 References


 Footnotes and Disclosure

The authors have no proprietary or commercial interest in any materials discussed in this article.

 Branch retinal vein occlusion associated with fingolimod treatment for multiple sclerosis

Visual manifestations are the presenting symptom in approximately 20% of patients with multiple sclerosis (MS). The management of relapsing-remitting forms of MS relies on disease-modifying drugs to reduce the frequency of recurrent episodes and slow progression.

Fingolimod is an orally administered medication that modulates the immune response by sequestering thymocytes and lymphocytes in lymph nodes through the activation of sphingosine-1-phosphate-1 (S1P) receptors.1 Reported adverse events include arterial vasospasm, bradycardia, infections, and macular edema (ME). We report here a case of MS treated with fingolimod resulting in a branch retinal vein occlusion (BRVO) that resolved with discontinuation of the medication.

A 31-year-old woman noted a 5-day history of decreased vision in her right eye. She denied pain with eye movement. She had a 16-year history of MS previously treated with interferon beta-1A and glatiramer acetate. Her MS regimen at the time of presentation included only fingolimod 0.5 mg for the previous 10 months. She denied oral contraceptive, tobacco, alcohol, or illicit drug use and reported no personal or family history of a coagulation disorder. Surgical history was significant for a splenectomy performed after abdominal trauma 18 years before the current presentation.

Her best-corrected visual acuity was 20/60-1 and 20/20 in the right and left eyes, respectively. Pupils were normal, with no relative afferent pupillary defect, dyschromatopsia, or brightness desaturation. Visual fields were full to confrontation. Dilated fundus examination of the right eye demonstrated disc and retinal hemorrhages and venous congestion consistent with a limited BRVO; optical coherence tomography (OCT) of the macula revealed ME (Fig. 1). The left eye was unaffected. Subsequent serological evaluation revealed a normal coagulation panel, all peripheral blood counts were within the normal range, and there were no other vasculopathic comorbidities. We suspected a potential association with fingolimod treatment, and the medication was discontinued the same day. No other form of treatment was initiated.

On follow-up examination 3 weeks later, acuity improved to 20/20 in the affected eye with near-complete resolution of the BRVO and intraretinal fluid (Fig. 2). The patient was transitioned to dimethyl fumarate with no reported issues on 1-year follow-up.

To date, there has been one reported case of a BRVO in a patient taking fingolimod. The reported patient was much older (an independent risk factor for BRVO), and a causal relationship between fingolimod and vein occlusion could not be clearly established as the patient received treatment with an intravitreal ranibizumab injection.2 In our case, fingolimod was discontinued, and relatively rapid spontaneous resolution of the BRVO was observed. The timing of resolution also coincided with fingolimod and fingolimod phosphate pharmacokinetics with an established half-life of 6–9 days.3 For a typical BRVO, retinal hemorrhages and intraretinal edema usually take many months to resolve.

The mechanism by which fingolimod could induce a vaso-occlusive event is speculative. Fingolimod is converted to fingolimod phosphate and binds to S1P receptor subtypes as an S1P analogue.1 Lymphopenia is mitigated by initial

Fig. 1—Fundus photography of the right eye demonstrating tortuous and congested veins (yellow arrows), intraretinal hemorrhages (white arrows), and disc congestion (arrowhead) consistent with a superior branch retinal vein occlusion, with inset optical coherence tomography image (horizontally oriented section through the fovea) showing intraretinal edema just superior to the foveal centre (asterisk).
SIP1 receptor activation and receptor internalization with disruption of normal receptor recycling. Without functional receptor expression, lymphocytes are sequestered in peripheral lymph nodes and unable to enter the systemic circulation. Tissue-specific expression of alternative SIP receptors also mediates a number of other cellular functions, including the upregulation of endothelial adhesion molecules and the disruption of intercellular adhesions.\(^4\) It is plausible that these unintended effects increase vascular adhesion, promote hemodynamic stasis, and degrade vessel integrity, resulting in adverse peripheral vascular events, ME, and retinal vein occlusions.

Our patient’s history of splenectomy may also be relevant. Having undergone a splenectomy increased her vaso-occlusive risk, including that of a retinal vein occlusion. The effectiveness of fingolimod in an asplenic patient should also be considered, given that fingolimod’s mechanism of action is to sequester lymphocytes in lymphoid tissue. Though animal studies of fingolimod in mice with splenectomies have demonstrated reductions in circulating peripheral lymphocytes, asplenia may represent a unique condition that should be considered in humans.\(^5\)

In summary, retinal vein occlusions should be considered as a potential adverse event in patients taking fingolimod. Cessation of fingolimod can be sufficient to allow for spontaneous resolution of venous occlusions and associated ME, avoiding potentially invasive treatments. The value of dilated retinal examination in addition to macular OCT evaluation in fingolimod-treated patients is emphasized by the fact that our patient demonstrated ME on OCT, indistinguishable for the typical OCT appearance of fingolimod-associated ME without associated BRVO.

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References


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Nomenclature: thyroid-associated orbitopathy, Graves ophthalmopathy, or thyroid eye disease?

Nomenclature in medicine affects scientific accuracy, patient perceptions, communication, and information retrieval. We opine that the terms “thyroid eye disease” (TED) or “Graves ophthalmopathy” (GOp) used to designate the most common nontraumatic orbitopathy we encounter as ophthalmologists are inappropriate; a better appellation for this autoimmune orbitopathy usually associated with dysthyroidism is “thyroid-associated orbitopathy” (TAO).

The reasons to adopt the nomenclature of TAO include (i) scientific accuracy, (ii) the disadvantages of eponyms, and (iii)