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► **To cite this version:**

Paul Maddison. The use of Rituximab in myasthenia gravis and Lambert-Eaton myasthenic syndrome. Journal of Neurology, Neurosurgery and Psychiatry, 2010, 82 (6), pp.671. 10.1136/jnnp.2009.197632 . hal-00591164

HAL Id: hal-00591164

<https://hal.science/hal-00591164>

Submitted on 7 May 2011

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The use of Rituximab in myasthenia gravis and Lambert-Eaton myasthenic syndrome.

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Key words: myasthenia gravis, Lambert-Eaton myasthenic syndrome, Rituximab

Word count: 1633

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Abstract

Aim: To assess the treatment effects of Rituximab in a population of patients with myasthenia gravis and Lambert-Eaton myasthenic syndrome.

Methods: Data on all treated patients in the United Kingdom were collected from referring physicians, with full case ascertainment and follow-up.

Results: Since 2004, 10 patients with generalised myasthenia gravis (three of whom were positive for muscle-specific tyrosine kinase (MuSK) antibodies), and two patients with Lambert-Eaton myasthenic syndrome (LEMS) were treated with Rituximab. Using the Myasthenia Gravis Foundation America postintervention status, three patients (25%) achieved remission, and a further 5 (42%) improved clinically over an 18 month period. Only one patient developed worsening symptoms. The probability of achieving remission was unrelated to the duration of neurological symptoms prior to treatment. All LEMS and MuSK antibody patients improved following Rituximab treatment.

Conclusion: In a relatively large, unselected group of patients with myasthenia gravis and LEMS, Rituximab treatment resulted in significant clinical improvement in two-thirds of cases. As a selective, B-cell targeted therapy, Rituximab should be considered as a treatment option for patients with either myasthenia gravis or LEMS for whom standard immunosuppressive treatments have been unsuccessful.

The use of Rituximab in myasthenia gravis and Lambert-Eaton myasthenic syndrome

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Introduction

Standard immune therapies are usually successful in the treatment of the autoimmune antibody-mediated disorder of generalised myasthenia gravis. However, a proportion of patients respond poorly to conventional immunosuppressant regimens, requiring significant ongoing courses of either plasma exchange (PEX) or intravenous immunoglobulin (IVIg), the beneficial effects of which are often unsustainable. Newer, effective therapeutic options are now being considered for these treatment-resistant patients. Rituximab is a chimeric IgG1 monoclonal antibody treatment (anti-CD20) that depletes the B-cell repertoire of the immune system.[1] It was initially licensed for treatment of B-cell malignancies, but has since been found to be a particularly effective therapy for autoimmune antibody-mediated conditions such as rheumatoid arthritis, where B cells are thought to play a prominent role in autoantibody production.[2] Initial case reports have suggested that Rituximab may also be an important, beneficial form of treatment for myasthenia gravis, a humoral immune-mediated autoimmune disorder of

neuromuscular transmission, when standard immunosuppressive regimens have failed.[3] To date, the experience of the effects of Rituximab in myasthenia gravis is limited to two separate reports of six treated patients,[4-5] two reports of three treated patients,[6-7] and 10 single case reports worldwide.[3, 8-16] A phase II open, pilot study has just commenced, intending to recruit 12 patients with myasthenia over the next 3 years (ClinicalTrials.gov identifier: NCT00774462). All but one of the published case reports to date have suggested that Rituximab is beneficial in treating recalcitrant symptoms of myasthenia. However, with all early reports of this nature, there is inevitably a high likelihood of a positive reporting bias. By using a countrywide search of all incidences of the use of Rituximab in patients with disorders of neuromuscular transmission, we have been able to collate the treatment outcomes in an unselected, larger number of patients, including for the first time, the effect of Rituximab treatment in Lambert-Eaton myasthenic syndrome (LEMS).

Methods

Data from all patients with myasthenia gravis or LEMS, treated with Rituximab, were collected retrospectively from the UK myasthenia interest group (with research ethics committee approval). Members of the group comprise all adult and paediatric neurologists in the UK who run specialist neuromuscular clinics. Responses were obtained from all physicians overseeing neuromuscular clinics in 28 centres in the UK, whether or not they had used Rituximab treatment. Additional responses were obtained from members of the British Muscle Society. It was thought likely that all cases of myasthenia or LEMS who had received Rituximab treatment were seen and assessed at some point by a member of the myasthenia interest group. We considered that the retrospective case ascertainment was complete for the UK. Full demographic details and treatment outcomes were obtained on each patient. Response to Rituximab treatment was graded according to the Myasthenia Gravis Foundation America (MGFA) postintervention status (PIS).[17]

Results

Twelve patients who received Rituximab treatment at least once were identified from eight centres retrospectively. Ten patients had generalised myasthenia gravis, and two LEMS. Eleven (92%) were female, with a median age at disease onset of 21 years (range 2 – 49). All patients had detectable antibodies: acetylcholine receptor antibodies in seven, MuSK antibodies in three, and voltage-gated calcium channel antibodies in the two LEMS cases. Diagnostic confirmatory investigations included positive Edrophonium tests done in seven patients, and abnormal single-fibre electromyography or repetitive nerve stimulation tests performed in nine. Thymic abnormalities were found in six myasthenia patients who underwent thymectomy (thymic hyperplasia in five, thymoma in one), all of whom had positive acetylcholine receptor antibodies. All patients were moderately or severely affected, with MGFA class of between IIIb/IV and V before Rituximab treatment. Bulbar dysfunction was prominent in eight patients (including two MuSK antibody positive patients), and there was evidence of neuromuscular respiratory weakness in six (five requiring invasive ventilation, and one LEMS patient who received nocturnal non-invasive ventilation). In total, ten patients (83%) had evidence of either respiratory failure or bulbar dysfunction.

Prior to Rituximab, all patients had previously been taking prednisolone and 11 at least one type of second line immunosuppressant (see table 1), and all but one had received IVIg with limited benefit. In addition, nine (75%) patients had received various courses of PEX, often used as maintenance therapy to control persistent myasthenic symptoms temporarily. The mean duration of myasthenic or LEMS symptoms prior to Rituximab therapy was 3.3 years (range 2 – 25 years).

Rituximab treatment was given at a standard dose of 375 mg/m² or equivalent in all patients. The commonest dosing schedule was weekly infusions on four consecutive weeks (eight patients), continued as once-monthly infusions in three. Four patients

(three from one institution) only received one or two initial infusions of Rituximab. The infusions were tolerated in all but one patient who developed side effects of fever and rigors after one dose. Over a four to 18 month period following Rituximab therapy, three patients (25%) achieved complete remission of symptoms (MGFA PIS status CSR or PR), only one of whom required any form of ongoing immunosuppression, a reducing dose of ciclosporin (table 1). During ongoing follow-up of 12 to 48 months, a further four

Table 1. Patient demographics and treatment outcomes.

Patient	Gender	Current age (years)	Age at onset (years)	Antibody status	MGFA pre-Rituximab	Previous treatments	Post-Rituximab PIS
1	F	11	5	AChR Ab+	IVa	Tx (normal thymus) PRED, PEX, IVIg	CSR
2	F	20	14	AChR Ab+	V	Tx (hyperplasia), PRED AZA, MMF, PEX, CYC	CSR
3	F	24	13	AChR Ab+	IIIb	Tx (hyperplasia), PRED AZA, IVIg, PEX	U
4	F	25	11 (LEMS)	VGCC Ab+	IVa	PRED, AZA, CIC, MMF IVIg, PEX	I
5	F	29	2	MuSK Ab+	IVb	PRED, AZA, CIC, IVIg PEX	PR
6	F	34	29	AChR Ab+	IIIb	Tx (hyperplasia), PRED AZA, MTX, MMF, IVIg	U
7	F	35	8	AChR Ab+	IVb	Tx (hyperplasia), PRED AZA, MTX, CIC, IVIg, PEX	W
8	F	36	28	AChR Ab+	V	Tx (hyperplasia), PRED AZA, IVIg	I
9	F	40	36	MuSK Ab+	V	PRED, MMF, IVIg, PEX	I
10	M	46	41 (LEMS)	VGCC Ab+	IVb	PRED, AZA, MTX, CIC IVIg, PEX	MM-1
11	F	46	42	AChR Ab+	V	Tx (thymoma), PRED AZA, IVIg	U

(Table 1 continued)

12	F	52	49	MuSK Ab+	IVb	PRED, AZA, MMF, IVIg PEX	I
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AChR Ab = acetylcholine receptor antibody; VGCC Ab = voltage-gated calcium channel antibody; MuSK Ab = muscle-specific tyrosine kinase antibody; Tx = thymectomy; PRED = prednisolone; AZA = azathioprine; MTX = methotrexate; CIC = ciclosporin; MMF = mycophenolate; CYC = cyclophosphamide; CSR = complete stable remission; U = unchanged; I = improved; PR = pharmacological remission; W = worse; MM-1 = minimal manifestations.

patients (33%) responded well to Rituximab, facilitating a significant reduction in their ongoing immunosuppression medication (MGFA PIS MM-1 or I). One patient was able to stop monthly maintenance infusions of IVIg, with moderate symptomatic improvement. Of the remaining four patients, one developed worsening myasthenic symptoms following Rituximab, and still requires ongoing courses of PEX or IVIg, and the other three patients were unchanged. Three patients, initially requiring invasive ventilation, who improved after Rituximab treatment were all weaned from ventilatory support.

Both LEMS patients improved, but did not achieve remission. All three MuSK antibody positive myasthenia patients improved to some degree, with one achieving pharmacological remission. Three of the four patients (patients 3, 6, 8, 11, table 1) who received fewer than four weekly consecutive infusions did not achieve clinical improvement.

Discussion

In a nationwide survey, we obtained data retrospectively on all patients with myasthenia gravis or LEMS in the UK who had received Rituximab therapy. Of twelve patients identified, with follow-up data available for 12 to 48 months, seven (58%) achieved remission, or a significant improvement in symptoms following treatment, with only one patient developing a worsening of symptoms. The lack of significantly beneficial response in 5 (42%) patients is higher than reported cases. Of 28 Rituximab treated cases of myasthenia reported to date, all have shown treatment benefit following Rituximab, except one case of status unchanged.[16] Often, initial reports of new treatments in single cases describe positive outcomes, with fewer accounts of published treatment failures, in the absence of randomised controlled trials. In this study, the inclusion of all treated cases from the whole of the UK has demonstrated a more complete overview of the treatment effects of Rituximab in patients with disorders of neuromuscular transmission.

The lack of response in four patients (including apparent worsening in one) may have been due in part to the lower treatment dosing schedule given to some of these patients. The retrospective nature of this data collection meant that there was no consensus among the treating neurologists in terms of the Rituximab dosing schedule, although patients receiving only one single initial Rituximab infusion came from one centre. In most studies, Rituximab has generally been used at the doses developed for the treatment of B-cell Non-Hodgkin's Lymphoma, 375mg/m² weekly for four weeks. However, the tumour burden in lymphomas is often high whereas in autoimmune disorders such as myasthenia the B cell mass is presumably normal. It was subsequently demonstrated in a retrospective study of patients with idiopathic thrombocytopenia that lower doses of Rituximab were still effective in inducing disease remission in a majority of patients with this B-cell mediated autoimmune disorder.[18] In our study, all three myasthenia patients who received one single Rituximab infusion had significantly depleted B-cell populations in peripheral blood samples taken several months after the Rituximab treatment. As yet, the optimum dosing schedule for Rituximab in autoimmune disorders such as myasthenia and LEMS has not yet been clarified.

In this series, the probability of achieving remission or sustained clinical benefit following Rituximab therapy seemed to be unrelated to the duration of neurological symptoms prior to treatment, with one patient achieving complete remission after 24 years of myasthenic symptoms. Conversely, those who failed to gain benefit from Rituximab infusions had previously had symptoms for between two and 10 years. Nevertheless, it is feasible that earlier, more aggressive treatment with Rituximab may achieve higher rates of remission, as has been seen in rheumatoid arthritis,[19] eliminating the need for potentially harmful, chronic use of steroids and other immunosuppressive agents.

In line with 12 other case reports of MuSK antibody positive myasthenia patients treated with Rituximab, the three MuSK antibody positive patients in this study all benefited from infusions, one achieving disease remission. These findings are reassuring and highlight the potential long term benefits of treatments like Rituximab for a subset of

patients with myasthenia who are often found to have recalcitrant symptoms, compared with acetylcholine receptor antibody positive myasthenia patients.[20] This report also emphasises the potential benefits of Rituximab in patients with LEMS for the first time: the doses of standard immunotherapies required to maintain remission are often high in patients with this disorder,[21] and alternative therapies need further evaluation. It should be noted that although no serious, significant side effects were encountered by our 12 patients, recent reports of the development of progressive multifocal leucoencephalopathy in other autoimmune diseases treated with Rituximab should be borne in mind when considering the use of Rituximab in future patients with myasthenia or LEMS. [22]

Overall, Rituximab seems to be a safe, effective treatment for patients with both myasthenia and LEMS, perhaps for patients requiring maintenance invasive therapy such as PEX or IVIg, but as yet the optimum timing of treatment commencement, and the lowest efficacious dosing schedule need to be established from randomised trials.

Competing interests: none.

Funding: none.

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