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Long-term outcomes in patients presenting with optic neuritis: Analyses of the MSBase registry

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ABSTRACT

Background: Short-term outcomes of optic neuritis (ON) have been well characterized. Limited data exists on longer-term visual outcomes in patients who present with ON. The large MSBase registry allows for characterization of long-term visual outcomes after ON.

Methods: Via the MSBase Registry, data on patients from 41 centers was collected during routine clinical and research visits. Physical and visual disability were measured using the expanded disability status scale (EDSS) and the visual function score (VFS). Inclusion criteria for this analysis included age $\geq$ 18 years, clinically isolated syndrome (CIS), ON-onset, baseline visit within 6 months of onset, and at least one follow-up visit. Survival analysis was used to evaluate the association of disease-modifying treatment with time to conversion to clinically definite MS or sustained EDSS/VFS progression.

Results: Data from 60,933 patients were obtained from the MSBase registry in July 2019. Of these, 1317 patients met inclusion criteria; 935 were treated at some point in disease course, while 382 were never treated. At baseline, mean age was 32.3 $\pm$ 8.8 years, 74% were female, median EDSS was 2 (IQR 1–2), and median VFS was 1 (IQR 0–2). Median follow-up time was 5.2 years (IQR 2.4–9.3). Treatment was associated with reduced risk and delayed conversion to clinically definite MS (HR = 0.70, $p < 0.001$), sustained EDSS progression (HR = 0.46, $p < 0.0001$) and sustained VFS (HR = 0.41, $p < 0.001$) progression.

Conclusions: In the MSBase cohort, treatment after ON was associated with better visual and neurological outcomes compared to no treatment. These results support early treatment for patients presenting with ON as the first manifestation of MS.

1. Introduction

Long-term data on visual function and disability after optic neuritis (ON) as the initial manifestation of MS have not been well characterized. Previous studies evaluating long-term clinical outcomes after acute ON have been limited to the optic neuritis treatment trial (ONTT). This trial, which began before the era of preventative immunomodulatory therapy, showed largely favorable visual outcomes 15 years after ON, even in those who met criteria for MS at baseline or converted to MS within the 15 year follow-up period [1].

Recent studies have shown that early treatment of MS not only reduces relapses and accumulation of disability in the short-term but can delay progression to secondary-progressive MS [2] in the long term. A meta-analysis of studies in clinically isolated syndrome (CIS) patients showed that treatment with disease-modifying therapies attenuated brain atrophy, which is a risk factor for worse cognitive and physical disability outcomes in MS [3]. However, longitudinal studies specifically evaluating the effect of early treatment in CIS patients with ON as an initial clinical demyelinating event are sparse and largely limited to shorter-term clinical trials [4].

This study uses an international dataset, MSBase, to evaluate the trajectory of visual function and long-term outcomes in CIS patients with an optic nerve onset. The size and diversity of patients represented in MSBase represents an opportunity to examine potential effects of MS treatment on disability and vision in a large cohort and among patients receiving a variety of disease-modifying therapies. Our specific purpose in this analysis was to examine long-term visual trajectory post-ON and to determine the association of treatment with sustained EDSS and VFS scores over time.

2. Methods

2.1. Study cohort

MSBase is an international collaborative group of physicians and their healthcare teams dedicated to sharing and evaluating outcomes data in MS and related disorders (www.msbase.org) [5,6]. MSBase, developed in 2004, is the largest organized repository of longitudinal data for people with MS. Data have been obtained from observational cohort studies, with over 63,000 records collected from 105 centers in 33 countries at the current time. Data prior to 2004 was entered into the registry retrospectively. The MSBase registry was approved by Melbourne Health Human Research Ethics Committee and by each site's institutional review board and is registered with the World Health Organization International Clinical Trials Registry Platform (ACTRN12605000455662). Written or verbal consent was obtained from all enrolled patients in accordance with local regulations [5,6]. Data from 60,933 patients from 41 centers were extracted from the MSBase registry in July 2019. Only sites with more than 10 patient records were included in these analyses.

Inclusion criteria for our study included an age of 18 years or older, a diagnosis of clinically isolated syndrome (CIS) at baseline visit (within 6 months of disease onset), optic neuritis (ON) as the first clinical demyelinating event, a baseline visit within 6 months of symptom onset, at least one follow-up visit, and VFS and EDSS scores measured at both baseline and follow-up visit(s). Participants were excluded if their baseline visit occurred before 1995 (introduction of first MS disease-modifying therapies in Europe, where the majority of data originates), they had a diagnosis of NMOSD, or if treatment status was unknown. Visits were excluded if they occurred within 30 days after a relapse, except for the baseline visit. A total of 1317 subjects from the data extraction met these inclusion criteria.

2.2. Clinical information

Date of MS onset and diagnosis, clinical course, treatment, relapse characteristics and EDSS, were recorded during routine clinical visits, anonymized and entered into the MSBase registry. Records were classified as complete and eligible for analyses if they met a minimum required data set, which included date of birth, sex, MS course, onset date, EDSS score, treatment and center. Baseline MRI was defined as an MRI of the brain within one year prior to or one year after the baseline visit, and was available in a subset of participants ($n = 927$). Presence or absence of lesions on brain MRI at baseline was categorized. Baseline epoch was categorized as before 2006, 2006–2009, and 2010 and later based on treatment paradigms and the introduction of new classes of disease-modifying therapies. Annualized relapse rates (ARR) were calculated at the group level as the number of relapses total divided by the number of years of follow-up. Conversion to clinically definite MS (CDMS) was defined at the second relapse at least three months after the initial ON attack at enrollment.

2.3. Treatment

Treatment data were collected at each visit and entered into the MSBase registry. Treatment type, start date, end date, and reason for stopping treatment were recorded. Patients were categorized for purposes of the present analyses as either 'ever treated' or 'untreated'. They were considered treated if they had received any treatment after the initial episode of ON. Patients treated only with corticosteroids and not with any disease-modifying therapy were characterized as untreated. Treatments were also categorized by type (and by potency (higher vs lowwer). Lower potency therapies included injectable therapies and teriflunomide, the latter of which had only 3 participants. Higher potency therapies included oral, monoclonal antibody or conventionally immunosuppressive agents. (e.g. azathioprine, methotrexate, mycophenolate).

2.4. Expanded disability status score

EDSS competency through online certification is required for MSBase in order to ensure quality of EDSS assessments. EDSS was scored by trained clinicians and rated on a scale of 0–10. For this analysis, physical disability was defined as an EDSS $\geq$4, as this is commonly regarded as the transition point to SPMS. Kurtzke's Functional System (KFS) and EDSS Scores have been measured periodically in MSBase, with the mean inter-score interval of 5.7 months; this is comparable data density (frequency of measurement) to that of most MS clinical trials [6]. Three-month confirmed EDSS progression events were defined as increases of $\geq$0.5 points for patients with a baseline EDSS score $>$ 5.5, $\geq$1.0 point for those with a baseline EDSS score between 1.0 and 5.5, inclusive, and $\geq$ 1.5 points for those with a baseline EDSS score of 0, confirmed at least 12-weeks after the visit when the increase was observed. Sustained EDSS progression was defined as having an EDSS worsening for 3 months or greater. Sustained progression of individual KFS scores was defined as a worsening by 1 point for a period of 3 months or longer. Annualized EDSS change for the cohort was calculated as the sum of the EDSS changes divided by the total follow-up time for the cohort.

2.5. Visual function score

The visual function score (VFS) was calculated as part of the EDSS evaluation. Visual acuity, visual field and optic disc status (evidence of optic atrophy or "pallor") were recorded [7,8]. Visual field exams were performed as part of a neurological clinical exam without ophthalmological consultation, although at one site ophthalmological exams were performed also. VFS has a range of 0 to 6. Scores are shown in Table 1. Sustained VFS progression was defined as having a visual function score worsening (increase) by 1 scale point for a period of 3 months or longer. For this analysis, visual disability was defined as a VFS $\geq$ 2. Annualized VFS change for the cohort was calculated as the sum of the VFS changes divided by the total follow-up time of the cohort.

Table 1
Visual function score.

0	Normal
1	Disc pallor and/or small scotoma and/or visual acuity of worse eye less than 20/20 (1.0) but better than 20/30 (0.67)
2	Worse eye with maximal visual acuity of 20/30 to 20/59 (0.67–0.34)
3	Worse eye with large scotoma and/or moderate decrease in fields and/or maximal visual acuity of 20/60 to 20/99 (0.33–0.21)
4	Worse eye with marked decrease of fields and/or maximal visual acuity of 20/100 to 20/200 (0.2–0.1); Grade 3 plus maximal acuity of better eye of 20/60 (0.33) or less
5	Worse eye with maximal visual acuity less than 20/200 (0.1); Grade 4 plus maximal acuity of better eye of 20/60 (0.33) or less
6	Grade 5 plus maximal visual acuity of better eye of 20/60 (0.33) or less

2.6. Statistics

Analyses were performed using Stata 16.0. Descriptive analyses were performed to calculate the mean and/or median values of demographic and disease characteristics and compared using standardized differences. Confidence intervals (95% CI) for annualized relapse rates (ARRs) were calculated using Poisson regression. Mixed effects models were used to evaluate trends in EDSS/VFS over time. In these models, age, time, baseline VFS, baseline EDSS and baseline epoch were included as fixed effects. An interaction term between treatment group and time was also included as a fixed effect to determine if the particular treatment groups were associated with different recovery trajectories over time. Due to repeated measures for VFS and EDSS for each patient, patient ID was included as a random effect. Country was also included as a random effect. Mixed effects models with fixed and random effects can account for more than one level simultaneously by using covariates measured at the individual level, group level (country), and patient-level repeated measures.

Survival analysis was used to evaluate time to CDMS and time to sustained EDSS/VFS progression calculated from the time of ON-onset. Cox proportional hazards models, adjusted for age, sex, baseline epoch, VFS, EDSS and country, were used to compare the effects of ever versus no treatment and of higher vs lower potency treatments on the following three outcomes: conversion to CDMS, sustained EDSS progression and sustained VFS progression. Differences in outcomes after ON related to treatment history (ever versus no treatment) were evaluated, as well as differences based on treatment category (higher vs lower potency). Participants were included in the no treatment group if there were no treatments administered at any visits prior to the outcome event (second clinical demyelinating event defining CDMS or sustained EDSS/VFS progression) or the last/ most recent MSBase visit. Subjects were censored at either a treatment change or at the last recorded visit if no outcome event had occurred (conversion to CDMS or sustained EDSS/VFS progression). Time to event comparisons were made using non-parametric ranksum tests.

Time to visual disability, defined as a VFS $\geq$ 2, and time to physical disability, defined as an EDSS$\geq$4, were also evaluated in exploratory analyses in patients with a baseline VFS $<$ 2 and baseline EDSS$<$4 respectively. A Sankey diagram to visualize the flow of VFS in participants was created using SankeyMATIC [9]. This is a method designed to depict a flow from one set of values to another. Since there was considerable variation in follow-up time between participants, only those with a follow-up time of less than 10 years were included.

Predictors of CDMS conversion or sustained EDSS/VFS progression were determined using Cox proportional hazards models, with baseline covariates of age, sex, epoch, country, EDSS, VFS, polysymptomatic onset of supratentorial, brainstem and/or spinal cord regions, and brain MRI activity.

2.7. Sensitivity analysis

Several sensitivity analyses were performed on the mixed effects regression and survival analysis (Cox proportional hazards) models. The first sensitivity analysis used propensity score weighting and matching to overcome any potential bias that may have been introduced if more severe patients were more likely to have received treatment. A propensity score was calculated and included in the models to account for pre-treatment differences in the treated vs. untreated groups. The propensity of treatment was estimated using a multivariable logistic regression model that accounted for baseline age, sex, baseline epoch, visual function and EDSS score. Models using propensity score weighting and matching were also adjusted for country. The second sensitivity analysis was restricted to patients with baseline visits in 2010 or later only, when treatment and diagnosis paradigms were more similar to those currently in place, to overcome any potential bias due to changes in available treatments and evolving MS diagnostic criteria. The third

sensitivity analysis involved analysis on only the country with the most participants to evaluate whether differences in policies and treatment patterns between sites could have affected the likelihoods of visual or EDSS progression or conversion to MS. Similarly, a sensitivity analysis excluding low-middle-income countries (LMIC) was conducted. Lastly, a sensitivity analysis re-classifying medium potency therapies (fingolimod and dimethyl fumarate) was performed excluding these treatments from the high-potency category.

3. Results

3.1. MSBase cohort demographics

Baseline demographics for the 1317 CIS patients with optic nerve onset meeting our study's inclusion criteria are shown in Table 2. The average age of included patients was 32.3 ± 8.8 years, with 74.1% being female. Race/ethnicity data were self-reported in 76% of the MSBase cohort, and composed of 86% Caucasians in those who reported. The median follow-up time was 5.2 years (IQR 2.4–9.3, range 0.3–24.3) with a median of 9 (IQR 5-17, range 2-77) follow-up visits. In terms of baseline health status, the patients had a median EDSS of 2 (IQR 1-2, range 0-6.5) and median VFS of 1 (IQR 0-2, range 0-6). The annualized relapse rate for the cohort was 0.25 relapses/year. Steroids were used in fairly equal distributions between the ever treated and never treated groups. In the group ever treated with disease-modifying therapy, 52% had also received steroid treatment and 48% had not received steroids. In the group never treated with disease-modifying therapy, 50% received steroid treatment additionally, and 50% did not receive steroid treatment.

3.2. CDMS conversion

Patients who converted to CDMS within 3 months of initial onset symptom were excluded from this analysis ($n = 198$). Conversion to CDMS was observed in 741 (66.2%) of the 1119 CIS patients, with a median time from enrollment in the cohort of 1.0 years (IQR 0.5–2.3, range 0.3–17.7). Of the 741 patients who converted to CDMS, 515 (69.5%) were not treated before conversion to CDMS, 204 (27.5%) were treated with lower -potency agents, 13 (1.8%) with higher potency agents, 4 (0.5%) switched from lower to higher potency treatments before CDMS conversion, and 5 (0.7%) were treated in a clinical trial with actual treatment being unknown before CDMS conversion. Exposure to any treatment was associated with reduced risk of CDMS (HR = 0.70, $p < 0.0001$, Cox proportional hazards model, adjusting for age, sex, baseline epoch, country, baseline EDSS, baseline VFS). Treatment was also associated with a delayed onset of CDMS (median 1.4 years [IQR 0.7–2.9, range 0.3–11.5] in the treated vs. 0.8 years [IQR 0.4–2.0, range 0.3–17.7] in the untreated group) (Fig. 2, Table 3). There was no difference in frequency of CDMS development between higher ($n = 28$) and lower ($n = 341$) potency treatment groups ($p = 0.154$) or in time to CDMS conversion between these groups ($p = 0.687$). Sensitivity analysis using weighted Cox proportional hazards models produced similar results for those treated vs. not treated before CDMS conversion. The sample size was too small to perform weighted analysis in the higher vs. lower potency treatment group. Annualized relapse rate (ARR) for the group was 0.25 (0.26 in never treated and 0.21 in treated group). (Table 3).

A sensitivity analysis examining those participants with symptom onset in 2010 and later ($n = 607$) showed similar results for any treatment ($n = 238$) vs. no treatment at onset ($n = 369$) (HR = 0.72, $p =$

Table 2
Baseline characteristics.

	Overall (n = 1317)	Never Treated (n = 907)	Any Treatment (n = 410)	Standardized differences (unweighted)	Standardized differences (weighted)*	Lower potency (n = 377)	Higher potency (n = 28)	Standardized Differences (unweighted)	Standardized Differences (weighted)*
Age, years, mean ± SD (range)	32.3 ± 8.8	32.3 ± 9.0 (18.1–62.1)	32.3 ± 8.4 (18.2–58.1)	0.001	0.003	32.2 ± 8.5 (18.2–55.8)	32.5 ± 8.4 (18.9–58.1)	−0.034	−0.031
Sex, n (% female)	976 (74.1%)	681 (75.1%)	295 (72.0%)	0.071	0.101	271 (71.9%)	19 (67.9%)	0.088	−0.043
EDSS Median (IQR)	2 (1–2)	1.5 (1–2)	2 (1–2)	−0.155	0.166	2 (1–2)	2 (1.25–2.25)	−0.129	0.146
VFS Median (IQR)	1 (0–2)	1 (0–2)	1 (0–3)	−0.182	0.190	1 (0–2)	2 (0.5–3)	−0.118	0.027
Epoch									
Before 2006	250 (19.0)	216(23.8)	34(8.3)	−0.433	−0.292	28 (7.4)	5 (17.9)	0.318	0.401
2006–2009	335 (25.4)	224(24.7)	111(27.1)	0.054	−0.003	104 (27.6)	7 (25.0)	−0.059	−0.122
2010 and later, n (%)	732 (55.6)	467(51.5)	265(64.6)	0.269	0.160	245 (65.0)	16 (57.1)	−0.161	−0.240
Country, n(%)									
IT	378 (28.7)	321(35.4)	57(13.9)			48(12.7)	8(28.6)		
CZ	173 (13.1)	16(1.8)	157(38.3)			151(40.1)	6(21.4)		
TR	235 (17.8)	175(19.3)	60(14.6)	−0.058	−0.071	53(14.1)	7(25.0)	−0.157	−0.227
ES	121(9.2)	98(10.8)	23(5.6)			23(6.1)	0(0)		
AU	85(6.5)	67(7.3)	18(4.4)			12(3.2)	2(7.1)		
CA	54(4.1)	34(3.7)	20(4.5			18(4.8)	2(7.1)		
Other	271 (20.6)	196(21.6)	75(18.3)			72(19.1)	3(10.7)		
EDSS≥4, n(%)	28 (2.1)	23 (2.5%)	5 (1.2%)	0.10	n/a	4 (1.1)	1 (3.6)	n/a**	n/a
VFS ≥ 2, n(%)	569 (43.2)	366(40.4%)	203 (49.5%)	0.18	n/a	187 (50%)	15 (54%)	0.079	n/a

SD = standard deviation, IQR = Inter-quartile Range, EDSS = Expanded Disability Status Scale, VFS = Visual Function Score, IT = Italy, CZ = Czech Republic, TR = Turkey, ES = Spain, AU = Australia, CA = Canada.

* propensity score weighting with baseline variables age, gender, epoch, EDSS, VFS.

** Sample size too small for comparison.

Table 3
Results CDMS Conversion.

	Overall (n = 1119)	Not Treated (n = 745)	Any Treatment (n = 374)	Hazard Ratio	p-value	Lower potency (n = 341)	Higher potency (n = 28)	Hazard Ratio	p-value
Conversion to CDMS, n(%)	741 (66.2)	515 (69.1)	221 (59.1)	0.70 (0.58–0.85)	$p <$ 0.001*	204 (59.8)	13 (46.4)	0.66 (0.37–1.17)	p = 0.154*
Conversion to CDMS time, years, median (IQR/range)	1.0 (0.5–2.3) (0.3–17.7)	0.8 (0.4–2.0) (0.3–17.7)	1.4 (0.7–2.9) (0.3–11.5)	–	p < 0.001**	1.4 (0.7-2.8) (0.3–11.5)	1.2 (0.6–3.2) (0.3–7.4)	–	p = 0.687**
Annualized Relapse Rate (95% CI)	0.25 (0.24–0.26)	0.26 (0.25–0.28)	0.21 (0.19–0.23)	–	–	0.21 (0.19–0.23)	0.21 (0.15–0.28)	–	–

CI = Confidence Interval, CDMS = Clinically Definite Multiple Sclerosis, IQR = interquartile range.
* Cox proportional hazards model adjusted for age, gender, epoch, country, baseline EDSS, baseline VFS.
** Wilcoxon rank-sum test.

0.013, Cox proportional hazards model adjusting for age, sex, baseline epoch, country, baseline EDSS, baseline VFS). The sample size in the higher potency treatment group (n = 16) was too small for analysis to compare the effect of higher vs. lower potency therapies in this group. Likewise, time to CDMS conversion was longer in the treated group compared to the untreated group (median survival time 1.0 years [IQR 0.7–2.3, range 0.3–6.2] vs median survival time 0.6 years [IQR 0.4–1.1, range 0.3–7.5], $p < 0.001$). For the overall cohort enrolled in 2010 and later, median survival time to CDMS conversion (n = 337/607) was 0.8 years (IQR 0.4–1.6, range 0.3–7.5).

3.3. Sustained EDSS/VFS progression

Sustained physical disability (defined as EDSS≥4 for 3 or more consecutive months), was observed in 106 (8%) of participants with a median time of 3.4 years (IQR 1.7–6.1, range 0.1–17.2) and sustained visual disability (defined as VFS ≥ 2) was observed in 154 (12%) participants with a median time of 2.2 years (IQR 1.4–4.0, range 0.1–16.3). Final EDSS score median was 1.5 (IQR 1–2, range 0–8.5) and final VFS score median was 0 (IQR 0–1, range 0–6), with an annualized EDSS change for the group of 0.023 (95% CI 0.020, 0.027) and annualized VFS change for the group of 0.158 (95% CI 0.150, 0.166), indicating improvement (Table 4). Changes in visual function score from baseline to follow-up are shown in Fig. 1.

Sustained EDSS progression was observed in 230 (17.5%) of participants. Sustained VFS progression was observed in 240 (18.2%) of participants. In the overall cohort, 736 (55%) experienced progression of EDSS or any functional score, but not all of these were sustained over 3 months. Before EDSS progression, 874 (66%) were treated (755 with lower potency, 110 with higher potency, 9 with unknown treatments), and 443 were not treated. Any treatment before sustained EDSS progression was associated with lower risk (HR = 0.46, p < 0.001, Cox proportional hazards model adjusted for age, sex, country, baseline epoch, EDSS and VFS) (Fig. 2). Unadjusted and weighted models showed similar results (HR = 0.41, p < 0.001 unadjusted/HR = 0.41, p < 0.001 weighted). We did not find evidence for a difference between higher vs. lower potency treatment groups with respect to sustained EDSS progression (HR = 0.56, p = 0.111 adjusted Cox models, HR = 0.58, p = 0.132 unadjusted, HR = 0.58 weighted, p = 0.149) (Table 5).

Before VFS progression, 889 (68%) were treated (767 on lower potency, 115 on higher potency, and 7 unknown) and 428 (32%) were untreated. In the treated group, 214 (24%) had VFS progression before switching treatments (26 switched treatments before VFS progression and were censored at treatment switch). Treatment overall was associated with lower risk of VFS progression (HR = 0.41, $p < 0.0001$ Cox proportional hazards model adjusted for age, sex, country, baseline epoch, EDSS and VFS). Unadjusted and weighted models showed similar results (HR = 0.59, $p \leq 0.001$ unadjusted, HR = 0.64, p = 0.002 weighted) (Fig. 2). We did not find evidence for difference in higher vs lower potency treatment groups for sustained VFS progression (HR = 0.56, p = 0.07 unadjusted, HR = 0.54, p = 0.07 adjusted, HR = 0.50, p = 0.07 weighted Cox proportional hazards models)(Table 5).

3.4. EDSS/VFS trends

When considering trends in the overall cohort across over all follow-up visits, annualized VFS change showed overall improvement of 0.158 points/year. VFS scores improved more (−0.17, p = 0.001, mixed effects model) in the ever-treated group (n = 934) compared to the never treated group (n = 383). Annualized EDSS change showed an

Table 4
Sustained EDSS/VFS Results.

	Overall (n = 1317)	Not Treated (n = 443)	Any Treatment before Progression (n = 874)	Hazard Ratio (95% CI)/ p-value	Lower Potency (n = 755)	Higher Potency (n = 110)	Hazard Ratio (95% CI)/ p-value
Sustained EDSS progression, n(%)	230 (17%)	85 (19%)	117 (13%)	HR = 0.46 (0.34–0.63) p < 0.0001	108 (14%)	8 (7%)	HR = 0.56 (0.27–1.14) p = 0.111
Time to Sustained EDSS progression, years, median (IQR/range)	2.8 (1.5–5.5) (0.1–19.9)	2.1 (1.0–3.9) (0.1–14.4)	3.4 (1.6–6.1) (0.1–17.4)	p < 0.001**	3.2 (1.6-6.1) (0.1–17.4)	5.5 (4.0–7.3) (0.8–13.3)	p = 0.043**
Sustained VFS Progression, n(%)*	240 (18%)	73 (17%)	141 (16%)	HR = 0.41 (0.30–0.56) $p <$ 0.0001	128 (17%)	10 (9%)	HR = 0.54 (0.28–1.05) p = 0.069
Time to Sustained VFS Progression, years, median (IQR/range)	2.3 (1.1–4.8) (0.0–24.3)	1.2 (0.5–2.5) (0.00–13.0)	2.7 (1.4–5.2) (0.2–17.4)	p < 0.001**	2.5 (1.4-4.8) (0.2–17.4)	5.9 (3.6–7.3) (1.8–12.7)	p = 0.138

EDSS = Expanded Disability Status Scale, VFS = Visual Function Score, CI = confidence interval, IQR = interquartile range.
* For Sustained VFS Progression: No Treatment: n = 428, Any Treatment Before Progression: n = 889, Low Potency: n = 767, High Potency: n = 115.
** Wilcoxon rank-sum test.

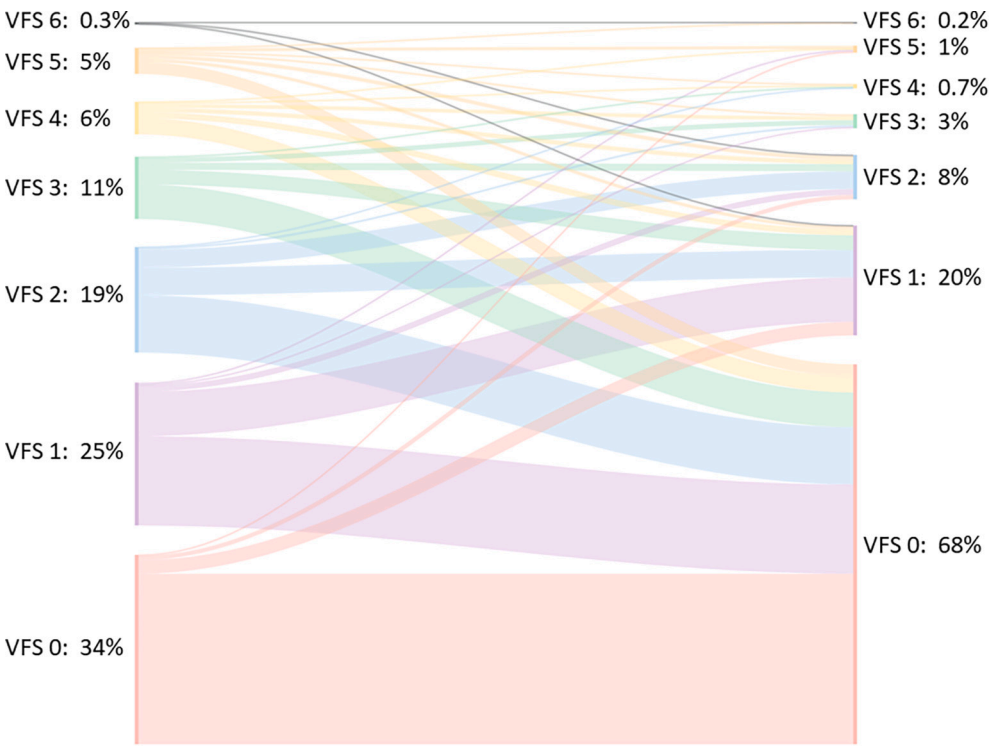

Fig. 1. Sankey Diagram for Baseline and Final VFS Scores.
Figure Legend: Baseline VFS scores are shown on left side of diagram. Final VFS scores are shown on the right side of diagram. Lines indicate flow of score from baseline to final follow-up visit. To account for variations in follow-up time, only those with a maximum of 10 years of follow-up were included (n==1036). VFS scores are shown in Table XX. For this analysis VFS ≥ 2 is considered visual disability. Note the majority of patients recovered to VFS score of 0 after initial optic nerve onset of CIS.

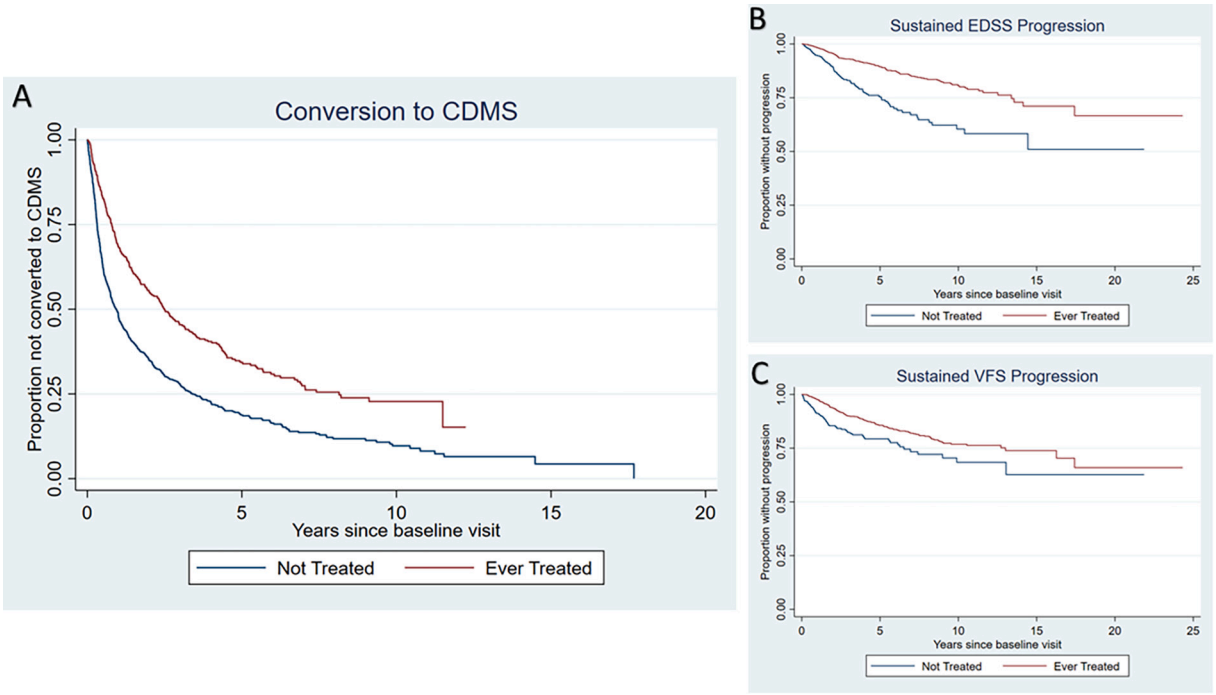

Fig. 2. Kaplan-Meier Survival Estimates for CDMS conversion, Sustained EDSS Progression and Sustained VFS Progression. A. Survival estimates of conversion to CDMS. B. Survival estimates of Sustained EDSS Progression. C. Survival estimates of VFS Progression. This figure illustrates that treatment before conversion to CDMS, sustained EDSS or VFS progression is protective. Frequency of the outcome is reduced and time to the outcome is delayed.

improvement of 0.23 points/year. There was no difference in EDSS score over time between the ever treated and never treated groups. These results were similar for models adjusting for age, sex, epoch, country, baseline EDSS and baseline VFS, as well as for models using propensity score weighting or propensity score matching. Overall, 599 (45%) participants (409 treated, 190 untreated) had improvement in EDSS from baseline to final visit, 365 (28%) participants (232 treated, 133 untreated) had no change and 353 (27%) participants (293 treated, 60 untreated) had worsening EDSS scores. Overall, 706 (54%) participants (515 treated, 191 untreated) had improvement in VFS from baseline to final visit, 526 (40%) participants (353 treated, 173 untreated) had no change and 85 (6%) participants (66 treated, 19 untreated) had

Table 5
Follow-up characteristics for overall cohort.

Follow-up Results	Overall Cohort (n = 1317)
Number of follow-ups, median (IQR, range)	9 (5–17, 2–77)
Follow-up time, years, median (IQR, range)	5.2 (2.4–9.3, 0.3–24.3)
Physical disability (Sustained EDSS≥ 4), n(%)	106 (8%)
Visual disability (Sustained VFS ≥2), n(%)	154 (12%)
Time to Sustained EDSS≥4, years, median (IQR, range)	3.4 (1.7–6.1, 0.1–17.2)
Time to Sustained VFS ≥ 2, years, median (IQR, range)	2.2 (1.4–4.0, 0.1–16.3)
Final EDSS, median (IQR, range)	1.5 (1–2, 0–8.5)
Final VFS, median (IQR, range)	0 (0–1, 0–6)
Annualized EDSS change, group* (95% CI)	−0.023 (0.020, 0.027)
Annualized VFS change, group* (95% CI)	−0.158 (0.150, 0.166)

IQR = interquartile range, EDSS = Expanded Disability Status Scale, VFS = Visual Function Score.

* Annualized rates calculated as the sum of the overall changes in scores for each individual in the cohort divided by the sum of the total follow-up time for each individual in the cohort. A negative value indicates improvement in scores.

worsening VFS scores.

3.5. Kurtzke's functional scores

Sustained progression was seen in all functional scores (Fig. 3). Median time to sustained functional score progression was similar for all 7 functional domains and ambulation (Table 6). Pyramidal and sensory domain sustained progression seemed to occur more frequently and earlier in this cohort. With the exception of pyramidal, cerebellar and sensory functional systems, disability progression appeared to plateau around 15 years after disease onset.

Table 6
Kurtzke's Functional System Scores Sustained Progression Results.

Functional Score	Sustained Progression, n (% out of 1317)	Time to Sustained Progression, years, median (IQR, range)
1 Pyramidal	515 (39%)	2.1 (0.8–4.1, 0.0–19.9)
2 Cerebellar	233 (18%)	2.9 (1.3–5.7, 0.1–21.1)
3 Brain	217 (16%)	2.4 (1.0–5.5, 0.0–19.9)
4 Sensory	384 (29%)	2.4 (1.1–5.2, 0.0–21.6)
5 Bladder/ Bowel	199 (15%)	3.4 (1.4–6.5, 0.0–18.6)
6 Vision	240 (18%)	2.3 (1.1–4.8, 0.0–17.4)
7 Mental	185 (14%)	2.5 (1.0–4.7, 0.1–15.7)
8 Ambulation	92 (7%)	3.9 (1.7–6.6, 0.0–16.5)

3.6. Predictors of CDMS conversion and EDSS/VFS progression

Age (HR = 0.98, $p < 0.001$), higher baseline EDSS (1.17, $p = 0.031$), polysymptomatic first onset symptoms (HR = 1.47, $p < 0.001$) and presence of brain MRI lesions at baseline (HR = 1.59, $p < 0.001$) were predictors of higher risk of conversion to CDMS (Table 7).

Baseline age (HR = 1.03, $p < 0.001$) and VFS scores (HR = 0.84, $p = 0.008$) were predictors of sustained EDSS progression. For each year of age, the risk of future sustained EDSS progression increased by 3%.

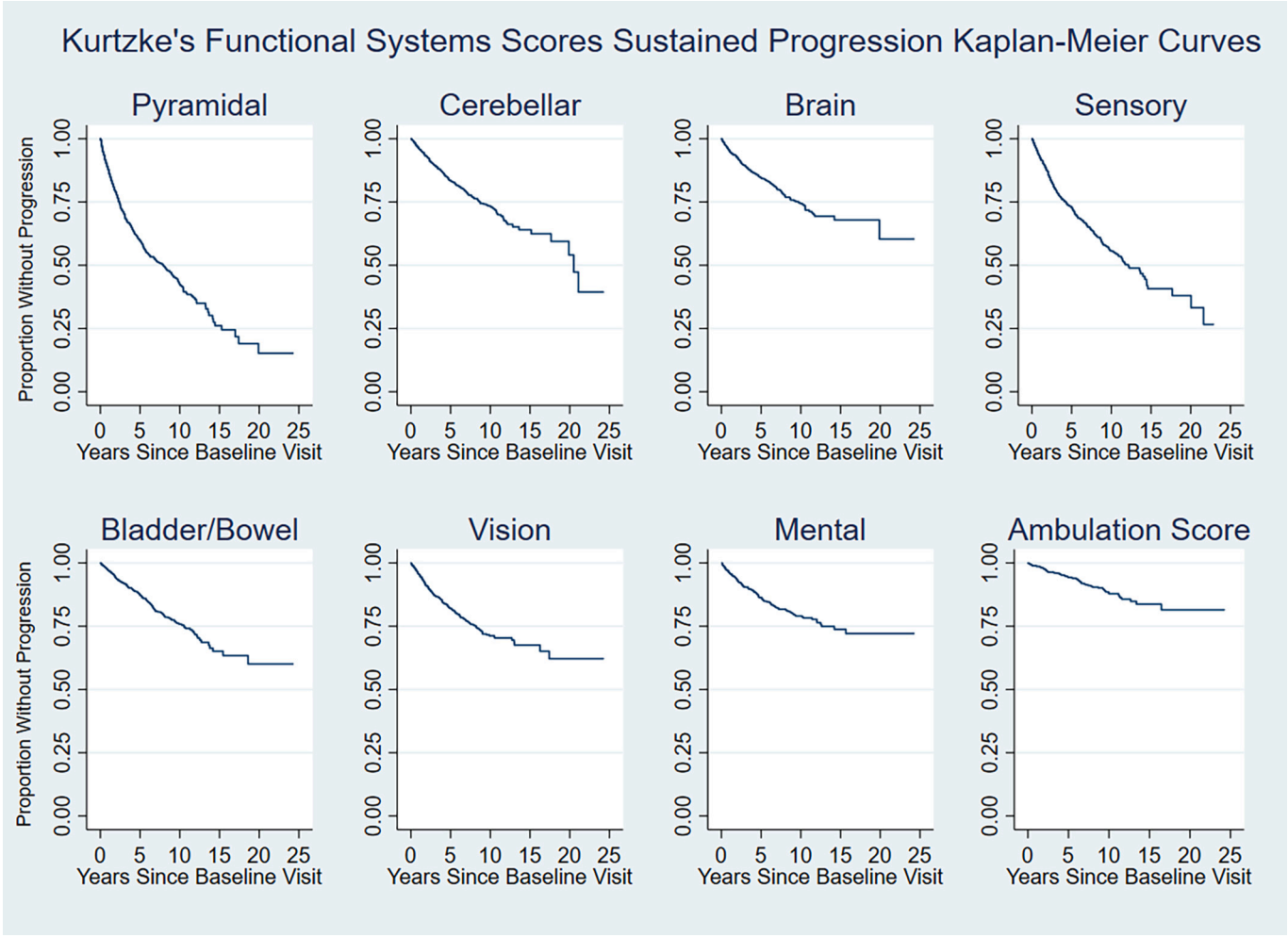

Fig. 3. Kaplan-Meier survival estimates for each of Kurtzke's Functional Systems Scores. This figure illustrates the trajectory of each of the functional scores recorded as part of EDSS assessment. Sustained progression for each of the scores is defined as a decline by 1 step for a period of 3 months or more.

Table 7
Baseline Predictors of Outcomes.

		CDMS Conversion		Sustained EDSS Progression		Sustained VFS Progression	
Predictor	Level	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value
Demographics							
Age	per 1 year	**0.98 (0.97–0.99)**	**<0.001**	**1.03 (1.01–1.04)**	**0.001**	1.01 (0.99–1.02)	0.370
Gender	Male	1.00	**–**	1.00	–	1.00	–
	Female	1.06 (0.89–1.29)	0.571	0.99 (0.73–1.34)	0.936	1.24 (0.92–1.68)	0.158
EDSS	per 1 point	**1.17 (1.01–1.34)**	**0.031**	1.10 (0.91–1.32)	0.341	**1.29 (1.07–1.55)**	**0.008**
VFS	per 1 point	0.98 (0.89–1.08)	0.705	**0.84 (0.73–0.96)**	**0.008**	0.98 (0.87–1.11)	0.781
Polysymptomatic Onset*		**1.47 (1.11–1.95)**	**<0.001**	1.23 (0.82–1.84)	0.317	**1.53 (1.02–2.29)**	**0.041**
Brain MRI lesions		**1.59 (1.28–1.98)**	**<0.001**	0.81 (0.54–1.21)	0.307	1.16 (0.78–1.73)	0.456

* Brainstem, Spinal Cord or Supratentorial.

Polysymptomatic onset and higher baseline EDSS were not predictors of sustained EDSS progression (Table 7).

Higher baseline EDSS (HR = 1.29, p = 0.008) and polysymptomatic onset symptoms (HR = 1.53, $p = 0.041$) were significant predictors of sustained VFS progression. Baseline VFS was not a predictor of sustained VFS progression (Table 7).

3.7. Sensitivity analyses

Sensitivity analyses were performed considering: (1) only the cohort subset with onset of symptoms during or after 2010, (2) incorporating propensity score weighting and matching, (3) including only the largest country (Italy) (4) excluding LMIC countries and (5) excluding medium potency therapies, except when the sample size was too small in the subset for valid results. Sensitivity analyses examining onset 2010 or later, including only the largest country, and excluding LMIC countries could not be performed when comparing higher vs lower potency treatment groups because the sample size was too small in the higher potency treatment group. Similar results were seen for all other sensitivity analyses as in the original models (See Supplementary Table 1).

4. Discussion

Results from this study demonstrate that treatment with disease-modifying therapies may delay onset and reduce risk of conversion to CDMS, sustained EDSS progression, and sustained VFS progression in CIS patients with an optic nerve onset. This multi-center observational study is, to our knowledge, the first study to evaluate long-term outcomes in CIS patients with optic nerve onset in the era of immunomodulatory therapy. These results may have more generalizability compared with clinical trials due to wider eligibility criteria and representation.

Recent discussions of the International Panel on Diagnosis of Multiple Sclerosis addressed inclusion of the optic nerve as a fifth MRI lesion site in the diagnostic criteria for MS. Although the optic nerve was not incorporated in the 2017 revisions to the McDonald Criteria, the committee discussed obtaining more data to justify inclusion [10,11]. This study evaluates long-term visual and physical disability outcomes for patients with an optic nerve onset of MS that may not have been classified as MS at onset under the current diagnostic criteria; some of these patients may be diagnosed earlier if the optic nerve were included as a lesion site. Sixty-six percent of this cohort of CIS patients with ON onset went on to develop CDMS. In the ONTT at the 15-year follow-up 50% of ON patients had developed MS [1]. Variances in frequency and time to CDMS conversion are likely due to different ascertainment patterns between the ONTT and the MSBase registry. Participants in the ONTT were evaluated at specified intervals (with some losses to follow-up) regardless of recurrence of ON or conversion to MS. Data included in the MSBase registry are from clinical practice, observational studies, and clinical trials with varied follow-up times and methods. In this context, it is more likely that a participant will have a follow-up visit if they had a second relapse and subsequent conversion to MS, which could explain the higher and faster rate of conversion in the MSBase cohort compared to the ONTT. There may also be other differences between the ONTT and the MSBase populations. For example, the ONTT had a large number of patients with normal baseline brain MRIs. Since the baseline brain MRI can predict risk of converting to MS, the two populations may have had different risk of converting to MS if for example, the MSBase population had more patients with abnormal baseline MRIs and therefore higher risk of converting sooner.

The association of treatment with better long-term outcomes for CIS patients with optic nerve onset is highly relevant. If CIS patients are diagnosed earlier as a result of inclusion of optic nerve lesions as a fifth anatomical site for dissemination in space and time, such patients can be treated with MS disease-modifying therapies earlier in their course, thus potentially preserving visual and physical function. On the other hand, because several neuroimmunologic diseases may manifest with optic neuritis (NMOSD, MOGAD, neurosarcoidosis), classification of monophasic acute ON as MS may increase the likelihood of MS misdiagnosis. Thus, it would be important to include the requirement that relevant MS mimics should be excluded in patients presenting with optic neuritis as with any new demyelinating event.

Mixed effects models evaluating overall trends in EDSS and VFS scores from baseline to final visit showed more improvement in VFS scores in the treated group, while there was no difference in EDSS scores. The lack of significant differences in the EDSS group is likely a reflection of the variability of EDSS, particularly with intermittent relapses, as well as inter- and intra-rater variability. These models consider all repeated measures from baseline to final visit and incorporate potential increases and decreases in the score and assume linearity, which may not be correct. Analysis of sustained EDSS/VFS progression is a more valid model because it considers changes that are consistent over time, rather than variability that may occur between individual visits. Further, when considering the EDSS/VFS changes in the entire cohort over all visits, the more severely affected participants may join the treated group as their disease progresses and contribute to the overall EDSS scores in that cohort. Additionally, there may be greater pressure to diagnose a case as MS to initiate treatment, so these cases may be evaluated and assessed more frequently. Again, this could contribute to an increase in the EDSS scores of the treated cohort. It is possible that without these sources of potential bias, EDSS scores would be lower (better) in the treated group. As such, the lack of differences seen may be an underestimation of an improvement in the treated group, as opposed to an actual lack of difference between the groups. Similarly, the improvement in VFS scores in the treated group may underestimate the actual difference between the groups, as the bias of more severe participants being in the treated group applies here as well.

In the Sankey diagram (Fig. 1), final VFS scores indicate overall improvement of VFS from baseline to final visit. As the baseline visit may have been during the initial symptom onset, many patients (43%) had a baseline VFS ≥ 2. Most of these recovered to VFS of 0 or 1, with a few having residual visual deficits, while others (12%) had sustained visual decline later in the course of their disease. Likewise, since baseline EDSS was measured close to the initial onset, improvement in EDSS

scores from baseline to final visits could be explained by recovering from initial relapse. Since follow-up time varied considerably in this observational study based on registry data, it is important to consider annualized changes, which also showed improvement overall for the group from baseline to final visit. Visual recovery after ON typically occurs in first 3–6 months [12]. Median follow-up time for this cohort was 5.2 years, so it is likely that visual recovery occurred initially after ON and patients continued to do well. There was an equal distribution of steroid use between the ever treated and never treated groups in this study. Since the ONTT and other studies have shown that steroid treatment had no effect on long-term recovery after ON, steroids were not considered in the main analysis of this paper [13]. Final results from the 15-year follow-up in the optic neuritis treatment trial were similar and showed most patients recovered visual function with regard to high-contrast acuity; however, patient-reported vision-specific quality of life scores continued to reflect subjective visual dysfunction even years after the acute episode [1].

Accumulation of disability in multiple domains in the Kurtzke's functional system scores suggests that MS is progressing in multiple systems in CIS patients with optic nerve onset. In all domains except pyramidal, cerebellar, and sensory, there was a decline that tended to stabilize around 15 years. These results are similar to a natural history study of MS using the North American Research Committee on Multiple Sclerosis (NARCOMS) registry where data on subjective symptoms across 11 domains showed a plateau after 15 years of disease duration in some domains [14].

The primary outcome for this study is VFS, which relies heavily on high-contrast visual acuity measurements that may vary between sites and uses confrontational visual field measurements instead of formal visual field testing. Numerous studies have shown that low-contrast acuity is a more sensitive measure of visual disability in MS, both at single time points and over time [15–17]. However, low-contrast acuity was not collected in MSBase. Using high-contrast acuity as a measure may underestimate the true amount of disability following ON and likely also underestimates the effects of treatment. This was demonstrated in the pivotal trials of natalizumab, in which there was no treatment effect on high-contrast visual acuity outcomes, but there was for low-contrast letter acuity outcomes [18]. EDSS scoring is heavily based on ambulation; the VFS often does not contribute heavily to the final EDSS. EDSS scores reflect more physical disability and may not reliably capture visual disability in MS patients.

Younger age, baseline EDSS score, polysymptomatic onset symptoms, and brain lesions at baseline were associated with increased risk of conversion to CDMS. Higher (worse) baseline VFS scores, however, were associated with a reduced likelihood of sustained EDSS progression. This may reflect the relatively poor contribution of VFS to EDSS scores for those with predominantly visual dysfunction as opposed to ambulation-related disability or that those presenting with ON may have milder disease overall as measured by EDSS. Also, the VFS scores may have been obtained close to the onset event, and may have subsequently recovered. Conversely, worse baseline EDSS was associated with increased risk for sustained VFS progression, potentially reflective of multi-dimensional accumulation of disability. Baseline VFS scores were not significantly associated with sustained VFS progression, suggesting that the severity of the initial high-contrast visual acuity score does not predict future visual disability as assessed with the VFS. In contrast to the risk of converting to CDMS, polysymptomatic onset symptoms, brain MRI findings, and baseline EDSS did not predict worse EDSS progression; this may also reflect the high contribution of ambulation to the EDSS score or relatively low overall disability in this patient subpopulation.

One of the main limitations of this study is the retrospective, observational design. Data were generally collected in the context of clinical protocols instead of standardized research protocols. Retrospective capture of clinical data can lead to systematic errors, reporting bias and heterogeneity between study sites. The MSBase registry has implemented systematic measures such as standardizing data quality and density [19] and requiring Neurostatus training for EDSS collection in order to reduce sources of error and bias. Suggested procedures for assessing MSBase data quality were followed [19]. Additionally, models used in these analyses were adjusted for country to attempt to overcome heterogeneity in treating patterns among sites; sensitivity analyses evaluating all models in only the largest contributing country (Italy) and excluding LMIC were constructed and showed similar results. Since this is a multicenter study in which participation is self-selected by site and is mainly composed of subspecialized academic centers and clinics treating MS, results may not be generalizable to larger populations. Race/ethnicity data are limited because is not part of the required minimum dataset. Of the 76% of patients who self-reported race/ethnicity, 86% were Caucasians. However, this statistic belies the wide diversity of ancestral origins of MSBase population. In our sample, a large proportion of patients come from counties where MS has been relatively understudied, such as Turkey (235 patients, or 18% of cohort) or Kuwait (52 patients, or 4% of cohort). MSBase has implemented standardized assessments that found greater generalizability for larger sites. Therefore, sites with less than 10 records were not included in the present analyses. Another potential source of bias includes the increased likelihood of treatment among patients with more severe disease at the time of enrollment into MSBase. Sensitivity analyses using propensity score weighting and matching showed similar results for all models, so it is not likely that this source of bias affected the results. Data showing the association of treatment overall with delayed conversion to CDMS and EDSS/VFS progression may nonetheless be an underestimate of the true effect.

Most patients in this observational study using the MSBase registry converted to CDMS over time, with 12% developing sustained visual disability. Treatment with disease-modifying therapies following an acute ON onset of CIS is associated with improved neurological and visual function as captured by the VFS. Further analyses of low-contrast letter acuity and optical coherence tomography (OCT) measures of structure will be essential to refine our understanding of treatment effects.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2021.118067.

Disclosure statements

Laura Balcer is editor in chief of the Journal of Neuro-Ophthalmology.

Steven Galetta has been a consultant for Biogen and Genentech.

Tomas Kalincik served on scientific advisory boards for BMS, Roche, Sanofi Genzyme, Novartis, Merck and Biogen, steering committee for Brain Atrophy Initiative by Sanofi Genzyme, received conference travel support and/or speaker honoraria from WebMD Global, Novartis, Biogen, Sanofi-Genzyme, Teva, BioCSL and Merck and received research or educational event support from Biogen, Novartis, Genzyme, Roche, Celgene and Merck.

Tim Spelman has received compensation for serving on scientific advisory boards, honoraria for consultancy and funding for travel from Biogen Inc.; speaker honoraria from Novartis.

Shiv Saidha has received consulting fees from Medical Logix for the development of CME programs in neurology and has served on scientific advisory boards for Biogen, Genzyme, Genentech Corporation, EMD Serono & Celgene. He has consulted for Carl Zeiss Meditec. He is the PI of investigator-initiated studies funded by Genentech Corporation and Biogen Idec, and received support from the Race to Erase MS foundation. He has received equity compensation for consulting from JuneBrain LLC, a retinal imaging device developer.

Alessandra Lugaresi has served as a Biogen, Merck Serono, Novartis, Roche, Sanofi/ Genzyme and Teva Advisory Board Member. She received congress and travel/accommodation expense compensations or speaker honoraria from Biogen, Merck, Mylan, Novartis, Sanofi/

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