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Research Article

Changes in Retinal Thickness and Brain Volume during 6.8-Year Escalating Therapy for Multiple Sclerosis

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Background. Different disease-modifying therapies (DMT) for multiple sclerosis (MS) have disparate effects on disability outcomes. Sweden has a leading position globally in initiating high-efficacy DMT instead of escalating DMT from 1st-line to high-efficacy DMT. With optical coherence tomography (OCT), retinal changes can be measured at a few micrometer level. OCT has been increasingly applied in diagnosing MS and monitoring disease course and therapeutic effect. *Objective.* We investigate the effects of 1st-line versus high-efficacy DMT for MS on retinal and brain atrophy and on functional outcomes during 6.8 years of escalating DMT. *Materials and Methods.* In this prospective longitudinal observational study, 18 MS patients were followed up for 6.8 years. Twelve of the patients were untreated at baseline. All patients underwent 1st-line DMT for median duration of 2.4 years and then switched to high-efficacy DMT for a median duration of 2.9 years. Findings from neurological examinations, MRI, and OCT measures were registered 2-4 times per year. *Results.* Ganglion cell-inner plexiform layer (GCIPL) thickness was significantly reduced during 1st-line DMT (73.75 μm, $p < 0.01$) compared to baseline (76.38 μm). During high-efficacy DMT, thickness reduction was slower (73.27 μm, $p < 0.05$), and MRI contrast-loading lesions vanished ($p < 0.01$). However, brain parenchymal fraction (BPF) decreased during high-efficacy DMT compared to 1st-line DMT. Estimated models showed similar results. *Conclusion.* GCIPL decline was most profound during 1st-line DMT and diminished during high-efficacy DMT. MRI contrast lesions vanished during high-efficacy DMT. However, brain atrophy continued regardless of high-efficacy DMT.

1. Introduction

Disease-modifying therapies (DMT) for relapsing-remitting multiple sclerosis (RRMS) have been gradually shifting from 1st-line to high-efficacy DMT [1, 2]. Sweden has a leading position globally in initiating early high-efficacy DMT, such as monoclonal antibody against CD20 B lymphocytes, instead of escalating DMT from 1st-line to high-efficacy DMT [3, 4]. The rationale for initiating high-efficacy DMT is to suppress inflammation and stop relapses as early and as effectively as possible, thereby preventing disease progression and functional disability [5–7]. Therapeutic use of

1st-line DMT with low potency for RRMS entered into clinical practice in the 1990s with injectable interferon-beta and glatiramer acetate (GA). Since 2013, teriflunomide and dimethyl fumarate in tablet form were used as alternative therapy for 1st-line DMT when interferon-beta or GA was unsuitable to be continued. Since then, the use of high-efficacy DMT either as switch therapy or first-line therapy has rapidly increased [4, 7]. Nowadays, injectable 1st-line DMT is rarely initiated and often discontinued in Sweden. The rise of high-efficacy DMT has resulted in better outcome for RRMS to achieve the "no evidence of disease activity" (NEDA) [8]. NEDA is measured according to

clinical activity, subclinical activity, inflammatory disease activity, and progressive activity, even in the absence of clinical relapses. MRI brain atrophy and neurofilament levels are also biomarkers used to measure NEDA, but at advanced levels [6]. Two recent Nordic studies have shown that early use of high-efficacy DMT yielded more favorable outcomes to achieve NEDA in early disease course and reduced the risk of disability progression [9, 10]. Optical coherence tomography (OCT) is an upcoming technique allowing to measure retinal microstructure changes and being increasingly used in monitoring MS course and therapeutic effect [11, 12]. OCT is a high-resolution imaging of the retina. The retinal microstructures studied with OCT are supposed to mirror the status of the whole brain [11, 13, 14]. OCT has been applied to diagnose MS and monitor disease course [11, 15, 16]. OCT measures including macular ganglion cell-inner plexiform layer (GCIPL) and peripapillary retinal nerve fiber layer (pRNFL) show strong association with visual functions [17–19] and correlate with brain atrophy [13, 20–22]. With OCT, the thickness of GCIPL and pRNFL can be measured at a few micrometer level with good reproducibility, thereby providing reliable and sensitive biomarkers to survey MS outcome [7, 11, 20, 23].

The aim of this study is to investigate the changes in the clinical outcomes of RRMS patients during 1st-line DMT and after therapy switch to high-efficacy DMT, compared to baseline with no therapy. The clinical outcomes included Expanded Disability Status Scale (EDSS), MS severity score (MSSS), number of brain lesions and brain volume assessed with magnetic resonance imaging (MRI), as well as brain parenchymal fraction (BPF). Additionally, changes in GCIPL and pRNFL thickness, measured with serial OCT examinations, were studied in parallel.

2. Materials and Methods

2.1. Study Design and Participants. This is a prospective, longitudinal, and observational study. The follow-up intervals and therapy switch are purely based on clinical need rather than research design. Eighteen patients with RRMS were consecutively recruited at the Neurological Clinic of Linköping University Hospital, Sweden, from February 2013 to December 2018. Inclusion criteria were that the patients fulfilled RRMS diagnosis according to 2010 McDonalds criteria [24], with ($n = 6$) or without ($n = 12$) 1st-line DMT at baseline. All 18 patients were later treated with the 1st DMT and then switched to high-efficacy DMT due to MS activity. The follow-up time for each DMT was at least 12 months. Interferon beta-1a (44 μg, subcutaneous injection every other day), interferon beta-1b (250 μg, subcutaneous injection every other day), dimethyl fumarate (240 mg, twice every day), and teriflunomide (14 mg, once every day) were included as 1st-line DMT. Natalizumab (300 mg, infusion every 4-5 weeks), rituximab (500 mg, infusion every 6 months), and cladribine (3.5 mg per kg body weight in total, administered during two treatment weeks per year over the course of two years) were included as high-efficacy DMT.

Enrollment and data acquisition were performed through convenience sampling. The revised 2017 McDonalds criteria [25] were not used since recruitment of patients had started before the new criteria were widely used in clinics in Sweden. However, cerebrospinal fluid (CSF) including cell count and oligoclonal IgG bands (OB) has been a routine investigation in MS diagnosis in Sweden.

2.2. Clinical Data Collection. MS severity was evaluated according to Expanded Disability Status Scale (EDSS), a globally accepted method to semiquantify disability of MS, and is widely used as a primary measurement of functional outcome [26, 27]. EDSS consists of a noncontinuous ordinal scale ranging from 0 to 10. Furthermore, MS Severity Score (MSSS) was included to correct EDSS for disease duration [28].

Clinical data were recorded at recruitment including MS symptoms at onset, MS duration, history of optic neuritis (ON), EDSS, MSSS, CSF findings including cell count and OB, and MRI lesions in the brain and the spinal cord (Tables 1 and 2). Visual function test including visual acuity on Snellen chart and OCT examination of peripapillary and macular areas were also performed at recruitment. Clinical examinations including EDSS and MSSS, as well as imaging (MRI and OCT), were registered 1-2 times per year.

2.3. Optical Coherence Tomography (OCT). OCT was performed at least 3 months prior to treatment; follow-up examinations with OCT were done according to clinical schedule. Examinations with a gap time less than 4 months were excluded. OCT examinations were performed in accordance with the consensus APOSTEL recommendation [29]; the same applied to presentation of results.

The OCT hardware used was Spectral Domain (SD) Cirrus HD-OCT (model 4000; Carl Zeiss Meditech), and the software was Cirrus HD-OCT 4000 version 6.5. Two trained operators oversaw collecting and reviewing of OCT data accordingly. Patients were examined in a dark room and without pupil dilation. Peripapillary and macular areas were studied in both eyes: macular GCIPL thickness was measured using macular cube 512×128 protocol with a 6 mm rim centered at the fovea; pRNFL thickness was measured using optic disk 200×200 protocol with a custom 3.4 mm ring centered at the optic disk. Scans with signal strength of 7/10 or above were included.

All patients had a visual function test including a Snellen visual acuity chart. Only non-ON or best eyes were included in the analysis.

2.4. Magnetic Resonance Imaging (MRI). The brain and spinal cord MRI was performed on all patients according to standard MS protocol [30]. T1-weight imaging with and without gadolinium enhancement, T2, and FLAIR were included. Quantitative images were retrieved using the QMAP sequence. Brain parenchymal fraction (BPF) was calculated using brain parenchymal volume (BPV) divided by intracranial volume (ICV) [31]. MRI examinations were performed and registered at least once per year.

2.5. Statistical Analysis. All data were analyzed using Statistical Package for the Social Sciences (SPSS) version 28.

TABLE 1: Demographic and clinical characteristics.

Female/male (ratio)	14/4 (3.5)
Age, years	36.9 ± 10.6
MS duration, years	4.20 ± 5.65
Follow-up duration, years	6.8 (4.2-8.3)
Untreated/treated, n/n	12/6
OB positive in CSF	17/17 (100)
OB count in CSF	10 (2–10)
History of ON	6 (33.3)
CSF cell count, $\times 10^6$/L	6.1 (0.5–11.6)
Pleocytosis in CSF, n/n	10/17 (58.8)

Abbreviations: OB: oligoclonal bands; DMT: disease-modifying treatment; OCT: optical coherence tomography; ON: opticus neuritis; CSF: cerebrospinal fluid. If not specified, values are n (%), mean ± SD, or median (interquartile range).

Thickness of GCIPL and pRNFL and score of EDSS and MSSS were used as outcome measurements.

The Cochranes Q test was used to analyze categorical data (periventricular, infratentorial, juxtacortical, gadolinium, and spinal cord lesions) over time.

Repeated measures ANOVA were used to analyze the differences in means between the measurements of each period for each patient. Friedman test was used for nonparametric data. Paired samples T-test was used to analyze changes of BPF.

Generalized linear mixed models (GLMM) were used to analyze GCIPL, pRNFL, BPF, EDSS, and MSSS during three periods: baseline and DMT periods. GLMM model was also used to adjust for time between OCT examinations.

3. Results

3.1. Demographic and Clinical Data. Eighteen patients were enrolled in the study, six of them had 1st-line DMT at baseline, and 12 were untreated. All 18 patients were later treated with 1st-line DMT and then switched to high-efficacy DMT due to MS activities. The mean age of patients was 36.9 ± 10.6 years. The ratio of females to males was 3.5. The average duration of MS diagnosis was 4.20 ± 5.65 years. The median follow-up duration was 6.8 (4.2–8.3) years. Six patients had a history of unilateral ON. Seventeen patients underwent lumbar puncture (LP). Ten of 17 had pleocytosis in cerebrospinal fluid (CSF), and all 17 patients showed OB in CSF (Table 1).

Twelve of 18 patients were untreated at baseline with follow-up period of 3.5 months and underwent 26 OCT examinations before initiating 1st-line DMT. Eighteen patients with 1st-line DMT (interferon-beta: $n = 15$; teriflunomide: $n = 2$; dimethyl fumarate: $n = 1$) underwent 66 OCT examinations during a period of 2.42 (1.17-8.44) years before switching to high-efficacy DMT. All 18 patients with high-efficacy DMT (rituximab: $n = 15$; natalizumab: $n = 2$; cladribine: $n = 1$) underwent 64 OCT examinations during a period of 2.92 (1.77-5.35) years.

3.2. EDSS, MSSS, and MRI Parameters at Baseline and during DMT. The mean EDSS was 0.75 at baseline (Table 2). The mean EDSS during 1st-line DMT was 0.86 and 0.44 during high-efficacy DMT. However, differences of EDSS did not reach statistical significance ($p = 0.649$). MSSS had a mean score of 1.34 at baseline, 0.75 during 1st-line DMT, and 0.70 during high-efficacy DMT. Changes of MSSS showed no statistical significance ($p = 0.779$).

The average number of MRI brain lesions was 14 (4–20) at baseline. The average number of lesions during 1st-line DMT was 19 (7–22) and 19 (10-23) during high-efficacy DMT. The number of lesions was significantly increased over time ($p = 0.015$) (Table 2). MRI gadolinium loading lesions were significantly reduced (baseline: $n = 7$; 1st-line DMT: $n = 4$; high-efficacy DMT: $n = 0$) over time during high-efficacy DMT compared to baseline ($p = 0.048$).

BPF data were not available at baseline. BPF data were available from 11 patients during both 1st-line and high-efficacy DMT period (Table 2). BPF was 88.09 ± 0.04% at 1st-line DMT and 87.24 ± 0.04% at high-efficacy DMT. The reduction of BPF from 1st-line to high-efficacy DMT was 0.85% ($p = 0.003$).

3.3. Changes of OCT Parameters during Treatment Compared to Baseline. Serial OCT examinations ($n = 156$) were recorded for a period of 6.83 (4.15–8.33) years (Table 1). The average time gap of OCT examinations was 8.06 (6.72–12.80) months. The mean GCIPL thickness at baseline was 76.38 μm (Table 2), 73.75 μm during 1st-line DMT, and 73.27 μm during high-efficacy DMT. The mean GCIPL thickness was significantly reduced over time according to repeated measures ANOVA ($p < 0.01$). The mean GCIPL thickness was significantly thinner during 1st-line DMT ($p = 0.004$) and during high-efficacy DMT ($p = 0.029$) compared to baseline (Figure 1(a)). However, the thickness of GCIPL between 1st-line DMT and high-efficacy DMT did not differ.

The mean pRNFL thickness did not differ significantly over time ($p = 0.094$) regardless of therapy periods, although it was slightly thicker at baseline (Table 2, Figure 1(b)).

3.4. Estimated Values of EDSS, MSSS, BPF, GCIPL, and pRNFL Thickness. The GLMM analysis showed similar results as repeated measures ANOVA (Table 3). EDSS (0–10, disability score normal to death) and MSSS (0–10, disability progression score normal to death) showed no significant changes over time. EDSS rate was estimated to increase by 0.02 per year, and MSSS was estimated to decrease by 0.07 per year.

BPF was significantly lower during high-efficacy DMT compared to 1st-line DMT ($p < 0.001$). Time-adjusted analysis showed reduction rate of BPF by 0.2% per year ($p < 0.001$).

GCIPL thickness was significantly thinner during therapy periods compared to baseline ($p < 0.001$ and $p < 0.05$) (Table 3, Figure 2(a)). Time-adjusted analysis showed a significant reduction rate of GCIPL thickness by 0.22 μm per year ($p < 0.001$).

pRNFL thickness was significantly thinner during 1st-line DMT compared to baseline ($p < 0.05$). Time-adjusted

Table 2: Results of clinical data and OCT parameters over time.

	Baseline (untreated)	1st-line DMT	High-efficacy DMT
Patients	12 (66.7)	18 (100)	18 (100)
Follow-up duration, years	0.25 (0.02–0.52)	2.42 (1.17–8.44)	2.92 (1.77–5.35)
EDSS	0.75 (0.00–1.00)	0.86 (0.32-1.13)	0.44 (0.00–1.50)
MSSS	1.34 (0.52-3.06)	0.75 (0.36-2.23)	0.70 (0.17-1.38)
MR findings			
Total brain lesions	14 (4-20)[1]*	19 (7-22)[1]*	19 (10-23)[1]*
Gd lesions	7 (53.8)	4 (22.2)	0(0.0)[2]*
Periventricular lesions	12 (100)	18 (100)	18 (100)
Juxtacortical lesions	10 (83.3)	16 (88.9)	15 (83.3)
Infratentorial lesions	4 (33.3)	7 (38.9)	8 (44.4)
Spinal cord lesions	10 (83.3)	15 (83.3)	15 (83.3)
BPF		88.09 ± 0.04	87.24 ± 0.04[3]**
OCT measures			
GCIPL, μm	76.38 ± 6.06	73.75 ± 7.37[4]**	73.27 ± 7.27[4]*
pRNFL, μm	88.44 ± 11.50	86.53 ± 11.16	86.28 ± 11.36

Abbreviations: NA: not applicable; DMT: disease-modifying treatment; EDSS: expanded disability status scale; MSSS: multiple sclerosis severity score; gd: gadolinium; BPF: brain parenchymal fraction; OCT: optical coherence tomography; GCIPL: ganglion cell inner-plexiform layer; pRNFL: peripapillary retinal nerve fiber layer. Values are n (%), mean ± SD, or median (interquartile range). [1]*Total brain lesions: Friedman's test ($p < 0.05$). [2]*Gd lesions: Cochran's Q test: pairwise comparison by McNemar's test: baseline vs. high-efficacy DMT ($p < 0.05$). [3]**BPF: paired samples T-test ($p < 0.01$). [4]**/*GCIPL: repeated measures ANOVA: post hoc pairwise comparison (Bonferroni corrected): baseline vs. 1st-line DMT (**$p < 0.01$), baseline vs. high-efficacy DMT (*$p < 0.05$).

analysis showed a significant reduction rate of pRNFL thickness by 0.48 μm per year ($p < 0.001$) (Table 3, Figure 2(b)).

4. Discussion

During the period of 2013 to 2018, we recruited 18 patients who were on 1st-line DMT and followed them systematically for a median duration of 6.8 years. Twelve of these patients had no therapy at baseline. After more than one year on 1st-line DMT, all the patients had been switched from 1st-line DMT to high-efficacy DMT with rituximab (off-label), natalizumab, or cladribine. All the patients were regularly assessed with neurological examinations including EDSS and MSSS, as well as MRI including BPF. Serial assessments of GCIPL and pRNFL were performed using OCT to ensure reliability and reproducibility. The results from this study demonstrate that GCIPL decline was most profound during 1st-line DMT. Reduction of GCIPL slowed down during high-efficacy DMT. MRI contrast loading lesions were reduced during 1st-line DMT and vanished during high-efficacy DMT. However, pathological loss of BPF remained during high-efficacy DMT.

In this study, duration of 1st-line DMT (2.4 years) and high-efficacy DMT (2.9 years) was comparable. EDSS and MSSS tended to be lower during high-efficacy DMT than during 1st-line DMT though without statistical significance. However, MRI gadolinium loading lesions disappeared during the 2.9 years of high-efficacy DMT indicating suppressed disease activity. Additional generalized linear mixed model (GLMM) adjusted to time demonstrated a minimal EDSS increment by 0.02 per year; on the contrary, it showed a decrement in MSSS by 0.07 per year indicating reduced

MS progression. MSSS is based on EDSS score with correction for disease duration, and it is considered to predict disease progression [28]. It is therefore not surprising that, with escalated therapy or high-efficacy DMT, disability progression can be delayed [3, 9, 10, 32].

BPF was lower during 1st-line DMT (88.1% ± 0.4) compared to healthy controls (89% ± 0.4), as it has been shown in other studies [33, 34]. A significant decline in BPF was observed during high-efficacy DMT (87.2% ± 0.4, $p < 0.01$). In this longitudinal study, BPF reduction was 0.84% over a time of 6.8 years, and the estimated reduction rate was 0.2% per year; this level of BPF reduction is clearly pathological. BPF decline in healthy adults is about 0.41% over a 10-year period according to Vågberg et al. [34]. The decline of BPF is faster in MS patients than in healthy controls and varies from 0.5 to 1.35% per year in untreated patients [35]. In general, studies of both traditional injectable treatments and high-efficacy treatments have shown various results, and a decline is still seen regardless of the therapy given [34–36]. High-efficacy DMT may slow down BPF reduction rate but it cannot normalize BPF reduction rate [37]. In a large cohort rituximab study, 822 MS patients were included, and annual BPF decline was 0.19% which is comparable to our result with annual BPF decline of 0.2% [4]. Pathological loss of BPF implies progressive neurodegeneration irrespective of suppressed CNS inflammation by DMT.

Serial OCT measures showed significant GCIPL reduction after 2.4 years on 1st-line DMT compared to baseline. During a 2.9-year duration of high-efficacy DMT, GCIPL reduction was minimal and did not differ from 1st-line DMT. pRNFL changes showed a similar trend of reduction as GCIPL, but without reaching statistical significance. We
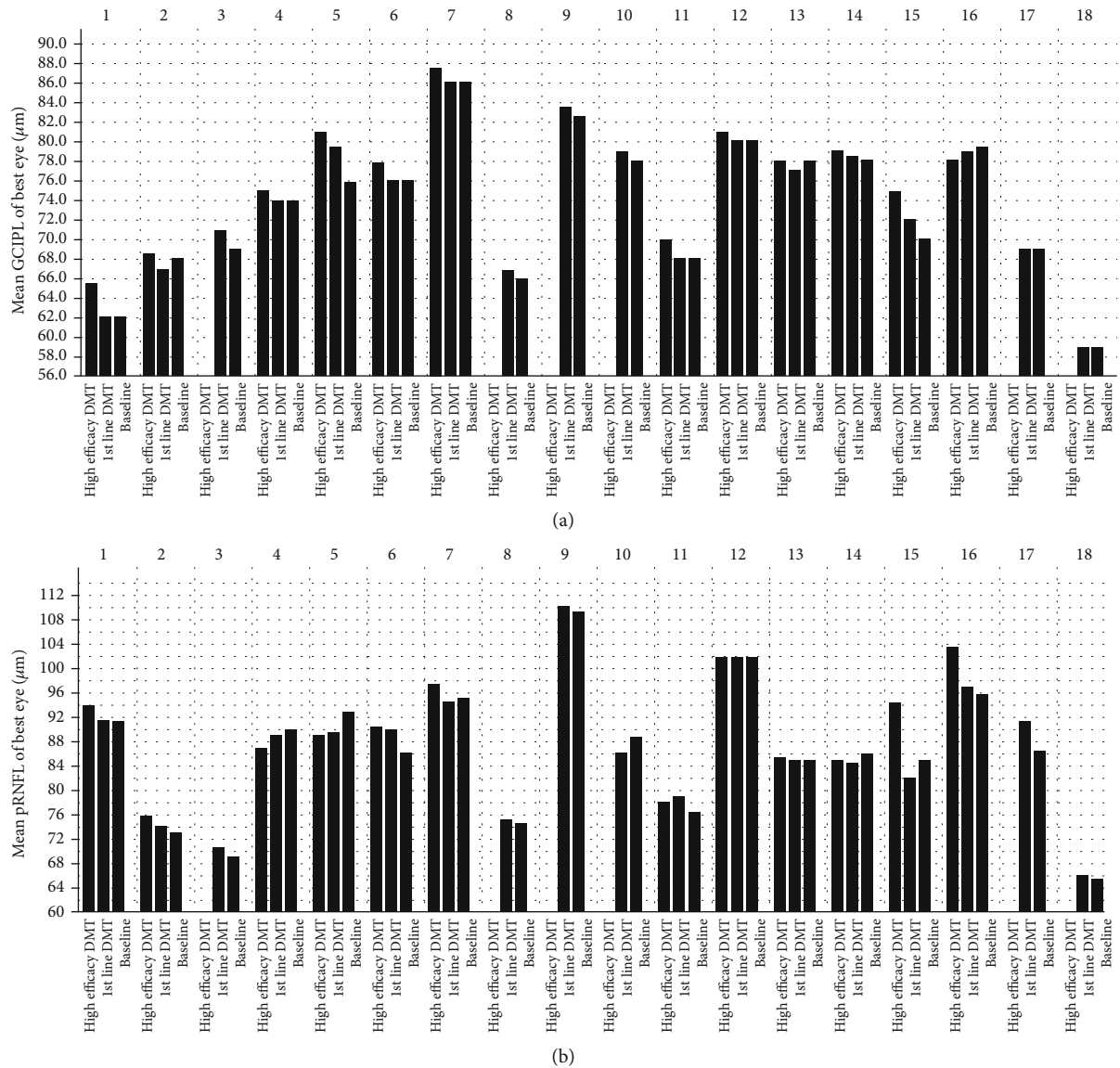
FIGURE 1: Changes of GCIPL and pRNFL thickness over time. Bar charts represent the individual GCIPL (a) and pRNFL (b) from best eye of each patient during three different time points. The thickness of GCIPL was significantly thinner during 1st-line DMT ($p < 0.01$) and high-efficacy DMT ($p < 0.05$) compared to baseline. There are no significant differences of pRNFL thickness among the three different time points. DMT: disease-modifying treatment; GCIPL: ganglion cell inner-plexiform layer; pRNFL: peripapillary retinal nerve fibre layer.

performed additional analysis of GCIPL and pRNFL with GLMM adjusted to OCT examination intervals at baseline vs. during 1st-line and high-efficacy DMT. Overall, during the whole follow-up period, the estimated reduction rate was 0.22 μm/year for GCIPL and 0.48 μm/year for pRNFL. Our GCIPL thinning rate was similar to the results reported by Lambe et al. [7]. The latter study reported a GCIPL thinning rate of 0.28 μm/year in rituximab-treated MS patients. However, the authors did not include pRNFL in their study. Our previous study showed that the annual thinning rate of GCIPL in RRMS patients was 0.43 μm/year, while the annual thinning rate of RNFL was 0.54 μm/year [38]. A study by Saidha et al. done in RRMS patients showed that GCIPL thinning rate was 0.31 μm/year and RNFL thinning rate was 0.41 μm/year [13]. The results from this study support

that high-efficacy DMT attenuate retinal atrophy. Tracking GCIPL thinning is more reliable and sensitive with better reproducibility than pRNFL and, therefore, of greater utility as a biomarker [7, 12, 13].

The major finding in our study is that GCIPL decline was most profound during 1st-line DMT and diminished during high-efficacy DMT, while brain atrophy continued regardless of high-efficacy DMT. These results partially indicate that GCIPL changes are more sensitive and precise detected with OCT compared to brain atrophy measured with MRI. Resolution of OCT parameters is about 5 micrometers [39], while with MRI a few millimeter changes can be detected [40]. Moreover, the involvement of visual pathway with inflammation and degeneration is more common in CNS demyelinating diseases such as MS than we have

TABLE 3: Estimated mean of GCIPL, pRNFL, BPF, EDSS, and MSSS.

	Baseline (untreated)		1st-line DMT		High-efficacy DMT		Changes per year	
Patients, n	12		18		18		NA	
Examinations, n	26		66		64		NA	
GCIPL, μm	74.57	(71.19–77.94)	73.48[1]**	(70.13-76.83)	73.85[2]*	(70.49–77.20)	-0.22[3]**	(-0.29--0.15)
pRNFL, μm	87.86	(82.53–93.19)	86.26[4]*	(81.02–91.49)	86.91	(81.96–92.77)	-0.48[5]**	(-0.68--0.28)
BPF, %	—	—	87.8	(85.8–89.7)	86.9[6]**	(84.9–88.8)	-0.2[7]**	(-0.3--0.1)
EDSS	0.64	(0.23–1.05)	0.90	(0.55–1.25)	0.81	(0.44–1.18)	0.02	(-0.02–0.06)
MSSS	1.10	(0.36–1.85)	1.13	(0.51–1.75)	1.25	(0.33–0.61)	-0.07	(-0.13--0.00)

Abbreviations: NA: not applicable; DMT: disease-modifying treatment; GCIPL: ganglion cell inner-plexiform layer; pRNFL: peripapillary retinal nerve fibre layer; BPF: brain parenchymal fraction; EDSS: expanded disability status scale; MSSS: multiple sclerosis severity score; estimated mean values according to generalized linear mixed models analyses (GLMM), mean (95% C.I.): [1]** $p < 0.01$ GCIPL: GLMM: pairwise comparison of fixed coefficients: baseline vs. 1st-line DMT. [2]* $p < 0.05$ GCIPL: GLMM: pairwise comparison of fixed coefficients: baseline vs. high-efficacy DMT. [3]** $p < 0.001$ GCIPL: GLMM: fixed coefficient changes over time. [4]* $p < 0.05$ pRNFL: GLMM: pairwise comparison of fixed coefficients: baseline vs. 1st-line DMT. [5]** $p < 0.001$ pRNFL: GLMM: fixed coefficient changes over time. [6]** $p < 0.001$ BPF: GLMM: pairwise comparison of fixed coefficients: 1st-line DMT vs. high-efficacy DMT. [7]** $p < 0.001$ BPF: GLMM: fixed coefficient changes over time.
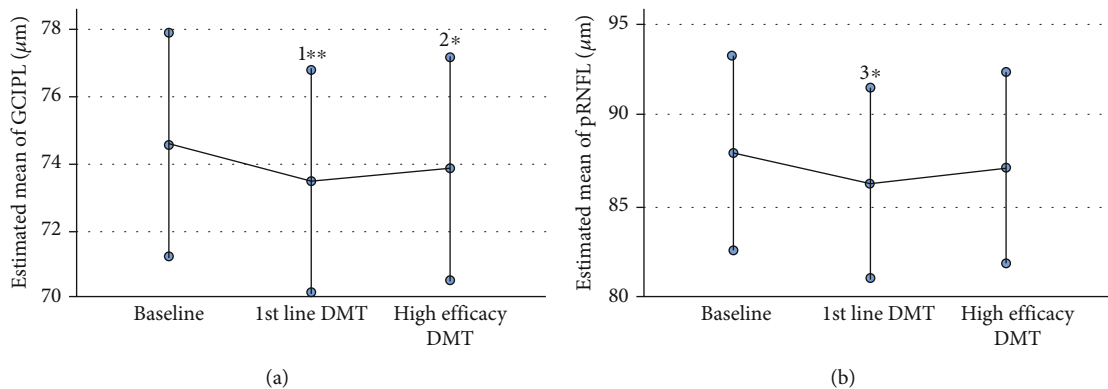

(a)

(b)

FIGURE 2: Estimated changes of GCIPL and pRNFL in the best eye over time. The estimated means of GCIPL (a) and pRNFL (b) thickness are generated from the generalized linear mixed models (GLMM) adjusted to time. The thickness of GCIPL was significantly thinner during 1st-line DMT ($p < 0.001$) and high-efficacy DMT ($p < 0.05$) compared to baseline. The thickness of pRNFL was significantly thinner during 1st-line DMT ($p < 0.05$) compared to baseline. 1[**]$p < 0.01$ GCIPL: GLMM: pairwise comparison of fixed coefficients: baseline vs. 1st-line DMT. 2[*]$p < 0.05$ GCIPL: GLMM: pairwise comparison of fixed coefficients: baseline vs. high-efficacy DMT. 3[*]$p < 0.05$ pRNFL: GLMM: pairwise comparison of fixed coefficients: baseline vs. 1st-line DMT. Error bars represents 95% C.I.

observed in clinical practice [41, 42]. The chronic inflammation and subsequent neurodegeneration occurring along the optic pathway can be quantified precisely and reliably by OCT.

Diminished GCIPL changes reflect that high-efficacy therapies block neuroinflammation more effectively than 1st-line therapy and eventually slow down neurodegeneration of visual pathway. However diffuse brain atrophy is continuing. This finding implies the need of searching for more effective anti-inflammatory therapy with neuroprotective effects.

In conclusion, this 6.8-year longitudinal study demonstrates that high-efficacy DMT significantly slows down retinal atrophy and markedly suppresses disease activity in patients with RRMS compared with 1st-line DMT. These results were in agreement with the decrease of MSSS. However, pathological brain atrophy progresses regardless of high-efficacy DMT, which corresponds to the increase of EDSS. GCIPL thinning and BPF loss are sensitive and reli-

able biomarkers to monitor MS course and therapeutic effects. Our results urge development of even more effective and neuroprotective therapies in MS. Moreover, OCT parameters are effective complement to MRI and potential markers for monitoring disease course and therapeutic response in MS.

4.1. Limitations. The main limitation of this study is the small number of enrolled patients and uneven follow-up intervals. The follow-up intervals and therapy switch are purely based on clinical need rather than research design. The OCT GCIPL software was on the market in 2012, and we started the project in 2013 when MS therapeutic strategy in Sweden was on the way to shift from conventional 1st-line DMT to high-efficacy DMT. Few new MS patients with 1st-line DMT fulfilled 1 year of therapy before switching to high-efficacy DMT due to the strategy of MS treatment in Sweden. MS patients are generally treated early with high-efficacy DMT instead of escalating therapy. Close clinical

follow-up and regular MRI examinations enabled us to identify disease activity in time and to switch to high-efficacy DMT quickly. Nowadays, very few MS patients are on injectable or tablet 1st-line DMT, and almost no new MS patients are initially treated with injectable 1st-line DMT.

Another limitation was no BPF measurement at baseline. BPF was not commonly used in clinical practice when this project was initiated. We have now access to BPF assessment for annual control of all treated MS patients.

Data Availability

The data presented in the study are available from the corresponding author upon reasonable request.

Ethical Approval

The study was approved by the Ethical Committee of Linköping University, Sweden (study number 2013/1411-31).

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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