eNeurologicalSci 21 (2020) 100279

Contents lists available at ScienceDirect

eNeurologicalSci

journal homepage: www.elsevier.com/locate/ensci

Case report

Severe lymphopenia after subcutaneous cladribine in a patient with multiple sclerosis: To vaccinate or not?

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ARTICLE INFO

Keywords:
Cladribine
Disease-modifying treatment
Lymphopenia
Adverse event
Influenza A virus
Multiple Sclerosis

ABSTRACT

Objective: To describe a fatal case of influenza A pneumonia in a patient with severe lymphopenia after receiving subcutaneous cladribine to treat her multiple sclerosis (MS).
Methods: Case report.
Results: A 53-year-old woman developed fatal influenza pneumonia associated with grade 4 lymphopenia two months after receiving a total dose of 60mg subcutaneous cladribine. Despite treatment with oseltamivir, her condition deteriorated and the patient passed away after developing respiratory failure.
Conclusion: Cladribine-related lymphopenia is usually mild to moderate, however severe lymphopenia may occur. People with MS, especially those who are immunosuppressed, should be offered the inactivated influenza vaccine annually.

1. Introduction

Cladribine is a synthetic purine nucleoside analogue originally developed as a treatment for haematologic malignancies. More recently, an oral formulation of cladribine (Mavenclad®) has been licensed for treating people with relapsing multiple sclerosis (pwRMS) [1]. We have been using subcutaneously administered (s.c.) cladribine (Litak®) to treat over 210 people with MS (pwMS) since November 2014 [2]. Whilst semi-selective lymphocyte depletion is considered key to the efficacy of cladribine in controlling MS, lymphopenia also leads to adverse risk, mainly of viral infections [3]. Although lymphopenia is usually mild to moderate, a small number of pwMS develop severe lymphopenia [4,5]. We report the case of a woman who developed grade 4 lymphopenia in the context of cladribine treatment for her MS, and died of influenza A pneumonia.

2. Case report

A 53-year-old woman with a 21-year history of RMS, was first diagnosed after an attack of lower limb weakness and numbness. Her only other significant medical history was hypothyroidism. She initially had a relatively mild course of the disease with no restriction in mobility. However, 15 years after disease onset she suffered a severe relapse associated with a new cervical lesion that left her with an Expanded Disability Status Scale (EDSS) score of 9.5. Treatment with natalizumab was started and although she gradually recovered over the following month, her new baseline EDSS score stabilised at 8.5. Eight months into the treatment she became seropositive for JC virus. Whilst her antibody titre remained below 0.9 for 5 years, it then increased up to 1.34. After discussing the risks of no treatment, for example rebound disease activity on natalizumab withdrawal, a decision was made to switch onto a different immunotherapy. Safety checks were successfully addressed and she was started on s.c. cladribine using a treatment schedule developed in-house [6]. At baseline, white blood cell count (WBC) was $8.5x10^9$/L (normal, $4\text{-}11x10^9$/L) and total lymphocyte count (TLC) was $3.6x10^9$/L (normal, $1\text{-}4.8x10^9$/L). In week 1 she received cladribine 10mg s.c. on three consecutive days. TLC at week 4 was $1.9x10^9$/L, and she was given another 10mg of s.c. cladribine on three consecutive days in week 5. At week 6 her TLC was $1.1x10^9$/L. At week 13, she presented to the emergency room with new onset dyspnoea. Her blood pressure was 96/57 mm Hg, pulse rate 81 bpm, respiratory rate 21/min and temperature 35,7°C. Peripheral oxygen saturation was 95% with a FiO2 of 0.5. Crackles were noted in both lower lung fields. Neurological examination showed no new findings compared to her baseline. Blood

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https://doi.org/10.1016/j.ensci.2020.100279
Received 2 June 2020; Received in revised form 7 September 2020; Accepted 30 September 2020
Available online 09 October 2020

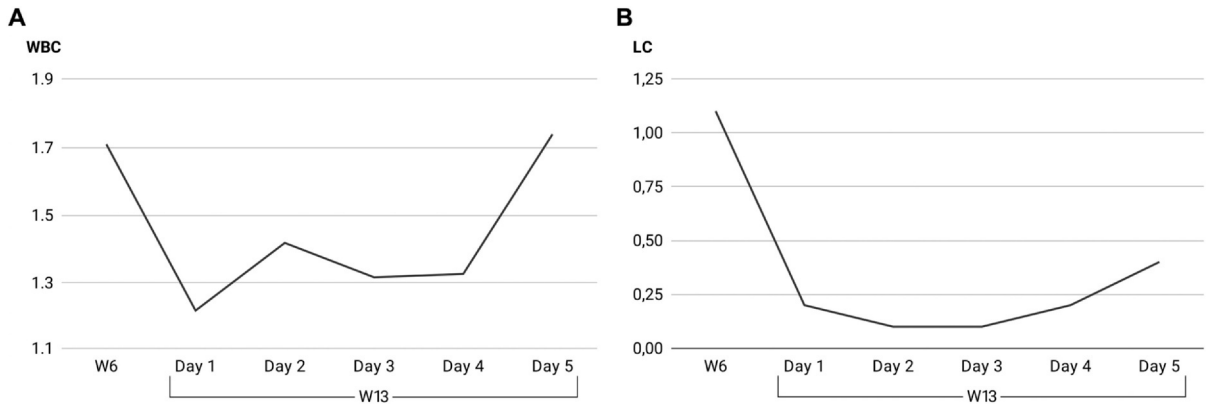

Fig. 1. White blood cells and lymphocytes counts.
Baseline white blood cells (1A) and lymphocytes (1B) counts at week 6 of treatment with cladribine and its course after hospital admission in week 13. LC: lymphocyte count. WBC: white blood cell. W6: week 6. W13: week 13.

tests revealed grade 4 lymphopenia with a TLC of $0.2x10^9$/L. WBC was $4.2x10^9$/L with $0.1x10^9$/L monocytes and $3.9x10^9$/L neutrophils. The time course of her WBC and TLC is shown in Fig.1. Her haemoglobin concentration was 88g/L and platelet count $120x10^9$/L. Her C-reactive protein was 182 mg/L. Chest X-ray revealed patchy opacification within the right lower zone suggesting pneumonia, and treatment with amoxicillin and clarithromycin was started. Influenza A virus target RNA was detected from a nose swab and treatment with oseltamivir was initiated. However, she gradually deteriorated and five days after admission she developed progressive respiratory failure and died. Since influenza vaccination would have coincided with the start of her immunotherapy, she did not receive her seasonal influenza vaccine.

3. Discussion

Cladribine has been shown to be a relatively safe and effective form of therapy for RMS [4]. Its mechanism of benefit is not fully understood but the most striking effect appears to be semi-selective, and relatively long-lasting, depletion of B and T lymphocytes with a particularly significant and long-lasting reduction for memory B cells [3]. Hence, lymphopenia is a regular observation in people treated with cladribine that relates to both its therapeutic mechanism of action as well as the potential associated risk, particularly viral infections or reactivations, such as shingles [3].

A previous study on pwRMS receiving s.c. cladribine reported a decrease of the mean TLC of approximately 40–45% compared to baseline [7]. The medication was administered monthly for six months, and an additional injection was given three months later. TLC reached a nadir approximately six months after treatment initiation with counts recovering thereafter, and no cases of grade 3 or grade 4 lymphopenia occurred [7]. Bearing in mind differences in the dosing schedule between studies, these results are comparable with data from our centre where only 2% of patients developed grade 3 lymphopenia [2]. However, the case presented here is a cautionary tale that grade 4 lymphopenia can occur even after following a personalised dosing protocol designed to prevent severe lymphopenia [6]. Another factor that could have contributed to lymphopenia in our patient is the influenza virus infection. However, grade 4 lymphopenia such as the one experienced by our patient is rare in otherwise immunocompetent patients with influenza virus infection [8,9].

Two large trials of oral cladribine in pwRMS and patients with a first clinical demyelinating event (CLARITY and ORACLE MS, respectively) evaluated the clinical effectiveness and safety profile of oral cladribine tablets [4,5]. In both studies, most of the lymphopenia events were classified as mild or moderate and occurred more frequently with higher doses. The CLARITY extension study confirmed these findings [10]. Additionally, a post-hoc analysis of the CLARITY and CLARITY extension studies showed no cases of grade 4 lymphopenia in pwRMS treated with cladribine tablets 3.5 mg/kg using a dosing schedule that took into account the TLC (i.e. Grade 0 lymphocyte count at the start of treatment and a maximum of grade 1 at the start of the second cycle) [10].

The WHO recommends that people who are most at risk of developing serious complications from influenza infection be vaccinated every year before the season begins. Clinical risk groups who should receive the influenza immunisation include adults with chronic neurological conditions, such as MS, and/or those who are immunosuppressed due to disease or treatment [11]. The patient reported here started immune reconstitution treatment with cladribine at a time when her seasonal influenza vaccination was due, and a decision was made to delay her immunisation. Whilst the inactivated influenza vaccine can generally be considered safe at any point of treatment, it will remain unclear whether this patient would have mounted an effective immune response during TLC depletion. Recent data suggest that the inactivated influenza vaccine will still provide some protection in patients already receiving B cell depletion therapy [12]. However, the vaccination response during lymphocyte depletion in pwMS treated with cladribine is uncertain and should be studied in a formal research protocol. The live attenuated influenza vaccine is given as a nasal spray and is contraindicated in people who are clinically severely immunocompromised and in their close contacts [11,13]. Cladribine treatment should not be initiated within four weeks after vaccination with an attenuated live vaccine and pwMS treated with cladribine should not receive live vaccines until their WBC and TLC have returned to within their normal reference ranges [14]. In line with WHO guidance and the UK national influenza immunisation programme [11,13], we recommend annual influenza vaccination with inactivated, but not live vaccines, in pwMS who have received cladribine and whose immune system is compromised. Nevertheless, inactivated vaccines should ideally be administered at least two weeks before commencing immunosuppressive treatments [13]. Influenza immunisation should also be recommended for household members and carers of pwMS, as well as healthcare and social care workers in direct contact with pwMS [13].

4. Conclusion

We report a case of lethal influenza A infection associated with grade 4 lymphopenia in an MS patient receiving s.c. cladribine. This incident occurred despite using a personalised dosing schedule that was adapted to both body weight and individual TLC. Influenza vaccination may de-risk the use of cladribine further. As some immunocompromised patients may have a suboptimal immunological response to the vaccine, the inactivated influenza vaccine should

ideally be administered prior to treatment initiation with cladribine.

Declaration of Competing Interest

MM-C has received presentation fees or grants from Sanofi-Genzyme and UCB Pharma. DB has received consultancy or presentation fees from Canbex Therapeutics, Japan Tobacco, Merck Roche and Sanofi Genzyme. KS has received presentation fees, meeting support or scientific advisory fees from Biogen, Lipomed, Merck Serono, Novartis, Roche and Teva. GG has received consultancy, presentation fees or grants from AbbVie Biotherapeutics, Bayer Healthcare, Biogen, Canbex, Celgene, Ironwood, Japan Tobacco, Novartis, Roche, Sanofi-Genzyme, Synthon, Takeda, Teva and Vertex. No other disclosures were reported.

Acknowledgements

We wish to thank ECTRIMS (European Committee for Treatment and Research in Multiple Sclerosis) for supporting SR through their MS clinical training fellowship programme.

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