Reduced inflammation in relapsing-remitting multiple sclerosis after therapy switch to rituximab

Pierre de Flon, MD
Martin Gunnarsson, MD, PhD
Katarina Laurell, MD, PhD
Lars Söderström, MSc
Richard Birgander, MD, PhD
Thomas Lindqvist, MD
Wolfgang Krauss, MD
Ann Dring, PhD
Joakim Bergman, MSc
Peter Sundström, MD, PhD
Anders Svenningsson, MD, PhD

Correspondence to Dr. de Flon: pierre.deflon@regionjh.se

ABSTRACT

Objective: To describe the effects of switching treatment from ongoing first-line injectable therapies to rituximab on inflammatory activity measured by MRI and levels of CSF neurofilament light chain (CSF-NFL) in a cohort of patients with clinically stable relapsing-remitting multiple sclerosis (RRMS).

Method: Seventy-five patients with clinically stable RRMS treated with the first-line injectables interferon-β (IFN-β) and glatiramer acetate (GA) at 3 Swedish centers were switched to rituximab in this open-label phase II multicenter study. After a run-in period of 3 months, 2 IV doses of 1,000 mg rituximab were given 2 weeks apart followed by repeated clinical assessment, MRI, and CSF-NFL for 24 months.

Results: The mean cumulated number of gadolinium-enhancing lesions per patient at months 3 and 6 after treatment shift to rituximab was reduced compared to the run-in period (0.028 vs 0.36, $p = 0.029$). During the first year after treatment shift, the mean number of new or enlarged T2 lesions per patient was reduced (0.01 vs 0.28, $p = 0.004$) and mean CSF-NFL levels were reduced by 21% ($p = 0.01$).

Conclusions: For patients with RRMS, a treatment switch from IFN or GA to rituximab is associated with reduced inflammatory activity measured by MRI and CSF-NFL.

Classification of evidence: This study provides Class IV evidence that rituximab has an equal or superior effect in reducing inflammatory activity in RRMS measured by MRI and CSF-NFL compared to first-line injectables during the first year after treatment shift. *Neurology®* 2016;87:141–147

GLOSSARY

AE = adverse events; **CSF-NFL** = CSF levels of neurofilament light chain; **GA** = glatiramer acetate; **Gd+** = gadolinium-enhancing; **IFN** = interferon; **MS** = multiple sclerosis; **PML** = progressive multifocal leukoencephalopathy; **RRMS** = relapsing-remitting multiple sclerosis; **SAE** = serious adverse events; **TE** = echo time; **TI** = inversion time; **TR** = repetition time.

Multiple sclerosis (MS) is an autoimmune disease presenting with a broad spectrum of neurologic deficits due to inflammatory induced nerve damage in the CNS.[1] Both T and B lymphocytes play important roles in the pathogenesis of MS and are potential treatment targets. The role of the B cells in the inflammatory process of MS is not fully understood.[2] Over the last decade, a large number of disease-modifying drugs have been approved. Differences in efficacy, risk profile, side effects, and treatment costs contribute to the rationale for treatment decisions.[3] With the increasing number of therapeutic alternatives and the ongoing discussion of therapeutic objectives and the possibility to achieve no evidence of inflammation comes a growing need for evaluation of treatment effect.[4] Regular clinical assessments are preferably accompanied by MRI investigations to detect relevant subclinical inflammation.[5,6] Biochemical markers such as CSF levels of neurofilament light chain (CSF-NFL) are being explored for the same purpose.[7]

Rituximab, an anti-CD20 monoclonal antibody depleting B lymphocytes, has been widely used in the treatment of rheumatoid arthritis and hematologic malignancies, providing long-term

From the Department of Pharmacology and Clinical Neuroscience, Unit of Neurology, Östersund (P.d.F., K.L.), Umeå University; Department of Radiation Sciences, Diagnostic Radiology (R.B., T.L.), and Department of Pharmacology and Clinical Neuroscience (A.D., J.B., P.S., A.S.), Umeå University; Department of Neurology, School of Medical Sciences (M.G.), Department of Radiology (W.K.), Faculty of Medicine and Health, Örebro University; Unit of Research, Education and Development (L.S.), Region Jämtland Härjedalen; and Department of Clinical Sciences (A.S.), Danderyd Hospital, Karolinska Institutet, Stockholm, Sweden.

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experience of both patient convenience and safety with long-term follow-up.[8] Rituximab has also been explored in MS, but effect data are limited.[9] In the Helping to Evaluate Rituxan in Relapsing-Remitting Multiple Sclerosis (HERMES) trial, gadolinium-enhancing lesions (Gd+) on MRI were significantly reduced.[10] The efficacy of anti-CD20 therapy is now being further exploited by new compounds such as ocrelizumab[11] and ofatumumab.[12]

The primary objective of this open-label multicenter phase II trial was to study safety and efficacy in reducing inflammatory activity upon switch from injectable first-line treatments to rituximab in patients with clinically stable relapsing-remitting MS (RRMS). Inflammatory activity was evaluated by the presence of Gd+ lesions and the development of new or enlarging T2 lesions and by CSF-NFL levels.

METHODS

Standard protocol approvals, registrations, and patient consents. The Ethics Committee in Umeå approved the study (2010-315-31M), which was registered at EU Clinical Trial Register with EudraCT (2010-023012-38). Written informed consent was obtained from each patient.

Study population. Main inclusion criteria were age 18–55 years, diagnosis of RRMS or clinically isolated syndrome according to published criteria,[13] ongoing treatment with any of the first-line injectables available at the time of inclusion (i.e., interferon [IFN] or glatiramer acetate [GA]) for at least 6 months, and no evidence of clinical relapse or worsening during the last 6 months prior to inclusion. Exclusion criteria were secondary progressive MS, contraindications or noncompliance for lumbar puncture or MRI, documented vulnerability for infections, simultaneous treatment with immunosuppressant drugs, pregnancy or lactation, or severe psychiatric illness.

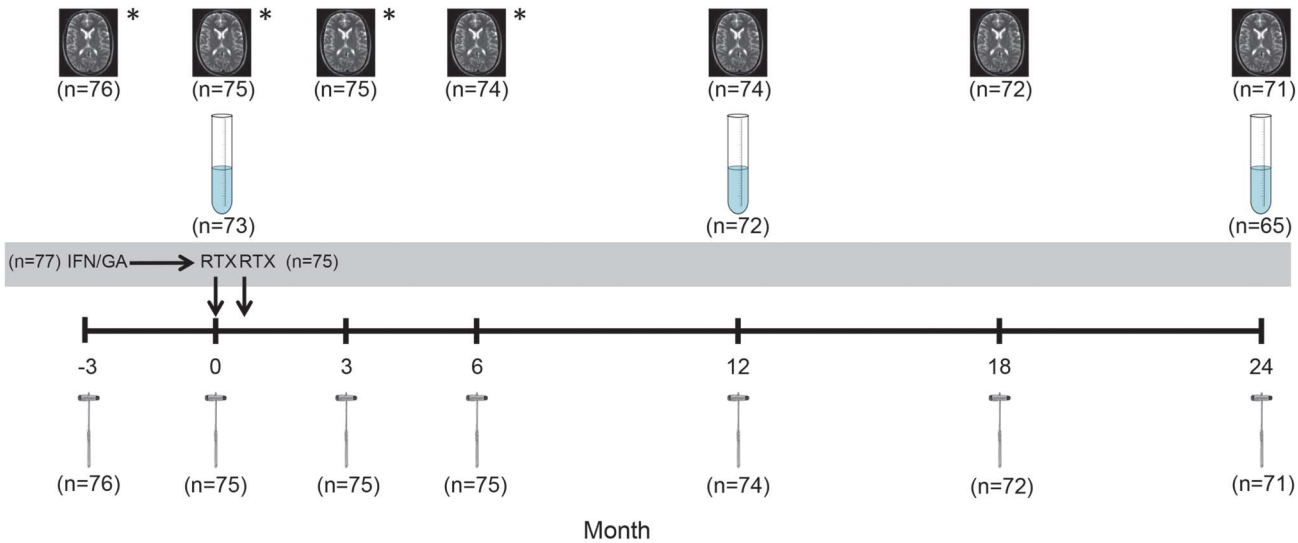
In order to avoid selection bias, the study population was identified from the Swedish MS Registry. All patients with RRMS treated with any of the available injectable first-line therapies registered at each participating center (Departments of Neurology in Umeå, Örebro, and Östersund, Sweden) were identified and randomly screened for inclusion in the study in a predetermined order.

Inclusion was begun in November 2011 and the last patient completed follow-up in March 2015.

Study design and outcome measures. This was a prospective, open-label, phase II, multicenter study. After a run-in period of 3 months with unchanged ongoing treatment with first-line injectables, therapy was shifted to rituximab (Mabthera; Roche AB, Stockholm, Sweden) without any intervening washout period. The patients were then followed clinically and by MRI for a period of 24 months according to the study protocol (figure 1). The 2 co–primary endpoints were the difference in mean number of Gd+ MRI lesions per patient calculated on the run-in examinations at month −3 and 0 compared with the examinations performed at months 3 and 6 and the change in mean CSF levels of NFL before and 1 year after rituximab treatment. Secondary endpoints were quality of life and health economic consequences from the treatment shift. Tertiary endpoints constituted the need for retreatment within the study as well as a number of additional MRI endpoints, one of which was the numbers of new and enlarged T2 lesions at time 0, 12, and 24 months. The study was determined to provide Class IV evidence for all listed research questions.

Study procedures. ***Treatment within the study.*** Patients continued treatment with their ongoing therapy during the run-in period and then switched to rituximab. The initial injection therapy was terminated at the time of the switch. Two doses of rituximab (1,000 mg IV) were given 2 weeks apart. Further doses

Figure 1 Study design and overview of completed events in the STRIX-MS study



The reflex hammer indicates timing of clinical assessment and the sample tubes the timing of lumbar puncture. *MRI performed with double dose contrast. The number of patients completing each event is shown in parentheses. GA = glatiramer acetate; IFN = interferon-β; RTX = treatment with rituximab 1,000 mg IV.

of rituximab or changes of treatment were given according to predetermined criteria of insufficient treatment effect, defined as the occurrence of clinical relapse or one or more Gd+ lesions on MRI performed with standard dose contrast or 2 or more new T2 lesions on MRI. If the patient met the criteria for insufficient treatment effect within the first year following switch to rituximab, it was classified as treatment failure. The patient was offered return to earlier injectable therapy or an alternative treatment regimen. If inflammatory activity as defined above occurred during the second year, the patient received a retreatment with 1,000 mg rituximab IV.

Clinical and laboratory assessment. Clinical assessment, including evaluation of relapses, Expanded Disability Status Scale grading, a number of functional and patient-reported outcome scales, and monitoring of adverse events (AE), was performed every 3 months during the run-in period and for the first 6 months after therapy switch, then every 6 months during the remaining study period. These assessments were done unblinded.

Laboratory assessment with blood cell count, differential count, liver function (aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase), thyroid function, and creatinine levels were assessed at the same occasion as clinical assessments. Samples for flow cytometry were collected before treatment switch, every 6 months during the study period. Samples for serum and CSF electrophoresis were collected at the time for lumbar punctures.

MRI. The Västerbotten and Jämtland populations were examined with an 8-channel head coil in a 3T Achieva system (Philips Healthcare, Best, the Netherlands) with the local standard clinical MS protocol including an axial T2-weighted sequence (repetition time [TR] 4,093 ms, echo time [TE] 80 ms, 3-mm slice thickness without intersecting gap, acquisition matrix 608 × 486), a sagittal 1.2-mm isotropic fat-suppressed fluid-attenuated inversion recovery (FLAIR) volume (TR 8,000 ms, TE 334 ms, inversion time [TI] 2,400 ms, acquisition matrix 228 × 226), and a sagittal 1-mm T1-weighted turbo field-echo volume with 0.72 × 0.72 mm in-plane resolution (TR 10.6 ms, TE 5.1 ms, acquisition matrix 348 × 322). The Örebro population was examined with an 8-channel head coil in a 1.5T Achieva system (Philips Healthcare) with the local standard clinical MS protocol including an axial T2-weighted turbo spin-echo sequence (TR 9,784 ms, TE 110 ms, 3-mm slice thickness with 0.3-mm intersecting gap, acquisition matrix 352 × 264), an axial FLAIR (TR 11,000 ms, TE 140 ms, TI 2,800 ms, 3-mm slice thickness with 0.3 mm intersecting gap, acquisition matrix 272 × 198), a sagittal FLAIR (TR 11,000 ms, TE 140 ms, TI 2,800 ms, 5-mm slice thickness with 0.5-mm intersecting gap, acquisition matrix 272 × 189), and an axial T1-weighted spin-echo (TR 475 ms, TE 12 ms, 3-mm slice thickness with 0.3-mm intersecting gap, acquisition matrix 224 × 168).

In all patients, the sequences were obtained after IV contrast administration (Magnevist; Bayer, Leverkusen, Germany). In the first 4 investigations, a double dose of contrast was used to enhance the sensitivity for detection of inflammatory activity.[14] During the trial, all MRI data were analyzed unblinded for safety monitoring and detection of treatment failure. After closing of the trial, 2 experienced senior neuroradiologists performed an independent blinded reassessment of the MRI data, displaying a 100% inter-rater agreement.

Lumbar puncture was performed immediately prior to therapy switch and 12 and 24 months thereafter. CSF was collected, according to internationally accepted guidelines, in 10 mL polypropylene tubes (Sarstedt, Nümbrecht, Germany), immediately put on ice, and centrifuged at 400*g* for 10 minutes.[15] The supernatant was dispensed into 9 aliquots of 1 mL in 1.5 mL polypropylene screw-cap tubes (Sarstedt) and stored at −80°C. NFL levels were measured using NFL enzymatic immunoassay (UmanDiagnostics, Umeå, Sweden) according to manufacturer's instructions. The NFL assays were conducted blinded to the clinical and radiologic data.

Statistical analyses. The sample size was calculated using data from published studies regarding comparable treatment effects on Gd+ lesions and NFL levels.[16] From these data, we estimate detecting a 40% difference with a power of 80% with a sample size of 70 individuals. For analysis of power on CSF-NFL data before and after change of treatment, we used data from studies on treatment shift from first-line injectables to natalizumab.[7] We then assumed a mean level of NFL being 850 ng/L before treatment change and an SD in this population to be 700, which will result in a power of 80% to detect a difference of 40% between the groups before and after treatment shift. Characteristics are presented as means ± SEM. Differences were tested by paired *t* test or Wilcoxon signed-rank test as appropriate. All statistics were done as 2-sided tests on 5% level of significance.

RESULTS

Patients. After screening of 175 patients, 77 fulfilled the inclusion criteria and provided informed consent for the study (for demographics, see the table). Two patients were unwilling to comply with the protocol after inclusion and were therefore excluded before therapy switch, and thus 75 patients received rituximab treatment according to protocol.

Four of the treated patients did not comply with the protocol during follow-up. In total, 71 patients completed all clinical and radiologic assessments during the study period of 24 months. Six patients chose not to undergo the final lumbar puncture (figure 1).

Clinical assessment. One patient reported a clinical relapse expressed as an optic neuritis 5 months after therapy switch. An independent ophthalmologist confirmed the diagnosis. No new lesions were seen on the MRI scan. Therapy was switched to natalizumab and the patient was followed according to study protocol without any further signs of inflammatory activity.

Four patients fulfilled the criteria for inflammatory activity during the second year after therapy switch. One patient reported a clinical relapse and all 4

Table Baseline characteristics of participants

Characteristics	Values
F/M, n (%)	52/25 (68/32)
Age, y, median (range)	41 (21–53)
Duration of disease, y, median (range)	7 (1–38)
Expanded Disability Status Scale, median (range)	1.5 (0–5)
Treatment at inclusion, no. (%) patients	
Interferon-β	66 (86)
Glatiramer acetate	11 (14)

fulfilled the MRI criteria and received repeated treatment with rituximab according to protocol.

The treatment was well-tolerated, with light to moderate infusion reactions being the most common side effect. Laboratory monitoring did not reveal any significant abnormalities. Six serious AE (SAE) were documented. Three of these were assessed as possibly related: 2 cases of pyelonephritis and 1 case of influenza. All required hospitalization and were followed by full recovery. The other 3 SAE, evaluated as nonrelated to study drug, were stroke, cholangitis, and suicidal attempt with intoxication. The stroke case presented as acute onset of left arm and facial paresis, improved by IV thrombolysis, and showed typical features of acute ischemic lesion in the thalamus on MRI diffusion-weighted images and apparent diffusion coefficient maps. The neurologic symptoms recovered fully within 1 month but the patient experienced increased fatigue after this episode. There were in total 17 non-serious AEs related or possibly related to the study drug comprising either infections or infusion-related events.

MRI activity. Seventy-two patients had valid data for analysis of Gd+ lesions. Ten patients had Gd+ lesions on MRI during the run-in period. None of them had any Gd+ lesions after treatment. Out of the 62 patients who had no Gd+ lesion in the run-in period, 2 had Gd+ lesions on MRI performed with double-dose contrast during the first 6 months after treatment. When MRI was repeated with standard dose contrast in those 2 patients, neither of them had any lesion and thus did not fulfill the criteria for treatment failure. The overall mean (±SEM) number of Gd+ lesions per patient dropped from 0.37 (±0.147) before treatment shift to 0.03 (±0.020) at the 6-month period after rituximab treatment ($p = 0.029$), which constituted the primary MRI endpoint of the study (figure 2A).

Seventy-four patients had valid data for evaluation of new or enlarged T2 lesions at month 0 and 12 and 71 patients for month 24. The mean number of new or enlarged T2 lesions per patient was significantly reduced ($p = 0.004$) from the baseline scan (0.28 ± 0.089) to the follow-up scan during at 12 months (0.01 ± 0.014). At month 24, there was a recurrence of MRI activity indicating a waning of effect of the rituximab treatment (figure 2B).

Neurofilament levels. Seventy patients had valid data from lumbar puncture at baseline and 1 year after treatment. Mean CSF-NFL levels (±SEM) dropped from 491 ng/L (±53.5) before to 387 ng/L (±39.4) 12 months after the therapy switch ($p = 0.010$) (figure 3).

Sixty-three patients had valid data from all 3 lumbar punctures. After 24 months, the CSF-NFL levels had increased to a mean of 418 ng/L (±43.6), not statistically significantly different from the baseline value.

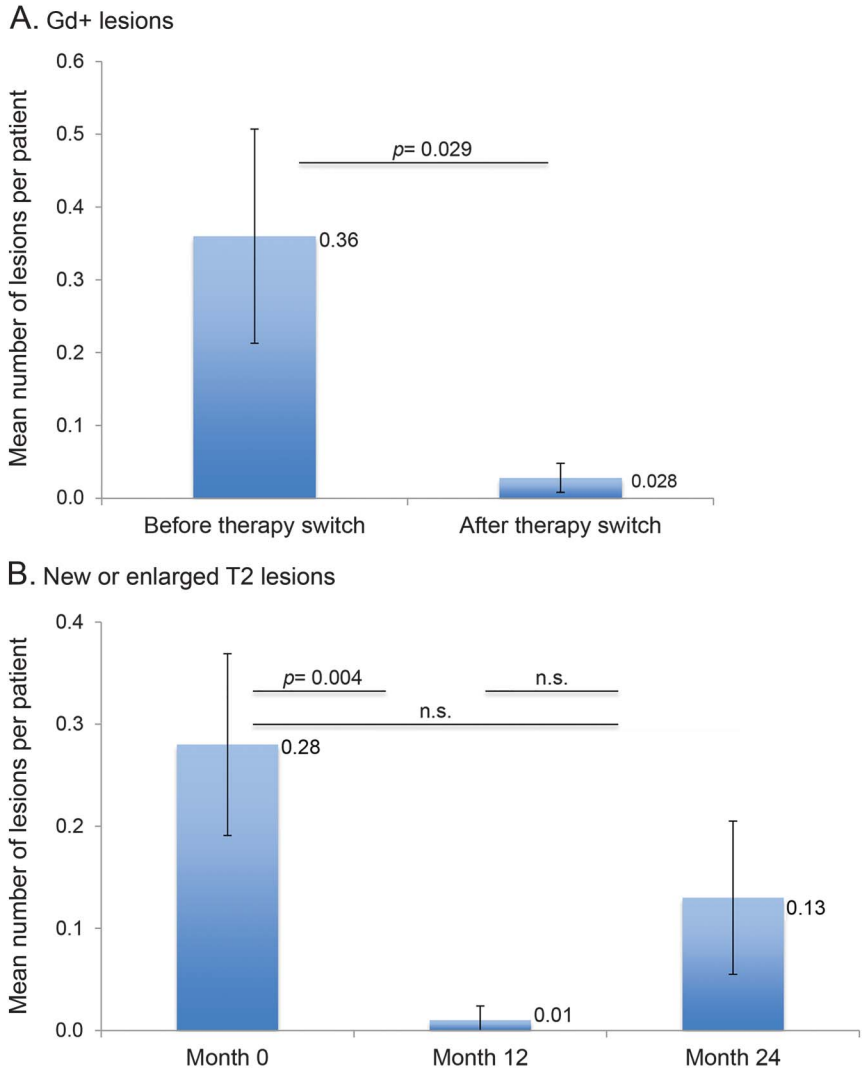
DISCUSSION In this study, we showed that switching treatment in clinically stable patients with RRMS from first-line injectables to rituximab was followed by an equal or superior control of MRI-based inflammatory activity during the subsequent year. Furthermore, there was a significant reduction in the CSF levels of the axonal injury marker NFL after therapy switch, indicating that rituximab treatment may yield a better protection from irreversible CNS damage than IFN/GA.[17] Only 1 of the 75 rituximab-treated patients fulfilled the predefined criteria of treatment failure during the first year after treatment switch and therefore changed to a different therapy.

Anti-CD20 therapy is effective in preventing inflammatory activity in MS, but so far only demonstrated in phase 2 settings with MRI measures as the primary endpoint.[10–12,18] Although our study population had low inflammatory activity at onset of the study, we could still document a significant reduction in both Gd+ and new T2 lesions upon treatment shift from IFN or GA to rituximab. Our data are therefore in line with the observations from the ocrelizumab study that suggested anti-CD20 treatment in monotherapy being superior to IFN treatment.[11]

Immunomodulatory drugs with potent anti-inflammatory effect in RRMS also reduce the level of CSF-NFL when compared with less effective treatments[7] or placebo.[19] Likewise, in the present group of clinically stable patients on first-line injectables, there was a significant reduction in the levels of NFL in the CSF 12 months after treatment shift to rituximab. Since CSF-NFL levels tend to increase with increasing age,[20] it is reasonable to conclude that this change does not represent a natural evolution of this marker. Considering the low inflammatory activity seen by MRI in the run-in period, it is particularly noteworthy that we were able to detect a significant reduction in CSF-NFL levels after switching to rituximab.

The optimal frequency for rituximab in order to retain efficient inflammatory control is currently unknown. A treatment course of 2 × 1,000 mg, given 2 weeks apart, conferred almost complete cessation of inflammatory activity for 48 weeks.[10] In our study, only one patient fulfilled the treatment failure criteria during the first year. However, during the second year after treatment switch, there was a clinical recurrence of inflammatory activity in 4 patients fulfilling the criteria of treatment failure. This, together with an increase, although not statistically significant, in both MRI activity and CSF-NFL levels, indicates that the protective effect from a single course of 2 × 1,000 mg rituximab lasts for more than 1, but less

Figure 2 MRI activity before and after therapy switch to rituximab



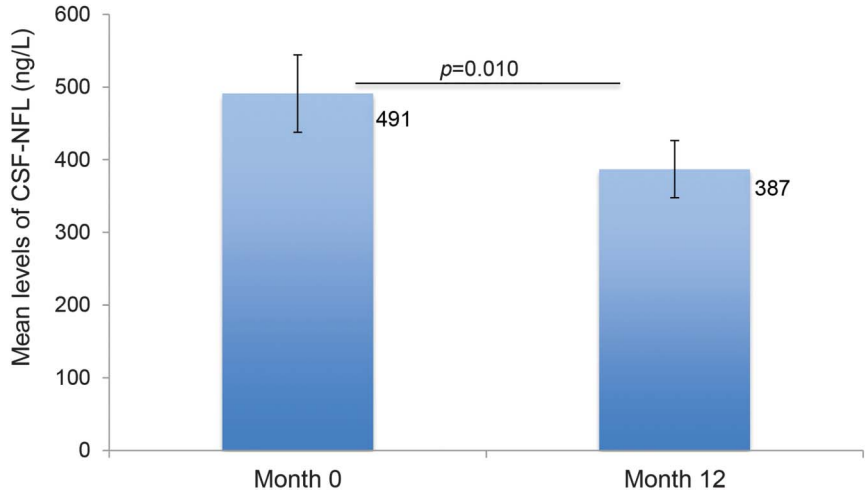
Mean number of gadolinium-enhancing (Gd+) lesions per patient before therapy during the run-in period (month −3 and 0) and the mean number after therapy switch from MRI performed at months 3 and 6. (A, B) Mean number of new or enlarged lesions on T2-weighted images. At month 0, the time from the previous MRI scans was 3 months; at months 12 and 24, the observation time was 6 months. Statistically significant differences are highlighted with *p* values depicted in the figure. Error bars represent SEM.

than 2, years. This agrees with data that describe recurrence of B cells occurring 6–12 months after depletion with rituximab.[10] The optimal dose and dosing frequency, as well as whether repeated doses of rituximab over time may induce long-term remission in MS, need to be studied further.

The long-term safety profile of rituximab is well-described in rheumatoid arthritis patient populations.[8] We found no unexpected adverse events during this study. The risk of progressive multifocal leukoencephalopathy (PML) has become a major concern in treating RRMS. To our knowledge, there is still no case of PML described with the use of rituximab in monotherapy for RRMS; however, the reporting rate of confirmed cases with rheumatoid arthritis is approximately 3 per 100,000 patients.[8]

Our study has the obvious weakness of not having a control group and thus involves a risk of evaluation biases. However, we employed great care in minimizing these kinds of errors within the framework of the chosen study design. First, we chose to study patients who were in a clinically stable phase of their disease to avoid the otherwise inevitable bias of regression to the mean. This necessitated the use of objective paraclinical measures of disease activity that could detect subclinical inflammatory activity. Second, we included a randomization step in the selection process for which patients should be asked to participate in the study. In this way we eliminated the bias of questioning only patients who for some reason were believed to be particularly suitable for treatment change. Third, we used 2 objective primary outcome measures of disease activity in the form of MRI activity

Figure 3 CSF levels of neurofilament light chain (CSF-NFL) before and after therapy switch to rituximab



Mean levels of CSF-NFL before therapy switch to rituximab (month 0) and 1 year after therapy switch (month 12). Error bars represent SEM.

and CSF-NFL levels before and after treatment shift, both of which were analyzed blinded for study-related data that could influence an objective evaluation. Both these objective measures of disease activity changed in a consistent manner after treatment switch with a recurrence of inflammatory activity during the second year, giving further support to our conclusions.

We provide Class IV evidence for equal or superior inflammatory control measured by MRI parameters and CSF-NFL during the first year when rituximab was used as an alternative to first-line injectable therapies in a realistic, real-life setting. Rituximab has a well-documented side effect profile as a generally safe medication in the setting of autoimmune disorders and therefore may confer an attractive treatment option in RRMS. Further ongoing analyses from the present study will give valuable information regarding patient-related outcome measures and health economic consequences of the investigated treatment switch.

AUTHOR CONTRIBUTIONS

Pierre de Flon participated in the design and conceptualization of the study, was principally responsible for patient management and data collection at the center in Östersund, participated in data analysis and interpretation, prepared the figures, and participated in writing and revision of the manuscript. Martin Gunnarsson participated in the design and conceptualization of the study, was principally responsible for patient management and data collection at the center in Örebro, and participated in data analysis and interpretation and in writing and revision of the manuscript. Katarina Laurell participated in data analysis and interpretation and in writing and revision of the manuscript. Lars Söderström was primarily responsible for design of the statistical analysis, participated in data analysis, and provided substantial intellectual input in revision of the manuscript. Richard Birgander participated in recording radiologic data and in writing and revision of the manuscript. Thomas Lindqvist participated in recording radiologic data and writing and revision of the manuscript. Wolfgang Krauss participated in recording and analysis of radiologic data. Ann Dring participated in data collection and analysis and interpretation of data. Joakim Bergman participated in data collection and analysis and interpretation of data. Peter Sundström participated in data collection, provided substantial input in data interpretation, and provided substantial intellectual input to manuscript revision. Anders Svenningsson was the principal investigator of the study and was principally responsible for the study design and conceptualization and patient management and data collection at the center in Umeå and participated in data analysis and interpretation and writing and reviewing the manuscript.

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DISCLOSURE

P. de Flon has served on an advisory board for BiogenIdec. M. Gunnarsson has served on an advisory board for Teva and has received travel funding and/or speaker honoraria from BiogenIdec, Novartis, Merck Serono, and Bayer Schering Pharma. K. Laurell and L. Söderström report no disclosures relevant to the manuscript. R. Birgander has received speaker honoraria from BiogenIdec on 2 occasions in 2012. T. Lindqvist, W. Krauss, A. Dring, and J. Bergman report no disclosures relevant to the manuscript. P. Sundström has received travel support to scientific meetings and honoraria for serving as a member of a stipend committee, both from BiogenIdec. A. Svenningsson has served on an advisory board for Sanofi-Genzyme and has received travel funding and/or speaker honoraria from BiogenIdec, Sanofi-Genzyme, Novartis, and Baxter Medical. Go to Neurology.org for full disclosures.

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REFERENCES

1. Compston A, Coles A. Multiple sclerosis. Lancet 2008; 372:1502–1517.
2. von Budingen HC, Palanichamy A, Lehmann-Horn K, Michel BA, Zamvil SS. Update on the autoimmune

pathology of multiple sclerosis: B-cells as disease-drivers and therapeutic targets. Eur Neurol 2015;73:238–246.
3. Piehl F. A changing treatment landscape for multiple sclerosis: challenges and opportunities. J Intern Med 2014; 275:364–381.
4. Ziemssen T, Derfuss T, de Stefano N, et al. Optimizing treatment success in multiple sclerosis. J Neurol Epub 2015 Dec 24.
5. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. Neurology 2014;83:278–286.
6. Wattjes MP, Rovira A, Miller D, et al. Evidence-based guidelines: MAGNIMS consensus guidelines on the use of MRI in multiple sclerosis: establishing disease prognosis and monitoring patients. Nat Rev Neurol 2015;11:597–606.
7. Gunnarsson M, Malmestrom C, Axelsson M, et al. Axonal damage in relapsing multiple sclerosis is markedly reduced by natalizumab. Ann Neurol 2011;69:83–89.
8. van Vollenhoven RF, Fleischmann RM, Furst DE, Lacey S, Lehane PB. Longterm safety of rituximab: final report of the rheumatoid arthritis global clinical trial program over 11 years. J Rheumatol 2015;42:1761–1766.
9. Castillo-Trivino T, Braithwaite D, Bacchetti P, Waubant E. Rituximab in relapsing and progressive forms of multiple sclerosis: a systematic review. PLoS One 2013;8:e66308.
10. Hauser SL, Waubant E, Arnold DL, et al. B-cell depletion with rituximab in relapsing-remitting multiple sclerosis. N Engl J Med 2008;358:676–688.
11. Kappos L, Li D, Calabresi PA, et al. Ocrelizumab in relapsing-remitting multiple sclerosis: a phase 2, randomised, placebo-controlled, multicentre trial. The Lancet 2011;378: 1779–1787.
12. Sorensen PS, Lisby S, Grove R, et al. Safety and efficacy of ofatumumab in relapsing-remitting multiple sclerosis: a phase 2 study. Neurology 2014;82:573–581.
13. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol 2011;69:292–302.
14. Gasperini C, Paolillo A, Rovaris M, et al. A comparison of the sensitivity of MRI after double- and triple-dose Gd-DTPA for detecting enhancing lesions in multiple sclerosis. Magn Reson Imaging 2000;18:761–763.
15. Teunissen CE, Petzold A, Bennett JL, et al. A consensus protocol for the standardization of cerebrospinal fluid collection and biobanking. Neurology 2009;73:1914–1922.
16. Cohen JA, Barkhof F, Comi G, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. N Engl J Med 2010;362:402–415.
17. Salzer J, Svenningsson A, Sundstrom P. Neurofilament light as a prognostic marker in multiple sclerosis. Mult Scler 2010;16:287–292.
18. Naismith RT, Piccio L, Lyons JA, et al. Rituximab add-on therapy for breakthrough relapsing multiple sclerosis: a 52-week phase II trial. Neurology 2010;74:1860–1867.
19. Kuhle J, Disanto G, Lorscheider J, et al. Fingolimod and CSF neurofilament light chain levels in relapsing-remitting multiple sclerosis. Neurology 2015;84:1639–1643.
20. Vagberg M, Norgren N, Dring A, et al. Levels and age dependency of neurofilament light and glial fibrillary acidic protein in healthy individuals and their relation to the brain parenchymal fraction. PLoS One 2015;10:e0135886.

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Alice in Wonderland syndrome: A systematic review (see the June 2016 issue of *Neurology*® *Clinical Practice*)

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