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Steroids may not be Immune to causing Hepatotoxicity

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Abstract

We report three cases of hepatocellular injury secondary to exposure to methylprednisolone. The first two patients were seen in the United States and the third in Austria. The pattern in all three cases suggests immune-mediated hypersensitivity reaction. The second and third patients fit the criteria for autoimmune–like, drug induced liver injury (AIH-DILI). One patient had a rechallenge with oral methylprednisolone to exclude excipients in the intravenous formulation as a cause of drug induced injury. The differences between AIH and AIH-DILI as well as evidence for rechallenge with a potentially harmful drug were also examined. The data strongly suggest that steroids can be associated with liver damage. In patients with worsening liver function during therapy with steroids, these drugs should be considered as potential culprits.

Keywords: *steroids, hepatotoxicity, hepatitis, HLA typing, rechallenge*

Background

Drug-induced liver injury (DILI) can be defined as a liver injury induced by a drug or herbal medicines leading to liver test abnormalities or liver dysfunction with reasonable exclusion of other etiologies. [1] DILI, like other adverse drug reactions, is underreported. A prospective, population-based study undertaken to study the incidence of DILIs in France, revealed an incidence of 13.9 per 100,000 inhabitants. [2] Another prospective population-based study, that systematically assessed the occurrence of drug-induced hepatitis, demonstrated a 16-fold higher rate than rates based on spontaneous reporting methods. [3]

Most drug-induced liver injuries have an acute onset, develop while the medication is being administered, and manifest histological patterns that can be categorized as hepatocellular, cholestatic, or mixed. [4,5] DILI can mimic almost all forms of acute and chronic liver disease.[1] There are three major mechanisms of DILI. The first involves direct damage to hepatocytes. Exposure reproducibly leads to hepatocyte necrosis, usually in a dose-dependent fashion. The lag time between exposure and onset of hepatocyte injury is generally brief. In most cases the chemical compound itself or its metabolite causes direct cellular damage. This type of injury is typified by acetaminophen overdose or ethanol abuse. [6] The second mechanism is an unpredictable, idiosyncratic reaction. Most cases of DILI are due to idiosyncratic or unexpected reactions. In contrast to acetaminophen induced hepatotoxicity, which occurs with dose-dependent overdose of the drug, idiosyncratic drug reactions have been traditionally considered dose independent. Most idiosyncratic drug reactions occur roughly between 1–2 weeks and 2–3 months from the start of drug therapy.[1] The third is a hypersensitivity response that is immune mediated. Initial exposure may not elicit a response but often, there is rapid recurrence of symptoms with re-challenge or re-exposure. The response is unpredictable from person to person, reflecting individual variability in recognizing protein adducts as foreign antigen.[3-7] Halothane,nitrofurantoin and minocycline, are a few drugs associated with drug-induced hypersensitivity reactions. [8,9] Drug-induced autoimmune-like hepatitis (AIH-DILI) is included within this profile of drug-induced liver injury but has certain specific features. [4]

Corticosteroids suppress inflammation and have been used to treat a variety of inflammatory disorders. Since their chemical structures are closely related to naturally occurring steroids,

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they are also generally not considered to be directly hepatotoxic. There are isolated case reports of steroid induced hepatotoxicity in literature, however, they are all in patients with autoimmune diseases treated with steroids.[10-13] Gutkowski et al. have nicely summarized and highlighted the characteristics of these patients from various case reports from 1996 to 2011.[14]

We report three cases of idiosyncratic hepatocellular injury secondary to exposure to methylprednisolone. The first two patients were seen in the United States and the third in Austria.

Case report

Patient 1:

The first patient was a 37 year old Caucasian female with multiple sclerosis (MS), diagnosed in 1999. In Dec 2001, she developed an MS flare and received three doses of 1000 mg methylprednisolone (Solumedrol®) intravenously, followed by 7 days of a prednisone taper. At that time her liver enzymes were normal: AST 15 IU/L, ALT 10 IU/L and total bilirubin was 0.4 mg/dL. No change in her liver profile was noted after the first course of steroids. In March 2002, she developed another MS flare and received the same course of treatment. One month later, she developed symptoms of hepatitis with elevations of liver enzymes (fig. 1). These tests normalized four months later, in September 2002. Her third exposure to a similar course of treatment, was in November 2002. She developed symptoms consistent with hepatitis within 10 days of completion of the course and her LFTs peaked in January 2003, with AST of 145 IU/L, ALT 195 IU/L and total bilirubin of 2.56 mg/dL. These resolved a month later. In May 2004, she received methylprednisolone (Solumedrol®) for one day, with seven days of prednisone taper. About 4 weeks after this, she again developed symptoms compatible with hepatitis, with peak AST of 1263 IU/L, ALT 1497 IU/L and total bilirubin of 8.4 mg/dL. These resolved a month later, by late July 2004. A liver sonogram in June, 2004 was unremarkable. Serological tests for viral hepatitis and autoimmune hepatitis were negative. Other etiologies of liver disease were excluded. She was on Solumedrol®, which in addition to the methylprednisolone, contains some excipients or fillers. It includes 12.8 mg of monobasic sodium phosphate anhydrous, 139.2 mg dibasic sodium phosphate and 66.8mg of benzyl alcohol as a preservative. She was also on oral contraceptives since age 19, namely Triphasil® (levonorgestrel and ethinyl estradiol) and, Yasmin® (drospirenone 3.0mg and ethinyl estradiol 0.030mg) although it is not known if she used a generic or specific brand. She received interferon beta 1 a (Avonex®, Biogen Idec, USA) with the first three steroid treatments. Then she was switched to glatiramer acetate (Copaxone®, Teva Pharmaceuticals, International). In between the courses of steroids, her liver function normalized, even though she continued to receive the other medications.

A re-challenge with oral methylprednisolone was performed in July 2005 in order to rule out potential reactions due to excipients in intravenous Solumedrol®. This resulted in a clinically symptomatic hepatitis nine days later. ALT increased from 16 IU/L to 87 IU/L and AST increased from14 IU/L to 45 IU/L. Liver function tests peaked one month later, with ALT of 848 IU/L, AST 243 IU/L and a bilirubin of 1.18 mg/dL. The liver function normalized over the next few weeks (fig. 1). Further follow-up is not available.

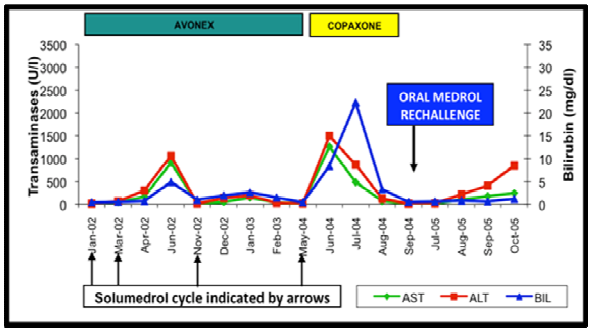

Fig 1. Laboratory data for patient 1 in relation to solumedrol doses.

Patient 2:

The second patient was a 44 year-old Caucasian female with MS. She was treated with the first course of methylprednisolone (Solumedrol®) in February 2006 with resolution of her symptoms. In December 2006, she was again treated with three weekly injections of *1000 mg of* methylprednisolone. Eleven days later, she was started on interferon beta 1 (Avonex®, Biogen Idec, USA). In January 2007, the third course of steroids was given. She also continued on interferon beta 1 injections. In February 2007, she developed a rash and fatigue. Laboratory tests showed elevated levels of serum ALT of 1541 IU/L, AST, 861 IU/L and a normal bilirubin. Avonex® (Biogen Idec, USA) was discontinued and in April 2007, she was started on daily glatiramer acetate (Copaxone®, Teva Pharmaceuticals, International).

In June 2007, her MS relapsed. At that time her serum ALT and AST levels were noted to be normal. She was treated with a fourth course of intravenous methylprednisolone. About a month later, she was readmitted with fatigue and jaundice. Her liver enzymes were significantly elevated at presentation and peaked three days later with ALT of 4102 IU/L, AST 3153 IU/L, Alkaline phosphatase 187 IU/L, bilirubin 28.9 mg/dL and INR 2.0 (fig 2). Her total serum IgG was 1940 mg/dl (Normal 700-1600 mg/dl), and SMA titer was 1:320. Chronic viral hepatitis and other causes of liver disease were excluded.

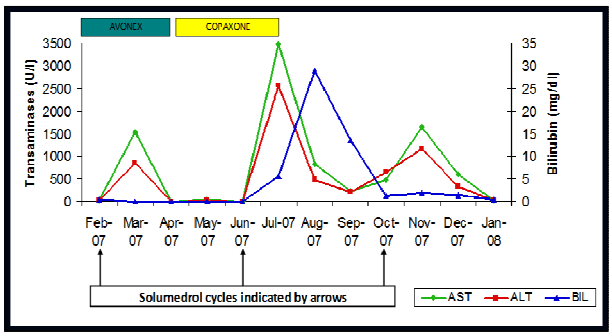

Fig 2. Laboratory data for patient 2 in relation to solumedrol doses.

Liver biopsy showed severe portal, periportal and moderate lobular, mixed inflammation composed of mononuclear cells, plasma cells and scattered eosinophils, with marked lobular disarray, numerous apoptotic hepatocytes, foci of bridging necrosis and hepatocyte dropout, involving less than 15% of the hepatic parenchyma (fig. 3 A-D). Mild bile duct proliferation with lymphocytic inflammation was also identified. These features are those of a severe, chronic active

hepatitis, most consistent with an immune-mediated drug effect or autoimmune hepatitis. Glatiramer acetate (Copaxone®, Teva Pharmaceuticals, International) was considered the cause of the liver damage and was discontinued in July, 2007.

In October, 2007 her MS relapsed again. After a single injection of methylprednisolone, she developed malaise and fatigue. Her laboratory tests showed an ALT of 483 IU/L, AST 636 IU/L, ALP 150 IU/L, total bilirubin 1.2 and the INR was 2.0. By day 12, post injection, LFTs had risen further, with an ALT of 1625 IU/L, AST 1591 IU/L, ALP 217 IU/L, total bilirubin, 1.9mg/dL and INR of 1.3. IgG was 1940 mg/dl, the anti-SMA titer was 1:160 but the ANA was negative. A month after presentation, her LFTs were normal. She has not been on any treatment for MS since and has no signs or symptoms of liver disease currently.

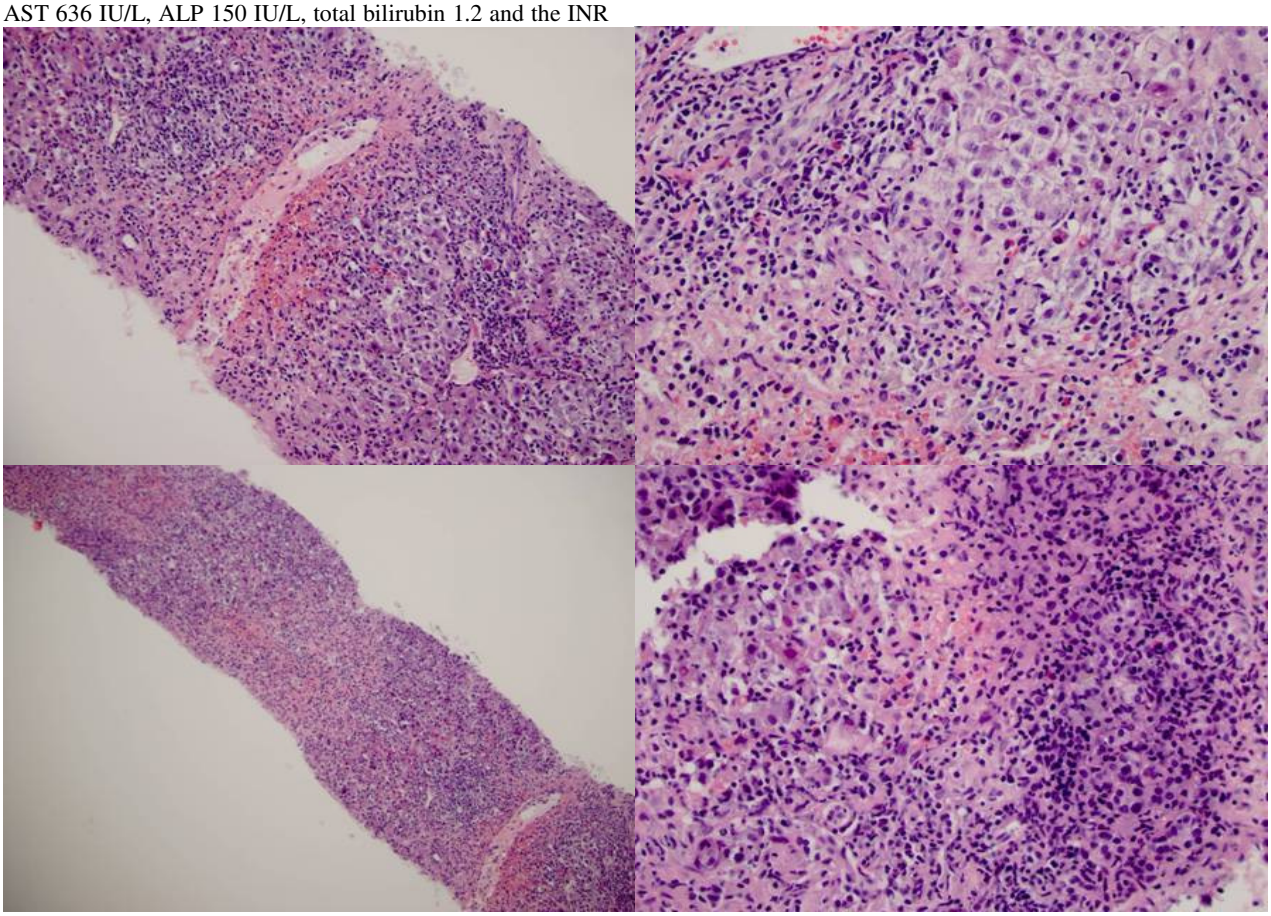

Fig 3 (A-D). Liver biopsy of patient 2, H&E stain. A (top left, 20x magnification), perivenular inflammation with hemorrhagic necrosis. **B** (top right, 40x magnification), mixed inflammation consisting of lymphocytes, plasma cells (lower left) and eosinophils. **C** (bottom left, 10x magnification), demonstrates perivenular hemorrhage (lower right), Marked pan-lobular inflammation and necrosis with drop-out and collapse. **D** (Bottom right, 40x magnification), necrosis and drop out (center) with lymphocytes infiltrating bile ducts (mid-right and lower left).

Patient 3:

A 45 year old female patient presented to the department of Internal Medicine in September 1990 with malaise, fever and jaundice but without signs of chronic liver disease. Her past history was uneventful except for the diagnosis of chorioretinitis in April 1988. She was on oral steroid maintenance therapy of 10 mg of methylprednisolone (Urbason^{R}) every other day, after several induction treatments using 40 to 60 mg methylprednisolone (Urbason^{R}) daily. She had no other maintenance medications including oral contraceptives.

Total bilirubin was 20.12 mg/dl (normal <1.14 mg/dl), AST 260 (normal <18 IU/L), ALT 388 IU/L (normal < 22 IU/L), GGT 69 IU/L (normal <19 IU/L), ALP 212 IU/L(normal <155 IU/L). International normalized ratio was 1.2 (normal 1.0-2.0). Her blood count was normal except for thrombocytopenia with 109,000 platelets/ml (normal > 150,000 platelets/ml). Fibrinogen was 131 (normal >210), iron and ceruloplasmin were normal and anti-thrombin III activity was 27%. Chronic viral hepatitis including B and C, Wilson's disease, hemochromatosis, HIV, CMV and EBV infection were excluded. ANA, AMA and ASMA were negative. Albumin level and C3 and C4 complement levels were decreased. Alpha-1-antitrypsin was negative.

Ultrasound and computed tomography scan, showed macro-nodular changes in the liver with mild splenomegaly, and no evidence of hepatic vein thrombosis or malignant disease. Liver biopsy showed large necrotic areas and the development of macro-nodular regeneration, massive lobular and peri-portal mixed lymphoplasmocytic and granulocytic infiltration with spotty necrosis and grade II to III fibrosis, compatible with acute hepatitis in remission. No evidence of fatty liver disease was found.

Corticosteroid therapy was discontinued. Liver function tests and other abnormal laboratory tests completely normalized in the following months except for the thrombocytopenia. There were no changes in LFTs in the next few years. Yearly bouts of chorioretinis (in 1991 and 1992, two episodes per year) were again treated with methylprednisolone tapers starting with 40 to 60 mg per day for 4 days, reduced by 10mg and followed by low dose maintenance therapy until vision had normalised in 1995. With each course of steroid treatment, elevations of transaminases, up to five times the normal limit, were observed, but ALP stayed within normal levels. From February 1999 to May 2004, one to two, short bouts of chorioretinitis occurred per year and responded to short courses of steroid therapy, followed by an increase in transaminase levels each time (fig. 4).

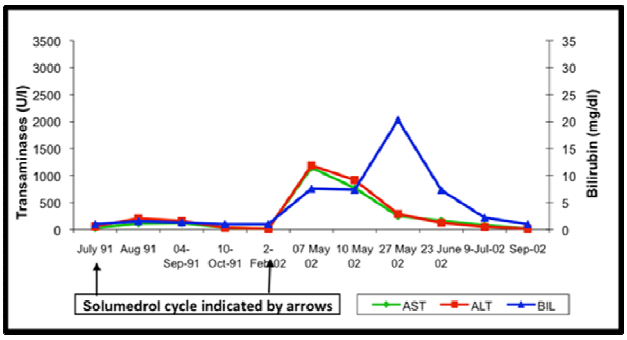

Fig 4. Laboratory data for patient 3 in relation to solumedrol doses.

In May 2004, she almost lost her vision, which prompted a 6 week course of steroids, improving her eye sight dramatically but causing severe acute cholestatic hepatitis. Total bilirubin rose to 7.4 mg/dl, AST 1030 IU/L, ALT 1090 IU/L, INR was 1.4 and platelets dropped to 78,000/ml. Again thorough exclusion of all causes for acute and chronic liver disease, including negative molecular and biologic tests was performed. Liver biopsy was showed acute portal and lobular hepatitis with eosinophils and porto-portal and porto-central fibrosis grade III to IV. All the specific tests for liver disease were repeated several times over the years without any change. On the basis of this histology and the absence of other causes of liver disease, and a negative drug history excluding corticosteroids, the working diagnosis of methylprednisolone induced chronic liver disease was made. No steroids were used thereafter. Transaminases and GGT levels remained one and a half times the upper limit of normal, bilirubin stayed at 2mg/dL and INR was 1.3. In December 2007, she presented with cirrhosis, de-compensated portal hypertension, encephalopathy, ascites and esophageal varices. As disease progressed, MELD (Model of End-stage Liver Disease) score was 12; the following year, liver transplantation was recommended.

Discussion

The initial courses of solumedrol were uneventful in the first patient. The subsequent courses were associated with hepatitis. Oral methylprednisolone tablets also induced hepatitis in the first patient. The lag time between exposure and development of hepatitis was progressively shorter with subsequent exposures (fig. 1). Rechallenge suggested that elevated LFTs were not due to excipients of the steroid formulation.

In the second patient, the temporal association with methylprednisolone became stronger as hepatitis continued to recur with administration of steroids, even after treatment with interferon and glatiramer acetate was discontinued. Liver biopsy was compatible with an immune mediated hypersensitivity drug reaction or more specifically drug-induced autoimmune-like hepatitis (AIH-DILI) (fig. 2).

In the third patient, the transaminases were minimally elevated after each round of steroids but returned to baseline, until she developed active hepatitis two years later (fig. 3). The autoimmune markers continued to be negative over the years. The imaging studies and first liver biopsy in 1990, did suggest pre-existing liver disease but no cause was ascertained. Steroids had already been on board for two years and it could be hypothesized that, they could have produced the changes suggestive of chronic liver disease. Among our patients, the third did progress to cirrhosis and decompensated liver disease in 2007.

Temporal association is a major contributor to the diagnosis of DILI. Each case had a strong temporality with methylprednisolone with low likelihood of other causes of hepatitis. Using the CIOMS or RUCAM (Roussel Uclaf Causality Assessment Method) scale for causality assessment, the first patient scored 12, the second patient scored 10 and the third patient scored 12, which are "highly probable" for DILI.[15] Using the Maria and Victorino system, the first patient scored 17, the second patient scored 15 and the third patient showed 12 which are "probable" for DILI.[16]

Each case was treated at a different institution and did not have an identical evaluation. The first two cases lack data on evaluation for atypical viral hepatitis including CMV and EBV, which is a limitation of the study. Other limitations include study design. This is a retrospective case study with possible confounders including other causes of hepatitis and use of other medications causing DILI.

Corticosteroids have long been the mainstay of treatment in patients with acute and chronic liver disease. [17-18] Thus, it appears almost counter-intuitive that this drug could induce liver damage. The fact that methylprednisolone continued to be used, even as the link with hepatitis got stronger, attests to clinical confidence in its lack of hepatotoxic potential.

Our first case is likely a hypersensitivity reaction. The second and third appear to be AIH-DILI with positive and negative autoimmune markers respectively. It could be argued that the second patient had AIH. Although anti-smooth muscle antibody was positive in the second patient, the total IgG was elevated less than 1.5 times normal and the clinical picture was deemed incompatible with autoimmune hepatitis per the AIH consensus criteria. [19] The third patient had features of hepatitis on histology in the setting of a negative workup for other causes of liver disease, including negative auto immune markers.

Several authors have attested to the fact that it is hard to distinguish between AIH and AIH-DILI[4,20,21], including differentiating them on the basis of histology.[21] Czaja suggests AIH-DILI differs from AIH mainly by its greater frequency for an acute onset, rarity of cirrhosis at presentation, and absence of relapse after corticosteroid withdrawal. [4] Castiella et al dispute the suggestion that cirrhosis is absent in AIH-DILI[9,22] or that patients invariably relapse after discontinuation of steroids in AIH but not AIH-DILI.[9,21-23]

Takahashi et al reported hepatitis in the setting of methylprednisolone in their patient with MS, and inferred that liver dysfunction in these patients might reflect rebound AIH, as steroids are withdrawn in patients with previously unrecognized autoimmune disease. [24-26] While Czaja has argued AIH can relapse even upto 22 years after treatment with steroids but Castiello, Bjornsson and Heurgue have suggested that relapse after withdrawl of steroids is not a reliable distinguishing feature between AIH and AIH-DILI.[9,20,22]

Features of AIH-DILI include a female predominance (80–90%) and latency intervals from 1 to 8 weeks (intermediate latency) to 3–12 months (long latency). AST and ALT are usually 5- to 20-fold above the upper limit of normal, whereas hypergammaglobulinemia and an abnormally increased serum IgG level reflect the chronic and immune-mediated aspects of the condition. Autoantibodies may be present in the absence of liver disease and are seen in both AIH and AIH-DILI. ANA, SMA , anti-LKM2 (antibodies to liver kidney microsome type 2) can also be seen in AIH-DILI but maybe absent upto 20-40% of the time. [4]

The histological features seen in AIH-DILI are said to be similar to those of classical autoimmune hepatitis, and they include interface hepatitis with portal and periportal infiltrates of lymphocytes, plasma cells, and eosinophils. The centrilobular zone 3 pattern is due to hepatotoxins that typically induce injury within 24–48 h of exposure but are not seen in late-onset, AIH-DILI.[27-30] Similar findings were noted in the 2nd and 3rd patients.

A recent article by Gutowski et al., summarizes case reports from existing literature, with a total of 13 patients, all of whom had autoimmune diseases. 1 patient had Crohn's disease, 1 had SLE, 2 had Graves Opthalomopathy, 1 with CNS vasculitis and 7 with MS. 12 out of the 13 patients were female.[14] Multiple sclerosis being an autoimmune disease lends credibility to having other autoimmune disease processes.

Genetic studies suggest an allele, HLA DR B1*1501 may be a genetic risk factor for DILI secondary to amoxicillin-clavulanic acid and other drugs. [31,32] There is evidence to support that this allele maybe a risk factor for MS. [33-34] One could postulate that MS patients, may have an increased risk of some forms of DILI, although we cannot generalize this to other autoimmune diseases. Other genetic associations regarding DILI include predominance of HLA-DR6 in hepatitis caused by chlorpromazine and HLA-A11 in tricyclic antidepressant induced hepatitis.[31-32] HLA genotyping would be of interest in MS patients with AIH-DILI, as a future study.

Re-challenge is another aspect that lends weight to the diagnosis of DILI. In practice, rechallenge is not advised as this carries significant morbidity and mortality. It would take an undefined time period to elicit symptoms and signs. It may be positive in about 50% of the cases and a negative response would not rule out causality. Hence, this approach is rarely justified and if no alternative medication exists, it should only be done with the patient's informed consent. [35-37]

Alternative etiology of hepatitis in our patients, include hepatitis due to interferon beta 1-a acetate or Avonex® (occurrence less 4:1000 patients, [38,39] and glatiramer acetate or Copaxone ® (occurrence less than 1:1000 patients), used to treat MS.[40] These drugs were discontinued. Nevertheless, hepatitis followed the administration of methylprednisolone, which continued to be used several times for both patients.

In conclusion, we report three cases linking methylprednisolone with drug induced liver injury. Future studies could focus on HLA typing in patients with MS who present with DILI and consideration of longer follow-up, both biochemical and histologic. A thorough history to exclude medication exposure, detailed work-up to diagnose alternative causes for liver disease and the establishment of registries for DILI (4,19) will be key. Physicians should consider this diagnosis in a patient who develops hepatitis while on treatment with methylprednisolone.

Acknowledgments

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