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ORIGINAL COMMUNICATION

Rituximab as induction therapy in refractory myasthenia gravis: 18 month follow-up study

Nishita Singh[1] · **Vinay Goyal**[1]

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Abstract

Background Myasthenia gravis is an immune-mediated disorder characterized by easy fatigability and diurnal variation in skeletal muscle weakness. Aim of therapy is to prevent crisis and maintain remission. However, despite standard therapy, some remain refractory to treatment.

Aims and objectives To look for efficacy of rituximab in treating refractory myasthenia gravis (MG) in the form of MGFA-PIS score, number of crisis, and dose reduction in immunotherapies.

Material and methods A retrospective study was performed in patients with myasthenia gravis (MG) referred to the All India Institute of Medical Sciences (AIIMS) from January 2012 to December 2017 with follow-up of at least 6 months.

Results Eight refractory MG patients (six AchR positive and two Musk-positive) were identified on oral corticosteroids and azathioprine. After four cycles of rituximab, all patients showed a dose reduction of whom seven were completely tapered off prednisone and there was a 53.8% dose reduction in azathioprine. All patients were continued on AZA after RTX infusion unless contraindicated. Seven achieved minimal manifestation (MM)—2 status as per the MGFA-PIS scale. None of the patients had infusion associated reactions or cytopenia post-RTX infusion.

Conclusion In this small retrospective study, we used RTX as induction therapy and results suggest that repeated RTX infusions may not be necessary as it adds to cost of therapy, especially in LMIC like India.

Keywords Myasthenia gravis · Rituximab · Refractory myasthenia gravis · Immunetherapy

Introduction

Myasthenia gravis is an immune-mediated disorder of the neuro-muscular junction NMJ) at post-synaptic level characterized by easy fatigability and diurnal variation in skeletal muscle weakness, sometimes, leading to respiratory failure. Recent studies have shown a prevalence of more than 200 in 1 million from 100 to 140 out of 1 million, and the incidence ranges between 9 and 30 out of 1 million [1].

Current therapy consists of symptomatic therapy with acetylcholinesterase inhibitors and immunotherapy such as corticosteroids, plasmapheresis (PLEX), and intravenous immunoglobulin (IVIg) for myasthenic crisis and azathioprine (AZA), mycophenolate mofetil (MMF), cyclosporine (CYC), and methotrexate (Mtx) as an immune modulating agent for long-term remission and for prevention of crisis. However, despite standard therapy, some patients remain symptomatic/refractory or may develop adverse effects of drugs. At this stage, newer therapeutics are, thus, desirable, particularly long-term steroid sparing agents with fewer adverse effects.

Immune pathogenesis of MG suggests an important role of autoreactive B cells which would, thus, be an appropriate target for therapy [2]. Currently, rituximab, a novel B-cell-directed biologic, has been used extensively [2]. Till date, the evidence for use of rituximab (RTX) in MG is based on case reports, clinical series and meta-analysis [3], and there is lack of evidence from randomized-controlled trial. In addition, evidence regarding superior utility of RTX in AchRAb positive, MusK antibody-positive, or double seronegative over other immunomodulating therapy needs to be evaluated.

We report our experience with rituximab in eight patients with refractory generalized MG. This is the largest study

✉ Nishita Singh
nishitaneurology@gmail.com

[1] Department of Neurology, Neurosciences Centre, All India Institute of Medical Sciences, New Delhi 110029, India

from single center in India with long follow-up of one and a half years.

Methods

This is a retrospective study of eight patients with refractory myasthenia gravis MG (defined as refractory as per the international consensus criteria by MGFA) [4] referred to the All India Institute of Medical Sciences (AIIMS) between January 2012 and December 2017 with follow-up of at least 6 months (Table 1). These were patients whose post-intervention status (PIS) was unchanged or had worsened after corticosteroids and at least two other immune-suppressive agents. Patients were evaluated before and after rituximab treatment and each patient was categorized as per the MGFA classification.

RTX was given at a standard dose of 375 mg/m^2. Each cycle was defined as one infusion per week for 4 consecutive weeks. Hemogram and liver function tests were checked, prior to every infusion. CD19/20 values were recorded if available. Repeat cycle was planned at 6 month interval if required. All patients were on prednisone and azathioprine prior to RTX therapy and their doses were modified as per the discretion of treating physician.

Table 1 Baseline characteristics

	1	2	3	4	5	6	7	8	Median, range
Age	29	40	32	57	52	43	28	24	36, 24–52
Gender	M	M	M	M	M	M	M	F	7M/ 1F
Follow-up at AIIMS (months)	36	51	204	18	168	208	240	8	109.5, 8–240
Antibody status	MusK	AchR	MusK	AchR	AchR	AchR	AchR	AchR	2 MUSK / 6 AChR
Antibody titres at baseline (nmol/l)	NA	> 40	NA	> 40	> 40	> 40	30	> 40	
Disease duration (months)	84	66	204	200	168	264	240	10	184, 10–264
No. of crisis/ impending crisis before RTX	3	5	1	1	1	1	3	4	2, 1–5
Treatment of crisis	PLEX	PLEX	IVIg	IVIg	PLEX	IVIg	PLEX	IVIg-2, PLEX-2	5 PLEX / 4 IVIg
Thymectomy	No	Yes	Yes	No	Yes	Yes	No	No	4 Thymectomy
Baseline MGFA	IIA	IIIB	IIB	IIIB	IIA	I	IIIB	IIIB	
MGFA worst grade	IVB	IVB	IVB	IVB	IVA	IIIB	IVB	IVB	
Baseline immunosuppressants	CS + AZA	CS + AZA	CS + AZA	CS + AZA	CS + AZA	CS + AZA	CS + AZA	CS + AZA	
Dose of AZA before RTX, mg	175	150	225	200	150	225	150	100	162.5
Baseline prednisone dose (mg/d)	20	10	10	30	30	30	30	40	30
Adverse effects	Abn LFT	Later HBsAg positive	None	Abn LFT	AVN	Abn LFT	None	None	

Abn Abnormal, *AZA* azathioprine, *AchRab* acetylcholine receptor antibody, *anti-MUSK* anti tyrosine receptor antibody, *AVN* avascular necrosis of femur, *CS* corticosteroids, *IVIg* IV immunoglobulin, *MG* myasthenia gravis, *MGFA* Myasthenia Gravis Foundation of America, *MMF* mycophenolate, mofetil, *PLEX* plasma exchange, *NA* not available

Results

Eight refractory MG patients were identified who were treated with RTX. All patients showed improvement in symptoms as well as signs along with dose reduction of various drugs (Table 2). All patients showed improvement (*I*) after RTX therapy and seven out of eight achieved minimal manifestation, MM 2 status as per the MGFA-PIS scale. None of the patients had reactions documented during rituximab infusion or cytopenia or opportunistic infection post-RTX infusion (Table 2).

In seven out of eight patients, steroids were completely tapered off after four infusions of rituximab. All patients were continued on AZA on the same dose after RTX infusion unless contraindicated. Three out of eight patients developed transaminitis which led to dose reduction of AZA in two patients and one patient was switched to mycophenolate mofetil due to recurrent episodes of transaminitis even at low doses of AZA and positive TPMT assay (Patient 1).

One patient developed avascular necrosis of femur secondary to steroid use. One patient was later found to be HBsAg positive, probably due to prior history of receiving multiple cycles of PLEX for treating myasthenic crisis (patient 2). He was started on anti-viral therapy and is now under gastroenterology follow-up. Three months after detection of Hepatitis B and after consulting the treating gastroenterologist, he was started on low dose of AZA (100mg) and is currently tolerating it well. All these patients received rituximab as they continued to have relapses despite being on steroids and add-on azathioprine (2 mg/kg for at least more than 3 months) (Table 1).

Discussion

The standard initial treatment of MG comprises of corticosteroids followed by add-on therapy with azathioprine, mycophenolate mofetil, cyclophosphamide, cyclosporine, methotrexate, or tacrolimus. Intravenous human immunoglobulin (IVIg) and plasma exchange (PLEX) can be used to treat acute exacerbations or as maintenance therapy or preoperatively before thymectomy. There are several drawbacks of corticosteroid therapy, including serious adverse effects with long-term use, lack of response in some patients, and need of add-on therapy in many other patients which, in turn, have their own side-effects [5].

About 10–15% patients referred to a tertiary center have refractory disease, thus, leading to substantial disease burden and economic loss. These are more likely younger females, undergone thymectomy, and are MusK-positive patients [6]. Hence, there is an emerging need to identify safe, faster, and effective treatment for this subgroup of patients.

Rituximab is an alternative treatment for refractory MG which is an appealing option due to its mechanism of action targeting CD20-positive B cells which are involved in the disease process of MG. However, it is still considered as a second-line therapy in MG when there is no response to the first-line agents.

Table 2 Outcomes at last visit

	1	2	3	4	5	6	7	8	Median
Baseline MGFA	IIA	IIIB	IIB	IIIB	IIA	I	IIIB	IIIB	
MGFA-PIS									
MM Change in status	MM-2 I	MM-1 I	MM-1 I	MM-1 I	MM-1 I	MM-2 I	MM-2 I	MM-2 I	
Immune medications at final visit, dose in mg	MMF 1500	AZA 100	AZA 200	AZA 100	AZA 100	AZA 100	AZA 100	AZA 100	
No. of crisis after RTX	None	None	None	None	None	None	None	None	
Add on drug apart from steroids at last visit	No	No	No	Yes	No	No	No	No	
Final prednisone dose (mg/d)	No	No	No	10	No	No	No	30	
On PLEX/IVIg after RTX	None	No	No	No	No	No	no	No	
No. of RTX Cycle, Infusions	1, 4	1, 4	1, 4	1, 4	1, 4	1, 4	1, 4	1, 4	
Duration of follow-up after RTX, mon	20	27	29	14	21	16	14	16	18
CD 19/CD 20 count at baseline (%)	28/18	18/12	14/12	30/16	24/18	22/19	22/16	18/11	
CD 19/CD 20 count at 6months after RTX (%)	< 1/ < 1	< 1/ < 1	< 1/ < 1	< 1/ < 1	< 1/ < 1	< 1/ < 1	< 1/ < 1	< 1/ < 1	
TLC at baseline (mm^3)	9820	8830	7520	9330	7330	6440	6560	8220	
TLC at 4 weeks after RTX (mm^3)	7650	7830	5540	8340	5900	4800	5900	7340	
TLC at 8 weeks after RTX (mm^3)	6680	7520	6100	8100	6200	4200	5100	6140	

AZA azathioprine, *IVIg* IV immunoglobulin, *MG* myasthenia gravis, *MGFA* Myasthenia Gravis Foundation of America, *MMF* mycophenolate mofetil, *PLEX* plasma exchange, *MM* minimal manifestation, *I* improvement

The protocol adapted for RTX infusion in MG is that used in treatment of non-Hodgkin lymphoma, comprising of 4 weekly infusions at 375 mg/m2 which represents one cycle. This was followed by repeat treatment every 6 months. For MG, no ideal dose has been established; however, some use peripheral B-cell count CD19 and CD20) as a marker to restart RTX infusions [7]. All our patients had a remarkable decrease in CD 19/20 counts and they continued to remain suppressed (< 1%) even 6 months after RTX infusion.

In a recent systematic review [3], 169 patients with refractory MG, treated with RTX showed significant reduction in the proportion of relapses in patients positive for AChR antibody (93% before vs. 26% after, $P < 0.001$) and MuSK antibody (100% before vs 14% after). In patients with MUSK antibodies, there was a larger reduction in the number of relapses ($p = 0.04$). Only one out of seven sero-negative MG patients responded to RTX. There was no effect of age of onset of myasthenia, gender, duration of disease, number of previous immunosuppressive therapies, number of pre-treatment relapses, and RTX dose regimen on improvement. On multi-variate analysis, predictors of improvement were: MuSK positivity MG, mild-to-moderate disease, and age less than 45 years at the time of treatment (OR 2.4 for age < 45 years). Better response in patients with MusK positivity is probably due to a lower frequency of IL-10 producing B cells in these patients [8]. Adverse reactions were seen in 14% patients (flushing in 3 and one each of agranulocytosis, pneumonia, bronchitis, dyspnoea, MI, altered sweet taste, chills and rigor, rash, pruritus, reactivation of oral herpes zoster, and spondylodiscitis) [3].

In present retrospective analysis of eight patients with refractory myasthenia gravis, we show that rituximab led to a sustained clinical improvement for median duration of 109.5 months along with reduction or discontinuation of corticosteroid therapy. At time of this analysis, all patients had been followed up for at least 6 months after the last RTX infusion and patients with less than 6 month follow-up were excluded. Our results support the hypothesis that rituximab can be helpful in managing refractory MG and is in agreement with the previous reports and meta-analysis [1, 3].

Unlike the usual belief that RTX is a relatively dangerous drug in terms of adverse effects, none of the patients in our study develop any infusion reaction after pre-treatment. All patients appeared to tolerate rituximab with no severe hematologic derangements. One patient had reactivation of hepatitis B after 1 year of RTX infusions (probably due to multiple PLEX, he had received in past) and is currently on antiviral therapy.

In this short follow-up study, RTX was used as drug to induce remission and none of the patients have had recurrence/worsening of symptoms post-induction nor did they require repeated infusions of RTX as they maintained their MGFA-PIS status on AZA post-RTX induction.

Like any low–middle-income countries (LMIC), in India too, cost of therapy is a huge burden on patient and family. It is a crucial factor in decision-making for long-term treatment. Post-RTX, there was a significant decrease in cost of long-term therapy by 15%, if we exclude one patient who was started on MMF post-RTX as cost of MMF is almost five times more than AZA. In addition, there was no crisis seen post-RTX which led to further cost reduction by 35%.

However, it should also be kept in mind that RTX in itself is an expensive drug and maintenance therapy every 6 months may not be feasible in every patient. This suggests that repeated RTX infusions may not be necessary as it adds to cost of therapy, especially in LMIC. AZA has been tried and tested for long-term use [9]. Adverse effects of long-term use of AZA are well defined and mentioned in the literature, whereas long-term adverse effects of RTX, a relatively new drug, are still under evaluation. We, thus, routinely favor AZA over RTX in terms of long-term use.

Apart from rituximab, yet another biologic which is the first drug approved for refractory MG and has shown to have promising results is eculizumab which acts against complement C5, thus, interfering the formation of membrane attack complex at the motor end-plate. This approval was based on a phase 2 REGAIN study which was followed by a phase III trial [10]. However, statistically significant results were found only in secondary end-points and primary end-points of the study were not met. In addition, the cost of therapy is a major deterrent in choosing it as a first option in patients with refractory MG.

The small, retrospective nature is a limitation of the current study and it emphasizes the need for a large prospective controlled trial to make more definitive conclusions regarding the efficacy of rituximab in the treatment of refractory MG.

Conclusion

In "conclusion", the marked effect of rituximab as induction therapy in patients with refractory MG in our clinic as well as its response in similar studies is promising, and suggests that further investigation of this agent in MG is warranted.

Compliance with ethical standards

Conflicts of interest There are no conflicts of interest in submission of this manuscript.

Ethical approval The study was approved by an ethics committee and/or follows the tenants of the Declaration of Helsinki.

Informed consent Informed consent was obtained from all the patients which should be included in the manuscript.

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