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Original article

Interrupting rituximab treatment in relapsing-remitting multiple sclerosis; no evidence of rebound disease activity

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ABSTRACT

Background: Rituximab (RTX) and other anti-CD20 therapies are increasingly used as disease modifying treatments (DMTs) in MS. However, data on reasons to interrupt treatment, alternative DMTs after anti-CD20 therapy and potential rebound disease activity are limited. The objective here was therefore to determine the rate and cause of RTX treatment interruptions and responses to subsequent DMTs in a large single centre cohort addressing also the hypothesis that there would not be rebound activity after discontinuation of RTX, regardless of reason for discontinuation and irrespective of subsequent treatments.

Methods: A retrospective observational study of all relapsing-remitting MS (RRMS) patients having received at least one dose of RTX at the Karolinska University Hospital from 2009 to 2018 and having either stopped treatment or had more than one year since last RTX infusion, as identified in the Swedish MS registry with additional data derived from clinical charts.

Results: As of February 2018, we identified 808 patients ever treated with RTX out of 1513 RRMS patients with current or previous DMT, 92 (11%) had terminated RTX; 27 (29%) stopped RTX due to pregnancy, 26 (28%) due to adverse events, 23 (25%) for other reasons, 9 (10%) due to stable disease and the remaining 7 (8%) due to lack of effect. The cohort of 92 patients was followed until April 2019, when 34 had restarted RTX, 27 switched DMT, 24 remained without DMT and 7 were lost to follow up. Of the 7 patients terminating RTX due to lack of effect, 4 started ofatumumab, 2 had autologous hematopoietic stem cell transplantation and 1 was lost to follow up. In all of the 92 patients, after initial RTX discontinuation, only 3 patients had relapses and 4 had new T2 lesions (one of which had both). Gadolinium was administered in 78% of follow up magnetic resonance imaging (MRI) with no enhancing lesions found (mean MRI follow up from RTX discontinuation 29 months, range 7–92 months, $n = =77$).

Conclusion: Findings are consistent with a low rate of RTX interruptions, with pregnancy and adverse events as most frequent reasons. A small proportion of patients switched due to breakthrough disease in context of incomplete B-lymphocyte depletion. Signs of ongoing disease activity in the remaining group was low regardless of whether a new DMT was started. These findings are consistent with a long acting effect of RTX in RRMS and absence of rebound disease activity phenomena upon stopping therapy.

1. Introduction

1.1. Background

Rituximab (RTX; Mabthera™, Roche, Basel, Switzerland) is a chimeric monoclonal antibody binding to the CD20 protein present on naïve and memory B-cells, but not B-cell progenitors and plasma cells, resulting in systemic B-cell depletion. It is approved for B-cell lymphoma, rheumatoid arthritis and certain forms of systemic vasculitis. Further development for other indications, such as relapsing-remitting multiple sclerosis (RRMS), has been terminated by the manufacturer. However, in a placebo-controlled phase II study in RRMS, RTX demonstrated a very strong reduction in new T2- and Gadolinium contrast-enhancing (Gd^+) T1-weighted lesions on magnetic resonance imaging (MRI), consistent with a potent effect on inflammatory disease activity (Hauser et al., 2008). Additional retrospective observational studies in real world populations have demonstrated high comparative effectiveness and drug persistence rates compared to other disease modifying therapy (DMT) options (Alping et al., 2016; Granqvist et al., 2018; Salzer et al., 2016). The notion of a very strong effect on inflammatory disease activity of B-cell depleting therapies in RRMS is also supported by more recent studies with other anti-CD20 DMTs. Thus,

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ocrelizumab (Ocrevus™, Roche, Basel, Switzerland), a humanized anti-CD20 monoclonal antibody, demonstrated an impressive 94 and 95% reduction, respectively, in contrast-enhancing T1-weighted MRI lesions compared to subcutaneous interferon-beta1a in two phase III trials in RRMS (Hauser et al., 2017). Furthermore, ofatumumab (Arzerra™, Novartis, Basel, Switzerland), a fully humanized anti-CD20 monoclonal antibody currently in phase III clinical testing showed > 99% suppression of new brain MRI lesion activity over placebo in a dose finding phase II study (Sorensen et al., 2014). Collectively, existing evidence indicates that the frequency of treatment failure with anti-CD20 therapy is very low.

There is, however, limited data on disease activity after discontinuation of RTX. As RTX is one of the most frequently used DMTs in RRMS patients in Sweden and other anti-CD20 are now increasingly used globally, studies addressing the rate and reasons of treatment discontinuation, response to subsequent therapies and possible rebound effects upon cessation are needed.

1.2. Objectives

To determine reasons for RTX cessation among all RRMS patients treated at our center, response to subsequent DMT if started and to evaluate possible rebound activity after RTX discontinuation.

2. Methods and material

2.1. Patients and clinical data

Data comprising all patients ever treated with RTX for RRMS at Karolinska University Hospital/Center for Neurology in Stockholm, Sweden, was retrieved from the Swedish MS registry (SMSreg) on February 10th, 2018. Additional follow up data for patients terminating RTX was collected from medical charts until April 11st, 2019. Reasons for discontinuation were noted for all patients terminating RTX treatment. Regarding the subgroup of patients terminating RTX due to lack of effect, the outcome variables obtained classifying these patients as non-responders are defined in Section 2.2. In this subgroup of patients B-cell counts were noted during and after RTX treatment and screening for anti-RTX antibodies in serum was performed in some cases using an electrochemiluminescence-based method; these procedures have been described previously (Dunn et al., 2018). Disease activity after RTX discontinuation is defined in Section 2.3.

One patient who only had previously received RTX at a different hospital together with four patients whose MS diagnoses prior to data extraction had been changed to neuromyelitis optica were excluded from the cohort. At review of medical charts a further three patients were excluded due to conversion to SPMS before RTX initiation, one patient whose disease diagnosis was changed to suspected vasculitis and one patient treated with one dose of RTX after natalizumab-induced progressive multifocal leukoencephalopathy. As standard regimen patients received infusions of 500 mg (mg) RTX every six months. A minority of patients had initially received 1000 mg at six-month intervals, with later dose reduction to 500 mg every six months. MRI was done using a standardized protocol on 1.5 or 3 Tesla MRI scanners with evaluation by two trained neuroradiologists (Vagberg et al., 2017).

All outcome variables entered prospectively in SMSreg were validated against medical records. Patients had given informed consent to registration in SMSreg and the study was approved by the Stockholm Regional Ethical Committee (2009/2107–31/12).

2.2. Definitions of categories for termination of treatment

Reasons for discontinuation were grouped as due to lack of effect, adverse events (AE), stable disease, confirmed or planned pregnancy, and other reasons. In patients with two or more reasons for RTX discontinuation only one was considered according to the priority order listed above. Lack of effect was defined as a verified clinical relapse or Gd^+ on T1-weighed MRI at least three months after first RTX administration or a new lesion on T2-weighed MRI compared with a reference scan performed at least three months after first RTX administration. AEs as reasons for RTX discontinuation were graded 1 to 5 according to the Common Terminology Criteria for Adverse Events (CTCAE version 4,0 published May 28, 2009). Infusion reactions (IR) were noted from infusion day to three days after the infusion and the remaining types of AEs were registered if occurring from three months after first RTX infusion until 12 months after the last RTX infusion. If another DMT had been started within 12 months since last RTX dose, any AEs occurring after this therapy change were acknowledged only if regarded as related to RTX by the treating neurologist. Increased susceptibility for infections and serum hypogammaglobulinemia were noted if occurring from three months after first RTX infusion until 12 months after the last RTX infusion. In a smaller proportion of patients further treatment was deemed unnecessary by the treating neurologist due to a mild disease course, denoted “Stable disease”. The category “Planned or confirmed pregnancy” included women planning to become or with confirmed pregnancy. Patients wishing to interrupt treatment were classified as “Other reasons” unless fulfilling any of the categories previously described. This category also included patients that were lost to follow up due to migration. For all discontinuation categories ≥ 1 year between RTX infusions were considered as terminated treatment, regardless of whether RTX later was reintroduced.

2.3. Outcome variables after RTX discontinuation indicating active disease

New T2 lesions after RTX treatment were noted from date of last RTX infusion until most recent MRI, regardless of subsequent therapies, with first reference MRI performed at least 3 months after the first RTX infusion. Presence of Gd^+ lesions on MRI and clinical relapses were noted from final RTX infusion date to most recent MRI, irrespective of RTX replacement therapies.

2.4. Statistics

Calculations were performed with IBM® SPSS® Statistics Version 22.0.

3. Results

3.1. Baseline characteristics

As of February 10th, 2018, 1513 RRMS patients were listed with current or previous DMT. Of these, 808 (53.4%) had ever been treated with RTX, with the first patient initiating RTX December 2010. Ninety-two patients (11.4%) had interrupted RTX, while 716 (88.6%) were listed with an ongoing treatment as depicted in the flow chart in Fig. 1. Baseline characteristics at RTX initiation of patients with ongoing and interrupted RTX treatment are given in Table 1 and were essentially similar between groups regarding age, disease duration, EDSS and number of previously used DMTs.

Two patients having received RTX at our center had died at time of data censoring, due to sigmoid cancer in one patient and cholangiocarcinoma in the other patient. Death occurred twenty-two and eight months after last RTX infusion, respectively. In both cases the detection of malignancies occurred after start of RTX, but was not stated as reason to discontinue the drug.

3.2. Reasons for RTX discontinuation

Twenty-seven patients interrupting RTX did so for family planning or with a confirmed pregnancy. At data censoring 24 had restarted RTX after delivery. Twenty-six patients interrupted RTX due to AEs. None of

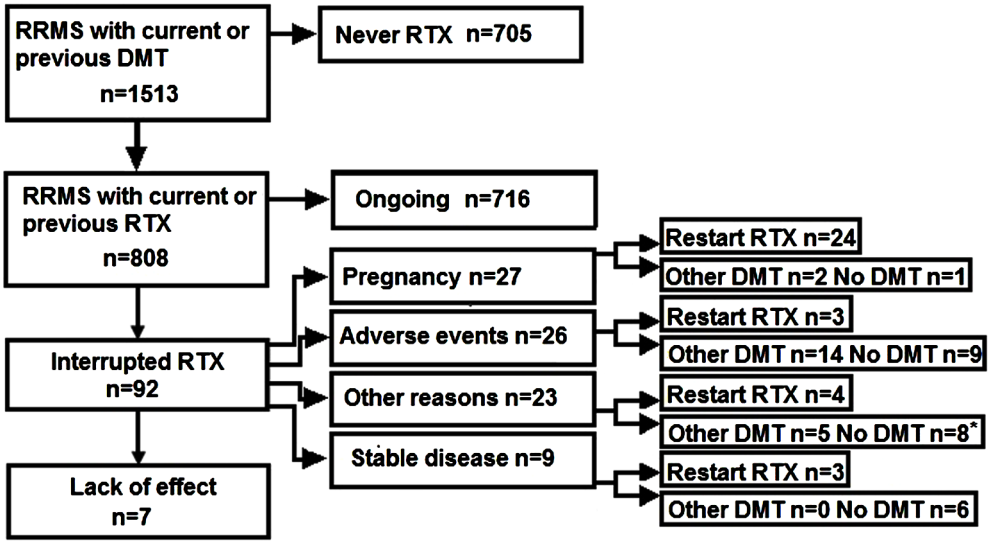

Fig. 1. Flow chart depicting the identification of the cohort terminating rituximab (RTX), with sub-classification into reasons for RTX discontinuation and initial subsequent therapies. The following descending priority order was used: 1) treatment failure; 2) adverse event; 3) stable disease; 4) planned or confirmed pregnancy, and; 5) other reasons. * Six patients in the group who terminated RTX due to other reasons were lost to follow up. DMT: disease modifying treatment.

these patients had a grade 4 AE or higher. Four patients in this group had a grade 3 AE, eleven had a grade 2 AE and four patients had a grade 1 AE. The remaining seven of these patients described increased susceptibility for infections since starting RTX, although grading of these AEs were not possible due to insufficient documentation in medical records. However, three of these seven patients displayed serum immunoglobulin G levels below reference values (< 6.7 g/liter). Twenty-three patients were classified as interrupting RTX for "Other reasons". In most cases this group consisted of patients wishing to terminate treatment due to fear of AEs, emigration or opting for non-proven alternative treatment methods. One patient underwent HSCT, though objective evidence of continued disease activity was lacking. An additional patient was switched to natalizumab one month after RTX initiation due to continued aggressive clinical and neuroradiological disease activity and subsequently underwent HSCT.

Nine patients terminated RTX treatment due to stable disease, as defined above. At data censoring six of these had not restarted RTX or any other DMT and in the remaining three patients treatment with RTX had been re-initiated although none displayed signs of active disease, as defined in Section 2.3.

Finally, a total of seven patients terminated RTX due to objective signs of lack of effect occurring more than three months after treatment start. The characteristics of these patients are given in Table 2.

Four of these patients displayed signs of continued diseased activity on MRI or had verified relapses. One of the three remaining patients, while classified as RRMS by the treating neurologist, displayed more progressive worsening without distinct relapses or new focal MRI lesions. The two remaining patients reported more diffuse worsening of MS symptoms, without fulfilling the criteria for a relapse and without signs of neuroradiological disease activity on MRI.

By the extended follow up date, two of the RTX non-responders had been subjected to HSCT, subsequently displaying a stabilization of disease progression. The other four patients, of which three displayed anti-RTX antibodies, all had incomplete B cell depletion and switched therapy to ofatumumab. Three of these patients displayed complete B cell depletion and no further signs of continued disease activity. The fourth patient had a CTCAE grade 3 IR immediately after the first infusion of ofatumumab, which then was discontinued and subsequently started treatment with fingolimod. The seventh patient was lost to follow up due to emigration from Sweden soon after terminating RTX.

3.3. Outcome after RTX discontinuation

Of the 92 patients terminating RTX treatment, 34 re-started RTX as initial subsequent therapy, mainly in the group stopping treatment due to pregnancy. By April 11, 2019, twenty-seven patients had switched DMT (most frequently to ofatumumab and natalizumab, $n = 7$ for both), twenty-four patients remained without DMT and seven were lost to follow up. Five patients received two, and three patients received three different DMTs after initial termination of RTX (data not shown). Notably, excluding events during RTX therapy in the subgroup of seven patients with lack of treatment effect, there were only relapses in three patients and new T2 lesions in four patients after RTX discontinuation among all 92 subjects (one of which had both). Among these patients with clinical relapse after RTX discontinuation, none had been treated with a subsequent DMT for more than three months when this occurred. Gadolinium was administered in 78% of follow up magnetic resonance imaging (MRI) with no enhancing lesions found (mean MRI follow up from RTX discontinuation 29 months, range 7–92 months, $n = 77$).

Outcome after RTX termination by discontinuation reason is depicted in Table 3.

4. Discussion

An increasing body of evidence supports the notion of a very potent abrogation of inflammatory disease activity in RRMS with anti-CD20

Table 1
Demographic data of patients with ongoing and interrupted treatment with RTX, respectively.

Sex	Ongoing RTX treatment, $n = 716$ Females $n = 502$ (70%)	Terminated RTX treatment, $n = 92$ Females $n = 77$ (84%)
Disease duration at RTX initiation (mean, years)	7.9 (SD 7.2)	8.0 (SD 7.0)
Age at RTX initiation (mean, years)	38.5 (SD 10.3)	38.6 (SD 10.0)
EDSS at RTX initiation (median, range)	2.0 (0–8)	2.0 (0–6)
Number of DMT´s prior RTX (mean)	1.2 (SD 1.0)	1.3 (SD 1.0)

RTX: rituximab; EDSS: Expanded Disability Status Scale; DMT: Disease-modifying therapy; SD: standard deviation.

Table 2
Patients terminating rituximab due to lack of effect.

Patient	1	2[a]	3	4	5	6	7
Sex	Woman	Woman	Man	Man	Woman	Woman	Woman
Age at RTX start (years)	39	41	41	36	32	32	56
Disease duration at RTX initiation (years)	6	7	10	11	2	3	10
Treatment prior RTX	INJ, DMF	INJ	DMF	INJ	INJ, NTZ, FGL, PLEX	DMF	none
Disease activity the year prior to RTX	T2	T2, Gd + (8), relapse	No	Gd + (3)	Relapse(3), Gd +	T2, Gd + (2)	Gd +
Disease activity > 3 months after first RTX dose	T2, Gd + (3), relapse	T2, Gd + (12), relapse(2)	No[b]	Gd + (7)	No[b]	T2, Gd +	No[c]
Complete B-cell depletion at any time point with RTX	Yes	No	Yes	No	N/A	Yes	Yes
Incomplete B-cell depletion at any time point with RTX	Yes	Yes	N/A	Yes	N/A	No	No
Normalized B-cell counts at any time point with RTX	No	No	N/A	No	N/A	Yes	Yes
Anti-RTX antibodies	Positive	Positive	N/A	N/A	N/A	Positive	N/A
Treatment after RTX	OFA	OFA	HSCT	N/A	HSCT	OFA	OFA[c]
Relapses after switch from RTX	No	No	No	N/A	No	No	No
Change in EDSS between RTX and post-RTX DMT	7 → 7.5	No change	5.5 → 5	N/A	3 → 2.5	3 → 2.5	N/A

RTX: rituximab; EDSS: Expanded Disability Status Scale; DMT: disease modifying therapy; INJ: interferon or glatiramer acetate; DMF: dimethyl fumarate; T2: T2-weighted magnetic resonance imaging; Gd + : Gadolinium contrast-enhancing (Gd^+) T1-weighted lesion; OFA: ofatumumab; N/A: not available; HSCT: autologous hematopoietic stem cell transplantation; NTZ: natalizumab; FGL: fingolimod; PLEX: plasma exchange. Disease activity defined as either of the following: relapse, new lesion on T2-weighted image or Gd + lesion (residual or newly formed). Newly formed T2 lesions considered signs of disease activity if reference scan performed at least three months after start of RTX treatment. Number of events indicated in parentheses if known. B-cell depletion defined as: complete: < 10 cells/microliter(μl); incomplete: 10 to < 90 cells/μl; Normalized B-cell count: ≥ 90 cells/μl.

[a] This patient is reported as patient 2 in Table 6 in the paper by Dunn et al., 2018.

[b] Patient number three and five reported overall worsening of MS symptoms during RTX treatment, although distinct relapses or signs of neuroradiological activity were lacking.

[c] Patient number seven reported general malaise including fatigue during RTX treatment, without relapses or signs of neuroradiological activity and discontinued OFA due to a grade 3 infusion reaction, as defined by the Common Terminology Criteria for Adverse Events.

DMTs. Thus, RCTs with three different anti-CD20 monoclonal antibodies have demonstrated impressive reductions in neuroradiological disease activity (Hauser et al., 2017, 2008; Kappos et al., 2011; Sorensen et al., 2014). In addition, comparative effectiveness studies in real world populations have shown that RTX outperforms fingolimod in patients switching from natalizumab due to John Cunningham virus serology positivity, as well as displaying equal or better performance than all more frequent DMT options in patients initiating a first line treatment (Alping et al., 2016; Granqvist et al., 2018). In both these studies RTX had a significantly lower rate of treatment interruptions compared to MS approved DMTs. The notion of a high persistence rate of RTX is replicated in this cohort, with a drug survival of close to 90%. Furthermore, the results regarding safety is in accordance with our previous retrospective observational study of the safety profile of RTX (Salzer et al., 2016). Thus, patients terminating RTX stating AEs mainly did so due to milder to moderate side effects, except for two cases of fatal malignancies detected after start of RTX. While no increased risk of malignancies was detected in a nationwide cohort of patients with rheumatoid arthritis treated with RTX, additional studies are needed to address this specifically in MS (Wadstrom et al., 2017). This is also underscored by the finding of a two-fold increase of cancer incidence in pooled data from all studies with ocrelizumab (Montalban et al., 2017). In contrast, we recently compared the incidence of malignant cancers in Sweden in a nationwide material of MS patients occurring during treatment with high effective DMTs, with similar rates in RTX treated patients as populations-based controls (Alping et al., 2018).

One of the main findings here is that disease activity is suppressed long after RTX discontinuation, regardless of whether another therapy is started or not. Of the patients interrupting RTX for more than 12 months, this also included a significant proportion later restarting RTX, mainly women after pregnancy, with no signs of disease reactivation during the interval. Hence, our findings are consistent with a low risk of rebound phenomena after RTX cessation, as opposed to other DMTs such as natalizumab or fingolimod (Miravalle et al., 2011; West and Cree, 2010). This was somewhat expected as recent immunological evidence shows that the effect of B cell depleting treatments likely is mediated through depletion of memory B-cells, which reconstitute much slower than naïve B cells (Jelcic et al., 2018; Roll et al., 2008).

Among the seven patients that terminated RTX due to objective signs of breakthrough disease activity, most patients displayed incomplete B-cell depletion and in some cases anti-RTX antibodies were present, one of which has been previously reported by Dunn et al. 2018 as detailed in Table 2. Notably, after switching to ofatumumab, these patients displayed depletion of B-cells and abrogation of disease activity. Due to the study design and small number of patients with insufficient RTX treatment effect, a confirmation of the association between anti-RTX antibodies, incomplete B-cell depletion and clinical outcomes cannot be determined here. However, our findings suggest

Table 3
Patient outcomes after termination of RTX treatment, grouped by discontinuation reason with total number of patients remaining free of DMT use versus ever restarting RTX, by April 11, 2019. RTX: rituximab; MRI: magnetic resonance imaging; T2: T2-weighted magnetic resonance imaging. Mean MRI follow up in months. New T2 lesions after RTX treatment were collected from date of last RTX infusion until most recent MRI, regardless of subsequent therapies. The last MRI performed before final RTX infusion served as a reference scan. Presence of Gadolinium contrast-enhancing (Gd^+) T1-weighted lesions on MRI and relapses were noted from final RTX infusion date to most recent MRI and April 11, 2019, respectively, irrespective of RTX replacement therapies. There were no Gd + lesions in any of the MRI follow up scans (data not shown).

RTX discontinuation reason	No. of patients	Mean MRI follow up	New T2 lesions	Relapse	No new therapy	Restarted RTX
Pregnancy	27 (29%)	28.9 (13.0–56.0)	1	0	1	25
Adverse events	26 (28%)	25.0 (7.0–57.0)	1	0	9	4
Other reasons	23 (25%)	32.4 (13.0–64.0)	1	3	8	4
Stable disease	9 (10%)	32.4 (10.0–92.0)	0	0	6	4
Lack of effect	7 (8%)	31.2 (19.0–62.0)	1	0	0	0

that a switch to a humanized anti-CD20 DMT can be meaningful in context of an inadequate treatment response and presence of anti-RTX antibodies.

A weakness with this study is the retrospective observational design, with a less structured follow up routine. In addition, we did not evaluate relapses and MRI findings in patients with ongoing RTX therapy, since this has been reported previously in a larger cohort (Salzer et al., 2016). Lastly, we cannot exclude that changes in the RTX dosing regimen (more frequent infusions or higher doses) could have affected efficacy outcomes.

5. Conclusions

This retrospective observational study of a large single center cohort of RRMS patients treated with RTX replicates previous findings of high efficacy and tolerability of this DMT, with a low rate of RTX interruptions, mainly due to pregnancy and AEs. Importantly, we also observe a very low rate of disease activity in those terminating RTX for reasons other than lack of effect regardless of whether RTX later is restarted, a switch to another DMT is performed or the patient remains without treatment. This is consistent with a long acting effect of RTX in RRMS and an absence of rebound disease activity phenomena. These findings are of relevance for risk-benefit assessments of subsequent treatment options in patients wanting to interrupt RTX treatment due to planning of pregnancy or AEs.

Conflict of Interest Statement

Drs Juto, Fink and Al Nimer do not report any conflicts of interest. Dr Piehl has received unrestricted academic research grants from Genzyme, Merck KGaA and Novartis, and fees for serving as Chair of DMC in clinical trials with Parexel.

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