



Središnja medicinska knjižnica

Adamec I., Pavlović I., Pavičić T., Ruška B., Habek M. (2018) *Toxic liver injury after high-dose methylprednisolone in people with multiple sclerosis*. Multiple Sclerosis and Related Disorders, 25. pp. 43-45. ISSN 2211-0356

<http://www.elsevier.com/locate/issn/22110348>

<http://www.sciencedirect.com/science/journal/22110348>

<http://dx.doi.org/10.1016/j.msard.2018.07.021>

<http://medlib.mef.hr/3505>

University of Zagreb School of Medicine Repository

<http://medlib.mef.hr/>

Toxic liver injury after high-dose methylprednisolone in people with multiple sclerosis

Ivan Adamec¹, Ivan Pavlović², Tin Pavičić², Berislav Ruška², Mario Habek^{1,2}

¹University Hospital Center Zagreb, Department of Neurology, Referral Center for Autonomic Nervous System Disorders, Zagreb, Croatia

²School of Medicine, University of Zagreb, Zagreb, Croatia

Corresponding author:

Mario Habek, MD, PhD

Department of Neurology, University Hospital Center Zagreb

Kišpatićeva 12

HR-10000 Zagreb

Croatia

Phone/Fax: +38512388033; e-mail: mhabek@mef.hr

Word count: 1316

Number of references: 8

Number of figures: 1

Authors' contributions

Study concept and design: Habek. Acquisition of data: Adamec, Pavlović, Pavičić, Ruška, Habek. Analysis and interpretation of data: Adamec, Pavlović, Pavičić, Ruška, Habek. Drafting of the manuscript: Adamec. Critical revision of the manuscript for important intellectual content: Adamec, Pavlović, Pavičić, Ruška, Habek. Administrative, technical, and material support: Adamec, Pavlović, Pavičić, Ruška, Habek.

Financial & competing interest disclosure

None of the authors have relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. No writing assistance was utilized in the production of this manuscript.

Funding

No funding was received for this study.

Highlights

- High-dose methylprednisolone for the treatment of MS may be associated with hepatic adverse events.
- Hepatotoxic effect of high-dose methylprednisolone seems to be an idiosyncratic reaction.
- Dexamethasone may be used in further treatment of MS relapses in such patients.

Abstract

The standard therapy of multiple sclerosis (MS) relapse is high-dose pulse corticosteroid therapy. Although commonly applied and usually well tolerated it may as well carry certain risks for people with MS, the more severe of them being hepatotoxicity. This report describes three cases of acute liver injury following pulse corticosteroid therapy with reference to other possible causative factors. Caution should be exercised when applying high-dose methylprednisolone given the potential liver related adverse events it may cause.

Key words: multiple sclerosis, hepatitis, methylprednisolone

1. Introduction

The standard therapy of multiple sclerosis (MS) relapse is high-dose pulse corticosteroid therapy. Although commonly applied and usually well tolerated it may as well carry certain risks for people with MS (pwMS). The most common patient-reported adverse events are change in taste, flushing, abdominal pain, sleep disturbances and behavioural changes, which can have a substantial impact on every-day activities (Jongen et al., 2016). Even more severe side effects may develop affecting the gastrointestinal, cardiovascular or central nervous system, however, these are usually associated with prolonged steroid application (Shacke et al., 2002). Recently, there have been several reports of pwMS developing hepatitis. The paper by Cacao et al. reports on five pwMS and autoimmune hepatitis (Cacao et al., 2018). What is notable in this report is the fact that four out of five patients were treated with high-dose methylprednisolone before presenting with hepatitis, indicating that drug toxicity served as a trigger in, until then, asymptomatic autoimmune hepatitis. Another recent article described a patient treated for MS relapse developing a methylprednisolone-induced liver injury (Bresteau et al., 2018). Both of the aforementioned papers performed literature searches revealing another 35 cases of MS and autoimmune hepatitis and 12 cases of corticosteroid induced liver injuries in MS patients. We report on three additional cases of acute liver injury following pulse corticosteroid therapy.

2. Case reports

Patient 1. A 37-year old woman developed right optic neuritis in 2008 and was diagnosed with relapsing remitting multiple sclerosis (RRMS) in 2010. She was treated with interferon beta-1a 44 mcg subcutaneously since 2011. In 2012 and in January 2015 she received intravenous high-dose methylprednisolone pulse therapy (1 gram daily for 3 consecutive days) due to relapses. In February 2015 she developed nausea and epigastric pain with blood tests revealing hepatic lesion with AST of 1095 U/L (11-38) and ALT of 2259 U/L (10-36) (Fig. 1). Serological and immunological studies were normal or negative, including anti-HAV IgM, anti-Hbc, anti-Hbs, anti-Hbe, HbsAg, HbeAg, anti-HCV. EBV EBNA, EBV VCA IgG and CMV IgG were positive while EBV VCA IgM and CMV IgG were negative. Interferon was promptly discontinued with a gradual decrease in liver enzyme values. Liver biopsy was

performed revealing centrilobular necrosis with some lymphocytic and eosinophilic infiltration compatible with toxic liver necrosis. She was diagnosed with toxic liver injury caused by interferon. On further follow-up liver enzymes returned to normal and the patient was started on alemtuzumab receiving the first cycle in September of 2015 and the second in September in 2016, both of the times with prophylactic intravenous high-dose methylprednisolone therapy (1 gram daily for 3 consecutive days). Three months after the last dose of alemtuzumab and steroids another increase in liver enzyme was noted with AST of 91 U/L (11-38) and ALT of 140 U/L (10-36) which again resolved spontaneously. Since then the patient has remained stable and has not received further corticosteroid therapy.

Patient 2. A 46-year old woman was diagnosed with RRMS in March 2015 and was started on vitamin D drops, 3000 IU per day. She received intravenous high-dose methylprednisolone pulse therapy (1 gram daily for 3 consecutive days) due to relapse in May 2015. In June 2015 elevated liver enzymes were noted with AST of 74 U/L and ALT of 395 U/L (Fig 2.). Serological studies were negative including anti-Hbc, anti-Hbs, HbsAg, anti-HCV . EBV EBNA, EBV VCA IgG and CMV IgG were positive while EBV VCA IgM and CMV IgG were negative. Immunological studies revealed presence of smooth muscle antibody (SMA) with a titre of 1:160 (negative <1:20). Vitamin D was promptly discontinued and in the following weeks liver enzyme values returned to normal. In April 2016 she experienced a relapse and was treated with intravenous high-dose methylprednisolone therapy (1 gram daily for 3 consecutive days) and subsequently experienced elevation of liver enzymes, AST of 79 U/L and ALT of 134 U/L. Liver biopsy was performed revealing mild diffuse hepatic steatosis. Hepatic enzyme values gradually decreased and the patient was started on glatiramer acetat. She experienced another relapse and was treated with lower-dose intravenous dexamethasone pulse therapy (50 mg for 3 consecutive days) in December 2017 with subsequent transient elevation in liver enzyme values, AST of 54 U/L and ALT of 85 U/L.

Patient 3. A 44-year-old woman was diagnosed with RRMS in 2007. She received intravenous high-dose methylprednisolone therapy (1 gram daily for 3 consecutive days) due to MS relapse in December 2011. In March 2012 she developed jaundice with nausea and anorexia. Liver enzymes were elevated with ALT of 1340 U/L (Fig. 3). Serological and immunological studies were normal or negative, including anti-Hbc, anti-Hbs, HbsAg, anti-HCV as well as EBV and CMV PCR. Liver biopsy demonstrated portoportal and portocentral

necrosis with some lymphocytic infiltration compatible with toxic liver necrosis. Liver enzymes gradually decreased with no specific therapy. The patient was started on glatiramer acetate in 2013 but continued to experience disease activity. Due to further relapses she repeatedly received lower-dose intravenous dexamethasone pulse therapy (16 mg for 5 consecutive days) without a significant increase in live enzyme values. She stopped glatiramer acetate and started natalizumab in 2015. She has since been neurologically stable and has not experienced further liver damage.

3. Discussion

The presented cases emphasize the potential toxic effect of high-dose methylprednisolone treatment of MS relapses. The exact hepatotoxic effect of corticosteroids is not completely elucidated and is proposed to be an idiosyncratic reaction with a latency period of weeks to months (D'Agnolo and Drenth, 2013). Therefore, monitoring liver enzyme values in this period might be warranted to detect this rare but potentially perilous adverse event. Furthermore, patients 1 and 2 were, as well, on interferon and vitamin D therapy, respectively, and it is known that these drugs may cause liver injury which might have produced an add-on effect to methylprednisolone-induced hepatotoxicity. However, as patient 1 had been receiving interferon therapy for four years prior to development of hepatic symptoms we believe this to be mainly methylprednisolone-related. A subsequent more modest rise in liver enzymes following methylprednisolone after a switch from beta-interferon to alemtuzumab suggests there may have been a synergistic hepatotoxic effect of methylprednisolone plus interferon beta.

Pathological finding of liver biopsy from patient 1 has shown centrilobular necrosis, from patient 2 diffuse steatosis and from patient 3 portoportal and portocentral necrosis. All of these patterns have been described in drug-induced liver injury which further substantiates the diagnosis in the presented patients (Kleiner et al., 2014). Infectious hepatitis serology was negative in all of the patients and a thorough screening is mandatory in such cases as toxic hepatitis is mainly a diagnosis of exclusion.

Another important aspect of this report is that two of the patients were treated with lower-dose dexamethasone therapy for relapses after the initial episodes of liver injury causing a modest (Case2) or no rise in liver enzymes. Such cases of pwMS who experienced methylprednisolone-induced liver injury and were subsequently treated with dexamethasone for MS relapses have been described before and it appears to be a safe strategy to avoid repeated hepatic injury (D'Agnolo and Drenth, 2013). As well, dexamethasone's efficacy was assessed in a small double-blind randomized study and has shown an effect comparable to high-dose methylprednisolone for treatment of MS relapses (Milanese et al.,1989).

Finally, the case of patient 2 is significant for positive autoimmune hepatitis markers (SMA) and negative biopsy finding. On one hand, the biopsy results may represent false negative findings. However, the patient's symptoms resolved after withdrawal of corticosteroid therapy which led us to a conclusion that the liver injury was drug-induced and that the presence of SMA was an epiphenomenon given that a proportion of MS patients may have positive immunological tests without a clinical expression of another autoimmune disease (Adamec et al., 2012).

In conclusion, although methylprednisolone represents standard therapy of acute neurological worsening in pwMS it needs to be applied with caution given the potential liver related adverse events it may cause.

References

Adamec I, Bošković M, Škvorc A, Posavec V, Radmilović M, Gabelić T et al. 2012. Do we need broad immunological work-up in all patients with CIS? *J Neurol Sci.* 315:86-8

Bresteau C, Prevot S, Perlemuter G, Voican C. Methylprednisolone-induced acute liver injury in a patient treated for multiple sclerosis relapse. 2018. *BMJ Case Rep.* 2018. pii: bcr-2017-223670. doi: 10.1136/bcr-2017-223670.

Caçõo G, Santos E, Martins Silva A. 2018. Concurrent autoimmune hepatitis in multiple sclerosis. *Mult Scler.* 24:350-353.

D'Agnolo HM, 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.

Jongen PJ, Stavrakaki I, Voet B, Hoogervorst E, van Munster E, Linszen WH et al. 2016. Patient-reported adverse effects of high-dose intravenous methylprednisolone treatment: a prospective web-based multi-center study in multiple sclerosis patients with a relapse. *J Neurol.* 263:1641-51.

Kleiner DE, Chalasani NP, Lee WM, Fontana RJ, Bonkovsky HL, Watkins PB et al.; Drug-Induced Liver Injury Network (DILIN). Hepatic histological findings in suspected drug-induced liver injury: systematic evaluation and clinical associations. *Hepatology.* 2014;59:661-70.

Milanese C, La Mantia L, Salmaggi A, Campi A, Eoli M, Scaioli V et al. Double-blind randomized trial of ACTH versus dexamethasone versus methylprednisolone in multiple sclerosis bouts. Clinical, cerebrospinal fluid and neurophysiological results. *Eur Neurol.* 1989;29:10-4.

Schacke H, Docke WD, Asadullah K. 2002. Mechanisms involved in the side effects of glucocorticoids. *Pharmacol Ther.* 96:23-43.

Figures

Figure 1. Graphical presentation of liver enzymes and steroid therapy in 3 presented patients.

The y-axis representing liver enzyme values in U/L, AST in blue and ALT in red. The x-axis representing time frame of corticosteroid application and liver enzyme dynamics. The green squares representing point in time when intravenous methylprednisolone therapy was given. The orange squares representing point in time when intravenous dexamethasone therapy was given. The bold horizontal line representing the upper limit for liver enzyme reference values.

