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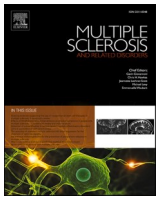

Reduced retinal neuronal injury as a consequence of high efficacy DMT treatment: an OCT study

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ABSTRACT

Objective: To assess the impact of disease-modifying treatments (DMTs) on retinal ganglion cell-inner plexiform layer (GCIPL) thickness.
Methods: We analyzed 174 retinal optical coherence tomography (OCT) scans from 90 MS patients (female-to-male ratio 3:1; mean age 39.3 years; median EDSS 2.0; mean disease duration 8.1 years). Bilateral macular scans were obtained at baseline and follow-up using spectral-domain OCT (Spectralis, Heidelberg Engineering, Germany) between 2017 and 2023. Patients were divided into moderate-efficacy (ME-DMT, $N = 34$) and high-efficacy (HE-DMT, $N = 56$) groups. The primary measure was global GCIPL thickness, with analysis conducted via independent *t*-tests and a mixed linear regression model to determine annualized GCIPL change.
Results: The HE-DMT group had a significantly lower annual GCIPL atrophy rate (0.07 ± 0.38 μm/year) compared to the ME-DMT group (0.64 ± 0.86 μm/year, $p < 0.0001$). Mixed linear regression confirmed these findings, accounting for covariates and baseline characteristics.
Conclusions: HE-DMTs appear to slow GCIPL atrophy, suggesting a potential neuroprotective effect. These results underscore the value of retinal imaging in tracking MS treatment efficacy and neurodegeneration.

1. Introduction

Optical coherence tomography (OCT) is a non-invasive imaging technique (Huang et al., 1991) that enables the quantification of retinal layer thickness and volume, providing insights into underlying neuroaxonal degeneration (Saidha et al., 2015). Additionally, its rapid execution and low cost make it a practical option for repeated, longitudinal use in clinical settings. Consequently, in recent years, numerous studies have employed OCT primarily to assess retinal damage following optic neuritis (ON) (Petzold et al., 2022), predict disability progression (Martinez-Lapiscina et al., 2016; Cordano et al., 2018), and monitor retinal markers of axonal and neuronal degeneration and inflammation in multiple sclerosis (MS) (Petzold et al., 2017; Nguyen et al., 2019; Cordano et al., 2022; Cordano et al., 2024; Olbert and Struhal, 2022; Knier et al., 2016; Cordano et al., 2021). Notably, OCT-measured retinal thinning in eyes without a history of ON has emerged as a reliable marker for MS-associated neuroaxonal damage, correlating with disability progression independently of relapse activity in MS (Bsteh et al., 2020).

Traditionally, brain atrophy measured via magnetic resonance imaging (MRI) has been used to evaluate the effectiveness of disease-modifying therapies (DMTs) in preventing MS-associated neuroaxonal damage. However, growing evidence suggests that OCT may also serve as a valuable clinical outcome measure for assessing DMT efficacy in relation to neurodegeneration (Saidha et al., 2015; Abalo-Lojo et al., 2014). Several high-efficacy DMTs (HE-DMTs) have demonstrated

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positive effects on reducing retinal atrophy in people with MS. For instance, natalizumab (NTZ), one of the most effective treatments for MS, has been shown to significantly reduce thinning of the peripapillary retinal nerve fiber layer (pRNFL)—a key marker of axonal loss—compared to moderate-efficacy DMTs (ME-DMTs) (Jakimovski et al., 2021). Alemtuzumab (ATZ) has demonstrated stabilization not only of the pRNFL but also of the ganglion cell and inner plexiform layer (GCIPL), a retinal marker of neuronal loss (Chan et al., 2020). Additionally, after the first year of treatment with rituximab (RTX), GCIPL atrophy rates were comparable to those observed with NTZ treatment (Lambe et al., 2021). Conversely, fingolimod has been associated with macular edema, which can mildly increase total macular volume and thus complicate the assessment of retinal atrophy (Nørgaard et al., 2020; D'Ambrosio et al., 2021).

Given the growing number of available DMTs, further prospective studies are needed to systematically compare the effects of various DMT categories on OCT-derived retinal atrophy.

In this monocentric study, we prospectively collected data from two groups of individuals with MS undergoing treatment with either HE-DMTs or ME-DMTs. Longitudinal OCT scans were acquired to assess the atrophy rate of the GCIPL.

2. Materials and methods

The study was conducted between 2017 and 2023 at the MS Centre of Cagliari, which serves as the reference center for MS in Sardinia, an island with the highest prevalence of the disease in Italy. It involved a quantitative descriptive analysis of individuals with relapsing-remitting multiple sclerosis (RRMS) who underwent OCT examination for clinical purpose. As required by standard clinical practice in our Multiple Sclerosis center, patients were asked to sign an informed consent form at the time of diagnosis and when they started a DMT, authorizing the anonymous use of their clinical data for research purposes.

Subjects with a confirmed diagnosis of RRMS, established according to McDonald criteria (Thompson et al., 2018), were prospectively included in the study. All participants had initiated a DMT and were followed at the MS Centre of Cagliari. Patients who were not receiving any DMT or who had a different MS phenotype were excluded from the study.

Patients were divided into two groups based on their medication. Those treated with interferon-beta, dimethyl fumarate, teriflunomide, and glatiramer acetate were assigned to the ME-DMT group, while those treated with ocrelizumab, NTZ, cladribine, ATZ, and RTX formed the HE-DMT group.

Patient demographics (sex, age) and clinical data, including age of onset, disease duration, and disability level as evaluated using the Expanded Disability Status Scale (EDSS), were collected at baseline (T0) and after a follow-up period (T24). A history of ON was obtained by retrospectively reviewing medical records; episodes of unilateral visual loss, particularly those associated with pain during eye movement, increased latency on visual evoked potential (VEP) testing, and recovery of vision after high-dose steroid treatment were classified as previous ON. Patients with ON occurring within the 6 months before enrollment were excluded. Atypical cases, such as simultaneous bilateral visual deficits, no recovery, or rapid resolution of deficits in $<$24 h without steroid treatment, were excluded from the ON classification. Eyes with ON occurrences during the follow-up period were also excluded from the analysis.

2.1. OCT scanning protocols

OCT scans were acquired at the MS Centre of Cagliari using a spectral-domain OCT (Spectralis, Heidelberg Engineering, Germany) at both T0 and T24, with the Trutrack function activated to ensure precise registration of the scanning position. The examinations were conducted without prior pupil dilation under ambient light by different operators during routine follow-up or scheduled day-hospital visits. Macular volume scans centered on the fovea were obtained with active eye tracking for both eyes using the following parameters: 25 vertical B scans with 20 $\times$ 20 degrees coverage, with each B scan composed of 1024 A-scans in high-resolution mode. The distance between slices was 240 μm, and the average eye tracking (ART) ranged from 2 to 49.

Quality assessment was conducted by S.C.H., and only images meeting the OSCAR-IB criteria for OCT analysis, with a quality index greater than 15, were included (Tewarie et al., 2012). Automatic segmentation of the ganglion cell layer (GCL) and inner plexiform layer (IPL) from the OCT images was performed using the manufacturer's software (Heyex version 1.10.2.0). The segmented images were visually examined by S.C.H. with the patient information masked, and manual corrections for segmentation errors were made when necessary. The 6 mm Early Treatment Diabetic Retinopathy (ETDRS) grid was utilized to extract the global GCIPL thickness, the primary outcome measure of this study. The OCT data report was prepared according to APOSTEL guidelines. (Aytulun et al., 2021)

2.2. Statistical analysis

Statistical analyses were performed using GraphPad Prism version 10.0 (GraphPad Software, San Diego, CA, USA) and MATLAB R2022a (MathWorks, Natick, MA, USA). Demographic and clinical characteristics, as well as GCIPL thickness at baseline and follow-up, were compared between groups using independent *t*-tests.

To assess longitudinal changes in GCIPL thickness while accounting for baseline differences, a multivariable linear regression model was applied. The annualized GCIPL atrophy rate—defined as the difference in GCIPL thickness between baseline and follow-up divided by the follow-up duration—was used as the dependent variable, with treatment group as the primary independent variable (ME-DMT vs HE-DMT). Covariates included eye (left/right), age, history of optic neuritis, baseline EDSS score, baseline DMT category, disease duration, and baseline GCIPL thickness. All covariates represented baseline characteristics measured prior to or at study entry. Statistical significance was set at a two-sided α level of 0.05.

3. Results

A total of 90 patients with a diagnosis of RRMS were enrolled, with an average follow-up period of 28.47 $\pm$ 5.79 months. Six eyes were excluded from both baseline and follow-up data for the following reasons: occurrence of optic neuritis (2 eyes) during the follow-up period, insufficient image quality (3 eyes), and inability to acquire images (1 eye). Ultimately, images from 174 eyes were collected, and patients were categorized into ME-DMT group and the HE-DMT group based on their ongoing treatment.

The ME-DMT group comprised 34 patients (25 females), with an average age of 41.47 $\pm$ 7.45 years, an age of onset of 34.82 $\pm$ 7.46 years, and disease duration of 6.62 $\pm$ 6.3 years. The median EDSS at baseline was 1.5 (ranging from 0 to 6.5). Prior to enrollment in the study, 32.35 % ($n = 11$) of patients in the ME-DMT group had experienced at least one episode of optic neuritis. A total of 16 subjects (47.06 %) were drug-naive before starting the study. The medications taken at baseline in this group included interferon-beta ($n = 14$), dimethyl fumarate ($n = 10$), teriflunomide ($n = 5$), and glatiramer acetate ($n = 5$). During the follow-up period, 7 patients switched DMTs to one of the medications classified as moderate efficacy. The baseline GCIPL thickness (averaged across both eyes) was 71.47 $\pm$ 6.03 μm and decreased to 70.33 $\pm$ 6.23 μm at follow-up.

The HE-DMT group included the remaining 56 participants (44 females), with a mean age of 38.04 $\pm$ 9.92 years, an age of onset of 29.04 $\pm$ 9.24 years, a mean disease duration of 9 $\pm$ 7.58 years, and a median EDSS at baseline of 2.0 (ranging from 0 to 7.5). At least one episode of ON prior to enrollment was recorded in 60.71 % ($n = 34$) of HE-DMT

subjects. In this group, 11 patients (19.64 %) were drug-naive at T0. The medications taken by participants in this group included ocrelizumab ($n = 33$), natalizumab ($n = 11$), cladribine ($n = 4$), alemtuzumab ($n = 6$), and rituximab ($n = 2$). Of these subjects, 2 changed their medication before the end of the follow-up period, switching to another DMT within the same efficacy tier. The mean baseline GCIPL thickness was 64.47 ± 8.44 μm and remained stable at follow-up (64.31 ± 8.52 μm) (Table 1).

At baseline, subjects in the HE-DMT group exhibited a younger age of onset ($p = 0.0012$) and a greater clinical burden, as indicated by a higher EDSS ($p = 0.0204$), a greater prevalence of ON, and a history of requiring stronger DMTs throughout their lives ($p < 0.0001$). No significant differences were observed in age or disease duration between the two groups. In terms of GCIPL thickness, patients in the HE-DMT group showed greater atrophy at baseline, likely associated with the increased severity of their MS ($p < 0.0001$). Additionally, the follow-up period was significantly longer for the HE-DMT group ($p = 0.0014$).

During the follow-up period, patients in the HE-DMT group exhibited a lower annual atrophy rate of GCIPL ($p < 0.0001$). The global GCIPL thickness in patients receiving ME-DMT showed an atrophy rate of −0.64 ± 0.86 μm/year. In contrast, subjects treated with HE-DMT demonstrated stability in GCIPL thickness throughout the follow-up, with no significant atrophy observed (−0.07 ± 0.38 μm/year). The longitudinal changes in GCIPL thickness are illustrated in the Fig. 1.

These findings were further examined using multivariable linear regression. The overall model was statistically significant (F-test $p = 0.0015$), explaining approximately 13.6 % of the variance in the annualized GCIPL atrophy rate ($R^2 = 0.1357$). Among all covariates included in the model, only the treatment group (HE-DMT vs ME-DMT) showed a statistically significant independent association with GCIPL atrophy rate. No other baseline variables reached statistical significance, indicating that the overall model significance was primarily driven by the treatment effect. The results of the multivariable linear regression analysis are summarized in Table 2.

Table 1
Demographic and clinical characteristics of the MS patients treated with ME or HE DMTs. IFN-B: interferon-beta; DMF: dimethylfumarate. TER: teriflunomide; GA: glatiramer-acetate; FIN: fingolimod; OCR: ocrelizumab; NAT: natalizumab; ALE: alemtuzumab; CLA: cladribine; RTX: rituximab.

Demographic Data	Total Patients ($N = 90$, 174 eyes)	ME Patients ($N = 34$, 64 eyes)	HE Patients ($N = 56$, 109 eyes)	
Sex (female)	69 (76.6 %)	25 (73.5 %)	44 (78.5 %)	$p = 0.7874$
Age (years ± SD)	39.3 ± 9.18	41.47 ± 7.45	38.04 ± 9.92	$p = 0.0663$
Age of onset (years ± SD)	31.2 ± 9.02	34.82 ± 7.46	29.04 ± 9.24	$p = 0.0017$
Disease duration (years ± SD)	8.1 ± 7.18	6.62 ± 6.3	9 ± 7.58	$p = 0.1116$
ON history	50 % ($n = 45$)	32.35 % ($n = 11$)	60.71 % ($n = 34$)	$p = 0.0091$
EDSS (median)	2.0 (0 to 7.5)	1.5 (0 to 6.5)	2.0 (0 to 7.5)	$p = 0.0111$
Baseline Treatment		IFN-$B = 14$ DMF = 10 TER = 5 GA = 5	OCR = 33 NAT = 11 ALE = 6 CLA = 4 RTX = 2	
Follow-up treatment		IFN-$B = 11$ DMF = 13 TER = 6 GA = 4	OCR = 33 NAT = 12 ALE = 6 CLA = 3 RTX = 2	
Follow-up period (months)	28.47 ± 5.9	26.45 ± 3,74	29.7 ± 6.46	$p = 0.0036$

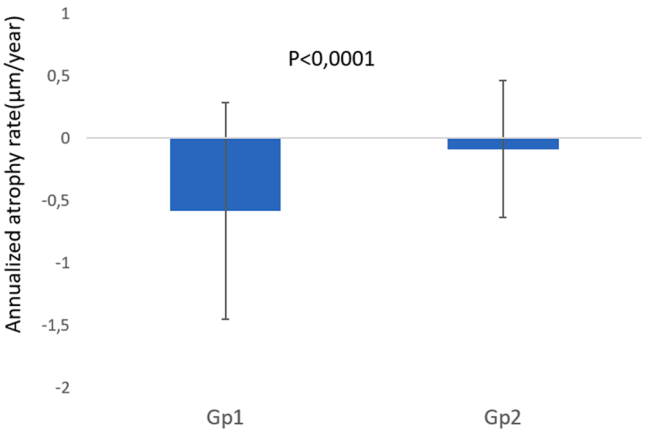

Fig. 1. Annual GCIPL Volume Loss ($p < 0,0001$)
Gp1: ME-DMT group. Gp2: HE –DMT group.

Table 2
Multivariable linear regression analysis of annualized GCIPL atrophy rate.

Predictor	β (95 % CI)	p-value
Group (HE-DMT vs ME-DMT)	0.0706 to 0.9235	0.0226
Eyes (left vs right)	−0.0074 to 0.0070	0.9550
ON history	−0.1115 to 0.3541	0.3050
Age	−0.0231 to 0.0049	0.2001
Disease duration	−0.0182 to 0.0206	0.9017
Baseline EDSS	−0.0254 to 0.1126	0.2136
Baseline DMT category	−0.2068 to 0.0454	0.2083
Baseline GCIPL thickness	−0.0015 to 0.0015	0.9749
Intercept	−1.4345 to 0.0673	0.0741

4. Discussion

Our study demonstrates that HE-DMTs significantly reduced the retinal atrophy rate during the follow-up period. This suggests that more aggressive treatment may slow down neuronal injury in MS (Saidha et al., 2015; Abalo-Lojo et al., 2014; Saidha et al., 2013). High-efficacy treatments, such as anti-CD20 agents and NTZ, are recognized for their effectiveness in mitigating the disease course by reducing relapse rates and preventing the formation of new lesions on T2-weighted MRI scans, as well as reducing brain atrophy (Lambe et al., 2021; Lanzillo et al., 2012; Pucci et al., 2011; Hauser et al., 2017; Hauser et al., 2020). In our cohort, participants receiving HE-DMTs, such as ocrelizumab and NTZ, exhibited substantially lower GCIPL atrophy compared to those treated with ME-DMTs, despite difference in baseline characteristics.

These findings align with some of the limited studies in the literature. For instance, Button et al. assessed the retinal atrophy rate in 157 patients with MS and found that NTZ was more effective in reducing GCIPL atrophy compared to conventional DMTs like interferon-beta and glatiramer acetate (Button et al., 2017). Conversely, a more recent study by Kabanovski et al. involving 67 patients found no significant differences in GCIPL atrophy among participants receiving different DMTs (Kabanovski et al., 2023).

Instead, our findings strongly support the notion that assessing retinal atrophy rates through serial OCT scans could serve as an effective strategy for monitoring treatment efficacy. This approach is particularly advantageous given that OCT is a rapid, affordable, and non-invasive examination that can be easily integrated into clinical practice.

Certainly, this study has several limitations. First, a limited number of participants were treated with specific DMTs, such as teriflunomide and glatiramer acetate for moderate-efficacy drugs, and cladribine, alemtuzumab, and rituximab for high-efficacy ones. A larger sample size and more complex stratification are necessary to understand how each individual DMT may affect retinal layer thinning. Second, the non-

randomized design introduces the potential for selection bias, as patients with more severe disease may have preferentially received more aggressive therapy."

Third, all patients included in the study were Caucasian and diagnosed with RRMS, making it impossible to extrapolate the influence of variables such as ethnicity and other MS phenotypes, including primary progressive (PPMS) or secondary progressive (SPMS) MS. However, a recent study involving 36 patients with PPMS suggests that ocrelizumab may decrease retinal atrophy, particularly in those subjects with no further clinical progression (Miscioscia et al., 2022). This indicates that outcomes in these phenotypes may be similar to those observed in our cohort.

A more comprehensive review is necessary to validate OCT measurements of retinal layer thickness and volume, ensuring that OCT can be reliably implemented in the routine evaluation of MS patients.

5. Conclusions

According to our data, HE-DMTs can significantly reduce the retinal atrophy rate, reinforcing the potential of aggressive treatments to alter the trajectory of neurodegeneration in MS. Conversely, the ME-DMT group continued to show GCIPL atrophy over time. Therefore, treatment efficacy should also be evaluated based on whether a DMT can effectively reduce the GCIPL atrophy rate. OCT has proven to be a cost-effective and rapid clinical tool that can easily be integrated into routine evaluations for individuals with MS. However, more studies focusing on a wider range of DMTs are needed to establish OCT as a more reliable instrument for assessing treatment efficacy in clinical practice.

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CRediT authorship contribution statement

Antonio Francesco Vacca: Writing – original draft, Investigation, Data curation. **Su-Chun Huang:** Writing – original draft, Software, Methodology, Data curation. **Elisa Idini:** Writing – original draft, Investigation, Data curation. **Giancarlo Coghe:** Writing – review & editing, Investigation, Data curation, Conceptualization. **Marzia Fronza:** Investigation, Data curation. **Lorena Lorefice:** Visualization, Conceptualization. **Eleonora Cocco:** Writing – review & editing, Supervision, Conceptualization. **Christian Cordano:** Writing – review & editing, Supervision, Methodology, Data curation. **Jessica Frau:** Writing – review & editing, Visualization, Supervision, Investigation, Conceptualization.

Declaration of competing interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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