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10-year-outcomes after rituximab for myasthenia gravis: Efficacy, safety, costs of inhospital care, and impact on childbearing potential

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ABSTRACT

Rituximab (RTX) has emerged as an attractive off-label treatment option for patients with myasthenia gravis (MG) refractory to other immune therapies. However, data on long-term outcome after RTX for MG are still scarce. Here we present the 10-year outcomes [median (range) 10.1 (6.7–11.2) years] with respect to efficacy, safety, costs of inhospital care, and impact on childbearing potential in all four MG patients treated by one of the authors with RTX. In all patients, RTX led to sustained clinical improvement and eventual tapering of other immune therapies. RTX was well tolerated, and complications were not observed. After the start of RTX, annual costs for hospital admissions were markedly reduced compared to costs in the year preceding RTX. Under close clinical observation, two patients had uncomplicated pregnancies giving birth to a healthy child. With regard to its efficacy, excellent tolerance, lack of complications, low frequency of repeat infusions and pending patent expiry in many countries, RTX appears to compare favourably with other immune therapies used for MG. Multicentre trials and registries are urgently needed to further address long-term safety issues and clarify the efficacy and role of RTX in managing MG.

1. Introduction

In patients with generalized myasthenia gravis (MG), long-term steroid-sparing, immunosuppressive treatment is usually needed. However, conventional immunosuppressive agents such as azathioprine, mycophenolate mofetil, or cyclosporine can have intolerable side effects, may fail, or take too long to achieve and maintain a sufficiently stable remission.

In recent years, rituximab (RTX), a monoclonal antibody that depletes B cells and B cell precursors by binding to the CD20 surface antigen, has evolved as a promising off-label treatment option for both anti-acetylcholine receptor antibodies positive (AchR+) MG and anti-muscle-specific tyrosine kinase antibodies (MuSK+) positive MG [1–11].

Despite increasing use of RTX for MG, data on its long-term efficacy, safety, costs, and impact on childbearing potential are still lacking. We report on the 10-year outcomes of all four MG patients treated with RTX and followed up by one of the authors (K.S.).

2. Patients and methods

This retrospective analysis covers all follow-up data obtained until May 31, 2016.

Short term outcomes of three of the four patients have been reported in the *Journal* [1].

Patients underwent regular neurological assessments including the Quantitative Myasthenia Gravis (QMG) score [12].

2.1. RTX protocol

Patients were treated with RTX at a dose of 375 mg/m^2 every week for two consecutive weeks. From 2005 to 2009, we used monitoring of B cell counts with flow cytometry to guide re-treatment with RTX (1 infusion at a dose of 375 mg/m^2). In 2010, concerns regarding potential complications of long-term high-dose treatment with RTX including progressive multifocal leukoencephalopathy (PML) led us to give RTX infusions only after symptoms or signs of clinical deterioration. In case of subjective deterioration patients were obliged to seek neurological consultation and undergo testing for B cell counts to enable further management decisions.

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Table 1
Overview of patient characteristics.

Patientno., sex	MG subtype	Age at Dx of MG	Age, at start of RTX	Follow-up after start of RTX (years)	No. of RTX infusions	All prior immune therapies	Current therapy	QMG score before RTX	QMG score since RTX, worst	QMG score since RTX, most recent	DRG-MG score in the year before RTX	DRG-MG score in years after RTX (mean)	Miscellaneous under therapy with RTX
1, F	AChR+	14	32	11.2	8	PR, AZA, TX, CYC, MMF, PE, IA	PYR as needed	20	12	5	2132	720	Childbirth 2013 (elective Caesarean delivery)
2, F	MuSK+	45	50	10.2	7	PR, IVIg, IA	PYR as needed	13	14	2	7118	815	None
3, F	AChR+	21	22	10.1	6	PR, AZA, TX	PYR as needed	7	6	1	2378	1003	Childbirth 2015 (vaginal delivery)
4, F	MuSK+	32	37	6.7	3	PR, AZA, IVIg	None	7	3	0	6257	625	None

AChR+, anti-acetylcholine receptor antibodies positive; AZA, azathioprine; CYC, cyclosporine; DRG-MG, Diagnosis Related Groups score of hospital admissions related to myasthenia gravis; Dx, Diagnosis; F, female; IA, immunoadsorption; IVIg, intravenous immunoglobulins; M, male; MG, myasthenia gravis; MMF, mycophenolate mofetil; MuSK+, anti-muscle-specific tyrosine kinase antibodies positive; n. a., not applicable; PE, plasma exchange; PR, prednisolone or other steroids; PYR, pyridostigmine; QMG, Quantitative Myasthenia Gravis; RTX, rituximab; TX, thymectomy.

2.2. Impact of RTX on costs of inhospital care

In Austria, RTX for MG represents off-label treatment. Hence, there is no proper reimbursement of the use of RTX itself. The basis for the Austrian reimbursement model of hospital care dates back to the year 2005, in which one DRG point corresponded to one euro. A detailed description of the Austrian healthcare system with its DRG system and heavy reliance on hospital care would go beyond the scope of this paper and can be found elsewhere [13]. We evaluated the impact of RTX on costs of inhospital care for each individual by using a surrogate marker: We compared the DRG score of hospital admissions related to myasthenia gravis (DRG-MG score) in the year before RTX and the mean DRG-MG score in the years after RTX. The DRG-MG score included hospital admissions for tests or treatment of MG, and complications of the disease or its treatment (e.g. immunosuppression-associated infection).

3. Results

Median (range) clinical follow-up after the start of RTX was 10.1 (6.7–11.2) years.

Table 1 gives details on patient characteristics and management of MG.

3.1. Efficacy of RTX

In all patients, the QMG score improved dramatically after initiating RTX therapy, with the worst individual QMG score during follow-up after RTX still substantially lower compared to the individual QMG score before RTX (Table 1; Fig. 1).

The disease course and management of patients 1–3 with follow-up until December 31, 2008 have been reported in the *Journal* [1]. Ever

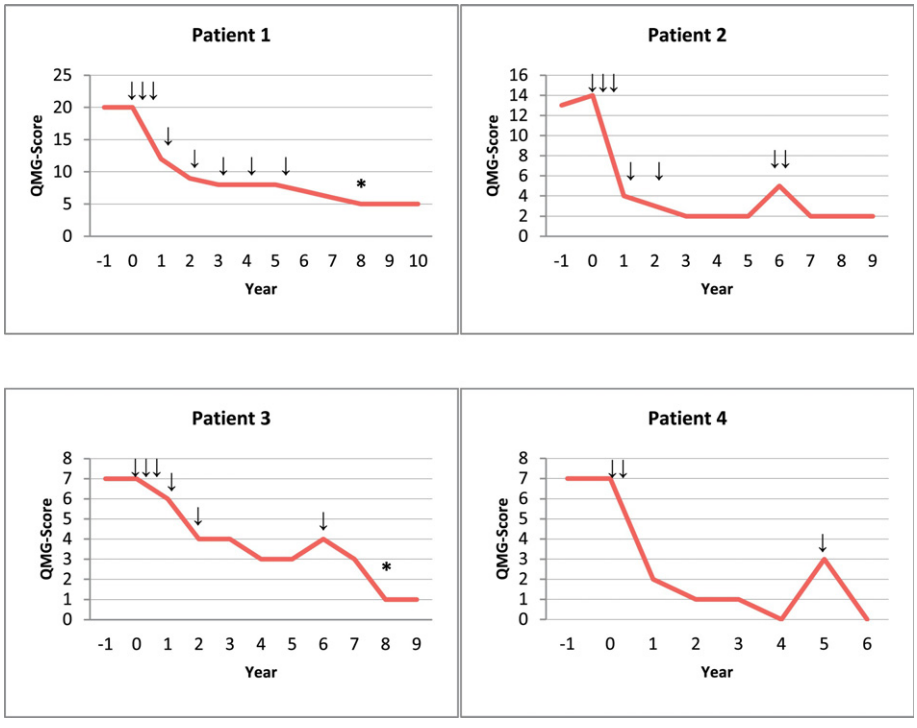

Fig. 1. Frequency of rituximab infusions and corresponding clinical scores QMG score: Quantitative Myasthenia Gravis score; ↓ = rituximab infusion at a dose of 375 mg/m^2; * = child delivery.