Occurrence of Liver Injury with drugs used for Multiple Sclerosis: signals emerging from the FDA Adverse Event Reporting System (FAERS)

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Background: Idiosyncratic drug-induced liver injury (DILI), albeit rare, represents the most common cause for stopping drug development or restricting indications after marketing authorization (Onakpoya et al., 2016). Recently, a case series raised concern on the occurrence of potentially severe DILI with dimethyl fumarate (Muñoz et al., 2017). However, the actual hepatic profile of drugs used in multiple sclerosis (MS) is unknown.

Aim: We assessed the possible association between MS drugs and DILI occurrence by analyzing the FDA Adverse Event Reporting System (FAERS).

Method: FAERS database collects over 12 million of adverse event reports. In this study, we extracted reports (2004-2016) associated with MS drugs, and performed disproportionality analysis (case/non-cases method) by calculating Reporting Odds Ratios (RORs) with 95% Confidence Interval (CI). Considering the heterogeneity of liver damage manifestations, different groups of liver events were created in increasing order of specificity and severity: from the System Organ Class (SOC) “Hepatobiliary disorders”, to the Standardized MedDRA Query (SMQ) “Drug-related hepatic disorders – severe events only”, to customized definitions of “Overall Liver Injury” and “Acute Liver Failure” (ALF) events (Suzuki et al., 2010; Raschi et al., 2014; Raschi et al., 2015). RORs were stratified for sex and adjusted for concomitant drugs with recognized DILI risk.

Results: The SOC, SMQ and ALF analyses showed significant disproportion emerging from different MS medications across the various types of hepatic events: fampridine, glatiramer acetate, interferon beta 1a and 1b and mitoxantrone. In particular, in SMQ analysis, 29 cases of fampridine (ROR=3.23; 95%Cl=2.22–4.68) were retrieved, 195 for glatiramer acetate (1.20;1.04–1.39), 2,265 interferon beta 1a (1.44; 1.35–1.52), 499 interferon beta 1b (2.17; 1.98–2.38) and 127 mitoxantrone (3.14; 2.62–3.76). The ALF query retained 39 cases for glatiramer acetate (1.90; 1.37–2.63), 275 interferon beta 1a (1.38; 1.17–1.62), 74 interferon beta 1b (2.52; 1.98–3.23) and 44 mitoxantrone (8.51; 6.25–11.60). Results were consistent after stratification and ROR adjustment.

Discussion: Our analyses highlight that the majority of MS drugs are associated with disproportionate reporting of liver injury, including well-known agents for DILI risk such as interferon and mitoxantrone. In addition, we found previously unknown associations with fampridine (used as symptomatic) and glatiramer acetate, a non-biotechnological agent potentially causing acute hepatic failure. Stratification in females and adjustment do not modify ROR values, thus increasing the likelihood of a real contribution of MS drugs in DILI occurrence. However, the multifactorial pathogenesis of DILI and MS together with the complex disease-modifying properties of MS drugs warrant further investigation to clarify the underlying mechanistic basis.

Conclusion: Considering the unpredictable nature of DILI, clinicians monitor the potential occurrence of DILI events in MS patients, including hepatic failure and consider, on a case-by-case basis, the potential responsibility of MS drugs when they diagnose hepatic damage.

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