Severe acute cholestatic hepatitis with prolonged cholestasis and bile-duct injury following atorvastatin therapy : a case report

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Abstract

We report the case of a patient who exhibited severe acute hepatitis with symptomatic cholestasis for more than 3 months and bile duct injury following the prescription of atorvastatin. After withdrawal the drug, the patient's wellbeing slowly improves and biological features normalize in 4 months. Therapy aimed at treating severe liver steatosis and hypercholesterolemia. Atorvastatin is a highly effective 3-hydroxy-3 methylglutamyl- coenzyme A reductase (statin) used to lower low-density lipoprotein. Reported frequent adverse events of the medication include nausea, depression, myalgia, abdominal pain and abnormal liver function tests. Although abnormal liver function tests is not an uncommon side effect of the medication, more serious liver injury is rare. In a recent literature review, about ten cases of serious hepatotoxicity have been documented. In the typical presentation, the duration of exposure prior to hepatic toxicity is variable. Liver injury is generally of the mixed type. A prolonged cholestasis for more than 3 months has been seldom reported. Morphological changes includes canalicular cholestasis, feathery degeneration but no cholangiolitis nor cholangitis under the form of cytological and inflammatory changes at the level of interlobular bile ducts. This case report provides further evidence that among statins, atorvastatin may be implicated in drug-induced liver injury and indicates for the first time that such liver injury may be followed by prolonged cholestasis and interlobular bile duct injury. Atorvastatin has thus to be added to the list of medication potentially responsible for bile duct injury. (Acta gastroenterol. belg., **2008**, 71, **318-320**).

Key words : atorvastatin, cholestatic hepatitis, bile duct injury.

Introduction

Atorvastatin is a highly effective 3-hydroxy-3 methylglutamyl- coenzyme A reductase (statin) used to lower low-density lipoprotein (LDL). Reported frequent adverse events of the medication include nausea, depression, myalgia, abdominal pain and abnormal liver function tests. In a recent literature review, about ten cases of serious hepatotoxicity have been documented (1). In the typical presentation, the duration of exposure prior to hepatic toxicity is variable (mean 9,4 weeks ; range 1-52 weeks).

Liver injury is generally of the mixed type, prolonged cholestasis for more than 3 months having been (mean 3,9 months ; range 1-12 months) seldom reported (1,2). In the latter, morphological changes included canalicular cholestasis, feathery degeneration but no cholangiolitis nor cholangitis under the form of cytological and inflammatory changes at the level of interlobular bile ducts (1,2,3).

We report the case of a patient who exhibited severe acute hepatitis with symptomatic cholestasis for more than 3 months and bile duct injury following the prescription of atorvastatin followed after 4 weeks by metformin. Therapy aimed at treating early type II diabetes mellitus together with severe liver steatosis and hypercholesterolemia.

Case report

A 52 year old portugese man with a recent history of type II diabetes mellitus was first treated by gliquidone (90mg per day) and atorvastatin (10 mg per day) starting on may 27th 2006. On June 26th gliquidone was replaced by metformin (1700 mg per day). On July 22nd and due to a hyperglycemic episode, a short course of gliquidone (90 mg per day) was again given for 4 days. On August 6th, the patient was referred to our intensive care unit for the suspicion of acute liver failure based on a clinical picture wich included fever, dyspepsia, nausea, arthralgia, jaundice and right upper abdominal discomfort lasting for 8 days.

A biochemical work up performed on August 5th had shown AST 6102 IU/L (N < 34 IU/L) and ALT 6838 IU/L (N < 44 IU/L) ; blood ammonia determination was at the upper limit of normal.Patient's previous clinical history was unremarkable. He did not drink any alcohol.At clinical examination, body temperature was slightly increased (38.5 °C) with a slight tenderness at the palpation of the right hypochondrium. Liver biochemistry on the next day showed : total bilirubin 5,87 mg/dl (N < 1 mg/dl), ASAT 6385 IU/L, ALAT 8275 IU/L, INR was increased at 1,93 (N < 1,1), factor V determination was 53%.Serological testing for hepatitis B surface antigen, hepatitis B core IgM, hepatitis A IgM and hepatitis C antibodies were all negative.Serological testing for Epstein Barr (EBV), cytomegalovirus (CMV),

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herpes simplex and hepatitis E did not show any evidence of recent infection. The search for anti-smooth muscle, antimitochondrial, anti-liver-kidney microsome, antinuclear and anti soluble liver antigen antibodies was also negative. Upper abdominal ultrasound showed a hyperreflectivity of liver parenchyma without other abnormality. A liver biopsy was performed by the transvenous approach. The wedge hepatic vein pressure gradient was normal. At liver biopsy examination, the liver parenchyma exhibited a normal architecture. Eight of nine portal triads were enlarged due to a mild bile duct proliferation and an extensive inflammatory infiltration mainly composed of lymphocytes, plasma cells, neutrophils and eosinophils. There was a mild interface hepatitis. Endothelitis was present in several portal veins. Interlobular bile ducts were irregular, with an epithelium slightly infiltrated with lymphocytes and neutrophils which were also present in their close vicinity (Fig. 1). Mild lobular collapses were seen in the periportal areas, sometimes expanding from the portal region to the center of the lobules. Acidophilic bodies were scarce and there was a slight macrovesicular steatosis. Perls staining showed discrete iron deposits in the Kuppfer cells and there was only few bile plugs in the lobules.

Due to cholestasis with bile duct injury under the form of cholangitis, a treatment with ursodeoxycholic acid was introduced together with insulin.

As shown on table I, the evolution was slowly favourable, the patient being discharged on August 25th with an improved general condition but the persistence of a deep jaundice (total serum bilirubin : 25 mg/dl).

During follow-up, a severe and invalidating pruritus persisting until mid-October was improved following rifampicine therapy (150 mg per day) started on September 12th. In spite of a total weight loss of 11 kg, the condition of the patient slowly improved, clinical and biochemical features of cholestasis having disappeared on December 8th.

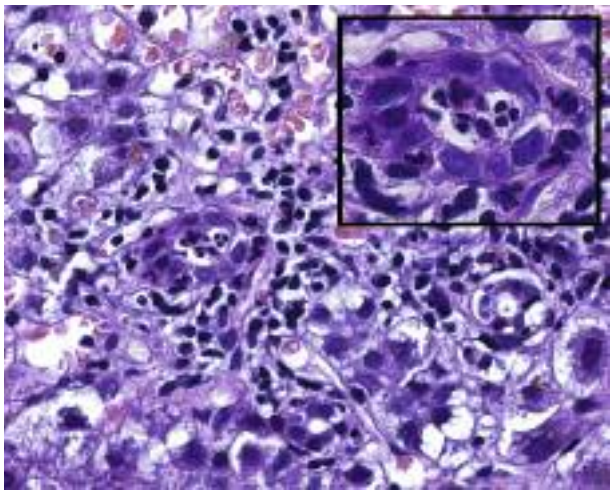
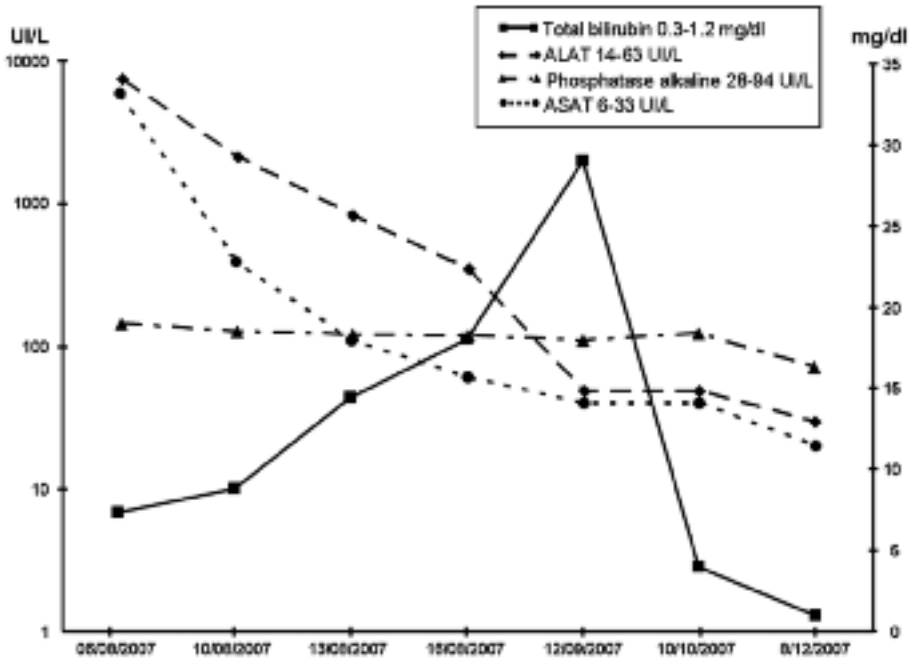


Fig. 1. — Irregular interlobular bile ducts, with an epithelium infiltrated with lymphocytes and neutrophils.

Discussion

We report the case of a 52 year old patient with type II diabetes mellitus who developed severe acute hepatitis with transient liver failure, symptomatic cholestasis for more than 3 months together with bile duct liver injury

Table 1. — **Liver-associated enzymes**



under the form of cholangitis and pericholangitis 9 weeks after the initiation of atorvastatin therapy and 4 weeks after the addition of metformin to the therapeutic regimen. This occurred in the absence of any other potential cause of liver disease and ensuing clinical cholestasis which lasted for 10 weeks with a weight loss of 11 kg Clinical and biochemical normalisation eventually occurred after 4 months.

The hypothesis of metformin-induced hepatitis is unlikely since such a side effect has been only seldom reported with a clinical and biochemical pattern mainly of the mixed cytolytic and cholestatic type without any reported evidence of bile duct injury at histological examination. In addition and in all reported cases, a favourable outcome was invariably reported after drug withdrawal (4,5,6,7). The pathogenesis of metformin-induced liver injury remains unknown, likely of immunoallergic origin.

Gliquidone is a sulphonylurea agent with proven efficacy and good safety profile. In this group of oral antidiabetic medications, the standardized incidence of acute liver failure per 1000 person-years is 0.08 (8). To our knowledge, drug induced hepatitis has been described for almost every sulphonylurea agents except gliquidone. Role of this medication in the present hepatitis seems therefore extremely unlikely.

With regard to atorvastatin, serious cases of hepatotoxicity have been reported in 14 patients so far. Persistent transaminase elevations greater than 3 times the upper limit of normal having been reported during treatment in 0,7% (9) and 0,5% (10) of treated patients. In the case of drug-induced hepatitis, the usual pattern is that of a mixed cholestatic and hepatocellular type with marked hyperbilirubinemia. Liver injury occurs after a variable duration of exposure to the drug (mean 9,4 weeks) (1).

The histology of liver biopsies was reported in 7 patients suffering from atorvastatin related hepatitis. The present case, as those previously described, was characterized by the presence of a mixed cholestatic/hepatocellular pattern of injury however in the absence of bile duct lesions or endotheliatis.To our knowledge and till now, there has been no such description of atorvastatin-induced morphological evidence of interlobular bile duct injury.

If the role of atorvastatin in the occurence of liver damage appears extremely likely, the question of a potential triggering event might be raised. The cytochrome CYP 3A4 is a well known pathway used by atorvastatin metabolism. In this regard, the short course of gliquidone given 2 weeks prior to the occurence of hepatitis might have played a role. Although strong evidence for potential interaction between gliquidone and CYP3A4 is still lacking.

The pathogenesis of atorvastatin associated liver dysfunction remains poorly understood. There is no cross-toxicity with simvastatin, which suggests an immunoallergic mechanism (11). Pelli *et al.* suggested an autoimmune process of atorvastatin induced hepatitis, but we have no serological evidence of this in our particular case (12). Finally, the observation of bile duct injury might be in favour of an immune origin possibly due to genetic predisposition as described for amoxycillin-clavulanic acid (13).

Conclusion

This case report provides further evidence that among statins, atorvastatin may be implicated in drug-induced liver injury and indicates for the first time that such liver injury may be followed by prolonged cholestasis and interlobular bile duct injury. Atorvastatin has thus to be added to the list of medication potentially responsible for bile duct injury.

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