Oral cladribine treatment and idiosyncratic drug-induced liver injury in multiple sclerosis

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ABSTRACT
Background Oral cladribine (OC) is approved for the treatment of highly active relapsing multiple sclerosis. Postmarketing safety assessments have reported rare, but occasionally severe cases of liver injury in temporal association with OC, with pathophysiologic mechanisms still unknown. In the only detailed case report on this topic, idiosyncratic drug-induced liver injury (iDILI) during OC treatment was well characterised for the first time, but occurred in the context of prior high-dose steroid exposure. Although high-dose steroids are known to induce iDILI in patients with multiple sclerosis with a delay of up to 12 weeks, OC was assumed to be the culprit agent for observed liver injury and the role of steroid exposure was not further investigated.

Case Herein, we describe a case of a 35-year-old women treated with high-dose oral prednisolone during the first treatment cycle OC and subsequently developed iDILI. A causality assessment of the role of prednisolone and OC was performed using the updated Roussel Uclaf Causality Assessment Method which also included a negative re-exposure test for OC during the second OC treatment cycle 1 year later.

Conclusion Our observations suggest that prednisolone or interactions between prednisolone and OC are more likely to foster development of iDILI rather than OC treatment itself.

INTRODUCTION
Oral cladribine (OC), a purine analogue, was approved for the treatment of highly active relapsing multiple sclerosis (RMS) in 2017. The recommended cumulative dose is 3.5 mg/kg, administered in 2 yearly treatment cycles, each comprising 2 weeks of treatment within 2 consecutive months.

Postmarketing safety assessments have reported rare, but occasionally severe cases of liver injury in temporal association with OC, whose pathophysiologic mechanisms are as yet unknown.1 2 These cases of liver dysfunction are unexpected as cladribine is not metabolised by the liver.3 4 Recently, the first case report detailing a suspected underlying OC-associated idiosyncratic drug-induced liver injury (iDILI) has been published.5 In that case report, hepatotoxicity occurred within the setting of a previous high-dose methylprednisolone (MP) therapy,5 raising the question whether previous steroid exposure might be a predisposing factor for observed hepatotoxicity or even the culprit agent.

Herein, we describe a similar case of a 35-year-old women treated with high-dose oral prednisolone during the first treatment cycle OC and subsequently developed iDILI. Causality assessment using the updated Roussel Uclaf Causality Assessment Method (RUCAM), which also included a negative re-exposure test for OC during the second OC treatment cycle 1 year later, suggests that prednisolone or interactions between prednisolone and OC may have fostered development of iDILI rather than OC treatment itself.

CASE REPORT
A 35-year-old woman with RMS diagnosed in 2016 and otherwise unremarkable medical history was referred to our multiple sclerosis (MS) centre in April 2021. Her Expanded Disability Status Scale score was 1.5. With the exception of peginterferon beta-1a and a low-dose oestrogen pill, she was not taking any other medications, drugs, herbal or nutritional supplements, or regular alcohol.

Because of recurrence of MRI activity, an escalation of the MS treatment with OC was proposed in August 2021 and treatment with peginterferon beta-1a was discontinued. Baseline blood examinations including complete blood count (CBC) with differential including lymphocyte count and liver tests (LTs) (alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), total bilirubin (BILI) and international normalised ratio (INR)) were normal. Infectious disease
serology was indicative of a past hepatitis A and otherwise unremarkable. The first course of the first cycle of OC treatment (total dosage: 60 mg, body weight 69 kg) was initiated on 4 October 2021. The patient received oral prednisolone (400 mg/day for 3 days) on 27 October 2021, for a suspected relapse which resolved within days. The second course of the first OC treatment cycle (total dosage: 60 mg) was started on 8 November 2021, and completed without complications.

On 14 December 2021, routine laboratory studies revealed acute hepatocellular liver injury in the clinically asymptomatic patient and iDILI was assumed. AST (690 U/L, 19 times the upper level of normal (ULN)) and ALT (912 U/L, 26×ULN) levels were significantly and GGT (71 U/L, 2×ULN) and total BILI (31 µmol/L, 1.3×ULN) slightly elevated. Alkaline phosphatase (ALP) was normal. Coagulation showed mild coagulopathy (INR: 1.3, normal range: 0.8–1.1) and CBC grade 2 lymphopaenia (760 cells/µL). Abdominal ultrasound was normal with no signs of liver disease. Infectious disease serology remained unchanged and/or genome tests revealed no evidence of active hepatitis A, B, C and E. The antinuclear antibody titre (ANA) was positive at 1:80 with negative SP100 and gp210 antibodies, which was considered non-specific. ANA is found in up to 27% of patients with relapsing-remitting MS. Diagnosis of autoimmune or drug-induced autoimmune hepatitis was unlikely, because immunoglobulins (IgA–IgG–IgM) were not elevated and autoantibodies to smooth muscle, liver–kidney microsomes-1 and liver cytosol-1 were negative.

A liver biopsy was performed on 20 December 2021 as is standard practice for an unexplained hepatopathy in our gastroenterology department. The liver biopsy findings were consistent, although not specific for iDILI (figure 1).

Liver enzymes started to decrease on 21 December 2021, while BILI reached its peak level 9 days later (45 µmol/L, 2×ULN). On 18 February 2022, LTs were within normal ranges again.

Because the MS was inactive after the first OC cycle and alternative disease-modifying therapies also posed potential liver-toxic effects, a decision was taken together with the patient to complete the second cycle of OC. Written informed consent was obtained. LTs were in the normal range on initiation of the first course of the second cycle OC on 1 September 2022, with an intentional re-exposure test to 10 mg OC, and continued on 19 September 2022 (total dosage: 50 mg). The final second course of the second cycle of OC began on 17 October 2022 (total dosage 60 mg) in the absence of any change in the closely monitored LTs over the next 4 months (see figure 2 for time-course of LTs).

**DISCUSSION**

iDILI is best defined as a rare, dose-independent adverse hepatic reaction that is unexpected on the basis of the pharmacological action of the administered drug. Similarly, the hepatic metabolism of OC is deemed negligible. The pathogenesis of iDILI is poorly understood, but could likely arise from complex interactions between genetic, non-genetic and environmental factors including drug–drug interactions. Recently, it has been suggested that a common human leucocyte antigen phenotype promotes both MS and iDILI and may help to explain the increased incidence of iDILI found in patients with MS.

In the present case, OC in combination with high-dose steroids during the first treatment cycle, but not without steroids during the second treatment cycle, led to moderate, hepatocellular iDILI, which was diagnosed based on clinical chemistry, liver biopsy findings and after ruling out other differential diagnoses including autoimmune hepatitis.

Regarding causality assessment, we used the updated RUCAM score which is a point-based, standardised and validated tool to estimate the likelihood that iDILI is due to OC or prednisolone treatment. Liver injury was classified as hepatocellular according to an ALT/ALP R ratio

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**Figure 1** Liver biopsy results. Acute hepatitis with necroinflammatory infiltrate and acute pericentral necrosis and bleeding, sinusoidal dilation. Mild cholestasis. H&E staining. Scale bars indicate 500 µm (A) and 200 µm (B).
of >5.7 Considering the negative re-exposure test for OC (~2 points) and the higher points of OC than for oral prednisolone (+2 vs +1 points) for officially labelled drug hepatotoxicity, a RUCAM score of +4 was calculated for OC and +5 for prednisolone, indicating a possible relationship between each drug and iDILI.7 Hepatotoxicity of OC, but not of oral prednisolone, has been officially labelled in the product characteristics in Germany. The higher RUCAM score of prednisolone compared with OC suggests a higher likelihood that prednisolone, rather than OC, was the precipitating factor in the development of iDILI. In fact, pulsed high-dose treatment with the steroid MP, which is structurally closely related to prednisolone, has prospectively been shown to cause liver injury in up to 8.6% of patients treated for MS10 which is a much higher rate than the estimated incidence of OC-associated liver injury of 1:1000 based on UK pharmacovigilance register data.9 Yet, no public information about concomitant steroid treatment is available in the register.

The RUCAM score of +4 we calculated for OC is significantly lower than that of +6 reported by the only published case report on suspected OC-induced iDILI.13 However, no re-exposure test was available in that case report resulting in a higher RUCAM score. Interestingly, the authors excluded previous high-dose MP treatment in their patient as a possible cause of iDILI and did not report the respective RUCAM score. In their opinion, a steroid-induced liver injury was unlikely due to the time lag of 6 weeks after MP administration. It should be noted, however, that a delayed onset of hepatotoxicity of up to 84 days after high-dose MP exposure has already been described in MS and other neurological patients.3–12

We cannot rule out the possibility that interactions between prednisolone and OC may have fostered development of iDILI rather than OC or prednisolone treatment itself. Indeed, several drug-drug interactions have been shown to influence the incidence and/or the severity of iDILI in an in vitro study using monocyte-derived hepatocyte-like cells from 48 patients with iDILI.13 Most iDILI events are thought to be mediated by the adaptive immune system which is activated by the respective drug, its metabolites or sublethal cell stress.13 Even though the exact mechanism remains speculative, it has been hypothesised that drug–drug interactions may lead to a delayed and prolonged immune activation causing iDILI.13 A relationship between the contraceptive oestrogen pill and iDILI seems unlikely because the former was also taken during the negative re-exposure test. The role of the interferon appears to be negligible, as it was discontinued approximately 2 months before OC intake.

In conclusion, OC is a highly efficient treatment option in MS with a favourable overall safety profile. However, concerns have been raised about the hepatotoxic potential of OC in some patients. In our case of iDILI associated with OC and steroid cotreatment, prednisolone received a higher causality score for the development of iDILI than OC. Our case study underlines the need for more information about concomitant steroid exposure in cases of liver injury attributed to OC treatment as well as potential drug–drug interactions with prednisolone and OC.

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