Rituximab vs placebo induction prior to glatiramer acetate monotherapy in multiple sclerosis

Justin M. Honce, MD, Kavita V. Nair, PhD, Stefan Sillau, PhD, Brooke Valdez, BA, Augusto Miravalle, MD, Enrique Alvarez, MD, PhD, Teri Schreiner, MD, MPH, John R. Corboy, MD, and Timothy L. Vollmer, MD

Neurology® 2019;92:e723-e732. doi:10.1212/WNL.0000000000006916

Correspondence

Dr. Vollmer
timothy.vollmer@ucdenver.edu

Abstract

Objective

To examine whether rituximab induction followed by glatiramer acetate (GA) monotherapy is more effective than GA alone for the treatment of relapsing multiple sclerosis with active disease.

Methods

This was a single-center, double-blind, placebo-controlled study. Fifty-five participants were randomly assigned (1:1 ratio) to either rituximab (R-GA) or placebo (P-GA) induction, followed by GA therapy initiated in all participants. Participants were followed up to 3 years. The primary endpoint was the number of participants with no evidence of disease activity (NEDA): those without relapse, new MRI lesions, and sustained change in disability.

Results

Twenty-eight and 27 participants received rituximab and placebo induction, respectively, with one participant in each arm withdrawing before 6-month MRI. There were no significant differences in baseline characteristics. At end of study, 44.44% of R-GA participants demonstrated NEDA vs 19.23% of P-GA participants ($p = 0.049$). Treatment failed for a smaller proportion of R-GA participants (37.04% R-GA vs 69.23% P-GA, $p = 0.019$), and time to treatment failure was longer (23.32 months R-GA vs 11.29 months P-GA, $p = 0.027$). Fewer participants in the R-GA arm had new lesions (25.93% R-GA vs 61.54% P-GA, $p = 0.009$), and there were fewer new T2 lesions (0.48 R-GA vs 1.96 P-GA, $p = 0.027$). Probability of demonstrating NEDA in the R-GA arm returned to baseline within the study period. There were no differences in adverse events.

Conclusions

Induction therapy with rituximab followed by GA may provide superior efficacy in the short term than GA alone in relapsing multiple sclerosis, but this benefit appears to wane within the study period. Larger studies are needed to assess sustainability of results.

ClinicalTrials.gov identifier

NCT01569451.

From the Departments of Radiology (J.M.H.) and Clinical Pharmacy (K.V.N.), University of Colorado Hospital, Aurora; Department of Neurology (K.V.N., S.S., B.V., E.A., T.S., J.R.C., T.L.V.), University of Colorado, and Rocky Mountain Multiple Sclerosis Center at the University of Colorado, Aurora; and Department of Neurology (A.M.), University of Florida, Gainesville. Dr. Miravalle is currently at Advanced Neurology of Colorado, Fort Collins, Colorado.

Go to [Neurology.org/N](https://www.neurology.org/N) for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

CIS = clinically isolated syndrome; **CUL** = combined unique lesion; **DMT** = disease-modifying therapy; **EDSS** = Expanded Disability Status Scale; **GA** = glatiramer acetate; **GEL** = gadolinium-enhancing lesion; **HERMES** = Helping to Evaluate Rituxan in Relapsing-Remitting Multiple Sclerosis; **Ig** = immunoglobulin; **MS** = multiple sclerosis; **NEDA** = no evidence of disease activity; **P-GA** = placebo–glatiramer acetate; **PRO** = patient-reported outcome; **R-GA** = rituximab–glatiramer acetate; **SAD** = sustained accumulation of disability.

Currently, the dominant approach in the selection of disease-modifying therapies (DMTs) for the initial treatment of multiple sclerosis (MS) is referred to as “escalation” therapy. This promotes the utilization of low-efficacy/low-risk treatments as first line, followed by switching to higher-efficacy/higher-risk treatments if participants demonstrate “treatment failure.”^{1,2} The challenge in implementing escalation therapy is in defining the threshold at which point a patient “fails” their initial DMT.^{3–7} The escalation approach allows many patients to accumulate preventable disability early in the disease.^{8,9} As a result, there is a growing argument to use highly efficacious DMTs as first-line agents even if there may be higher risk.^{1,10,11}

Another approach is induction therapy, in which the goal is to initiate treatment with a highly effective immunosuppressive DMT, used for a short time to minimize risk, with or without a low-efficacy/low-risk agent for long-term immunomodulation.^{10,12–14} Given the significant costs and degradation of quality of life experienced by patients with poorly controlled MS,^{15,16} and the importance of initiation of early treatment,¹⁷ the risks associated with short-term immunosuppression followed by conventional immunomodulatory agents may be outweighed by risks associated with inadequate control of disease activity.

The emerging role of B lymphocytes in the pathogenesis of MS^{18,19} suggests that induction strategies utilizing B cell-depleting therapies may provide long-standing control of MS disease activity with a tolerable risk profile.²⁰ Rituximab (Rituxan; Genentech, South San Francisco, CA) is an anti-CD20 monoclonal antibody that depletes B lymphocytes. It is approved for the treatment of non-Hodgkin lymphoma and rheumatoid arthritis.²¹ Studies of off-label rituximab in relapsing-remitting MS have shown substantial clinical effects on relapses and MRI activity, with an acceptable short-term safety profile.^{20,22–24}

Glatiramer acetate (GA) (Copaxone; Teva, North Wales, PA), is one of the oldest and safest approved therapies for patients with relapsing-remitting MS,^{25–27} but the efficacy of GA is modest in comparison to several other presently available DMTs.²⁸ The rationale for using GA as the maintenance therapy after rituximab induction is the observation that a key mechanism of action for GA may be the induction of regulatory B cells through interaction of GA with the B cell receptor, and subsequent inhibition of MS-related proinflammatory B and T cells through bystander suppression.²⁹

This study examines whether using rituximab as an induction agent followed by GA monotherapy is more effective than GA alone for the treatment of relapsing forms of MS with active disease.

Methods

Standard protocol approvals, registrations, and patient consents

The study protocol was approved by the Colorado Multiple Institutional Review Board, and all study participants provided written informed consent before undergoing study procedures. Details on this clinical trial are recorded at clinicaltrials.gov (NCT01569451).

Participants

Inclusion criteria

This study population was recruited from the Rocky Mountain MS Center at the University of Colorado in Aurora and included patients between 18 and 55 years of age with a diagnosis of clinically isolated syndrome (CIS) or relapsing MS as determined by 2005 revised McDonald criteria.³⁰ Patients with CIS who were eligible for the study had a history of one unifocal neurologic event and an MRI within the last year with at least 2 T2-weighted brain lesions measuring at least 6 mm in diameter. Relapsing patients eligible for the study demonstrated at least one clinically defined relapse and at least one (but not ≥ 15) gadolinium-enhancing lesion (GEL) on MRI within the year before enrollment.

Exclusion criteria

Medication-related exclusion criteria for the study were as follows: treatment with systemic corticosteroids within 30 days of randomization; previous treatment with interferon β , fingolimod, teriflunomide, or natalizumab within 3 months of randomization; treatment with mitoxantrone, cyclophosphamide, or any other chemotherapeutic agent for MS or malignancy within 12 months of randomization; or any prior treatment with alemtuzumab or cladribine. The following were other exclusion criteria: history of cardiac arrhythmias, angina or any other significant cardiac abnormalities; history of hepatitis B and/or C infection; history of any other clinically significant chronic disease of the immune system or a known immunodeficiency syndrome (such as HIV); attenuated live virus vaccination within 4 weeks of randomization; and white blood cell count less than $2.5 \times 10^9/L$.

or lymphocyte count below $0.4 \times 10^9/L$. No female participant was pregnant or lactating and all were required to practice an acceptable method of birth control during the study period.

Study design

This was a double-blind, placebo-controlled, randomized, single-center study. Enrollment was conducted between October 2011 and April 2013, and the study was completed on the last follow-up visit, which occurred in May 2015. For randomization, patients were divided into blocks of 4, and within each block, 2 were randomly assigned to the rituximab-GA (R-GA) treatment, and the remaining 2 were assigned to the placebo-GA (P-GA) treatment by an independent statistician. These results were placed in sequentially numbered envelopes and sent to the dispensing pharmacy at the University of Colorado Hospital. The study pharmacist selected the envelopes for the next randomized patient in order of randomization and issued identical infusions bags of either rituximab (R-GA) or saline (P-GA). A disclosure envelope was prepared for each randomization number in case emergency unblinding becomes necessary.

The study, with 45 patients planned per group, was powered on a 2 independent-sample proportion test for difference in the proportion of patients with disease events within 24 weeks. For a P-GA proportion of 45%, and an R-GA proportion of 15%, a decrease of 0.3, similar to the HERMES (Helping to Evaluate Rituxan in Relapsing-Remitting MS) trial,²⁰ a 2-sample proportion test, at $\alpha = 0.05$, would achieve approximately 90% power. Our final sample sizes, 26 and 27 for P-GA and R-GA, respectively, would have 65% power, under the same inputs.

Within 60 days of informed consent, all patients were randomized in a 1:1 ratio to either rituximab (R-GA arm) or placebo (P-GA arm) in a blinded fashion. Participants received an IV infusion of 1,000 mg of rituximab or placebo (normal saline) on study days 1 (baseline visit) and 15. On study day 28 (visit 1), GA therapy was initiated in all participants: 20 mg injected subcutaneously daily up to a maximum of 144 weeks.

Study visits occurred every 3 months with phone calls every month to assess for possible adverse events and relapses between study visits. The Expanded Disability Status Scale (EDSS), Multiple Sclerosis Functional Composite score, and MRI scans of the brain with and without contrast were measured at baseline and months 6, 12, 18, 24, 30, and 36. Additional patient-reported outcomes (PROs), including Patient Determined Disease Steps and various other performance scales (Modified Fatigue Impact Scale, 36-Item Short Form Health survey, Symptom Inventory–Short Form), were collected every month and every 6 months, respectively.

Complete blood counts with differential and CD19⁺ lymphocyte levels were collected at baseline and every 3

months during the study period. CD19⁺ was analyzed as a surrogate of CD20⁺ as it has similar expression and rituximab interferes with flow cytometric analysis of CD20⁺ lymphocytes.

Primary endpoint

The primary endpoint was the proportion of participants demonstrating no evidence of disease activity (NEDA), defined as those without any new combined unique lesions (CULs) on MRI, *and* without any protocol defined relapse following treatment initiation, *and* without a 3-month sustained accumulation of disability (SAD). The primary endpoint was also used to calculate the probability of being disease-free throughout the study for both treatment groups. A CUL is any new lesion defined as a T2 or proton density high-signal lesion ≥ 3 mm in diameter not seen on an immediate prior examination *or* a new gadolinium-enhancing T1 lesion unless they were in the exact anatomical region of a new T2 hyperintense lesion.

Protocol-defined relapses were a new or worsening neurologic symptom(s) with an objective change on the EDSS of at least 1.5 points for participants with baseline EDSS scores of 0 or 0.5, at least 1-point change for participants with EDSS of 1 to 5.5, or at least a 0.5-point change for participants with EDSS of 5.5 to 6.5. Symptoms must have been attributable to MS, last ≥ 48 hours, been present at normal body temperature, and preceded by at least 30 days of clinical stability. Participants were evaluated by a treating physician after a suspected relapse, with EDSS evaluations performed by an examining physician blinded to treatment assignment. SAD was met if these EDSS changes were sustained for at least 3 months. All 3 primary outcome measures were evaluated by a blinded examiner.

Secondary endpoints

The major secondary endpoints measured were the proportion of participants whose treatment failed, and the time to treatment failure, defined as having 2 or more CULs on an MRI, *or* developing a protocol defined relapse, *or* development of SAD. In practice then, a single new CUL, in the absence of relapse or SAD, categorizes a participant as no longer meeting NEDA, but not as having failed treatment. Additional clinical secondary endpoints included the proportion of participants with no clinical relapses, the annualized relapse rate, and the proportion of participants experiencing multiple (≥ 2) relapses during the study period. In addition, the proportion of participants requiring treatment with corticosteroids for relapse management and proportion of participants with SAD were also assessed.

The following were MRI secondary endpoints: (1) the proportion of participants with new CULs, (2) the number of new CULs, (3) the proportion of participants with new T2 lesions, (4) new GELs, as well as the numbers of (5) new T2 lesions and (6) new GELs in each arm.

Exploratory endpoints

Descriptive changes in overall longitudinal scores between baseline and 1- and 2-year follow-up over the study period were assessed for multiple PRO instruments including the quality-of-life 36-Item Short Form Health survey–Mental and Physical Summary score, the Performance Scales, the Patient Determined Disease Steps, the Modified Fatigue Impact Scale score, and the Symptom Inventory–Short Form.

Statistical analysis

Continuous variables were transformed when necessary and possible to render the distributions more gaussian. Rank-based methods were performed for highly skewed distributions.

Binary outcomes over time were analyzed with Poisson rate models. Time to treatment failure was analyzed with Kaplan-Meier curves and with Cox proportional hazards models. Counting of events was also performed using negative binomial models, and Cox proportional hazards models were considered as well. Change scores and mixed-model regression models were used for repeated measures for continuous outcomes, such as the PRO scales. These analyses were conducted in SAS version 9.4 (SAS Institute, Cary, NC). Participants were analyzed under intention-to-treat analysis.

Data availability

The study protocol and anonymized data from this study will be shared when requested by a qualified investigator.

Results

Recruitment and study flow

Recruitment for this study occurred over a 27-month period. The flow of participants through the study is depicted in figure 1. A total of 64 participants were screened for the study

and 55 were randomized to either P-GA or R-GA induction. Twenty-six and 27 completed the baseline visit in the P-GA and R-GA groups, respectively. One participant in each arm withdrew before the 6-month MRI.

Baseline characteristics

As seen in table 1, there were no statistically significant differences between the R-GA and P-GA arms for any baseline measure. Two-thirds of participants were women, and mean age was 36.6 years. The vast majority of participants in both groups had relapsing forms of MS, with only 2 participants with CIS in each group. There was an apparently greater T2 lesion burden in the R-GA arm but this did not meet clinical significance (3,293 mm³ R-GA vs 1,629 mm³ P-GA, $p = 0.0854$). R-GA participants also had an apparently overall longer disease duration that did not meet statistical significance (R-GA 5.56 years vs P-GA 2.72 years, $p = 0.0761$). Participants were followed for a mean of 1.63 years (SD 0.83) in the R-GA arm and 1.52 years (SD 0.77) in the P-GA arm ($p = 0.3974$).

Primary endpoint

At the close of the study, a greater proportion of participants in the R-GA arm (12 of 27, 44.44%) than in the P-GA arm (5 of 26 participants, 19.23%) demonstrated NEDA ($p = 0.0493$). The probability of achieving NEDA over the study period is depicted by a Kaplan-Meier survival curve (figure 2). The R-GA arm revealed a greater probability of demonstrating NEDA beginning about 6 months from induction. This effect does not appear to be sustained, with the R-GA arm nearing the P-GA baseline within the study period.

Secondary endpoints

As is seen in table 2, over the study period, there were 10 participants (37.04%) in the R-GA arm and 18 participants (69.23%) in the P-GA arm whose treatment failed (≥ 2 new

Figure 1 *Study sample includes those patients who had at least 1 follow-up MRI after baseline

P-GA = placebo-glatiramer acetate; R-GA rituximab-glatiramer acetate.

Table 1 Baseline characteristics of treatment groups

	R-GA arm (n = 27)	P-GA arm (n = 26)	p Value	Total/mean
Sex, female, n (%)	19 (70.4)	18 (69.2)	0.9280	37 (69.8)
Age, y, mean (SD)	36.46 (8.31)	36.64 (9.15)	0.9391	36.55
Race, n (%)				
Caucasian	22 (81.5)	21 (80.8)	0.5188	43 (81.1)
Hispanic	3 (11.1)	1 (3.9)		4 (7.6)
Unknown	2 (7.4)	4 (15.4)		6 (11.3)
Type of MS, n (%)				
Relapsing	25 (92.6)	24 (92.3)	1.0000	49 (92.4)
CIS	2 (7.4)	2 (7.7)		4 (7.6)
EDSS score, mean (SD)	2.80 (1.78)	2.63 (1.57)	0.7270	2.72
MSFC z score, mean (SD)	−0.0659 (0.7082)	0.0685 (0.7956)	0.5275	0 (by definition)
MS disease duration, y, mean (SD)	5.56 (7.08)	2.72 (3.50)	0.0761	4.17
Treatment-naïve, n (%)	21 (77.8)	18 (64.3)	0.4805	44 (80.0)
Natalizumab within 6 mo of randomization, yes, n (%)	5 (18.5)	4 (15.4)	1.0000	9 (17.0)
No. of GELs, mean (SD)	1.07 (2.53)	0.54 (2.16)	0.4001	0.81
T2 lesion volume, mm ³ (geometric mean ± SD on the log scale)	3,293.43 (763.39, 14,208.53)	1,629.27 (379.03, 7,003.54)	0.0854	2331.87

Abbreviations: CIS = clinically isolated syndrome; EDSS = Expanded Disability Status Scale; GEL = gadolinium-enhancing lesion; MS = multiple sclerosis; MSFC = Multiple Sclerosis Functional Composite; P-GA = placebo-glatiramer acetate; R-GA rituximab-glatiramer acetate.

CULs, relapses, and/or SAD) ($p = 0.0189$). For the R-GA group, 3 failed treatment for new CULs, 6 had relapses, and 1 failed for SAD. For the P-GA group, 8 failed treatment for new CULs, 8 had relapses, and 2 failed because of SAD. Median time for a participant to reach treatment failure was twice as long for R-GA compared to P-GA ($p = 0.0268$). There were

more participants with no relapses in the R-GA arm ($n = 20$, 74.07%) compared with the P-GA arm ($n = 13$, 50%), but this did not meet statistical significance ($p = 0.0707$). Figure 3 depicts the Kaplan-Meier curve for relapses in this study. One participant in the R-GA arm experienced multiple (2) relapses, as did 3 in the P-GA arm. There were also no significant differences regarding corticosteroid use, SAD, or annualized relapse rate.

Figure 2 Probability of being disease-free between treatment groups during the study period

P-GA = placebo-glatiramer acetate; R-GA rituximab-glatiramer acetate.

Blinded analysis of MRI demonstrated less MRI activity within the R-GA arm as compared with the P-GA arm, with a smaller proportion of R-GA participants having new CULs, and there were fewer new CULs in total in the R-GA arm (table 2). New T2 lesions drove the changes in CULs, with fewer participants in the R-GA arm with new T2 lesions ($n = 7$, 25.93%) than in the P-GA arm ($n = 16$, 61.54%) ($p = 0.0089$). There were also fewer total numbers of new T2 lesions in the R-GA arm, but there were no significant differences in the number of participants with new GELs or differences in the mean number of GELs between each arm.

Exploratory endpoints

There were no significant group differences in self-reported disability or quality of life for any of the tested PRO scales between baseline assessment and the end of study visit. Baseline scores for each group are presented in data available from Dryad (table e-1, doi.org/10.5061/dryad.f43591n).

Table 2 Secondary outcome differences between treatment groups

	R-GA arm (n = 27)	P-GA arm (n = 26)	p Value	Ratio (95% CI)
Clinical outcomes				
Participants whose treatment failed, n (%)	10 (37.04)	18 (69.23)	0.0189 ^a	0.5350 (0.2820–0.9,338)
Median time to treatment failure, mo (95% CI)	23.32 (14.64, ∞)	11.29 (5.25, 23.39)	0.0268 ^a	Hazard ratio: 0.452 (0.200–0.961)
Participants with relapses during the study period, n (%)	6 (22.22)	9 (34.62)	0.3167	0.6420 (0.2325–1.5542)
Participants with multiple relapses during the study period, n (%)	1 (3.70)	3 (11.54)	0.3507	0.3210 (0.0125–3.0166)
Annualized relapse rate	0.1550	0.3706	0.1219	0.4182 (0.1586–1.1031)
Participants treated with corticosteroids for relapses, n (%)	4 (14.81)	9 (34.62)	0.0940	0.4280 (0.0667–1.1823)
Participants who achieved sustained accumulation of disability, n (%)	4 (14.81)	3 (11.54)	1.0000	1.2840 (0.2956–8.3752)
MRI outcomes				
Participants with new T2 lesions, n (%)	7 (25.93)	16 (61.54)	0.0089 ^a	0.4213 (0.1679–0.8675)
No. of new T2 lesions, mean (SD)	0.48 (1.22)	1.96 (3.09)	0.0270 ^a	0.2455 (0.0808–0.7453)
Participants with any GELs, n (%)	3 (11.11)	6 (23.08)	0.2935	0.4815 (0.0656–1.7313)
No. of GELs, mean (SD)	0.11 (0.32)	0.38 (0.80)	0.1081	0.2889 (0.0767–1.0881)
Participants with any new T2/GEL CUL, n (%)	9 (33.33)	17 (65.38)	0.0196 ^a	0.5098 (0.2459–0.9301)
No. of any new T2/GEL CUL, mean (SD)	0.59 (1.24)	2.35 (3.37)	0.0164 ^a	0.2526 (0.0978–0.6526)

Abbreviations: CI = confidence interval; CUL = combined unique lesion; GEL = gadolinium-enhancing lesion; P-GA = placebo-glatiramer acetate; R-GA rituximab-glatiramer acetate.

^a Significant.

Since this was an exploratory analysis, comparisons in PRO overall scores for each of these scales was limited between baseline to 12 and 24 months within each study group and

between groups. There were no differences found in any within- or between-group differences.

Pharmacodynamics

The R-GA arm demonstrated >95% reduction of CD20⁺ lymphocytes (as measured by CD19⁺ counts) at the first follow-up visit at 3 months, and depletion was sustained for a mean of 9.83 months (95% confidence interval, 8.46–11.20) and median of 8.61 months (95% confidence interval, 8.29–11.36). By 25 months, mean CD19⁺ lymphocytes had returned to 60.4% of baseline values. In the P-GA arm, CD19⁺ lymphocytes remained relatively stable over the course of the study (figure 4).

Immunoglobulin (Ig) levels were measured at screening, 1 year, and on the last study visit. At the screening visit, IgG levels were below the lower limit of baseline in 5 R-GA participants (mean 619 mg/dL) and 2 P-GA participants (mean of 767 mg/dL). At 1 year, of the 5 R-GA participants with abnormal baseline values, 3 (60%) remained below the lower limit of normal with a mean IgG of 607 mg/dL. Both P-GA participants with baseline IgG levels below normal had normalized by 1 year. By the final end of study visit, IgG levels were within normal range for all participants (100% recovery).

Figure 3 Probability of protocol-defined relapse between treatment groups during the study period

P-GA = placebo-glatiramer acetate; R-GA rituximab-glatiramer acetate.

Figure 4 CD19⁺ lymphocytes

IQR = interquartile range; P-GA = placebo-glatiramer acetate; R-GA rituximab-glatiramer acetate.

For IgM, at the screening visit, 3 R-GA participants had IgM levels below the lower limit of normal (mean 35 mg/dL), while no P-GA participants were below normal. Three R-GA participants remained below the lower limit of normal at year 1 (mean 34 mg/dL), and one P-GA participant had IgM of 30 mg/dL. At the final end of study visit, 3 participants from R-GA and one from P-GA remained below the lower limit of normal, with an additional P-GA participant now also below normal (mean of 32 mg/dL for R-GA and 33 mg/dL for P-GA). IgA levels remained above the lower limit of normal for all participants throughout the study.

Safety and tolerability

All participants receiving rituximab or placebo induction experienced at least one adverse event, and the summary of adverse events is depicted in table 3. In the R-GA arm, there were 18 participants who experienced a combined total of 42 infusion-related reactions, while 11 P-GA participants experienced 12 total infusion-related reactions. All of these were mild grade 1 or 2 reactions that did not require hospitalization (data available from Dryad, table e-2, doi.org/10.5061/dryad.f43591n). Regarding serious adverse events, there were 4 hospitalizations of participants in the R-GA arm and 5 in the P-GA arm during the study period. One participant in each arm was hospitalized for pneumonia, and the participant from the P-GA arm hospitalized for pneumonia was separately hospitalized for MS relapse. Other hospitalizations in both groups were deemed unrelated to treatment (R-GA: knee surgery; P-GA: shoulder surgery, fibromyalgia, fall).

Discussion

Our results suggest that for participants with recent active disease, induction therapy with rituximab followed by GA was

Table 3 AE summary table

AE summary table for specific AEs	Rituximab, 1 g (2 infusions) (n = 28)	Placebo, 500 mL (2 infusions) (n = 27)
Total no. of patients with ≥ 1AE	22 (79)	22 (81)
Injury, poisoning, and procedural complications	18 (64)	11 (41)
Infusion-related reaction	18 (64)	11 (41)
General disorders and administration-site conditions	22 (79)	22 (81)
Influenza-like illness	18 (64)	13 (48)
Injection-site erythema	2 (7)	5 (19)
Fatigue	15 (54)	13 (48)
Injection-site reaction	8 (29)	8 (30)
Infections and infestations	14 (50)	14 (52)
Upper respiratory tract infection	13 (46)	10 (37)
Urinary tract infection	7 (25)	7 (26)
Bronchitis	3 (11)	2 (7)
Nervous system disorders	9 (32)	10 (37)
Headache	9 (32)	10 (37)
Psychiatric disorders	10 (36)	7 (26)
Depression	5 (18)	3 (11)
Insomnia	2 (7)	1 (4)
Anxiety	7 (25)	5 (19)
Musculoskeletal and connective tissue disorders	4 (14)	0 (0)
Back pain	2 (7)	0 (0)
Arthralgia	2 (7)	0 (0)
Gastrointestinal issues	9 (32)	7 (26)

Abbreviation: AE = adverse event.
Data represent n (%).

superior to placebo induction and GA monotherapy, with 44.44% of participants in the R-GA arm demonstrating NEDA vs 19.23% in the P-GA arm, although the effect appears to be temporally limited. Participants in the R-GA arm had fewer treatment failures, and longer median time to reach treatment failure, as well as fewer new T2 lesions, while no differences were observed for GELs. The lack of an effect on GELs may be attributable to the relative infrequency of MRI (obtained every 6 months), as GELs typically only last for 2 to 8 weeks,³¹ while the residual T2 hyperintense lesions remain for years and are usually permanent. While there were a greater number of infusion-related reactions in the R-GA arm compared with P-GA, these reactions were mild/moderate and there were no differences in serious adverse

events. This further supports the growing body of literature that demonstrates that CD20 therapy is generally well tolerated with an acceptable safety profile.^{24,32}

The role of immunosuppressive therapy with maintenance immunomodulation to provide increased efficacy compared with immunomodulation alone has been primarily addressed with mitoxantrone^{12,33,34} and natalizumab.^{35,36} Mitoxantrone was the first high-efficacy drug to be studied, as originally it was the primary immunosuppressant approved for treatment of MS. In one study of mitoxantrone induction followed by maintenance interferon beta-1b, when compared with participants receiving interferon beta-1b with concurrent methyl prednisone for the first 6 months, the mitoxantrone group demonstrated delayed time to sustained confirmed disability, and the mean and cumulative numbers of new T2 lesions and GEL ions were significantly lower in the mitoxantrone group over 3 years.³³ In another study comparing mitoxantrone induction to placebo and then followed by maintenance GA, the mitoxantrone induction group showed an 89% greater reduction in number of GELs vs GA alone, and mean relapse rates in the mitoxantrone group (0.16) were half that of the GA group (0.32).¹²

Other therapeutic strategies combining high- and low-efficacy treatments have also shown promise. A post hoc analysis³⁵ of the SENTINEL study³⁷ compared participants treated with interferon beta-1a and placebo to participants on interferon beta-1a plus natalizumab. Interferon beta-1a plus natalizumab had a greater risk reduction in sustained disability progression and reduced annualized relapse rates across all participants, with reductions of up to 58% for disability progression and 76% for annualized relapse rate in participants with highly active disease. Natalizumab added to GA maintenance also appears to outperform GA therapy alone, with a phase II, randomized, placebo-controlled study showing that the arm receiving natalizumab rather than placebo induction experienced reduced mean numbers of new GELs and T2 lesions and similar rates of infection and infusion reactions during 6 months of therapy.³⁶ Combination therapies utilizing 2 lower-efficacy treatments have not shown similar benefits. In the Combi-Rx (Combination Therapy in Patients with Relapsing-Remitting MS) study, the combination of interferon beta-1a and GA was not superior to GA plus placebo in risk of relapse, although an effect was seen on some MRI metrics.³⁸

Despite the promising results of induction/maintenance and dual-therapy approaches described above, very little research has been performed with other treatment combinations. In this study, the induction effect of rituximab appears to be limited to about 30 months after a single course (figure 1). This apparent failure of rituximab induction to result in a sustained reduction in the probability of being disease-free compared with the P-GA arm might be related to normalization of the immune system after the use of a single induction course. The decrease in probability of being disease-free in this study appears to mirror the repopulation of CD19⁺ B cells in R-GA to 60.4% of baseline by 25 months. Repopulation

plateaued after 25 months reaching no more than 63.2% of baseline by month 33 and IgG levels were within normal range in all patients by this point. Given interindividual variations in B cell repopulation in participants receiving rituximab,³⁹ repeat dosing within the first year may be necessary, perhaps based on individual B cell repopulation responses, and may provide a more sustained response, but the growing evidence about the safety and efficacy of long-term CD20 therapy suggests that perhaps continuous therapy is the most appropriate treatment course in many patients.^{18,24} An alternative explanation is that induction with rituximab does not enhance the effect of GA once the effect of rituximab wanes.

There are several limitations in this study. It is unclear from the results how much of the enhanced effect in the R-GA arm was the result of GA maintenance therapy after induction, given that the HERMES trial data²⁰ show that compared with placebo induction, rituximab induction without subsequent maintenance dosing results in reduced mean numbers of relapses, annualized relapse rate, and reduced numbers of new GELs at 48 weeks after induction. In our trial, with far longer follow-up, the reduction in probability of being disease-free for the R-GA arm was evident up to 30 months (120 weeks). The sample size was small, with limited power as a result; a larger study may have identified a more prolonged effect. We were unable to perform subgroup analysis, for example, looking at the effect of prior treatment. It also is unclear whether the longer disease duration of the R-GA group, though not statistically significant, may have had a role in the waning early benefit in the R-GA group. Whether the effect of rituximab induction lasts beyond 48 weeks is not known. The addition of a third treatment arm of rituximab induction alone with placebo maintenance therapy might have answered this question. However, such a study would have required a much larger number of participants and more resources than were available for this project.

In relapsing forms of MS with active disease, rituximab induction followed by maintenance GA therapy appears to be superior to GA monotherapy, but the effect is not sustained. Thus, a single dose of rituximab is, by itself, an inadequate induction agent in MS. It is unknown whether multiple doses of rituximab every 6 months would have a more sustained effect, including beyond the expected return of B lymphocytes after cessation of the intervention. The results of this study are also a reminder that successful therapies for MS either must be continued or change the underlying biology of the immune response to maintain effectiveness for a prolonged period of time.

Acknowledgment

The authors thank Brandi Vollmer, MPH, for her contributions related to the analysis and presentation of adverse event data and table preparation.

Study funding

This study was a University of Colorado Denver investigator sponsored trial funded by Teva Pharmaceuticals.

Disclosure

J. Honce has received research support from Biogen and Novartis and has received honorarium from Roche Genentech. K. Nair reports research support from Genentech, Biogen, and Novartis and consulting from Sanofi Genzyme and Astellas. S. Sillau and B. Valdez report no disclosures relevant to the manuscript. A. Miravalle reports consulting from Teva Neuroscience, Bayer, Genzyme, Biogen Idec, Questcor, and Medscape CME. Dr. Miravalle reports research support from Roche, Biogen Idec, NIH, Genentech, Teva Neuroscience, and Osmotica. E. Alvarez reports research support from Acorda, Biogen, Novartis, and Rocky Mountain MS Center and consulting from Biogen, Celgene, EMD Serono, Genentech, Genzyme, Teva, Novartis, and TG Therapeutics. T. Schreiner reports research support from Novartis, Biogen Idec, NIH, and MSDx. J. Corboy reports research support from the Patient-Centered Outcomes Research Institute, National Multiple Sclerosis Society, Rocky Mountain MS Center, Biogen, Novartis, and MedDay; receives compensation as editor, *Neurology®: Clinical Practice*; and consultant on legal issue for Mylan Pharmaceuticals. T. Vollmer reports compensation for activities such as advisory boards, lectures, and consultancy from Academic CME, Alcimed, Anthem Blue Cross, Genentech/Roche, Biogen Idec, Novartis, Celgene, Epigene, Rocky Mountain MS Center, GLG Consulting, Ohio Health, TG Therapeutics, Topaz Therapeutics, Dleara Lawyers, and Teva Neuroscience. Dr. Vollmer reports research support from Teva Neuroscience, NIH/NINDS, Rocky Mountain MS Center, Actelion, Biogen, Novartis, Roche/Genentech, UT South Western, and TG Therapeutics, Inc. Go to Neurology.org/N for full disclosures.

Publication history

Received by *Neurology* June 1, 2018. Accepted in final form October 5, 2018.

Appendix 1 Authors

Investigator	Location	Role	Contribution
Justin M. Honce, MD	University of Colorado	Coinvestigator	Study design, image analysis, data analysis, manuscript preparation
Kavita V. Nair, PhD	University of Colorado	Coinvestigator	Patient recruitment, data analysis, manuscript preparation
Stefan Sillau, PhD	University of Colorado	Coinvestigator	Data analysis, manuscript preparation
Brooke Valdez, BA	University of Colorado	Coinvestigator	Patient recruitment, data analysis, manuscript preparation
Augusto Miravalle, MD	University of Colorado	Coinvestigator	Study design, patient recruitment, EDSS evaluations, data analysis, manuscript preparation

(continued)

Investigator	Location	Role	Contribution
Enrique Alvarez, MD, PhD	University of Colorado	Coinvestigator	Patient recruitment, EDSS evaluations, data analysis, manuscript preparation
Teri Schriener, MD, MPH	University of Colorado	Coinvestigator	Study design, patient recruitment, manuscript preparation
John R. Corboy, MD	University of Colorado	Coinvestigator	Study design, patient recruitment, data analysis, manuscript preparation
Tim L. Vollmer, MD	University of Colorado	Principal investigator	Study design, patient recruitment, data analysis, manuscript preparation

References

- Comi G, Radaelli M, Soelberg Sørensen P. Evolving concepts in the treatment of relapsing multiple sclerosis. *Lancet* 2017;389:1347–1356.
- Comi G. Induction vs escalating therapy in multiple sclerosis: practical implications. *Neurol Sci* 2008;29:253–255.
- Río J, Nos C, Tintoré M, et al. Defining the response to interferon- β in relapsing-remitting multiple sclerosis patients. *Ann Neurol* 2006;59:344–352.
- Río J, Comabella M, Montalban X. Predicting responders to therapies for multiple sclerosis. *Nat Rev Neurol* 2009;5:553–560.
- Sormani M, Río J, Tintoré M, et al. Scoring treatment response in patients with relapsing multiple sclerosis. *Mult Scler J* 2013;19:605–612.
- Banwell B, Giovannoni G, Hawkes C, Lublin F. Editors' welcome and a working definition for a multiple sclerosis cure. *Mult Scler Relat Disord* 2013;2:65–67.
- Bermel RA, Naismith RT. Using MRI to make informed clinical decisions in multiple sclerosis care. *Curr Opin Neurol* 2015;28:244.
- Dobson R, Rudick RA, Turner B, Schmierer K, Giovannoni G. Assessing treatment response to interferon- β : is there a role for MRI? *Neurology* 2014;82:248–254.
- He A, Spelman T, Jokubaitis V, et al. Comparison of switch to fingolimod or interferon beta/glatiramer acetate in active multiple sclerosis. *JAMA Neurol* 2015;72:405–413.
- Merkel B, Butzkueven H, Traboulsee AL, Havrdova E, Kalincik T. Timing of high-efficacy therapy in relapsing-remitting multiple sclerosis: a systematic review. *Autoimmun Rev* 2017;16:658–665.
- Giovannoni G. Multiple sclerosis should be treated using a step-down strategy rather than a step-up strategy—YES. *Mult Scler J* 2016;22:1397–1400.
- Vollmer T, Panitch H, Bar-Or A, et al. Glatiramer acetate after induction therapy with mitoxantrone in relapsing multiple sclerosis. *Mult Scler J* 2008;14:663–670.
- Havrdova E, Arnold DL, Cohen JA, et al. Alemtuzumab CARE-MS I 5-year follow-up: durable efficacy in the absence of continuous MS therapy. *Neurology* 2017;89:1107–1116.
- Coles AJ, Cohen JA, Fox EJ, et al. Alemtuzumab CARE-MS II 5-year follow-up: efficacy and safety findings. *Neurology* 2017;89:1117–1126.
- Kobelt G, Berg J, Atherly D, Hadjimichael O. Costs and quality of life in multiple sclerosis: a cross-sectional study in the United States. *Neurology* 2006;66:1696–1702.
- Kobelt G, Berg J, Lindgren P, Fredrikson S, Jönsson B. Costs and quality of life of patients with multiple sclerosis in Europe. *J Neurol Neurosurg Psychiatry* 2006;77:918–926.
- Kavaliunas A, Manouchehrinia A, Stawiarz L, et al. Importance of early treatment initiation in the clinical course of multiple sclerosis. *Mult Scler J* 2017;23:1233–1240.
- Torres IM, García-Merino A. Anti-CD20 monoclonal antibodies in multiple sclerosis. *Expert Rev Neurother* 2017;17:359–371.
- Staun-Ram E, Miller A. Effector and regulatory B cells in multiple sclerosis. *Clin Immunol* 2017;184:11–25.
- Hauser SL, Waubant E, Arnold DL, et al. B-cell depletion with rituximab in relapsing-remitting multiple sclerosis. *N Engl J Med* 2008;358:676–688.
- van Vollenhoven RF, Fleischmann RM, Furst DE, Lacey S, Lehane PB. Longterm safety of rituximab: final report of the Rheumatoid Arthritis Global Clinical Trial Program over 11 years. *J Rheumatol* 2015;42:1761–1766.
- Hawker K, O'Connor P, Freedman MS, et al. Rituximab in patients with primary progressive multiple sclerosis: results of a randomized double-blind placebo-controlled multicenter trial. *Ann Neurol* 2009;66:460–471.

23. Alvarez E, Vollmer B, Jace B, et al. Effectiveness of switching to rituximab over fingolimod or dimethyl fumarate after natalizumab in preventing disease activity in multiple sclerosis. (P3.288). *Neurology* 2015;84. Abstract. Available at: n.neurology.org/content/84/14_Supplement/P3.288. Accessed August 20, 2018.
24. Granqvist M, Boremalm M, Poorghobad A, et al. Comparative effectiveness of rituximab and other initial treatment choices for multiple sclerosis. *JAMA Neurol* 2018; 75:320–327.
25. Ford C, Goodman A, Johnson K, et al. Continuous long-term immunomodulatory therapy in relapsing multiple sclerosis: results from the 15-year analysis of the US prospective open-label study of glatiramer acetate. *Mult Scler J* 2010;16: 342–350.
26. Comi G, Filippi M, Wolinsky JS. European/Canadian multicenter, double-blind, randomized, placebo-controlled study of the effects of glatiramer acetate on magnetic resonance imaging–measured disease activity and burden in patients with relapsing multiple sclerosis. *Ann Neurol* 2001;49:290–297.
27. Johnson KP, Brooks BR, Cohen JA, et al. Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind, placebo-controlled trial. *Neurology* 1995;45:1268–1276.
28. Tice JA, Chapman R, Kumar V, et al. Disease modifying therapies for relapsing remitting and primary progressive multiple sclerosis: effectiveness and value. Available at: icer-review.org/wp-content/uploads/2016/08/CTAF_MS_Evidence_Report_012617.pdf. Accessed August 20, 2018.
29. Jackson LJ, Selva S, Niedzielko T, Vollmer T. B cell receptor recognition of glatiramer acetate is required for efficacy through antigen presentation and cytokine production. *J Clin Cell Immunol* 2014;5:185.
30. Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the “McDonald Criteria.” *Ann Neurol* 2005;58:840–846.
31. Guttmann CR, Ahn SS, Hsu L, Kikinis R, Jolesz FA. The evolution of multiple sclerosis lesions on serial MR. *Am J Neuroradiol* 1995;16:1481–1491.
32. Barun B, Bar-Or A. Treatment of multiple sclerosis with anti-CD20 antibodies. *Clin Immunol* 2012;142:31–37.
33. Edan G, Comi G, Le Page E, et al. Mitoxantrone prior to interferon beta-1b in aggressive relapsing multiple sclerosis: a 3-year randomised trial. *J Neurol Neurosurg Psychiatry* 2011;82:1344–1350.
34. Le Page E, Leray E, Taurin G, et al. Mitoxantrone as induction treatment in aggressive relapsing remitting multiple sclerosis: treatment response factors in a 5 year follow-up observational study of 100 consecutive patients. *J Neurol Neurosurg Psychiatry* 2008; 79:52–56.
35. Hutchinson M, Kappos L, Calabresi PA, et al. The efficacy of natalizumab in patients with relapsing multiple sclerosis: subgroup analyses of AFFIRM and SENTINEL. *J Neurol* 2009;256:405–415.
36. Goodman AD, Rossman H, Bar-Or A, et al. GLANCE: results of a phase 2, randomized, double-blind, placebo-controlled study. *Neurology* 2009;72:806–812.
37. Rudick RA, Stuart WH, Calabresi PA, et al. Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. *N Engl J Med* 2006;354:911–923.
38. Lublin FD, Cofield SS, Cutter GR, et al. Randomized study combining interferon and glatiramer acetate in multiple sclerosis. *Ann Neurol* 2013;73:327–340.
39. Greenberg BM, Graves D, Remington G, et al. Rituximab dosing and monitoring strategies in neuromyelitis optica patients: creating strategies for therapeutic success. *Mult Scler J* 2012;18:1022–1026.