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CASE SERIES

Novel Finding of Retinal Aneurysmal Alterations in Patients Undergoing Fingolimod Therapy for Multiple Sclerosis

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ABSTRACT

***Introduction*:** Fingolimod (Gilenya®), commonly used for relapsing-remitting multiple sclerosis (RRMS), is the first approved oral immunomodulatory agent. While its primary mechanism involves lymphocyte sequestration in lymphoid tissues, emerging studies report a potential link between fingolimod therapy and retinal vascular complications such as central serous chorioretinopathy and macular oedema. This study aims to describe the novel evidence on retinal aneurysmal alterations in patients receiving fingolimod, exploring possible mechanisms and clinical implications.

***Methods*:** Case series of five eyes of five patients with retinal aneurysmal alterations and in therapy with fingolimod for multiple sclerosis. Multimodal imaging scans and medical records of patients on fingolimod therapy were reviewed. Outcome measures included best-corrected visual acuity (BCVA), central subfield thickness (CST) on spectral-domain optical coherence tomography (SD-OCT), presence of retinal aneurysmal alterations and analysis of their change in appearance over time using OCT angiography (OCTA).

***Results*:** Findings indicate a possible association between fingolimod therapy and unilateral retinal aneurysmal changes in certain patients. The proposed mechanisms include endothelial retinal dysfunction, altered retinal vascular permeability and immune modulation effects. The clinical significance of these changes remains uncertain, necessitating further investigation.

***Conclusions*:** Fingolimod may contribute to unilateral retinal aneurysmal vascular changes in a subset of patients. Clinicians should remain vigilant for potential retinal vascular complications, and further research is needed to clarify the underlying mechanisms, the evolution and the long-term risks associated with fingolimod therapy. Notably, in the reported cases, the

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retinal aneurysmal alterations showed regression following the discontinuation of fingolimod, suggesting a potential reversibility of these changes upon cessation of treatment.

Keywords: Retinal aneurysmal alterations; Retinal vascular complications; Fingolimod; Gilenya; Multiple sclerosis; Sphingosine-1-phosphate receptors; Cerebrovascular disease

Key Summary Points

Why carry out this study?

Fingolimod is a widely used oral therapy for relapsing-remitting multiple sclerosis (RRMS) and is known to cause ocular side effects such as macular oedema. However, other retinal vascular complications remain poorly characterized. Because retinal integrity is essential for preserving vision, it is important to investigate whether fingolimod may also induce new, reversible vascular alterations in the retina

Does fingolimod therapy lead to retinal aneurysmal alterations, and are these vascular changes reversible after drug discontinuation?

What was learned from the study?

Retinal aneurysmal alterations were identified in five patients with multiple sclerosis undergoing fingolimod therapy. In all cases, the vascular changes regressed after cessation of fingolimod without any additional treatment, suggesting a reversible, drug-related effect

Although these alterations were not associated with visual loss, they represent a newly recognized and potentially reversible retinal vascular manifestation of fingolimod therapy. Regular retinal imaging and close collaboration between neurologists and ophthalmologists are essential for early detection, monitoring and safe therapeutic management

INTRODUCTION

Fingolimod (Gilenya®) is a widely used immunomodulatory drug for the treatment of relapsing-remitting multiple sclerosis (RRMS), a chronic autoimmune disease characterized by recurrent inflammatory attacks on the central nervous system (CNS) [1]. As the first oral disease-modifying therapy (DMT) approved for RRMS, fingolimod has transformed MS management by effectively reducing disease activity, decreasing relapse rates and delaying disability progression. Its mechanism of action primarily involves the modulation of sphingosine-1-phosphate (S1P) receptors, which regulate immune cell trafficking [2]. By acting as a functional antagonist of these receptors, fingolimod sequesters lymphocytes within lymphoid tissues, thereby preventing their migration into the CNS and reducing neuroinflammation [3].

While fingolimod has demonstrated significant benefits in MS treatment, emerging evidence suggests that its pharmacological effects extend beyond immune modulation, influencing vascular homeostasis and endothelial function [4]. The S1P signalling pathway plays a crucial role in maintaining vascular integrity, endothelial barrier function and vascular tone. Given fingolimod's interaction with S1P receptors, concerns have arisen regarding its potential impact on the cardiovascular system, including blood pressure regulation, heart rate alterations and endothelial health [5]. Clinical trials and post-marketing surveillance have documented cardiovascular side effects such as bradycardia and hypertension [6].

Moreover, fingolimod has been associated with several ocular side effects, primarily affecting the retina and the optic nerve [7]. The most well-documented side effect is fingolimod-associated macular oedema [8–10]. This condition typically develops within the first few months of treatment and is more common in patients with preexisting risk factors such as diabetes mellitus or uveitis. Management often involves regular monitoring, potential discontinuation of the drug in severe cases and, if necessary, adjunctive treatments such as carbonic anhydrase inhibitors or anti-VEGF intravitreal

therapy [11]. Another reported ocular side effect associated with fingolimod is central serous chorioretinopathy (CSCR), which, unlike macular oedema, lacks clear management guidelines in the context of fingolimod therapy [12]. Indeed, while drug discontinuation is generally recommended in cases of macular oedema, there are no established indications for stopping the medication in patients with CSCR. Notably, Ziccardi et al. [13] described a case of CSCR that resolved without discontinuation of the medication, suggesting a potentially different clinical course and management approach for this condition.

Beyond macular oedema and CSCR, other less frequent retinal vascular abnormalities have been described in patients receiving fingolimod. Some individuals developed retinal capillary dilation and vascular tortuosity resembling microvascular changes seen in diabetic retinopathy [14] and more rarely reported. Retinal haemorrhages have also been observed, likely because of endothelial dysfunction and compromised vascular stability [15]. Also, choroidal alterations, including choroidal effusion leading to serous retinal detachment, have been documented, further confirming that fingolimod influences vascular homeostasis within the eye [16, 17].

In this context, emerging concern, not yet described, is the finding of retinal aneurysmatic alterations, which could predispose patients to visual impairment, since they develop in the macular area. In this study, we describe retinal aneurysmal alterations identified in five patients undergoing fingolimod therapy for multiple sclerosis and provide detailed multimodal imaging documentation for two representative cases. Understanding these alterations is crucial for early detection and optimal management for visual sparing.

CASE PRESENTATIONS

This was a case series report including five patients with MS and retinal aneurysmal alterations, visited at the Clinical and Research Center of Neurophthalmology, Genetic and Rare Diseases of the Eye of IRCCS Fondazione Bietti between April 2024 and March 2025, as outpatients for ophthalmological clinical surveillance for being on fingolimod therapy. Clinical data were collected following the procedures in adherence with the Helsinki Declaration (1964 and further revisions). Ethical approval was not required as this case series originated from a retrospective analysis of existing anonymized data and did not involve any experimental interventions. Patients were informed and consented to the use of their medical records and data for scientific purposes. Written informed consent was obtained from each patient for publication of data. Explicit permission was obtained to publish the OCT and OCTA scans by the subjects involved in the study.

Electronic medical records of the five patients in therapy with fingolimod for RRMS were reviewed, and data collected included: demographic information, Snellen best corrected visual acuity (BCVA) at the time of presentation and at the last available follow-up, and clinical examination findings. Patients with retinal aneurysmal alterations were identified through manual revision of macular OCT angiography scans executed for clinical surveillance of patients on fingolimod therapy for RRMS. Multimodal imaging was performed including color fundus photographs, near-infrared reflectance (NIR), spectral-domain OCT (SD-OCT), short wavelength fundus autofluorescence and OCT angiography (OCTA).

Multimodal retinal imaging was acquired with the Heidelberg Spectralis® (Heidelberg Engineering, Heidelberg, Germany). Central subfield thickness (CST) measurements were obtained from serial eye-tracked volumetric OCT scans at the time of presentation and at the last available follow-up appointment, conducted after a 1-year observation period.

The five patients included two men and three women. The demographic and clinical data of the patients are shown in Table 1. The mean ± standard deviation (SD) age at the time of presentation was 59.2 ± 3.4 years; the mean ophthalmological follow-up time was 10.5 ± 4.5 months; the mean fingolimod (Gilenya®) treatment duration for RRMS was 0.5 mg daily for 14.8 ± 6.6 years. In all cases, only one eye was affected, while the contralateral eye

Table 1 Demographic and clinical data of the patients

	Age (years)	Sex	Affected eye	BCVA[5] (Snellen)	Haemorrhages on fundoscopy	SD-OCT	OCTA	Fingolimod treatment duration (years)	Other known systemic diseases
Case 1	59	F[1]	RE[3]	20/20	No	ME[6] + RAA[7]	SVP[8]	24	HTN[10]
Case 2	57	M[2]	LE[4]	20/20	No	ME + RAA	DVP[9]	7	None
Case 3	64	F	LE	20/25	No	Only RAA	SVP	18	HypoT[11]
Case 4	61	M	RE	20/22	No	Only RAA	SVP	10	CAD[12]
Case 5	55	F	RE	20/25	No	ME + RAA	SVP	15	None

[1] F = female; [2] M = male; [3] RE = right eye; [4] LE = left eye; [5] BCVA = best-corrected visual acuity; [6] ME = macular oedema; [7] RAA = retinal aneurysmal alteration; [8] SVP = superficial vascular plexus; [9] DVP = deep vascular plexus; [10] HTN = systemic arterial hypertension; [11] HypoT = hypothyroidism; [12] CAD = coronary artery disease

remained unaffected. Best-corrected visual acuity (BCVA) was generally good across the cohort. No retinal haemorrhages or signs of hypertensive retinopathy were observed in any patient on fundoscopy. Retinal aneurysmal alterations were variably associated with macular oedema, being present in three cases and absent in two.

Of these five patients, we report in detail the complete 12-month follow-up and explanatory imaging of two patients—one male and one female. Of the five patients identified, two were selected for detailed description based on the completeness of longitudinal imaging data and follow-up documentation, allowing a full assessment of lesions, with one occurring at the level of the superficial vascular plexus and one at the level of the deep vascular plexus, and the evolution before and after fingolimod discontinuation.

Case 1

A 59-year-old woman with a history of systemic arterial hypertension and RRMS (Expanded Disability Status Scale [EDSS] 3.5) was followed up with routine ophthalmological evaluations. She was diagnosed with multiple sclerosis in 2001 following an episode of optic neuritis in the left eye according to the McDonald criteria [18], later reclassified according to the 2017 revisions [19]. Since 2001, she had been receiving fingolimod (Gilenya®) 0.5 mg daily as part of her long-term disease-modifying therapy, not showing any macular abnormalities at her baseline (pre-administration) ophthalmological evaluation, as described in her clinical reports by her private ophthalmologist.

She was admitted as an outpatient to our clinical center on 15 October 2015 and exhibited temporal pallor of the optic nerve in the left eye, in the absence of delayed neural conduction, with no other abnormalities attributable to Gilenya® therapy. At a routine follow-up in June 2024, structural SD-OCT and OCTA revealed macular focal oedema and retinal aneurysmal vascular alterations in the right eye (RE), despite preserved best-corrected visual acuity (20/20 Snellen), absence of metamorphopsia and a fundoscopy result within normal limits not showing retinal haemorrhages or other visible changes (Fig. 1). The retinal aneurysmal changes were observed on structural SD-OCT as localized hyperreflective round lesions at the level of the inner retina and on OCTA scans as focal dilations of capillaries predominantly located in the superficial vascular plexus. The contralateral (left) eye was also examined and showed no abnormalities on ophthalmoscopy or structural or angiographic imaging.

These retinal ultrastructural findings were newly detected, as previous ophthalmological assessments including OCT scans performed on 16 May 2023 had shown no abnormalities.

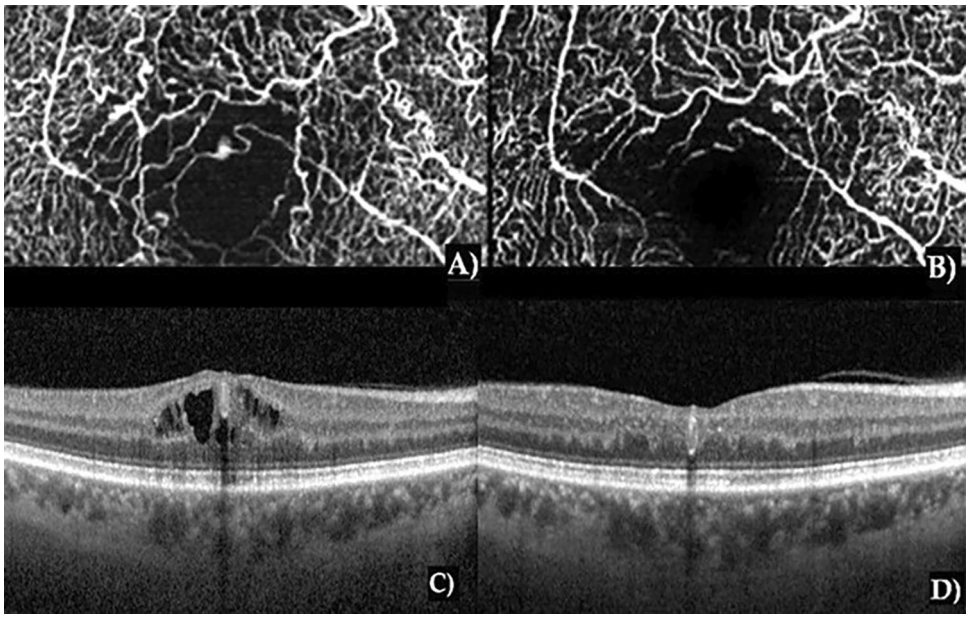

Fig. 1 Evolution of a retinal aneurysmal alteration on optical coherence tomography angiography (OCTA) (**A**, **B**) and spectral-domain optical coherence tomography (SD-OCT) (**C**, **D**) in Case 1. **A** At presentation, an isolated macular aneurysmal dilation at the level of the superficial vascular plexus associated with macular oedema (**C**) was observed in the right eye. **B** Four months after discontinuing fingolimod, absence of detectable retinal aneurysmal alterations was evident on OCTA (**B**), and regression of macular oedema with residual tubular morphological sequelae at the sites of the prior aneurysmal alteration was observed on SD-OCT (**D**)

Given the presence of retinal vascular alterations and oedema, fingolimod therapy was discontinued in June 2024 and replaced after 5 months with cladribine (Mavenclad®) 60 mg per week.

Four months after the discontinuation of fingolimod, the patient was re-evaluated using OCTA, which demonstrated regression of the retinal aneurysmal alteration, and SD-OCT, which revealed resolution of the macular oedema but persistence of a residual hyporeflective, tubular structure with a hyperreflective contour line as morphological sequelae at the sites of the prior aneurysmal alteration. The spontaneous regression of the retinal vascular phenotype following fingolimod withdrawal, without the need for additional therapeutic intervention, supports a potential causal relationship between the drug and the observed microvascular changes.

Case 2

A 57-year-old man with RRMS (EDSS 4.5) and no known systemic comorbidities was under regular ophthalmological follow-up during the course of his disease-modifying therapy. He experienced disease onset in 2018 with motor symptoms and was diagnosed according to the 2017 McDonald criteria [19]. Since diagnosis, he had been receiving fingolimod (Gilenya®) 0.5 mg daily as part of his long-term management.

The patient first presented to our clinical center as an outpatient on 25 September 2020. His last ophthalmological evaluation before the development of ocular findings, performed on 12 June 2023, was unremarkable, showing no abnormalities related to fingolimod therapy on fundoscopy and SD-OCT. However, during

routine follow-up in May 2024, multimodal imaging revealed unilateral macular oedema and retinal aneurysmal vascular alterations in the left eye (LE), without associated retinal haemorrhages (Fig. 2). Despite these findings, his BCVA remained stable at 20/20 Snellen during follow-up assessments.

On structural SD-OCT, focal macular oedema was detected, while OCTA imaging demonstrated the presence of a localized aneurysmal dilation primarily in the deep capillary plexus. The contralateral (right) eye was also thoroughly examined and showed no abnormalities on either structural or angiographic imaging.

The patient's ocular history also included a diagnosis of bilateral macular dystrophy in January 2024, with genetic testing ongoing to determine the underlying cause.

Given the newly detected vascular abnormality, fingolimod therapy was discontinued in May 2024. At 10 months following the discontinuation of fingolimod, the patient underwent re-evaluation. OCTA demonstrated a regression of the previously identified retinal aneurysmal alteration, while structural SD-OCT revealed complete resolution of the macular oedema. Nonetheless, discrete residual hyperreflective foci persisted at the former sites of the aneurysmal alteration. The spontaneous resolution

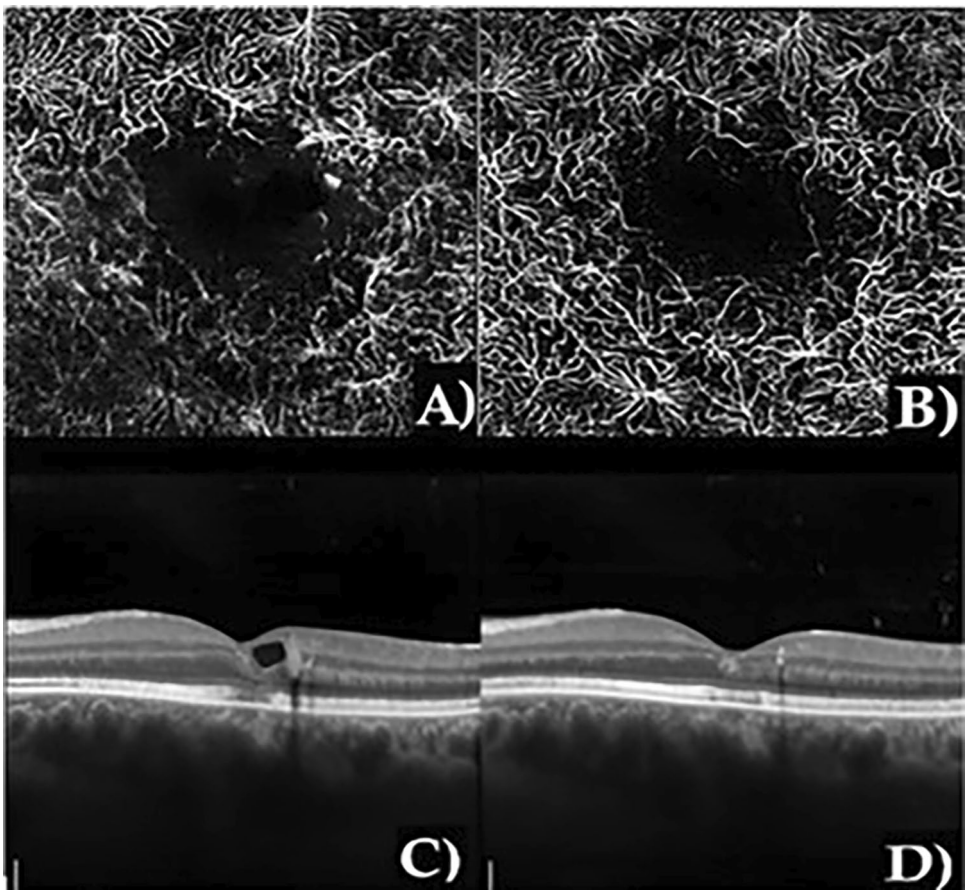

Fig. 2 Evolution of a retinal aneurysmal alteration on optical coherence tomography angiography (OCTA) (**A**, **B**) and spectral-domain optical coherence tomography (SD-OCT) (**C**, **D**) in Case 2. **A** At presentation, an isolated macular aneurysmal dilation at the level of the deep vascular plexus associated with macular oedema (**C**) was observed in the left eye. **B** Ten months after the discontinuation of fingolimod, absence of detectable retinal aneurysmal alterations was evident on OCTA (**B**), and regression of macular oedema with residual hyperreflective foci at the sites of the prior aneurysmal alteration was observed on SD-OCT (**D**)

of the retinal aneurysmal abnormality in the absence of additional therapeutic intervention further substantiates a potential causal relationship between fingolimod therapy and the development of the observed microvascular changes.

DISCUSSION

To the best of our knowledge, our study is the first case to describe the occurrence of benign unilateral retinal aneurysmal alterations in patients undergoing therapy with fingolimod for RRMS. This novel finding expands the spectrum of vascular complications potentially associated with fingolimod and highlights the importance of careful ophthalmological monitoring in patients receiving this therapy, even when they do not report visual abnormalities.

Fingolimod's ability to modulate sphingosine-1-phosphate (S1P) receptors has raised concerns regarding its effects on vascular health. The S1P signalling pathway is essential for maintaining endothelial function, vascular tone regulation and permeability. Specifically, activation of the S1P1 receptor promotes endothelial barrier integrity, whereas S1P2 and S1P3 receptors are involved in vasoconstriction and vascular remodelling [20, 21]. Fingolimod, acting as an S1P receptor modulator, initially activates but subsequently downregulates these receptors, potentially leading to endothelial dysfunction and altered vascular homeostasis. Downregulation of S1P1 receptors has been shown to increase vascular permeability, impair nitric oxide production and destabilize endothelial cells—factors that may contribute to vascular abnormalities, including aneurysm formation [22].

Moreover, fingolimod's immunomodulatory effects may also contribute to vascular pathology. While the drug effectively reduces systemic immune activation by sequestering lymphocytes, it may also cause imbalances in local immune responses, particularly within the vasculature. Chronic low-grade vascular inflammation, a known contributor to aneurysm development, could be exacerbated by such localized immune dysregulation under fingolimod therapy [23, 24].

Another proposed mechanism involves haemodynamic and structural changes within the vasculature. Fingolimod-induced alterations in vascular tone and endothelial permeability may result in disturbed blood flow dynamics. This can lead to increased mechanical stress on the vessel wall and progressive remodelling, predisposing susceptible vessels to aneurysmal dilation [25]. Additionally, dysfunction of vascular smooth muscle cells—mediated by disrupted S1P signalling—could impair extracellular matrix maintenance and further weaken the vessel wall, contributing to aneurysmal changes [26, 27].

Lately, a growing body of evidence suggests an elevated risk for intracranial aneurysms and other vascular complications in patients treated with fingolimod, particularly those with underlying risk factors [20, 28]. Observational studies have also reported cases of arterial dissections, subarachnoid haemorrhage and other vascular abnormalities, implying a possible link between prolonged fingolimod exposure and structural vessel remodelling [28, 29].

Until now, no retinal aneurysmal abnormalities related to fingolimod administration have been documented. Our case series highlights this rare but noteworthy ocular manifestation. Importantly, in all five patients we observed that following the discontinuation of fingolimod therapy, the retinal aneurysmal alterations regressed, as confirmed by OCTA. This finding reinforces the plausibility of a causal relationship between fingolimod and retinal vascular changes. The timing of re-examination (4 and 10 months after fingolimod withdrawal) was determined by scheduled clinical follow-up intervals. In both patients, retinal aneurysmal alterations had completely regressed by the time of reassessment. Based on earlier OCTA scans in other patients, we estimate that regression may occur within 1–3 months after drug cessation, although this requires confirmation in larger cohorts. The resolution of these alterations in the absence of any additional intervention further supports a direct pharmacological effect of the drug on retinal microvasculature.

In our series, retinal aneurysmal alterations were observed in patients undergoing long-term

fingolimod therapy for RRMS. Despite the presence of these microvascular abnormalities, BCVA was generally preserved, the patients were asymptomatic, and no retinal haemorrhages or signs of hypertensive retinopathy were observed on fundoscopy. These findings suggest that the observed vascular changes are not secondary to systemic hypertension or other common retinal vascular pathologies. Notably, the presence of macular oedema was inconsistent, being associated with retinal aneurysmal changes in some but not all cases. This variability may reflect differences in lesion location, duration or individual retinal vascular response. Importantly, retinal aneurysmal alterations were identified in both the superficial and deep vascular plexuses, suggesting that multiple retinal capillary layers may be vulnerable to fingolimod-associated vascular effects. Interestingly, all retinal aneurysmal alterations observed in our series were unilateral. We are currently unable to provide a definitive explanation for this finding, which may be due to the limited number of patients included or to the prompt discontinuation of fingolimod therapy after the initial detection of abnormalities, potentially limiting further bilateral involvement. The unilateral nature of involvement and the absence of systemic vascular complications further support the hypothesis of a localized, drug-related microvascular effect rather than a systemic vascular aetiology. All these findings suggest that fingolimod-related aneurysmal changes are generally benign and reversible, with a low likelihood of causing vision-threatening complications. Nevertheless, early detection remains important for monitoring potential progression and guiding clinical decision-making. Interestingly, intracranial aneurysms have already been described in association with fingolimod therapy, indicating that vascular wall alterations may not be limited to the ocular microcirculation. However, it remains uncertain whether similar changes might affect other systemic organs.

The main limitations of this study include the small sample size and retrospective design, which restrict generalization of findings. Additionally, the lack of intermediate follow-up imaging limits precise determination of the time course of lesion regression. The precise mechanisms underlying fingolimod-induced retinal aneurysmal changes remain incompletely understood, and further investigation is warranted. Future larger prospective studies are needed to assess retinal microvascular integrity in patients initiating or undergoing fingolimod therapy. It is important to underline the role of a non-invasive and innovative technique such as OCTA, which could serve as a valuable tool for early detection of subclinical vascular alterations, enabling timely therapeutic decisions and preventing potential visual complications. Moreover, identifying predictive biomarkers for susceptibility to vascular side effects may help stratify risk and personalize MS treatment strategies.

CONCLUSIONS

Retinal aneurysmal alterations represent a potential ocular complication of fingolimod therapy in patients with MS [30]. While the pathophysiological mechanisms remain under investigation, evidence suggests that endothelial dysfunction, blood-retinal barrier disruption and altered vascular tone contribute to these changes [31]. Additionally, the natural evolution of these retinal aneurysmal alterations remains unknown, particularly in the hypothetical scenario where fingolimod treatment is continued. In our study, the vascular abnormalities regressed in all patients following drug discontinuation; however, it remains unclear whether such changes would have persisted, worsened or resolved spontaneously if treatment had been maintained. Further studies are necessary to clarify this aspect and to determine the potential progression or long-term stability of these findings in the absence of drug withdrawal.

Early detection through ophthalmological screening and multimodal imaging is crucial for preventing vision-threatening complications. A collaborative approach involving neurologists and ophthalmologists is essential for optimizing patient outcomes while maintaining disease control. Ongoing research is necessary to further elucidate the mechanisms and develop targeted strategies for mitigating these vascular disorders

in patients undergoing long-term fingolimod therapy.

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Data Availability. The data used to support the findings of the study are included within the article.

Declarations

Conflict of Interest. Feliciana Menna, Lucilla Barbano, Carmen Dell'Aquila, Mattia D'Andrea, Vincenzo Parisi and Lucia Ziccardi declare that they have nothing to disclose.

Ethical Approval. The study was conducted in accordance with the tenets of the Declaration of Helsinki (1964 and later amendments). Ethical approval was waived by the institutional ethics committee of IRCCS-Fondazione Bietti (Rome, Italy) because this study involved a retrospective review of anonymized patients' data under clinical out-patient evaluation. Patients were informed and consented to the use his/her medical records and data for scientific purposes. Written informed consent has been obtained from each patient for publication of data. Explicit permission was obtained to publish the OCT and OCTA scans by the subjects involved in the study.

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