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CASE REPORT

Methylprednisolone liver toxicity: A new case and a French regional pharmacovigilance survey

Jérôme Dumortier[a,b,*], Judith Cottin[c], Caroline Lavie[b,d], Olivier Guillaud[a], Valérie Hervieu[b,e], Christine Chambon-Augoyard[a], Jean-Yves Scoazec[f], Sandra Vukusic[b,d], Thierry Vial[c]

[a] *Service d'Hépato-gastro-entérologie, Hôpital Edouard Herriot, Hospices Civils de Lyon, Lyon, France*
[b] *Université Claude Bernard Lyon 1, Lyon, France*
[c] *Centre de Pharmacovigilance, Service Hospitalo-Universitaire de Pharmacotoxicologie, Hospices Civils de Lyon, Lyon, France*
[d] *Service de Neurologie A, Hôpital Neurologique Pierre Wertheimer, Hospices Civils de Lyon, Bron, France*
[e] *Service d'anatomopathologie, Hôpital Edouard Herriot, Hospices Civils de Lyon, Lyon, France*
[f] *Service d'anatomopathologie, Institut Gustave Roussy, Villejuif, France*

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Summary Reported hepatotoxicity induced by corticosteroids is very rare, and the diagnosis is highly challenging in the context of auto-immune disease. We report here a case of high-dose methylprednisolone (MP)-induced acute hepatitis confirmed by liver histology in a patient with multiple sclerosis (MS) and a case series ($n = 4$) notified to the French Pharmacovigilance center of Lyon. In all 5 cases, other common causes of hepatitis were excluded. The causal relationship with MP pulse therapy was supported by the fact that MP was the only culprit drug. In addition, 3 of these 5 patients underwent unintended single or multiple positive MP rechallenge. Our 5 patients scored a RUCAM score from 6 (probable) to 10 (highly probable). MP-induced liver injury is probably very rare, since only less than 30 cases have been reported in the literature. Nevertheless, our cases strongly illustrates that many cases could have been unrecognized; final diagnosis in 3 of 5 of our patients was made after the second or third episode of acute hepatitis. In conclusion, these cases we report here strongly illustrates that high-dose MP-induced liver injury can occur in patients treated for MS or auto-immune disorder. Unintended re-challenge can confirm the diagnosis and can help to distinguish it from autoimmune hepatitis. Performing liver function tests routinely both before and after MP administration would be beneficial, as the timely recognition of this complication and early drug withdrawal may prevent progression of severe necrosis hepatic injury.

* Corresponding author at: pavillon L, Hôpital Edouard Herriot, 69437 Lyon Cedex 03, France.
E-mail address: jerome.dumortier@chu-lyon.fr (J. Dumortier).

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Drug-induced liver injury is a common cause of acute hepatitis, and the diagnosis is performed after excluding other causes for liver diseases [1—3]. Reported hepatotoxicity induced by corticosteroids is very rare, and the diagnosis is highly challenging in the context of auto-immune disease. We report here a case of high-dose methylprednisolone (MP)-induced acute hepatitis confirmed by liver histology in a patient with multiple sclerosis (MS) and a case series notified to the French Pharmacovigilance center of Lyon.

Cases description

In November 2015, a 27 year old woman was hospitalized in our department because of severe acute hepatitis of unknown etiology. She suffered from MS since 2004 but had no other medical antecedent. Since initial diagnosis, the patient received corticosteroid pulses (2004—2005 and 2015—2016), beta-1a interferon (2005), azathioprine (2006—2007), glatiramer acetate (2007—2010) and teriflunomide (2014—2015). The treatment with teriflunomide had been stopped in September 2015, and an indication of a new treatment line by fingolimod was planned. The patient had no family history of liver disease and she did not consume alcohol on a regular or irregular basis. There was no skin reaction. Abdominal Doppler ultrasound was normal. At that time, she presented with mild asthenia and her laboratory findings were as follows: AST 2235 U/l (normal: 0—55), ALT 1704 U/l (normal: 5—34), gamma glutamyl transferase (GGT) 124 U/l (normal: 9—36), total bilirubin 63 μmol/l (normal: 0—20), albumin 3.6 g/dl (normal: 3.5—5.0), globulins 14.8 g/l (normal: 8.0—13.5), prothrombin rate 45%, and INR 2.1. Serum HBsAg, anti-HBs, anti-HBc IgM, anti-HCV, anti-HAV IgM, anti-HEV IgM, EBV VCA IgM, anti-HHV6 IgM, anti-CMV IgM (ELISA), HCV-RNA (PCR), CMV-DNA (PCR), antinuclear, anti-mitochondrial, anti-SLA, anti-liver kidney microsomal (LKM) and anti-smooth muscle antibodies were negative. There was no change in polymorphonuclear blood count. Serum protein electrophoresis and serum level of alpha-1 anti-trypsin were within normal limits. Serum ceruloplasmin level was normal. Since usual aetiologies of acute hepatitis were ruled out, a drug-induced liver toxicity of teriflunomide, recently started, was suspected, even if the treatment had been stopped few weeks earlier. A liver biopsy was performed and showed the presence of severe necro-inflammatory lesions. The overall architecture was preserved, without any sign suggestive of chronic liver disease. Portal tracts were slightly expanded; they contained a moderate inflammatory infiltrate made of lymphocytes, rare plasma cells and some eosinophils; bile ducts were not altered. Lobular damage was severe. Large, well-delimited areas of centrilobular necrosis was present in all lobules; necrotic areas were surrounded by apoptotic hepatocytes and inflammatory cells, including lymphocytes, plasma cells and eosinophils. Residual central veins were usually inflammatory; their wall was invaded by immune cells with features of endothelialitis in some vessels. In periportal areas, residual hepatocytes were large, sometimes clarified and multinucleated. There was no steatosis. The final diagnosis was probable severe toxic hepatitis. The treatment consisted in N-acetylcysteine. Liver function tests progressively improved and returned to normal (Fig. 1). In March 2016, the treatment of fingolimod was started under close monitoring of liver function tests, showing no recurrence of hepatitis in March and April. The patient received in addition a pulse of 1 g/d for 3 days MP in May 2016, and the patient presented a new acute episode of hepatitis. Laboratory findings were as follows: AST 353 U/l (normal: 0—35), ALT 144 U/l (normal: 0—35), GGT 28 U/l (normal: 0—40), total bilirubin 21 μmol/l (normal: 0—20). Therefore a drug-induced liver toxicity of high dose MP was suspected. A review of history of past MP pulses disclosed a first episode of acute hepatitis in 2004 (Fig. 1); 2 other pulses were done in 2005, but liver function tests were not performed after these pulses. Retrospectively, the episode of November 2015 was also following a MP pulse. The final diagnosis was recurrent high dose MP-induced liver toxicity. All episode of acute hepatitis occurred less than 1 month after MP pulses. The treatment with fingolimod was maintained. In November 2016, laboratory findings were as follows: AST 21 U/l (normal: 0—35), ALT 15 U/l (normal: 0—35), GGT 7 U/l (normal: 0—40).

This case prompted our regional pharmacovigilance Center to review all cases of hepatotoxicity related to MP and reported since 1985. After exclusion of poorly informative cases and cases more probably related to another drug or non-drug cause, 4 cases of serious liver injury associated with MP treatment were retained. Main characteristics of the patient, drug treatment and type of liver injury are summarized on Table 1. All patients received high-dose intravenous MP pulse for the treatment of an auto-immune disease (multiple sclerosis in 2 and alopecia areata in 2). The mean time to onset of the liver injury after the last MP pulse therapy was 52 ± 18 days in patients who all had previously and uneventfully received 2—4 MP pulse therapy. The median cumulative MP dose was 6.5 g (range 3—12 g). According to an international report for classifying drug-induced liver injury [21], all patients had a hepatocellular type of injury and one developed severe hepatocellular insufficiency with a prothrombin time lower than 32%. To assess the causal relationship with MP pulse therapy, the RUCAM score was determined for each patient and ranged from 6 (probable) to 10 (highly probable) with a mean score of 7.75 ± 2.06 [5]. All patients fully recovered within an average of 3 months. In one patient, liver injury recovered despite a treatment with low doses of corticosteroid. A liver biopsy performed in three patients was compatible with a toxic or drug-induced injury and showed the presence of severe necrosis inflammatory lesions. Two patients underwent unintended rechallenge of MP pulse. Both had recurrence of liver injury with a time to onset and a severity of liver injury similar to the previous episode. One of these patients had a second positive rechallenge test.

Discussion

We report here a case of recurrent liver injury episodes associated with pulse MP therapy in a patient with MS, including one severe episode and a series of 4 additional cases notified to the Pharmacovigilance center of Lyon. The confirmation of diagnosis required the exclusion of alternative viral or immunological diagnoses, especially autoimmune hepatitis, which can be associated, very rarely, with MS [4].

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