This is the published version of a paper published in Neurology.

Citation for the original published paper (version of record):

Rituximab in multiple sclerosis: a retrospective observational study on safety and efficacy.
Neurology, 87(20): 2074-2081
https://doi.org/10.1212/WNL.0000000000003331

Access to the published version may require subscription.

N.B. When citing this work, cite the original published paper.

Permanent link to this version:
http://urn.kb.se/resolve?urn=urn:nbn:se:umu:diva-132168
Rituximab in multiple sclerosis
A retrospective observational study on safety and efficacy

ABSTRACT

Objective: To investigate the safety and efficacy of rituximab in multiple sclerosis (MS).

Methods: In this retrospective uncontrolled observational multicenter study, off-label rituximab-treated patients with MS were identified through the Swedish MS register. Outcome data were collected from the MS register and medical charts. Adverse events (AEs) grades 2–5 according to the Common Terminology Criteria for Adverse Events were recorded.

Results: A total of 822 rituximab-treated patients with MS were identified: 557 relapsing-remitting MS (RRMS), 198 secondary progressive MS (SPMS), and 67 primary progressive MS (PPMS). At baseline, 26.2% had contrast-enhancing lesions (CELs). Patients were treated with 500 or 1,000 mg rituximab IV every 6–12 months, during a mean 21.8 (SD 14.3) months. During treatment, the annualized relapse rates were 0.044 (RRMS), 0.038 (SPMS), and 0.015 (PPMS), and 4.6% of patients displayed CELs. Median Expanded Disability Status Scale remained unchanged in RRMS (p = 0.42) and increased by 0.5 and 1.0 in SPMS and PPMS, respectively (p = 0.10 and 0.25). Infusion-related AEs occurred during 7.8% of infusions and most were mild. A total of 89 AEs grades ≥2 (of which 76 infections) were recorded in 72 patients. No case of progressive multifocal leukoencephalopathy was detected.

Conclusions: This is the largest cohort of patients with MS treated with rituximab reported so far. The safety, clinical, and MRI findings in this heterogeneous real-world cohort treated with different doses of rituximab were similar to those reported in previous randomized controlled trials on B-cell depletion therapy in MS.

Classification of evidence: This study provides Class IV evidence that for patients with MS, rituximab is safe and effective. Neurology® 2016;87:2074–2081

GLOSSARY

AE = adverse event; ARR = annualized relapse rate; BPF = brain parenchymal fraction; CEL = contrast-enhancing lesion; CTCAE = Common Terminology Criteria for Adverse Events; DMD = disease modulatory drug; EDSS = Expanded Disability Status Scale; HACA = human antichimeric antibody; HERMES = Helping to Evaluate Rituxan in Relapsing-Remitting Multiple Sclerosis; IgG = immunoglobulin G; JCV = JC virus; MS = multiple sclerosis; OLYMPUS = A Study to Evaluate the Safety and Efficacy of Rituximab in Adults With Primary Progressive Multiple Sclerosis; PML = progressive multifocal leukoencephalopathy; PPMS = primary progressive multiple sclerosis; RCT = randomized controlled trial; RRMS = relapsing-remitting multiple sclerosis.

Rituximab (Mabthera; Roche, Basel, Switzerland), a chimeric monoclonal B-cell-depleting anti-CD20 antibody, has shown beneficial effects in 2 randomized placebo-controlled phase 2 trials (RCTs): the Helping to Evaluate Rituxan in Relapsing-Remitting Multiple Sclerosis (HERMES) trial for relapsing-remitting multiple sclerosis (RRMS) and A Study to Evaluate the Safety and Efficacy of Rituximab in Adults With Primary Progressive Multiple Sclerosis (OLYMPUS) trial for primary progressive multiple sclerosis (PPMS).\(^1\)\(^2\) The notion of a positive effect of anti-CD20 antibody treatment in RRMS is supported by 2 recent RCTs with 2 new antibodies:

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Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article. The Article Processing Charge was paid by the authors.

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ocrelizumab (humanized) and ofatumumab (human).3,4 Three large, unpublished RCTs with ocrelizumab in RRMS (A Study of Ocrelizumab in Comparison with Interferon Beta 1a [Rebiif] in Patients with Relapsing Multiple Sclerosis [OPERA] I and II) and PPMS (A Study of Ocrelizumab in Patients with Primary Progressive Multiple Sclerosis [ORATORIO]) were presented at the European Conference for Treatment and Research in MS 2015 (ECTRIMS).5 In these studies, ocrelizumab showed significant benefit over interferon-β-1a for RRMS and over placebo for PPMS. Furthermore, we recently provided evidence that rituximab is superior to fingolimod regarding disease reactivation in patients switching from natalizumab due to positive JC virus (JCV) serology.6

Available data from rituximab in rheumatoid arthritis indicate a high tolerability and low risks for serious opportunistic infections or secondary malignancies.7 Progressive multifocal leukoencephalopathy (PML) has been reported in rituximab-treated patients, but to our knowledge, no case of PML has been reported from natalizumab due to positive JCV serology.6

The primary aim of this retrospective study performed at specialized MS centers at 3 university hospitals in Sweden was to investigate the safety of rituximab in MS (level of evidence IV). The secondary aim was to report the efficacy of rituximab in MS on clinical and MRI measures (level of evidence IV).

Available data from rituximab in rheumatoid arthritis indicate a high tolerability and low risks for serious opportunistic infections or secondary malignancies.7

The source population was all patients with MS ever treated with rituximab recorded in the Swedish MS register launched in 2001 (neuromag.se)9 at the Umeå (until April 12, 2015), Sahlgrenska (Gothenburg, until April 18, 2015), and Karolinska (Stockholm, until February 24, 2015) University Hospitals. Patients treated with rituximab for other concomitant conditions or with no follow-up data available were excluded (figure 1). Medical charts were reviewed according to a prespecified data collection protocol. Time on treatment was defined as time from first rituximab infusion until data censure. For those who discontinued treatment, data collection was extended until 1 year after the last rituximab infusion or time for data censure, whichever came first.

Treatment and follow-up monitoring. Patients were usually treated with single infusions of 500 or 1,000 mg rituximab IV every 6–12 months, in some cases after an initial higher dose treatment course (1,000–2,000 mg subdivided into 2 infusions given within 1 month). Clinical examinations and cerebral 1.5 or 3T MRI were performed routinely every 6–12 months or as clinically indicated. Blood samples for safety and B-cell monitoring were drawn immediately before rituximab infusions. B-cell levels were not used to guide treatment decisions.

Outcome data collection. Clinical and MRI data were retrieved from the Swedish MS register and medical charts. The baseline MRI was defined as the most recent MRI before rituximab treatment initiation. We recorded the presence and numbers of contrast-enhancing lesions (CELs) on all MRIs. The brain parenchymal fraction (BPF) is estimated in clinical routine since 2009 at Umeå University Hospital, and was recorded when available. The BPF was calculated using the SyMap method.11 Postprocessing was performed using SyMRI BrainStudio version 7.0 (SyntheticMR AB, Linköping, Sweden) with minor manual adjustments to the automated brain segmentation. Patients who discontinued rituximab were considered treated until 1 year after discontinuation. The dates of the most recent relapse before rituximab and all relapses on treatment were recorded. The Expanded Disability Status Scale (EDSS) scores prior to rituximab and the latest EDSS on treatment were recorded. The immunoglobulin G (IgG, g/L) levels and the number of B cells, expressed as the percentages of CD19-positive cells among the

This flowchart depicts how the 822 rituximab (RTX)-treated patients with multiple sclerosis (MS) were identified. The source population was all MS cases registered in the Swedish MS register at the 3 participating MS centers (Umeå University Hospital, Umeå, until April 12, 2015; Karolinska University Hospital, Stockholm, until February 24, 2015; and Sahlgrenska University Hospital, Gothenburg, until April 18, 2015). We excluded patients lost to follow-up and patients treated with RTX for reasons other than MS (e.g., rheumatoid arthritis, systemic lupus erythematosus, and neuromyelitis optica).

METHODS

The primary aim of this retrospective study performed at specialized MS centers at 3 university hospitals in Sweden was to investigate the safety of rituximab in MS (level of evidence IV). The secondary aim was to report the efficacy of rituximab in MS on clinical and MRI measures (level of evidence IV).

Standard protocol approvals, registrations, and patient consents. The study was approved by the local ethics committees in Umeå (2013/445-31) and Stockholm (2009/2107-3/11/2). Formal patient consent was waived by the ethics committees.

Study population. The source population was all patients with MS ever treated with rituximab recorded in the Swedish MS register launched in 2001 (neuromag.se) at the Umeå (until April 12, 2015), Sahlgrenska (Gothenburg, until April 18, 2015), and Karolinska (Stockholm, until February 24, 2015) University Hospitals. Patients treated with rituximab for other concomitant conditions or with no follow-up data available were excluded (figure 1). Medical charts were reviewed according to a prespecified data collection protocol. Time on treatment was defined as time from first rituximab infusion until data censure. For those who discontinued treatment, data collection was extended until 1 year after the last rituximab infusion or time for data censure, whichever came first.
A total of 822 patients with MS (557 interferon-modulatory drug (DMD), and the remainder switched. One-fifth had received rituximab as their first disease. Baseline characteristics are presented in table 1. 

### Adverse events (AEs) occurring during rituximab treatment were registered from medical records covering all medical sub-specialities at the hospitals, and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v 4.03, June 2010. The following AEs were recorded: deaths, malignancies, autoimmune disorders, and infections. We did not record grade 1 AEs or uncomplicated lower urinary or upper respiratory tract infections, since we expected the sensitivity to be low. For the same reason, unspecific symptomatic diagnoses were also excluded. Herpes and herpes zoster infections requiring antiviral treatment were recorded as these may indicate compromised cellular immunity.12 Infusion-related AEs (all CTCAE grades) were actively interrogated and recorded in medical charts by the MS nurses at each infusion.

### Statistical analyses. SPSS version 23 was used for statistical analyses. Normally distributed variables were presented as mean (SD), parametric variables as median (range). The independent samples t test or 1-way analysis of variance were used to compare means, the Mann-Whitney U test or 1-way analysis of variance were used to compare medians. The Pearson χ² test was used to compare proportions and Fisher exact test if one category had less than 5 observations. The numbers of MRIs with CELs per year of treatment, the annualized relapse rates (ARRs), and the proportions of infusions with infusion reactions were compared using the Upton N-1 χ² in Win-pepi software version 2.72. We calculated the atrophy rate as the change in BPF (ΔBPF) divided by years elapsed between each MRI. For patients who had ≥2 ΔBPF estimations, we calculated the mean atrophy rate. The α was set at <0.05.

### RESULTS A total of 822 patients with MS (557 RRMS, 198 SPMS, 67 PPMS) ever treated with rituximab fulfilling the inclusion criteria were identified (figure 1). Of the 557 RRMS cases, 114° and 713 patients, respectively, were included in 2 other recently published studies. Baseline characteristics are presented in table 1. One-fifth had received rituximab as their first disease modulatory drug (DMD), and the remainder switched from other DMDs, most commonly natalizumab and interferon-β (table 1). Median (range) washout periods for first- and second-line therapies were 0.48 (0–176.9) and 1.22 (0–65.2) months, respectively. Patients were treated with rituximab during a total of 1,490 and followed during 1,580 patient-years. The mean (SD) treatment duration was 21.8 (14.3) months, median 18.4 (range 0–88), and the mean follow-up time was 23.1 (15.3) months. In total, 313 patients were on treatment for >24 months. The median rituximab dose was 1,000 mg (100–1,000) per infusion (table 1). One-third had received 2,000 mg during the first treatment course (1,000 + 1,000 mg given within 1 month, table 1). These patients were more likely to have had CELs on their baseline MRI (32.5 vs 22.9%, p = 0.003), making further analyses based on first treatment course dose difficult.

The mean B-cell levels decreased and remained low over the observed time period (figure 2). IgG levels decreased only slightly on the aggregate level, but 3% (25 cases) had IgG levels below the lower normal reference value at some point during treatment (n = 1,107 sampling occasions, figure 2). The JCV serostatus at baseline was known in 342 patients, of which 285 (83%) were seropositive. The mean absolute JCV index, determined in 198 patients, was 1.96 (1.22).

### Clinical efficacy data. A total of 59 relapses occurred on rituximab treatment, which corresponded to the following ARRs: 0.044 for RRMS, 0.038 for SPMS, and 0.015 for PPMS (figure 3). The relapses occurred at a median of 4.7 (0.16–23.9) months after the most recent infusion. The ARRs on rituximab treatment in patients with RRMS differed across previous treatment categories: 0.016 for treatment-naïve patients (n = 119), 0.033 for patients previously on first-line DMDs (interferons, glatiramer acetate, dimethylfumarate; n = 180), and 0.067 for patients previously on second-line DMDs (natalizumab, alemtuzumab; n = 243) (p = 0.015) (15 patients not classifiable). The baseline EDSS (n = 630) was assessed mean 1.8 (2.75) months before rituximab initiation, the latest available follow-up EDSS (n = 613) 22.2 (14.5) months later. During the observation time, the median EDSS remained unchanged in patients with RRMS (p = 0.42), and increased 0.5 and 1.0 for patients with SPMS and PPMS, respectively (p = 0.10 and 0.25).

### MRI efficacy data. Data for 2,208 MRI examinations were retrieved, including the baseline MRIs. Each patient had a median of 2 (1–9) MRIs including baseline. A baseline MRI was performed in 99.5% (818 out of 822) of patients, and 77.3% (635 out of 822) of patients had performed at least 1 MRI after rituximab initiation. The mean time between baseline MRI and rituximab initiation was 4.5 (8.4), and the mean interval between the MRI scans during treatment was 10.6 (6.1) months. At baseline, 26.2% (214 out of 818) of patients had CELs (a total of 636 CELs, mean [SD] 0.8 [2.3] CELs/MRI, table 1). After treatment initiation, 4.6% (29 out of 635) of patients had CELs (total 75 CELs on 31 MRIs). When counting all 1,390 MRIs performed after treatment initiation, this yielded a ratio of 0.054 CELs/MRI, or CELs in 2.2% of MRIs. The CELs appearing during treatment were more common during the first 6 months vs later (p < 0.001) (figure 3). Among the 432 patients with RRMS with data on CELs after rituximab initiation, the numbers of CELs/MRI on treatment were 0.16 in naive patients (n = 82), 0.06 in patients previously on first-line DMDs (n = 138), and 0.23 in patients previously on second-line DMDs (n = 198) during the first 6 months after the first.
rituximab infusion (p = 0.02). The corresponding figures during months 6–18 were 0.01, 0.01, and 0.04, respectively (p = 0.12).

Atrophy rate. The mean annual change in BPF on rituximab treatment was −0.19% (0.95). This was assessed in 160 patients at the Umeå University Hospital who had ≥2 ΔBPF estimations available (726 MRIs).

Rituximab dosing. The 2 most common rituximab protocols in Sweden are 500 and 1,000 mg every 6 months as single maintenance doses after an initial dose that may vary from 500 to 2,000 mg, sometimes

| Table 1 | Baseline characteristics and rituximab (RTX) treatment data for 822 patients with multiple sclerosis (MS) treated with rituximab at 3 Swedish MS centers (Umeå, Karolinska, and Sahlgrenska University Hospitals), by multiple sclerosis subtype |
|-----------|-----------------|-----------------|-----------------|-----------------|
| Female, n (%) | Relapsing disease (n = 557) | Secondary progressive (n = 198) | Primary progressive (n = 87) | Total (n = 822) |
| Age at MS onset, y, mean (SD) | 30.7 (10.3) | 30.0 (8.9) | 40.5 (12.4) | 31.3 (10.5) |
| Age at RTX start, y, mean (SD) | 39.6 (10.6) | 49.1 (8.5) | 48.7 (10.6) | 42.6 (11.1) |
| Disease duration at RTX start, y, mean (SD) | 8.9 (7.2) | 19.1 (7.9) | 8.2 (6.2) | 11.3 (8.5) |
| Years since conversion to SPMS, mean (SD) | — | 6.5 (5.4) | — | — |
| EDSS at RTX start, median (range) | 2 (0–8.5) | 5.5 (1.5–9) | 5 (1–9) | 3 (0–9) |
| CELs at baseline, n (%) | 141 (25.4) | 78 (23.9) | 26 (38.8) | 214 (26.2) |
| Most recent MRI to RTX start, mo, mean (SD) | 4.1 (7.5) | 5.8 (11.3) | 3.8 (3.9) | 4.5 (8.4) |
| No. of DMTs prior to RTX, median (range) | 1 (0–7) | 2 (0–6) | 0 (0–3) | 1 (0–7) |
| RTX dose/infusion, mg, median (range) | 1,000 (100–1,000) | 750 (100–1,000) | 1,000 (500–1,000) | 1,000 (100–1,000) |
| Infusion interval, excluding the first treatment course, mo, mean (SD) | 7.2 (3.7) | 7.2 (4.2) | 6.8 (3.7) | 7.1 (3.8) |
| Follow-up time since RTX start, mo, mean (SD) | 21.9 (15.4) | 24.8 (14.7) | 27.9 (15.2) | 23.1 (15.3) |
| Treatment-naive, n (%) | 119 (21.4) | 21 (10.6) | 35 (52.2) | 175 (21.3) |
| Months between last relapse and RTX start in treatment-naive, median (range) | 3.3 (0–117) | 56.8 (2.9–343.5) | 3.9 (0.5–358.1) | 4.0 (0.1–358.1) |
| Last DMT before RTX | n = 438 | n = 177 | n = 32 | n = 647 |
| Natalizumab | 167 (38.1) | 53 (29.9) | 7 (21.9) | 227 (35.1) |
| Interferons | 140 (32.0) | 57 (32.2) | 4 (12.5) | 201 (31.1) |
| Fingolimod | 71 (16.2) | 11 (6.2) | 4 (12.5) | 86 (13.3) |
| Glatiramer acetate | 30 (6.8) | 16 (9) | 3 (9.4) | 49 (7.6) |
| Other | 30 (6.8) | 40 (22.6) | 14 (43.8) | 84 (13.0) |
| Reason for changing to RTX | Disease activity* | 156 (35.6) | 77 (43.8) | 12 (37.5) | 248 (38.5) |
| JCV+ | 114 (26.0) | 33 (18.8) | 5 (15.6) | 152 (23.5) |
| Adverse event | 68 (15.5) | 19 (10.8) | 3 (9.4) | 90 (13.9) |
| Other | 100 (22.1) | 48 (27.1) | 12 (37.5) | 157 (24.3) |

Abbreviations: CEL = contrast-enhancing lesion; DMT = disease-modifying treatment; EDSS = Expanded Disability Status Scale; JCV = JC virus; SPMS = secondary progressive multiple sclerosis.

Data are n (%), mean (SD) for continuous variables, or median (range) for nonparametric variables.

* There were 41 patients with relapsing-remitting MS with EDSS scores ≥4.5. Although some of these may have the progressive form of MS, we did not have enough data to reclassify them.

** Four cases (3 relapsing-remitting MS and 1 SPMS) did not have a baseline MRI.

* Values are median (range) of means for each patient.

* 1 month between first and second infusions.

* These patients had experienced a recent relapse, had new or enlarged T2 lesions or CELs on MRI, or were for other reasons deemed to have ongoing disease activity by the treating physician.
levels are shown as mean percentage of CD19
3 (the Karolinska University Hospital, the B-cell levels are shown as mean absolute numbers of cases used to estimate the means and SDs are shown below the figure for IgG (top row) (106) of CD19
12 were merged due to few cases. Figure 2 B-cell and immunoglobulin G (IgG) levels before and during rituximab treatment in multiple sclerosis cases

B-cell and IgG levels did not differ (table e-1). Non-infusion-related AEs per patient-year of treatment were slightly less common in the 500 vs 1,000 mg groups (0.083 vs 0.125) but B-cell and IgG levels did not differ (table e-1).

Adverse events. A total of 89 non-infusion-related AEs grades 2–5 were detected. The most common types of AE were infections (n = 76); this was also true for severe AEs (table 2). Three grade 2 malignancies were detected, and 4 patients died. Causes of death were cardiac arhythmia, respiratory failure, vascular surgery, and suicide by intoxication, respectively (table e-2). Infusion reactions (malaise, headache, chills, nausea) occurred during 7.8% of infusions (234 out of 3,002). Such reactions were more common during the first 3 infusions, 10.1% (213 out of 2,108), compared with subsequent infusions, 2.3% (21 out of 894) (p < 0.001). Infusion-related AE grades were 3 (n = 3), 2 (n = 72), and 1 (n = 159).

Drug survival. In total, 10.3% (85 out of 822) discontinued rituximab treatment during the study, 43 of these (20 RRMS, 16 SPMS, and 7 PPMS) due to AEs or disease activity. The remainder, 42 patients, stopped treatment due to stable condition, secondary progressive MS, pregnancy, or other reasons (figure e-1). The drug survival (proportion of patients who had not discontinued rituximab due to disease activity or AEs) at data censure was 94.8% (779 out of 822, figure e-1).

DISCUSSION We report the largest retrospective observational study so far investigating off-label rituximab treatment in MS. Although data were retrieved from 3 MS centers with different treatment regimens and different selection principles for rituximab treatment, they add important information on safety and tolerability of rituximab in a heterogeneous clinical real-world sample. Due to the design of the study, efficacy data are less reliable but support those achieved in previous RCT studies on rituximab and other B-cell-depleting therapies as well as an observational study in a high inflammatory group switching from natalizumab.

In this study, a large proportion of decisions to initiate rituximab treatment were based on MRI. Although we included a relatively high proportion of progressive patients, the formation of new lesions on MRI was high at baseline. Despite this, the observed ARR and MRI disease activity were low during rituximab treatment. Based on the observed ARRs in this study, rituximab-treated patients with RRMS may be expected to experience one relapse every 23rd year. This is low compared to first-line-agent treated patients with MS, and even compared with alemtuzumab- and natalizumab-treated patients. Furthermore, the drug survival, reflecting both effectiveness and safety/tolerability, was divided into 2 infusions within 1 month. To compare these 2 treatment regimens, we subdivided the RRMS cohort into those who had received ≤750 mg/infusion and those who had received >750 mg/infusion as maintenance dose. A total of 478 patients with RRMS had received at least 2 infusions and were included in this analysis. The low-dose group (n = 220) had received median 500 (100–750) and the high-dose group (n = 258) 1,000 (786–2,000) mg rituximab per maintenance treatment course. The majority, 78.2% in the low-dose group and 82.2% in the high-dose group, had received 500 and 1,000 mg, respectively, per maintenance infusion. The groups did not differ with regards to most important baseline characteristics, such as proportions with CELs at baseline and previous treatment with natalizumab. However, the lower dose group was slightly older at treatment initiation, 41.1 (10.7) vs 38.6 (10.8) years, p = 0.01, and had shorter follow-up time, 17.9 (9.6) vs 28.7 (15.7) months, p < 0.01 (table e-1 at Neurology.org). As CELs were more common on early MRIs, and as the follow-up times for the 2 groups differed, we compared MRI data for the time periods <6 and 6–18 months separately. Efficacy data suggested no differences in numbers of CELs/MRI (0.14 vs 0.15; p = 0.85) during <6 months after treatment initiation, or during months 6–18 (0.02 vs 0.02; p = 0.67), in the 500 vs 1,000 mg groups (table e-1). Also, the ARRs for the entire follow-up period were similar (0.040 vs 0.047, p = 0.61). Non-infusion-related AEs per patient-year of treatment were slightly less common in the 500 vs 1,000 mg groups (0.083 vs 0.125) but B-cell and IgG levels did not differ (table e-1).
high compared with earlier reports. Most of the CELs that were detected appeared early (within 6 months) after rituximab initiation, suggesting lingering disease activity, which eventually disappeared. However, compared with RCTs, the frequencies of visits and MRI scannings were lower in our study. This probably underestimates numbers of clinical events and transient MRI lesions. Although the different maintenance dose groups, 500 vs 1,000 mg every 6 months, were not identical regarding all baseline parameters, including age, which might have influenced the results, our data suggested no major difference regarding efficacy based on these different dose regimens. Furthermore, slightly fewer AEs per patient-year of treatment occurred in the 500-mg group. Since the emergence of these data, the lower dose treatment protocol has been largely implemented at the 3 sites.

We did not record grade 1 AEs (mild, not treated) for non–infusion-related AEs, as the sensitivity for such events was expected to be low, and it is also likely that some grade 2 AEs (mild, needing intervention) may have been overlooked. However, the expected sensitivity for severe AEs is high since these are likely to be reported by patients or recorded in medical charts. The 4 deaths in this study were not interpreted as rituximab-related (table e-2). We detected no cases of PML, despite the fact that 83.3% were seropositive among those with known JCV serostatus. However, fewer than half of our patients were on treatment for >24 months, and given the low risk of PML even in natalizumab-treated patients during the first 24 months, a longer-term follow-up will be needed to define the PML risk in this patient population. As for infusion-related AEs, for which the sensitivity is expected to be high as such events are logged by MS nurses, most were mild (grades 1 or 2). In addition, infusion-related AEs were most common during the first 1–3 infusions, indicating that the potential immunogenicity of rituximab is a minor clinical problem. This is of interest in context of human antichimeric antibodies (HACAs). Such antibodies were detected at week 48 in 24.6% of rituximab-treated patients in the HERMES trial, although no association between the presence of HACAs and AEs or efficacy was seen. Several authors have speculated about the potential benefits of
Causes of death in these 4 cases were cardiac arrhythmia, respiratory failure, vascular surgery, and suicide, respectively. More detailed data are available in table e-2.

Table 2  Non-infusion-related adverse events (AEs) by severity, type, and frequency for 822 patients with multiple sclerosis treated with rituximab at 3 Swedish multiple sclerosis centers (Umeå, Sahlgrenska, and Karolinska University Hospitals)

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any</strong></td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>66 [8.0]</td>
</tr>
<tr>
<td>Grade 3</td>
<td>17 [2.1]</td>
</tr>
<tr>
<td>Grade 4</td>
<td>2 [0.2]</td>
</tr>
<tr>
<td>Grade 5</td>
<td>4* [0.5]</td>
</tr>
<tr>
<td><strong>Severe (CTCAE grades 3 and 4)</strong></td>
<td></td>
</tr>
<tr>
<td>Infections (pneumonia, pyelonephritis, sepsis, sinusitis, appendicitis, enteritis, bronchitis, erysipelas, intestinal abscess, tubulointerstitial nephritis)</td>
<td>14 [1.7]</td>
</tr>
<tr>
<td>Cardiac disorder (acute coronary syndrome)</td>
<td>1 [0.1]</td>
</tr>
<tr>
<td>Respiratory disorder (interstitial pneumonitis)</td>
<td>1 [0.1]</td>
</tr>
<tr>
<td>Nervous system disorder (bilateral facial palsy)</td>
<td>1 [0.1]</td>
</tr>
<tr>
<td>Immune system disorder (rheumatoid arthritis)</td>
<td>1 [0.1]</td>
</tr>
<tr>
<td>Skin disorder (Sweet syndrome)</td>
<td>1 [0.1]</td>
</tr>
<tr>
<td><strong>Malignancies (all CTCAE grade 2)</strong></td>
<td></td>
</tr>
<tr>
<td>Basalioma</td>
<td>2 [0.2]</td>
</tr>
<tr>
<td>Pyoderma gangrenosum</td>
<td>1 [0.1]</td>
</tr>
<tr>
<td><strong>Most common (≥4 cases) infections</strong></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>19 [2.3]</td>
</tr>
<tr>
<td>Otitis</td>
<td>12 [1.5]</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>10 [1.2]</td>
</tr>
<tr>
<td>Herpes</td>
<td>6 [0.7]</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>5 [0.6]</td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>4 [0.5]</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>4 [0.5]</td>
</tr>
<tr>
<td><strong>AEs by disease course</strong></td>
<td></td>
</tr>
<tr>
<td>Relapsing-remitting MS</td>
<td>68 [12.2]</td>
</tr>
<tr>
<td>Secondary progressive MS</td>
<td>16 [3.9]</td>
</tr>
<tr>
<td>Primary progressive MS</td>
<td>5 [0.6]</td>
</tr>
</tbody>
</table>

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events, version 4.03; MS = multiple sclerosis.

*Grade 1 AEs were not recorded due to low sensitivity.

The mechanisms of action for anti-CD20 treatment in MS are unknown, but may include immune modulation through a reduction in B-cell-dependent antigen presentation, less B-cell-dependent granulocyte macrophage-colony stimulating factor secretion, or lower levels of autoreactive antibodies. The concordance of efficacy data across different B-cell-depleting agents suggests that the results represent a class effect rather than specific effects mediated by different binding epitopes or the balance between different effector mechanisms between the different anti-CD20 monoclonal antibodies.1-5

Weaknesses of this study apart from those already mentioned include the lack of a control group and the retrospective design, which has inherent methodological issues. These concern data quality, e.g., insufficient documentation in medical charts, and low outcome sensitivity, which prevented grade 1 AE reporting. Also, different methods of reporting B-cell levels prevented complete analyses of this variable on the cohort as a whole, and the low number of patients with cerebral volumetric estimations as well as the lack of a control group for this measure limits the usefulness of atrophy data.

This observational study provides level IV evidence that rituximab is safe and effective for treating MS for up to 2 years. A phase 3 RCT is motivated and may be performed as an investigator-driven effort. This should be given high priority for public funding agencies given the potential patient and societal (low treatment costs) benefits.

**AUTHOR CONTRIBUTIONS**

The study was conceived and designed by A.S., J.S., F.P., P.A., and J.L. Data collection was performed by R.S., P.A., L.N., A.B., K.F., P.I.-J., C.M., M.A., A.S., J.S., and F.P. Statistical analyses were performed by J.S. The report, tables, and figures were drafted by J.S., who had full access to all data. All authors provided comments and intellectual input on the tables, figures, analyses, interpretation of data, and manuscript draft. All authors approved the final version for publication.

**ACKNOWLEDGMENT**

The authors thank Carl Pihl for primary data collection in the Stockholm cohort and doctors and nurses at all 3 sites for providing clinical data on their patients.

**STUDY FUNDING**

No targeted funding reported.

**DISCLOSURE**

J. Salzer has received lecture honoraria from BiogenIdec, Teva Pharmaceuticals, and Genzyme/Sanofi, has received travel support from BiogenIdec, and has received research support from Synapsys. R. Stenningsson and P. Alping report no disclosures relevant to the manuscript. L. Novakova has received travel support and/or lecture honoraria from Biogen and Novartis and unconditional research grant from Biogen. A. Björk reports no disclosures relevant to the manuscript. K. Fink has received an unrestricted research grant from Biogen. P. Isak-Jacobsson reports no disclosures relevant to the manuscript. C. Malmström has received lecture honoraria and had travel expenses partially reimbursed from Biogen, Merck-Serono, and Novartis. He has received a nonconditional research grant from Biogen and served on advisory boards for Biogen, Novartis, and Roche. M. Auksoon has received travel support and/or lecture and writing honoraria from Biogen, Novartis, and Genzyme/Sanofi/Aventis, has served on scientific advisory boards for Biogen, Novartis, and Genzyme/Sanofi/Aventis, and has received unconditional research grants from Biogen. M. Vågberg has received unconditional research grants from BiogenIdec AB and Neuro Sweden, has received lecture honoraria from BiogenIdec AB, has received travel grants from BiogenIdec AB, Novartis, and Baxter Medical AB, has received writing honoraria from Pharma Industry and BestPractice Multiple Sclerosis. P. Sandstrom has received honoraria from Biogen for serving as a member of a stipend committee. J. Lycke has received travel support and/or lecture honoraria from Biogen, Novartis, Teva, and Genzyme/Sanofi/Aventis, has received travel support and/or lecture honoraria from Biogen, Novartis, Teva, and Genzyme/Sanofi/Aventis, has received honoraria from Genzyme/Sanofi/Aventis for serving as an investigator, and has served as a member of the Biogen advisory board.

J. Selmaj has received research support from BiogenIdec, Genzyme/Sanofi, and Teva Pharmaceuticals and has received travel support from BiogenIdec and Genzyme/Sanofi. M. Alping has received travel support and/or lecture honoraria from Biogen, Teva Pharmaceuticals, and Genzyme/Sanofi. C. Malmström, L. Alping, J. Lycke, E. Schmeling, and M. Vågberg report no disclosures relevant to the manuscript. Individuals who served as members of the editorial boards of Neurology, Multiple Sclerosis, and Journal of Neurology, Neurosurgery, and Psychiatry report no disclosures relevant to the manuscript.

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served on scientific advisory boards for Almirall, Teva, Biogen, Novartis, and Genzyme/SanofiAventis, serves on the editorial board of Acta Neurologica Scandinavica, and has received unconditional research grants from Biogen, Novartis, and Teva. F. Piehl has received unrestricted academic research grants from Biogen and Novartis. A. Svenningsson has served on an advisory board for Sanofi-Genzyme and has received travel funding from Biogen Idec. Go to Neurology.org for full disclosures.

Received February 8, 2016. Accepted in final form June 2, 2016.

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Neurology 2016;87;2074-2081 Published Online before print October 19, 2016
DOI 10.1212/WNL.0000000000003331

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