MSJ Experimental Translational Clinical

Original Research Paper

An exploratory analysis of the efficacy of ocrelizumab in patients with multiple sclerosis with increased disability

Multiple Sclerosis Journal—Experimental, Translational and Clinical

January–March 2020, 1–7

DOI: 10.1177/2055217320911939

Jerry S Wolinsky, Natalie J Engmann, Jinglan Pei, Ashish Pradhan, Clyde Markowitz and Edward J Fox

Abstract

Background: Ocrelizumab, an anti-CD20 humanized monoclonal antibody, reduced disease progression in pivotal trials of patients with relapsing (OPERA I, OPERA II) and primary progressive (ORATORIO) multiple sclerosis (MS). These effects may be particularly important among patients with increased disability.

Objective: In this post hoc exploratory analysis, we evaluated the efficacy of ocrelizumab on disability progression among a subgroup of patients with MS who had increased baseline disability levels (Expanded Disability Status Scale scores $\geq$4.0) in the pivotal trials.

Methods: During the double-blind period, patients received ocrelizumab 600 mg intravenously every 24 weeks for 96 weeks in the OPERA trials (versus interferon β-1a 44 μg subcutaneously three times per week) and for 120 weeks in ORATORIO (versus placebo). Kaplan–Meier and Cox survival analyses were used to assess disability outcome measures.

Results: Baseline demographic, disease, and treatment characteristics were generally comparable across treatment groups in patients with increased disability from the OPERA and ORATORIO trials. Ocrelizumab treatment numerically, and in some instances significantly, reduced confirmed disability progression versus the comparator in these patients.

Conclusions: In patients with increased baseline disability, ocrelizumab reduced the risk of confirmed disability progression versus interferon β-1a in patients with relapsing-onset MS and versus placebo in patients with progression-onset MS.

Keywords: Ocrelizumab, disease-modifying therapy, relapsing multiple sclerosis, primary progressive multiple sclerosis, disease progression, disability, ambulation

Date received: 21 November 2019; revised 6 February 2020; accepted: 16 February 2020

Introduction

Worsening of neurological symptoms in multiple sclerosis (MS) results in progression of disability, reduced mobility and other functional impairments, and decreased independence in the majority of patients.[1–4] The Expanded Disability Status Scale (EDSS) is the most widely used tool for benchmarking disability in patients with MS.[4] An EDSS score of 4.0 serves as an important milestone, as it signifies a transition to impaired walking (unaided walking distance limited to 500 m without rest).[5] However, clinical trials often enroll patients with lower EDSS scores, limiting information on the efficacy of disease-modifying therapy (DMT) among patients with MS who have increased disability.

Ocrelizumab is a humanized monoclonal antibody that selectively targets CD20-expressing B cells.[6,7] The efficacy of ocrelizumab has been demonstrated in three pivotal phase III clinical trials: OPERA I

Correspondence to:
Jerry S Wolinsky,
McGovern Medical School, The University of Texas Health Science Center at Houston, 6431 Fannin Street, Houston, TX 77030, USA.
jerry.s.wolinsky@uth.tmc.edu

Jerry S Wolinsky,
McGovern Medical School, The University of Texas Health Science Center at Houston, TX, USA

Natalie J Engmann, **Jinglan Pei**, **Ashish Pradhan**, Genentech, Inc., South San Francisco, CA, USA

Clyde Markowitz, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

Edward J Fox, Central Texas Neurology Consultants, Round Rock, TX, USA

(NCT01247324) and OPERA II (NCT01412333) in patients with relapsing MS (RMS)[8] and ORATORIO (NCT01194570) in patients with primary progressive MS (PPMS).[9] In these trials, ocrelizumab treatment was associated with lower rates of disease activity and progression than interferon (IFN) β-1a treatment in patients with RMS and reduced rates of clinical and magnetic resonance imaging–measured disease progression compared with placebo in patients with PPMS. We conducted an exploratory analysis of the effect of ocrelizumab on disability progression among a subgroup of patients with increased EDSS-defined disability levels from the OPERA and ORATORIO trials.

Methods

Details of the OPERA I, OPERA II, and ORATORIO trials, including patient eligibility criteria and study design, were previously described.[8,9] Briefly, patients received ocrelizumab 600 mg intravenously every 24 weeks for 96 weeks in OPERA I and OPERA II (versus IFN β-1a 44 μg subcutaneously three times weekly) and for ≥120 weeks (until a predefined number of disability events occurred) in ORATORIO (versus placebo).[8,9]

The primary goal of this analysis was to assess disability outcomes among ocrelizumab-treated patients with RMS or PPMS who had a baseline EDSS score ≥4.0 at the start of the OPERA I/OPERA II or ORATORIO clinical trials, respectively. Endpoints were assessed during the double-blind treatment period (baseline through Week 96 for OPERA I/OPERA II and through Week 120 for ORATORIO) using Kaplan–Meier and Cox survival analyses and included the following:

- Time to 24-week confirmed disability progression (CDP) on the EDSS (CDP-EDSS), defined as an increase from baseline EDSS score of ≥1 point in patients with a baseline EDSS score of ≤5.5 or ≥0.5 point in patients with a baseline EDSS score of >5.5.
- Time to confirmed 20% increase in Nine-Hole Peg Test (9HPT) time for ≥24 weeks (CDP-9HPT). In this test, the patient was instructed to place nine pegs into nine empty holes, one at a time, as quickly as possible. Two consecutive timed trials were conducted using the dominant hand, immediately followed by two consecutive timed trials with the non-dominant hand.
- Time to confirmed 20% increase in Timed 25-Foot Walk (T25FW) time for ≥24 weeks (CDP-T25FW). In this test, the patient was instructed to walk 25 feet as quickly as possible while being timed (e.g. trial 1). Upon reaching the 25-foot mark, the patient was timed while walking the same distance again (e.g. trial 2).
- Composite assessment of CDP-EDSS, CDP-9HPT, and CDP-T25FW, defined as progression on one or more of these three measures.

Preservation of function is arguably more meaningful among patients who are more disabled. Moreover, accumulation of disability at higher levels on the EDSS may more directly reflect clinical expression of underlying pathological manifestations of disease progression. We conducted an exploratory sensitivity analysis on subsets of patients with more advanced disability at baseline to explore possible differential effects of ocrelizumab at later stages in relapse-onset and progression-onset disease phenotypes. Among patients with RMS (OPERA I/OPERA II), outcomes were also evaluated in a more restricted subset of those with a baseline EDSS score >5.0, which signifies disability severe enough to preclude full participation in daily activities. In the PPMS (ORATORIO) population, a baseline EDSS threshold score of >6.0 was used to define a more restricted subset of patients who at baseline required bilateral assistance to walk 20 m without rest.

Due to the exploratory nature of this analysis, no adjustments for multiplicity testing or accounting for assistive device use or inability to complete the 9HPT or T25FW assessments were made. No missing data imputation was done for EDSS. Missing data were imputed for 9HPT time and T25FW time as follows:

- 9HPT: If the test results were not available due to a "physical limitation," the maximum possible value for the scale was imputed. If the test results were not available and it was not due to a "physical limitation," the missing test score was imputed using the result from the other trial of the same hand. If the result from the other trial of the same hand was also missing, the average score from the other hand (or available score from one trial if the result from only one trial was available) was imputed.
- T25FW: If the test results were not available due to a "physical limitation," the maximum possible value for the scale was imputed. If the test results were not available and it was not due to a "physical limitation," the result from the other trial was used to impute the missing value.

Results

Among patients with increased disability in the pivotal trials, the baseline EDSS score ≥4.0 (OPERA I/OPERA II, $n = 375$) and ORATORIO ($n = 507$) cohorts had a larger sample size than the baseline EDSS score >5.0 (OPERA, $n = 92$) and >6.0 (ORATORIO, $n = 88$) cohorts. Baseline demographics, disease characteristics, and treatment history (Table 1) were generally comparable in ocrelizumab- and comparator-treated patients. In this exploratory analysis, patients experienced numerically and directionally attenuated risks of CDP with ocrelizumab treatment versus the comparator during the double-blind treatment period of 96 weeks in OPERA I/OPERA II and 120 weeks in ORATORIO, as assessed by CDP-EDSS, CDP-9HPT, CDP-T25FW, and the composite confirmed-progression endpoint (Figure 1, Table 2, Supplementary Figures 1 and 2).

In particular, in the OPERA I/OPERA II analysis, the confirmed disability risk reductions reached statistical significance only for time to CDP-EDSS for the baseline EDSS score ≥4.0 ($p = 0.013$) cohort and trended towards significance for the baseline EDSS score >5.0 ($p = 0.097$) cohort (Table 2, Supplementary Figure 1). All analyses trended positively or reached statistical significance for the ORATORIO baseline EDSS score ≥4.0 (CDP-EDSS, $p = 0.017$; CDP-9HPT, $p = 0.013$) and EDSS score >6.0 (CDP-EDSS, $p = 0.046$; CDP-T25FW, $p = 0.026$) cohorts (Table 2, Supplementary Figure 2). It is worth noting that the limited effect on CDP observed in the OPERA I/OPERA II cohorts may have been influenced by comparator-treated patients receiving an active drug, IFN β-1a 44 μg subcutaneously three times weekly, which may have had an effect on slowing disease progression during the 96-week double-blind treatment period. Moreover, because this was an exploratory analysis and no adjustments for multiple comparisons were made, additional research evaluating the efficacy of DMTs in patients with increased disability is needed.

Discussion

Early and intensive intervention in MS is increasingly being recognized as a critical factor in minimizing disability progression. However, according to the trial data on which this concept is based, there is a question of the impact of therapy on patients who have already accumulated appreciable disability. A common implicit presumption is that treatments may not effectively modify disease once a certain disability threshold, typically measured via the EDSS, is crossed. Unfortunately, this may contribute to what are likely artificial treatment barriers for patients with higher disability levels.

The present analysis focused on clinical outcomes using multiple measures of disability progression among patients with RMS and those with PPMS with greater baseline disability based on EDSS scores. Treatment benefits with ocrelizumab relative to the active comparator or placebo were observed for EDSS-based outcomes in patients with RMS and PPMS; additionally, benefits were also observed for other measures of disability, including the T25FW and 9HPT in patients with PPMS. Performance-based measures such as these have superior psychometric properties[10] and may be more meaningful to patients than the EDSS at higher levels of that scale. Preservation of upper extremity function, for example, may be particularly valuable to patients who require the use of a walking aid or are confined to a wheelchair versus patients without walking impairment. In a recent survey of patients with MS, approximately 90% of respondents ranked upper limb function above lower limb function as key for maintaining independence, and 95% of respondents felt that patients in wheelchairs should not be excluded from clinical trials.[11] In order for the benefits of DMT in patients with advanced disability to be seen, clinical trials must include endpoints that are sensitive to functions that can be preserved or regained in this population.

Limitations of this analysis include the small sample size and post hoc nature of the investigation. Moreover, because this analysis was exploratory, we did not adjust for multiplicity of testing as we were primarily interested in the direction of the data. In addition, patients with increased baseline disability were identified using the EDSS, which, despite being the most accepted measure of disability in MS clinical trials, has a number of important and well-known limitations, including high variability, non-linearity of staying time at the different stages, limited sensitivity, and failure to adequately capture other domains considered by patients to be an important part of daily functioning, such as upper extremity function and cognition.[4] Lastly, the limited effect observed in patients with RMS may have also been driven by the use of a conventional fixed baseline EDSS value; it has previously been shown that a roving EDSS reference value (i.e. resetting the reference EDSS score after ≥24- or ≥48-week confirmation of a new score) may more efficiently detect progression events independent of relapse

Table 1. Baseline demographics and disease characteristics of patients enrolled in OPERA I/OPERA II and ORATORIO with walking impairment and in the sensitivity population.

	Patients with walking impairment			
	RMS (OPERA I/OPERA II) BL EDSS score ≥4.0		PPMS (ORATORIO) BL EDSS score ≥4.0	
	OCR ($n = 183$)	IFN β-1a ($n = 192$)	OCR ($n = 341$)	PBO ($n = 166$)
Age, mean (SD), years	40.2 (9.3)	41.4 (8.6)	44.7 (7.9)	44.9 (8.0)
Female, *n* (%)	114 (62.3)	129 (67.2)	177 (51.9)	83 (50.0)
Duration of disease, mean (SD), years				
Time since symptom onset	10.25 (6.99)	10.09 (7.19)	7.17 (4.33)	6.73 (3.79)
Time since MS diagnosis	6.16 (5.65)	6.32 (5.96)	3.29 (3.43)	3.21 (3.68)
No. of relapses in the previous 12 months, mean (SD)	1.34 (0.67)	1.36 (0.79)	NA	NA
Previous treatment, *n* (%)				
Yes	61 (33.3)	61 (31.8)	45 (13.2)	22 (13.3)
No	122 (66.7)	131 (68.2)	296 (86.8)	144 (86.7)
EDSS score, mean (SD)	4.63 (0.62)	4.69 (0.63)	5.31 (0.91)	5.34 (0.90)
EDSS score, median (range)	4.50 (4.0–6.0)	4.50 (4.0–6.0)	5.50 (4.0–7.0)	5.50 (4.0–6.5)
9HPT time, mean (SD), s	31.05 (23.26)	29.34 (12.68)	34.85 (27.04)	33.23 (14.97)
T25FW time, mean (SD), s	12.87 (16.86)	11.80 (17.54)	17.98 (24.07)	16.06 (17.89)
Patients without Gd-enhancing lesions, *n* (%)	112 (61.9)[a,b]	124 (64.9)[a,c]	230 (67.8)[a,d]	124 (75.2)[a,e]
No. of T2 lesions, mean (SD)	65.29 (43.82)	62.41 (41.34)	50.41 (39.53)	48.25 (41.94)
Volume of T2 lesions, mean (SD), cm^3	16.15 (16.80)	13.85 (14.04)	14.30 (16.33)	11.87 (13.88)
Normalized brain volume, mean (SD), cm^3	1461.48 (89.70)	1450.45 (86.92)	1457.44 (82.23)	1465.27 (85.95)

	Sensitivity population			
	RMS (OPERA I/OPERA II) BL EDSS score >5.0		PPMS (ORATORIO) BL EDSS score >6.0	
	OCR ($n = 42$)	IFN β-1a ($n = 50$)	OCR ($n = 63$)	PBO ($n = 25$)
Age, mean (SD), years	40.1 (9.7)	41.0 (7.8)	44.1 (9.1)	43.2 (7.1)
Female, *n* (%)	29 (69.0)	38 (76.0)	34 (54.0)	9 (36.0)
Duration of disease, mean (SD), years				
Time since symptom onset	10.98 (7.47)	12.71 (8.12)	9.57 (4.84)	9.65 (4.52)
Time since MS diagnosis	7.15 (6.56)	9.09 (6.75)	5.41 (4.27)	5.03 (5.29)
No. of relapses in the previous 12 months, mean (SD)	1.40 (0.89)	1.47 (1.00)	NA	NA
Previous treatment, *n* (%)				
Yes	14 (33.3)	19 (38.0)	15 (23.8)	6 (24.0)
No	28 (66.7)	31 (62.0)	48 (76.2)	19 (76.0)
EDSS score, mean (SD)	5.50 (0.18)	5.52 (0.17)	6.51 (0.06)	6.50 (0.00)
EDSS score, median (range)	5.50 (5.5–6.0)	5.50 (5.5–6.0)	6.50 (6.5–7.0)	6.50 (6.5–6.5)
9HPT time, mean (SD), s	35.81 (44.16)	34.52 (19.33)	52.97 (54.32)	48.25 (23.07)
T25FW time, mean (SD), s	23.98 (30.02)	16.71 (20.71)	43.32 (39.66)	36.90 (30.11)

(continued)

Table 1. Continued

	Sensitivity population			
	RMS (OPERA I/OPERA II) BL EDSS score >5.0		PPMS (ORATORIO) BL EDSS score >6.0	
	OCR ($n=42$)	IFN β-1a ($n=50$)	OCR ($n=63$)	PBO ($n=25$)
Patients without Gd-enhancing lesions, *n* (%)	25 (59.5)	30 (60.0)	39 (62.9)[a,f]	16 (66.7)[a,g]
No. of T2 lesions, mean (SD)	67.31 (42.94)	73.48 (44.95)	55.59 (44.09)	55.96 (35.67)
Volume of T2 lesions, mean (SD), cm^3	14.75 (15.15)	15.81 (13.10)	17.52 (19.82)	13.88 (12.32)
Normalized brain volume, mean (SD), cm^3	1462.44 (70.63)	1428.60 (78.74)	1432.92 (85.42)	1447.93 (76.66)

[a]Patients had missing baseline T1 lesion data.
[b]Denominator = 181.
[c]Denominator = 191.
[d]Denominator = 339.
[e]Denominator = 165.
[f]Denominator = 62.
[g]Denominator = 24.
9HPT: Nine-Hole Peg Test; BL: baseline; EDSS: Expanded Disability Status Scale; Gd: gadolinium; IFN: interferon; MS: multiple sclerosis; NA: not applicable; OCR: ocrelizumab; PBO: placebo; PPMS: primary progressive multiple sclerosis; RMS: relapsing multiple sclerosis; T25FW: Timed 25-Foot Walk.

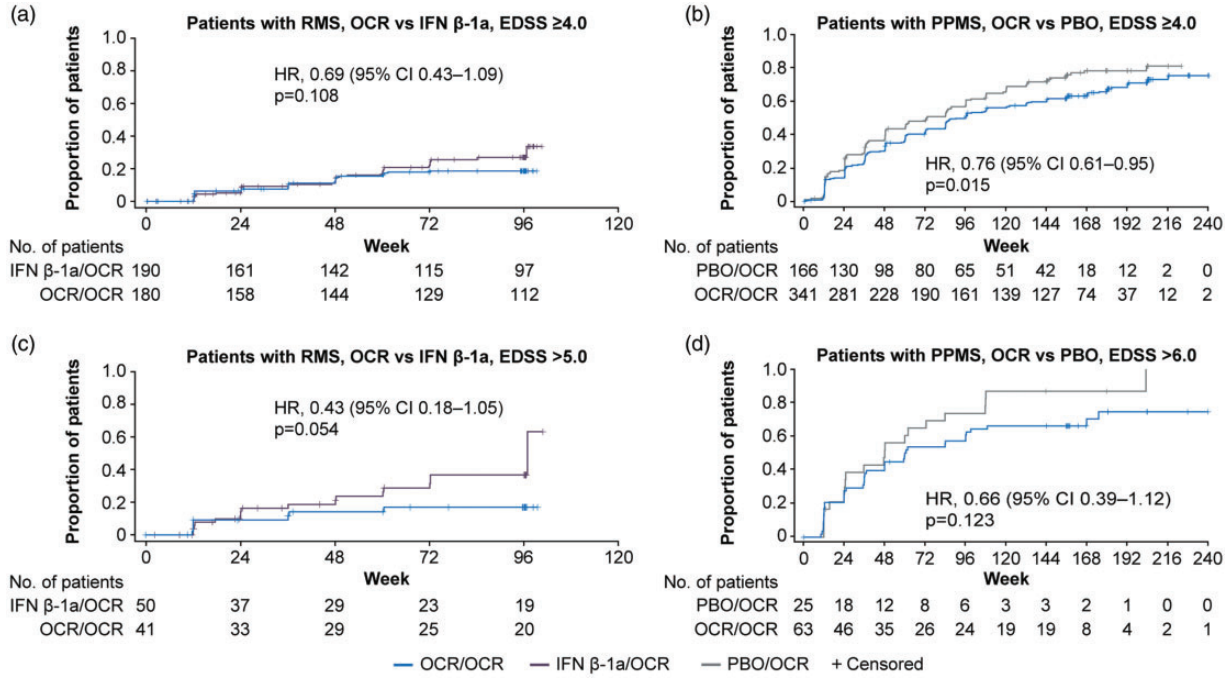

Figure 1. Effect of ocrelizumab versus that of comparator on composite disability measure in patients with RMS (OPERA I/OPERA II) and patients with PPMS (ORATORIO) who had baseline EDSS score ≥4.0 ((a) and (b)); baseline EDSS score >5.0 (RMS only; (c)) and baseline EDSS score >6.0 (PPMS only; (d)).
CI: confidence interval; EDSS: Expanded Disability Status Scale; HR: hazard ratio; IFN: interferon; OCR: ocrelizumab; PBO: placebo; PPMS: primary progressive multiple sclerosis; RMS: relapsing multiple sclerosis.

Table 2. Effect of ocrelizumab on measures of confirmed progression in patients enrolled in OPERA I/OPERA II and ORATORIO with walking impairment and in the sensitivity population.

	Patients with walking impairment	
	RMS (OPERA I/OPERA II) BL EDSS score ≥4.0	PPMS (ORATORIO) BL EDSS score ≥4.0
	HR (95% CI) OCR ($n = 183$)/IFN β-1a ($n = 192$)	HR (95% CI) OCR ($n = 341$)/PBO ($n = 166$)
Time to CDP-EDSS	0.37 (0.16–0.84) $p = 0.013$	0.71 (0.54–0.94) $p = 0.017$
Time to CDP-9HPT	0.60 (0.22–1.64) $p = 0.311$	0.64 (0.45–0.91) $p = 0.013$
Time to CDP-T25FW	0.88 (0.51–1.52) $p = 0.634$	0.80 (0.63–1.02) $p = 0.070$
Time to composite confirmed progression	0.69 (0.43–1.09) $p = 0.108$	0.76 (0.61–0.95) $p = 0.015$
	Sensitivity population	
	RMS (OPERA I/OPERA II) BL EDSS score >5.0	PPMS (ORATORIO) BL EDSS score >6.0
	HR (95% CI) OCR ($n = 42$)/IFN β-1a ($n = 50$)	HR (95% CI) OCR ($n = 63$)/PBO ($n = 25$)
Time to CDP-EDSS	0.29 (0.06–1.39) $p = 0.097$	0.51 (0.25–1.00) $p = 0.046$
Time to CDP-9HPT	0.28 (0.03–2.50) $p = 0.222$	0.58 (0.30–1.11) $p = 0.095$
Time to CDP-T25FW	0.61 (0.22–1.65) $p = 0.321$	0.55 (0.32–0.94) $p = 0.026$
Time to composite confirmed progression	0.43 (0.18–1.05) $p = 0.054$	0.66 (0.39–1.12) $p = 0.123$

9HPT: Nine-Hole Peg Test; BL: baseline; CDP: confirmed disability progression; EDSS: Expanded Disability Status Scale; HR: hazard ratio; IFN: interferon; OCR: ocrelizumab; PBO: placebo; PPMS: primary progressive multiple sclerosis; RMS: relapsing multiple sclerosis; T25FW: Timed 25-Foot Walk.

activity in patients with RMS and relapsing-remitting MS treated with a DMT.[12,13]

In conclusion, there is currently a limited understanding of the potential benefits of DMT in patients with increased disability. Findings from this study provide evidence that ocrelizumab may have a meaningful benefit for patients with RMS and PPMS with demonstrable impairment (EDSS score ≥4.0) and for patients with PPMS with even more advanced disability (EDSS score >6.0). A strong directional trend for reduced disability risk was also observed in patients with RMS with advanced disability (EDSS score >5.0). Due to the exploratory nature of this analysis, additional prospective studies are warranted to assess treatment benefit in patients with MS with advanced disease using qualified, sensitive, and meaningful assessments of disability.

Acknowledgments

We thank all patients and the investigators for their participation in these trials. Writing and editorial assistance was provided by Liz LaFlamme, Jumaah Goldberg, and Angela Morris of Health Interactions, Inc., USA, and funded by Genentech, Inc., South San Francisco, CA, USA.

Author contributions

Conception and design of the study: JSW, NJE, JP, AP, CM, EJF; acquisition and analysis of data: JP, AP, NJE; drafting a significant portion of the manuscript or figures: JSW, JP, NJE. All authors had full access to all data in the study and participated in writing the manuscript, and the corresponding author had final responsibility for the decision to submit the manuscript for publication.

Conflict of Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: JSW has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities from Actelion, Alkermes, BrainStorm Cell Therapeutics, Celgene, Clene Nanomedicine, EMD Serono, Forward Pharma A/S, GeNeuro, GW Pharmaceuticals, MedDay Pharmaceuticals, NervGen Pharma Corp., Novartis, Otsuka, PTC Therapeutics, F. Hoffmann-La Roche Ltd and Genentech, Inc., and Sanofi Genzyme; he received

royalties for outlicensed monoclonal antibodies through The University of Texas Health Science Center at Houston from Millipore Corporation. NJE, JP, and AP are employees of Genentech, Inc., and shareholders of F. Hoffmann-La Roche Ltd. CM has received consultancy fees from Bayer HealthCare, Biogen, F. Hoffmann-La Roche Ltd and Genentech, Inc., Mallinckrodt Pharmaceuticals, EMD Serono, Mylan, Novartis, Sanofi Genzyme, and Teva Pharmaceutical Industries. EJF has received speaker honoraria and travel expense reimbursement from, participated in clinical research or speakers bureaus for, or served on advisory/consulting/steering committees for AbbVie, Acorda, Allergan, Bayer, Biogen, Celgene, Chugai, EMD Serono, F. Hoffmann-La Roche Ltd, Mallinckrodt Pharmaceuticals, MedDay Pharmaceuticals, Novartis, Sanofi Genzyme, Teva Pharmaceutical Industries, and TG Therapeutics.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The OPERA I, OPERA II, and ORATORIO clinical trials were funded by F. Hoffmann-La Roche Ltd, Basel, Switzerland.

ORCID iD

Jerry S Wolinsky https://orcid.org/0000-0002-8197-2762

Supplemental Material

Supplemental material for this article is available online.

References

1. Jones E, Pike J, Marshall T, et al. Quantifying the relationship between increased disability and health care resource utilization, quality of life, work productivity, health care costs in patients with multiple sclerosis in the US. *BMC Health Serv Res* 2016; 16: 294.
2. Salter AR, Cutter GR, Tyry T, et al. Impact of loss of mobility on instrumental activities of daily living and socioeconomic status in patients with MS. *Curr Med Res Opin* 2010; 26: 493–500.
3. Souza A, Kelleher A, Cooper R, et al. Multiple sclerosis and mobility-related assistive technology: systematic review of literature. *J Rehabil Res Dev* 2010; 47: 213–223.
4. Uitdehaag BMJ. Disability outcome measures in phase III clinical trials in multiple sclerosis. *CNS Drugs* 2018; 32: 543–558.
5. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 1983; 33: 1444–1452.
6. Genentech, Inc. OCREVUSTM [ocrelizumab] Full prescribing information, 2017.
7. Roche Pharma AG. OCREVUS [ocrelizumab] Summary of product characteristics, 2018.
8. Hauser SL, Bar-Or A, Comi G, et al. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. *New Eng J Med* 2017; 376: 221–234.
9. Montalban X, Hauser SL, Kappos L, et al. Ocrelizumab versus placebo in primary progressive multiple sclerosis. *New Eng J Med* 2017; 376: 209–220.
10. LaRocca NG, Hudson LD, Rudick R, et al. The MSOAC approach to developing performance outcomes to measure and monitor multiple sclerosis disability. *Mult Scler* 2018; 24: 1469–1484.
11. Thomson A, Giovannoni G, Marta M, et al. Importance of upper limb function in advanced multiple sclerosis. ECTRIMS Online Library, 2016.
12. Kappos L, Wolinsky JS, Giovannoni G, et al. Relapse-associated worsening and progression independent of relapse activity in patients with relapsing multiple sclerosis in the phase III OPERA I and OPERA II studies. ECTRIMS Online Library, 2018.
13. Kappos L, Butzkueven H, Wiendl H, et al. Greater sensitivity to multiple sclerosis disability worsening and progression events using a roving versus a fixed reference value in a prospective cohort study. *Mult Scler* 2018; 24: 963–973.