Alemtuzumab-induced remission of multiple sclerosis-associated uveitis

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Abstract

Purpose: To report a case of multiple sclerosis (MS)-associated uveitis refractory to conventional immunosuppressants, with subsequent remission following treatment with alemtuzumab.

Methods: Case report. Patient was treated with intravenous alemtuzumab, a lymphocyte depleting anti-CD52 monoclonal antibody that has recently been approved for use in relapsing MS.

Results: A 17-year old female presented with bilateral optic neuritis and subsequently bilateral intermediate uveitis and secondary macular oedema. She was diagnosed with active relapsing MS for which she received treatment with alemtuzumab. The intraocular inflammation previously refractory to conventional immunosuppressants responded to alemtuzumab, inducing remission.

Conclusions: To our knowledge this is the first such report of alemtuzumab treatment in MS-associated ocular inflammatory disease and may demonstrate a potential utility for this drug in related conditions.

Keywords:

Multiple Sclerosis

Uveitis

Alemtuzumab

Intraocular inflammation

Introduction

Alemtuzumab is an anti-CD52 monoclonal antibody recently approved for use in relapsing multiple sclerosis (MS). It has been shown to be highly effective at reducing clinical relapse rates and in some studies slowing, or even reversing, disability outcomes.[1-3] CD52 is present on approximately 5% of the cell surface of lymphocytes and is also expressed, albeit at lower levels, on monocytes, macrophages, eosinophils and NK cells.[4,5] Treatment with alemtuzumab results in a rapid depletion of circulating lymphocytes with subsequent beneficial reconstitution.[6]

Optic neuritis is the most commonly associated ocular manifestation of MS, however intraocular inflammation is reported to occur in 0.4% to 26.9% of patients.[7] Intermediate uveitis is the most common type but all anatomic sub-types of uveitis have been reported.[7,8] Secondary complications including cystoid macular oedema can also occur; at which point the disease is difficult to manage and may be refractory to standard immunosuppressive treatments.[7,8] Although the exact prevalence of macular oedema in MS-associated uveitis is unknown, it is estimated to affect 37% of patients with MS-associated intermediate uveitis.[8] Alemtuzumab has previously been shown to be beneficial in ocular inflammatory disease initially in a single case refractory to treatment and complicated by standard therapeutic side effects, then a case series of 10 patients with systemic autoimmune disease and associated ocular inflammatory disease and finally in 18 patients with Behçet's disease.[9-11]

Although the association between MS and uveitis is well established, the effect of alemtuzumab on MS-associated intraocular inflammation is unknown. We present a patient with MS and alemtuzumab-induced remission of uveitis.

Case report

A 17-year-old female presented with an episode of optic neuritis (ON) affecting the right eye, followed by ON of the left eye 10 months later. One month after this she was diagnosed with bilateral intermediate uveitis with peripheral retinal vasculitis and associated macular oedema (figure 1). Routine uveitis screening was performed to exclude common systemic associations. Syphilis serology, antinuclear and antinuclear cytoplasmic antibodies and QuantiFERON® Gold tests were negative, and a chest X-ray was unremarkable. Following initial screening she was referred for a neurological opinion. Subsequent cranial magnetic resonance imaging (MRI) was normal with an unremarkable cerebrospinal fluid examination other than positive CSF oligoclonal bands unpaired in a serum sample. For her ophthalmological symptoms the patient commenced immunomodulatory treatment with a combination of oral prednisolone and cyclosporine, which was then switched to tacrolimus.

Three years after initial presentation the patient experienced transient limb sensory symptoms with a repeat cranial MRI scan demonstrating a single, left sided deep white matter lesion as well as non-specific abnormal cord signal at C6. In the following 3 years the patient experienced a further 5 episodes of transient neurological dysfunction including 4 in one 12-month period. A further MRI demonstrated new lesions in the medulla, cerebellum, anterior pons and in the left periventricular region and a diagnosis of relapsing-MS was made. Of note, high resolution computerised tomography of the thorax and anti-aquaporin-4 antibodies were negative.

As a result of highly active disease, alemtuzumab was commenced with a 5-day treatment of 12mg/day intravenously with a routine, second, 3-day course of alemtuzumab 12 months later. Following a further clinical relapse 3 years after treatment initiation and repeat imaging demonstrating new and enhancing lesions the patient received a 3rd, 3-day course of alemtuzumab.

Ophthalmological management has proved difficult throughout with the patient requiring regular courses of oral steroids and been intolerant/failed treatment with cyclosporine, tacrolimus and mycophenolate mofetil after. In particular, the left eye required periocular and intraocular steroids (Figure 2). After the first course of alemtuzumab, macular oedema was present in the left eye despite

two orbital floor injections of triamcinolone for approximately 6 months after infusion. Following this, visual acuity and central macular thickness remained stable until the second course of alemtuzumab. Following the second treatment, the patient experienced a flare in symptoms lasting approximately 3 months. However, stabilisation of disease was again observed for a period of 9 months. Macular oedema subsequently worsened, was difficult to control and required an intraocular dexamethasone implant in order to control the inflammation in the left eye. Following this she received the 3rd course of alemtuzumab and despite the effect of intraocular dexamethasone wearing off she has remained well controlled for the last 12 months not even requiring oral steroids. Recent ophthalmological review has demonstrated stable vision with OCT showing a healthy macular in the right eye and minute cysts in the left eye. Of note, the patient has developed Graves' disease with associated thyroid eye disease following the second course of alemtuzumab; a well described autoimmune side effect of the drug.

Discussion

We present a case of MS-associated uveitis refractory to conventional immunomodulatory therapy with subsequent remission achieved following alemtuzumab treatment. Alemtuzumab has previously been used for treating intraocular inflammation, albeit with scarce case series and case reports in the literature but with promising results.[9-11] In contrast to previously reported cases in which patients received 1 cycle of treatment, our patient received 3 cycles of treatment. In our patient the macular oedema resolved and improvement was maintained for approximately 6 months after the addition of alemtuzumab without other significant changes on the systemic or local treatment after the first and the second infusion of alemtuzumab. Similarly in a case report using alemtuzumab for undifferentiated unilateral panuveitis, the patient experienced 2 flare-ups of intraocular inflammation during the 4 months after treatment with posterior induced remission, which coincides with the response in our patient.[10]

Uveitis is traditionally considered an autoimmune disease initiated by loss of immune tolerance to retinal proteins and tyrosinase-related products, orchestrated by two subsets of CD4+ T cells: Th1 and Th17 cells.[12] The mechanism of action of alemtuzumab helps to explain its potential effect on uveitis. Following treatment with alemtuzumab there is a rapid and profound reduction in lymphocytes with recovery varying by cell type. B lymphocytes recover the quickest, followed by CD8+ and CD4+ T lymphocytes.[13-15] The population of lymphocytes is altered following treatment, with regulatory T cells (Tregs) dominating the milieu, which is thought to be beneficial.[16-18] This time to repopulation with Tregs may explain the delayed effect seen on ocular disease in our case.

The main side effects of alemtuzumab are well established and relate to acquired autoimmune diseases, with a particular predilection for the thyroid gland.[19] Although serious, these side effects are predictable and can be anticipated with an active surveillance program. Despite these side effects, this case demonstrates the potential utility of alemtuzumab for treatment of MS-associated uveitis, which was more efficacious than all other standard immunomodulatory treatment used. Patients with

concomitant MS and uveitis may therefore expect improvement in ocular symptoms following treatment with alemtuzumab.

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Figure Captions:

Fig 1 Fluorescein angiography (FA) and optical coherence tomography (OCT) at presentation. Top figures show FA for the right and left eye with peripheral vascular leakage, macular leakage and hyperfluorescent optic disc in both eyes. Inferior figures show the OCT at the level of the fovea disclosing bilateral macular oedema. A and C corresponds to images of the right eye and B and D to the left eye.

Fig 2 Visual acuity (VA) and central macular thickness (CMT) diagrams, showing the evolution of both parameters during the follow-up. Arrows sign the changes on treatment according to the superior legend. Vertical lines in the graphs represent a time interval of approximately 6 months. RE: right eye; LE: left eye; VA: visual acuity; CMT: central macular thickness.