




# Liver injury after methylprednisolone pulses: A disputable cause of hepatotoxicity. A case series and literature review

Miguel Eugenio Zoubek<sup>1,2</sup>, José Pinazo-Bandera<sup>1</sup>, Aida Ortega-Alonso<sup>1</sup>,  
Nelia Hernández<sup>3</sup>, Javier Crespo<sup>4,7</sup>, Fernando Contreras<sup>5</sup>,  
Inmaculada Medina-Cáliz<sup>1</sup>, Judith Sanabria-Cabrera<sup>1,6</sup>,  
Rocío Sanjuan-Jiménez<sup>1,6</sup>, Andrés González-Jiménez<sup>1</sup> ,  
Miren García-Cortés<sup>1</sup>, M Isabel Lucena<sup>1,6,7</sup> , Raúl J Andrade<sup>1,7,\*</sup>  
and Mercedes Robles-Díaz<sup>1,7,\*</sup> 

## Abstract

**Background and Objectives:** Corticosteroids are often empirically used to treat idiosyncratic hepatotoxicity with severe features. Interestingly, intravenous methylprednisolone (MP) is increasingly being recognized as being responsible for liver injury. We aimed to characterize MP-induced liver injury by analyzing demographical, clinical, laboratory and outcome data of three MP-induced hepatotoxicity cases and compared this information with that of previously published cases.

**Case series:** Three females with multiple sclerosis (MS) were treated intravenously with MP, mean daily dose 767 mg. Liver damage occurred 2 to 6 weeks after exposure. Severity was mild to moderate. Two patients suffered positive rechallenge.

**Literature review:** We identified 50 published cases of MP hepatotoxicity. Most of these cases were female (86%) and main treatment indications were MS (29 cases) and Graves' ophthalmopathy (13 cases). Hepatocellular damage predominated and mean time to onset was 6 weeks. Four patients died and rechallenge occurred in 19 cases.

**Conclusion:** MP pulses can induce severe liver injury, often with an autoimmune phenotype, particularly in patients with MS and Graves' ophthalmopathy. Consequently, these patient groups should have liver tests monitored when treated with MP to provide safer patient care.

## Keywords

Methylprednisolone-induced liver injury, steroid pulses, multiple sclerosis, Graves' ophthalmopathy, AIH

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## Key summary

Corticosteroids, which are used in severe forms of acute liver injury due to their potent immunomodulatory activity, are considered non-hazardous agents to the liver, and indeed they are underrepresented in drug-induced

<sup>1</sup>UGC Digestivo y Farmacología Clínica, Instituto de Investigación Biomédica de Málaga (IBIMA), H U Virgen de la Victoria, Málaga, Spain

<sup>2</sup>Department of Toxicology, School for Nutrition, Toxicology and Metabolism (NUTRIM), Maastricht University, Maastricht, The Netherlands

<sup>3</sup>Hospital de Clínicas, Clínica Gastroenterología, F Medicina, Montevideo, Uruguay

<sup>4</sup>Unidad de Gestión Clínica de Enfermedades Digestivas, Hospital Marqués de Valdecilla, Instituto de Investigación Biomédica Marqués de Valdecilla (IDIVAL), Santander, Spain

<sup>5</sup>Departamento de Gastroenterología, National University Pedro Henríquez Ureña, Santo Domingo, Dominican Republic

<sup>6</sup>Unidad Investigación Clínica y Ensayos Clínicos (UICEC)-Instituto de Investigación de Biomedicina de Málaga (IBIMA), Plataforma Spanish Clinical Research Network (SCReN), Málaga Spain

<sup>7</sup>Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas, CIBERehd, Madrid, Spain

\*Co-senior authorship

### Corresponding author:

Mercedes Robles-Díaz, UGC Digestivo, H U Virgen de la Victoria, Málaga 29010, Spain.

Email: mrobles@uma.es

liver injury (DILI) databases. However, cases of methylprednisolone (MP)-DILI have been increasingly reported in recent years.

### Main findings of our study

- Liver injury associated with MP typically appears during the first weeks after receiving high doses of the agent, manifesting with a hepatocellular pattern of damage, and commonly goes unnoticed favouring rechallenge with the drug.
- MP-induced liver injury frequently presents with an autoimmune phenotype, particularly in patients with multiple sclerosis and Graves' ophthalmopathy, which suggests that the drug may unmask AIH in susceptible subjects.
- Liver tests in patients with autoimmune disorders should be monitored when treated with high-dose courses of MP in order to diagnose liver injury early and to provide a better management of these patients.

## Introduction

Methylprednisolone (MP), a synthetic glucocorticoid drug, exerts potent anti-inflammatory and immunomodulatory effects, therefore it is prescribed to treat severe inflammatory, autoimmune and neoplastic disorders, as well as in the setting of transplant rejection, among other uses. High-dose intravenous MP is the standard therapy for relapsing autoimmune disorders such as multiple sclerosis, where doses ranging from 500 mg/day for 5 days to 1 g/day for 3 days are commonly used.

Corticosteroids are considered to be safe, in terms of hepatotoxicity, thus, they are underrepresented in hepatotoxicity databases.<sup>1</sup> However, a number of liver injury cases, particularly those related to high-dose methylprednisolone, have been reported in recent years. This situation has triggered controversy, in terms of the attribution of causality since corticosteroids have been empirically advocated for the management of severe forms of idiosyncratic drug-induced liver injury (DILI), as well as in cases of hepatotoxicity presenting with autoimmunity and systemic hypersensitivity features.

In the present study, we aimed to characterize the clinical phenotype of MP-induced liver injury (DILI) by analyzing three cases included in Spanish (from 1994 to 2018) and Latin-American (from 2013 to 2018) DILI registries. Both databases share the same standardized operating procedures, which have been published elsewhere.<sup>2</sup> Information from newly reported cases was then compared with that of 50 previously published cases retrieved from an extensive literature review.

## Case series

### Patient 1

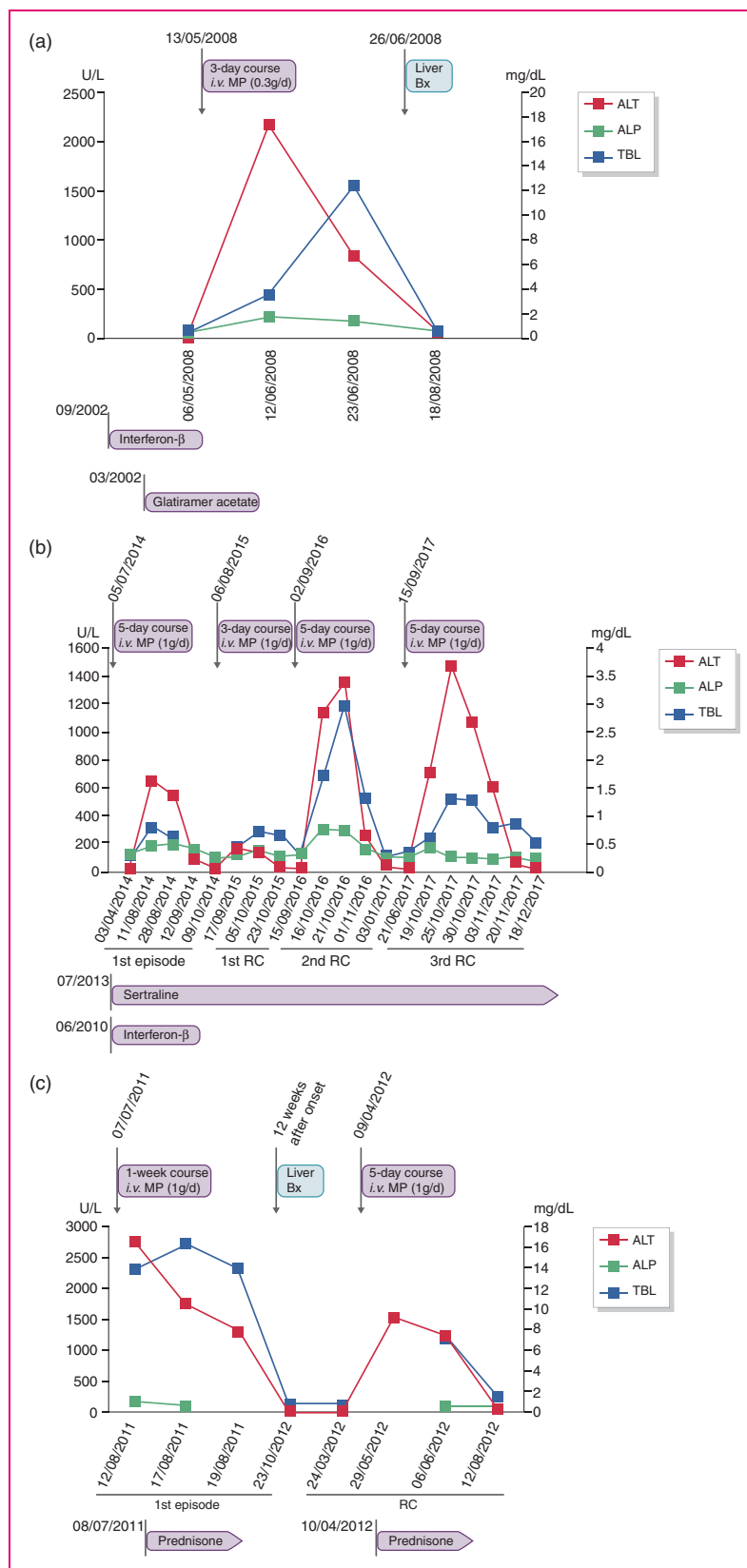
A 31-year-old female with a 3-year history of multiple sclerosis (MS) under treatment with interferon beta (IFN- $\beta$ ) and glatiramer acetate for the last 9 and 3 months, respectively, was admitted to the hospital due to acute relapsing disease.

The patient received a 3-day course of 300 mg/day intravenous pulse MP. Two weeks later, weakness, nausea, weight loss and jaundice ensued. Total bilirubin was 3.6 mg/dL (TBL < 1.0 mg/dL), aspartate aminotransferase 1420 U/L (AST < 31 U/L), alanine aminotransferase 2194 U/L (ALT < 31 U/L) and alkaline phosphatase 229 U/L (ALP < 129 U/L), indicating hepatocellular injury. All medications were stopped at this point (Figure 1(a)). The patient's liver tests at the time of starting MP therapy were normal (Figure 1(a)). Serology tests for viral hepatitis A (HAV), B (HBV), C (HCV), cytomegalovirus (CMV), Epstein-Barr virus (EBV) and human immunodeficiency virus (HIV) were negative. Immunoglobulins, ceruloplasmin, copper, iron and transferrin serum levels were within normal ranges. Antinuclear (ANA), antimitochondrial (AMA) and anti-smooth muscle antibodies (ASMA) were negative. However, positive ANA titers of 1/320 were found at the time of biochemistry normalization. Liver imaging (CT scan, cholangiography) were normal. Liver biopsy performed 1 month after initiating MP treatment showed centrilobular necrosis with portal fibrosis and mixed inflammatory infiltrates. A maximum TBL value of 12.6 mg/dL was reached 5 weeks after onset.

Liver tests returned to normal within 70 days. Causality assessment using the Council for International Organizations of Medical Sciences (CIOMS) scale<sup>3</sup> scored 7 points (probable) for MP.

### Patient 2

A 36-year-old female with a previous history of MS, depressive disorder and non-alcoholic fatty liver disease and with normal liver tests (Figure 1(b)) and stable body weight (60 kg) was treated with IFN- $\beta$  for 4 years and sertraline for the last year. She presented with relapsing MS and received a 5-day course of high-dose (1 g/day) intravenous methylprednisolone and then prednisone 60 mg/day, which was gradually reduced and ultimately withdrawn in 3 weeks. Laboratory tests 5 weeks after starting the MP



**Figure 1.** Temporal relationship between courses of intravenous MP pulse and liver biochemistry in four patients. The data shown correspond to patient 1 with a single episode after exposure to MP (a), patient 2 who developed after a first episode up to three more events of MP hepatotoxicity (b) and patient 3 who after a first event of MP-induced liver injury suffered from rechallenge due to MP (c). Concomitant treatments present at onset of each liver dysfunction episode are displayed. Abbreviations: MP: methylprednisolone; TBL: serum total bilirubin (mg/dl); ALT: alanine aminotransferase (U/L); ALP: alkaline phosphatase (U/L); interferon-β: interferon beta; Bx: biopsy; g: gram; d: day; i.v.: intravenous; RC: rechallenge; CaC: calcium carbonate; CaG: calcium gluconate; MCP: metoclopramide; *prn*: *pro re nata*.

showed acute hepatocellular injury: TBL 0.8 mg/dL ( $< 1.1$  mg/dL), AST 419 U/L ( $< 27$  U/L), ALT 630 U/L ( $< 33$  U/L), and ALP 193 U/L ( $< 270$  U/L). Serology for HAV, HBV, HCV, CMV and EBV was negative. ANA, AMA, ASMA and anti-liver/kidney microsomal antibody type 1 ([anti-LKM-1]) were all negative. An abdominal ultrasound showed normal liver parenchyma and biliary ducts and a thin-walled gallbladder containing biliary sludge. Laboratory chemistries were normal 8 weeks later; the patient remained on sertraline, however IFN- $\beta$  was discontinued. Several months later during follow-up, liver tests remained normal.

One year later, a similar episode occurred following MS exacerbation and administration of intravenous MP (1 g/day for 3 days) and the same course of dose titration. Two weeks after MP cessation, abnormal liver parameters were found: TBL 0.46 mg/dL, AST 122 U/L, ALT 165 U/L and ALP 125 U/L (Figure 1(b)). Viral hepatitis was excluded, and autoantibodies were negative. Eleven weeks later, liver tests were normal.

Over the next 2 years, due to relapsing–remitting MS, she received subsequent 5-day courses of high intravenous dose of MP, which were followed by flares of aminotransferases (first year: TBL 1.75 mg/dL, AST 896 U/L, ALT 1151 U/L and ALP 314 U/L; second year: TBL 0.57 mg/dL, AST 485 U/L, ALT 696 U/L, ALP 172 U/L) (Figure 1(b)). Screening for viral hepatitis was again negative.

CIOMS scale yielded a score of 9 (highly probable) for MP hepatotoxicity with three positive rechallenges.

### Patient 3

A 33-year-old female with a 12-year history of MS was referred to the clinic due to marked jaundice, pruritus and elevated transaminases. The patient had up to six MS exacerbations in the past and had received bolus, high-dose (1 g/day) MP for 3 to 7 days, followed by oral prednisone, with complete neurological remission. Routine biochemistry after each treatment was normal.

Following a new MS relapse and administration of intravenous MP (1 g/day for 1 week) and 12 days of oral prednisone, laboratory tests were performed 6 weeks later, indicating severe hepatocellular injury: TBL 13.9 mg/dL ( $< 1.0$  mg/dL), AST 1823 U/L ( $< 104$  U/L), ALT 2737 U/L ( $< 52$  U/L) and ALP 169 U/L ( $< 104$  U/L). Serology ruled out viral causes. Screening for autoantibodies was negative, serum ceruloplasmin; globulin levels were normal, as was abdominal ultrasonography. Clinical and laboratory findings 2 weeks later showed spontaneous improvement. Three months later, a liver biopsy specimen showed minimal residual hepatitis.

Ten months later, similar acute hepatitis-like symptoms occurred following MS exacerbation and

intravenous MP administration (1 g/day for 5 days). Laboratory tests showed the following results: TBL 2.47 mg/dL, AST 1113 U/L, ALT 1500 U/L and INR 1.31, which returned to normal several weeks later. The CIOMS scale provided a score of 7 (probable) for MP with positive re-exposure.

### Literature review

A total number of 50 cases presented in 7 case series and 24 single case reports were retrieved from 2000 to 2018, carefully reviewed and analyzed in this study (Tables 1 and 2).<sup>4–34</sup>

Most patients were female (86%), with a mean age of 40 years (range 11–74 years). The primary indications for MP therapy were exacerbated episodes of demyelinating diseases (29 cases of MS), followed by Graves' ophthalmopathy (GO) (13 cases).

MP was mainly administered intravenously (96%). The cumulative MP doses ranged from 0.2 to 15 g, and the average MP treatment duration was 22 days (range 3–136 days), with a mean duration of 5 days for demyelinating disorders and 47 days for GO.

Twenty-one patients presented weakness, generalised malaise, nausea, abdominal pain and pruritus. Jaundice was a common feature in symptomatic patients (76%). In addition, 21 patients were asymptomatic, and the diagnosis of liver injury was based on a routine blood test. No information regarding symptoms was available for the remaining eight cases. The mean time to symptoms onset was 6 weeks (range 1–20 weeks) (Table 1).

The mean values for peak liver tests were as follows: TBL 6.5 mg/dL (range, 0.8–24 mg/dL), AST 874 U/L (range, 39–3315 U/L), ALT 1393 U/L (range, 122–3768 U/L) and ALP 181 U/L (range, 80–498 U/L). Sixteen cases presented with positive autoantibody titers (36%). Of those cases, eight had ANA titers, three cases ASMA titers and one case had anti-LKM-1 titers. Three additional cases presented simultaneously with ANA and ASMA titers, and one case had positive AMA and ANA autoantibodies. In 29 cases autoimmunity titers were negative, while autoantibody information was not available in five cases (Table 2).

Liver biopsy information was available for 32 (64%) patients. The primary findings were necrosis in 22 cases and apoptotic changes in two cases (Table 1). Interestingly, the pattern of liver injury, based on biochemical parameters, was hepatocellular in all cases with available information ( $n = 39$ ). Seventeen of 22 patients for whom sufficient information was available met new Hy's (nHy) law criteria (Table 2).

Most MP-DILI patients recovered (94%), but four patients died. The mean time to resolution was

**Table 1.** Summarized demographic and clinical information of methylprednisolone-induced liver injury events reviewed in literature (n=50).

Case no.- author	Age (yr)/ sex (M/F)	Indication for MP treatment	Cumulative MP dosage g; (treatment duration, d)	Time to onset, wks <sup>a</sup>	Concomitant medication	Clinical presentation	Time to resolution, wks <sup>a</sup>	Liver biopsy	Outcome	Re- challenge, (n)
1.-Davidov et al.	23/F	MS	3 (3)	3	-	Jaundice, fever, nausea, vomiting	12	Hepatocyte dropouts in central areas, congestion and chronic inflammation; portal tracts enlarged due to chronic inflammation (lymphocytes, eosinophils and plasma cells); in par- enchyma, acidophilic bodies accompanied by inflammatory cells; hep- atocytes showed signs of regeneration	R	Yes (1)
2.-Moleti et al. (1)	58/M	GO	3.2 (84)	5	-	Asymptomatic	6	-	R	-
3.-Moleti et al. (2)	50/F	GO	1.5 (84) + oral prednisone during interpulse periods	3	Methimazole	Asymptomatic	16	-	R	-
4.-Grilli et al.	35/F	MS	5 (5)	4	-	Jaundice	4	Nodular parenchyma partially surrounded by fibrotic septa emerging from portal tracts; moderately dense inflammatory infil- trate (lymphocytes, plasma cells, eosinophils and neu- trophils); bridging and confluent necrosis	R	Yes (1)
5.-Ferraro et al. (1)	50/F	MS	1 (5)	1	Lisinopril	N/A	4	-	R	-
6.-Ferraro et al. (2)	30/F	MS	1 (5)	1	-	N/A	2	-	R	-
7.-Ferraro et al. (3)	38/F	MS AITD	1 (5)	8	-	N/A	4	Inflammatory infiltrate, patched focal necrosis, periportal fibrosis and numerous ceroid-laden macrophages	R	-
8.-Ferraro (4) et al.	24/F	MS	1 (5) + 1-mo taper	16	-	N/A	16	Inflammatory infiltrate, patched focal necrosis, periportal fibrosis and numerous ceroid-laden macrophages	R	Yes (3)

(continued)

Table 1. Continued

Case no.- author	Age (yr)/ sex (M/F)	Indication for MP treatment	Cumulative MP dosage g; (treatment duration, d)	Time to onset, wks <sup>a</sup>	Concomitant medication	Clinical presentation	Time to resolution, wks <sup>a</sup>	Liver biopsy	Outcome	Re- challenge, (n)
9.-Oliveira et al.	33/F	MS	1 (N/A) + oral maintenance	N/A	Cyclophosphamide, glatiramer acetate	Jaundice	N/A	Severe interface hepatitis and centrilobular hepatocyte necrosis with mild fibrotic changes	R	Yes (4)
10.-Melamed et al.	52/M	GO	0.5 (14)	2	Atorvastatin, ciprofibrate, levothyroxine	Jaundice, weakness, arthralgia	28	-	R	Yes (1)
11.-D'Agnolo et al.	48/F	MS	1 (3)	3	-	Abdominal pain, nausea	N/A	-	R	Yes (1)
12.-Carrier et al.	30/F	MS	1 (N/A)	2	APAP (levels below toxic doses)	Jaundice, asthenia	N/A	Significant bridging necrosis between central veins and portal tracts/ portal spaces; in necrotic foci, inflamma- tory lymphocytic infiltrate with plasma cells eosino- phils; intrahepatic cholestasis	R	Yes (2)
13.-Alva et al.	38/F	ILD	0.96 <sup>b</sup> (30)	N/A	N/A	Jaundice, rash, pruritus	24	Cholestatic hepatitis with early stage fibrosis	R	-
14.-Furutama et al.	11/F	MS	3 (3)	6	-	Febricula, fatigue	2	-	R	Yes (2)
15.-Gutkowski et al.	24/F	MS	3 (N/A)	4	IFN- $\beta$ (2 ij) + APAP (single dose at each ij)	Jaundice	3	-	R	Yes (1)
16.-Loraschi et al. (1)	33/M	DE	2.5 (4)	5	-	Asymptomatic	3	Focal necrosis (acinar zones II and III), monocyte/macro- phage infiltration, Kupffer cell hyperplasia, acido- philic bodies and focal microvesicular steatosis	R	-
17.-Loraschi et al. (2)	27/F	RBON	4.5 (6)	1	-	Asymptomatic	1	-	R	-
18.-Maamouri et al.	37/F	MS	3 (3)	3	-	Asymptomatic	N/A	Lymphoplasmacytic portal inflammatory infiltrate with interphase hepatitis and bridging fibrosis	R	-
19.-Rivero et al.	57/F	MS	3 (3)	1	-	Asymptomatic	12	Lytic necrosis and macrophage hyperplasia with ceroid- laden macrophages	R	Yes (2)

(continued)

Table 1. Continued

Case no.- author	Age (yr)/ sex (M/F)	Indication for MP treatment	Cumulative MP dosage g; (treatment duration, d)	Time to onset, wks <sup>a</sup>	Concomitant medication	Clinical presentation	Time to resolution, wks <sup>a</sup>	Liver biopsy	Outcome	Re- challenge, (n)
20.-Takahashi et al.	43/F	MS	3 (3)	4	IFN- $\beta$	Nausea, vomiting	N/A	Perivenular bridging necrosis with inflammatory infiltra- tion including eosinophils and interphase hepatitis	R	Yes (1)
21.-Reuß et al.	42/F	MS	5 (N/A)	3	-	Asymptomatic	N/A	Active hepatitis with portal lymphocyte infiltration and fibrosis	-	-
22.-Topal et al.	47/F	CNSV, self- medication	0.224/d <sup>b</sup> (7)	1	Topiramate	Jaundice, weakness, anorexia, nausea, pruritus, acholia, choluria	7	-	R	-
23.-Das et al.	48/F	MS	N/A	6	-	Jaundice, nausea, vomiting	N/A	Infiltrate with lymphocytes, eosinophils and plasmatic cells; more apparent in perivenular acinar region III; increasing presence of councilman bodies	R	Yes (1)
24.-Hofstee et al.	46/F	MS	1 (3)	6	-	Asymptomatic	16	-	R	Yes (2)
25.-Marinó et al.	43/F	G0	4.7 (N/A)	6	-	Asymptomatic	9	Lymphoplasmacytic infiltrate affecting interlobular bile conducts; focal centrilobu- lar necrosis	R	-
26.-Marinó et al. (1)	56/N/A	G0	15 (56)	8	Oestrogens	Jaundice, fatigue, anorexia, diarrhoea	7 <sup>§</sup>	Massive necrosis	Exitus	-
27.-Marinó et al. (2)	63/N/A	G0	9.3 (49)	8	Atenolol, propafenone, quinapril	Jaundice, fatigue, anorexia, diarrhoea	7 <sup>§</sup>	N/A	Exitus	-
28.-Marinó et al. (3)	47/N/A	G0	8.3 (35)	18	-	Jaundice, fatigue, anorexia, diarrhoea	5 <sup>§</sup>	N/A	Exitus (post- LTx)	-
29.-Marinó et al. (4)	45/N/A	G0	9.3 (49)	15	Ciprofloxacin	Asymptomatic	23	Moderate necrosis	R	-
30.-Marinó et al. (5)	30/N/A	G0	7.2 (35)	18	-	Asymptomatic	18	Lobular and portal lymphocytic infiltrate with eosinophilia	R	-
31.-Marinó et al. (6)	55/N/A	G0	10.7 (35)	16	Trandolapril	Asymptomatic	9	N/A	R	-

(continued)

Table 1. Continued

Case no.- author	Age (yr)/ sex (M/F)	Indication for MP treatment	Cumulative MP dosage g; (treatment duration, d)	Time to onset, wks <sup>a</sup>	Concomitant medication	Clinical presentation	Time to resolution, wks <sup>a</sup>	Liver biopsy	Outcome	Re- challenge, (n)
32.-Marinó et al. (7)	54/N/A	GO	4 (21)	4	Oestrogens	Asymptomatic	20	Confluent necrosis; lympho- cytic and plasma cell infiltrates	R	-
33.-Salvi et al.	43/F	HT	5.5 (136)	8	N/A	Asymptomatic	18	Lobular hepatitis with central necrosis, presence of lymphocytes and plasma cell infiltrates, acidophilic bodies and Kupffer cell hyperplasia	R	-
34.-Weissel et al.	71/F	GO	15 (N/A)	4	Methimazole, cortisone	N/A	2 <sup>§</sup>	Necrosis of liver parenchyma	Exitus	-
35.-Dumontier et al. (1)	40/F	Alopecia Areata	N/A	7	N/A	N/A	30	-	R	-
36.-Dumontier et al. (2)	26/F	MS	N/A	11	N/A	N/A	4	Portal fibrosis, no signs of autoimmune hepatitis, cholestasis or steatosis (performed 2 months after the second episode)	R	Yes (2)
37.-Dumontier et al. (3)	27/F	MS	N/A	9	N/A	N/A	11	Focal liver cell necrosis in acinar zone 3	R	Yes (1)
38.-Dumontier et al. (4)	36/M	Alopecia Areata	N/A	5	N/A	N/A	7	Central lobular necrosis (30% of liver parenchyma)	R	-
39.-Dumontier et al. (5)	27/F	MS	N/A	4	Teriflunomide	Mild asthenia	154	Central lobular necrosis	R	Yes (2)
40.-Hidalgo et al. (1)	28/F	MS	1.5 (9)	7	-	Jaundice, choluria, acholia, nausea, vomiting	4	Lymphocyte-oedematous background and fibrotic changes related to mild chronic hepatitis	R	Yes (1)
41.-Hidalgo et al. (2)	37/M	Transverse myelitis	1 (5)	6	-	Asymptomatic	N/A	No inflammatory changes (biopsy performed 2 months after episode)	R	-
42.-Hidalgo et al. (3)	35/F	MS	1 (5)	1	-	Asymptomatic	N/A	-	R	-
43.-Abramavicius et al.	74/F	GO	4 (57)	5	Methimazole	Asymptomatic	N/A	-	R	-
44.-Lee et al.	34/M	MS	1 (5) + 1/mo maintenance dose	20	-	Asymptomatic	30	Centrilobular necrosis	R	-

(continued)



Table 1. Continued

Case no.- author	Age (yr)/ sex (M/F)	Indication for MP treatment	Cumulative MP dosage g; (treatment duration, d)	Time to onset, wks <sup>a</sup>	Concomitant medication	Clinical presentation	Time to resolution, wks <sup>a</sup>	Liver biopsy	Outcome	Re- challenge, (n)
45.-Kadle et al.	51/F	AITD, MS	0.5 (10)	7	-	Weakness, anorexia, weight loss, jaundice	22	-	R	-
46.-Adamec et al. (1)	37/F	MS	3 (3)	4	IFN- $\beta$	Nausea, epigastric pain	N/A	Centrilobular necrosis with lymphocytic and eosino- philic infiltrates	R	Yes (1)
47.-Adamec et al. (2)	46/F	MS	3 (3)	4	Vitamin D	Asymptomatic	N/A	Mild diffuse hepatic steatosis	R	Yes (1)
48.-Adamec et al. (3)	44/F	MS	3 (3)	12	-	Jaundice, nausea, anorexia	N/A	Portoportal and portoportal necrosis with lymphocytic infiltrate	R	-
49.-Bresteau et al.	35/F	MS	5 (5)	8	-	Asymptomatic	6	Confluent necrosis, severer at terminal hepatic venule, portal tract inflammation, no bile duct damage	R	-
50.-Rotondo et al.	16/F	MS	5 (5)	4	-	Urticaria, angioedema, nausea, vomiting	8	Focal centrilobular hepatocyte necrosis with interface hepatitis	R	-
<b>Our cases</b>										
Patient 1	31/F	MS	0.9 (3)	2	IFN- $\beta$ , glatiramer acetate	Jaundice, weakness, nausea	N/A	Acute hepatitis, portal fibrosis and mixed infiltration including eosinophils; centrilobular necrosis	N/A	-
Patient 2	36/F	MS	3 (3) + 60 mg/day p.o. (21 days)	2	IFN- $\beta$ , sertraline	Asymptomatic	12	-	R	Yes (3)
Patient 3	33/F	MS	7 (7) + prednisone p.o. (12 days)	6	-	Jaundice, intermittent pruritus	N/A	Minimal residual hepatitis without fibrosis	R	Yes (1)

Summarized demographic, clinical, histological and laboratory data correlated with a first exposure of methylprednisolone (in case accidental rechallenge applied) or with the episode described in the manuscript and/or displaying enough information.

<sup>a</sup>Time units were registered as weeks, and when days were indicated in the original publication, they were rounded up (e.g., 1–7 days equals 1 week; 8–14 days equals 2 weeks, etc.).

<sup>b</sup>MP was administered exclusively p.o. in contrast to the rest of the cases where MP was administered intravenously only.

Abbreviations: MP: methylprednisolone; M: male; F: female; y: years; N/A: not available; mo: month; wk: weeks; d: days; g: gram; MS: multiple sclerosis; GO: Graves' ophthalmopathy; AITD: autoimmune thyroid diseases; IFN- $\beta$ : interferon beta; ILD: interstitial lung disease; DE: demyelinating encephalopathy; CNSV: central nervous system vasculitis; RBON: retrobulbar optic neuritis; post-LTX: after liver transplantation; HT: Hashimoto's thyroiditis; EP: enoxiparin; CaC: calcium carbonate; PP: pantoprazole; MMZ: metimazole; APAP: acetaminophen; AV: *Aloe vera*; ij: injections; R: recovery; <sup>§</sup>: time to exitus.

**Table 2.** Summarized biochemical, liver injury pattern and autoimmunity information of methylprednisolone-induced liver injury events at peak reviewed from literature ( $n = 50$ ) and new reported cases ( $n = 3$ ).

Author	Case	TBL (mg/dL)	AST (U/L)	ALT (U/L)	ALP (U/L)	Type of injury	Autoantibodies; meeting nHy's law criteria
Davidov et al.	1	6.3	N/A	2287	123	HC	ASMA+; nHy
Moleti et al. (1)	2	N/A	486	809	N/A	N/A	-
Moleti et al. (2)	3	N/A	338	903	N/A	N/A	ANA + (low titers)
Grilli et al.	4	24	1104	2000	114	HC	nHy
Ferraro et al. (1)	5	N/A	136	355	N/A	N/A	-
Ferraro et al. (2)	6	N/A	157	627	N/A	N/A	-
Ferraro et al. (3)	7	N/A	109	260	N/A	HC <sup>a</sup>	ANA + (1:640); ASMA + (1:80)
Ferraro et al. (4)	8	N/A	315	671	N/A	HC <sup>a</sup>	-
Oliveira et al.	9	16	710	2308	92	HC	ANA + (1:40), nHy
Melamud et al.	10	3.4	283	465	80	HC	nHy
D'Agnolo et al.	11	1.7	2384	3028	N/A	HC <sup>a</sup>	-
Carrier et al.	12	N/A	3315	3768	N/A	HC <sup>a</sup>	ANA + (1:160); nHy <sup>d</sup>
Alva et al.	13	3.3	1428	2618	134	HC	nHy
Furutama et al.	14	0.8	278	428	N/A	N/A	ANA + (1:80)
Gutkowski et al.	15	18	900	1740	186	HC	ASMA + (>1:320); nHy
Loraschi et al. (1)	16	N/A	349	1042	N/A	HC <sup>a</sup>	-
Loraschi et al. (2)	17	N/A	39	122	N/A	N/A	-
Maámouri et al.	18	1	229	553	228	HC	ANA + (1:100); ASMA + (1:100)
Rivero et al.	19	N/A	1328	2685	115	HC	-
Takahashi et al.	20	3.4	1102	1067	377	HC	ANA + (1:80); ASMA+; nHy
Reuß et al.	21	N/A	485	1082	N/A	HC <sup>a</sup>	N/A
Topal et al.	22	10	1600	2478	138	HC	nHy
Das et al.	23	N/A	1500	1600	200	HC	nHy <sup>d</sup>
Hofstee et al.	24	N/A	755	1095	140	HC	-
Marinó et al.	25	N/A	990	1419	N/A	HC <sup>a</sup>	-
Marinó et al. (1)	26	N/A	2280	2490	498	HC	ANA + (low titers); nHy <sup>d</sup>
Marinó et al. (2)	27	N/A	68	179	100	HC	N/A
Marinó et al. (3)	28	N/A	N/A	N/A	N/A	N/A	N/A
Marinó et al. (4)	29	N/A	888	1971	178	HC	N/A
Marinó et al. (5)	30	N/A	457	930	237	HC	anti-LKM-1
Marinó et al. (6)	31	N/A	635	1044	245	HC	-
Marinó et al. (7)	32	N/A	948	1815	183	HC	-
Salvi et al.	33	N/A	634	1152	N/A	HC <sup>a</sup>	ANA + (high titers)
Weissel et al.	34	N/A	N/A	N/A	N/A	HC <sup>a</sup>	N/A
Dumontier et al. (1)	35	N/A	29 <sup>b</sup>	34 <sup>b</sup>	N/A	HC <sup>c</sup>	-
Dumontier et al. (2)	36	N/A	14 <sup>b</sup>	33 <sup>b</sup>	N/A	HC <sup>c</sup>	-
Dumontier et al. (3)	37	N/A	5.3 <sup>b</sup>	9.6 <sup>b</sup>	N/A	HC <sup>c</sup>	-
Dumontier et al. (4)	38	N/A	N/A	50 <sup>b</sup>	N/A	HC <sup>c</sup>	-
Dumontier et al. (5)	39	3.7	2235	1704	N/A	HC <sup>c</sup>	nHy
Hidalgo et al. (1)	40	N/A	N/A	N/A	N/A	HC <sup>a</sup>	nHy <sup>d</sup>
Hidalgo et al. (2)	41	N/A	N/A	N/A	N/A	N/A	-
Hidalgo et al. (3)	42	N/A	N/A	N/A	N/A	N/A	-
Abramavicius et al.	43	N/A	89	194	N/A	N/A	AMA + (1/40); ANA + (1/40)
Lee et al.	44	1.6	660	1242	N/A	HC <sup>a</sup>	-
Kadle et al.	45	N/A	1774	1047	175	HC	ANA + (1/160); nHy <sup>d</sup>

(continued)

Table 2. Continued

Author	Case	TBL (mg/dL)	AST (U/L)	ALT (U/L)	ALP (U/L)	Type of injury	Autoantibodies; meeting nHy's law criteria
Adamec et al. (1)	46	N/A	1095	2259	N/A	HC <sup>a</sup>	-
Adamec et al. (2)	47	N/A	74	395	N/A	N/A	ASMA + (1/160)
Adamec et al. (3)	48	N/A	N/A	1340	N/A	HC <sup>a</sup>	nHy <sup>d</sup>
Breseau et al. (1)	49	2.9	778	1512	86	HC	ANA + (1/80); nHy
Rotondo et al.	50	2.1	1142	2438	N/A	HC <sup>a</sup>	nHy
<b>Our cases</b>							
Patient 1		3.6	1420	2194	229	HC	ANA + (1/320), nHy
Patient 2		1.30	771	1459	106	HC	-
Patient 3		13.9	1823	2737	169	HC	nHy
<b>Mean U/L (range)<sup>e</sup></b>		6.5 mg/dL (0.8–24)	907 (39–3315)	1443 (122–3768)	180 (80–498)		

<sup>a</sup>When ALT values and/or pathological findings were suggestive of hepatic cytolytic features, but ALP values were not available.

<sup>b</sup>Normalized values provided by author and rough parameters not available in U/L.

<sup>c</sup>Ratio provided by author.

<sup>d</sup>When TBL values were not available, but patient had presented jaundice.

<sup>e</sup>Mean was calculated based on reports which included AST, ALT and ALP in U/L.

Abbreviations: TBL: serum total bilirubin; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase; ANA: antinuclear antibody titres; ASMA: anti-smooth muscle antibody titres; anti-LKM-1: anti-liver/kidney microsomal antibody type 1; AMA: antimitochondrial antibody; N/A: not available; nHy: new Hy's law criteria were applied, where  $nR > 5 + TBL > 2 \times ULN$ , and  $nR$  was calculated as  $(ALT \text{ or } AST \text{ (whichever was highest)}) / ULN$  /  $(ALP / ULN)$ ; ULN: upper limit of normal.

16 weeks (range, 1–154 weeks), and in the four fatal cases, the mean time to exitus was 5 weeks (range, 2–7 weeks). Rechallenge was observed in 19 cases, and in eight of those re-exposure to MP occurred more than two times. MP was the only administered drug in 26 cases; 18 cases had other associated medications on long-term use or with a low hepatotoxic potential. In six cases no information was provided (Table 1).

## Discussion

MP is an unexpected cause of DILI, in fact, it is used as treatment of choice for severe hepatitis, as well as liver disease with autoimmune features, due to its anti-inflammatory and immunosuppressive activities.<sup>20</sup> However, our case series and review of the literature indicate that intravenous high-dose courses of MP can induce severe hepatitis that recurs with repeated administration of the drug and, occasionally, can lead to a fatal progression.<sup>24,26</sup>

Our analysis shows that MP hepatotoxicity can be severe. All four fatal cases were diagnosed with GO relapse (31% lethality within the GO subgroup) and were exposed to higher cumulative MP doses (mean 12 g) compared to the remaining patients (mean cumulative MP dose 2 g (range, 0.18–10.7 g)). Seventeen of the earlier reported events (81%), as well as two of our cases (patients 1, 3) met nHy's law criteria, defined as hepatocellular injury (new ratio,  $nR \geq 5$ ) calculated as  $ALT \text{ or } AST \text{ (whichever was highest/upper limit of normal, ULN)} / (ALP / ULN)$  accompanied by total

bilirubin  $> 2 \times ULN$ .<sup>2</sup> In the majority of cases analyzed in this study, MP was administered to treat exacerbations of an underlying autoimmune disease. Although MP is more commonly used in patients with indications other than autoimmune disorders (e.g., asthma, COPD exacerbations and medullar compression), there are no reported cases of MP-DILI when used in these indications, which suggests that patients with an underlying autoimmune disease, particularly MS or GO, have a higher risk of developing MP-DILI. Indeed, a recent prospective observational single-centre study by Nociti et al. (2018)<sup>37</sup> conducted in 175 MS patients treated with i.v. MP pulses showed an 8.6% prevalence of liver injury. Together, these observations highlight that MP-DILI may be a growing concern in the management of patients with autoimmune disorders and a new challenge in the field of hepatotoxicity.

It is worth noting that patients 11, 14, 43 and 48 responded favourably to dexamethasone therapy, with no subsequent flares in transaminases or only mild liver dysfunction (case 43). Thus, dexamethasone might be a safe glucocorticoid alternative in patients with a previous episode of MP-DILI.<sup>13,32</sup>

Out of the 50 reported cases, 16 patients had positive autoantibody titers as did one of our cases. However, most likely positive autoantibodies in these cases were one of the features of the underlying autoimmune disease rather than of the DILI episode.<sup>35</sup>

In five of the reviewed MP-DILI cases, a diagnosis of AIH triggered by MP was established (cases 18, 20, 21, 25 and 33). In cases 20, 25 and 33, baseline liver

tests were within normal ranges, making less probable an underlying non-diagnosed AIH.

The adaptive immune response is believed to play an important role in the mechanism of DILI.<sup>35</sup> Steroids exert a potent immunosuppressive effect and have often been empirically used in severe forms of liver injury. Hence, one may hypothesize that the MP-induced transient immunosuppression, followed by an immune reconstitution, could awake an autoimmune-like reaction in a susceptible host. This condition may then unmask AIH in predisposed patients.

Once a diagnosis of liver damage was made in cases 20, 25 and 33, therapy was switched to oral corticoids (prednisolone in case 20 and prednisone in the other cases). In case 18, treatment with azathioprine and oral prednisone followed the AIH diagnosis. However, not all cases had this type of progression.

Furthermore, the time to resolution lasted 9 and 18 weeks for cases 25 and 33, respectively, and remained unknown in case 18, although the authors described transaminase normalization within 2 weeks after starting immunosuppressant treatment. Similarly, for the remaining MP-induced liver injury events, the mean time to spontaneous recovery was 15 weeks (range, 1–154 weeks). Thus, the profile of serum liver enzyme recovery and the time to resolution suggest an independent course from the immunosuppressive therapy administered. It is difficult to distinguish MP-induced liver injury from AIH unmasked by MP. Nevertheless, there is a well-defined timeline between the treatment initiation with MP and the development of liver injury, with a mean time to onset of 6 weeks (range, 1–20 weeks). Hence, the relationship between liver injury and intake of MP is undeniable.

Another aspect of interest in MP-DILI is the high rate of rechallenge episodes. It is already known that positive rechallenge due to a suspected causative agent strengthens causality in DILI.<sup>36</sup> In the published cases 38% had a positive rechallenge. Most of our patients had positive re-exposure to MP, which led to a new ALT flare. Most likely, the frequent rechallenge to MP occurs due to lack of awareness of MP hepatotoxicity potential. The elevated numbers of re-exposure, as well as the fact that fatal progression has been described in MP-DILI, are concerning. Thus, an accurate diagnosis of MP-DILI is key for an early discontinuation of the drug and to prevent rechallenge.

In conclusion, MP-induced liver injury, which remains a rare cause of hepatotoxicity, mainly presenting with hepatocellular injury, should be considered in patients having an underlying autoimmune disorder, especially MS and GO, who receive high pulsed i.v. doses of the drug in a short period of time. Liver injury appears frequently during the first weeks after treatment initiation and the severity ranges from

asymptomatic or mild to severe and even fatal. Patients presenting an underlying autoimmune disease require a closer follow-up and liver monitoring during and after high-dose MP therapy.

#### Author contributions

Conceptualization: RJA, MRD; investigation and data analysis: MEZ, JPB, MRD, AOA, NH, JC, FC, IMC, JSC, RSJ, AGJ, MGC; writing: MEZ, JPB, MRD, MIL, RJA.

#### Declaration of conflicting interests

None declared.

#### Ethics approval

This study was reviewed and approved by the Ethical Review Board H U Virgen de la Victoria 9 July 2010.

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#### Informed consent

All three DILI patients provided informed consent prior to study enrolment.

#### ORCID iD

Andrés González-Jiménez  <http://orcid.org/0000-0002-7059-1577>

M Isabel Lucena  <http://orcid.org/0000-0001-9586-4896>

Mercedes Robles-Díaz  <http://orcid.org/0000-0002-2365-2787>

#### References

1. Andrade RJ, Lucena MI, Fernandez MC, et al. Drug-induced liver injury: an analysis of 461 incidences submitted to the Spanish registry over a 10-year period. *Gastroenterology* 2005; 129: 512–521.
2. Robles-Díaz M, Lucena MI, Kaplowitz N, et al. Use of Hy's law and a new composite algorithm to predict acute liver failure in patients with drug-induced liver injury. *Gastroenterology* 2014; 147(1): 109–118.
3. Danan G and Benichou C. Causality assessment of adverse reactions to drugs – I. A novel method based on the conclusions of international consensus meetings: application to drug-induced liver injuries. *J Clin Epidemiol* 1993; 46(11): 1323–1330.
4. Davidov Y, Har-Noy O, Pappo O, et al. Methylprednisolone-induced liver injury: Case report and literature review. *J Dig Dis* 2016; 17: 55–62.
5. Moleti M, Giuffrida G, Sturniolo G, et al. Acute liver damage following intravenous glucocorticoid treatment for Graves' ophthalmopathy. *Endocrine* 2016; 54(1): 259–268.

6. Grilli E, Galati V, Petrosillo N, et al. Incomplete septal cirrhosis after high-dose methylprednisolone therapy and regression of liver injury. *Liver Int* 2015; 35: 674–676.
7. Ferraro D, Mirante VG, Losi L, et al. Methylprednisolone-induced toxic hepatitis after intravenous pulsed therapy for multiple sclerosis relapses. *Neurologist* 2015; 19: 153–154.
8. Oliveira AT, Lopes S, Cipriano MA, et al. Induced liver injury after high-dose methylprednisolone in a patient with multiple sclerosis. *BMJ Case Rep* 2015; pii: bcr2015210722.
9. Melamud B, Lurie Y, Goldin E, et al. Methylprednisolone-induced liver injury: a diagnostic challenge. *Isr Med Assoc J* 2014; 16: 180–181.
10. D'Agnolo HM and Drenth JP. High-dose methylprednisolone-induced hepatitis in a patient with multiple sclerosis: a case report and brief review of literature. *Neth J Med* 2013; 71: 199–202.
11. Carrier P, Godet B, Crepin S, et al. Acute liver toxicity due to methylprednisolone: consider this diagnosis in the context of autoimmunity. *Clin Res Hepatol Gastroenterol* 2013; 37: 100–104.
12. Alva AS, Bhasin A and Vijayaraghavan S. A rare case of methylprednisolone induced hepatitis. *J Clin Exp Hepatol* 2013; 3(Suppl 1): S37.
13. Furutama D, Kimura F, Shinoda K, et al. Recurrent high-dose intravenous methylprednisolone succinate pulse therapy-induced hepatopathy in a patient with multiple sclerosis. *Med Princ Pract* 2011; 20: 291–293.
14. Gutkowski K, Chwist A and Hartleb M. Liver injury induced by high-dose methylprednisolone therapy: a case report and brief review of the literature. *Hepat Mon* 2011; 11: 656–661.
15. Loraschi A, Banfi P, Mauri M, et al. Hepatotoxicity after high-dose methylprednisolone for demyelinating disease. *Clin Neuropharmacol* 2010; 33: 52–54.
16. Maàmour N, Ketari S, Ben Hariz F, et al. Bolus de méthylprednisolone révélant une hépatite auto-immune chez une patiente atteinte de sclérose en plaques. *J Afr Hépatol Gastroentérol* 2009; 3: 195–197.
17. Rivero Fernandez M, Riesco JM, Moreira VF, et al. Recurrent acute liver toxicity from intravenous methylprednisolone. *Rev Esp Enferm Dig* 2008; 100: 720–723.
18. Takahashi A, Kanno Y, Takahashi Y, et al. Development of autoimmune hepatitis type 1 after pulsed methylprednisolone therapy for multiple sclerosis: a case report. *World J Gastroenterol* 2008; 14: 5474–5477.
19. Reuß R, Retzlaff K, Vogel S, et al. Autoimmune hepatitis after high-dose intravenous methylprednisolone pulse in RR-MS. *Central European Journal of Medicine* 2007; 2(3): 356–359.
20. Topal F, Ozaslan E, Akbulut S, et al. Methylprednisolone-induced toxic hepatitis. *Ann Pharmacother* 2006; 40: 1868–1871.
21. Das D, Graham I and Rose J. Recurrent acute hepatitis in patient receiving pulsed methylprednisolone for multiple sclerosis. *Indian J Gastroenterol* 2006; 25: 314–316.
22. Hofstee HM, Nanayakkara PW and Stehouwer CD. Acute hepatitis related to prednisolone. *Eur J Intern Med* 2005; 16: 209–210.
23. Marino M, Morabito E, Altea MA, et al. Autoimmune hepatitis during intravenous glucocorticoid pulse therapy for Graves' ophthalmopathy treated successfully with glucocorticoids themselves. *J Endocrinol Invest* 2005; 28: 280–284.
24. Marino M, Morabito E, Brunetto MR, et al. Acute and severe liver damage associated with intravenous glucocorticoid pulse therapy in patients with Graves' ophthalmopathy. *Thyroid* 2004; 14: 403–406.
25. Salvi M, Vannucchi G, Sbrozzi F, et al. Onset of autoimmune hepatitis during intravenous steroid therapy for thyroid-associated ophthalmopathy in a patient with Hashimoto's thyroiditis: case report. *Thyroid* 2004; 14: 631–634.
26. Weissel M and Hauff W. Fatal liver failure after high-dose glucocorticoid pulse therapy in a patient with severe thyroid eye disease. *Thyroid* 2000; 10: 521.
27. Dumortier J, Cottin J, Lavie C, et al. Methylprednisolone liver toxicity: A new case and a French regional pharmacovigilance survey. *Clin Res Hepatol Gastroenterol* 2017; 41: 497–501.
28. Abramavicius S, Velickiene D and Kadusevicius E. Methimazole-induced liver injury overshadowed by methylprednisolone pulse therapy: Case report. *Medicine (Baltimore)* 2017; 96: 8159.
29. Hidalgo de la Cruz M, Miranda Acuna JA, Lozano Ros A, et al. Hepatotoxicity after high-dose intravenous methylprednisolone in multiple sclerosis patients. *Clin Case Rep* 2017; 5: 1210–1212.
30. Lee HM, Ditelberg JS and Kaplan MM. Pericentral liver cell necrosis associated with the use of high-dose intravenous methylprednisolone. *Dig Dis Sci* 2007; 52: 1533–1534.
31. Kadle MAH and Mazurchik NV. Hepatotoxicity induced by high dose of methylprednisolone therapy in a patient with multiple sclerosis: a case report and brief review of literature. *Open J Gastroenterol* 2016; 6: 146–150.
32. Adamec I, Pavlović I, Pavičić T, et al. Toxic liver injury after high-dose methylprednisolone in people with multiple sclerosis. *Mult Scler Relat Disord* 2018; 25: 43–45.
33. Bresteau C, Prevot S, Perlemuter G, et al. Methylprednisolone-induced acute liver injury in a patient treated for multiple sclerosis relapse. *BMJ Case Rep* 2018; 5: 2018.
34. Rotondo E, Graziosi A, Di Stefano V, et al. Methylprednisolone-induced hepatotoxicity in a 16-year-old girl with multiple sclerosis. *BMJ Case Rep* 2018; 11: e226687.
35. Stephens C, Castiella A, Gomez-Moreno EM, et al. Autoantibody presentation in drug-induced liver injury and idiopathic autoimmune hepatitis: the influence of human leucocyte antigen alleles. *Pharmacogenet Genomics* 2016; 26(9): 414–422.
36. Andrade RJ, Robles M and Lucena MI. Rechallenge in drug-induced liver injury: the attractive hazard. *Expert Opin Drug Saf* 2009; 8: 709–714.
37. Nociti V, Biolato M, De Fino C, et al. Liver injury after pulsed methylprednisolone therapy in multiple sclerosis patients. *Brain Behav* 2018; 8(6):e00968.