shows that: 30 patients (57.69%) achieved a total score that allowed their inclusion in the category of mild depression, 19 patients (36.54%) were classified as medium severity and the remaining 3 patients (5.77%) developed a depression of severe intensity.

Application of MADRS in patients diagnosed with depression gives information about clinical aspects and about the intensity of depression secondary to antiviral treatment, somewhat superimposable to those of the HAMD.

**Evolution of a depression secondary to antiviral therapy**

**Antidepressant therapy**

The 52 patients diagnosed with major depression secondary IFN received antidepressant medication from different classes: SSRI (18 patients), NASSA (7 patients), SNRI (8 patients) and Tianeptine (19 patients).

**Evolution of MADRS score scale**

Upon diagnosis of major depression secondary antiviral therapy in the 52 patients, the mean MADRS score was 20.8. Tracking the evolution of patients, undergoing antidepressant treatment, with the MADRS scale, shows that in the second month, the mean MADRS score is slightly down from the first month:
17.8. In the sixth month, the mean score reached 6.8. Standard deviation value decreases from 3.8 in the first month to 2.4 in the sixth month.

Evolution of MADRS score scale

Therapeutic response - decrease of MADRS score of 50% of baseline, has never been reached in the second month of antidepressant therapy in any patient. In the third month of evolution, only 6 patients were responders, then increasing the number from 25 in the fourth, 44 in fifth and 51 in the sixth month.

Evolution of CGI-S scale score

CGI-S scale application in patients diagnosed with major depression secondary to antiviral therapy in the moment of establishing this diagnosis, shows that recorded scores have values between 2 (borderline ill) and 6 (severely ill), meaning an average of 3.7 in the first month.

Average scores for CGI-S decreased to almost half in the third month, reaching a value of 2. In the sixth month reaches the lowest value: 0.6.

The dropout rate of antiviral therapy

The dropout rate of antiviral therapy due to the emergence of depression for the entire group is 2.03% (3 patients).

Conclusions

Statistically significant risk factors for developing depression secondary antiviral therapy in patients with HCV were: taking peginterferon α2b 1.5 mg/kg/week in combination with ribavirin 1200mg/day, 35-44 year age group and psychiatric status at the start of therapy antivirals.

Psychiatric evaluation performed immediately before initiation of antiviral therapy and monitoring for 3 months with proper care, are likely to bring significant benefits to patients with HCV by reducing psychiatric contraindications to antiviral therapy and especially by reducing the dropout rate due to the threat of depression.
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