Choriocapillaris Integrity in Relapsed Central Serous Chorioretinopathy in a Patient Treated With Fingolimod for Multiple Sclerosis: New Insights From Optical Coherence Tomography Angiography

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Fingolimod (FTY), the first oral disease-modifying therapy for relapsing–remitting multiple sclerosis (RRMS), is a structural analog of intracellular sphingosine and acts as a modulator of sphingosine-1-phosphate (SIP) receptors. By crossing the blood–brain barrier, FTY reduces the trafficking of autoreactive lymphocytes and inhibits their infiltration into the central nervous system, reducing local inflammation and neurodegeneration (1).

Nevertheless, SIP receptors are ubiquitous in human tissues (1), and at the level of the blood–ocular barrier, they regulate the endothelial cells’ integrity and the consequent vascular permeability (2).

Among the unwarranted off-target ocular side effects associated with FTY, cystoid macular edema, resulting from endothelial damage and consequent accumulation of the intraretinal fluid, as well as central serous chorioretinopathy (CSCR), acute anterior uveitis, and retinal hemorrhages have been reported (2,3). CSCR is usually a benign condition, characterized by focal retinal ischemia and choriocapillaris (CC) attenuation, with reactive hyperperfusion that may lead to subretinal fluid (SRF) leakage (4). Spectral domain optical coherence tomography (SD-OCT) and OCT angiography (OCTA) are noninvasive innovative imaging tools useful for investigating the structure and integrity of the retinal and choroidal vasculature in several retinal disorders, particularly CSCR. Different from macular edema, for which FTY interruption is recommended, there are no clear indications to manage CSCR during treatment with FTY. Discontinuing the drug (5) and adding on oral acetazolamide, topical anti-inflammatory drops, and sub-Tenon or intravitreal steroid injections have been proposed as rescue approaches (2). However, FTY interruption may result in severe inflammatory MS rebound and should be considered only if there is no alternative strategy for managing drug-related complications (5).

Here, we report a case of a 44-year-old male patient with RRMS diagnosed in 1999, who started FTY on July 2016 (Gilena, Novartis, 0.5-mg oral capsule once daily) after radiological reactivation in the spinal cord associated with disability worsening (EDSS 6.0). At that time, he was not taking any concurrent drug.

As for Gilena summary of product characteristics, before starting the treatment (June 2016), the patient subjected to blood tests and full cardiological, dermatological, and ophthalmological screening. In his right eye (RE), signs of CSCR, that were already known since June 2012, were found, and vision was not affected. Because of the risk of ocular complications, alternative treatment options were considered. However, owing to contraindications to other MS treatments and tolerability issues posed by the patient, the decision of starting FTY and monitoring the patient for macular adverse events was made. He was therefore referred for macular follow-up thereafter.

On his first visit at our neuro-ophthalmology unit (November 2017), we found 20/20 Snellen best-corrected visual acuity, normal chromatic function, intraocular pressure, and anterior and posterior segments in both eyes. SD-OCT scans showed focal retinal thinning in the macular nasal and inferior sectors by horizontal scans in the RE and a small neurometinal detachment (NRM) in the macular inferior sector by vertical scans, suggesting relapsed CSCR. Morphology of choroid by enhanced-depth imaging OCT showed macular choroidal thickening. Short-wave fundus autofluorescence showed diffuse hyperautofluorescence corresponding to the NRM with a gravitational track, as for typical chronic CSCR.

Two months later (January 2018), increased NRM with extension of fluid to the inferior portion of the fovea and gravitational fluid along the inferior vascular arcade.
in the RE was observed (Fig. 1A). Indocyanine green angiography showed signs of focal choroidal hyperpermeability in the nasal and inferior macular sectors (Fig. 1C, D), whereas OCTA did not show evident CC and choroidal abnormalities (Fig. 1E). Complementary multifocal electroretinogram recorded normal bioelectric responses indicating the absence of photoreceptor and bipolar cells' dysfunction, despite abnormal SRF accumulation (Fig. 1F).

After consulting the patient's neurologist and based on the OCTA findings, we decided to follow-up the patient closely and to continue FTY therapy because of the likelihood of MS relapse and disability accrual in case of interruption (5). No other ophthalmological therapy was added.

One month later (February 2018), we noticed reduced NRD height and partial reabsorption of the SRF on SD-OCT (Fig. 2A). Subsequent examinations, performed monthly up to 6 months from the first observation (May 2018), showed complete SRF reabsorption (Fig. 2D–F) that remained stable at 12 months of follow-up (November 2018). OCTA images confirmed the absence of ischemic features at the level of both the CC and choroid.

The use of FTY is believed to downregulate SLP signaling, responsible for maintaining cell-to-cell and

**FIG. 1.** Multimodal study of a patient with relapsed central serous chorioretinopathy (CSCR) in his right eye (RE) during fingolimod treatment. Two months after the presentation of relapsed CSCR, macular spectral domain optical coherence tomography (SD-OCT—Spectralis HRA; Heidelberg Engineering, Heidelberg, Germany) scans showed increased height of the neuroretinal detachment (NRD) with extension of fluid to the inferior portion of the fovea and gravitational fluid along the inferior vascular arcade (A). Short-wave fundus autofluorescence revealed diffuse hyperautofluorescence corresponding to the NRD with a gravitational track, as for typical chronic CSCR (B). In the nasal and inferior macular sectors, a hyperfluorescent area appeared in the early phase of indocyanine green angiography (ICGA) (C) and persisted in the late phase of the examination (D), corresponding to focal choroidal hyperpermeability. In the context of this area, retinal pigment epithelial atrophy areas appeared hyperfluorescent in the early phase (C) because of window defect and hypofluorescent in the late phase of ICGA (D). Swept-source OCTA scans (PLEX Elite 9000; Carl Zeiss Meditec Inc, Dublin, CA) did not show any evident abnormalities at the level of the choriocapillaris except mild changes that are shadowing artifacts because of the NRD seen in the RE structural SD-OCT scans (E). Multifocal electroretinograms, recorded from retinal annular areas (rings) centered to the fovea up to 20° of eccentricity, presented normal values of P1 implicit time (IT) and N1-P1 response amplitude density (RAD), describing the absence of photoreceptor and bipolar cells' dysfunction (F). OCTA, optical coherence tomography angiography.
cell-to-matrix adhesion complexes (1,2), thus leading to increased retinal vascular permeability resulting in edema (2). Vascular permeability is at the base of CSCR (3,4), and innovative imaging techniques, such as OCTA, can help attain new insights related to disease staging and mechanisms. In detail, hyporeflective flow signal void lesions have been described as suggestive of focal choroidal ischemia with surrounding reactive hyperperfusion in both acute and chronic CSCR, and the number and area of lesions increase with the disease severity (4).

Contrary to typical CSCR OCTA features, consisting of the dysfunctional retinal pigment epithelium or hyperpermeable CC associated with focal ischemic signs (3,4), our patient with atypical CSCR relapsed during treatment with FTY did not show evident CC and choroidal abnormalities, as well as flow signal void lesions, except for the mild changes due to the NRD during follow-up (Figs. 1E, 2C–F).

The OCTA findings of CC integrity, with transitory choroidal hyperpermeability and no ischemic CC changes, supported the choice of not suspending FTY in this atypical CSCR case with stable vision. However, in a different reported case of subfoveal CSCR with the consequent decrease of visual acuity, FTY was suspended based on recurrent NRD (3). This and our CSCR case let us to remark caution and serial strict monitoring of FTY-treated patients (2,5).

In conclusion, our results indicate that FTY administration did not adversely influence retinal and choroidal vascular integrity, even in the presence of pre-existing CSCR, with relevant implications for the treatment and long-term management.

STATEMENT OF AUTHORSHIP

REFERENCES