Toxic hepatitis by interferon Beta-1a

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Abstract

Interferon beta-1a is one of the most commonly used drugs for the treatment of patients with multiple sclerosis. Some of the side effects of this drug are known, such as, reactions at the injection site, increase in hepatic enzymes, *livedo reticularis*, autoantibody positivity, and hematological or neuropsychiatric abnormalities.

The authors report a case of a patient with multiple sclerosis treated with interferon beta-1a, who developed acute hepatitis associated with the introduction of this drug, on two separate occasions.

In addition to this clinical case, we present a bibliographic review of the theme.

Key words: Toxic hepatitis, liver tests, interferon-beta, multiple sclerosis.

Introduction

Hepatocellular dysfunction is common (around 50% to 75%) in patients with multiple sclerosis (MS) treated with interferon beta-1a (IfB1a). However, data from various the studies involving MS patients with hepatocellular dysfunction are limited.[1]

IfB1a, administered subcutaneously (SC) 3 times a week, is a preparation derived from the ovarian cells of Chinese rats. Its main functions in MS are: 1) to reduce recurrences; 2) to decrease radiological progression; 3) to reduce conversion of the recurrent-remittent form of MS to its definitive form.[2]

There are a number of adverse effects caused by IfB1a, namely, appearance of Raynaud's phenomenon, *livedo reticularis,* presence of autoantibodies, hematological alterations (e.g. : Pancytopenia and hemolytic anemia), hepatocellular dysfunction, flu syndrome, reactions at the injection site, and depression. Hepatotoxicity to IfB1 is manifested by an asymptomatic increase in hepatic enzymes, but severe symptomatic cases have already been described, particularly in two patients who required hepatic transplant, due to fulminant toxic hepatitis.[2]

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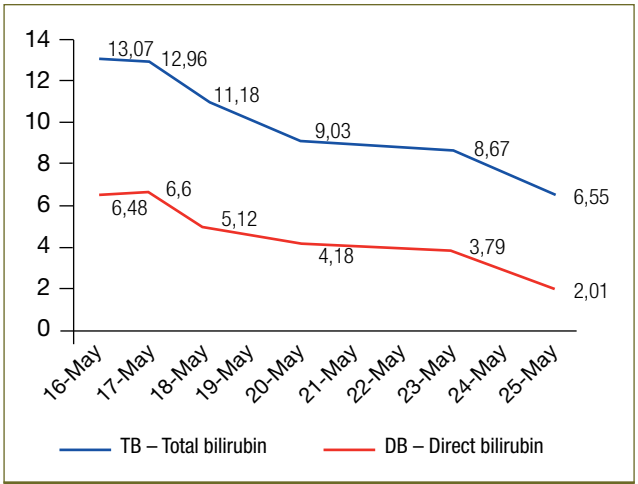
The lesion mechanism has not been fully elucidated. It is known that IfB1a interferes with Cytochrome P450, through a decrease in isoenzyme activity, and also interferes with the metabolization of other drugs. The association of IfB1a with certain drugs, such as methylprednisolone**,** tricyclic antidepressives, benzodiazepines and oral contraceptives, also increases the likelihood of its hepatoxicity.[2, 3]

The literature does not give much information in relation to the exact number of described cases of hepatotoxicity to IfB1a, as these cases are not always reported to the bodies responsible for this supervision. However, it was possible to calculate that in the United States of America, toxic hepatitis is the main cause of fulminant acute hepatitis requiring liver transplant.[1]

Clinical Case

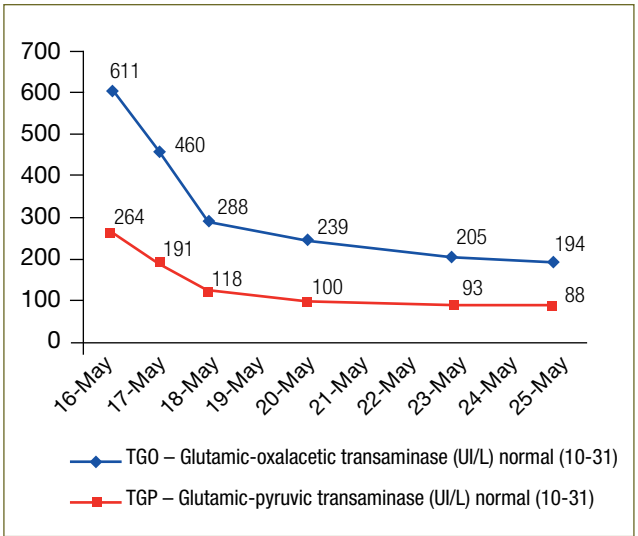
B.M.R, women, aged 40 years, Caucasian, retired, born and residing at Trofa, with a known personal history of MS diagnosed in November 2004, medicated with IfB1a (3x/week, SC); hospitalized four times at the Neurology Service (between November 2004 and April 2005), for episodes of MS treated with methylprednisolone; use of oral contraceptive (OC); up-to-date National Vaccination Plan; claimed no use of illicit drugs or sexual behaviors of risk.

Onset of asthenia and choluria seven days prior to admission. Three days before being admitted to the Emergency Service (ES), facial jaundice and chemoses were observed. On the 16 May 2005 she went to the ES and was admitted. Since the start of the symptoms, the patient reported no arthralgias, rash, visible hema-



Evolution of total and direct bilirubin during hospitalization.

FIG. 1



Evolution of transaminases during hospitalization.

FIG. 2

tic losses, itching, fever, vomiting or abdominal pain. There were no alterations in frequency, consistency or color of the feces, and she reported that she had not consumed mushrooms or water unfit for drinking. On objective examination, she was conscious, collaborative and oriented, with normal color, and hydrated, with jaundice of the skin and sclera, without flapping, and neurological exam without focal signs; cardiac and pulmonary auscultation were unaltered, abdomen with palpable liver 3 cm below the costal border of the right midclavicular line, normotensive and eupneic. Tests following admission showed: platelets 100 000/uL (150-350 000/uL); renal function normal (calculated creatinine clearance:101 ml/min); TGO/TGP:611/264 UI/L (N:10-31); total bilirubin (TB):13.07 mg/dL (N<1) and direct bilirubin (DB): 6.48 mg/dl (N<0,2); alkaline phosphatase and GGT normal; prothrombin time (PT): 16.2' (10.5'-13.5'); abdominal echography: "liver of dimensions at the upper limit of normal, of around 15 cm ; parenchyma texture heterogenous, with no evidence of nodular lesions. Gallbladder without stones/acalculous. Without free fluid". Patient was admitted to the Internal Medicine Service with acute hepatitis, and alterations in the coagulation tests. IfB1a and oral contraceptive were suspended.

In the 1st week of hospitalization, choluria and jaundice persisted, without the appearance of any other complaints, with objective exam identical to that on admission, and vital parameters stable. Analytically, she presented a gradual reduction in levels of hepatic enzymes or bilirubinemia *(Fig.1 and 2)* and normalization of the coagulation study. The study carried out for etiological investigation showed: negativity for infections (hepatitis A, B, C, E, HIV virus, cytomegalovirus, Epstein-Barr virus, herpes simplex 1 and 2, toxoplasmosis, Wright, Widal and Paul-Brunell reactions) and for autoimmunity (antinuclear antibodies, antiDNAds, antiSm, antiSSA/SSB, antimytochondrials, antiRNP, anti-smooth muscle, antiLKM). The proteinogram, iron kinetic and alfa$_1$-anti-trypsin were normal. Patient was discharged on 25th May 2005, and referred to the External Internal Medicine Service, with indication to maintain suspension of IfB1a and oral contraceptive.

The Assistant Neurologist resumed IfB1a in August 2005. The patient remained asymptomatic for four months, after which symptoms of nausea, vomiting, jaundice of the sclera and choluria occurred, and she was referred to the ES. She had fever, cutaneous alterations or coloration of the feces, weight loss or algic complaints. On objective examination, she presented jaundice of the sclerotic tissue, the remainder of the evaluation being normal. From the analytical point of view, she had thrombocytopenia -103 000/µL (150-350 000/µL), TGO/TGP: 1013/975 UI/L (N:10-31), TB: 8.48 mg/dL (N<1) and DB: 4.78 mg/dl (N<0,2); alkaline phosphatase, GGT, total albumin

and proteins within the normal limits. Prothrombin time: 17.7' (10.5-13.5). Abdominal ultrasound was carried out, showing no alterations. Patient was admitted with acute hepatitis with alterations in coagulation, and IfB1a was suspended. In the 1st week of hospitalization, choluria persisted, with onset of generalized itching. Etiological study was repeated, resulting in exclusion of infectious, metabolic, vascular and auto-immune causes. Analytically, there was a gradual deterioration in the hepatic tests, with TB values ranging from 8.49 to 25.42 mg/dL (N<1), TGO: 804-1013 UI/L, TGP: 537-975 UI/L, PT:17'-19,9' (10.5'-13.5'). Due to the presence of acute hepatitis with severity criteria indicated by TB>3 mg/dL and serum albumin:3-3,5 g/dL, PT>6', although without ascites or encephalopathy, the Hepatic Transplant Center was contacted, which advised an attitude of daily analytical expectancy and surveillance. In the 2nd week she remained clinically stable. She was seen by an Ophthalmologist, who excluded the presence of Kayser-Fleischer rings, and observed a normal result for urinary copper levels. From the analytical point of view, and in view of the alterations described above, the medical attitude remained one of expectancy. In the 3rd week of hospitalization, she did not report any "repeat" complaints and the objective examination was similar. Hepatic biopsy was performed, revealing "preserved trabecular architecture, portal spaces with moderate fibrosis, ductular proliferation and polymorphic inflammatory infiltrate, with some eosinophiles and lymphocytes. No cholestasis, steatosis, siderosis or necrosis were identified. Alterations in the hepatic parenchyma compatible with toxic/medicamentous hepatitis". Patient was discharged, with fortnightly analytical control and suspension of IfB1a. She is presently asymptomatic and analytically shows normal hepatic function. MS-targeted glatiramer acetate was initiated.

Discussion

In view of a clinical state of acute hepatitis with alterations in coagulation, various diagnostic hypotheses can be proposed, according to the patient's history, and clinical suspicion. It is important to think of the most frequent causes, notably, infectious causes (hepatitis A, B, C, D, E; HIV virus; cytomegalovirus; Epstein-Barr; herpes simplex), alcohol consumption, metabolic/genetic diseases (Wilson disease, hemochromatosis, ∞1 antitrypsin deficiency), systemic pathology (tuberculosis, sarcoidosis, amyloidosis), auto-immune etiology (auto-immune hepatitis, primary biliary cirrhosis, sclerosing cholangitis), consumption or exposure to toxins and other less frequent causes (paraneoplastic syndrome, family intra-hepatic cholestasis, and Budd-Chiari syndrome).[4]

Although drug-related hepatotoxicity is rare, with incidences varying between 1/10 000 and 1/100 000 inhabitants/year, its exact incidence is difficult to determine, due to the difficulty of diagnosis and the failure to report cases detected, to the regulatory authorities.[1]

The risk of hepatotoxicity is described as being higher in adults (> 50 years), obese and malnourished women, and where there is concomitant use of other drugs (e.g.: Methylprednisolone, tricyclic antidepressives, benzodiazepines and oral contraceptives).[1,5]

The etiopathogenic mechanisms involved may be predicted, according to the drugs used. The three known forms of hepatic lesion are: 1 – hepatic cytolysis, with increase in transaminases (TGP 3 times higher than normal). Examples: isoniazid, troglitazone; 2 – cholestasis, with an increase in alkaline phosphatase (two times higher than normal) and total bilirubin (two times higher than normal). Examples: Amoxicillin-clavulanic acid, chlorpromazine; 3 – Mixed, with an increase in transaminases, alkaline phosphatase and total bilirubin. Examples: Phenytoin, nitrofurantoin.[1,3] It is known that when the hepatic lesion causes jaundice, the mortality rate can be as high as 10% to 50%, with a higher probability of requiring liver transplant.[1]

Direct toxic hepatitis is dose-dependant, with a short latency period from the time of exposure to the hepatic lesion, although clinical manifestations can emerge 24-48h after introducing the drug. In the case of idiosyncratic reactions, hepatitis is unpredictable and not dose-dependant, and it can emerge after a long exposure period. The underlying pathogenic mechanisms in idiosyncratic reactions are not fully known, but it is known that it is an immuno-mediated process, with the formation of a neoantigen (cellular component linked metabolites). It is believed that this last mechanism is involved in the pathogenesis of hepatotoxicity caused by IfB1a.[4]

The diagnosis is difficult to establish, and involves excluding the other causes referred to above. Combinations of various exams should be used, notably, serological, imagiological and histological exams.[1,4]

In the majority of cases, the treatment consists of suspending the drug and instituting support measures. Resolution is generally complete, but can take several weeks or months until analytical normalization is obtained. However, some rare cases have been described in which progression of the chronic hepatic lesion/disease.[1-5] IfB1a is responsible for the increase in transaminases in 59% of patients at the end of 6 months, in 64% at 12 months and in 67% at 24 months. These enzyme increases are generally asymptomatic and dose-independant.[2, 5, 6] However, hepatic dysfunction is not specific to IfB1a, but rather, an effect of the class. Cases of hepatotoxicity with IfB1b have also been documented, although these alterations are transitory and less severe.[3, 5]

The association of IfB1a with methylprednisolone increases the likelihood of adverse effects.[6] This combination becomes problematic, particularly in patients with MS, as occurrences/relapses of the disease are generally controlled with methylprednisolone EV. Another situation that can increase the possibility of hepatotoxicity to IfB1a is the concomitant use of paracetamol for symptomatic relief of the "flu" symptoms of IfB1a.[3, 5, 6]

In the case presented, there was an initial hepatotoxic reaction six months after the start of IfB1a, in a patient who used oral contraceptives, concomitantly, who had four episodes of MS which were controlled with methylprednisolone. It is known that after an initial toxic reaction to IfB1a, there is production of antibodies, through a process of sensitization/immuno-medication, which are subsequently reactivated with the reintroduction of IfB1a. Predictably, the second contact with IfB1a caused an exuberant response in the organism, with indicators of analytical severity, which led to the hypothesis of the need for a liver transplant. Our clinical conduct included, from the start, on both occasions, suspension of the drug(s) and the institution of support measures.

Conclusion

Nowadays, a strong clinical suspicion is fundamental and crucial, and this enabled correct medical conduct that led us to a rapid and accurate diagnosis of a case of toxic hepatitis. After establishing this diagnosis, it is important to evict the etiological agent, subsequently explaining to the patient the need to suspend a drug that is supposed to have a therapeutic, non-toxic effect.

It is important to remember that in the majority of cases, evolution is benign, but we should always bear in mind exponential cases, which may prompt a more severe form of manifestation. ■

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