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Baseline Retinal Nerve Fiber Layer Thickness and Macular Volume Quantified by OCT in the North American Phase 3 Fingolimod Trial for Relapsing–Remitting Multiple Sclerosis

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Abstract

Background—Patients with multiple sclerosis (MS) demonstrate thinning of peripapillary retinal nerve fiber layer (RNFL) and decreased macular volume as measured by optical coherence tomography (OCT). To our knowledge, there are no previous reports from a large MS OCT database with strict quality control measures that quantitate RNFL and macula in patients with relapsing–remitting multiple sclerosis.

Methods—The University of California Davis OCT Reading Center gathered OCT data at baseline as part of the North American phase 3 trial of fingolimod (Gilenya). Average RNFL thickness (RNFLT) and macular volume (TMV) were measured using time domain OCT (TD-OCT). RNFL quadrants, clock hours, and macular subfields were included. With strict quality control and accounting for signal strength differences, scans were categorized as “reduced” or “not reduced” for each field, based on being less than 5th percentile for age-matched controls derived from the normative database in the scanner software. Patients were deemed “abnormal” if at least 1 eye had reduced values for a given parameter. Patients with abnormalities in corresponding RNFL and macular subfields were compared by cross-tabulation.

Results—The TD-OCT data were prospectively collected from 939 of the 1,083 trial patients, 712 of whom met all final quality and data inclusion criteria. Of the final cohort, 242 (34.0%) demonstrated reduced (less than 5th percentile) average RNFLT in at least 1 eye. One hundred seventy-eight (25.0%) patients had reduced TMV. One hundred twenty-eight (18.0%) demonstrated both reduced TMV and RNFLT in the same eye, whereas 42 (5.8%) had reduced TMV and RNFLT in both eyes. Of the 242 patients with reduced average RNFL thickness, 128 (52.9%) also had reduced TMV. Fifty patients had reduced TMV in the absence of reduced RNFLT in at least 1 eye, a cohort prevalence of 7.0%. Quadrant and subfield analysis showed a

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predominance of temporal and inferior RNFL thinning, with inferior macular thinning corresponding best to RNFL thinning.

Conclusion—RNFL and macular thinning/volume loss is common at baseline in relapsing–remitting multiple sclerosis, as measured by TD-OCT. When the RNFL is thin, the macular volume is reduced in more than half of the patients. There is a population of reduced TMV without any reduction in RNFLT. Documenting the prevalence and distribution of these structural abnormalities supports recent reports and suggests new retinal areas to probe for functional vision changes in MS.

Retinal nerve fiber layer (RNFL) degeneration and the resulting optic nerve atrophy is a widely accepted measure of disease burden in patients with multiple sclerosis (MS) (1,2). It is thought that both anterograde and retrograde transsynaptic axon degeneration may be responsible for the loss of neural tissue in the brain and the eye affecting both the white and gray matter (3). It is evident both in magnetic resonance imaging lesion burden and on pathological specimens showing gliosis and neuronal loss, in addition to retinal ganglion cell axon degeneration (4–7).

Optical coherence tomography (OCT) has gained increasing popularity in quantifying RNFL thickness (RNFLT) as a measure of axon disease in the MS population. Both time domain and spectral domain platforms are reproducible and reliable in quantifying these changes (1,8–12). Furthermore, peripapillary RNFL thinning correlates over time with clinical measures of low-contrast letter acuity and contrast sensitivity, as well as the expanded disability score and disease duration, giving clinicians an objective way to follow disease burden (9,12–15). Even patients with MS without a history of optic neuritis have shown thinner RNFL than controls (16,17), providing evidence that at baseline, patients with MS have abnormal optic nerves.

It is now recognized that macular volume is reduced in MS vs normal eyes, and some studies have shown that macular volume loss is associated with RNFL loss (18,19). Approximately 34% of the macular volume is made up of ganglion cells and their axons, so it may be expected that macular volume loss would follow RNFL loss (8). However, OCT evidence of macular thinning has recently been demonstrated even in the absence of RNFL thinning, with new evidence of inner and outer macular atrophy (20). Thus, in early MS, there are significant fundamental structural changes of the retina that can be quantified in vivo.

The purpose of our study was to use the largest known quality-controlled database of time domain OCT (TD-OCT) in a phase 3 MS trial to describe and map the baseline thickness and/or volume of the RNFL and macula in the relapsing–remitting MS population.

METHODS

In this retrospective observational study, OCT data were collected from all screening TD-OCT scans performed for FREEDOMS 2, the phase 3 North American trial of fingolimod (Gilenya), a sphingosine 1-phosphate receptor modulator that is the first Food and Drug Administration–approved oral treatment in the relapsing–remitting MS population (21,22). Institutional review board approval was obtained at University of California Davis for this substudy.

Patients

Patients were recruited for FREEDOMS 2 based on the following inclusion criteria: men or nonpregnant women, 18–55 years of age, a diagnosis of MS as defined by 2005 revised McDonald criteria, a relapsing–remitting course with at least 1 documented relapse during

the previous 1 year or 2 documented relapses during the 2 years before randomization, and an expanded disability status scale score of 0–5.5 inclusive (Novartis Protocol for North American Phase 3 Fingolimod Clinical Trial NCT00355134, 2006). During randomization, those patients in whom a suspicion of macular edema by dilated ophthalmoscopy or OCT (increased central foveal thickness or cystic changes in the fovea) failed screening and were not randomized into the study.

Optical Coherence Tomography

OCT scans were collected at the time of randomization and in follow-up over the 2-year study, using a single alignment and capture on the time domain platform (Stratus OCT; Carl Zeiss Meditec, Inc, Dublin, CA). Fast RNFLT protocols measured A-scans in a nominal 1.73-mm radius circle of peripapillary RNFL. Data for average RNFLT, 4 quadrants, and 12 clock hours were collected. The left eye from a sample MS patient with reduced RNFLT is shown in Figure 1A. Total macular volume (TMV) and the 9 Early Treatment of Diabetic Retinopathy Study (ETDRS) sectors were also collected, using fast macular thickness protocols to measure A-scans over the 1-mm central fovea, 4 quadrants of the 1- to 3-mm inner macular ring, and 4 quadrants of the 3- to 6-mm outer macular ring (23). The same MS patient as in Figure 1A is shown in Figure 1B with reduced macular thickness.

Data from both eyes of each subject were submitted to the study sponsor and to a centralized review by masked investigators at the University of California Davis OCT Reading Center. As published previously, scans were excluded from the final database if they met any of the following criteria: signal strength less than 7 (except in the case of a few clearly visible fovea or optic nerve scans with correct centration), exported data missing, extra scans, decentered scans, wrong scans or scanner used, or they required redraw by the technician due to segmentation artifact (24).

Only patients with complete data for both eyes were included in the final OCT analysis. Measurements for each eye were categorized as “reduced” (less than 5th percentile of normal limits) or “normal, not reduced” (within or above normal limits) based on the manufacturer’s normative database of age-matched controls (25). Study analysts were masked to all clinical information beyond gender, date of birth, and eye that was measured. Thus, the number of patients with a history of optic neuritis or glaucoma was unknown.

Analysis

Percentages of age-matched individuals who had abnormal results in a given field were graphed and summarized (See Supplemental Digital Content, Figure 1, <http://links.lww.com/WNO/A81>). Scans from reduced and normal eyes were also plotted according to measured field of interest (See Supplemental Digital Content, Figure 2, <http://links.lww.com/WNO/A82>, and Figure 3, <http://links.lww.com/WNO/A83>). Average OCT thicknesses were measured in micrometers \pm one standard deviation (SD; type 1 error rate set at 0.05). Based on retinal ganglion cell axon distribution in the fundus, cross-tabulations of anatomically corresponding RNFL and macula quadrants were created. McNemar test was used to compare proportions of patients who had thinning in an RNFL quadrant and the corresponding outer or inner sector of the macula. Linear repeated-measures regression models, assuming an exchangeable correlation structure to account for the intercorrelation between eyes from the same person, were used to compare signal strength and mean thicknesses between reduced eyes and not reduced eyes (26). Models for mean thicknesses included signal strength as a covariate to ensure that differences were not due to differences in signal strength.

RESULTS

One thousand eighty-three patients were enrolled in the clinical trial. The OCT Reading Center received 18,733 scans from 939 patients at 96 sites. From this database, 2,880 high-quality representative OCT scans determined by the above strict quality control criteria (24) were selected. Only patients with complete data of each eye's macula and RNFL were used, representing 1,434 eyes in 717 patients. Across the 1,434 eyes, the average signal strength was 8.1 ± 1.5 for RNFL and 7.7 ± 1.5 for TMV. During final analysis, total average RNFLT and TMV were missing in five patients, but all subfield measures for these patients were included.

Average RNFL Thickness vs Total Macular Volume

Table 1 summarizes results of total average RNFLT and TMV. Of 712 patients, 242 (34.0%) had reduced average RNFLT. TMV was reduced in 178 (25.0%) patients. Average RNFLT and TMV were reduced in the same eye of 128 (18.0%) patients. Of the 242 patients with reduced average RNFLT, 128 (52.9%) also demonstrated reduced TMV. Fifty patients had reduced TMV without reduction in RNFLT in the same eye, representing 7.0% of all patients in the study cohort and 10.6% of all patients with a normal RNFLT.

Of the 712 patients with average RNFLT and TMV available for both eyes, 153 (21.5%) demonstrated bilaterally reduced values for one or both categories: bilateral RNFLT in 115 individuals, bilateral TMV in 80 individuals, and bilateral RNFLT and TMV in 42 patients. Twenty-one patients had bilaterally reduced TMV without RNFLT reduction in either eye.

RNFL and Macular Subfield Thickness

Figure 1A (See Supplemental Digital Content, <http://links.lww.com/WNO/A81>) summarizes the percent of patients with reduced RNFLT in at least one eye by quadrants and clock hours. RNFLT was most often reduced in the temporal quadrant (34.3% of the patients) and in clock hours 2 (41.7%) and 7 (52.7%). Reduced eyes had significantly lower signal strength for all RNFL measures (Table 2), but even after accounting for these differences, the average RNFL values were significantly different between normal and thin eyes (Table 3, $P < 0.001$ for all RNFL measures). Figure 1B (See Supplemental Digital Content, <http://links.lww.com/WNO/A81>) summarizes the percent of patients with reduced macular thickness in at least one eye by ETDRS subfield. TMV was $5.97 \pm 0.20 \text{ mm}^3$ for normal eyes and $6.83 \pm 0.38 \text{ mm}^3$ for reduced eyes. In general, the frequency of reduced thickness in the inner quadrants was higher than that in the outer quadrants. The highest frequency of macular thinning was found in the inner temporal (37.4%) and inner inferior (34.9%) subfields. The lowest frequency regions of thinning were the central 1-mm fovea (7.8%) and the outer nasal quadrant (2.5%). Reduced eyes had significantly lower signal strength for TMV and the outer quadrants (Table 4), but even after accounting for these differences, all macular values were significantly different between normal and thin eyes (Table 5; $P < 0.001$ for all macular measures).

RNFL quadrants and macular sectors that corresponded anatomically are compared in Table 6. The percentage of patients with thinning in the RNFL quadrant that were also thin in the macula quadrant is also presented. The highest frequency of concurrent thinning in RNFL and macula quadrants occurred in the superior RNFL and inner temporal macula (17.1%). Thinning of the inferior RNFL was associated with the inner temporal macula (16.9%), inner inferior macula (16.5%), and outer inferior macula (15.5%). In most cases, percentages between inner and outer macula quadrant and RNFLT were significantly different ($P < 0.001$, McNemar test).

DISCUSSION

Our study demonstrated baseline thinning of the RNFL reduced macular volume in the largest quality-controlled data set of OCT from a phase 3 MS trial cohort to date. In this population, about one third of the patients had RNFL thinning at baseline and one-quarter of patients had reduced TMV. Average RNFLT and TMV were collectively reduced in 18.0%. When the RNFLT was reduced, the macular volume was reduced in over half of the patients (52.9%). In other words, individuals with RNFL reduction were much more likely to have TMV reduction (128 of 242 patients, 52.9%) than individuals without RNFL reduction (50 of 470 patients, 10.6%). In total, macular volume was reduced in the absence of RNFL reduction in 7.0% of the trial cohort. Additionally, many subfields of RNFL and macula were abnormal, with the inferior RNFL and inferior and temporal macula showing the most collectively reduced values. There is no doubt that a significant fraction of this cohort had objective OCT evidence of structural damage to not only the optic nerve but the macula as well at baseline.

The fact that RNFL and macular thinning are linked in this population is not a new idea (8,17,19). However, this study is arguably the largest database of the MS OCT trial data that has undergone strict quality control with a centralized OCT reading center. Additionally, this study detailed which subfields of the macula and quadrants or clock hours of the optic nerve were preferentially affected. They were often affected together, particularly in the inferior region, likely representing inferior peripapillary RNFL from ganglion cells with axons originating in the inferior macula.

Our study also supported the notion that a subset of patients with MS may have structural damage to the macula in the absence of damage to the RNFL. Saidha et al (20) described the preferential macular involvement in 10% of their 450 patients with MS as measured by the spectral domain OCT, who appeared to have worse disease severity scores and more severe macular function by multifocal electroretinography. Our results showed that 7.0% of 712 patients (10.6% of the patients with a normal RNFLT) had reduced TMV in the absence of thin average RNFL. Our data collected with TD-OCT supported the findings of Saidha et al. Reduced central foveal area in 7.8% of our patients also demonstrated that MS can affect the outer retinal layers. This has been observed in patients with long-standing MS using adaptive optics (27,28).

Patients with a history of MS tend to develop peripapillary RNFL thinning in the temporal quadrant, which preferentially affects the papillomacular bundle (29). In our study, the papillomacular bundle region showed great thickness variability. Thinning of the temporal optic nerve quadrant occurred in 246 patients (34.3%). The inner nasal macula was thin in 20.8%, and the outer nasal macula was thin in only 2.5%. The inner macular ring encompasses a thicker ganglion cell layer than that of the outer macular ring (30), which may offer a possible explanation for this disparity because ganglion cells in the inner sector would contribute proportionally more to overall macular thickness than other retinal layers. Nevertheless, other macular sectors did not demonstrate such a dramatic difference.

Although the temporal RNFL was the most commonly thinned quadrant, as reported in previous studies (29), the clock hours of greatest thinning were in the inferior quadrant. Since the inferior RNFL is traditionally the thickest quadrant, it is not surprising that the inferior RNFL would show the most thinning since there are more nerve fibers at risk.

A true comparative subfield analysis was limited by predetermined normative database and analysis plots for ETDRS sectors in the macula and RNFL quadrants. These regions may not optimally correspond in anatomical distribution. For example, the superior and inferior RNFL both represent axons from the temporal macula. Also, nominal categories of reduced

and not reduced did not allow for continuous variable analysis to determine which patients had values near but not beyond the threshold of 5% (i.e., low-normal, just above 5%), the analysis of which may clarify any linear relationships between RNFL and macular thinning.

The lack of segmentation algorithms in TD-OCT precludes further interpretation of our data set. As technology improves and time domain platforms give way to spectral domain and high-resolution OCT, intraretinal OCT segmentation algorithms and volume mapping are now beginning to detail how much of macular thinning is due to ganglion cell death or RNFL loss vs damage to outer retinal layers (20,27,28,31,32).

In conclusion, our study showed that both the RNFL and macula are commonly thinned in the relapsing–remitting MS population at baseline. We confirmed that when the average RNFL is thin, the macula showed reduced volume at baseline. We also documented a population of patients in whom the macula was preferentially affected, despite normal RNFL as measured by TD-OCT. Future assessment of the longitudinal and clinical data from the MS fingolimod trial should provide insights into the populations at risk of macular pathology and loss of visual function.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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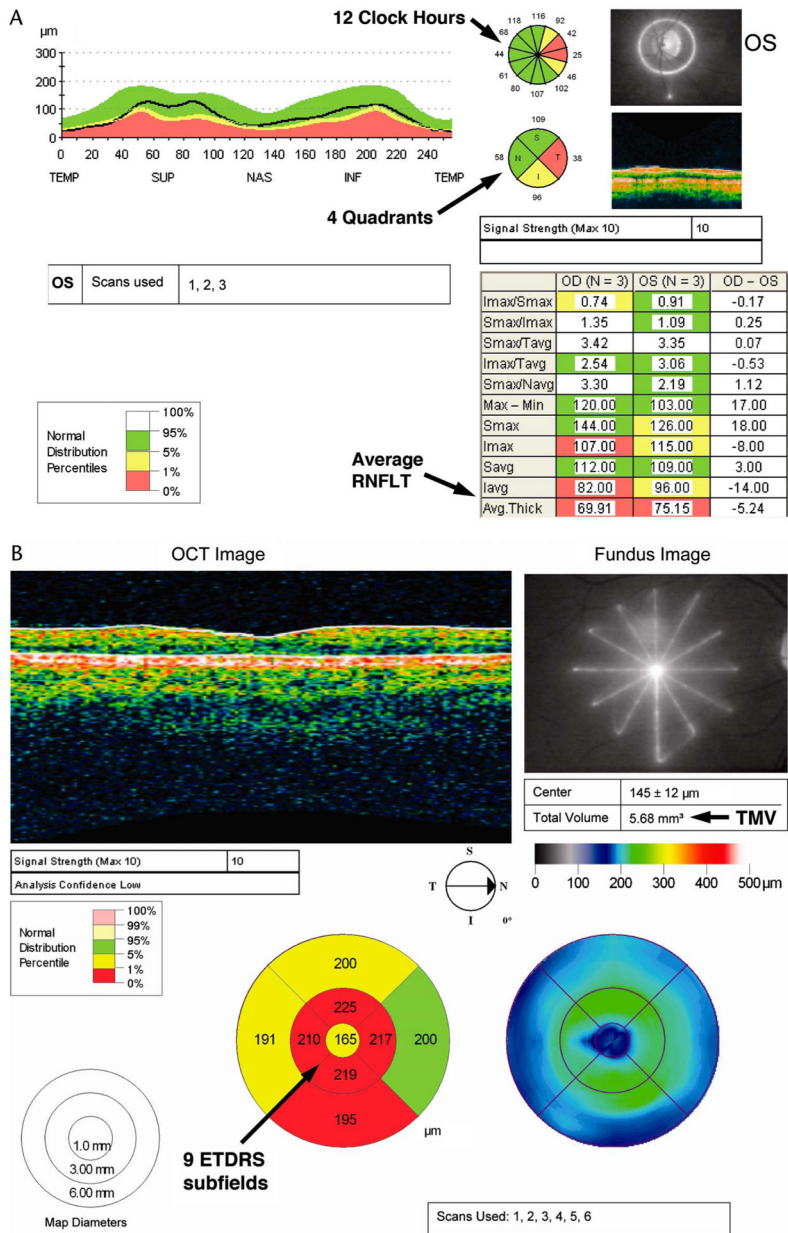


FIG. 1. Left eye of a patient with relapsing-remitting multiple sclerosis. **A.** Fast retinal nerve fiber layer thickness (RNFLT) protocol shows reduced RNFLT. **B.** Fast macular thickness protocol reveals reduced total macular volume and macular sector thickness. ETDRS, Early Treatment of Diabetic Retinopathy Study; OCT, optical coherence tomography; OS, left eye; TMV, total macular volume.

TABLE 1

Patients with abnormal TMV vs abnormal average RNFLT in at least one eye

	RNFLT Normal, n (%)	RNFLT Abnormal, n (%)	
TMV normal	420 (59.0)	114 (16.0)	534 (75.0)
TMV abnormal	50 (7.0)	128 (18.0)	178 (25.0)
Total	470 (66.0)	242 (34.0)	712

RNFLT, retinal nerve layer thickness; TMV, total macular volume.

TABLE 2

Signal strength differences in reduced and not reduced eyes for retinal nerve fiber layer thickness

RNFL Region	Average Signal Strength of Reduced Eyes (SD)	Average Signal Strength of Not Reduced Eyes (SD)*	P
Average thickness RNFL	7.75 (1.54)	8.31 (1.44)	<0.001
Superior average RNFL	7.86 (1.52)	8.25 (1.46)	<0.001
Inferior average RNFL	7.71 (1.51)	8.29 (1.45)	<0.001
Temporal average RNFL	7.79 (1.56)	8.27 (1.45)	<0.001
Nasal average RNFL	7.78 (1.45)	8.23 (1.49)	<0.001
Clock hour 1 [†]	7.79 (1.59)	8.27 (1.45)	<0.001
Clock hour 2	7.89 (1.48)	8.27 (1.49)	<0.001
Clock hour 3	7.75 (1.51)	8.30 (1.45)	<0.001
Clock hour 4	7.76 (1.62)	8.27 (1.44)	<0.001
Clock hour 5	7.69 (1.56)	8.23 (1.48)	<0.001
Clock hour 6	7.76 (1.50)	8.24 (1.47)	<0.001
Clock hour 7	7.93 (1.50)	8.25 (1.49)	0.007
Clock hour 8	7.73 (1.58)	8.29 (1.44)	<0.001
Clock hour 9	7.75 (1.57)	8.26 (1.45)	<0.001
Clock hour 10	7.78 (1.57)	8.25 (1.46)	<0.001
Clock hour 11	7.70 (1.57)	8.30 (1.44)	<0.001
Clock hour 12	7.89 (1.54)	8.20 (1.47)	0.009

* Includes all normal eyes of individuals with both eyes not reduced.

[†] Clock hours are standardized such that left eyes have been flipped to correspond with right eye orientation, that is, 9-o'clock position corresponds to the temporal quadrant and 3-o'clock position corresponds to the nasal quadrant.

RNFL, retinal nerve fiber layer; SD, standard deviation.

TABLE 3

Distribution of RNFL thinning by quadrant and clock hour in relapsing–remitting multiple sclerosis patients with at least one eye affected

RNFL Region	Percent of Patients With at Least One Eye <5% Normal Thickness, %	Average Value of Reduced Eyes, μm (SD)	Average Value of Not Reduced Eyes, μm (SD)*
Average thickness RNFL	34.0 [†]	73.3 (8.2)	100.1 (9.9)
Superior average RNFL	28.3	86.2 (11.1)	123.9 (15.2)
Inferior average RNFL	26.6	85.4 (10.9)	126.2 (16.6)
Temporal average RNFL	34.3	41.1 (6.1)	68.4 (11.8)
Nasal average RNFL	17.6	46.8 (6.2)	81.1 (17.0)
Clock hour 1 [‡]	27.6	70.3 (11.7)	118.8 (21.1)
Clock hour 2	41.7	51.7 (10.2)	92.0 (19.7)
Clock hour 3	36.4	34.3 (5.1)	61.4 (16.0)
Clock hour 4	29.8	40.7 (6.9)	75.3 (17.6)
Clock hour 5	15.6	60.3 (9.5)	117.7 (25.9)
Clock hour 6	21.8	79.0 (13.8)	136.5 (23.8)
Clock hour 7	52.7	78.3 (14.0)	127.6 (20.7)
Clock hour 8	27.7	40.2 (5.9)	73.8 (17.1)
Clock hour 9	27.6	32.6 (4.0)	57.7 (14.7)
Clock hour 10	24.5	46.5 (7.8)	87.5 (20.6)
Clock hour 11	32.5	80.5 (13.8)	126.3 (19.6)
Clock hour 12	21.1	73.2 (11.7)	126.3 (22.4)

* Includes all normal eyes of individuals with both eyes not reduced.

[†] Average RNFL% is out of 712 patients due to 5 patients missing only this measurement. All sectors and clock hours are percentage out of 717 patients.

[‡] Clock hours are standardized such that left eyes have been flipped to correspond with right eye orientation, that is, 9-o'clock position corresponds to the temporal quadrant and 3-o'clock position corresponds to the nasal quadrant.

RNFL, retinal nerve fiber layer; SD, standard deviation.

TABLE 4

Signal strength differences in reduced and not reduced eyes for macula

Macular Subfield	Average Signal Strength of Reduced Eyes (SD)	Average Signal Strength of Not Reduced Eyes (SD)*	P
Total macular volume	7.44 (1.53)	7.79 (1.51)	0.01
Outer superior average thickness	7.30 (1.42)	7.78 (1.53)	0.
Outer nasal average thickness	7.09 (1.37)	7.75 (1.53)	0.04
Outer inferior average thickness	7.40 (1.52)	7.82 (1.50)	<0.001
Outer temporal average thickness	7.43 (1.53)	7.84 (1.51)	<0.001
Inner superior average thickness	7.61 (1.49)	7.76 (1.52)	0.24
Inner nasal average thickness	7.61 (1.50)	7.76 (1.53)	0.28
Inner inferior average thickness	7.59 (1.54)	7.76 (1.50)	0.21
Inner temporal average thickness	7.68 (1.56)	7.74 (1.51)	0.52
Central foveal area thickness	7.84 (1.59)	7.72 (1.53)	0.49

* Includes all normal eyes of individuals with both eyes not reduced.

TABLE 5

Distribution of macular thickness by subfield in relapsing–remitting multiple sclerosis patients with at least one eye affected

Macular Subfield	Percent of Patients With at Least One Eye <5% Normal, %	Average Value of Reduced Eyes, μm (SD) [*]	Average Value of Not Reduced Eyes, μm (SD) [†]
TMV	25.3 [‡]	5.97 (0.20)	6.83 (0.38)
Outer superior average thickness	14.1	200.8 (6.9)	234.5 (14.9)
Outer nasal average thickness	2.5	193.3 (3.8)	245.8 (19.9)
Outer inferior average thickness	28.4	199.0 (7.7)	230.8 (13.8)
Outer temporal average thickness	28.3	193.8 (6.8)	221.4 (15.5)
Inner superior average thickness	23.7	233.5 (9.5)	270.8 (15.1)
Inner nasal average thickness	20.8	229.2 (10.5)	269.6 (16.9)
Inner inferior average thickness	34.9	236.0 (12.3)	271.0 (18.0)
Inner temporal average thickness	37.4	228.9 (9.8)	261.1 (17.1)
Central foveal area thickness	7.8	159.6 (7.3)	203.6 (21.6)

* Except for TMV, which is measured in cubic millimeters.

[†] Includes all normal eyes of individuals with both eyes not reduced.

[‡] TMV% is of 712 patients due to 5 patients missing only this measurement. All sectors are percent of 717 patients.

TMV, total macular volume.

TABLE 6

Comparison of reduced retinal nerve fiber layer thickness to reduced macular thickness by quadrant or sector

RNFL Quadrant	Macular Subfield	Percent of Patients With Reduced RNFLT and Macular Thickness in the Same Eye, %
Superior	Outer superior	7.9
Superior	Inner superior	11.4
Superior	Outer temporal	12.4
Superior	Inner temporal	17.1
Inferior	Outer inferior	15.5
Inferior	Inner inferior	16.5
Inferior	Outer temporal	13.7
Inferior	Inner temporal	16.9
Temporal	Outer nasal	2.1
Temporal	Inner nasal	11.8
RNFL average	Total macular volume	17.8
RNFL average	Central 1 mm thickness	3.8

RNFL, retinal nerve fiber layer; RNFLT, retinal nerve fiber layer thickness.