





COMBAT-MS: A Population-Based Observational Cohort Study Addressing the Benefit–Risk Balance of Multiple Sclerosis Therapies Compared with Rituximab

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Objective: To assess comparative effectiveness, safety, and tolerability of off-label rituximab, compared with frequently used therapies approved for multiple sclerosis (MS).

Methods: A Swedish cohort study of persons with relapsing–remitting MS, age 18 to 75 years at inclusion and with a first therapy start or a first therapy switch between 2011 and 2018. Low-dose rituximab was compared with MS-approved therapies. Primary outcomes were proportions with 12 months confirmed disability worsening and change in MS Impact Scale-29 (MSIS-29) scores, respectively. Secondary endpoints included relapses, therapy discontinuation, and serious adverse events. Analyses used an intention-to-treat approach and were adjusted for demographics, MS features, and health characteristics.

Results: We included 2,449 participants as first therapy start and 2,463 as first therapy switch. Proportions with disability worsening at 3 years were 9.1% for rituximab as first therapy and 5.1% after therapy switch, with no differences to MS-approved comparators. Worsening on rituximab was mostly independent of relapses. MSIS-29 with rituximab at 3 years improved by 1.3/8.4 points (physical/psychological) for first disease-modifying therapy (DMT) and 0.4/3.6 for DMT switch, and was mostly similar across therapies. Rituximab had lower relapse rates and higher therapy persistence

View this article online at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com/doi/10.1002/ana.27012). DOI: 10.1002/ana.27012

Received Feb 20, 2024, and in revised form May 28, 2024. Accepted for publication Jun 4, 2024.

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in both groups. The rate of hospital-treated infections was higher with rituximab after a therapy switch, but not as a first therapy.

Interpretation: This population-based real-world cohort study found low rates of disability progression, mostly independent of relapses, and without significant differences between rituximab and MS-approved comparators. Rituximab led to lower rates of inflammatory activity and higher treatment persistence, but was associated with an increased rate of serious infections.

ANN NEUROL 2024;96:678–693

Relapsing–remitting multiple sclerosis (RRMS) is the most common presentation of multiple sclerosis (MS) and a leading cause of neurological disability in the young and middle-age population.^{1,2} RRMS is characterized by episodes of neurological worsening, followed by a variable degree of recovery. Natural history studies have shown that a majority of people with RRMS develop a more continuous worsening with time, known as secondary progressive MS (SPMS).¹ Several disease-modifying therapies (DMTs) are approved for RRMS based on data from randomized controlled trials (RCT), using lowered risk of relapses as the primary effect variable. Extrapolation from multiple studies indicates a 30 to 69% reduction in annualized relapse rate (ARR) with DMTs, compared with placebo.^{3,4} Older injectable therapies (interferon-beta and glatiramer acetate) make up the lower span of this range, whereas monoclonal antibodies (eg, alemtuzumab and natalizumab) are in the higher span, and oral DMTs (eg, teriflunomide, dimethyl fumarate, and fingolimod) in-between.³ Recent RCTs with the B-cell–depleting antiCD20 monoclonals ocrelizumab, ofatumumab, and rituximab (off-label) have demonstrated lower ARRs, compared with interferon-beta, teriflunomide, and dimethyl fumarate, respectively.^{5–8} However, available data are incomplete for important outcomes, such as disability accrual and safety, beyond the normal 2-year duration of a phase 3 trial. For example, no difference in rate of neither mild nor severe infections were discernible in phase 3 trials with ocrelizumab and ofatumumab compared with interferon-beta and teriflunomide, respectively, whereas an increased risk with antiCD20 monoclonals, especially of severe infections, emerges in real-world populations with longer observation time.^{5,6,9} Importantly, because RCTs and most register-based studies do not have a population-based setting, the external validity for more heterogeneous patient populations, as seen in clinical practice, is not fully known.¹⁰ Real-world populations are also subject to frequent switching of therapy, which may have great impact on treatment outcomes.^{11,12} The objective of the Comparison Between All Immuno-Therapies For Multiple Sclerosis (COMBAT-MS) study was to assess long-term outcomes of effectiveness, safety, and patient experience, in a large population-based sample of people with MS initiating either a first-ever MS DMT or a first DMT switch.

A particular focus was placed on off-label treatment with rituximab, which has become a common treatment option for RRMS in some settings (including Sweden), despite not having formal approval for MS and limited available RCT data for this indication.

Methods

We conducted a nationwide, observational study in a population-based RRMS cohort followed at any of Sweden's 10 university-affiliated MS centers, which cover approximately half of the Swedish MS population. The study was approved by the regional ethics committee in Stockholm (no. 2017/32-31/4, with last amendment no. 2021-04978) and the Swedish Medical Products Agency (no. 5.1-2017-18037, EU no. 2016-003587-39), with collection of written informed consent from each study participant.

The tax-funded Swedish health care system provides universal access, with annual out-of-pocket costs for outpatient health care visits and prescription drugs capped at \$120 and \$240, respectively. Out of pocket inpatient care costs are capped at \$13 per day, whereas all hospital-administered drugs are free of charge, thereby having a limited economic impact on MS DMT choice for the individual. Study inclusion criteria were a first-ever MS DMT or a first DMT switch (switches between different interferons or between interferon and glatiramer-acetate were disregarded) between January 1, 2011 and October 31, 2018 (the index DMT); age 18 to 75 years at inclusion; having decision-making capacity; and in the case of fertile women, had been given information about potential DMT-related teratogenic effects and safe contraception in relation to the DMT used. Exclusion criteria were progressive forms of MS at the start of the index DMT; other neurological or medical conditions interfering with study assessments or decision-making capacity; subjects with contraindications to medicinal products used in the study (eg, gadolinium); and ongoing participation in trials with blinded study medication. See Fig 1. for the study flow chart. The study design (including endpoint definitions) was developed together with stakeholder representatives through questionnaires to people with MS and neurologists working with MS, in the United States (US) and Sweden. The study protocol was pre-registered

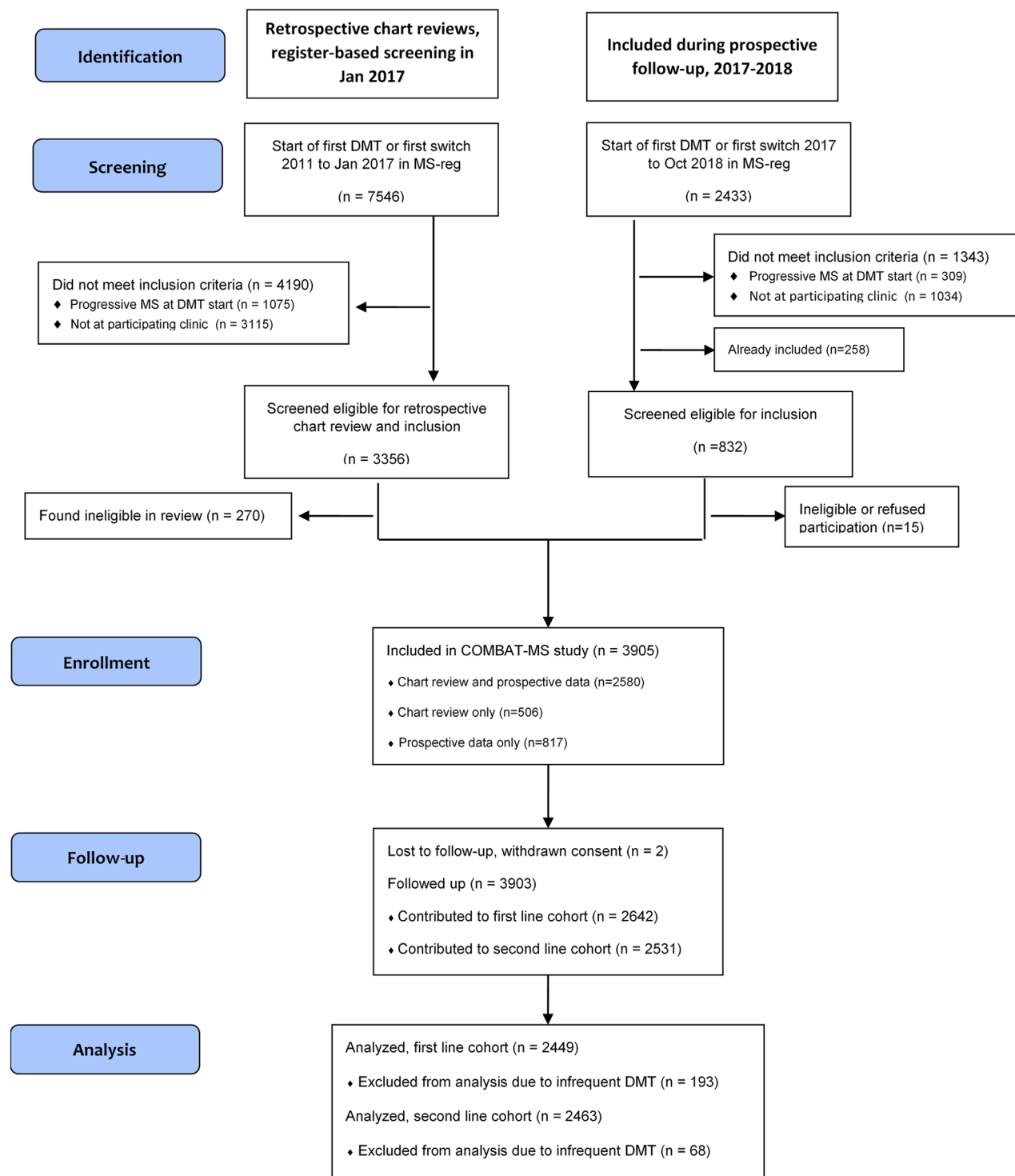


FIGURE 1: Study flowchart. Flowchart depicting the enrollment, follow-up, and analysis of the study. [Color figure can be viewed at www.annalsofneurology.org]

(full protocol in Appendix 2; [ClinicalTrials.gov](https://clinicaltrials.gov), NCT03193866; EU Trials Register, EudraCT 2016–003587-39). Some secondary outcomes listed in the protocol have not yet been analyzed and will be addressed in future publications.

Participants were recruited for prospective data collection between June 2, 2017 and June 30, 2019. Annual

assessment of disability status and patient-reported outcomes were registered in the Swedish MS register, from the date of recruitment until March 31, 2022. Pre-recruitment data available in the Swedish MS register were validated and updated through clinical chart review using a pre-specified data dictionary, as previously described.¹³ Additional data were sourced from Sweden's national

medical and demographic registers, by linkage using the national personal identity number assigned to all Swedish residents at birth or immigration. Demographic factors (Statistics Sweden) included age, sex, country of birth, educational level, and proportions with sick leave (≥ 2 weeks) and disability pension. Medical history comprised diagnoses coded with the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) for all inpatient and specialized outpatient care (Patient Register), as well as all collected prescription drugs coded with the Anatomical Therapeutic Chemical (ATC) classification system (Prescribed Drugs Register).^{14,15}

Exposures

DMTs included in analyses were rituximab, natalizumab, fingolimod, dimethyl fumarate, interferon, and glatiramer acetate. These therapies were further stratified based on if the therapy was a first-ever DMT (first DMT) or a first DMT switch (DMT switch). All therapies are assumed to be used according to their individual labels, except for rituximab where no official label is available. A previous study assessing rituximab use in the COMBAT-MS cohort found that the most common treatment pattern was a low-dose regimen of 500mg of rituximab every 6 months, but in most cases with a higher initial dose (usually 1,000mg as a single infusion).¹⁶

Endpoints

Primary endpoints were proportion of participants with 12-months confirmed disability worsening (CDW) and change in disease-related impact on daily life, both at 3 years after therapy start. Following discussions with patient partners and other stake-holders, our registered protocol defined CDW differently for those with low and high disability at treatment start. An Expanded Disability Status Scale (EDSS) score < 2.5 at baseline progressing to EDSS ≥ 3 or an EDSS score ≥ 2.5 at baseline increasing ≥ 1 point. However, to align with earlier studies, we also opted to use the standard definition for CDW, that is, a ≥ 1.5 -point increase in EDSS from a previous score of 0, a ≥ 1.0 -point increase in EDSS from a previous score of 1.0–5.0, or a ≥ 0.5 -point increase in EDSS from a previous score of > 5.5 as main outcome. This standard CDW measure is presented overall, as well as stratified by presence of relapses (yes/no) during the same 3-year assessment period.

In all assessments of CDW, EDSS scores within 30 days of a registered relapse were ignored. To be considered confirmed, disability worsening was required on at least two visits separated by ≥ 12 months with no intermediary visit with reversal of the worsening. The choice of

12 months was to align with the annual follow-up visits recommended by national guidelines during the study period. Disease-related impact on daily life was defined as the change in physical or psychological subscale points of the MS Impact Scale-29 (MSIS-29).¹⁷ Secondary endpoints included change in EDSS, ARR, proportion remaining on therapy, and proportion with no evidence of disease activity (NEDA)-3 (defined as no clinical relapse, no new/enlarging T2 lesions or contrast-enhancing lesions on magnetic resonance imaging [MRI], and no CDW as defined by the standard definition of the primary endpoint). Pre-specified safety outcomes were rates of serious infections (defined as infections requiring hospitalization), invasive cancer, major adverse cardiovascular events (MACE) (defined as acute coronary syndrome, stroke, or death from any cardiovascular cause), and all-cause mortality. In post-hoc analyses we additionally assessed all primary and secondary endpoints at 5 years from start of the index therapy.

Analyses

Main analyses used an intention-to-treat approach, including all patients in the analyses even if they changed from or discontinued their index DMT. For example, a patient starting rituximab as a first ever DMT, then switching to natalizumab after 2 years, and subsequently discontinuing natalizumab after one more year would be included in the analysis of the first DMT cohort as exposed to rituximab, and in the DMT switch cohort as exposed to natalizumab. DMT groups with < 100 participants were excluded, which affected DMTs such as alemtuzumab, ocrelizumab, and cladribine that were marketed only at the end of the inclusion period. Multivariable regression models were used to adjust for differences in baseline characteristics (with continuous variables as second-degree polynomials): age; sex; region of residence; country of birth; educational level; time since MS diagnosis; any relapse in the last 12 months; EDSS, MSIS-29, and Symbols Digit Modalities Test scores at baseline; any hospitalized infection; invasive cancer; MACE and/or arrhythmia within 5 years; and any dispensed antidepressants and antidiabetic drugs within 12 months before start of the index DMT. Missing values in outcomes and covariates were addressed with multiple imputations by chained equations, with 20 imputations and 10 burn-in iterations. Variables with missing values were imputed from all other outcome and baseline variables used in the analyses, including polynomial terms. Predictive mean matching was used for continuous variables and (multinomial) logistic regression for categorical variables. Proportions with missing data are shown in Table S1.

For all non–time-to-event endpoints, mean differences between rituximab and the MS-approved DMTs were estimated using linear regression, which for binary endpoints corresponds to mean differences in proportions.¹⁸ For time-to-event endpoints, Cox regression was used to estimate hazard ratios (HRs) with time since therapy start as the timescale. Robust standard errors (Huber-White) were estimated for each imputed dataset and combined using Rubin's rules, yielding 95% confidence intervals (CIs) by the normal approximation.

Post-hoc and Sensitivity Analyses

As previously mentioned CDW with a standard definition was added as an additional outcome and split by relapse activity. After the start of the study, the prospective data collection was extended from July 1, 2021 to March 31, 2022, making it meaningful to analyze outcomes also at 5 years after start of the index therapy. Because of low treatment persistence with several DMTs, on-drug effectiveness and safety endpoints were included as sensitivity analyses. We additionally assessed effectiveness endpoints restricted to participants with a 3-year follow-up evaluation in the prospective follow-up period (2017–2022). At reviewer request, we also present main analyses restricted to the population age ≥ 50 at start of the index therapy as a supplementary analysis (Table S6). At further reviewer request, the main analysis was also performed using inverse probability of treatment weighting as an alternative way to adjust for confounding factors. Stabilized weights were assigned as the sample proportion with the DMT received multiplied by the individual's inverse probability of receiving this DMT, with probabilities predicted from multinomial logistic regression, including the same potential confounders as the main analyses, and were truncated to the 99th percentile. The calendar year differed too much between some treatments for acceptable balance to be achieved, and it was instead included in the weighted outcome regression models.

Results

A total of 3,764 unique patients with MS contributed to the evaluation of the 3-year outcomes. A total of 2,449 in first DMT and 2,463 in DMT switch (1,148 patients [30%] contributed to both cohorts). Baseline characteristics are shown in Tables 1 and 2. As expected, compared with DMT switch, first DMT participants were younger, had shorter disease duration, and a larger proportion with relapse in the year before index DMT start (particularly with natalizumab as a first DMT). Because of changing treatment practices over time, older injectable DMTs, natalizumab, and fingolimod were dominating in the first part of the inclusion period (2011–2014), whereas

dimethyl fumarate, teriflunomide, and rituximab became more common in the later part. Baseline EDSS scores with natalizumab and rituximab were on average higher, compared with the other DMTs. Treatment patterns were markedly different across the participating centers, indicating that regional differences in prescribing practices had a large impact on the choice of DMT, independent of patient characteristics.

Primary Endpoints

Proportions fulfilling standard CDW criteria with rituximab at 3 years were 9.1% for first DMT and 5.1% for DMT switch (Tables 3 and 4). Most instances of CDW on rituximab were in subjects with no relapse within 3 years of treatment start. Among those starting with low EDSS (<2.5), a confirmed worsening to EDSS ≥ 3 (a change highlighted as particularly meaningful by patient partners at study registration) was seen in 4.1% on rituximab as a first DMT and 1.8% on rituximab after a DMT switch. After adjustment for baseline characteristics, proportions with CDW were similar for all therapies, both overall with the standard definition of CDW and in the subgroups with baseline EDSS <2.5 and ≥ 2.5 . The only significant difference was in the proportion with CDW according to the standard definition and at least one relapse, which was 3.0 percentage points higher (95% CI, 0.4–5.6) for interferons vs rituximab.

MSIS-29 scores with rituximab at 3 years had decreased (indicating an improvement) by 1.3 and 8.4 points for first DMT and 0.4 and 3.6 points for DMT switch, on the physical and psychological subscores, respectively (see Tables 3 and 4). Adjusted for baseline characteristics, MSIS-29 physical subscale scores decreased more with natalizumab, both as a first DMT and after a DMT switch, compared with rituximab, although absolute differences were small. Data on MSIS-29 change was missing for $>90\%$ of those on injectable therapies and are at reviewer request omitted from the table (missingness caused by patient reported outcomes historically only collected for “high efficacy” DMTs).

At 5 years, CDW proportions with rituximab were 14.0% and 12.5% for first DMT and DMT switch, respectively, and again without significant differences compared with the other DMTs, except for a higher proportion with CDW combined with relapse on interferons versus rituximab (Tables 4 and 5). The only significant difference in MSIS-29 change at 5 years was a greater decrease in the physical subdomain scores with natalizumab, compared with rituximab, as a first DMT (the difference was borderline significant after a DMT switch).

TABLE 1. Patient Characteristics at Treatment Start First DMT Cohort

First DMT Cohort	Rituximab	Natalizumab	Dimethyl fumarate	Interferon	Glatiramer acetate
No. of patients	591	334	416	992	116
Yr of DMT start, median (IQR)	2016 (2015–2017)	2014 (2013–2016)	2015 (2014–2017)	2013 (2012–2014)	2013 (2012–2014)
Age in yr, mean (SD)	36.9 (11.3)	31.6 (9.2)	34.4 (9.7)	35.8 (10.5)	36.9 (11.7)
Female, n (%)	399 (67.5)	242 (72.5)	283 (68.0)	705 (71.1)	90 (77.6)
Born in Sweden, n (%)	494 (83.7)	278 (83.2)	337 (81.0)	782 (78.8)	98 (84.5)
Education, 12+ yr, n (%)	307 (52.7)	154 (48.1)	226 (55.5)	514 (53.0)	57 (49.6)
Yr since MS diagnosis, mean (SD)	1.3 (4.0)	0.5 (1.9)	0.6 (2.3)	0.9 (3.1)	1.7 (4.5)
Any relapse last yr, n (%)	367 (62.1)	252 (75.4)	265 (63.7)	648 (65.3)	62 (53.4)
EDSS, mean (SD)	2.0 (1.3)	2.1 (1.3)	1.5 (1.1)	1.6 (1.2)	1.4 (1.2)
EDSS <2.5, n (%)	297 (62.8)	154 (60.6)	283 (80.2)	499 (76.3)	58 (77.3)
MSIS-29 physical, mean (SD)	1.8 (0.8)	2.0 (0.9)	1.7 (0.8)	1.6 (0.7)	1.7 (0.6)
MSIS-29 psychological, mean (SD)	2.4 (1.0)	2.6 (1.0)	2.3 (1.0)	2.2 (0.9)	2.6 (0.9)
SDMT, mean (SD)	52.0 (11.4)	50.6 (13.3)	53.4 (12.5)	55.2 (12.3)	54.4 (11.4)
Medical history, n (%) ^a					
Serious infection	15 (2.5)	16 (4.8)	7 (1.7)	21 (2.1)	1 (0.9)
Cancer	4 (0.7)	3 (0.9)	4 (1.0)	10 (1.0)	3 (2.6)
MACE	9 (1.5)	3 (0.9)	2 (0.5)	10 (1.0)	4 (3.4)
Arrhythmia	10 (1.7)	2 (0.6)	2 (0.5)	7 (0.7)	0 (0.0)
Diabetes	13 (2.2)	7 (2.1)	4 (1.0)	17 (1.7)	2 (1.7)
Antidepressant use	88 (14.9)	35 (10.5)	64 (15.4)	98 (9.9)	25 (21.6)

DMT = disease-modifying therapy, EDSS = expanded disability status scale, IQR = interquartile range, MACE = major adverse cardiovascular event, SD = standard deviation; SDMT = Symbols Digit Modalities Test.

^aAny diagnosis in the last 5 years or a filled prescription during the last year.

Secondary Endpoints

Mean EDSS scores with rituximab at 3 years decreased slightly for first DMT and remained stable for DMT switch (see Tables 3 and 4), compared with baseline. This

was explained by a larger proportion with a ≥ 1 -point EDSS reduction compared with those with an increase in first DMT (28.7% vs 19.0%), whereas the two proportions were similar for DMT switch (18.8% vs 19.1%).

TABLE 2. Patient Characteristics at Treatment Start Switch DMT cohort

Switch DMT cohort	Rituximab	Natalizumab	Dimethyl fumarate	Fingolimod	Teriflunomide
No. of patients	748	541	570	443	161
Yr of DMT start, median (IQR)	2016 (2014–2017)	2013 (2012–2014)	2015 (2014–2016)	2013 (2012–2014)	2015 (2015–2017)
Age in yr, mean (SD)	39.0 (10.5)	35.1 (9.6)	40.6 (10.6)	37.3 (9.4)	46.3 (9.8)
Female, n (%)	560 (74.9)	406 (75.0)	418 (73.3)	292 (65.9)	116 (72.0)
Born in Sweden, n (%)	605 (80.9)	460 (85.0)	466 (81.8)	361 (81.7)	139 (86.3)
Education, 12+ yr, n (%)	403 (54.5)	272 (50.9)	309 (55.2)	234 (53.7)	89 (55.3)
Yr since MS diagnosis, mean (SD)	5.6 (5.5)	4.7 (4.8)	7.1 (5.9)	5.6 (4.8)	9.3 (6.9)
Any relapse last yr, n (%)	254 (34.0)	288 (53.2)	120 (21.1)	172 (38.8)	30 (18.6)
EDSS, mean (SD)	2.0 (1.3)	2.2 (1.4)	1.6 (1.3)	1.8 (1.3)	1.8 (1.6)
EDSS <2.5, n (%)	369 (61.9)	226 (52.9)	330 (75.5)	227 (70.7)	78 (64.5)
MSIS-29 physical, mean (SD)	1.7 (0.8)	1.9 (0.9)	1.6 (0.7)	1.7 (0.8)	1.7 (0.7)
MSIS-29 psychological, mean (SD)	2.2 (1.0)	2.4 (1.0)	2.0 (0.9)	2.2 (0.9)	2.1 (1.0)
SDMT, mean (SD)	51.5 (11.5)	52.1 (11.9)	52.8 (11.8)	53.3 (12.6)	53.3 (9.9)
Medical history, n (%) ^a					
Serious infection	21 (2.8)	21 (3.9)	17 (3.0)	12 (2.7)	6 (3.7)
Cancer	10 (1.3)	2 (0.4)	10 (1.8)	6 (1.4)	7 (4.3)
MACE	6 (0.8)	5 (0.9)	6 (1.1)	1 (0.2)	4 (2.5)
Arrhythmia	11 (1.5)	8 (1.5)	5 (0.9)	6 (1.4)	1 (0.6)
Diabetes	17 (2.3)	6 (1.1)	12 (2.1)	5 (1.1)	2 (1.2)
Antidepressant use	124 (16.6)	108 (20.0)	92 (16.1)	81 (18.3)	42 (26.1)

DMT = disease-modifying therapy, EDSS = expanded disability status scale, IQR = interquartile range, MACE = major adverse cardiovascular event, SD = standard deviation; SDMT = symbols digit modalities test.

^aAny diagnosis in the last 5 years or a filled prescription during the last year.

These proportions did not differ significantly between the DMTs in either of the two groups. Mean EDSS scores with rituximab were slightly lower compared with baseline also at 5 years for first DMT (27.1% with improvement vs 20.8% with worsening) (see Tables 5 and 6). In contrast, EDSS had increased slightly for DMT switch at 5 years (17.9% with improvement vs 26.4% with worsening), but still without differences across DMTs.

Rituximab had the lowest ARR over 3 years, 0.03 for both first DMT and DMT switch. The adjusted ARRs were statistically significantly higher than for the other DMTs, except for natalizumab as a first DMT. The greatest difference to the rituximab group was with interferons as a first DMT (+0.13, ie, 13 additional relapses per 100 patients per year) and teriflunomide (+0.08) after a DMT switch. Similar differences were evident also at

TABLE 3. Comparative Effectiveness at 3 Years After Treatment Start First DMT cohort

First DMT cohort	Reference	Mean difference to Rituximab (95% confidence interval)			
	Rituximab (mean or %)	Natalizumab	Dimethyl fumarate	Interferon	Glatiramer acetate
No. of patients	591	334	416	992	116
CDW, standard (%)	9.1	-2.6 (-8.3; 3.0)	0.3 (-4.9; 5.5)	1.9 (-4.4; 8.3)	-2.6 (-12.3; 7.2)
With ≥1 relapse	0.9	-0.1 (-2.3; 2.2)	2.0 (-0.1; 4.1)	3.0 (0.4; 5.6)	-0.5 (-4.8; 3.8)
With no relapse	8.3	-2.6 (-7.6; 2.5)	-1.7 (-6.2; 2.8)	-1.1 (-6.8; 4.6)	-2.1 (-10.7; 6.6)
CDW, protocol					
EDSS <2.5 reaching 3+	4.1	-1.7 (-6.1; 2.8)	0.9 (-3.4; 5.1)	1.1 (-2.9; 5.1)	-2.4 (-12.3; 7.4)
EDSS ≥2.5, ≥1 unit incr.	8.4	-2.1 (-9.7; 5.5)	0.2 (-8.5; 8.8)	2.0 (-7.2; 11.1)	-5.7 (-24.7; 13.2)
MSIS-29 Phys. change	-1.3	-4.3 (-7.3; -1.3)	-0.6 (-3.1; 1.9)	n/a	n/a
MSIS-29 Psych. change	-8.4	-3.0 (-6.6; 0.7)	0.9 (-2.5; 4.3)	n/a	n/a
EDSS change	-0.2	-0.1 (-0.3; 0.1)	-0.1 (-0.3; 0.1)	0.1 (-0.1; 0.2)	-0.3 (-0.6; 0.1)
EDSS increase + 1 (%)	19.0	-2.9 (-9.8; 3.9)	-2.2 (-8.4; 4.0)	2.4 (-4.9; 9.7)	-0.2 (-14.6; 14.2)
EDSS decrease - 1 (%)	28.7	3.6 (-4.4; 11.7)	3.6 (-3.2; 10.5)	-0.8 (-7.6; 6.1)	5.6 (-11.2; 22.5)
ARR	0.03	0.02 (-0.00; 0.05)	0.06 (0.03; 0.08)	0.13 (0.10; 0.16)	0.09 (0.04; 0.14)
NEDA-3 (%)	75.7	-3.8 (-12.1; 4.4)	-19.9 (-26.6; -13.3)	-33.2 (-40.9; -25.5)	-30.7 (-46.5; -15.0)
Remaining on drug (%)	89.1	-42.8 (-49.3; -36.2)	-47.3 (-52.9; -41.7)	-71.7 (-76.8; -66.7)	-66.4 (-76.1; -56.6)

Mean differences to rituximab estimated as each DMT mean or percentage minus rituximab mean or percentage. Adjusted for age, sex, year of treatment start, country of birth, geographical region, education level, duration since MS diagnosis, baseline EDSS, SDMT, and MSIS-29 scores, history of serious infection, malignancy, major adverse cardiovascular event, arrhythmia, use of antidepressants, diabetes. Estimated with multivariable linear regression with robust confidence intervals (Huber-White). MSIS-29 data on interferons and glatiramer acetate omitted because of high missingness. ARR = annualized relapse rate, CDW = confirmed disability worsening, DMT = disease-modifying therapy, EDSS = expanded disability status scale, MS = multiple sclerosis, MSIS-29 = MS impact scale-29, NEDA-3 = no evidence of disease activity three components; Phys. = physical; Psych. = psychological.

5 years, with significantly higher ARR with all other DMTs compared with rituximab, except for natalizumab, in both the first DMT and DMT switch groups.

NEDA-3 status, which also includes proportions without new brain lesions detected by neuroimaging, at 3 years with rituximab was fulfilled by 75.7% and 82.1% of participants in first DMT and DMT switch, respectively. This was greater than for all comparators, except natalizumab as a first DMT (see Tables 3 and 4).

Proportions fulfilling NEDA-3 status at 5 years were higher with rituximab than with all comparators in both cohorts (see Tables 5 and 6).

Unadjusted survival curves for proportions free of CDW and relapses up to 9 years after start of index DMT indicated that the results at 3 and 5 years persisted also over the longer term, without any indication of differences between the therapies emerging later on (Fig 2).

TABLE 4. Comparative Effectiveness at 3 Years After Treatment Start Switch DMT Cohort

Switch DMT cohort	Reference	Mean difference to rituximab (95% confidence interval)			
	Rituximab (mean or %)	Natalizumab	Dimethyl fumarate	Fingolimod	Teriflunomide
No. of patients	748	541	570	443	161
CDW, standard (%)	5.1	2.3 (−2.1; 6.7)	1.9 (−2.1; 5.9)	2.4 (−2.6; 7.3)	2.7 (−3.6; 9.0)
With ≥1 relapse	0.7	0.4 (−1.7; 2.6)	1.2 (−0.5; 2.9)	0.9 (−1.3; 3.0)	2.8 (−0.7; 6.2)
With no relapse	4.5	1.8 (−2.0; 5.7)	0.7 (−3.0; 4.3)	1.5 (−3.0; 5.9)	−0.1 (−5.6; 5.4)
CDW, protocol					
EDSS < 2.5 reaching 3+	1.8	1.4 (−1.9; 4.7)	0.6 (−2.0; 3.2)	0.8 (−2.7; 4.3)	2.2 (−2.9; 7.3)
EDSS ≥ 2.5, ≥1 unit incr.	5.7	−0.0 (−6.2; 6.1)	1.5 (−6.0; 9.1)	−1.6 (−7.9; 4.7)	0.2 (−10.1; 10.5)
MSIS-29 Phys. change	−0.4	−2.4 (−4.8; 0.0)	−0.8 (−2.7; 1.2)	−2.0 (−4.2; 0.2)	2.0 (−1.2; 5.3)
MSIS-29 Psych. change	−3.6	−1.8 (−5.2; 1.5)	0.0 (−3.0; 3.1)	−1.7 (−5.1; 1.8)	1.6 (−3.0; 6.2)
EDSS change	0.0	−0.1 (−0.2; 0.1)	−0.0 (−0.1; 0.1)	−0.0 (−0.2; 0.1)	0.1 (−0.1; 0.3)
EDSS increase + 1 (%)	18.8	0.5 (−6.6; 7.6)	−2.9 (−9.1; 3.3)	−2.0 (−9.3; 5.3)	4.1 (−5.9; 14.0)
EDSS decrease − 1 (%)	19.1	4.2 (−2.2; 10.6)	0.3 (−5.1; 5.8)	−1.2 (−7.8; 5.3)	−1.6 (−9.0; 5.8)
ARR	0.03	0.03 (0.01; 0.05)	0.05 (0.03; 0.07)	0.05 (0.02; 0.07)	0.08 (0.04; 0.11)
NEDA-3 (%)	82.1	−9.7 (−16.7; −2.6)	−21.7 (−29.0; −14.5)	−25.4 (−34.0; −16.7)	−22.7 (−33.2; −12.3)
Remaining on drug (%)	88.6	−34.6 (−40.5; −28.7)	−41.4 (−46.5; −36.2)	−34.4 (−40.3; −28.6)	−50.4 (−58.7; −42.2)

Mean differences to rituximab estimated as each DMT mean or percentage minus rituximab mean or percentage. Adjusted for age, sex, year of treatment start, country of birth, geographical region, education level, duration since MS diagnosis, baseline EDSS, SDMT, and MSIS-29 scores, history of serious infection, malignancy, major adverse cardiovascular event, arrhythmia, use of antidepressants, diabetes. Estimated with multivariable linear regression with robust confidence intervals (Huber-White). MSIS-29 data on interferons and glatiramer acetate omitted because of high missingness. ARR = annualized relapse rate, CDW = confirmed disability worsening, DMT = disease-modifying therapy, EDSS = expanded disability status scale, MS = multiple sclerosis, MSIS-29 = MS impact scale-29, NEDA-3 = no evidence of disease activity three components; Phys. = physical; Psych. = psychological.

Proportions remaining on index DMT were substantially higher with rituximab, compared with all other DMTs, at both 3 and 5 years. In the first DMT group the difference compared with rituximab ranged from −42.8% (natalizumab) to −71.7% (interferons), and in the DMT switch group from −34.4% (fingolimod) to −50.4% (teriflunomide). A Sankey diagram of the change in DMTs between baseline and at year 3 is shown in Fig 3 (with exact numbers in Table S2), showing that the

most common DMT change by year 3 was a switch to rituximab.

Incidence rates of severe infections for first DMT ranged from 5.8 per 1,000 patient years (glatiramer acetate) to 12.7 (rituximab, Table 7). Corresponding rates with DMT switch ranged from 5.9 (dimethyl fumarate) to 20.3 (rituximab), with HRs between 0.23 (natalizumab) and 0.55 (teriflunomide), compared with rituximab. A higher rate of severe infections with rituximab remained also at

TABLE 5. Comparative Effectiveness at 5 Years After Treatment Start First DMT Cohort

First DMT cohort	Reference	Mean difference to rituximab (95% confidence interval)			
	Rituximab (mean or %)	Natalizumab	Dimethyl fumarate	Interferon	Glatiramer acetate
No. of patients	395	276	307	955	107
CDW, standard (%)	14.0	-4.3 (-10.7; 2.2)	-1.3 (-7.5; 4.8)	1.5 (-5.3; 8.3)	-8.5 (-19.6; 2.7)
With 1+ relapse	2.1	0.2 (-3.3; 3.6)	2.3 (-1.1; 5.7)	5.0 (1.3; 8.6)	-2.9 (-8.4; 2.6)
With no relapse	12.0	-4.4 (-9.9; 1.0)	-3.7 (-9.1; 1.8)	-3.5 (-9.1; 2.2)	-5.6 (-14.8; 3.6)
CDW, protocol					
EDSS <2.5 reaching 3+	5.5	-0.0 (-0.1; 0.0)	0.0 (-0.0; 0.1)	0.0 (-0.0; 0.1)	-0.0 (-0.1; 0.1)
EDSS ≥2.5, ≥1 unit incr.	14.6	-0.0 (-0.1; 0.1)	-0.1 (-0.2; 0.1)	0.0 (-0.1; 0.1)	-0.1 (-0.4; 0.1)
MSIS-29 Phys. change	-0.9	-5.2 (-9.1; -1.2)	-0.2 (-4.0; 3.5)	n/a	n/a
MSIS-29 Psys. change	-9.1	-3.1 (-8.2; 1.9)	3.1 (-1.3; 7.5)	n/a	n/a
EDSS change	-0.1	-0.2 (-0.4; 0.0)	-0.1 (-0.3; 0.1)	0.1 (-0.2; 0.3)	-0.4 (-0.8; 0.0)
EDSS increase +1 (%)	20.8	-4.0 (-12.2; 4.2)	-4.3 (-12.2; 3.6)	6.3 (-1.9; 14.6)	-6.3 (-21.1; 8.5)
EDSS decrease -1 (%)	27.1	8.9 (-0.8; 18.7)	2.2 (-6.3; 10.8)	-1.9 (-10.1; 6.3)	10.2 (-2.9; 23.2)
ARR	0.02	0.02 (-0.00; 0.04)	0.04 (0.02; 0.05)	0.09 (0.07; 0.11)	0.05 (0.01; 0.09)
NEDA-3 (%)	67.7	-12.8 (-22.7; -3.0)	-24.7 (-33.4; -16.1)	-35.8 (-44.7; -26.9)	-31.2 (-46.3; -16.1)
Remaining on drug (%)	77.7	-40.5 (-48.0; -33.0)	-43.2 (-50.2; -36.2)	-68.9 (-74.6; -63.2)	-66.8 (-76.4; -57.3)

Mean differences to rituximab estimated as each DMT mean or percentage minus rituximab mean or percentage. Adjusted for age, sex, year of treatment start, country of birth, geographical region, education level, duration since MS diagnosis, baseline EDSS, SDMT, and MSIS-29 scores, history of serious infection, malignancy, major adverse cardiovascular event, arrhythmia, use of antidepressants, diabetes. Estimated with multivariable linear regression with robust confidence intervals (Huber-White). MSIS-29 data on interferons and glatiramer acetate omitted because of high missingness. ARR = annualized relapse rate, CDW = confirmed disability worsening, DMT = disease-modifying therapy, EDSS = expanded disability status scale, MS = multiple sclerosis, MSIS-29 = MS impact scale-29, NEDA-3 = no evidence of disease activity three components; Phys. = physical; Psys. = psychological.

5 years in DMT switch (see Table S3). Rates of invasive cancer, MACE, and all-cause mortality were low and did not differ at either 3 or 5 years across DMTs (see Tables 7 and S3).

Sensitivity Analyses

The on-drug analysis, restricted to those remaining on the index DMT at 3 years, showed a greater proportion with

≥1-point EDSS reduction with natalizumab, compared with rituximab, but no other differences in EDSS outcomes between the DMTs. Furthermore, almost all differences in measures reflecting inflammatory disease activity between the DMT groups had disappeared, except for a higher rate of relapses with interferons as a first DMT and a lower proportion fulfilling NEDA-3 status with fingolimod after a DMT switch, compared with rituximab (Table S4).

TABLE 6. Comparative Effectiveness at 5 Years After Treatment Start Switch DMT Cohort

Switch DMT cohort	Reference	Mean difference to Rituximab (95% confidence interval)			
	Rituximab (mean or %)	Natalizumab	Dimethyl fumarate	Fingolimod	Teriflunomide
No. of patients	559	514	504	415	125
CDW, standard (%)	12.5	-1.7 (-7.1; 3.6)	2.6 (-3.3; 8.5)	-0.9 (-6.8; 5.0)	2.7 (-6.0; 11.4)
With 1+ relapse	2.1	0.1 (-2.8; 3.0)	1.9 (-0.8; 4.6)	1.2 (-1.7; 4.2)	3.6 (-1.6; 8.8)
With no relapse	10.3	-1.8 (-6.7; 3.0)	0.7 (-4.5; 5.8)	-2.1 (-7.2; 3.0)	-0.9 (-8.0; 6.3)
CDW, protocol					
EDSS <2.5 reaching 3+	3.4	0.0 (-0.0; 0.1)	0.0 (-0.0; 0.1)	0.0 (-0.0; 0.1)	0.0 (-0.0; 0.1)
EDSS ≥2.5, ≥1 unit increase	15.3	-0.0 (-0.1; 0.1)	-0.0 (-0.1; 0.1)	-0.1 (-0.2; 0.0)	0.0 (-0.1; 0.2)
MSIS-29 Phys. change	-0.6	-2.4 (-5.0; 0.3)	-0.0 (-2.1; 2.0)	-1.1 (-3.5; 1.3)	-0.9 (-4.0; 2.1)
MSIS-29 Psys. change	-3.4	-4.1 (-7.6; -0.6)	1.3 (-1.8; 4.4)	-1.1 (-4.6; 2.3)	1.5 (-3.0; 6.0)
EDSS change	0.1	-0.1 (-0.3; 0.1)	-0.1 (-0.3; 0.1)	0.1 (-0.1; 0.3)	-0.0 (-0.3; 0.2)
EDSS increase + 1 (%)	26.4	-0.7 (-8.8; 7.4)	-3.2 (-10.8; 4.4)	4.4 (-3.9; 12.8)	-5.5 (-15.9; 4.9)
EDSS decrease - 1 (%)	17.9	5.6 (-1.5; 12.8)	6.2 (-0.4; 12.9)	-1.6 (-8.7; 5.5)	1.1 (-6.9; 9.0)
ARR	0.02	0.02 (0.00; 0.04)	0.04 (0.03; 0.06)	0.04 (0.02; 0.06)	0.06 (0.03; 0.08)
NEDA-3 (%)	71.4	-9.4 (-17.7; -1.2)	-27.9 (-35.9; -19.9)	-26.4 (-35.5; -17.3)	-24.1 (-36.6; -11.6)
Remaining on drug (%)	75.0	-34.6 (-41.4; -27.8)	-42.0 (-47.9; -36.0)	-35.2 (-42.0; -28.4)	-45.6 (-54.9; -36.2)

Mean differences to rituximab estimated as each DMT mean or percentage minus rituximab mean or percentage. Adjusted for age, sex, year of treatment start, country of birth, geographical region, education level, duration since MS diagnosis, baseline EDSS, SDMT, and MSIS-29 scores, history of serious infection, malignancy, major adverse cardiovascular event, arrhythmia, use of antidepressants, diabetes. Estimated with multivariable linear regression with robust confidence intervals (Huber-White). MSIS-29 data on interferons and glatiramer acetate omitted because of high missingness. ARR = annualized relapse rate, CDW = confirmed disability worsening, DMT = disease-modifying therapy, EDSS = expanded disability status scale, MS = multiple sclerosis, MSIS-29 = MS impact scale-29, NEDA-3 = no evidence of disease activity three components; Phys. = physical; Psys. = psychological.

A second sensitivity analysis, including only participants with a 3-year evaluation after the start of the structured prospective follow-up, found the same patterns as in the main analyses, although the size of some therapy groups, especially injectable DMTs, were greatly reduced (Table S5).

Analyses restricted to those age ≥50 at treatment start (13.6% of the full sample) revealed substantially higher rates of CDW (Table S6) (18.4% among those

≥50, compared with 9.1% with rituximab cohort as first DMT), despite similar or lower rates of relapses (0.02 vs 0.03). Similar differences were seen for all DMTs and although statistical power was low, point estimates did not indicate meaningful differences between DMTs. Inverse probability weighting gave overall balanced baseline characteristics (Table S7), and results that were very close to those from the main analysis (Table S8).

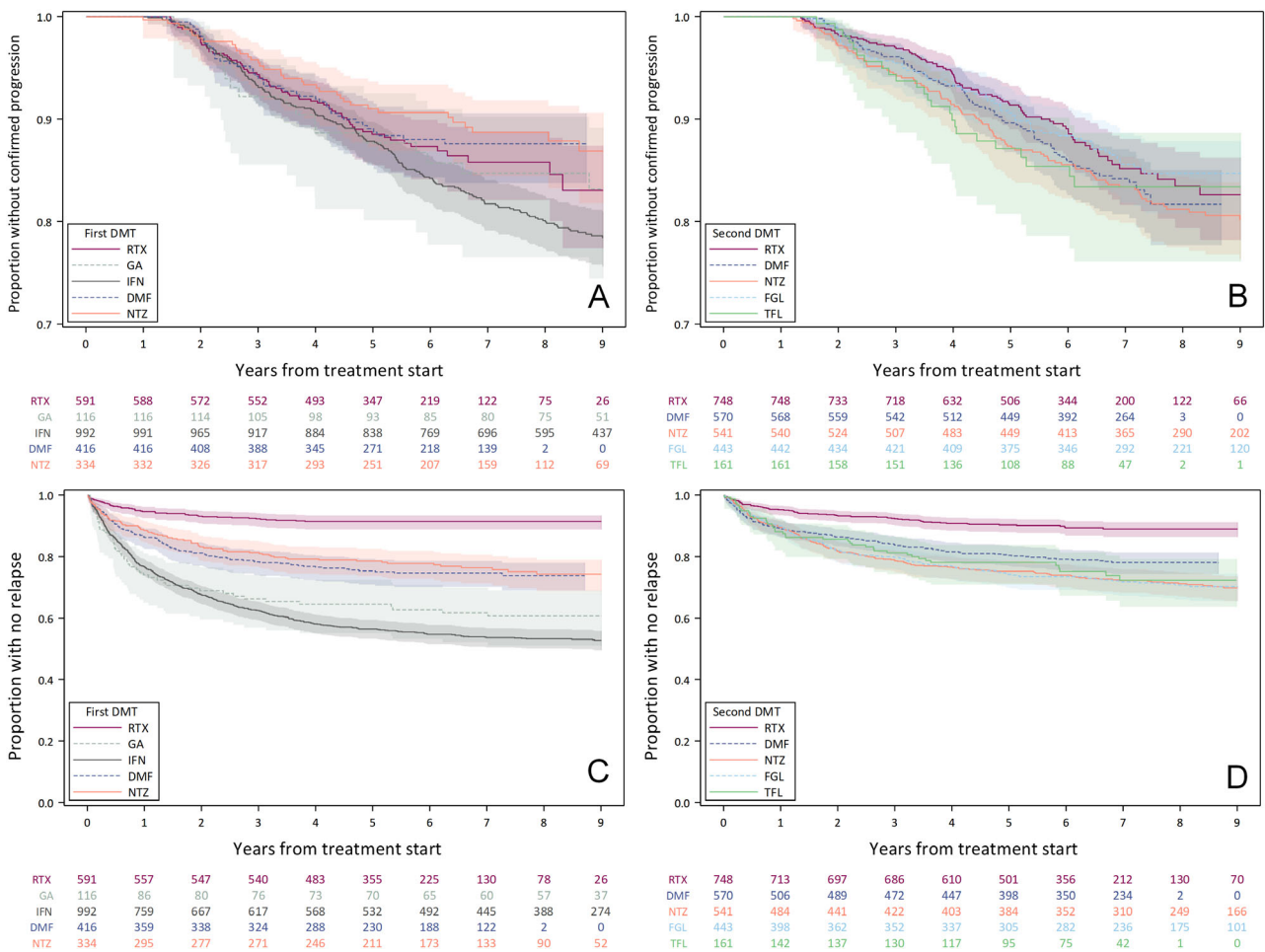


FIGURE 2: Proportions without confirmed disability progression and relapses over time unadjusted Kaplan Meier estimates of the survival functions for confirmed disability progression (A,B) and relapses (C,D) up to 9 years after start of index disease-modifying therapy. RTX = rituximab, GA = glatiramer acetate, IFN = interferon, DMF = dimethyl fumarate, NTZ = natalizumab, FGL = fingolimod, TFL = teriflunomide. [Color figure can be viewed at www.annalsofneurology.org]

Discussion

In this large population-based cohort study, we found only minor differences across DMTs for the primary endpoints: CDW and disease-related impact on quality of life (QoL). With rituximab as reference, the only statistically significant differences were greater mean reductions in MSIS-29 physical subscale scores with natalizumab, although less than what is generally considered a clinically meaningful effect.¹⁹ In contrast, we found robust differences in secondary endpoints reflecting inflammatory disease activity at both 3 and 5 years after treatment start (ie, relapses and the neuroimaging metrics included in the NEDA-3 measure) favoring rituximab over all other DMTs, except for natalizumab in some of the subgroups. Furthermore, a substantially higher proportion of participants remained on rituximab, compared with other DMTs. Apart from a higher risk of severe infections with rituximab in the DMT switch cohort, only minor differences in safety outcomes were recorded.

This is the first comprehensive assessment of effectiveness, safety, and patient-reported outcomes in a large population-based cohort reflecting contemporary clinical treatment practices. Although the intention-to-treat approach of the main analyses (used to avoid introducing selection bias) meant that therapy switching likely impacted results by diluting potential underlying differences between DMTs, robust differences favoring rituximab were seen for endpoints reflecting inflammatory disease activity and treatment persistence. Regular monitoring by MS specialists with imaging may have contributed to earlier therapy escalation compared with in more resource-limited settings and the fact that a stepped therapy approach may be less suitable in other contexts is highlighted by a recent US study, where implementation of preferred formulary DMTs (natalizumab and rituximab) led to both decreased health care expenditures and improved clinical outcomes.²⁰ The preference specifically for natalizumab and rituximab is supported by our findings.

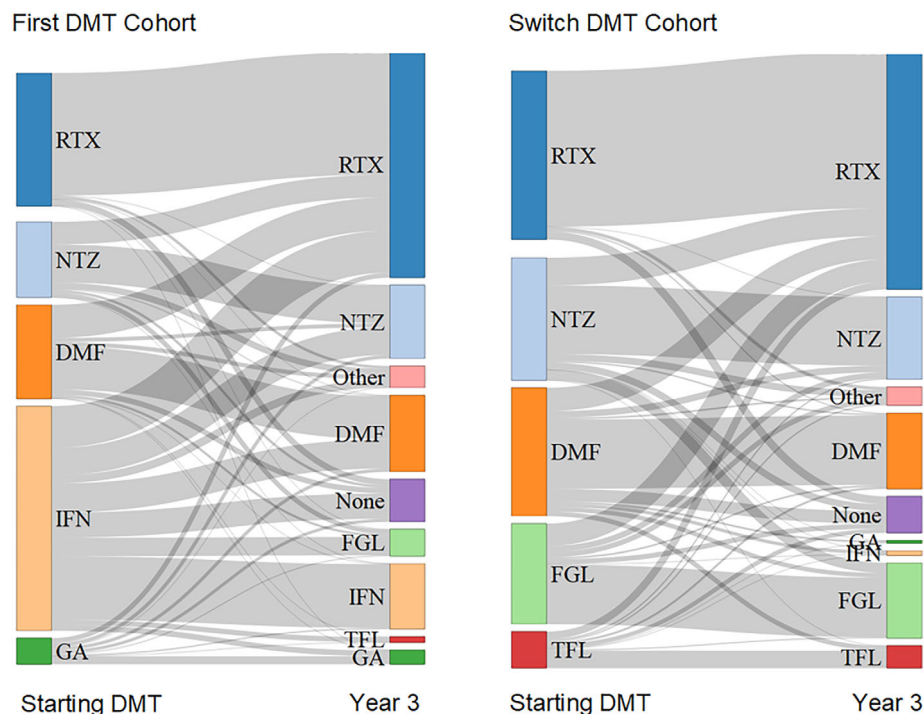


FIGURE 3: Switch in active therapy between baseline and year 3A Sankey diagram of the change in disease-modifying therapies between baseline and year 3. The colored blocks represent the proportion of participants with a specific therapy at the 2 timepoints. The lines between the blocks represent the flow of participants between baseline and year three. RTX = rituximab, NTZ = natalizumab, DMF = dimethyl fumarate, IFN = interferon, GA = glatiramer acetate, FGL = fingolimod, TFL = teriflunomide. [Color figure can be viewed at www.annalsofneurology.org]

TABLE 7. Rate of Pre-Selected Serious Adverse Events in 3 Years After Treatment Start

First DMT cohort	Rituximab	Natalizumab	Dimethyl fumarate	Interferon	Glatiramer acetate
Death (IR)	0.6 (0.0–3.2)	0.0 (0.0–3.7)	0.0 (0.0–3.0)	0.0 (0.0–1.2)	0.0 (0.0–10.6)
Cancer (IR)	0.6 (0.0–3.2)	3.0 (0.6–8.8)	0.0 (0.0–3.0)	2.4 (1.0–4.9)	2.9 (0.1–16.2)
MACE (IR)	1.7 (0.4–5.0)	0.0 (0.0–3.7)	0.8 (0.0–4.5)	1.4 (0.4–3.5)	0.0 (0.0–10.6)
Infection (IR)	12.7 (8.0–19.2)	12.2 (6.3–21.3)	9.8 (5.1–17.1)	6.8 (4.2–10.5)	5.8 (0.7–21.1)
Infection (HR)	Ref	1.01 (0.44–2.33)	0.92 (0.42–2.00)	0.73 (0.33–1.62)	N/A ^a
Switch DMT cohort	Rituximab	Natalizumab	Dimethyl fumarate	Fingolimod	Teriflunomide
Death (IR)	0.0 (0.0–1.7)	0.0 (0.0–2.3)	0.0 (0.0–2.2)	0.0 (0.0–2.8)	2.1 (0.1–11.6)
Cancer (IR)	1.3 (0.3–3.9)	1.2 (0.1–4.5)	3.0 (1.0–6.9)	4.6 (1.7–9.9)	0.0 (0.0–7.7)
MACE (IR)	1.3 (0.3–3.9)	1.2 (0.2–4.5)	0.6 (0.0–3.3)	0.0 (0.0–2.8)	4.2 (0.5–15.1)
Infection (IR)	20.3 (14.8–27.3)	6.2 (3.0–11.5)	5.9 (2.8–10.9)	10.0 (5.3–17.0)	14.9 (6.0–30.7)
Infection (HR)	Ref	0.23 (0.10–0.53)	0.26 (0.12–0.54)	0.40 (0.19–0.83)	0.55 (0.23–1.34)

Unadjusted IR per 1,000 person-years and adjusted HR for infection with rituximab as the reference. HRs adjusted for age, sex, year of treatment start, country of birth, geographical region, education level, duration since MS diagnosis, baseline EDSS, SDMT, and MSIS-29 scores, history of serious infection, malignancy, major adverse cardiovascular event, arrhythmia, use of antidepressants, diabetes. HRs estimated with Cox regression with robust confidence intervals (Huber-White).

DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; HR = hazard ratios; IR = incidence rates; MACE = major adverse cardiovascular event; MSIS-29 = Multiple Sclerosis Impact Scale-29.

^aToo few events to include in analysis.

The risk of CDW did not differ between DMTs, which contrasts previous uncontrolled register studies.^{21–23} This may be because of several factors. First, prior studies were not population-based and included longer case identification periods, during which the MS diagnostic criteria were changed, possibly leading to a case mix with more active and/or severe disease. Indeed, the overall risk of CDW appears lower in our cohorts compared with previous studies.^{21–23} Second, adherence to guidelines recommending therapy escalation with a clinical relapse or signs of neuroradiological disease activity minimize time on insufficiently effective DMTs,²⁴ whereas enriching for individuals with a beneficial therapy response with the initial DMT. Third, as previously mentioned, the use of an intention-to-treat strategy likely diluted possible underlying differences across the included therapies, affecting the power to detect differences. Additionally, it should be noted that the risk of disability progression increase from the fifth decade of life.^{25,26} Therefore, longer observation will be required to rule out any differences materializing later on.^{27,28}

Our observations add to an increasing body of evidence suggesting that most instances of CDW are not driven by relapses, even in the relapsing–remitting disease stage.²⁹ The relative contributions of progression independent of relapse activity and relapse-associated worsening toward CDW differs across studies, likely resulting from differences in outcome definitions and study participants' clinical characteristics.³⁰ Given the overall low ARR in our study, particularly with rituximab, a notable finding here is that approximately 80 to 90% of individuals experiencing CDW had been relapse-free during the observation period, and among those with at least one relapse, only those with interferon as a first therapy had a higher proportion of CDW compared with rituximab. Further, proportions with CDW were substantially higher in individuals above the age of 50 years, although they constituted a minority of the study cohort. Combining the first DMT and DMT switch groups, only 114 therapy starts (2.3%) were among people age ≥ 60 years, and 669 (13.6%) were among people age ≥ 50 . A recent register study from the United Kingdom found that 9.6% of people with MS have an onset after 50 years of age.³¹ Those with late-onset MS displayed a higher proportion with progressive disease features, including primary-progressive MS, a faster rate of disability accrual, and a lower likelihood of starting highly effective DMTs, compared with the younger age groups. Our study complements these results by providing data on treatment outcomes, although the only difference reaching statistical significance was treatment persistence, favoring rituximab over all other DMTs apart from fingolimod in the switch

cohort. We note that point estimates for ARR and NEDA-3 also favored rituximab among the elderly, but the lack of significant difference would be in line with meta-analyses of RCT data, showing that the relative benefit of treatment decrease with older age.³² This highlights the unmet clinical need for therapies with effect on disease processes associated with the later stages of MS.³³

There is an ongoing debate about how treatment effectiveness should be weighed against safety concerns to optimize the benefit–risk for individual patients.¹⁰ It is, therefore, of interest that the outcomes rated highest by the stakeholders involved in designing this study (ie, QoL [patients]) and disability accumulation [neurologists]) were not noticeably impacted by DMT choice. As a result of regular monitoring for residual inflammatory disease activity and no substantial economic or structural barriers for switching therapy, those with an insufficiently effective or tolerable first DMT switched to an alternative, as shown by small remaining differences between DMTs in the on-drug sensitivity analysis. Nevertheless, it should be noted that especially younger individuals with older injectable drugs as a first DMT, or teriflunomide after a DMT switch, were prone to switch therapy, most often to rituximab. On the other hand, the increased rate of severe infections with rituximab after a DMT switch should be noted and risk mitigation strategies, such as routine vaccinations and extension of rituximab infusion intervals,^{34,35} should be further explored.

From a health care perspective, it is striking that low-dose rituximab performed equally well on disability and patient-reported outcomes and outperformed several MS-approved DMTs regarding relapses and treatment persistence. Drug costs in MS are high compared with other chronic diseases and have tripled in the United States between 2011 and 2017.^{36,37} Cost-effective DMT options are even more warranted in resource-limited settings, because most MS-approved drugs are neither accessible nor affordable.³⁸ In light of this, our findings support the World Health Organization's recent decision to include rituximab on their *Model List of Essential Medicines for MS*.³⁹ Additional support is also provided by a recent Swedish cost-effectiveness study in a nationwide RRMS cohort (partly overlapping with the present study's cohort), which found that rituximab, compared with fingolimod, dimethyl fumarate, and natalizumab was associated with mean cost savings of \$35,000 to \$66,000 and 0.12 to 0.22 mean prevented relapses per started therapy over 5 years, resulting in the rare situation of a drug being both more effective and less costly.¹⁶ Importantly, the drug cost savings and higher effectiveness were not offset by other increased health care costs.

The main limitation of this study is the lack of randomization, which means that residual confounding may

bias our results despite our efforts to adjust for a broad range of factors. Second, the sample size limited our ability to test for differences in the rates of rare safety outcomes. However, some of these outcomes have been addressed by leveraging the entire Swedish MS population, compared with a general-population reference cohort.^{9,40} Third, data missingness affected DMT groups differently, where a lack of patient-reported outcomes at baseline before the start of the structured follow-up period, particularly for older injectable DMTs, made the effectiveness of imputation less certain. Multiple imputation allows for adjustment for covariates even in the presence of substantial missingness, but should be interpreted as an extrapolation, assuming the same conditional covariance between clinical variables among the patients missing data (more often those starting injectables in the earlier part of the study period) as among those with complete data (more often those starting high-efficacy treatments). We believe this extrapolation can be defended, in particular because most adjustments had a very minor effect on the observed treatment differences. Of perhaps bigger importance, we also completely lacked data on several potentially important confounders, including smoking, physical exercise, diet, and body mass index. Fourth, the coronavirus disease 2019 pandemic impacted the study's follow-up procedures, resulting in higher missingness of EDSS assessments and neuroradiological examinations. Fifth, because of being approved only at the end of the inclusion period, treatments such as cladribine or ocrelizumab had too few exposures to be included in the analysis. Last, extrapolation of findings to more resource-limited settings or fragmented health care systems should be done with caution.

In conclusion, the findings of the COMBAT-MS study suggest that impact of initial DMT choice on disability accrual and patient-reported outcomes is small in a dynamic real-world context with regular monitoring and low barriers for DMT switches. However, those starting or switching to off-label low-dose rituximab had a lower risk of relapses and were less likely to switch therapy, compared with those starting the MS-approved alternatives. Implementation of risk mitigation strategies to reduce the risk of infection with rituximab may further improve the benefit–risk balance of this therapeutic modality in RRMS.

Acknowledgements

We thank all study participants, in particular patient stakeholder representatives E. Helmersson, D. Stoner, J. Roussel Jr, J. Roussel Sr, L. Roussel, and J. Johansson, clinical staff at involved centers, other researchers involved

in the COMBAT-MS study program, in particular T. Granberg, I. Kockum, and A. Mattsson, the scientific advisory board representatives N. LaRocca, G. Gronseth, and G. Giovannoni, and Patient-Centered Outcomes Research Institute (PCORI) and its board of governors and project management team. Research reported in this publication was funded through a PCORI Award (MS-1511-33196). The views in this publication are solely the responsibility of the authors and do not necessarily represent the views of the PCORI, its Board of Governors or Methodology Committee.

Author Contributions

F.P., A.L.G., A.S., and T.F. contributed to the conception and design of the study; F.P., P.A., S.V., S.E., J.B., K.F., A.F.H., M.G., J.H., A.L.G., J.L., J.M., P.N., T.O., J.S., A.S., and T.F. contributed to the acquisition and analysis of data; F.P., P.A., S.V., S.E., and T.F. contributed to drafting the text or preparing the figures.

Potential Conflicts of Interest

Relevant entities are Roche (market authorization holder for MabThera/rituximab), Biogen (Avonex/interferon-beta-1a, Tysabri/natalizumab and Tecfidera/dimethyl fumarate), Bayer (Betaferon/interferon-beta-1b), Novartis (Gilenya/fingolimod, Extavia/interferon-beta-1b), Merck (Rebif/interferon-beta-1a), and Teva (Copaxone/glatiramer acetate). F.P.: research grants outside of this study from Merck; fees for serving on DMCs in clinical trials with Roche; expert testimony for Novartis. K.F.: served on scientific advisory boards for Biogen, Merck, Novartis, and Roche; received financial research support from Merck. A.F.H.: received unrestricted funding from Biogen; speaking honoraria from Merck; consulting fees from Roche. J.H.: research grants outside of this study from Biogen, Merck, Novartis, and Roche; speaker's fees or fees for serving on advisory boards for Biogen, Merck, Novartis, and Teva. J.L.: received travel support and/or lecture honoraria and has served on scientific advisory boards for Biogen, Merck, Novartis, and Roche; received unconditional research grants from Biogen and Novartis. J.M.: received honoraria for advisory boards and lecture honorarium for Merck. T.O.: received advisory board/lecture honoraria; unrestricted research grants from Biogen, Novartis, and Merck. P.A. S.V., S.E., J.B., M.G., A.L.G., P.N., J.S., A.S., and T.F.: nothing to declare.

Data Availability

Requests for sharing of de-identified data will be considered on reasonable request and in accordance with current legislation regarding protection of personal data (see Supplementary material). Additional group level data has been

deposited with clinicaltrials.gov and the EU clinical trials register.

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