

*Case Report***Suicidal Thoughts Leading to Pegylated Interferon Therapy Discontinuation in a Hepatitis C Patient**Artan Shkoza¹, Mirlinda Likmeta², Sokol Myftiu³, Gentian Vyshka¹¹Biomedical and Experimental Department, Faculty of Medicine, University of Medicine in Tirana, Albania.²Hospital Pharmacy, Department of Pharmaceutical Technology and Bio-pharmacy, Faculty of Pharmacy, University of Medicine in Tirana, Albania.³Cardiology and Internal Service, University Hospital Centre "Mother Theresa", Tirana, Albania.

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*Received: 20/07/2015**Revised: 12/08/2015**Accepted: 18/08/2015***ABSTRACT**

Chronic hepatitis C is an invalidating medical condition whose prognosis has been substantially improved following the discovery of new effective drugs. A golden standard therapy with antiviral drugs has been proven efficacious in promoting a sustained virological response rate. However, such therapies are not deprived from side effects, and some of those might be serious enough to lead to discontinuation of therapy. We report the case of a female patient that formulated severe and stable suicidal thoughts during the first course of peginterferon and ribavirin combined treatment. The patient discontinued therapy against medical advice albeit a psychiatric consultancy and ad hoc therapy was suggested. The case clearly demonstrates the need for a multidisciplinary approach of chronic hepatitis C patients, especially when under aggressive therapeutical schemata, to promote adherence to treatment and thus to improve the final outcome of the disease.

Keywords: suicidal thoughts, pegylated interferon, ribavirin, chronic hepatitis, therapy discontinuation.

INTRODUCTION

Discontinuation and dose modification of therapeutic principles are a factor of major concern for treating clinicians, since these changes might influence directly the final outcome and the efficacy of any treatment. Adherence to therapeutic schemata is a complex process, and the fact that non-adherence might be encountered in an increased frequency due to a diversity of factors, has raised serious concerns. [1, 2]

Patients can discontinue efficacious therapies for chronic hepatitis because of

side-effects, which seem to have a particular appearance profile depending on the genotype of hepatitis C, among other. [3] In their review, Chopra et al. number several bothersome adverse effects that can easily led unprepared and uncollaborative patients to discontinue therapy against medical advice. Among these adverse effects, 'flu'-like symptoms (fatigue, myalgia, fever, and lassitude), skin rash, anal discomfort and dysgeusia are frequent, albeit relatively easily manageable. [3]

The pharmacological boom of new and highly effective agents has led some

authors to extremes of optimism, forecasting the eradication of hepatitis C. [4] the medical and laymen personal taking care for chronic hepatitis patients should however be aware of major obstacles that could prevent patients from profiting with an efficacious therapy. Pegylated-interferon (PEG-IFN)- α , ribavirin (RBV) and boceprevir (BOC), as the golden standard state-of-the art therapy, are not deprived from serious side effects; and even the mere fear of side effects might stop patients from accessing treatment. [5, 6]

CASE STUDY

A Caucasian woman aged fifty years old, was put under PEGASYS® therapy (pegylated interferon [peginterferon] alfa-2a, 180 mcg SC once weekly), combined with peroral ribavirin (800 milligrams, four tablets daily), in conformity with well-known and approved therapeutic schemata for chronic hepatitis C. [7] Higher dosages of both these active drugs have been tried in other settings. [8]

A summary of the clinical and laboratory data of the patient before the initiation of this combined therapy is described below (including Tables 1, 2).

Following the first week of this combined therapy (Pegasys-ribavirin) the patient showed a febrile status during two days, malaise and general fatigue. The fever subsided thereafter, but migrant arthralgias persisted. Five days after the initiation of the therapy epigastric pain was referred, directly linked with the oral assumption of ribavirin. A gastroscopy showed only erosive mucosal changes in the stomach, related to the overuse of non-steroidal anti-inflammatory drugs for the treatment of a lumbar disc hernia during several months prior to the diagnosis of chronic hepatitis C.

The palpation of abdomen uncovered no mass presence and was painless; the genotyping analysis for HCV detected a genotype 1b. The patient received the

following therapy for not longer than three months; in fact, during a follow-up visit in the third month she reported suicidal thoughts, emotional liability, severe insomnia and depressed mood. In spite of the fact that she showed nonfatal suicidal thoughts and behaviours, and never attempted or planned to complete suicide, the obsessive perseveration of this ideation was enough for the patient to stop completely the therapy, against medical advice. An ambulatory consultancy with the psychiatrist resulted inconclusive, albeit an antidepressant was prescribed (Fluoxetine twenty milligrams daily) and consumed during a two-month period of time.

Table 1: Patient's laboratory data at the initiation of INF therapy

Variables	Value	Normal range
Blood chemistry		
ALT (U/L)	131	0 – 45
AST (U/L)	102	0 – 35
GGT (U/L)	38	0 – 55
Total bilirubin (mg/dL)	2.5	0.3 – 1.2
Direct bilirubin (mg/dL)	1.6	0.0 – 0.2
ALP (U/L)	55	30 – 120
Glucose (mg/dL)	98	74 – 106
Urea (mg/dL)	20	10 – 43
Creatinine (mg/dL)	0.6	0.6 – 1.2
CRP (mg/L)	2.15	1.10 – 8.00
Total protein (g/dL)	7.2	6.0 – 8.3
Albumin (g/dL)	4.6	3.5 – 4.2
Alpha-1 globulin (%)	4.4	2.9 – 4.9
Alpha-2 globulin (%)	9.8	7.1 – 11.8
Beta-1 globulin (%)	6.2	4.7 – 7.2
Beta-2 globulin (%)	4.8	3.2 – 6.5
Gamma globulin (%)	14.2	11.1 – 18.8
Sodium (mmol/L)	132	136 – 146
Chloride (mmol/L)	104	98 – 106
Potassium (mmol/L)	3.9	3.4 – 4.5
Cholesterol (mg/dL)	121	120 – 220
Triglyceride (mg/dL)	71	50 – 150
Viral markers		
HCV-RNA level (IU/mL)	6.05 x 10 ⁵	-
Virus genotype	1b	-
Anti HCV (Hepatitis C virus)	Positive	-
HBsAg	Negative	-
HBcAb	Negative	-
Hematology		
RBC (x10 ⁶ cells/mm ³)	4.66	3.80 – 5.80
Hemoglobin (g/dL)	14.2	11.0 – 16.5
WBC (x10 ³ cells/ μ l)	7.1	3.5 – 10.0
Platelet count (x10 ³ cells/ μ l)	221	150 – 390

Table 2: Clinical characteristics at the initiation of the treatment with INF

Variables	Initiation of treatment
HCV-RNA (IU/mL)	6.05 x 10 ⁵
Clinical course	
Fatigue	Yes
Fever	No
Abdominal pain	Yes
Jaundice	No
Pruritus	No
Ascites	No
Encephalopathy	No

The patient never started again the over mentioned therapy for chronic hepatitis C, although she turned back twice for a hepatologist consultancy. She formulated clearly to the clinicians that ‘she feared ideas of suicide’ and that such ideas were clearly caused from the therapy she was receiving for HCV.

DISCUSSION

Depression and suicidality might be a major adverse event of some medications, here including peginterferon and ribavirin. Some authors refer its frequency to some 22% of the patients treated with this combination, with other adverse effects being even more frequent, such as fatigue (54%), headache (47%) and so on. [9]

Different pathophysiological mechanisms might explain the appearance of neuropsychiatric side effects during peginterferon and ribavirin therapy, but as for the depression, depressive mood, and suicidality, obviously all roads will lead to the serotonergic neurotransmission processes. [10,11] As a precursor of serotonin, even tryptophan has been scrutinized, with its disequilibrium imputed among other as a possible consequence of interferon therapy. [12] In spite of the fact that depression is the most encountered psychiatric medically-induced occurrence following peginterferon therapy, mania has been reported as well, generally following the discontinuation of such therapy. [13]

When considering long-term application and efficacy of chronic hepatitis C therapy, authors suggest that only hepatitis C genotype (precisely patients infected with genotypes 2 or 3 have a better chance of achieving sustained virological response rate), but not the psychiatric morbidity, will influence the response rate. [14] However, there is a general consensus that all patients are eligible for interferon and ribavirin treatment, regardless of their psychiatric status. [15] The lower responses ratios to peginterferon and ribavirin combination treatment in a population of chronic hepatitis C patients composed mainly from individuals infected with genotype 1b has become another issue of concern, that will probably be circumvented with the discovery of new therapeutic agents. [16]

CONCLUSION

In spite of potential side effects and suspicious response ratios, available therapeutic options for HCV treatment have to be put into place, as long as this infection reflects a severe and potentially invalidating medical condition. Difficult-to-treat patients should be taken in charge from a multidisciplinary team, composed from psychologists and psychiatrists, when necessary. Our case witnesses the necessity of such a team, with a patient suffering from suicidal thoughts to the point of being forced to discontinue therapy.

Drug-related suicidality is an important medical issue, with wide societal, legal and forensic implications. Initially this phenomenon was considered and reported as strictly related to the use of certain psychotropic drugs (mainly the new generation antidepressants), alcohol and illicit substances. [17-19] Actually, the field of research has been expanded with the uncovering of adverse effects even among drugs that are not strictly or primarily acting

on the nervous system. Since suicidality is clearly no longer a peculiar side effect of only antidepressants, tight monitoring of every adverse event during the use of potent and new drugs, will help clinicians to early detect suicidal thoughts or behaviors, and thus to make the necessary therapeutic changes accordingly.

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