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-modulating 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). The notion of a positive effect of anti-CD20 antibody treatment in RRMS is supported by 2 recent RCTs with 2 new antibodies:...
ocrelizumab (humanized) and ofatumumab (human). 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 (EC-TRIMS). 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. Available data from rituximab in rheumatoid arthritis indicate a high tolerability and low risks for serious opportunistic infections or secondary malignancies. Progressive multifocal leukoencephalopathy (PML) has been reported in rituximab-treated patients, but to our knowledge, no case of PML has been reported among rituximab-treated patients with multiple sclerosis (MS).

Since the publication of the HERMES1 and OLYMPUS2 trials, rituximab has been increasingly used off-label to treat MS in Sweden, in progressive MS with signs of disease activity, and in JCV-positive RRMS with active disease course.

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 (2009/2107-31/2). 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 (neuroreg.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.

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. 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 T cells, were used to follow B-cell levels.

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).

| Source | Umeå (n = 536) | Gothenburg (n = 1,559) | Stockholm (n = 3,551) |
|--------|----------------|------------------------|-----------------------|
| Ever been treated with RTX | (n = 287) | (n = 104) | (n = 454) |
| Excluded | (n = 14) | (n = 4) | (n = 6) |
| Not MS (1) | Lost to follow-up (13) | Lost to follow-up (4) | Not MS (4) Lost to follow-up (1) |
| Included | (n = 273) | (n = 100) | (n = 449) |
| Total | (n = 522) | | |

Figure 1: Flowchart of case ascertainment
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 ARR: 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 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 $-0.19\%$ (95). This was assessed in 160 patients at the Umeå University Hospital who had $\geq 2$ 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...
Figure 2  B-cell and immunoglobulin G (IgG) levels before and during rituximab treatment in multiple sclerosis cases

![Diagram showing B-cell and IgG levels with data points and lines indicating levels before and during rituximab treatment.]

B-cell and IgG levels at samplings immediately before rituximab infusions 1–12. The numbers of cases used to estimate the means and SDs are shown below the figure for IgG (top row) and B cells (lower row). aAt Umeå Hospital and Sahlgrenska University Hospital, the B-cell levels are shown as mean percentage of CD19⁺ cells within the CD45⁺ cell population. bAt the Karolinska University Hospital, the B-cell levels are shown as mean absolute numbers (×10⁶) of CD19⁺ cells/mL blood. cInfusions 8–12 were merged due to few cases.

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 RMS may be expected to experience one relapse every 23rd year. This is low compared with 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

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).

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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

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**Figure 3** Radiologic and clinical disease activity over time, and by disease subtype, in 822 rituximab-treated Swedish patients with multiple sclerosis (MS)

The percentage of MRIs with contrast-enhancing lesions (CELs, left y-axis, blue bars), as well as the annualized relapse rate (right y-axis, green bars), for patients with MS treated with rituximab, by time period after rituximab treatment initiation, or MS subtype (x-axis). The numbers of patients at risk were calculated as the number of patients entering each time period. The person-time variable was calculated as number of years from treatment initiation to data censure, or 12 months after last infusion in case of treatment discontinuation, whichever came first. ARR = annualized relapse rate; PPMS = primary progressive multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis.
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.

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