Association of Age With Contrast-Enhancing Lesions Across the Multiple Sclerosis Disease Spectrum

Marcus W. Koch, MD, PhD, Jop Mostert, MD, PhD, Yinan Zhang, MD, Jerry S. Wolinsky, MD, Fred D. Lublin, MD, Eva Strijbis, MD, PhD, and Gary Cutter, PhD

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Correspondence
Dr. Koch
mwkoch@ucalgary.ca

Abstract

Background and Objectives

To investigate the association of age and the presence of contrast-enhancing lesions (CELs) on cranial MRI scans in different disease courses of multiple sclerosis (MS), we describe the frequency of CELs as a function of age in 4 large randomized controlled trial (RCT) datasets.

Methods

Using original trial data from CombiRx (Combination Therapy in Patients With Relapsing-Remitting Multiple Sclerosis; clinicaltrials.gov identifier NCT00211887), a trial in relapsing-remitting MS; ASCEND (A Clinical Study of the Efficacy of Natalizumab on Reducing Disability Progression in Participants With Secondary Progressive Multiple Sclerosis; clinicaltrials.gov identifier NCT01416181), a trial in secondary progressive MS; and the 2 primary progressive MS trials PROMISE and INFORMS; clinicaltrials.gov identifier NCT00731692), we describe the occurrence of CELs per age group at baseline for the entire trial cohort and at 1 year follow-up in the treatment arms.

Results

CombiRx included 1,008, ASCEND 889, PROMISE 943, and INFORMS 970 participants. At baseline, CEL frequency differed between datasets according to disease course: 39.6% of CombiRx, 23.9% of ASCEND, 14.0% of PROMISE, and 12.3% of INFORMS participants had CELs. This distribution by disease course was largely preserved within each age group. In all datasets, there was an almost linear decrease of the percentage of participants with CELs with advancing age. After 1 year of experimental treatment, CEL occurrence was reduced in all trial datasets, and almost absent in ASCEND. The decrease of CEL occurrence with advancing age was preserved in CombiRx, PROMISE, and INFORMS after 1 year of treatment. We investigated the association of the baseline factors age, disease duration, sex, and EDSS with having CELs at baseline with multivariable binary logistic regression models. Age was the only characteristic associated with the risk of CELs at baseline in all datasets, with higher age associated with a lower risk of CELs (odds ratios for having CELs at baseline per year increase in age: CombiRx: 0.96, 95% confidence interval [CI] 0.95–0.98; ASCEND: 0.94, 95% CI 0.92–0.97; PROMISE: 0.94, 95% CI 0.91–0.96; INFORMS: 0.97, 95% CI 0.94–0.99).

Discussion

Our analysis of 4 large, well-characterized RCT datasets shows that the association of age and CEL occurrence is a general phenomenon across the spectrum of MS disease courses. Our findings should be replicated in real-world MS datasets.

From the Departments of Clinical Neurosciences (M.W.K.) and Community Health Sciences (M.W.K.), University of Calgary, Alberta, Canada; Department of Neurology (J.M.), Rijnstate Hospital, Arnhem, the Netherlands; Department of Neurology (Y.Z., F.D.L.), Icahn School of Medicine at Mount Sinai, New York, NY; Department of Neurology (J.S.W.), McGovern Medical School, University of Texas Health Science Center at Houston (UTHealth); Department of Neurology (E.S.), MS Center Amsterdam, Amsterdam University Medical Centers, the Netherlands; and Department of Biostatistics (G.C.), University of Alabama at Birmingham.

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Glossary

ASCEND = A Clinical Study of the Efficacy of Natalizumab on Reducing Disability Progression in Participants With Secondary Progressive Multiple Sclerosis; **CEL** = contrast-enhancing lesion; **CombiRx** = Combination Therapy in Patients With Relapsing-Remitting Multiple Sclerosis; **EDSS** = Expanded Disability Status Scale; **MS** = multiple sclerosis; **PPMS** = primary progressive multiple sclerosis; **RCT** = randomized controlled trial; **RRMS** = relapsing-remitting multiple sclerosis; **SPMS** = secondary progressive multiple sclerosis.

The disease process of multiple sclerosis (MS) is characterized by inflammation as well as neurodegeneration.[1] Common to all forms of MS are foci of inflammation in the brain and spinal cord, which can be visualized with MRI. Active inflammatory demyelination within such lesions leads to damage to the blood–brain barrier, so that actively demyelinating lesions can be identified using a gadolinium-based contrast agent. Contrast-enhancing lesions (CELs) on MRI scans are indicative of active inflammatory demyelination at the time of the scan, and are therefore seen as a reliable radiologic biomarker of current inflammatory disease activity. The presence and number of CELs are an important secondary outcome in relapsing-remitting MS (RRMS) trials, but CELs occur in all disease courses of MS.

Several studies showed that CEL frequency decreases with age,[2-5] a finding that is in keeping with the observation that relapses decrease with age and disease duration,[6] and with the general idea that inflammatory disease activity in MS is more pronounced in younger and less prevalent in older people. However, these studies were dominated by patients with RRMS, and it is less clear whether the observed association of age and CEL occurrence is present across all MS disease courses.

In this study, we used the datasets from 4 large randomized controlled trials (RCTs) in RRMS, secondary progressive MS (SPMS), and primary progressive MS (PPMS) to investigate the relation of age on the presence of CELs at baseline and after 1 year of experimental treatment.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

The dataset of CombiRx (Combination Therapy in Patients With Relapsing-Remitting Multiple Sclerosis) was obtained from the Coordinating Center at the University of Alabama at Birmingham. The ASCEND (A Clinical Study of the Efficacy of Natalizumab on Reducing Disability Progression in Participants With Secondary Progressive Multiple Sclerosis) and PROMISE and INFORMS RCT datasets were obtained from Biogen, TEVA, and Novartis, the pharmaceutical companies that conducted and oversaw these trials. Ethical approval for the original trial is described in the original publications.[7-10] Ethical approval for this analysis was sought and granted by the University of Calgary Conjoint Health Research Ethics Board.

Trial Datasets

CombiRx

CombiRx[7] was a multicenter phase 3 RCT of interferon-β plus placebo (25%) or glatiramer acetate plus placebo (25%) or combination of the 2 active agents in RRMS (50%), so that all included participants received a form of immunomodulatory treatment. The inclusion criteria were a diagnosis of RRMS by Poser[11] or 2001 McDonald[12] diagnostic criteria, age 18–60 years inclusive, and Expanded Disability Status Scale (EDSS) score[13] of 0–5.5 inclusive, with at least 2 exacerbations in the 3 years before inclusion (where one exacerbation could be an MRI change meeting the 2001 McDonald MRI criteria for dissemination in time). CombiRx participants were naive to immunomodulatory treatment at the time of enrollment.[7]

ASCEND

ASCEND[8] was a multicenter phase 3 RCT investigating the efficacy of natalizumab treatment in SPMS. Entry criteria included age 18–58 years inclusive, SPMS for 2 or more years, disability progression over the previous year (as assessed using a standardized form), and a screening EDSS of 3.0–6.5 inclusive.

PROMISE

PROMISE[9] was a multicenter phase 3 RCT investigating the efficacy of glatiramer acetate treatment in PPMS. Key inclusion criteria included a participant age between 30 and 65 years with an entry EDSS score of 3.0–6.5 inclusive and a diagnosis of PPMS confirmed by the principal investigator at each study site. Participants with a history of relapses were excluded.[9]

INFORMS

INFORMS[10] was a multicenter phase 3 RCT investigating the efficacy of fingolimod treatment in PPMS. Key inclusion criteria were age 25–65 years, a clinical diagnosis of PPMS, disease progression for 1 year or more, a disease duration of 2–10 years, and objective evidence of disability worsening in the 2 years before inclusion.[10]

Outcome Measures

All clinical trials included gadolinium-enhanced cranial MRI scans at the beginning and throughout the trial. Technical details of the postcontrast scans are shown in Table 1. We selected the first scan before treatment initiation (performed at the screening visit in ASCEND and at baseline in the other trials) for the entire trial cohorts and the 1-year follow-up scan (performed at 48 weeks in ASCEND) of the treatment arm

for our analyses. We determined the number of patients with CELs on these scans.

To investigate whether patients with CELs at baseline also had CELs at 1 year follow-up, we constructed 2×2 tables and performed χ^2 tests.

We investigated the association of the baseline factors age, disease duration, sex, and EDSS at baseline with having CELs at baseline with multivariable binary logistic regression models. We also investigated the possible interaction of age and disease duration with an interaction term in these models.

Given the heterogeneity of the datasets, we decided not to perform further analyses. All statistical analyses were performed with the R statistical software package for Windows, version 4.0.2.[14] Statistical significance was taken to be at the 2-tailed 0.05 level.

Data Availability

CombiRx
Access to the CombiRx dataset can be requested from the Coordinating Center or MS Center at the University of Alabama at Birmingham by completing a data use agreement that is reviewed by a committee overseeing the use of the data. Qualified researchers have or will obtain appropriate institutional review board approval for the study request. Depending on the complexity of the request, researchers may need to cover the cost of producing the deidentified data.

ASCEND
The ASCEND dataset is available upon request from Biogen. Individual participant data collected during the trial will be shared after anonymization and on approval of a research proposal and data sharing agreement. Research proposals can be submitted online (biogenclinicaldatarequest.com).

PROMISE
The PROMISE dataset was acquired through TEVA Pharmaceutical's Data Sharing and Transparency office after agreeing on a research proposal and data sharing agreement. It is available to other qualified researchers upon request from TEVA Pharmaceuticals.

INFORMS
The INFORMS dataset is available upon request from Novartis. Individual participant data collected during the trial will be shared after anonymization and on approval of a research proposal and data sharing agreement. Research proposals can be submitted online (clinicalstudydatarequest.com).

Results

Baseline Characteristics
The baseline characteristics of the trial datasets are shown in Table 2. The datasets reflect the disease course included in each trial, with CombiRx including younger patients than the

Table 1 Technical Details of the T1-Weighted Postcontrast MRIs for Each Trial

	CombiRx	ASCEND	PROMISE	INFORMS
Contrast agent used	Gadolinium DTPA	Gadolinium (various)	Gadopentetate dimeglumine	Gadolinium (various)
Dose of the contrast agent, mmol/kg	0.1	0.1	0.1	0.1
Time between contrast administration and image acquisition, min	5	10	5	5
Sequence description	—	3D spoiled gradient-recalled echo with slab-selective excitation	Contiguous, interleaved, T1-weighted transaxial images using a spin echo pulse sequence with magnetization transfer, both before and following the contrast infusion	Conventional spin echo
TR, ms	600–660	30	400	500–700
TE, ms	10–15	11	11	10–20
Field of view, cm	24	25	24	25
Excitations, n	1	1	1	1
Slices, n	44	60	44	≥46
Slice thickness, mm	3	3	3	3
Field strength	1.5T or 3.0T	1.5T or 3.0T	1.5T	1.5T or 3.0T

Abbreviations: ASCEND = A Clinical Study of the Efficacy of Natalizumab on Reducing Disability Progression in Participants With Secondary Progressive Multiple Sclerosis; CombiRx = Combination Therapy in Patients With Relapsing-Remitting Multiple Sclerosis; DTPA = diethylenetriaminepentaacetic acid; TR = repetition time; TE = echo time.

Table 2 Baseline Characteristics in the Included Trial Datasets

	CombiRx	ASCEND	PROMISE	INFORMS
Participants, n	1,008	889	943	970
Participants in the treatment arm	1,008 (100)	440 (49.5)	627 (66.5)	483 (49.8)
MS disease course	RRMS	SPMS	PPMS	PPMS
Women/men	730/278	550/339	483/460	469/501
Age, y	37 (30–45)	48 (42–53)	51 (44–57)	49 (43–55)
Age groups, y				
Up to 30	261 (25.9)	29 (3.3)	11 (1.2)	12 (1.2)
31–40	351 (34.8)	139 (15.6)	116 (12.3)	145 (14.9)
41–50	278 (27.6)	373 (42.0)	324 (34.4)	368 (37.9)
51–60	118 (11.7)[a]	348 (39.1)	393 (41.7)	341 (35.2)
Above 60	—	—	99 (10.5)	104 (107.)
Disease duration, y	2 (1–5)	16 (11–21)	9 (5–14)	5 (4–7)
EDSS at baseline	2.0 (1.0–2.5)	6.0 (5.0–6.5)	5.0 (4.0–6.0)	4.5 (4.0–5.5)
EDSS at baseline groups				
0.0–3.0	876 (87.1)	13 (1.5)	55 (5.8)	34 (3.6)
3.5–5.5	130 (12.9)	610 (68.6)	708 (75.1)	679 (71.9)
6.0 and above	—	266 (29.9)	180 (19.1)	231 (24.5)

Abbreviations: ASCEND = A Clinical Study of the Efficacy of Natalizumab on Reducing Disability Progression in Participants With Secondary Progressive Multiple Sclerosis; CombiRx = Combination Therapy in Patients With Relapsing-Remitting Multiple Sclerosis; DTPA = diethylenetriaminepentaacetic acid; EDSS = Expanded Disability Status Scale; PPMS = primary progressive multiple sclerosis; MS = multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis.
Values are n (%) or median (interquartile range).
[a] Includes one 61-year-old participant.

3 progressive trials. As expected, and as a consequence of the inclusion criteria and disease definitions, disability at baseline was much higher in the progressive trials. We divided age at baseline into 5 categories: up to 30 years, 31–40 years, 41–50 years, 51–60 years, and above 60 years. One participant in CombiRx was 61 years of age at baseline; we decided to include this participant's data in the 51–60 years group.

CELs at Baseline by Age

CEL occurrence differed between datasets according to disease course, with 39.6% of CombiRx participants having CELs, followed by ASCEND participants with 23.9%, and PROMISE and INFORMS participants with 14.0% and 12.8%. This distribution by disease course was largely preserved within each age group (Table 3 and Figure). In all datasets, there was an almost linear decrease of the percentage of participants with CELs with advancing age (Table 3 and Figure).

CELs in the Treatment Arms at 1 Year

After 1 year of experimental treatment, CEL occurrence was meaningfully reduced in all trial datasets. As expected, this reduction was less pronounced in CombiRx and PROMISE, which used the platform treatments interferon-β and

glatiramer acetate, and in which the percentage of CEL occurrence was reduced to about half of the baseline percentage after 1 year of treatment (CombiRx: from baseline overall 39.6% to 14.8% at 1 year in the treatment arm; PROMISE: from 14.0% to 7.6%) (Table 3 and Figure). After 1 year of fingolimod treatment in INFORMS, CELs were reduced to about a quarter of their baseline frequency (from 12.8% to 3.3%), and 1 year of natalizumab treatment almost abolished CELs in ASCEND (from 23.9% to 1%) (Table 3 and Figure). The almost linear decrease of CEL occurrence with advancing age, however, was preserved in CombiRx, PROMISE, and INFORMS after 1 year of treatment. Table 4 shows the resulting 2 × 2 tables for CELs at baseline and 1 year follow-up for the treatment arms of the trials. Significantly more trial participants with CELs at baseline remained CEL positive at 1 year follow-up compared to those without CELs at baseline in CombiRx (with 27% of participants with CELs at baseline also having CELs at follow-up, compared to only 7% of participants without CELs at baseline being CEL positive at follow up, χ^2 $p < 0.0001$), PROMISE (21% vs 5%, $p < 0.0001$), and INFORMS (14% vs 2%, $p < 0.0001$). In ASCEND, there were so few CELs at 1 year follow-up that the 2 × 2 table could not be interpreted (Table 4).
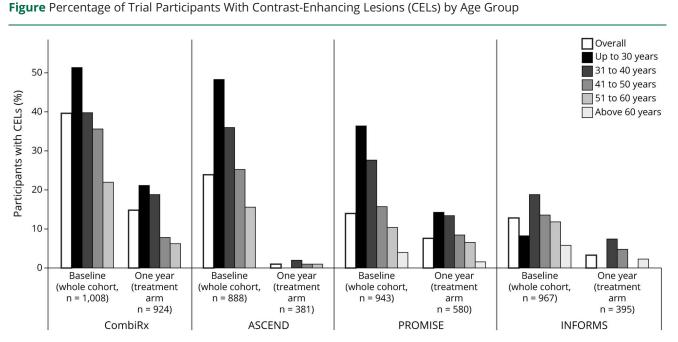
Table 3 Percentage of Participants With Contrast-Enhancing Lesions by Age Group at Baseline in the Whole Cohort and at 1 Year in the Treatment Arms in the Included Datasets

	CombiRx	ASCEND	PROMISE	INFORMS
Whole group at baseline	39.6 (1,008)	23.9 (888)	14.0 (943)	12.8 (967)
Overall up to 30 y	51.3 (261)	48.3 (29)	36.4 (11)	8.3 (12)
31–40 y	39.8 (351)	36.0 (139)	27.6 (116)	18.8 (144)
41–50 y	35.6 (278)	25.2 (373)	15.7 (324)	13.6 (368)
51–60 y	22.0 (118)[a]	15.6 (347)	10.4 (393)	11.8 (340)
Above 60 y	—	—	4.0 (99)	5.8 (103)
Treatment arm at 1 y				
Overall	14.8 (924)	1.0 (381)	7.6 (580)	3.3 (395)
Up to 30 y	21.1 (227)	0.0 (12)	14.3 (7)	0.0 (7)
31–40 y	18.8 (329)	2.0 (52)	13.4 (67)	7.4 (54)
41–50 y	7.8 (255)	1.0 (171)	8.5 (200)	4.8 (165)
51–60 y	6.2 (113)[a]	1.0 (146)	6.6 (242)	0.0 (126)
Above 60 y	—	—	1.6 (64)	2.3 (43)

Abbreviations: ASCEND = A Clinical Study of the Efficacy of Natalizumab on Reducing Disability Progression in Participants With Secondary Progressive Multiple Sclerosis; CombiRx = Combination Therapy in Patients With Relapsing-Remitting Multiple Sclerosis; DTPA = diethylenetriaminepentaacetic acid.
The numbers in parentheses are the total number of observations per category.
[a] Includes one 61-year-old participant.

CELs and Baseline Characteristics

Table 5 shows the results of the multivariable logistic regression models on the association of baseline characteristics and CEL occurrence. Age was the only baseline characteristic associated with the risk of CELs at baseline in all datasets, with higher age associated with a lower risk of CELs. The strength of the association of age and CEL occurrence was similar between trial datasets, with odds ratios of between 0.94 and

Figure Percentage of Trial Participants With Contrast-Enhancing Lesions (CELs) by Age Group

Percentage of trial participants with CELs by age group at baseline in the 4 included trial datasets. The percentage of individuals with CELs decreases as a function of age and disease course both at baseline and after 1 year of treatment.

Table 4 Two-By-Two Tables of Trial Participants in the Treatment Arms With Contrast-Enhancing Lesions (CELs) at Baseline and at 1-Year Follow-up

CELs at baseline	CELs at 1 year follow-up		
	Yes	No	p^a
CombiRx			
Yes	98	269	<0.0001
No	39	518	
ASCEND			
Yes	1	102	0.93
No	3	275	
PROMISE			
Yes	17	64	<0.0001
No	27	472	
INFORMS			
Yes	7	44	<0.0001
No	6	338	

Abbreviations: ASCEND = A Clinical Study of the Efficacy of Natalizumab on Reducing Disability Progression in Participants With Secondary Progressive Multiple Sclerosis; CombiRx = Combination Therapy in Patients With Relapsing-Remitting Multiple Sclerosis; DTPA = diethylenetriaminepentaacetic acid.
Significantly more participants with CELs at baseline have CELs at 1 year follow-up in CombiRx, PROMISE, and INFORMS. There are so few CELs at 1 year follow-up in ASCEND that the table cannot be interpreted.
[a] χ^2 test.

datasets, higher EDSS at baseline was associated with a higher risk of CELs at baseline (odds ratio per EDSS point increase 1.20, 95% confidence interval 1.03 to 1.41).

Discussion

Our investigation into 4 large phase 3 RCT datasets shows that the age dependence of CELs is a general phenomenon across the spectrum of disease courses in MS. The observation that CELs occurrence decreases with age was previously described in several observational and interventional studies, including an observational study of 200 untreated people with RRMS and SPMS,[4] a cohort including 1,543 individuals with all forms of MS and clinically isolated syndrome,[5] and in the linomide in RRMS and SPMS trial.[2] Two studies using triple-dose gadolinium contrast in 45 people showed that CELs decrease with time in PPMS, from 32% at baseline[15] to 26% 5 years later.[16] Our investigation confirms the observation that CELs are also age-dependent in PPMS, and adds that the effect of age on CEL occurrence is preserved in treated patients.

In the ASCEND dataset, we see a very powerful treatment effect of natalizumab in SPMS, which almost abolishes CELs 1 year after treatment. It should be kept in mind, however, that ASCEND was a negative trial and that natalizumab treatment, despite its impressive effect on CEL occurrence, could not prevent the steady functional decline the participants experienced in this trial over the observation period.[8] This lacking effect on functional outcomes despite a powerful effect on CELs supports the idea that disease progression in SPMS is driven by a pathophysiology that is separate from focal inflammatory demyelination. The hypotheses about the nature of this pathophysiology range from a different form of inflammation[17] to the idea that MS may be primarily a neurodegenerative disease in which inflammation is an early reaction to neurodegenerative processes.[18]

0.96 per year increasing age and comparable 95% confidence intervals between trial datasets (Table 5). Disease duration was not significantly associated with CELs and there was no significant interaction between age and disease duration in any of the datasets. In PROMISE, but not in the other

Table 5 Results of the Multivariable Logistic Regression Models on the Association of Baseline Characteristics on the Risk of Having Contrast-Enhancing Lesions (CELs) at Baseline

	CombiRx	ASCEND	PROMISE	INFORMS
Age[a]	0.96 (0.95–0.98)	0.94 (0.92–0.97)	0.94 (0.91–0.96)	0.97 (0.94–0.99)
Disease duration[a]	0.99 (0.96–1.01)	0.99 (0.97–1.02)	0.98 (0.95–1.01)	0.96 (0.88–1.04)
Sex				
Female (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Male	1.10 (0.83–1.47)	0.89 (0.64–1.23)	0.80 (0.55–1.18)	1.19 (0.81–1.76)
EDSS[b]	1.07 (0.95–1.21)	1.00 (0.84–1.20)	1.20 (1.03–1.41)	0.98 (0.81–1.19)

Abbreviations: ASCEND = A Clinical Study of the Efficacy of Natalizumab on Reducing Disability Progression in Participants With Secondary Progressive Multiple Sclerosis; CombiRx = Combination Therapy in Patients With Relapsing-Remitting Multiple Sclerosis; DTPA = diethylenetriaminepentaacetic acid; EDSS = Expanded Disability Status Scale.
Age is the only baseline characteristic associated with the risk of CELs at baseline, with higher age associated with a lower risk of CELs. Disease duration is not significantly associated with CELs in any of the models. In PROMISE, but not in the other datasets, higher EDSS at baseline was associated with a higher risk of CELs at baseline. Values are odds ratio (95% confidence interval).
[a] Per year increase.
[b] Per point increase.

In the CombiRx dataset we see the natural decrease of inflammatory disease activity in RRMS as a function of age, even though the inclusion criteria of this trial selected for patients with comparatively active RRMS, with at least 2 demyelinating events (2 relapses or 1 relapse and new MRI activity in the 3 years before inclusion). Furthermore, it recruited previously treatment naive participants so that the CEL positivity in the higher age groups may also indicate a more benign preexisting disease course in the older participants, since they were recruited in their 40s or 50s without prior exposure to immunomodulatory drugs. Nevertheless, the almost linear relation between age and CEL occurrence is preserved after 1 year of treatment with the platform therapies interferon-β, glatiramer acetate, or their combination. The effect of aging on disease activity can also be seen in relapse frequency measured in clinical practice. A study in 2,477 people with RRMS in the British Columbia Natural History Cohort showed that annualized relapse rates decline with age.[6]

In our study, disease duration was not significantly associated with CELs at baseline in any of the trial datasets, nor did we find a significant interaction between age and disease duration for the risk of having CELs. These findings contrast the investigation of factors associated with gadolinium enhancement in the linomide in RRMS and SPMS trial, where disease duration as well as age were associated with having CELs.[2] The previously mentioned study on relapse frequency in the British Columbia Natural History Cohort also found that disease duration was associated with decreasing relapse frequency in addition to age, and across age groups.[6]

Taken together, these investigations suggest that there is a natural "mellowing" of focal inflammatory disease activity with age across the MS disease spectrum. There is some support for this idea from an autopsy study investigating the characteristics of demyelinating white matter lesions in 120 individuals with different MS disease courses.[19] This study showed that "active" white matter lesions dominate in younger individuals and make up around 80% of demyelinating lesions at age 20, but decline almost linearly to around 20% at age 60. In older individuals, "inactive" and "smoldering" lesions form the majority of white matter lesions.[19] It has been speculated that this reduction in active focal inflammatory demyelination is due to a shift from adaptive T- and B-cell mediated immunity underlying active focal inflammation to innate immunity resulting in chronic inflammation and microglial activation.[20] For RRMS, this suggests that younger patients may benefit from a more aggressive treatment approach. On the other hand, it also suggests that older patients may naturally age out of the risk of highly active disease, and that immunomodulatory treatment focused on focal inflammation may be less beneficial with advancing age. Weideman et al.[21] examined the effect of immunomodulatory drug treatment on disability progression in a meta-analysis of 38 clinical trials in MS and

found that the efficacy of such treatment decreases with age, to the point where it may not reduce disability progression in participants above age 53. Based on these findings, several RCTs are underway to investigate whether immunomodulatory drugs can be safely discontinued in older patients or in patients without disease activity for a prolonged period. In the DISCOMS trial (Discontinuation of Disease Modifying Therapies in Multiple Sclerosis; clinicaltrials.gov identifier NCT03073603), participants are randomized to either remain on their current treatment or to discontinue it, and are then followed clinically and with cranial MRIs every 6 months to determine differences in clinical and radiologic disease activity. Other trials following a similar design are the STOP-I-SEP trial (Disease Modifying Therapies Withdrawal in Inactive Secondary Progressive Multiple Sclerosis Patients Older Than 50 Years; clinicaltrials.gov identifier NCT03653273) and the DOT-MS trial (Discontinuing Disease-modifying Therapies in Stable Relapsing-Onset Multiple Sclerosis; clinicaltrials.gov identifier NCT04260711). These trials will contribute to a better understanding of age as a determinant of inflammatory disease activity and treatment response in different forms of MS. Similarly, the effect of age demonstrated in our study could also be used to enrich a trial cohort, for example by including younger patients for a phase 2 study of a treatment for active inflammatory demyelination, or by deliberately including older participants for trials targeting smoldering lesions or chronic microglial activation.

Our study has several limitations. While our investigation shows that the effect of aging on focal inflammatory demyelination is present in all MS disease courses, we caution against comparing between these datasets, and against generalizing the findings from these datasets to the general clinical population of people with MS. Clinical trials always include a selected subgroup of the real-world population of people with MS, and are often enriched for activity to increase or enhance the occurrence of outcome events. Our findings should be replicated in real-world datasets, ideally in population-based cohorts including people with all subtypes of MS.

Author Statement

The principal author takes full responsibility for the data, the analyses and interpretation, and the conduct of the research; the principal author had full access to all of the data and has the right to publish any and all data separate and apart from any sponsor.

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Disclosure

Publication History

Appendix Authors

Name	Location	Contribution
Marcus Werner Koch, MD, PhD	Departments of Clinical Neurosciences and Community Health Sciences, University of Calgary, Alberta, Canada	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data

Appendix (continued)

Name	Location	Contribution
Jop Mostert, MD, PhD	Department of Neurology, Rijnstate Hospital, Arnhem, the Netherlands	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Yinan Zhang, MD	Department of Neurology, Icahn School of Medicine at Mount Sinai, New York, NY	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Jerry S. Wolinsky, MD	Department of Neurology, McGovern Medical School, University of Texas Health Science Center at Houston (UTHealth)	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Fred D. Lublin, MD	Department of Neurology, Icahn School of Medicine at Mount Sinai, New York, NY	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Eva M.M. Strijbis, MD, PhD	Department of Neurology, MS Center Amsterdam, Amsterdam University Medical Centers, the Netherlands	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Gary Cutter, PhD	Department of Biostatistics, University of Alabama at Birmingham	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data

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