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Original Research Paper

Improved treatment satisfaction after switching therapy to rituximab in relapsing–remitting MS

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Abstract

Objective: New disease-modifying treatment strategies in multiple sclerosis offer possibilities for individualised treatment. In this study, we evaluated patient-reported outcome measures before and after a switch in therapy from first-line injectable treatments to rituximab.

Method: A total of 75 patients with clinically stable relapsing–remitting multiple sclerosis (RRMS) receiving ongoing first-line injectable treatment at three Swedish centres had their treatment switched to rituximab in this open-label phase II multicentre study. Assessment of treatment satisfaction, patient-perceived impact of the disease on daily life, fatigue, cognitive symptoms and disease progression was performed 3 months before and at the time of the treatment shift and then for a subsequent 2-year period.

Results: The overall treatment satisfaction rating improved significantly from a mean of 4.8 (scale range: 1–7), while on injectable therapies, to a mean of 6.3 after 1 year of rituximab treatment ($p < 0.001$). This improvement was sustained after 2 years. There was no significant change in scores for patient-perceived impact of disease, fatigue or disease progression.

Conclusion: A shift in therapy from first-line injectables to rituximab in a cohort of clinically stable RRMS patients was followed by improved treatment satisfaction. This is clinically relevant as it may influence long-term adherence to immunomodulating therapy.

Keywords: Multiple sclerosis, rituximab, B-cell depletion therapy, treatment satisfaction, patient-reported outcome measures, clinical trial

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Introduction

Multiple sclerosis (MS) is an inflammatory disease affecting the central nervous system (CNS) causing neurological deficit.[1] In the last two decades, injectable disease-modifying therapies (iDMTs), that is, interferon-beta (IFN-beta) and glatiramer acetate (GA) have been the main first-line therapies in relapsing–remitting multiple sclerosis (RRMS). During recent years, an increasing number of new multiple sclerosis (MS) treatments have come onto the market, each with a unique profile regarding mechanism of action, efficacy, side effects as well as routines and routes of administration and safety.[2,3] In addition to the disease-modifying effect, the outcome of MS treatment is dependent on the patient's compliance and long-term adherence to therapy.[4–6] Differences in definitions of adherence complicate comparisons between studies, but in MS, the overall adherence rate to injection therapies varies between 41% and 88%.[5] A comprehensive understanding of the various factors affecting adherence is valuable when making clinical treatment decisions, which is well described for IFN-beta and GA.[7,8] The increasing number of new treatment options emphasises the need for knowledge about patient-reported outcome measures (PROMs), in addition to efficacy and risks, in order to make treatment decisions in concordance with the patient.[9]

Rituximab, a monoclonal antibody that depletes B-lymphocytes by targeting the CD20 surface antigen, is administered as intravenous infusions, most commonly at 6- to 12-month intervals when used as treatment for MS today. The disease-modifying effect of rituximab in RRMS has been demonstrated in several studies,[10,11] including our own Switch-To-RituXimab-in MS (STRIX-MS) trial.[12] The objective

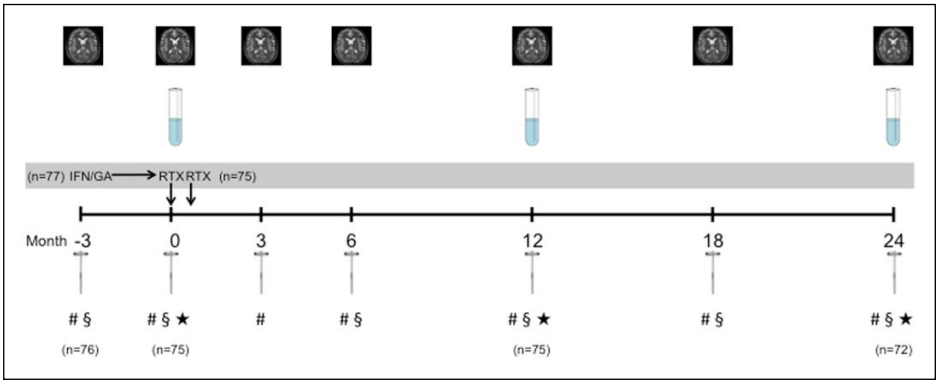


Figure 1. MRI pictures indicate timings for MRI investigations. Test tubes indicate timings for lumbar punctures. The reflex hammers indicate timings for clinical visits, and the symbols indicate timings for evaluation of different PROMs (#EDSS; §MSIS-29, FSMC and SDMT and ★TSQM-10). The numbers in brackets indicate the number of patients seen at different points in time.
IFN: interferon-beta; GA: glatiramer acetate; RTX: Rituximab 1000 mg.

of this study was to analyse PROMs and disability development after the therapy switch to rituximab in the STRIX-MS trial.

Method

Ethics and regulatory statement

This study was approved by the Ethics Committee in Umeå (Dnr 2010-315-31M) and registered in the European Union (EU) Clinical Trials Register with EudraCT number 2010-023012-38. Written informed consent was obtained from each patient.

Study population

The main inclusion criteria were age 18–55 years, diagnosis of RRMS or clinically isolated syndrome (CIS) according to the McDonald criteria[13] and ongoing treatment with IFN-beta or GA for at least 6 months with no clinical relapse or disease progression during the 6 months prior to inclusion. Exclusion criteria were secondary progressive MS, contraindications or non-compliance for lumbar puncture and/or magnetic resonance imaging (MRI), documented vulnerability to infections, simultaneous treatment with immunosuppressant drugs, pregnancy or lactation or severe psychiatric illness.

Patients fulfilling the inclusion criteria were identified by searching the Swedish MS registry at participating centres without knowing patient identification. Each centre had an estimated coverage in the registry of over 90% of the target population, that is, patients with RRMS with ongoing treatment with iDMT. Eligible patients were screened for inclusion in the study according to a predetermined algorithm. The inclusion period began in November 2011, and the last follow-up visit was completed in March 2015.

A total of 175 patients were screened for inclusion; out of whom, 63 did not fulfil all the inclusion criteria, 28 declared unwillingness to comply with the study protocol and 7 were planning for pregnancy. The inclusion process was closed when 77 patients were accepted for inclusion according to the power calculation performed for the trial. Two patients withdrew their consent before treatment was switched; thus, a final sample of 75 patients made the treatment switch, all of whom were available for follow-up at month 12. At month 24, another three patients had terminated the trial due to pregnancy ($n=1$), planning for pregnancy ($n=1$) and a request for earlier rituximab treatment than specified by the protocol ($n=1$). For one patient, the Symbol Digits Modalities Test (SDMT) and Fatigue Scale for Motor and Cognitive functions (FSMC) results at month 0 were missing due to administrative failure.

Study design

This was a prospective, open-label multicentre study. After a run-in period of 3 months with unchanged injection therapy, treatment was shifted to rituximab (Mabthera®; Roche AB, Stockholm, Sweden), and the patients were followed up through regular clinical visits, MRI and lumbar punctures for a period of 24 months (Figure 1). The results of the MRI and cerebrospinal fluid (CSF) analysis, being the primary outcome measures of the STRIX trial, are presented in an earlier publication[12] and will not be further discussed in this article. Patients from Östersund performed all

Table 1. Clinical and patient-reported outcome measures in the STRIX study.

Parameter	PROM	Reference
Treatment satisfaction	TSQM-10 (Treatment Satisfaction Questionnaire for Medicine)	Atkinson et al.[16] and Bharmal et al.[17]
Perceived impact of disease on daily life	MSIS-29 (Multiple Sclerosis Impact Scale)	Hobart et al.[18]
Fatigue	FSMC (Fatigue Scale for Motor and Cognitive functions)	Penner et al.[19]
Cognitive performance	SDMT (Symbol Digits Modalities Test)	Van Schependom et al.[20]
Neurologic impairment	EDSS (Expanded Disability Status Scale)	Kurtzke[14] and Meyer-Moock et al.[15]

STRIX: Switch-To-RituXimab, PROM: patient-reported outcome measure.

MRI and CSF procedures at the centre in Umeå. Clinical visits included evaluation of relapses, disability according to the Expanded Disability Status Scale (EDSS),[14,15] SDMT, adverse events and PROMs at time points indicated in Figure 1. Patients were reimbursed for all costs exceeding clinical routine, except for possible loss of income.

Treatment within the study

Two doses of rituximab (1000 mg intravenous (IV)) were given 2 weeks apart. Further doses of rituximab or changes in treatment were administered according to predetermined criteria for insufficient treatment effect defined as the occurrence of a clinical relapse or the occurrence of one or more Gd+ lesions on MRI performed with standard dose contrast or two or more new T2 lesions on MRI compared with the last performed investigation. If a patient met the criteria for insufficient treatment effect within the first year following the switch to rituximab, this was classified as treatment failure, and the patient was offered to switch back to earlier injectable therapy or an alternative treatment regimen. If inflammatory activity occurred during the second year, the patient received a re-treatment with 1000 mg rituximab IV.

Outcome measures

A summary of the PROMs and disability measures used in this study are presented in Table 1.

Treatment satisfaction was evaluated using the Treatment Satisfaction Questionnaire for Medicine (TSQM).[16] We used the modified form TSQM-9[17] supplemented with one question on side effects as applied by the Swedish MS Registry (TSQM-10). The questionnaire is shown in detail in Figure 2. We evaluated the individual questions, the total score of questions 1–9 (maximum of 59) and the 'global satisfaction' rating (question 10) separately. Higher scores indicate greater satisfaction. Questions 1–7 and the 'global satisfaction' rating had a maximum score of 7, while questions 8–9 had a maximum score of 5.

Perceived impact of the disease on daily living was assessed using the Multiple Sclerosis Impact Scale (MSIS-29)[18] with the results presented separately for the physical and psychological subscales.[21] High points indicate high impact of the disease on daily life.

Fatigue was assessed using the FSMC.[19] The results are expressed as a total score. Higher scores indicate more severe fatigue.

Cognitive performance was evaluated using the SDMT.[20] Values for all outcome measures are presented as at the time before therapy switch and at 1 and 2 years thereafter as an intention-to-treat (ITT) analysis.

Statistics

Descriptive statistics were reported for all variables with calculation of mean values, median values, standard deviation (SD) and range. Missing values were not replaced.

The Wilcoxon signed-rank test was used to test paired significance between the separate time points. In order to compensate for multiple testing, an overall level of significance $p < 0.01$ was used in accordance with Bonferroni.

Results

In the final study population of 75 patients, the mean (SD) age was 41.1 (8.1) years, and the mean duration of MS was 9.5 (6.8) years, with gender distribution as expected (F/M: $n = 52/25$) (for demographics, see Table 2).

TSQM-10 (Treatment Satisfaction Questionnaire)

Take some time to think through how satisfied or dissatisfied you are with the medication you are taking at the moment. We are interested in your assessment of the medicine effectiveness, side effects and how easy or difficult it has been to take your medication in the last 2 - 3 weeks or since you last took it or received it in the hospital. Please select the option that most closely reflects your experiences.

1. How satisfied or dissatisfied are you with the medicine's ability to prevent or treat your condition?

1. Extremely dissatisfied
2. Very dissatisfied
3. Dissatisfied
4. Somewhat satisfied
5. Satisfied
6. Very satisfied
7. Extremely satisfied

2. How satisfied or dissatisfied are you with the way the medicine relieves your symptoms?

1. Extremely dissatisfied
2. Very dissatisfied
3. Dissatisfied
4. Somewhat satisfied
5. Satisfied
6. Very satisfied
7. Extremely satisfied

3. How satisfied or dissatisfied are you with the time it takes for the medicine to start working?

1. Extremely dissatisfied
2. Very dissatisfied
3. Dissatisfied
4. Somewhat satisfied
5. Satisfied
6. Very satisfied
7. Extremely satisfied

4. How easy or difficult is it to use the medication in its current form?

1. Extremely difficult
2. Very difficult
3. Difficult
4. Quite easy
5. Easy
6. Very easy
7. Extremely easy

5. How easy or difficult it is to plan every time you have to take the medicine?

1. Extremely difficult
2. Very difficult
3. Difficult
4. Quite easy
5. Easy
6. Very easy
7. Extremely easy

6. How easy or difficult is it to take the medicine as directed?

1. Extremely difficult
2. Very difficult
3. Difficult
4. Quite easy
5. Easy
6. Very easy
7. Extremely easy

7. How easy or difficult is it to live with the side effects of the medicine?

1. Extremely difficult
2. Very difficult
3. Difficult
4. Quite easy
5. Easy
6. Very easy
7. Extremely easy

8. How confident are you that this medicine is suitable for you?

1. Not at all confident
2. Somewhat confident
3. Confident
4. Very confident
5. Completely confident

9. How confident are you that the positives of the medicine outweigh the negatives?

1. Not at all confident
2. Somewhat confident
3. Confident
4. Very confident
5. Completely confident

10. If you take everything into consideration, how satisfied or dissatisfied are you with this medicine?

1. Extremely dissatisfied
2. Very dissatisfied
3. Dissatisfied
4. Somewhat satisfied
5. Satisfied
6. Very satisfied
7. Extremely satisfied

Figure 2. English translation of the version of TSQM-10 used in this study.

Clinical results

One patient had a clinical relapse (optic neuritis) during the first year. Therapy was changed to natalizumab (NTZ), and the patient continued follow-up in accordance with protocol. During the second year, four patients fulfilled the criteria of inflammatory activity. Three of these were due to radiological activity at month 18 (one by Gd+ lesions, one by two new

Table 2. Patient demographics in the STRIX study.

Women/men, *n* (%)	52 (69)/23 (31)
Age at inclusion, mean (SD), years	41.1 (8.1)
Duration of disease, mean (SD), years	9.5 (6.8)
Duration of treatment, mean (SD), months	61 (40)
Min–max, months	10–172
EDSS at inclusion, median (range)	1.5 (0–5)
Treatment at inclusion, *n* (%)	
Interferon beta	65 (87%)
Glatiramer acetate	10 (13%)

STRIX: Switch-To-RituXimab, SD: standard deviation; EDSS: Expanded Disability Status Scale.

T2 lesions and one by the combination of Gd+ lesions and more than two new T2 lesions). One patient had a clinical relapse 20 months after rituximab treatment. An extra MRI at this time point revealed new T2 and Gd+ lesions. All four patients displaying inflammatory activity were treated with a repeated dose of rituximab as specified in the study protocol. EDSS did not show any statistically significant changes over the course of the study. The SDMT showed a significant ($p < 0.001$) improvement from a mean (SD) of 53.6 (12.4) to 56 (12.7) during the first year with unchanged results during the second year.

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 adverse events (SAEs) were documented. Three of these were assessed as possibly treatment related: two cases of pyelonephritis and one case of influenza, all required hospitalisation and were followed by full recovery. The other three SAEs considered as non-related to treatment were stroke, cholangitis and suicidal attempt with intoxication. There were in total 17 non-SAEs related or possibly related to the study drug comprising either infections or infection-related events.

Results of PROMs

Results for the PROMs are summarised in Table 3, and the detailed results for each sub-question in the TSQM are presented in Figure 3.

For the TSQM-10 mean (SD), the sum of the scores of questions 1–9 significantly improved from 39.4 (7.0) to 51.4 (6.0) points (see Figure 4).

The scores for all sub-questions in TSQM-10 improved significantly after the first year. The improvement was most prominent in question 4 ('How easy or difficult is it to use the medication in its current form?') and question 7 ('How easy or difficult is it to live with the side effects of the medicine?'). The 'global satisfaction' rating score improved from 4.8 (1.0) to 6.3 (0.8) at 12 months after the therapy switch (Figure 3). In all, 2 of the 75 patients lowered their 'global satisfaction' rating at month 12. For the remaining 73 patients, the 'global satisfaction' rating improved. The change in the proportions between the different 'global satisfaction' rating categories is shown in Figure 5. At month 12, while on treatment with rituximab, the fraction of patients that rated their 'global satisfaction' with treatment as 'very satisfied' or 'extremely satisfied' was 87%. This compares with 24%, while on injectables, before the therapy switch. For all questions, the mean improvement was sustained without any statistically significant changes at 24 months.

The MSIS-29 and FSMC values did not change significantly during the study.

Discussion

As far as we are aware, this is the first study to explore PROMs among MS patients treated with rituximab. In this group of clinically stable patients with RRMS, a switch from injection therapies to rituximab was followed by a significant increase in treatment satisfaction. In contrast, scores related to disease progression, fatigue or disease impact on everyday life did not improve.

Studies of patients' perception of satisfaction with their treatment are relatively rare, although satisfaction has been shown to be an independent predictor of adherence to therapy in MS[8] as well as for other diseases.[22] An earlier study using the TSQM scale to compare different iDMTs and monthly infusions of NTZ did not show any significant difference in overall treatment satisfaction, but patients treated with NTZ gave significantly higher satisfaction scores for treatment convenience.[23] A significant improvement in TSQM overall satisfaction, calculated as change in least-square mean from baseline, has been shown after switching therapy from iDMT to fingolimod.[24] The link between satisfaction and adherence is important since adherence to therapy is a prerequisite for optimal long-term treatment outcomes.[4,5]

The discrepancy found in this study between the prominent increase in patient treatment satisfaction

Table 3. Results of PROMs and disability assessments during the STRIX trial.

Variable	Month 0	Month 12	Month 24	Levels of significance
TSQM-1–9	$n=75$	$n=75$	$n=72$	
Median (min–max)	40 (24–55)	52 (33–59)	52 (34–59)	Months 0–12, $p<0.001$
Mean ± SD	39.4 ± 7.0	51.4 ± 6.0	50.8 ± 5.9	Months 0–24, $p<0.001$
TSQM-10	$n=75$	$n=75$	$n=72$	
Median (min–max)	5 (2–6)	6 (4–7)	6 (4–7)	Months 0–12, $p<0.001$
Mean ± SD	4.8 ± 1.0	6.3 ± 0.8	6.2 ± 0.8	Months 0–24, $p<0.001$
SDMT	$n=74$	$n=75$	$n=72$	
Median (min–max)	53.5 (18–84)	57 (18–90)	57 (17–86)	Months 0–12, $p<0.001$
Mean ± SD	53.6 ± 12.4	57.0 ± 12.7	56.8 ± 12.5	Months 0–24, $p<0.001$
MSIS-29 phys.	$n=75$	$n=75$	$n=72$	
Median (min–max)	1.30 (1.0–2.9)	1.25 (1.0–3.3)	1.35 (1.0–3.4)	n.s.
Mean ± SD	1.44 ± 0.48	1.43 ± 0.49	1.52 ± 0.57	
MSIS-29 psyc.	$n=75$	$n=75$	$n=72$	
Median (min–max)	1.67 (1.0–3.78)	1.56 (1.0–4.22)	1.56 (1.0–4.11)	n.s.
Mean ± SD	1.79 ± 0.70	1.66 ± 0.68	1.80 ± 0.78	
FSMC total points	$n=74$	$n=75$	$n=72$	n.s.
Median (min–max)	55 (20–96)	52 (20–94)	52 (20–95)	
Mean ± SD	52.7 ± 20.1	50.6 ± 20.3	51.8 ± 21.3	
EDSS	$n=75$	$n=75$	$n=72$	
Median (min–max)	1.5 (0–5)	1.0 (0–5)	1.25 (0–5)	n.s.
Mean ± SD	1.6 ± 1.2	1.5 ± 1.3	1.7 ± 1.4	

STRIX: Switch-To-RituXimab; PROMs: patient-reported outcome measures; TSQM: Treatment Satisfaction Questionnaire for Medicine; SDMT: Symbol Digits Modalities Test; MSIS: Multiple Sclerosis Impact Scale; FSMC: Fatigue Scale for Motor and Cognitive functions; EDSS: Expanded Disability Status Scale; SD: standard deviation.

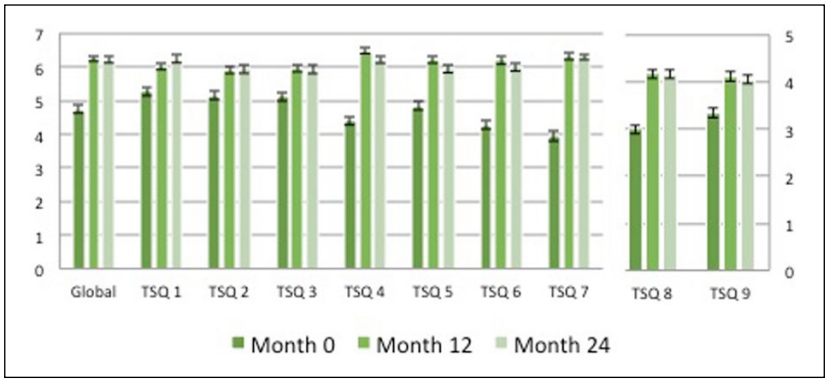


Figure 3. Mean value of TSQM sub-question scores (SEM) before the therapy switch (month 0) and 12 and 24 months thereafter (months 12 and 24). The change from months 0 to 12 and from months 0 to 24 is statistically significant ($p<0.001$) for all sub-questions.
The 'global satisfaction' rating corresponds to question 10.
Note that the scale on the left *y*-axis corresponds to the overall rating and questions 1–7 and 10 with a maximum value of 7, while the *y*-axis on the right corresponds to questions 8 and 9 with a maximum value of 5.

and the lack of clinically significant improvements in the other PROMs and functional scales is noteworthy. It may have several explanations. First, the overall low disability in the investigated population with a median EDSS of 1.5 indicates that the impact of the disease on daily life was low even at the time of treatment shift. This was confirmed by the low level of the MSIS-29 score at baseline, both physical and psychological, which does not leave room for major improvement. Likewise, the FSMC score at the time of switching to rituximab indicated low-to-moderate fatigue, which may partly explain why this PROM did

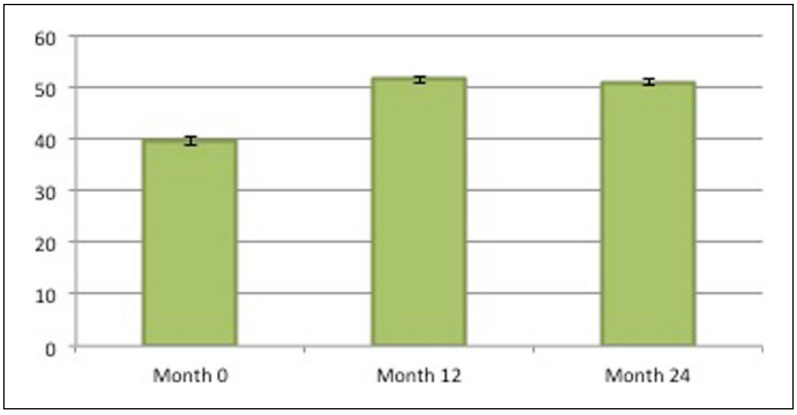
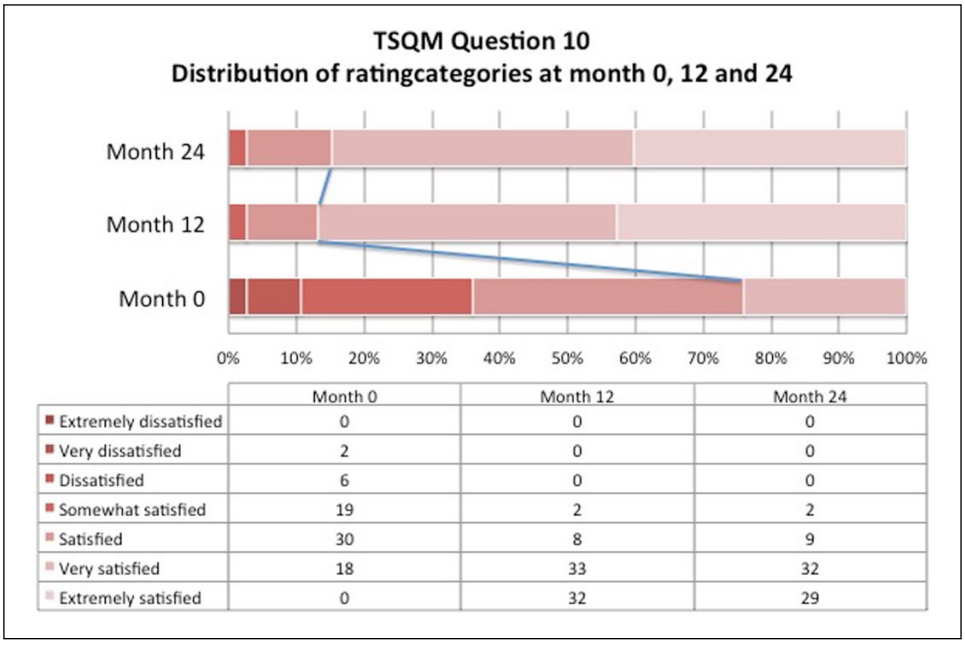


Figure 4. Mean value (SEM) for TSQM, summarised scores for questions 1–9 before the therapy switch (month 0) and after 12 and 24 months. Maximum score rating is 59.



	Month 0	Month 12	Month 24
Extremely dissatisfied	0	0	0
Very dissatisfied	2	0	0
Dissatisfied	6	0	0
Somewhat satisfied	19	2	2
Satisfied	30	8	9
Very satisfied	18	33	32
Extremely satisfied	0	32	29

Figure 5. Proportion of patients per rating category in TSQM sub-question 10 ('global satisfaction' rating) before the therapy switch (month 0) and 12 and 24 months after. Lighter colours represent a higher degree of satisfaction. The line between the columns indicates the amount of patients evaluating that they were extremely or very satisfied with their treatment. This number of patients increased from 18 (24%) at month 0 with injectable therapies to 65 (87%) and 61 (85%) at 12 and 24 months, respectively, after switching to rituximab treatment.

not improve significantly either. Second, the patients were selected as being clinically stable for a period of at least 6 months before inclusion in the trial, leaving a clinical variable such as EDSS unlikely to improve from a treatment change. The small, but statistically significant, improvement in SDMT results may at least in part be explained by a learning effect. However, the fact that the patients had already performed the test during the visit 3 months before the treatment switch, which also included at least one training set, argues against the learning effect as the only explanation for this improvement. Since the improvement occurred early and then remained stable may also indicate a real improvement. The lack of control group makes this speculative, however.

A strength of this study is that it describes aspects of MS treatment that are intimately connected to the patients' everyday experience of their chronic disease. With the improving efficacy of MS treatments, the goal of treatment should not only be to eliminate the inflammatory activity but also to diminish patients'

treatment-related perception of having a chronic disease. It is not likely that the improved treatment satisfaction in this study is related to reduction in MS-related symptoms, since the low-average EDSS at baseline indicates an already low level of such symptoms. Instead, the improved treatment satisfaction might be due to more convenient treatment schedule and low occurrence of side effects with probably less interference with daily activities. Treatment with rituximab might offer the possibility for patients to avoid being reminded about their disease by medication and side effects in their everyday life. We speculate this being one important reason for the high satisfaction with the rituximab treatment. Whether this can be extrapolated to MS patients with more active disease remains to be shown.

The lack of control group is an obvious weakness of the study. Using the patients as their own controls is suboptimal from a scientific point of view, but on the other hand, it better reflects the real-life clinical situation. Although the study included a run-in period, this was considerably shorter than the follow-up after the shift in treatment, and the frequent contact with the care provider during the study period could possibly have had an effect on the perception of treatment satisfaction and overall impact of the disease. More frequent visits create a closer contact between care provider and patient, but at the same time, they are time-consuming for the patient. More frequent MRI and yearly lumbar punctures can potentially lead to a comforting feeling of having more thorough control of disease activity. At the same time, such investigations may cause an increased level of discomfort. The geographical circumstances might also affect the perception of the follow-up routine. The participating centres in Östersund and Umeå are located in a rural part of Sweden, requiring some of the patients to travel a distance of up to 200 km one-way to attend the follow-up meetings. All the patients from Östersund had to travel 400 km one-way to perform their MRI and lumbar punctures at the medical centre in Umeå, which also required an overnight stay for logistical reasons. Thus, it cannot be assumed that the study's follow-up routines contributed to an increase in treatment satisfaction. Taking all of these factors into consideration, we believe it is unlikely that study-related confounding factors can explain the clearly improved and sustained treatment satisfaction that was detected after switching treatment from injectable therapies to rituximab.

In this study, we show a marked increase in treatment satisfaction when patients with RRMS using iDMTs switch treatment to rituximab, despite being clinically stable on their earlier injectable medication. The average overall rating of the treatment satisfaction with rituximab was rated as between 'very satisfied' and 'extremely satisfied', which was sustained over the entire 2-year study period. This quality of rituximab treatment, together with its potent anti-inflammatory property and favourable safety profile, provides support for rituximab as an important treatment option in RRMS.

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Declaration of Conflicting Interests

P.d.F. has served on an advisory board for Biogen Idec. K.L. declares that there is no conflict of interest. L.S. declares that there is no conflict of interest. M.G. has served on an advisory board for Teva and has received travel funding and/or speaker honoraria from Biogen Idec, Novartis, Merck Serono and Bayer Schering Pharma. A.S. has served on an advisory board for Sanofi Genzyme and has received travel funding and/or speaker honoraria from Biogen Idec, Sanofi Genzyme and Novartis.

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