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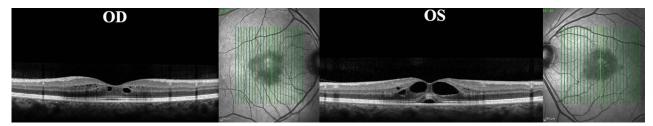
## Siponimod-Related Bilateral Macular Edema: A Transient and Completely Reversible Disorder

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**S** iponimod, a selective sphingosine-1-phosphate receptor (S1PR) 1 and 5 modulator, was recently approved for treatment of active secondary progressive multiple sclerosis (SPMS). Macular edema (ME) is the build-up of fluid in the macula, namely between the inner and outer plexiform retinal layers, and can be observed during treatment with S1P modulators that sometimes can be massive and alarming (1). We report a case of severe and bilateral siponimod-associated ME, completely resolved 13 days after immediate therapy discontinuation.

A 50-year-old relapse-onset multiple sclerosis (RMS) female patient had been treated for 12 years with natalizumab since the diagnosis. Her past and current medical history were free of other pathologies, namely diabetes mellitus, uveitis, or other diseases potentially affecting the retina. The patient remained stable until 2 years ago when she complained of a limitation in walking and entered the secondary progressive disease phase, characterized by Expanded Disability Status Scale progression from 5.0 to 6.0 in absence of relapses. Spinal cord MRI disclosed a

modest enlargement of a pre-existing lesion at C2 level. John Cunningham Virus (JCV) index was 0.92, and antinatalizumab antibodies were absent. In line with European Medicines Agency indications, the patient then was switched to siponimod 2 mg/day after a detailed ophthalmologic examination, optical coherence tomography (OCT) included, that gave completely normal findings. Therapy was well-tolerated, but after 3 weeks, she complained of acute bilateral blurry vision, in absence of ocular pain or dyschromatopsia. Ophthalmologic examination revealed a best-corrected visual acuity (BCVA) of 20/50 in the right eye and 20/70 in the left eye, and no significant alteration of automated visual field test. Fundus oculi examination showed loss of foveal reflex and OCT examination revealed a quite severe cystoid ME in both eyes, with mild foveal neuroretinal detachment in the left eye (Fig. 1). Ocular anterior segment examination was normal. Siponimod was immediately discontinued, and after 13 days, the patients reported visual function recovery. BCVA turned 20/20 in both eyes, and OCT scan showed complete reabsorption of ME (Fig. 2). The patient did not



**FIG. 1.** Spectral domain optical coherence tomography scan after 3 weeks from starting siponimod treatment showed bilateral cystoid macular edema, moderate in right eye and severe in left eye.

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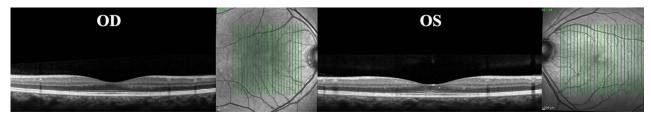
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show signs of ME relapse at monthly OCT during the following 2 months.

Siponimod has been approved for treatment of active SPMS on the basis of the Phase III RCT EXPAND data that demonstrated a significant reduction in the 3- and 6-month confirmed disability progression (CDP) and in brain atrophy (2). In this trial, ME was observed in 1.8% of siponimod-treated patients, a percentage slightly higher than that observed under Fingolimod (1). No detailed data on ME clinical presentation and outcome in siponimod-treated patients enrolled in the RCT were reported.



**FIG. 2.** Spectral domain optical coherence tomography scan after 13 days from Siponimod discontinuation resulted normal, as well as visual function of the patient.

In S1PR-modulator-treated patients, ME usually appears mainly within 3–4 months after therapy start, but onset 24 hours after the first administration was also observed. Our case is worthy of interest and of clinical utility because it differs in the timing of appearance (i.e., very early) and evolution (i.e., rapidly benign) from the only case of siponimod-induced ME available in literature (3). Despite the severity of clinical and OCT presentation, our case had a rapid and complete resolution of the clinical course after therapy discontinuation. The correct management of ME implies the early recognition of symptoms and an accurate periodic OCT examination during the first months after therapy start to intercept ME, possibly before visual function impairment.

The exact pathologic mechanism underlying S1PR modulator-induced ME has not been fully clarified. A dysfunction of the inner blood—retina barrier (iBRB) may be hypothesized. The iBRB, which regulates the movement of solutes from the retinal vasculature to the neuroretina, is composed of tight junctions located between retinal vascular endothelial cells, regulated by perivascular astrocytes, pericytes, and Müller cells. S1PR 1 was found highly expressed in endothelial cells and it is believed to play a role in the correct functioning of the intercellular tight junctions (4,5). Thus, siponimod may modulate S1PR1 on endothelial cells, resulting in the internalization of the receptors, transient dysfunction of the iBRB and impairment of retinal hydric homeostasis leading to intraretinal edema and foveal detachment.

In conclusion, siponimod-related ME may rapidly and completely resolve after treatment cessation, even when the clinical and instrumental picture appears severe.

## STATEMENT OF AUTHORSHIP

Conception and design: A. Miscioscia, F. Rinaldi; Acquisition of data: A. Miscioscia, E. Pilotto; Analysis and interpretation of data: A. Miscioscia. Drafting the manuscript: A. Miscioscia; Revising the manuscript for intellectual content: P. Gallo, P. Perini. Final approval of the completed manuscript: P. Gallo, P. Perini.

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