Bilateral Cotton Wool Spots After Use of an Endothelin Receptor Antagonist

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ABSTRACT: Ambrisentan (Letairis; Gilead Sciences, Foster City, CA) is an endothelin receptor antagonist approved by the U.S. Food and Drug Administration for the treatment of pulmonary arterial hypertension. The authors describe the occurrence of bilateral cotton wool spots soon after initiation of ambrisentan treatment in a 29-year-old woman. Fluorescein angiography, optical coherence tomography, and fundus autofluorescence were performed. After discontinuation of ambrisentan, the cotton wool spots resolved without recurrence. To the authors’ knowledge, this is the first report of retinopathy in the form of cotton wool spots associated with the use of an endothelin receptor antagonist.

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INTRODUCTION

The differential diagnosis of cotton wool spots is broad, including but not limited to diabetes mellitus, hypertension, collagen vascular diseases, HIV, anemia, blood cell dyscrasias, embolic events, coagulopathy, interferon pharmacotherapy, giant cell arteritis, trauma, and radiation therapy.1,2 A manifestation of microvascular retinal disease, ischemia of the retinal nerve fiber layer leads to accumulation of axonal debris,3 visible on ophthalmic examination as a white lesion known as a cotton wool spot.

This is the first report describing the occurrence of cotton wool spots after initiation of ambrisentan (Letairis; Gilead Sciences, Foster City, CA), a selective endothelin receptor antagonist used in the treatment of pulmonary arterial hypertension.
small nerve fiber layer hemorrhages were also noted. Fluorescein angiography revealed no early perfusion defect but demonstrated focal areas of late hyperfluorescence and leakage in the distribution of the cotton wool spots (Figure 2). Optical coherence tomography highlighted edema at the inner retinal layers (Figure 3).

The complete laboratory work-up to rule out collagen vascular disease and diabetes mellitus was unremarkable. Given the temporal relationship between the patient’s symptoms and the initiation of ambrisentan, medication side effect was considered and the patient was followed up in clinic.

At the 2-week follow-up examination, best corrected visual acuity was 20/25 in both eyes and resolution of the cotton wool spots was observed on dilated fundus examination (Figure 4). Vital signs at follow-up remained stable, with blood pressure of 140/85 mm Hg and mean arterial pressure of 103.3 mm Hg.

The patient was subsequently started on tadalafil 40 mg daily as an alternative treatment for pulmonary arterial hypertension, without recurrence of visual symptoms or cotton wool spots on clinical examination.

DISCUSSION

Endothelin is an endothelium-derived peptide found in three isoforms (ET-1, ET-2, ET-3) that act on three receptors (ETA, ETB1, and ETB2). The ET-1 isoform in particular has been implicated in vascular disease. Actions of endothelin on ETA and ETB2 are thought to promote vascular remodeling and vasoconstriction, whereas action on ETB1, in a counter-regulatory manner, promotes vasodilation and clear-
ance of ET-1 from circulation.\(^7\) Endothelin has known effects in the eye,\(^8\) and its role as a potential therapeutic target for common conditions such as diabetic retinopathy\(^9\) and open-angle glaucoma\(^10,11\) has been proposed.

Ambrisentan is a selective ETA endothelin receptor antagonist approved by the FDA for the treatment of pulmonary arterial hypertension. Clinical trials have demonstrated delay in clinical worsening and improvement in exercise capacity for patients with World Health Organization functional class 2 or 3 pulmonary arterial hypertension.\(^12-14\) Its most notable adverse effects include liver toxicity and birth defects. Ocular adverse effects were not noted while under investigation in clinical trials.\(^13,14\)

Given the known functionality of the endothelin receptor pathways, it is unusual that ETA receptor antagonism seemed to impair rather than improve retinal vascular hemodynamics in this patient, resulting in ischemia and hemorrhage of the nerve fiber layer. It is also unusual that the patient reported symptoms of visual blurring. Prior reports have noted scotomata and visual field defects correlating to cotton wool spots,\(^15,16\) but visual symptoms are not typical. The temporal relationship of the patient’s findings with initiation of ambrisentan and rapid resolution of such findings after discontinuation suggest a causal role.

Whether this could be a primary mechanism and side effect of the drug or a secondary effect is not known. As mentioned above, action of endothelin on ETB1 promotes vasodilation and clearance of ET-1, serving as a counter-regulatory effect to ETA receptor-mediated vasoconstriction. The ETA/ETB selectivity of ambrisentan has been shown to range from 29:1 to 4000:1, with a ratio of at least 2000:1 necessary for selective action in humans.\(^17\) One hypothesis in this patient may be that ambrisentan nonselectively antagonized ETB1 receptors, blunting its vasoprotective effect. Ambrisentan use has been associated with increased plasma levels of ET-1, further suggesting a nonselective action and blunted effect of the ETB1 receptor-mediated pathway.\(^17\) Recent preclinical studies noted endothelins mitigate vasoconstriction by different downstream signaling pathways in cerebral versus mesenteric vasculature in an animal model.\(^18\) Irregularities in these downstream pathways unique to this patient may also explain the observed alterations in retinal hemodynamics. A clear explanation is elusive, and an idiosyncratic reaction to endothelin receptor blockade in this patient also remains possible.

While the presence of essential hypertension could provide an explanation for cotton wool spots in this case, systemic blood pressure remained well-controlled, with average mean arterial pressure of

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**Figure 3.** Optical coherence tomography highlights edema of the retinal nerve fiber layer.

**Figure 4.** Fundus photography at 2-week follow-up revealing improvement or resolution of cotton wool spots in the right (A) and left (B) eyes.
100.3 mm Hg across all visits. As posited by Brown et al in 1985, the presence of a single cotton wool spot requires systemic evaluation.\(^1\) To our knowledge, this is the first report of cotton wool spots occurring with use of an endothelin receptor antagonist, namely ambrisentan. In patients treated with such agents, medication adverse effect should be considered in the differential diagnosis of cotton wool spots.

REFERENCES