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CHRONIC HEPATITIS C WITH SIGNIFICANT MORBIDITY AND END-ORGAN DAMAGE DEVELOPMENT DURING PEG-INTERFERON ALPHA-2A/RIBAVIRIN THERAPY

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Abstract

Objective: To report a case of significant morbidity and end-organ damage development during Peg-interferon Alpha-2a/Ribavirin therapy.

Case report: A 27-year-old woman patient with chronic hepatitis C diagnosis, genotype1b, Anti HCV positive, and HCV-RNA 6. 05 x 10^5 IU/mL, presented to our clinic in order to initiate the approved treatment regimen with subcutaneous peginterferon alfa 2a (PEG-INF-a2a, s.c.) plus oral ribavirin. There were no evident abnormalities in the patient's physical examination and laboratory data prior to the treatment, except for general asthenia and arthralgias and, above normal biliriubin levels plus positive smooth muscle antibodies (SMA). The patient was started on 180 mcg PEG interferon alpha-2a s. c. once a week with ribavirin 1000 mg/day. Four months later, despite undetectable HCV-RNA, she developed anemia, neutropenia, thrombocytopenia, and high transaminase levels, due to which the staff opted for a half-dose of Peg-interferon Alpha-2a/Ribavirin. After that, she suffered deterioration in liver function (Child class C, MELD score = 23.4) in association with non-invasive predictors of liver fibrosis, and with common radiologic changes of liver cirrhosis.

Conclusion: Patients with preexisting auto antibodies and chronic hepatitis C, especially women, may be predisposed to autoimmune hepatitis during interferon and ribavirin therapy. These patients require careful monitoring if IFN is considered as first line treatment.

Keywords: Chronic HCV infection, Peg-interferon Alpha-2a/ribavirin, Adverse Events, Autoimmune Diathesis, End-organ Damage

Introduction

Intereferon alpha (IFN-a) monotherapy was the first approved treatment for chronic hepatitis. As cited in Fried at. al., 2002, results of randomized, controlled trials subsequently indicated that the addition of ribavirin (Rbv) to IFN-a produces improved sustained virologic response rates (SVR). However, due to treatment-related adverse effects, combination therapy significantly increased the risk of dose modifications and discontinuations and, as has been observed clinically, dose modifications appeared to be less than optimal for HCV eradication**.** 19-22% of patients treated with Peginterferon alfa-2a and ribavirin, required reduction of ribavirin dose during therapy (Hadzyannis, 2002).

Side effects of IFN-a, Rbv, and IFN-a/Rbv combination therapy include depression, persistent fatigue, transient flulike symptoms (headache, fatigue, myalgia, chills, and fever), and bone marrow suppression leading to anemia and neutropenia (Maddrey,1999).

Other authors, as Karim et al. (2001), Boonyapisit et al. (2002), Li SD et al. (2002), Teragawa et al. (1996), Wesche et. al. (2001), reported that treatment with standard interferon with or without ribavirin may be associated with more specific and serious adverse events, with the potential to cause significant morbidity and end-organ damage, like hearing loss, retinopathy, acute renal failure, congestive heart failure and, according to Dalekos et al. (1999), induction or exacerbation of autoimmune diseases.

Patients with documented hepatitis C infection may deteriorate during IFN treatment if an underlying autoimmune hepatitis is present. This has been observed particularly in individuals with LKM positive antibody (Todros, Saracco, Durazzo, et al. 1995). Even though IFN seems to be safe in most HCV/anti - LKM-1 positive patients, these patients require careful monitoring if IFN is considered as first line treatment therapy. On the other hand, previously, it has been showed that INF therapy should be stopped due to occurrence or exacerbation of autoimmune phenomenon (Okanoue T, Sakamoto S, Itoh Y, Minami M, Yasui K, Sakamoto M, et al. 1996).

Hereby, we present a case of a female patient with preexisting auto antibodies and chronic hepatitis C who developed significant morbidity and liver failure during Peg-interferon Alpha-2a/Ribavirin therapy**.**

Case report

A 27-year-old woman, presented in January 2014 at University Clinic of Gastrohepatology, University Hospital Center "Mother Teresa" in Tirana, Albania, with the diagnosis of chronic hepatitis C. She presented to our clinic in order to initiate the approved treatment regimen with subcutaneous PEG-INF-alfa2a plus oral ribavirin. She was carrier of hepatitis C virus genotipe 1b, and HCV-RNA was 6. 05 x 10^5 IU/ml, as determined by Cobas AmpliPrep/TaqMan HCV test.

She did not smoke, drink alcohol, or use drugs. She weighed 69 kg, and was on a semi-vegetarian diet, excluding grapefruits. There was a history of two cesarean section deliveries. There were no evident abnormalities in the patient's physical examination prior to the treatment. The skin was pale and the abdomen was soft and nontender, with no organomegaly.

At the initial visit, the results of laboratory tests, including complete blood count, electrolytes, and albumin were normal, as were the results of coagulation test and renal function. Transaminase levels, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin level showed a slight elevation. Immunological test showed the titer of smooth muscle antibodies (SMA) 1:40. The other results of laboratory tests are shown in table 1. Also, according to Schiavon at. al. (2014), we evaluated the non-invasive serum fibrosis markers such as fibrosis-4 score based on age, ALT, AST and platelet count (FIB-4), AST to platelet ratio index (APRI), platelet count to spleen diameter (PC/SD), AST-to-ALT ratio (AST/ALT), and age-spleen-to-platelet ratio index (ASPRI) before initiating treatment with INF, and during follow-up (table 2). The treatment to the patient was started on 180 mcg PEG interferon alpha-2a s. c. once a week with ribavirin 1000 mg/day orally in 2 divided doses.

After three months, on March 2014, there was no detectable HCV-RNA. Two months later, on May 2014, the patient was not feeling well, complaining of a persistent fatigue and generalized malaise. Laboratory results showed deterioration of hematologic indices and transaminase values. Due to the anemia, neutropenia, thrombocytopenia, and high transaminase levels, the medical staff decided to continue the treatment with half-dose of PEG interferon alpha-2a/ribavirin (90 mcg PEG interferon once a week with 500 mg/day ribavirin).

On June 2014, she re-admitted in our clinic for closer monitoring, because despite having the treatment dose, the patient felt continuously tired. The physical examination revealed hepatosplenomegaly and jaundice on bulbar conjunctiva and skin, with no spider angiomas or palmar erythemas. The platelet, erythrocyte and leukocyte count continued to decline ($101x10^3$ cells/µl, $2.87x10^6$cells/mm^3 and $3.6x10^3$ cells/µl, respectively), hemoglobin level dropped to 6.8g/dL and bilirubin, and transaminase levels continued to

rise (bilirubin level to 2.8mg/dL, AST to 612 U/L, ALT to 311U/L). Also, the noninvasive biomarkers of fibrosis were worse than before (table 2), so the interferon therapy was interrupted. HCV-RNA level remained undetectable even after the treatment interruption. However, the bilirubin level continued to rise (to 11.1mg/dL), serum gamma globulin reached its peak (3.23g/dl), and noninvasive biomarkers were further worsened (tabel 2). Also, after the termination of INF therapy, the prognostic markers of cirrhosis continued to worsen (Child class C and MELD score=23.4). Furthermore, the total score of autoimmune hepatitis (AIH) revised in 1999, was increased to 11 (probable AIH) (table 2). The abdominal ultrasound examination showed enlargement of liver with macronodular parenchyma and abnormalities in its contour; there were ascites in abdominal cavity, and splenomegaly.

The patient was discharged from hospital at the request of the family members with the diagnosis of decompensated liver cirrhosis, with biological activity and severe liver failure, and with intrahepatic cholestasis. She went to Italy with the hope to be included in a liver transplant list.

Discussion

Chapman, Stace, Edgar, et al. (2001), concluded that PEG -IFN-alfa2a/Rbv treatment (180 mcg of PEG-IFN-alfa2a once weekly s.c. and 1000–1200 mg/day oral Rbv) resulted in an overall much better SVR rate than PEG-IFN-alfa2a alone. In addition, Moreno-Monteagudo, Castro, De Pedro, et al. (2002), suggested that that IFN-alfa/Rbv combination therapy is effective for patients who experience relapse or do not respond to IFN-alfa monotherapy. Combination therapy also produces a greater reduction in liver fibrosis than does IFN-alfa monotherapy.

However, the adverse effects of HCV treatment may compromise the success of therapy. Anemia has been found to be more pronounced with combination therapy than with IFN-a monotherapy. The results from a large population treated with combination Peginterferon alfa-2a and ribavirin (Hadzyannis, 2002) have showed that 19-22% of patients required reduction of ribavirin dose during therapy. This was somewhat more than patients requiring dose reduction in the trial with peginterferon alfa-2b/ribavirin (12-13%). In addition, dose reductions due to neutropenia and thrombocytopenia were more common in association with PEG-IFN-alfa/Rbv therapy than with standard IFN-alfa/Rbv therapy. High incidence of neutropenia and thrombocytopenia associated with PEG-IFN-a may be due to the longer bone marrow exposure, because of longer half-life of the agent; however, the recommended weekly dosages for combination therapy of both formulations of PEG-IFN-alfa (1.5 mg/kg of PEG-IFN-alfa2b once weekly and 180 mg of

PEG-IFN-alfa2a once weekly) are also greater than the recommended weekly dose of IFN-alfa (3 million IU of IFN-alfa2b 3 times/week).

IFN-alfa/Rbv treatment–induced anemia has been called a "mixed" anemia, because the effects of both drugs contribute to its etiology. Van Vlierbergh et al. (2001) found out that the major side effect of treatment with Rbv is hemolytic anemia. At Rbv doses of 800 mg/day, Rbv-induced hemolytic anemia causes a dramatic reduction in hemoglobin levels (of 2–3 g/dL), usually 4 weeks of initiation of treatment. When combination therapy with IFN-a/Rbv is used, 25%–30 % of patients develop hemoglobin levels <11g/dL. In addition to hemolysis Cacoub, Poynard, Ghillani, Charlotte, Olivi, Piette, et al., stated that Rbv induced anemia can occur by various mechanisms, including suppression of hematopoietic progenitor cell proliferation, activation of programmed cell death (apoptosis) in erythroid progenitor cells, provocation of immune hemolysis, and impairment of renal function.

Hepatitis C virus (HCV) is associated with different autoimmune manifestations. Based on different studies, 40-74% of HCV infected patients may experience other complications during the course of the disease that are principally immunological. The prevalence of HCV infection is much higher among some of these conditions and suggests a pathogenetic role of the virus. HCV is a trigger for the autoimmune reactions resulting in production of autoantibodies.

In recent years, Cacoub et al. found positive antinuclear antibodies in 41% of patients, rheumatoid factor in 38%, anticardiolipin antibodies in 27%, and antithyroglobulin antibodies in 13% of patients. Some of these antibodies such as anti-C-reactive protein correlated with the severity of liver disease. Papo, Marcellin, Bernuau, et al. (1992) underlined that in chronic liver disease anti-HCV high seropositivity may also point to autoimmune processes. Molecular mimicry of amino acid sequences of the hepatitis C virus with the human cytochromes and cellular structures may contribute to virus-triggered autoimmunity. There is a striking prevalence of autoimmune phenomena in patients who express circulating cryoglobulins, rheumatoid factor and nonspecific autoantibodies such as, smooth muscle antibodies, liver kidney microsomal (LKM)-1 antibodies, antinuclear antibodies, and antithyroid antibodies. Shindo, Di Bisceglie, Hoofnagle (1992) stated that autoimmune hepatitis can develop during treatment of chronic hepatitis B and C with interferon. Although generally considered to be rare, in one report of 144 patients with hepatitis C, deterioration in liver function and the development of autoantibodies occurred in seven percent during interferon therapy, all of whom were women. Sezaki, Arase, Tsubota, et al. (2003), demonstrated that some of these patients had preexisting autoantibodies,

suggesting that they may be predisposed to autoimmune hepatitis during interferon therapy.

Conclusion

Even though infrequently reported (<1%), one of the most serious adverse events associated with standard interferon therapy, is induction or exacerbation of autoimmune diseases. In this case, we came to the conclusion that the patient developed an autoimmune hepatitis, with deterioration in liver function. Patients with preexisting autoantibodies and chronic hepatitis C, especially women, may be predisposed to autoimmune hepatitis during interferon and ribavirin therapy. These patients require careful monitoring if IFN is considered as first line treatment. Further investigations are warranted to consider re-administration of interferon at low dose or interferon free therapy in chronic hepatitis C virus infection with preexisting autoimmune phenomenon.

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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	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/µl)	7. 1	3.5 – 10.0
Platelet count (x10^3 cells/µl)	221	150 – 390
Coagulation test		
International Normalized Ratio (INR)	1.15	0.850 – 1.200
APTT (sec)	32.2	25 – 35
Immunology		
Anti mitochondrial antibodies (AMA)	Negative	-
Smooth muscle antibodies (SMA)	1:40	-
TSH (µIU/ml)	1.13	0.27-4.2

Table 2. Clinical course, non-invasive biomarkers and AIH scoring system before, during, and after treatment with INF

Variables	**Initial of treatment**	**4 Months Later**	**6 Months Later**
HCV-RNA (IU/mL)	6. 05 x 10^5	No detectable	No detectable
Clinical course			
Fatigue	Yes	Yes	Yes
Fever	No	No	No
Abdominal pain	No	Yes	Yes
Jaundice	No	Yes	Yes
Pruritus	No	Yes	Yes
Ascites	No	Yes	Yes
Encephalopathy	No	No	No
AIH scoring system			
Female sex	+2	+2	+2
ALP/AST	+2	+2	+2
Gamma globulin g/dl	0	0	+3
Anti mitochondrial antibodies (AMA)	+3	+3	+3
Smooth muscle antibodies (SMA)	+1	+1	+1
Hepatitis viral markers	-3	-3	-3
Drug history	+1	+1	+1
Alcohol intake	+2	+2	+2
Other AI diseases	-	-	-
Other additional parameters	-	-	-
Total score	*8*	*8*	*11*
Prognostic markers			
Child-Pugh class	A	B	C
MELD score	11.5	12.8	23.4
Non-invasive biomarkers			
FIB-4 score	1.09	11.59	10.72
APRI	1.03	16.82	16.76
ASPRI	4.97	13.41	15.84
AST/ALT	0.77	2.01	2.11
PL/SD	2009.1	585.7	631.2

APRI, AST to platelet ratio index; ASPRI, age–spleen-to-platelet ratio index; AST/ALT, AST-to-ALT ratio; FIB-4, fibrosis-4 score based on age, ALT, AST and platelet count; MELD, Model for End-stage Liver Disease; PC/SD, platelet count to spleen diameter.