Effective Early Treatment of AChR Antibody-Positive Myasthenia Gravis with Rituximab; the Experience from a Neuroimmunology Clinic in a Developing Country

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ABSTRACT

BACKGROUND: Rituximab is reserved for treating refractory myasthenia gravis (MG) patients. Here we report our experience with rituximab in AChR antibody positive generalized MG (gMG) and impending myasthenic crisis (IMC).

METHODS: This retrospective, observational study, conducted at a tertiary care, neuroimmunology clinic, analyzed the data of patients with AChR antibody positive gMG, treated with rituximab between 1st January 2016 and 30th October 2018.

RESULTS: Eleven patients with AChR antibody positive gMG received rituximab. Mean age of the cohort was 50.54 ± 18.71 years with 9 males. Seven out of 11 patients received rituximab in the early stage (<2 years from onset) and had good response to treatment. Four of the 5 patients with IMC improved with rituximab alone. In the 10 patients who regularly followed up, there was a significant difference between the QMG scores at baseline and at 1, 2, 6, 12, and 18 months ($P < .0001$).

CONCLUSION: Rituximab appears to be a potentially effective early treatment option for AChR antibody positive generalized MG and impending myasthenic crisis.

KEYWORDS: Rituximab, myasthenia gravis, impending myasthenic crisis, B cell therapy, acetyl choline receptor antibody, early generalized myasthenia

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Introduction

Myasthenia gravis (MG) is an autoimmune disorder affecting neuromuscular transmission. It is caused by antibody mediated attacks on the nicotinic acetylcholine receptors (AChR), muscle specific tyrosine kinase (MuSK), and various other novel targets like anti-lipoprotein-related protein 4 (LRP4).[1,2] It is treated symptomatically with acetylcholinesterase inhibitors while the autoimmune attack is treated with conventional immunosuppressants like steroids, azathioprine, mycophenolate, cyclosporine, tacrolimus, and methotrexate.[3–7] Approximately 15% to 20% patients with MG experience at least 1 myasthenic crisis (MC) episode in their life.[8] Intravenous immunoglobulin (IVIg) or therapeutic plasma exchange (TPE) is used for acute treatment of MC and also for moderate to severe worsening of myasthenia gravis. A subgroup of patients, estimated to be about 10% to 20%, do not respond adequately to conventional immunosuppressants, develop adverse events or require continous treatment with IVIg or TPE and are termed refractory.[9] Refractory MG patients have more frequent clinical exacerbations, more often need rescue treatments with IVIg or TPE and escalation of immunosuppressive drugs and are more vulnerable to side effects. Treatment of refractory MG is a challenge and often requires newer agents like rituximab or eculizumab.[10,11]

Immunomodulation in MG is difficult as there are several challenges associated with the existing immunosuppressive treatments. Steroids, though effective, have the potential to worsen myasthenic symptoms and precipitate MC, especially at higher doses, within the first 2 to 3 weeks of the initiation of therapy. The long-term side effects of steroids include hyperglycemia, hypertension, hypokalemia, acneiform eruptions, cushingoid features, cataract, avascular necrosis, gastric ulcers, and opportunistic infections like tuberculosis.[12,13] Immunomodulators like azathioprine or mycophenolate take 3 to 4 months or longer to produce clinical improvement. Azathioprine has the potential to cause bone marrow suppression and liver dysfunction in certain patients.[5,13] Mycophenolate is known to be associated with leucopenia and an increased risk of infections.[12,13] IVIg is prohibitively expensive for most patients in developing countries and the effect lasts only for a few weeks. TPE is less expensive than IVIg but is still beyond the resources of many patients in developing countries. It is also inconvenient, uncomfortable, cumbersome, and needs specific equipment and a specialized team. It also carries the risk of infection at the vascular access site and hypotension during treatment.[5] Overall, the conventional treatment options for MG have many associated side effects and, in addition, resistance to treatment is reported in 10 %to 15% of patients.[14,15]

This has led to a search for alternative therapies that can overcome these limitations.

Rituximab has been used off-label as an effective treatment for MG refractory to other immune therapies. Rituximab is a genetically engineered mouse/human IgG1-kappa chimeric monoclonal antibody directed against CD20 surface antigens on B-cells. A systematic review and meta-analysis of case reports and case series have shown that rituximab is effective for MG patients refractory to immune therapies.[16–18] Most of these patients were AChR positive and had refractory disease, which may account for the less impressive effect of rituximab. Rituximab has several advantages: it has a faster onset of action when compared to other immunosuppressants, longer duration of action, less frequent infusions, and favorable side effect profile.[19,20] Rituximab might be more efficacious if administered during the early stages of gMG. This study aims to analyze the efficacy of rituximab in AChR antibody positive generalized Myasthenia Gravis (gMG) patients especially those who received it within 2 years of onset of MG and in those with impending myasthenic crisis (IMC).

Methods

This retrospective, observational study was conducted in the neuroimmunology clinic, at a tertiary care center, Bengaluru, in south India. The study analyzed the data of patients with gMG who were treated with rituximab between 1st January 2016 and 30th October 2018. MG was diagnosed based on the clinical features, electrophysiological findings, and AChR antibody assay.

For practical purposes we discriminated MGFA II, III, and IV based on the severity of muscle weakness as assessed by MRC muscle power grading. MGFA II—MRC grade 4/5 or fatigable weakness, MGFA III—MRC grade 3/5, MGFA IV—MRC grade 1-2/5. All patients with gMG who were AChR antibody positive and treated with rituximab with a minimum follow-up period of 18 months were included. MuSK antibody positive patients were excluded. Clinical details, QMG scores and adverse effects were collected from the case records of the patients.

For the purposes of this report, early stage MG (ESMG) was defined as generalized MG of less than 2 years from symptom onset and late stage MG (LSMG) as more than 2 years. MG was classified in accordance with the Myasthenia Gravis Foundation of America (MGFA) Clinical Classification.[21] MG patients with worsening muscle weakness resulting in respiratory failure, weakness of the pharyngeal, and upper airway musculature, or both, that requires mechanical ventilation and intubation was considered as having myasthenic crisis (MC).[20] Impending Myasthenic Crisis (IMC) was defined as "rapid clinical worsening of MG that, in the opinion of the treating physician, could lead to crisis in the short term (days to weeks)."[5]

Data was tabulated on Microsoft Excel and analyzed using MINITAB Express 1.5.1. One-way analysis of variance (ANOVA) and the Tukey simultaneous range test was used to compare QMG scores at baseline, 1, 2, 6, 12, and 18 months to evaluate the efficacy of rituximab. The results of these tests were considered statistically significant if $P < .05$.

Results

The study included 11 patients (9 male, 2 female) with AChR antibody positive gMG treated with rituximab. The mean age of the cohort was 50.54 ± 18.71 years (range 18-75). Based on the MGFA clinical classification, 1 patient had class IIb, 3 IIIa, 2 IIIb, 3 IVa, 1 IVb, and 1 class V MG, at the time of rituximab initiation (Table 1). 7/11 patients who had early stage of myasthenia (<2 years) received prednisolone and azathioprine only for a short period ranging from 2 weeks to 3 months. Of 4/11 patients who had late stage myasthenia (>2 years), 3 were on prednisolone and azathioprine for 3 to 5 years, while 1 was on azathioprine and methotrexate for three 3 years. There was no recent change in the dosage of any ongoing immunosuppressants. Thymectomy was performed only in 2 patients. Patient 3 underwent thymectomy after 6 months of MG diagnosis, while in patient 7 it was performed after 1 year. Patient 3 presented with MC after 12 months of thymectomy, while patient 7 presented with worsening of myasthenia 10 months after thymectomy. Patient 5 received TPE 12 months before and patient 6 received IVIG 6 months before starting rituximab. Patient 8 received IVIG 12 hours after his rituximab as his respiratory distress progressed rapidly.

All patients received at least 2 doses of 500 mg rituximab 2 weeks apart. Three patients received an additional rescue dose of rituximab (500 mg 2 weeks apart) as their clinical improvement was unsatisfactory after 1 to 2 months. Of these 3 patients, 2 responded favorably to the rescue dose and the third patient had dropped out due to lack of significant improvement. Details and outcomes of patients are shown in a flow chart (Figure 1). In the 10 patients who regularly followed up, 1-way ANOVA and Tukey simultaneous tests revealed that there was a significant difference between the QMG scores at baseline and at 1, 2, 6, 12, and 18 months ($F(5, 56) = 13.65$, $P < .0001$). Seven out of 10 patients received rituximab in the early stage of gMG (ESMG) and 3 patients received after 2 years of disease onset (LSMG). All patients with ESMG had a significant response to rituximab. The changes in the QMG scores over the 18-month period for whole cohort is shown in Figure 2. Once the rituximab was started the baseline medications were continued in the same dosages for the first 1 to 3 months. There after a slow taper was started and by 6 to 18 months we could wean majority (7/11) of the patients from steroids and other immunosuppressive medications.

Five patients with IMC were initiated on rituximab directly without IVIg or TPE (Figure 3). Four out of 5 patients stabilized over a period of 1 week and were discharged from the inpatient care by the end of the second week. They were managed with rituximab alone with standard dose of oral

Table 1. Baseline characteristics of the rituximab cohort.

PATIENT NO.	AGE	SEX	DURATION OF MYASTHENIA	PAST TREATMENT	MYASTHENIA GRAVIS CLASSIFICATION	QMG BASELINE	NO. OF PAST MYASTHENIC CRISES	IMPENDING MYASTHENIC CRISIS
1	62	M	1 Year	P, Az	IVa	21	0	Yes
2	45	F	11 Years	P, Az	IVa	24	2	Yes
3	66	M	1.5 Years	P, T	IVa	18	1	Yes
4	68	M	12 Years	Az, MTX	IVb	15	1	Yes
5	60	M	1.5 Years	P, Az, TPE	IIIa	13	1	No
6	61	M	1 Year	P, Az, IVIG	IIIb	17	3	No
7	75	M	1 Year 10 months	P, Az, T	IIIb	11	2	No
8	40	M	1 Year	IVIG	V	29	0	Yes
9	27	M	1 Year	P, Az	IIIa	12	0	No
10	34	M	12 Years	P, Az	IIb	11	1	No
11	18	F	1 Year 11 months	None	IIIa	16	0	No

P, prednisolone; Az, azathioprine; MTX, methotrexate; TPE, therapeutic plasma exchange; IVIG, intravenous immunoglobulin; T, thymectomy.

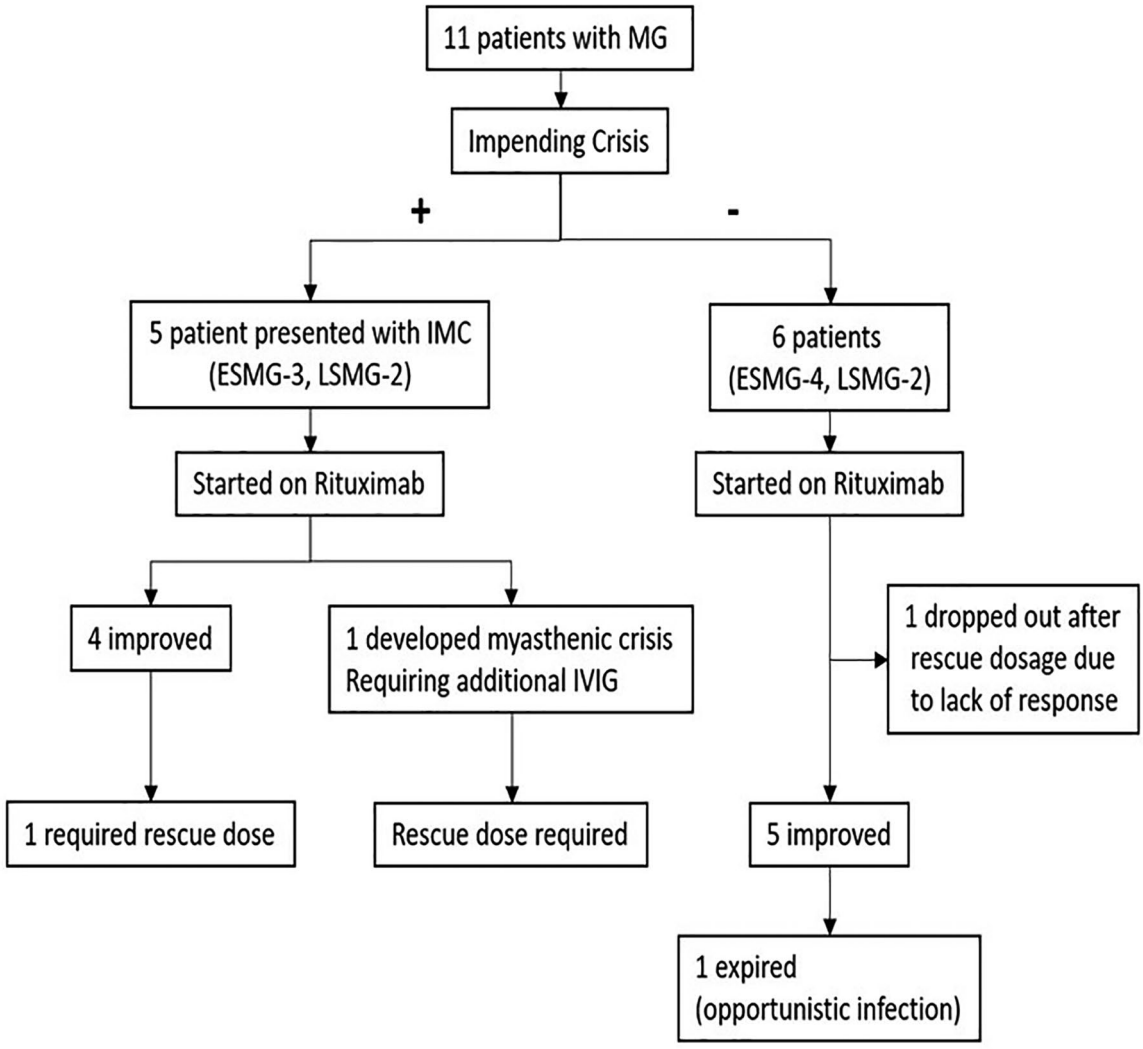

Figure 1. Summary flowchart.

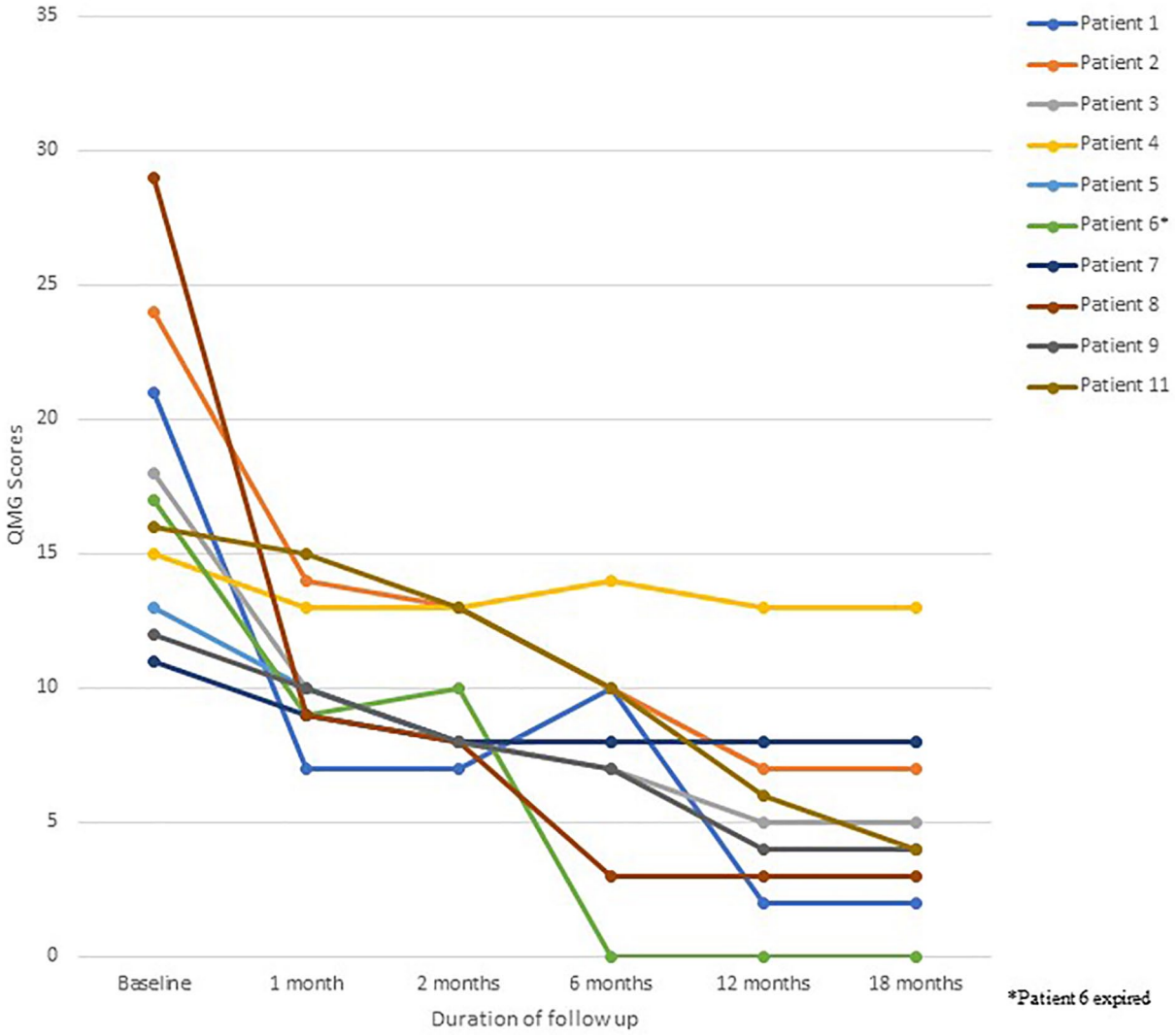

Figure 2. Changes in QMG scores of the rituximab cohort.
The QMG scores at baseline, 1, 2, 6, 12, and 18 months while on rituximab infusion are depicted for all patients in the study.

pyridostigmine. Improvement in bulbar and respiratory muscle weakness was noted by the second to third day post-infusion of rituximab. Only 1 out of the 5 patients had a rapidly progressive course and required ventilation and IV immunoglobulin administration within 12 hours of starting rituximab. This patient was discharged after a period of 2 weeks after receiving another 500 mg of rituximab. All these patients were maintained on 500 mg rituximab infusion every 6 to 12 months, based on their myasthenic symptoms. At 1 year follow up all the 5 patients with impending crisis had achieved Myasthenia Gravis foundation of America post intervention status scale of Minimum Manifestations (MM-3).

Rituximab was well tolerated by most patients. Rituximab infusion was not associated with any serious infusion reactions. Most of the patients received a very slow infusion of rituximab over 10 to 12 hours. Two patients with late MG with history of previous immunosuppressive drug exposure in the past had infectious complications. One had tuberculous lymphadenitis and another Pott's spine. The patient with tuberculosis of the spine developed anti-tubercular drugs induced liver injury and succumbed to the illness. Two patients aged 63 and 65, had malignancies discovered at 16 and 18 months after receiving rituximab, 1 carcinoma of prostate and 1 squamous cell carcinoma of stomach.

Discussion

Over the past decade, rituximab has been used in refractory MG by neurologists worldwide with encouraging results.[12] Rituximab has been found extremely effective in MuSK myasthenia, but its usefulness in AChR positive myasthenia is debated. In the current study riruximab was found to be potentially useful in AChR positive myasthenia, especially for patients in the early stages (<2 years) and for patients with impending myasthenic crisis. Ten of the 11 patients improved on treatment with rituximab, as indicated by their QMG scores. Rituximab produced an early improvement and this

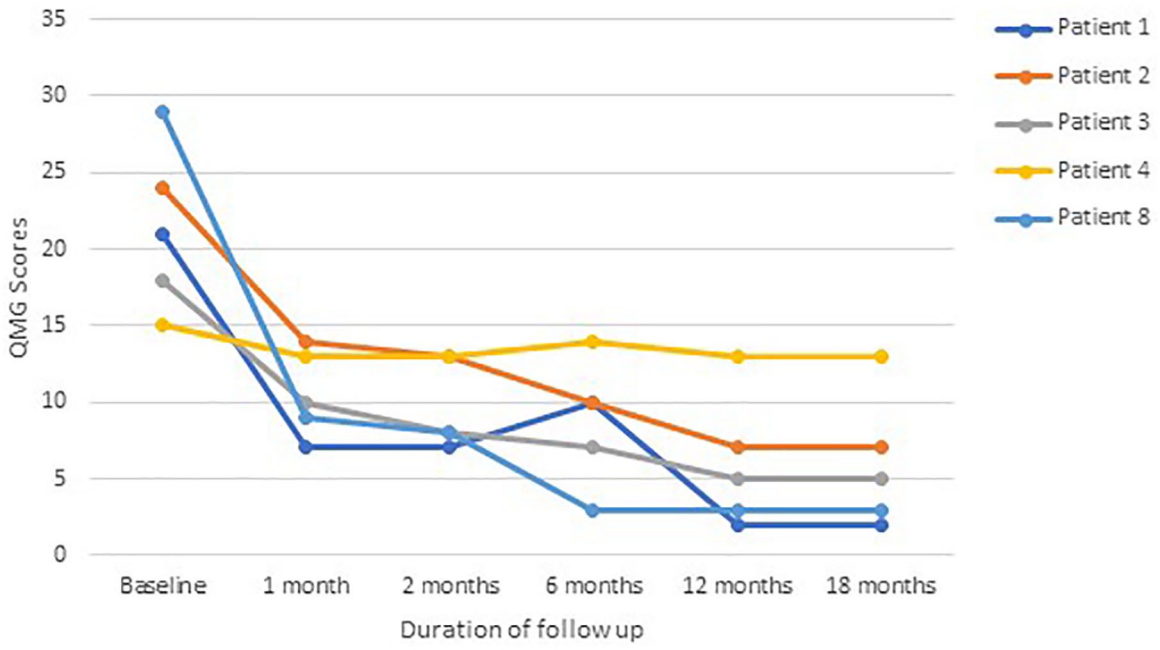

Figure 3. Changes in QMG scores in impending myasthenic crisis.

effect was sustained over a period of 18 months. Lindberg and Bokarewa[22] reported 5 cases of AChR positive MG patients who were treated with rituximab. The study demonstrated that rituximab was effective in the treatment of patients with recent onset MG as well as in patients with long-standing MG with marked decrease in the QMG scores after rituximab treatment. Maddison and colleagues also demonstrated in a relatively large, unselected group of patients with MG and Lambert-Eaton myasthenic syndrome (LEMS) that rituximab was associated with a significant clinical improvement in two-thirds of cases.[23]

Brauner et al[24] showed that rituximab was much better than conventional immunosuppressants and was more effective when administered within 12 months of disease onset. In our cohort also those with early stage generalized MG responded well to the treatment and had the least side effects.

In this study we used a lower dose protocol (500 mg 2 weeks apart) of rituximab unlike the standard protocol of 375 mg/m^2 weekly for 4 consecutive weeks or 1000 mg twice 2 weeks apart. This lower dose protocol was chosen due to following reasons:

a. Based on our experience with rituximab in multiple sclerosis, where we use low dose regimens.[25,26]
b. Pure B cell mediated disorders may respond well to smaller doses of rituximab.[27,28]
c. If lower doses are not effective, there is always a possibility of re-dosing at a later time.
d. The less frequent injections also may reduce cost in resource limited settings.
e. Adverse effects due to immunosuppression may be less with low intensity regimen.

In a recent report by Brauner et al,[24] from Sweden a low-dose protocol used for multiple sclerosis consisting of a single infusion of rituximab 500 mg every 6 months was used for treating myasthenia gravis and was found to be effective when compared to conventional immunosuppressants.

There may be a confounding effect of previous treatment and thymectomy on the improved outcomes with rituximab. However, the beneficial effect of rituximab is unlikely due to previous treatments in our patients as they presented with worsening symptoms and impending myasthenic crisis while on these medications and post thymectomy.

There were only 2 patients who underwent thymectomy and presented with worsening of myasthenia at or within 1 year post thymectomy. Thymectomy is unlikely to account for the improvement seen immediately after rituximab treatment. However thymectomy may have a role in the long term good outcome in these patients.

These observation though from a small cohort may argue for an early use of rituximab rather than reserving rituximab for refractory cases. In early stage generalized MG, rituximab may be a good option for several reasons. In the first place, its onset of action is much faster than azathioprine or mycophenolate. Ninety percent of circulating CD 20 B-cells are lysed within 3 days of the first infusion of rituxmab.[19] In 4 patients in whom we had checked pre and post rituximab CD 19 cell counts, 3 had CD19 cell count of 0 at 24 to 48 hours after infusion (unpublished data). Secondly, it has fewer side effects than other conventional immunosuppressants due to highly specific mechanism of action targeting only CD 20 B cells; thirdly, infectious complications are much less when rituximab is administered as first-line treatment rather than being given

after the trial of 1 or more immunosuppressants; fourthly the effect of rituximab can easily be monitored by checking the CD19/CD20 levels unlike other conventional immunosuppressants and finally infrequent infusions due to long lasting immune depletion (6-12 months) results in good compliance and adherence to treatment, which is a major issue with chronic diseases especially in developing countries.[13] The disadvantage of this prolonged effect is that it is not reversible, in case of any unexpected adverse events, when compared to other conventional immunosuppressants.

The patients who benefitted most from rituximab, in the context of a developing country were those with impending myasthenic crisis. It is not standard practice to give rituximab directly in impending mysathenic crisis. We started using rituximab out of necessity, due to severe financial constraints in a resource limited setting. The decision to start rituximab (Cost-215$) was made by the treating physician as the patients were unable to afford both IV immunoglobulin (Cost-5000$) and plasma exchange (Cost-1500$). Steroids were not initiated in these patients with IMC due to the risk of further worsening of mysathenic weakness resulting in MC.

We gave a single dose of rituximab 500 mg to our first patient of IMC in 2016 and her respiratory and bulbar weakness improved from third day and she was discharged on the seventh day. She came for her next dose of 500 mg after 2 weeks. On follow up she improved to minimal manifestation status (MM2) and is currently on yearly maintenance dose of 500 mg rituximab. She is not any other immunosuppressants and only on maintenance dose of pyridostigmine 60 mg 3 times daily. Based on this experience we started using rituximab for other patients with IMC who could not afford standard care.

Four of 5 patients with IMC were successfully treated with rituximab alone without IVIg or TPE. In our small cohort the effect of rituximab on bulbar muscles and respiratory muscles were evident on the third day and improved significantly by first 2 weeks. The effect on ptosis and ocular muscles were not as dramatic when compared to bulbar and respiratory muscles. The exact reason for this dissociation is not known but we presume that it may be due to the fact that the neuromuscular junctions of the ocular muscles and levator palpebrae may be more sensitive to the already existing anti-AChR antibodies. In these patients we have given additional doses of rituximab (500-1000 mg) after 1 month as our baseline dosages were only 500 mg 2 weeks apart. An early onset of action makes rituximab useful in patients with impending myasthenic crisis. As we had prior experience with rituximab for treatment of multiple sclerosis, we knew that the action of rituximab starts faster than usually perceived. The rituximab action on B cells starts immediately after the infusion as evidenced by the infusion reaction which is a cytokine release reaction due to the lysis of B cells. It is not an anaphylactic reaction and hence occurs usually with the first dose. CD 19/20 drops significantly within first 3 days after rituximab infusion.[19] The rapid onset and long duration of action noted above, makes rituximab the only available immunosuppressant which takes care of both acute and chronic phases of myasthenia. These patients with IMC did well on follow up and required a minimum maintenance dose of 500 mg every 6 to 12 months. Only 1 out of the 5 patients had a rapidly progressive course and required ventilation and IV immunoglobulin administration within 12 hours of starting rituximab. This case highlights the fact that rituximab may be less effective in rapidly worsening myasthenia and established MC. Patient with IMC appears to be the ideal candidates for rituximab. In developing countries with limited resources like India where the generic brands of rituximab are available at low cost, the economic benefit of using rituximab in impending myasthenic crisis is huge. These findings from a small cohort without any control group need to be verified further by randomized controlled trials in larger patient populations. If proved effective, early treatment with rituximab may lead to a paradigm shift in MG management, especially for those in early stages and in impending myasthenic crisis.

Conclusion

Rituximab may be an effective treatment option in patients with Acetylcholine receptor antibody positive generalized MG in early stages. Patients with impending myasthenic crisis seem to benefit the most, with huge economic advantage in developing countries like India. Those in late stage myasthenia gravis, who have been previously exposed to immunosuppressants seem to have higher chance of infections. A slight increase in risk of malignancies seen in this study needs further evaluation in larger studies with long term follow up.

Author Contributions

Thomas Mathew: leading role in concept and design, study supervision, identification and contribution of cases ,data analysis/interpretation, review of literature, writing of the manuscript. Kurian Thomas: supporting role in concept, design. Identification and acquisition of data, data analysis/interpretation, review of literature, writing of the manuscript. Saji K John: supporting role in concept and design, data collection, data analysis/interpretation, preparation and editing of manuscript. Shruthi Venkatesh: data collection, data analysis/interpretation. Raghunandan Nadig: data analysis/interpretation, review of literature, writing of the manuscript. Sagar Badachi: data analysis/interpretation, preparation and editing of manuscript. Delon D Souza: data analysis/interpretation, review of literature, preparation and editing of manuscript. G R K Sarma: data analysis/interpretation, review of literature, preparation and editing of manuscript. Gareth J Parry: data analysis/interpretation and editing.

Ethics Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is

consistent with those guidelines and follows the tenets of Helsinki Declaration. The study was approved by the Institutional Review Board of St. John's Medical College Hospital, Bengaluru, India (IEC Study Ref No.175/2018). A written informed consent was taken from all the study participants.

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