Asymptomatic ozanimod-related macular edema: a case report

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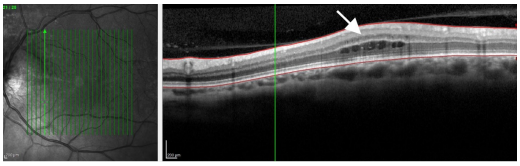
BACKGROUND

Ozanimod is a **sphingosine 1-phosphate receptor 1 and 5** (S1PR1, S1PR5) modulator approved for relapsing-remitting multiple sclerosis (RRMS). **Macular edema (ME)** has been reported as a rare adverse event in patients treated with all S1PR modulators (fingolimod, siponimod, ponesimod, ozanimod collectively referred to as "-imod"). According to the European Medicines Agency, ME may occur in patients with pre-existing risk factors such as diabetes, uveitis, or prior retinal disease, and ophthalmological monitoring is recommended.

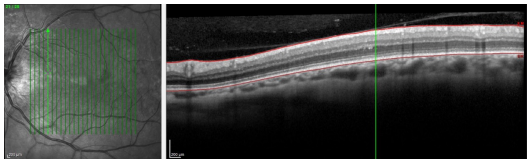
CASE REPORT

We report the case of a **61-year-old man** with RRMS who **developed asymptomatic ME three months after starting ozanimod**. The patient had a 20-year disease history, with clinical and radiological stability until recently. In September 2024, brain MRI revealed a new juxtacortical parietal lesion, and his EDSS was 3.5. As he declined treatment in the past, ozanimod was initiated in November 2024. Siponimod was not eligible due to age-related reimbursement restrictions in Italy. **Pre-treatment screening, including ophthalmological evaluation, was unremarkable** except for a prior, completely resolved central serous choroidopathy (CSC) in the right eye. At 3-month follow-up, the patient reported improved fatigue and stable EDSS. Blood tests showed moderate lymphopenia ($0.53x10^{12}$/L). Routine OCT, however, revealed asymptomatic ME in the left eye. **Ozanimod was discontinued, and follow-up OCT over the next 61 days showed progressive and near-complete ME resolution.**

3 months after ozanimod 1st administration



61 days after ozanimod discontinuation



DISCUSSION

This case aligns with prior evidence. A meta-analysis of randomized trials reported an ME **incidence of 0.8 per 1000 patient-years**, with four of seven cases linked to ozanimod. All had identifiable risk factors and developed ME within 15/366 days from treatment initiation. Most improved after drug discontinuation. The pathogenesis of -imod-induced ME is not fully understood but may involve **S1PR1 internalization** at the **inner blood-retina barrier (iBRB), altering fluid homeostasis** and leading to **intraretinal edema**. Notably, S1PR1 is a shared target across all -imods, supporting a class effect. In our case, ME resolution took about two months, likely influenced by the patient's history and ozanimod pharmacokinetics. Its main metabolite, CC112273, has a long half-life (11 days), with ~98% elimination by day 66 post-discontinuation.

CONCLUSION

In conclusion, ME can occur in **ozanimod-treated patients**, **even without symptoms, OCT surveillance is crucial in patients with predisposing conditions**, and drug withdrawal generally leads to spontaneous resolution, albeit potentially delayed due to prolonged drug elimination.

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