Journal of Neurology (2019) 266:699–706
https://doi.org/10.1007/s00415-019-09191-6

ORIGINAL COMMUNICATION

High efficacy of rituximab for myasthenia gravis: a comprehensive nationwide study in Austria

Raffi Topakian[1] · Fritz Zimprich[2] · Stephan Iglseder[3] · Norbert Embacher[4] · Michael Guger[5] · Karl Stieglbauer[6] · Dieter Langenscheidt[7] · Jakob Rath[2] · Stefan Quasthoff[8] · Philipp Simschitz[9] · Julia Wanschitz[10] · David Windisch[11] · Petra Müller[1] · Dierk Oel[1] · Günther Schustereder[1] · Stefan Einsiedler[1] · Christian Eggers[3] · Wolfgang Löscher[10]

Received: 18 November 2018 / Revised: 1 January 2019 / Accepted: 6 January 2019 / Published online: 16 January 2019

Abstract

Background Most patients with myasthenia gravis (MG) need long-term immunosuppressive therapy. However, conventional agents may have intolerable side effects, take too long or fail to achieve disease control. Rituximab (RTX) has emerged as an off-label treatment for refractory MG, but data on its use are still sparse.

Methods We conducted a retrospective nationwide study contacting all Austrian neurologists to provide anonymized data of all adult MG patients treated with RTX and minimum follow-up of 3 months. The Myasthenia Gravis Foundation of America Postintervention Status scale was used to assess outcomes.

Results 34 (60.7%) of a total of 56 patients were women. Median (IQR) age at diagnosis of MG and start of RTX were 41.5 (24.3; 65.8) and 47.5 (33; 71) years, respectively. Antibodies (ab) against acetylcholine receptor (AchR) and muscle-specific tyrosine kinase (MuSK) were present in 69.6% and 25% of patients, respectively (seronegative: 5.4%). Before RTX, 47 (83.9%) patients had had plasma exchange, immune adsorption or immunoglobulins. Three months after RTX, 14 of 53 (26.4%) patients were in remission. At last follow-up after a median of 20 (10; 53) months, remission was present in 42.9% of patients and another 25% had minimal manifestations. Remission was more frequent in patients with MuSK ab vs. those with AchR ab (71.4% vs. 35.9%, $p=0.022$). RTX was safe. The presence of MuSK ab independently predicted remission after RTX.

Conclusion In this retrospective study on RTX for MG, the largest to date, RTX appeared safe, efficacious and fast acting. Benefit from RTX was greatest in MuSK ab + MG.

Keywords Myasthenia gravis · Rituximab · Efficacy · Anti-MuSK · Outcome

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00415-019-09191-6) contains supplementary material, which is available to authorized users.

✉ Raffi Topakian
raffi.topakian@hotmail.com

1 Department of Neurology, Academic Teaching Hospital Wels-Grieskirchen, Grieskirchner Str. 42, 4600 Wels, Austria

2 Department of Neurology, Medical University of Vienna, Vienna, Austria

3 Department of Neurology, Krankenhaus Barmherzige Brüder, Linz, Austria

4 Department of Neurology, University Clinic St. Pölten, St. Pölten, Austria

5 Clinic for Neurology 2, Med Campus III, Kepler University Clinic, Linz, Austria

6 Neurologist in Private Practice, Linz, Austria

7 Department of Neurology, Landeskrankenhaus Rankweil, Rankweil, Austria

8 Department of Neurology, Graz Medical University, Graz, Austria

9 Department of Neurology, Klinikum Klagenfurt, Klagenfurt, Austria

10 Department of Neurology, Medical University Innsbruck, Innsbruck, Austria

11 Department of Neurology, Landeskrankenhaus Bruck, Bruck, Austria

Introduction

Myasthenia gravis (MG) is an autoimmune disorder of the neuromuscular junction in which antibodies (ab) bind to acetylcholine receptors (i.e. AchR ab + MG) or to functionally related molecules at the postsynaptic membrane of the neuromuscular junction. Most patients with MG develop fluctuating, generalized weakness and need long-term immunosuppressive medication to meet the treatment goal of minimal manifestations or better [1]. However, steroids and conventional steroid-sparing, oral immunosuppressive agents such as azathioprine or cyclosporine can have intolerable side effects, take too long, or even fail to achieve and maintain sufficient control of symptoms [2]. Patients with MG refractory to conventional treatment are at increased risk of MG crisis and may repeatedly need high-cost therapies such as intravenous immunoglobulins (IVIG), plasma exchange (PLEX), immunoadsorption (IA), or eculizumab, a monoclonal antibody recently approved for generalized AchR ab + MG [3].

Rituximab (RTX), a monoclonal antibody that leads to rapid depletion of B cells and their precursors, has emerged as a potentially efficacious off-label treatment option for patients with MG. The increasing use of RTX in many centres worldwide still lacks supportive evidence from randomized trials. Most data on RTX for MG are derived from small, retrospective single-centre studies. Several narrative reviews and two systematic reviews of published cases concluded that RTX constitutes a well-tolerated, promising treatment option, especially for MG patients with anti-muscle-specific tyrosine kinase antibodies (MuSK ab + MG). However, data are still sparse and there may be a bias due to insufficient publication of treatment failures [4–8].

To study the current use, efficacy and safety of RTX in adult patients with MG in a real-world setting, we conducted a comprehensive, nationwide, retrospective study.

Patients and methods

Study design and ethics approval

All departments of neurology in Austrian hospitals and all members of the Austrian Neurological Society (ANS) were invited by email in March, 2017, through the ANS to participate in this retrospective study. The deadline for forwarding of anonymized data was June 15, 2017. The study was approved by the principal ethics committee of Upper Austria (Study no. K-129-17) and the Medical University of Vienna, and was carried out in accordance with the declaration of Helsinki.

Inclusion criteria and variables of interest

To minimize reporting bias, participating physicians were required to report all adult MG patients treated with RTX. Patients had to be diagnosed with MG according to the guideline of the ANS [9] with a minimum length of follow-up after the start of RTX of 3 months.

By reviewing the charts and reports of patients, data on the following variables were collected: gender; age at diagnosis of MG; age at start of treatment with RTX; detected antibodies and titers; subtype of MG according to [1]; all previous treatments used for MG; criteria for the start of RTX; medication at the time of RTX start and at last follow-up with particular attention to the use of high-cost therapies (IVIG, PLEX and immunoadsorption therapies), steroids and cholinesterase inhibitors; protocols used for RTX induction and maintenance therapy; number of RTX infusions and length of follow-up. To assess disease severity at the time of start of RTX, the Myasthenia Gravis Foundation of America-Clinical Classification (MGFA-CC) was used [10]. Safety of RTX was evaluated by systematically ascertaining infusion reactions, infections, neoplasms, and other potential side effects and complications resulting in morbidity and mortality. To retrospectively assess outcomes after the start of RTX at 3 months (± 2 weeks), at 6 months (± 2 weeks), at 12 months (± 2 weeks), and at the time of last follow-up, the Myasthenia Gravis Foundation of America-Postintervention Status (MGFA-PiS) was used. The MGFA-PiS evaluates the patient's status (complete stable remission, pharmacologic remission, minimal manifestations) and the change of status since the initiation of treatment (improved, unchanged, worse, exacerbation, and death) as described previously [10].

Statistical analyses

All data were collected, entered in a spreadsheet, and double-checked for plausibility by the principal investigator (R.T.) before analyses were carried out using SPSS software (version 23.0, SPSS Inc., Chicago, IL, USA).

We compared baseline and treatment-related characteristics between patients who had achieved `remission´ (pharmacological remission or complete stable remission on the MGFA-PiS) at last follow-up vs. patients without remission at last follow-up. To identify independent predictors of remission on last follow-up, stepwise logistic regression models were analyzed entering age, gender and all variables with $p < 0.05$ on univariate analyses.

Categorical variables are reported as numbers and percentages. Continuous variables with normal distribution are expressed as means (standard deviation, SD) and skewed data are presented as medians (interquartile range, IQR). For univariate analyses of categorical variables, we used

the chi-square test or Fisher's exact test as appropriate. For continuous variables, intergroup differences were assessed by the two-tailed independent samples *t* test (data with normal distribution) and Mann–Whitney *U* test (skewed data).

To identify independent predictors of remission at the time of last follow-up, multivariate logistic regression analyses were carried out including all variables with $p < 0.05$ in univariate analyses of Table 2 plus the variables age and sex.

Results

Cohort characteristics

A total of 56 adult patients treated with RTX for MG were reported by ten departments of neurology and one neurologist in private practice. Individual patient demographics and treatment-related characteristics are given in the supplementary table. Shorter follow-up data of four patients (cases 23–26 in the supplementary table) were reported previously [2, 4].

34 (60.7%) patients were women. Median age at diagnosis of MG and start of RTX therapy was 41.5 (24.3; 65.8) and 47.5 (33; 71) years, respectively. 39 (69.6%) patients had anti-acetylcholine receptor antibodies (AchR ab+), 14 (25%) patients had anti-muscle-specific tyrosine kinase antibodies (MuSK ab+), and 3 (5.4%) patients with generalized MG were 'double seronegative'. Other antibodies were not systematically tested.

Regarding the clinical subtypes of MG [1], 16 (28.6%) patients had late onset MG (LOMG, defined as AchR ab + generalized MG and age ≥ 50 years at onset), 13 (23.2%) patients had early onset MG (EOMG, defined as AchR ab + generalized MG and age < 50 years at onset), 8 (14.3%) patients had AchR ab + thymoma-associated MG, 2 (3.6%) patients had AchR ab + ocular MG, 14 (25%) patients had MuSK ab + MG, and 3 (5.4%) patients had seronegative MG.

Severe disease before the start of RTX, defined by an MGFA-CC of IIIb or higher [7], was present in 33 (58.9%) patients.

The mean disease duration of MG before RTX was 4 (1.3; 10.8) years, and the median length of follow-up after initiation of RTX was 20 (10; 53.5) months.

Treatments before RTX start

For each patient, all previous therapies were recorded.

At the time of start of RTX, all patients had been or were still being treated with steroid prednisolone. Other oral immunotherapies that had been used or were still being used included azathioprine ($n = 44$, 78.6%), mycophenolate mofetil ($n = 13$, 23.2%), methotrexate ($n = 7$, 12.5%), ciclosporin ($n = 5$, 8.9%), tacrolimus ($n = 1$; 1.8%), and cyclophosphamide ($n = 1$, 1.8%). Thymectomy had been performed in 26 (46.4%) patients. 47 (83.9%) patients had already received one or more of the following `high-cost therapies´: PLEX/IA ($n = 26$, 46.4%) and IVIG ($n = 41$, 73.2%).

We studied the number of steroid-sparing immunotherapies used before the initiation of RTX. For this, thymectomy, whether for thymoma or other reasons, was counted as steroid-sparing therapy according to recent evidence [11]. In patients with both PLEX and IA, this was counted as one steroid-sparing therapy modality. The mean number of steroid-sparing therapies before RTX was 2.9 (SD ± 1.4).

Pyridostigmine was the only oral cholinesterase inhibitor used in this cohort. At the time of RTX start, 44 (78.6%) patients were still taking pyridostigmine (daily dose 60–720 mg).

Clinical criteria for RTX start, treatment protocols and length of follow-up

Clinical criteria for the start of RTX were (1) inability to lower immunotherapy without clinical relapse ($n = 18$, 32.1%); (2) lack of clinical control on immunotherapy regimens ($n = 48$, 85.7%); (3) intolerable side effects ($n = 33$, 58.9%); and (4) concomitant B-cell non-Hodgkin lymphoma along with the diagnosis of MG ($n = 1$). 37 (66.1%) patients fulfilled ≥ 1 clinical criterion.

RTX infusions were given after pretreatment with anti-allergic and anti-pyretic medication under close monitoring of blood pressure and heart rate. The protocols of RTX treatment, being induction therapy or maintenance therapy, varied across centres and between patients treated in a single centre. The majority of patients ($n = 47$, 83.9%) had induction therapy consisting of two RTX infusions within 2 weeks at a dose of 2×375 mg/m^2 body surface area ($n = 17$, 30.4%), 2×500 mg fixed dose ($n = 15$, 26.8%) or 2×1000 mg fixed dose ($n = 15$, 26.8%). Other protocols were used in nine (16.1%) patients, with one of these patients receiving RTX as part of R-CHOP (RTX, cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy for concomitant B-cell non-Hodgkin lymphoma.

Regimens of maintenance therapy showed great variations as well. For decision-making on repeat RTX infusions, the reappearance of B cells in peripheral blood detected by flow cytometry was used in 24 (42.9%) patients. 17 (30.4%) patients were re-treated with RTX on the grounds of new clinical deterioration observed during regular follow-up visits. Only three (5.4%) patients underwent a preplanned fixed-time/fixed-dose maintenance therapy protocol. The median number of RTX infusions (including induction and maintenance treatment) was 3 (2; 6). At the time of our analysis, 12 (21.4%) patients had only undergone RTX induction

therapy, while their future maintenance therapy regimen was still undecided.

Safety of RTX

RTX was generally well tolerated. Reported side effects and complications potentially related to RTX therapy included infusion reactions ($n=3$), respiratory tract infections ($n=3$), chronic pain syndromes ($n=2$), enteritis ($n=2$), herpes zoster ($n=1$), erysipelas ($n=1$), cholecystitis ($n=1$), unspecified mental disorder ($n=1$), and alopecia areata ($n=1$).

There was one death during follow-up. A 59-year-old man (patient 50 in the supplementary table) with recently diagnosed, highly refractory LOMG died 4.5 months after the start of RTX following combined treatment with high-dose steroids and pyridostigmine, PLEX, and IVIG; a cardiac cause of death was assumed, as 2 days prior to his death he reportedly had complained of symptoms suggestive of angina pectoris but had refused to seek medical help. He had had no known history of cardiac disease, and inpatient cardiac monitoring during treatment with PLEX, IVIG and RTX had been unremarkable. Autopsy was not performed.

Efficacy of RTX: MGFA-PiS outcomes and sparing of steroids and high-cost therapies

Table 1 summarizes MGFA-PiS outcomes at various follow-up time points after RTX therapy. Outcomes data were near-complete ($n=53$) at follow-up after 3 months and complete at the time of last follow-up after a median of 20 (10; 53.5) months.

After 3 months, 26.4% of patients had already reached remission. The proportion of patients in remission steadily rose over subsequent follow-up time points, reaching 42.9% at last follow-up. The proportions of patients with an MGFA-PiS of minimal manifestations (MM) or better were 45.3% after 3 months and 67.9% at last follow-up, respectively.

At last follow-up, remission was achieved in 71.4% (10/14) of MuSK ab+ patients and 35.9% (14/39) of AchR ab+ patients, respectively ($p=0.022$).

An outcome of MM or better was achieved in 85.7% (12/14) of MuSK ab+ patients and 64.1% (25/39) of AchR ab+ patients, respectively. Of the three patients with SNMG, one patient achieved MM and two patients showed some improvement.

Interestingly, none of the 13 patients with EOMG had reached remission at last follow-up.

At last follow-up, 'high-cost therapies' were given to 13 (23.2%) patients: 11 patients were treated with immunoglobulins (10 IVIG, 1 SCIG), and two patients were receiving IA on a non-regular basis. 33 of 39 (84.6%) patients who were still taking steroids at the time of RTX start had steroids stopped altogether ($n=23$; 59%) or the dose had been tapered to 50% or less ($n=10$; 25.6%).

Antibody levels after RTX

20 (35.8%) patients had antibody levels re-tested after start of RTX (Table 2). 13 (65%) of these patients showed some decrease of antibody levels, but this seemed unrelated to outcome. Interpretation of data was further compromised by the widely varying time points of antibody level testing.

Characteristics of patients with remission at last follow-up and predictors of remission

We compared baseline and follow-up characteristics in patients who had achieved remission at last follow-up vs. patients without remission (Table 2). In the remission group, median age at diagnosis of MG and at start of RTX were significantly higher [58 (33; 71) vs. 29.5 (20; 57.5)] years, $p=0.01$, and 67 (40; 72) vs. 40.5 (31; 64.3) years, $p=0.029$, respectively) and there was a trend towards shorter duration of disease before start of RTX (2.5 (1; 6.8) vs. 6 (2; 12) years, $p=0.09$). In the remission group, MuSK ab + MG

Table 1 MGFA-PiS outcomes after RTX initiation during follow-up

Variables	MGFA-PiS after 3 months (±2 weeks) ($n=53$)	MGFA-PiS after 6 months (±2 weeks) ($n=52$)	MGFA-PiS after 12 months (±2 weeks) ($n=41$)	MGFA-PiS at median 20 months (10; 53.5 months) ($n=56$)
Death	0	1 (1.9)	1 (2.4)	1 (1.8)
Worse	1 (1.9)	1 (1.9)	–	–
Unchanged	6 (11.3)	2 (3.8)	1 (2.4)	1 (1.8)
Improved	22 (41.5)	18 (34.6)	15 (36.6)	16 (28.6)
Minimal manifestation	10 (18.9)	12 (23.1)	8 (19.5)	14 (25.0)
Remission[a]	14 (26.4)	18 (34.6)	16 (39.0)	24 (42.9)

Numbers are counts (percentages)

[a]Complete stable remission, i.e. no medication for MG (including RTX infusions) for at least 12 months was achieved in five patients at last follow-up; all other patients were rated as pharmacological remission

Table 2 Characteristics of patients with remission vs. patients without remission at last follow-up

Variables	Total ($n=56$)	Remission at last follow-up ($n=24$)	No remission at last follow-up ($n=32$)	p value
Baseline characteristics before RTX start				
Female gender	34 (60.7)	14 (58.3)	20 (62.5)	0.75
Age at diagnosis of MG in years, median (IQR)	41.5 (24.3; 65.8)	58 (33; 71)	29.5 (20; 57.5)	0.01
Age at RTX start in years, median (IQR)	47.5 (33; 71)	67 (40; 72)	40.5 (31; 64.3)	0.029
Duration of diagnosed MG before RTX start in years, median (IQR)	4 (1.3; 10.8)	2.5 (1; 6.8)	6 (2; 12)	0.09
Antibody type				
Anti-AchR-ab	39 (69.6)	14 (58.3)	25 (78.1)	0.11
Anti-MuSK-ab	14 (25.0)	10 (41.7)	4 (12.5)	0.013
Double seronegative	3 (5.4)	0	3 (9.4)	
Thymoma	8 (14.3)	4 (16.7)	4 (12.5)	0.71
Number of steroid-sparing therapies before RTX start, mean (SD)	2.9 (1.4)	2.2 (1.1)	3.4 (1.4)	0.001
High-cost therapies (PLEX/IA or IVIG) before RTX start	47 (83.9)	17 (70.8)	30 (93.8)	0.03
Disease severity before RTX start according to MGFA-CC				
I	3 (5.4)	3 (12.5)	0	
IIa	4 (7.1)	3 (12.5)	1 (3.1)	
IIb	8 (14.3)	4 (16.7)	4 (12.5)	
IIIa	8 (14.3)	2 (8.3)	6 (18.8)	
IIIb	15 (26.8)	6 (25)	9 (28.1)	
IVa	5 (8.9)	0	5 (15.6)	
IVb	12 (21.4)	6 (25)	6 (18.8)	
V	1 (1.8)	0	1 (3.1)	
Mild disease (MGFA-CC < 3)	15 (26.8)	10 (41.7)	5 (15.6)	0.029
Moderate to severe disease (MGFA-CC ≥ 3b)	33 (58.9)	12 (50)	21 (65.6)	0.24
RTX, induction therapy				0.9
2 × 375 mg/m^2 within 1–2 weeks	17 (30.4)	8 (33.3)	9 (28.1)	
2 × 500 mg within 2 weeks	15 (26.8)	7 (29.2)	8 (25)	
2 × 1000 mg within 2 weeks	15 (26.8)	6 (25)	9 (28.1)	
Other protocols	9 (16.1)	3 (12.5)	6 (18.8)	
Follow-up characteristics				
RTX, maintenance therapy				0.87
B-cell counts as guide for repeat infusion	24 (42.9)	10 (41.7)	14 (43.8)	
Symptom worsening as guide for repeat infusion	17 (30.4)	7 (29.2)	10 (31.3)	
Fixed dose and interval regardless of B-cell counts and symptom control	3 (5.4)	2 (8.3)	1 (3.1)	
Other protocols or n/a	12 (21.4)	5 (20.8)	7 (21.9)	
Follow-up in months, median (IQR)	20 (10; 53.5)	19.5 (6.3; 41)	20.5 (11.3; 61)	0.20
RTX infusions, median (IQR)	3 (2; 6)	3 (2; 6)	4 (2; 6)	0.24
Medication at last follow-up				
Prednisolone dose tapered at least by 50% compared to RTX start	33/39 (84.6)	15/16 (93.8)	18/23 (78.3)	0.37
Prednisolone discontinued compared to RTX start	23/39 (59)	10/16 (62.5)	13/23 (56.5)	0.71
High-cost therapies (PLEX/IA, IVIG)	13 (23.2)	1 (4.2)	12 (37.5)	0.003
Decrease of antibody titer after RTX therapy	13/20 (65)	4/9 (44.4)	9/11 (81.8)	0.16

Data given are counts (percentages) unless indicated otherwise

anti-AChR-ab Anti-acetylcholine receptor antibodies positive, *IA* immunoadsorption, *IQR* interquartile range, *IVIG* intravenous immunoglobulins, *MG* myasthenia gravis, *MGFA-CC* Myasthenia Gravis Foundation of America-clinical classification, *anti-MuSK-ab* anti-muscle-specific tyrosine kinase antibodies positive, *PLEX* plasma exchange, *RTX* rituximab

was significantly more prevalent, (41.7% vs. 12.5%, $p=0.013$), while the mean number of steroid-sparing therapies before start of RTX was lower and the use of high-cost therapies was less frequent compared to patients without remission (Table 2).

Multivariate logistic regression analysis identified the presence of MuSK antibodies as the only baseline variable independently predicting remission at last follow-up, but confidence intervals were wide (OR 13.33, 95% CI 2.02–87.95; $p=0.007$).

Discussion

We report the largest cohort of MG patients treated with RTX. This is the first comprehensive nationwide study on the topic. In Austria, RTX for adult patients with MG is an off-label, hospital-based treatment given by neurologists. As Austria is a small country with good communication lines between neuromuscular specialists, we assume that, if any, only very few Austrian MG patients treated with RTX would not have been captured by our study.

In line with prior reports and two systematic reviews, we observed that RTX was safe and efficacious [2, 6, 7]. At time of last follow-up (after a median of 20 months), > 40% of patients had pharmacological or complete stable remission, and overall two-thirds of the cohort had at least achieved an MGFA-PiS of MM or better. Correspondingly, the need for high-cost therapies such as IVIG, PLEX or IA had decreased substantially at last follow-up, and in the large subgroup of 39 patients with steroid treatment at the time of RTX, steroids could be stopped or the dose tapered to less than half of starting dose in five of every six patients.

The good response in our cohort is consistent with many previous reports [2, 6, 7, 12–17], though some authors have observed a less favourable response to RTX [18]. Differences in patient selection, intensity of treatment, and definitions of `refractory MG´ may influence reported outcomes after RTX.

In spite of supportive retrospective data in the literature, conclusive evidence for the efficacy of RTX in MG is still lacking. The abundance of literature on the topic comes from retrospective single-centre studies and only few groups have reported small prospective data on RTX for MG [13, 17, 19]. As prospective randomized studies are notoriously problematic in MG, we deem studies reporting national multi-centre cohorts as important for a balanced judgement of this treatment. A recently concluded phase 2 trial of RTX vs. placebo in 52 patients with AchR ab + MG, presented as posters at the American Academy of Neurology Conference in Los Angeles 2018 and the International Congress on Neuromuscular Diseases in Vienna 2018, reported disappointing results [20].

Confirming prior reports, benefit was greatest in patients with MuSK ab + MG [6, 7, 13, 21]. This preponderance of MuSK ab + MG among the subgroup of patients with remission at last follow-up after RTX may be related to the specific pathophysiology of MuSK-ab + MG as a predominantly IgG4-related disorder [22].

The optimal timing of RTX for patients with MG is a matter of debate. For MuSK ab + MG, RTX may well become the first-line treatment in the near future. In contrast, for AchR ab + MG, current guidelines state that RTX should be reserved as escalation therapy [9]. Interestingly, none of our 13 patients with EOMG achieved remission after RTX. This may be due to a selection bias of severely affected patients with longstanding refractory disease. In univariate analysis, longer duration of MG was associated with less favourable response to RTX. An inverse correlation of MG duration and response to RTX has been reported before [6] and may be related to the selection of specific memory B-cell clones through multiple preceding immunosuppressive therapies. These CD27 + IgD- class-switched memory B cells could be more resistant to RTX [18, 23].

In this study, RTX appeared to be relatively fast acting. Despite the high proportion of nearly 60% severely affected patients, defined by an MGFA-CC of 3b or higher before the start of RTX, 3 months after induction therapy pharmacological remission was found in every fourth patient. In a large, retrospective Japanese study in patients with generalized MG, early fast-acting treatment strategies (including high-dose intravenous methylprednisolone, IVIG and PLEX) more frequently and earlier led to an outcome of minimal manifestations or better while keeping the dose of oral prednisolone at ≤ 5 mg/day [24]. Future studies of early aggressive treatment of MG may well consider to include RTX as another relatively fast-acting agent.

In our cohort, RTX was well tolerated and there were no serious safety issues. One patient with refractory LOMG died 4.5 months after the start of RTX, but his death appeared unrelated to RTX, though an association cannot be completely excluded. Despite its increasing use in patients with various autoimmune neurological disorders, long-term safety data of RTX are sparse. A recent study on this topic did not reveal any concerning signals [25]. However, thorough patient counselling and long-term follow-up are mandatory, as there are multiple safety concerns with prolonged RTX use including hepatitis B reactivation, severe hypogammaglobulinemia and late-onset neutropenia [4, 26]. Reactivation of the JC virus is another feared complication following RTX. Our literature search identified two patients with MG who developed progressive multifocal leukoencephalopathy after RTX in combination with other immunosuppressants [18, 27].

The incidence of MG increases with advanced age and shows a clear male preponderance. People above the age

of 65 years constitute more than 50% of the newly diagnosed [28]. In older patients, co-morbidities and co-medications may make treatment choices more complex. In our cohort, RTX was well tolerated, safe and efficacious in older patients, even in octogenarians. Our limited data suggest the consideration of RTX in the aged MG patient.

There is no generally accepted protocol for the use of RTX in MG. In our study, protocols for RTX induction and maintenance therapy varied widely across centres. The majority of patients received an induction therapy consisting of two RTX infusions within 2 weeks. Regarding maintenance therapy, a preplanned fixed-time/fixed-dose protocol (such as 1000 mg every 6 months) was used only in 5.4% of patients, while many patients received repeat RTX infusions either on the grounds of B-cell resurgence at flow cytometry or because of objective clinical deterioration observed during regular follow-up visits. The mode and intensity of induction and maintenance treatment remains controversial [5, 14, 29, 30]. Some authors have suggested that more aggressive treatments result in a more durable response and less relapses [30], while others have observed benefit from relatively low doses of RTX [12, 15]. Apart from the good safety and efficacy data, lower doses and the pending or existent patent expiry in many countries may further improve the cost-effectiveness of RTX for MG [2]. In fact, an ongoing randomized trial in 60 MG patients tests the efficacy of a single RTX infusion of 500 mg vs. placebo, alone or on top of corticosteroid medication [31].

Fixed-time/fixed-dose maintenance protocols may be favourable in previously severely affected patients with repeated episodes of rapid clinical deterioration. However, overtreatment with RTX should be avoided. Following RTX, prolonged B-cell depletion may last many years [32], potentially complicating issues such as the successful treatment of serious immunesuppression-related infections and the finding of a time window for recommended vaccinations.

The limitations of our study originate from its retrospective design. In MG, the assessment of efficacy of a single therapeutic intervention such as RTX can be difficult due to fluctuations of disease severity inherent to MG, overlapping therapies and concomitant diseases. Apart from the potential for selection bias and recall bias, the retrospective nature of the study could lead to an overestimation of favourable outcomes, as MGFA-PIS assessments were constructed from reviewing patients´ charts and letters. Length of follow-up of patients varied, so the association of risk factors and RTX treatment with outcome may have changed with time. We tried to account for this by assessing outcome not only at the time of last follow-up, but also at defined time points after the start of RTX.

In conclusion, this study found that RTX is a well tolerated, safe, efficacious, and relatively fast-acting treatment for patients with MG. Benefit from RTX was greatest in MuSK ab + MG. Placebo-controlled, randomized trials are needed to further clarify the role of RTX in MG.

Funding This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

References

1. Gilhus NE (2016) Myasthenia gravis. N Engl J Med 375:2570–2581
2. Stieglbauer K, Pichler R, Topakian R (2017) 10-year-outcomes after rituximab for myasthenia gravis: efficacy, safety, costs of inhospital care, and impact on childbearing potential. J Neurol Sci 375:241–244
3. Howard JF Jr, Utsugisawa K, Benatar M et al (2017) Safety and efficacy of eculizumab in anti-acetylcholine receptor antibody-positive refractory generalised myasthenia gravis (REGAIN): a phase 3, randomised, double-blind, placebo-controlled, multicentre study. Lancet Neurol 16:976–986
4. Stieglbauer K, Topakian R, Schäffer V et al (2009) Rituximab for myasthenia gravis: three case reports and review of the literature. J Neurol Sci 280:120–122
5. Benveniste O, Hilton-Jones D (2010) The role of rituximab in the treatment of myasthenia gravis. Eur Neurol Rev 5:95–100
6. Iorio R, Damato V, Alboini PE et al (2015) Efficacy and safety of rituximab for myasthenia gravis: a systematic review and meta-analysis. J Neurol 262:1115–1119
7. Tandan R, Hehir MK, Waheed W et al (2017) Rituximab treatment of myasthenia gravis: a systematic review. Muscle Nerve 56:185–196
8. Morren J, Li Y (2018) Myasthenia gravis with muscle-specific tyrosine kinase antibodies: a narrative review. Muscle Nerve 58:344–358
9. https://www.dgn.org/leitlinien/3005-ll-68-ll-diagnostik-und-therapie-der-myasthenia-gravis-und-des-lambert-eaton-syndroms. Access 18 Nov 2018
10. Jaretzki A 3rd, Barohn RJ, Ernstoff RM et al (2000) Myasthenia gravis: recommendations for clinical research standards. Task Force of the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America. Neurology 55:16–23
11. Wolfe GI, Kaminski HJ, Aban IB et al (2016) Randomized trial of thymectomy in myasthenia gravis. N Engl J Med 375:511–522
12. Blum S, Gillis D, Brown H et al (2011) Use and monitoring of low dose rituximab in myasthenia gravis. J Neurol Neurosurg Psychiatry 82:659–663
13. Díaz-Manera J, Martínez-Hernández E, Querol L et al (2012) Long-lasting treatment effect of rituximab in MuSK myasthenia. Neurology 78:189–193
14. Lebrun C, Bourg V, Bresch S et al (2016) Therapeutic target of memory B cells depletion helps to tailor administration frequency of rituximab in myasthenia gravis. J Neuroimmunol 298:79–81
15. Jing S, Song Y, Song J et al (2017) Responsiveness to low dose rituximab in refractory generalized myasthenia gravis. J Neuroimmunol 311:14–21
16. Nowak RJ, Dicapua DB, Zebardast N, Goldstein JM (2011) Response of patients with refractory myasthenia gravis to rituximab: a retrospective study. Ther Adv Neurol Disord 4:259–266

17. Beecher G, Anderson D, Siddiqi ZA (2018) Rituximab in refractory myasthenia gravis: extended prospective study results. Muscle Nerve 58:452–455
18. Afanasiev V, Demeret S, Bolgert F et al (2017) Resistant myasthenia gravis and rituximab: a monocentric retrospective study of 28 patients. Neuromuscul Disord 27:251–258
19. Landon-Cardinal O, Friedman D, Guiguet M et al (2018) Efficacy of rituximab in refractory generalized anti-AChR myasthenia gravis. J Neuromuscul Dis 5:241–249
20. https://clinicaltrials.gov/ct2/show/NCT02110706. Access 18 Nov 2018
21. Hehir MK, Hobson-Webb LD, Benatar M et al (2017) Rituximab as treatment for anti-MuSK myasthenia gravis: Multicenter blinded prospective review. Neurology 89:1069–1077
22. Raibagkar P, Ferry JA, Stone JH (2017) Is MuSK myasthenia gravis linked to IgG4-related disease? J Neuroimmunol 305:82–83
23. Möller B, Aeberli D, Eggli S et al (2009) Class-switched B cells display response to therapeutic B-cell depletion in rheumatoid arthritis. Arthritis Res Ther 11:R62
24. Utsugisawa K, Nagane Y, Akaishi T et al (2017) Early fast-acting treatment strategy against generalized myasthenia gravis. Muscle Nerve 55:794–801
25. Memon AB, Javed A, Caon C et al (2018) Long-term safety of rituximab induced peripheral B-cell depletion in autoimmune neurological diseases. PLoS One 13:e0190425. https://doi.org/10.1371/journal.pone.0190425
26. Kronbichler A, Windpessl M, Pieringer H et al (2017) Rituximab for immunologic renal disease: what the nephrologist needs to know. Autoimmun Rev 16:633–643
27. Kanth KM, Solorzano GE, Goldman MD (2016) PML in a patient with myasthenia gravis treated with multiple immunosuppressing agents. Neurol Clin Pract 6:e17–e19
28. Alkhawajah NM, Oger J (2015) Treatment of myasthenia gravis in the aged. Drugs Aging 32:689–697
29. Muto K, Matsui N, Unai Y et al (2017) Memory B cell resurgence requires repeated rituximab in myasthenia gravis. Neuromuscul Disord 27:918–922
30. Cortés-Vicente E, Rojas-Garcia R, Díaz-Manera J et al (2018) The impact of rituximab infusion protocol on the long-term outcome in anti-MuSK myasthenia gravis. Ann Clin Transl Neurol 5:710–716
31. https://clinicaltrials.gov/ct2/show/NCT02950155. Access 18 Nov 2018
32. Yi JS, Decroos EC, Sanders DB et al (2013) Prolonged B-cell depletion in MuSK myasthenia gravis following rituximab treatment. Muscle Nerve 48:992–993