MSJ Experimental Translational Clinical

Short Report

Short-term outcomes of pediatric multiple sclerosis patients treated with alemtuzumab at a Canadian University multiple sclerosis clinic

Multiple Sclerosis Journal—Experimental, Translational and Clinical

January–June 2020, 1–3

DOI: 10.1177/2055217320926613

David Jure Hunt and Anthony Traboulsee

Abstract

There is a lack of literature documenting the use of alemtuzumab in pediatric multiple sclerosis (MS) patients. Here we describe a 16-year-old and a 17-year-old patient receiving alemtuzumab and being followed for 37 months and 20 months, respectively. Both patients experienced a 1.0 decrease in Expanded Disability Status Scale since initial alemtuzumab infusion and had stable disease. No serious infusion reactions, infections, or definite relapses were recorded on follow-up. Alemtuzumab has been relatively well-tolerated and effective; however, larger, longer-term studies are necessary to understand the specific risks and benefits of alemtuzumab in pediatric MS.

Keywords: Alemtuzumab, disease-modifying therapies, immunology, multiple sclerosis, second-line treatment, teriflunomide

Date received: 29 October 2019; accepted: 4 April 2020

Introduction

Despite the paucity of completed phase 3 trials for treatment interventions in pediatric-onset multiple sclerosis (POMS), more patients are being treated with new-generation disease-modifying therapies (DMTs).[1,2] While there has been a recent report of alemtuzumab use in POMS patients,[3] there is an absence of literature on alemtuzumab use in POMS patients under the age of 18. A phase 3 trial evaluating alemtuzumab in POMS is set to be completed in 2026 (NCT03368664). Due to this delay, it is important that smaller studies help inform physicians in the meantime in using this highly efficacious therapy, as have been previously done for most DMTs in the POMS population.[1,2,4] Here we report alemtuzumab therapy in two POMS patients under the age of 18 and comment on safety and effectiveness following infusion.

Methods

A retrospective chart review was performed at the University of British Columbia multiple sclerosis (MS) clinic to identify MS patients who received alemtuzumab prior to their 18th birthday and consented to retrospective chart review. Data collection forms captured date and symptoms at MS onset, history of DMT use, history of relapses, Expanded Disability Status Scale (EDSS) changes, infections post-alemtuzumab, and laboratory monitoring from the patients' electronic medical records.

Patient 1

A 14-year-old male presented in October 2014 with left leg weakness and partial foot drop. Fluid-attenuated inversion recovery imaging captured several lesions, including one in the right motor strip accounting for the left lower limb symptoms (Figure 1(a)). One year later, the patient developed new brain lesions in the absence of clinical relapse, and both the clinical and radiological findings supported a diagnosis of MS.[5] Due to the rapid accumulation of disease burden, alemtuzumab was the preferred first-line treatment, but drug coverage was not approved. With the absence of phase 3 trials for treatment interventions in POMS at the time, teriflunomide (14 mg/day) was started based

Correspondence to:
Anthony Traboulsee, 2211 Wesbrook Mall, Room S199, Vancouver V6T 2B5, Canada.
Traboulsee.assistant@ubc.ca

David Jure Hunt, Faculty of Medicine, University of British Columbia,Canada

Anthony Traboulsee, Division of Neurology, Department of Medicine, University of British Columbia, Vancouver, Canada

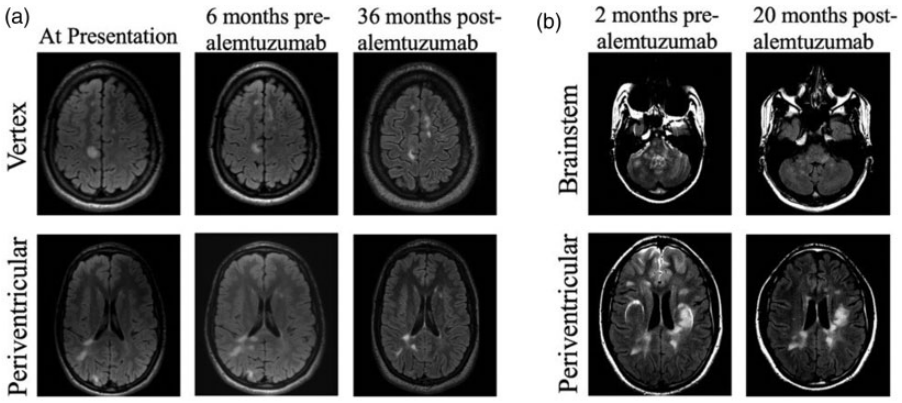

Figure 1. Axial fluid-attenuated inversion recovery images of Patient 1 and Patient 2.
(a) At presentation (October 2014), six months prior to starting alemtuzumab (January 2016), and 36 months after starting alemtuzumab therapy (June 2019).
(b) Two months prior to starting alemtuzumab (October 2017), and 20 months after starting alemtuzumab (August 2019). The artifact in the periventricular images pre-alemtuzumab is due to the patient's dental braces.

primarily on patient preference. Over the following year, the patient's EDSS increased from 2.0 to 2.5 following a brainstem relapse, with seven new brain and brainstem lesions. The 16-year-old patient was started on alemtuzumab in June 2016 (60 mg over 5 days) and received a second course one year later (36 mg over 3 days). The infusions were unremarkable for significant adverse reactions. In 37 months of follow-up, the patient has not developed secondary autoimmunity, radiological worsening of disease, or clinical relapse, and has had a stable EDSS of 1.5 since August 2016.

Patient 2

A 16-year-old male, diagnosed with POMS in South America at age 8, developed a relapse in February 2017 with vertigo, diplopia, and facial numbness, and was treated with intravenous (IV) steroids for 3 days. Two more brainstem relapses with radiological worsening occurred in May and August 2017, both of which were treated with IV steroids. His EDSS at this time was 2.5. Anti-MOG tests were not available at the time of investigation; however, both lesion quantity and location, as well as the disease course, supported the initial diagnosis of MS.[5,6] He was briefly placed on teriflunomide (14 mg/day) but was transitioned to alemtuzumab after drug coverage approval in December 2017. The initial (60 mg over 5 days) and subsequent infusions one year later (36 mg over 3 days) were unremarkable for significant infusion reactions. Six months after initiating alemtuzumab, the patient developed a presumed viral illness, with increased fatigue for two weeks and mild headache for five days. He had no fever or signs of meningeal involvement and had complete recovery. Eight months after starting alemtuzumab, he retrospectively reported increased fatigue and non-specific balance and coordination issues that resolved within one week without the use of steroids. There was no evidence of radiological worsening on follow-up one year after this report of transiently decreased coordination and fatigue (Figure 1(b)). Moderate asymptomatic neutropenia (absolute neutrophil count (ANC) of 0.6×10^9/L) developed in May 2019, which recovered to an ANC of 1.2×10^9/L the following month and has remained at this level since last follow-up in July 2019. In June 2019, the patient had an EDSS of 1.5.

Discussion

After two courses of alemtuzumab and 37 and 20 months of follow-up, both patients have had a 1.0 decrease in EDSS and currently have stable disease. Since initiating alemtuzumab, there have been no serious infections or MS relapses. On routine follow-up, Patient 2 retrospectively reported transiently decreased coordination and fatigue that resolved within one week, eight months after beginning alemtuzumab. Due to the lack of radiological worsening or new neurological symptoms, a return back to baseline, and the inability to rule out fever or infection at this time, we did not interpret this as a relapse. While the sample size is limited, these cases document the successful treatment of two POMS patients using alemtuzumab with no serious short-term adverse events.

In the phase 3 trials for alemtuzumab in adult-onset MS (AOMS), moderate neutropenia (ANC ≥ 0.5 to $<1.0 \times 10^9$/L) was observed in 11/798 participants

in the second year after initial infusion.[7] Patient 2 developed moderate afebrile neutropenia 18 months after starting alemtuzumab that may be of autoimmune origin. As neutrophil counts recovered to a less depleted state the following month, further investigations or treatment have not been pursued, but confirm the need for monthly hematological monitoring in POMS patients post-alemtuzumab.

The high risk of secondary autoimmunity associated with alemtuzumab often relegates it to a second- or third-line DMT. The mechanism driving secondary autoimmunity is unknown; however, high pre-treatment IL-21 levels and an elevated B cell:T regulatory cell ratio following partial lymphocyte reconstitution have been hypothesized as contributing factors.[8,9] After bone marrow ablation and transplant, T cells are reconstituted two to three times more rapidly in children compared with adults.[10] This observation may be important in the context of alemtuzumab, due to it causing potent lymphocyte depletion. Laboratory monitoring post-alemtuzumab does not routinely capture lymphocyte subsets, so we cannot comment on T cell dynamics in POMS patients post-alemtuzumab. Future studies should evaluate if POMS and AOMS patients differ with regards to B and T cell reconstitution following alemtuzumab therapy, and the effect this has on secondary autoimmunity and infection.

Author contributions

David Jure Hunt: data acquisition, analysis and interpretation; drafted the manuscript; study design; and conceptualization. Anthony Traboulsee: data interpretation; manuscript review; study design; and conceptualization.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: David Jure Hunt has no conflicts of interest to declare. Anthony Traboulsee has received grant funding from the Multiple Sclerosis Society of Canada, Canadian Institute for Health Research, F Hoffmann-La Roche, and Sanofi Genzyme; he has also received honoraria or travel grants from Teva Canada Innovation, F Hoffmann-La Roche, Merck/EMD Serono, Sanofi Genzyme, and Chugai Pharmaceuticals.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

David Jure Hunt https://orcid.org/0000-0003-0842-7538

References

1. Krysko KM, Graves J, Rensel M, et al. Use of newer disease-modifying therapies in pediatric multiple sclerosis in the US. *Neurology* 2018; 91: e1778–e1787.
2. Otallah S and Banwell B. Pediatric multiple sclerosis: an update. *Curr Neurol Neurosci Rep* 2018; 18: 76.
3. Margoni M, Rinaldi F, Miante S, et al. Alemtuzumab following natalizumab in highly active paediatric-onset multiple sclerosis. *Mult Scler J Exp Transl Clin* 2019; 5: 2055217319875471.
4. Rensel M. Long-term treatment strategies of pediatric multiple sclerosis, including the use of disease modifying therapies. *Children (Basel)* 2019; 6: pii E73.
5. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol* 2018; 17: 162–173.
6. Jurynczyk M, Geraldes R, Probert F, et al. Distinct brain imaging characteristics of autoantibody-mediated CNS conditions and multiple sclerosis. *Brain* 2017; 140: 617–627.
7. Baker D, Giovannoni G and Schmierer K. Marked neutropenia: significant but rare in people with multiple sclerosis after alemtuzumab treatment. *Mult Scler Relat Disord* 2017; 18: 181–183.
8. Baker D, Herrod SS, Alvarez-Gonzalez C, et al. Interpreting lymphocyte reconstitution data from the pivotal phase 3 trials of alemtuzumab. *JAMA Neurol* 2017; 74: 961–969.
9. Jones JL, Phuah CL, Cox AL, et al. IL-21 drives secondary autoimmunity in patients with multiple sclerosis, following therapeutic lymphocyte depletion with alemtuzumab (Campath-1H). *J Clin Invest* 2009; 119: 2052–2061.
10. Small TN, Papadopoulos EB, Boulad F, et al. Comparison of immune reconstitution after unrelated and related T-cell-depleted bone marrow transplantation: effect of patient age and donor leukocyte infusions. *Blood* 1999; 93: 467–480.