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Stopping oral steroid-sparing agents at initiation of rituximab in myasthenia gravis

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Abstract

Rituximab is a chimeric monoclonal antibody that binds CD20 and causes the depletion of B-cell subsets. Although initially designed to treat lymphoma, it has found wide use in the management of various autoimmune conditions, including myasthenia gravis (MG), an autoimmune disorder of the neuromuscular junction. Treated myasthenia patients are often on an oral steroid-sparing agent. To determine the safety of stopping oral steroid-sparing agents at the initiation of rituximab therapy and its effectiveness we reviewed the records of 27 MG patients with rituximab, including 13 with anti-MuSK+ MG, 10 with anti-AChR+ MG, and 4 double seronegative MG patients. All patients that were on an oral steroid-sparing agent (21 of 27) were able to stop it, and they did not require re-introduction of the medication. Also, the daily prednisone dosage was significantly decreased in 20/24 patients across all three serotype groups. MGFA post intervention status analysis also showed 15/27 of all patients achieved minimal manifestation status or remission across all groups. Antibody titers decreased dramatically and promptly in anti-MuSK+ MG patients. Our data suggests that stopping oral steroid-sparing agents at initiation of rituximab therapy is safe. Also, our data indicates that rituximab is highly effective in the management of seropositive MG patients.

Keywords: Myasthenia gravis; Rituxan; Rituximab; Muscle specific kinase; Acetylcholine receptor.

1. Introduction

Myasthenia Gravis is an autoimmune disorder in which antibodies develop against components of the post-synaptic neuromuscular junction membrane [1]. Patients present with skeletal muscle weakness involving extraocular, bulbar and appendicular muscles and, less commonly, the diaphragm. The two most common antigens are the acetylcholine receptor [2] in 85% of patients and muscle specific kinase [3–6] in 10% of patients. Other newly discovered rarer antigens include low-density lipoprotein receptor-related protein 4 (Lrp4) [7–9] and agrin [10–12].

Evolving insights suggest different disease mechanisms associated with the pathogenicity of AChR and MuSK autoantibodies. Anti-AChR antibodies are IgG1-3 subclass which trigger complement-dependent NMJ impairment, AChR endocytosis, or receptor blockade, whereas anti-MuSK antibodies are IgG4 subclass which inhibits NMJ transmission in a complement-independent manner affecting the MuSK/Lrp4 interactions and thereby impairing AChR clustering at the NMJ [13,14].

Prior to the discovery of effective immunosuppressive treatments, the mortality of MG was close to 30% [1]. Steroids, one of the earliest immunosuppressant treatments, proved highly effective in MG and remain a mainstay of therapy, limited by many dose-limiting side effects and adverse effects [15]. Current treatment strategies for MG include symptomatic treatment with acetylcholinesterase inhibitors, thymectomy, immunosuppression with steroids or oral steroid-sparing agents such as azathioprine, mycophenolate, cyclosporine, and/or short-term immunomodulation such as human immune globulin or plasma exchange. Despite a dramatic reduction in mortality with these treatments, complete clinical remission is not always achieved, and in some cases disability from poor responsiveness to treatment, complications from treatment, or a growing risk profile associated with prolonged use of

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oral steroid-sparing agents, make acute and chronic MG management challenging for the patient and clinician.

Rituximab is a chimeric monoclonal antibody that binds CD20 and causes the depletion of B-cell subsets [16]. There is a growing body of evidence over the past two decades that rituximab is a particularly effective therapy for both anti-AChR+ and anti-MuSK+ MG patients, particularly the anti-MuSK+ subtype, and in patients refractory to other standard treatments [17–25]. This study reports the success of stopping oral steroid-sparing agents at initiation of rituximab and the effectiveness of rituximab in one of the largest number of MG patients reported to date across anti-MuSK+ and anti-AChR+ subtypes.

2. Patients and methods

2.1. Patients

MG patients in the Johns Hopkins Neuromuscular Division treated with rituximab and seen for follow-up between January 2000 and January 2018 were included in this study. Patients were diagnosed as having MG based on a history consistent with MG and AChR or MuSK autoantibodies, or in the case of double seronegative patients, based on a history consistent with MG and abnormal SFEMG or repetitive nerve stimulation testing. The patients' electronic records were reviewed and demographic information, diagnostic data, treatment course, adverse effects and clinical status were collected. Establishment of MGFA grade for disease staging was determined from the documented neurologic exams. Patients received rituximab either 375 mg/m2 weekly for four consecutive weeks or rarely 1000 mg at weeks 1 and 3. Retreatment was based on clinical course. On rare occasions a patient received only partial doses due to scheduling or complications from treatment. Patients were selected for treatment with rituximab either because they had anti-MuSK+ MG or, in the case of anti-AChR+ or double seronegative MG, had a suboptimal clinical response on standard therapies, had intolerable side effects or adverse effects on standard therapies, or had a protracted exposure to oral steroid-sparing agents and growing cumulative risks of adverse effects.

2.2. Ethical approval

This study has been approved by the Johns Hopkins University Institutional Review Board (IRB00144068).

2.3. Statistical analyses

This study uses descriptive statistics including mean, median, standard deviation and standard error of the mean. Percentages were used for categorical variables. A paired two sample means *t*-test (one-tail) was used to determine significance in the average daily prednisone dose reduction.

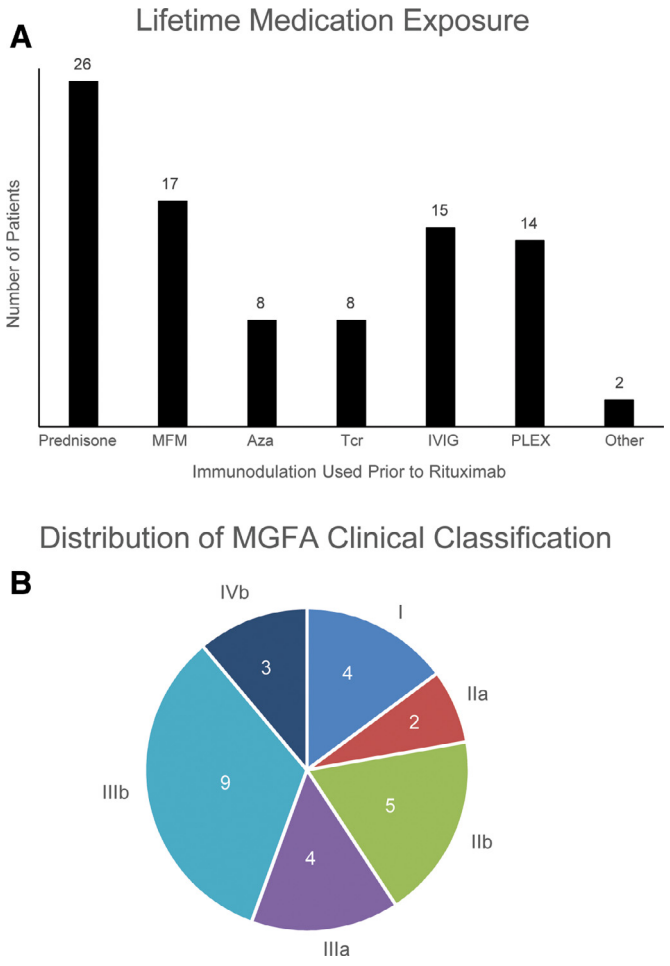

Fig. 1. *Lifetime immunomodulation and patient disease severity at diagnosis.* **(A)** All treatment from diagnosis to time of rituximab infusion for each patient. **(B)** Disease severity according to the MGFA classification scale at the time of diagnosis for all 27 patients. Mycophenolate mofetil (MFM), azathioprine (Aza), plasma exchange (PLEX), tacrolimus (Tcr), intravenous immunoglobulin (IVIG), cyclosporine and cyclophosphamide (other).

3. Results

3.1. Patient demographics

Twenty-seven patients with MG were included in this study (Table 1), including 13 anti-MuSK+, 10 anti-AChR+, and 4 double seronegative patients. The majority (22/27 patients) were female. The median age for the anti-MuSK+ cohort 32 yo (range 20–62) was younger than the anti-AChR+ cohort 49 yo (range 26–80), and both were considerably younger than the double seronegative cohort 56 yo (range 26–61). Thymectomy was performed on 9 of 10 anti-AChR+, 2 of 4 double seronegative, and 2 of 13 anti-MuSK+ patients.

Most patients had received treatment with more than one immunosuppressant over the duration of their disease (Fig. 1A). Nearly all patients, 26 of 27, were or had been on prednisone. The second most common agent used was mycophenolate mofetil (17/27), followed by IVIG (15/27), plasma exchange (14/27), tacrolimus (8/27), and azathioprine

Table 1
Response to treatment.

Patient	MGFA Classification			MGFA PIS		Medications			Prednisone ADD	
	At Diagnosis	Before Rituximab	At Last Visit	At 1 year	At Last Visit	Immediately Prior to Rituxan	Current	Stopped SSA	Pre	Post
Ach-01	I	I	I	PR	PR	Pr, MFM	Pr	Y	20	10
Ach-02	I	IIb	IIb	I	I	Pr, MFM, IVIG	Pr, IVIG	Y	55	20
Ach-03	IIIa	IIa	IIa	I	U	Pr, Aza	Pr	Y	10	10
Ach-04	IIa	IIIb	IIb	I	I	Pr, PLEX	Pr, PLEX	N/A	20	10
Ach-05	IIIa	IIa	0	I	MM-3	Pr, IVIG	None	N/A	5	0
Ach-06	I	IIb	IIb	I	I	Pr, MFM, IVIG	Pr, IVIG	Y	15	10
Ach-07	IIIb	IIIb	IIb	I	I	Pr, Aza, PLEX	Pr, PLEX	Y	5	5
Ach-08	IIIa	No Sx **	No Sx	PR	PR	Pr	Pr	N/A	6.13	2.5
Ach-09	IIIb	IIa	I	MM-1	MM-1	Pr, MFM	Pr	Y	20	12.5
Ach-10	IIb	IVb	IIb	*	I	Pr, MFM, IVIG	Pr	Y	40	20
DS-1	IIb	IIIa	I	I	MM-1	Pr, Tcr, IVIG	Pr	Y	35	6
DS-2	IIIb	IIIb	IIb	I	I	MFM, PLEX	PLEX	Y	0	0
DS-3	IIb	IIIb	IIb	MM-3	MM-3	Pr, Tcr, IVIG	Pr	Y	25	20
DS-4	IIIb	IIIb	IIIb	U	U	Pr, MFM, PLEX	Pr, PLEX	Y	15	30
Mu-01	IIIb	IIIb	IIb	*	I *	Pr, PLEX (1/wk), Aza	Pr, PLEX	Y	40	35
Mu-02	IVb	IIIb	I	MM-0	MM-0	Pr, MFM	None	Y	20	0
Mu-03	IVb	IVb	IIb	MM-1	MM-1	Pr, MFM, IVIG	None	Y	20	0
Mu-04	IIIb	IIIb	0	CSR	CSR	Pr, PLEX	None	N/A	10	0
Mu-05	IIa	IIb	IIb	I	I	Pr, Tcr, Aza, PLEX	Pr	Y	30	5
Mu-06	IIIb	IIIb	0	CSR	CSR	IVIG	None	N/A	0	0
Mu-07	IIIa	IVb	IIb	E	I	Pr, Tcr, PLEX	Pr	Y	20	20
Mu-08	IIIb	IIIb	IIa	PR	CSR	Pr, MFM	None	Y	20	0
Mu-09	IIb	IIb	I	PR	MM-1	Pr,Tcr, Aza, PLEX	Pr	Y	6.13	2.5
Mu-10	IIb	IIb	0	E	PR	Pr	None	N/A	30	0
Mu-11	I	I	I	*	MM-1 *	Pr	Pr	N/A	20	12.5
Mu-12	IIIb	IIIb	IIa	MM-1	PR	PLEX	None	N/A	0	0
Mu-13	IVb	IVb	IIIb	*	I *	Pr, Aza, PLEX	Pr	Y	50	45

PIS= Post Intervention Status, ADD= average daily dose (mg), SSA= steroid sparing agent, N/A= not applicable.
*Indicates that a year has not yet elapsed, **Patient placed on rituximab to treat MG and NMO.

(8/27). A single patient was on cyclosporine and another one was on cyclophosphamide.

The distribution of disease severity using the MGFA clinical classification scale at the time of diagnosis showed 9/27 class IIIB, 5/27 class IIb, 4/27 class IIIa, 4/27 class I, 3/27 class IVb and 2/27 IIa (Fig. 1B).

3.2. Response to treatment

Treatment response to rituximab in our patient population was assessed based on three variables: (1) efficacy of stopping oral steroid-sparing agents upon initiation of rituximab, (2) ability to reduce the average daily prednisone dose, and (3) improvement in the MGFA post intervention status.

3.2.1. Cessation of oral steroid-sparing agents

On rituximab, all 19 patients on oral steroid-sparing agents (O-SSA) were eventually completely tapered (Table 1); 12 were stopped at the time of initiating rituximab therapy. As successive patients demonstrated stable or improved MG control with rituximab, our practice shifted to abrupt cessation upon initiation of the rituximab. In the two patients (Mu-05 and Mu-09) that were on two oral steroid-sparing agents, one agent in both patients was stopped upon initiation of rituximab and the second was tapered off over months. The medication to stop in those two patients at the time of infusion was chosen based on its perceived prior effectiveness and long-term cumulative risk. No patients worsened when the steroid-sparing agent was stopped. None of the patients required re-introduction of an oral steroid-sparing agent after rituximab. None of the patients required an increased frequency of IVIG or PLEX. In fact, IVIG was discontinued in 6 out of 8 and PLEX in 6 out of 11 patients (Table 1). Among those still receiving PLEX, all but one (DS-4) had lower frequencies of exchanges.

3.2.2. Decrease in average daily prednisone dose

The average daily prednisone dose was calculated both at the time of the initial rituximab infusion and the last clinic visit. There was no specific protocol for the prednisone taper,

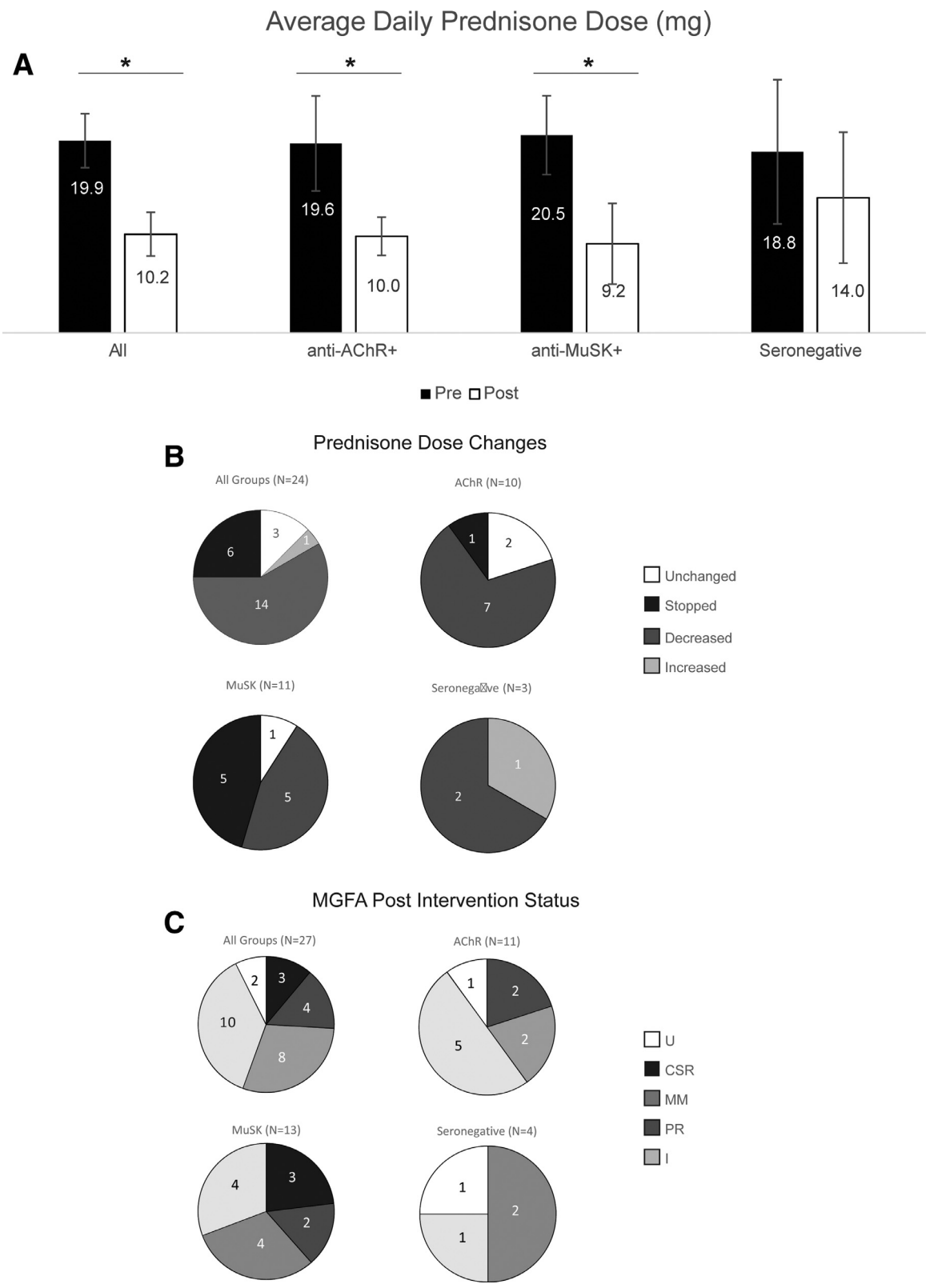

Fig. 2. *Response to treatment*. **(A)** Daily prednisone use before rituximab treatment ("pre", dark bars) and after treatment ("post", white bars). Three groups were statistically significant: all groups ($P<0.0009$), anti-MuSK+ ($P<0.009$) and anti-AChR+ ($P<0.001$). Both the change in prednisone dose **(B)** and MGFA post-intervention status **(C)** are plotted for each serotype. Complete Stable Remission (CSR), Pharmacologic Remission (PR), Minimal Manifestations (MM), Improved (I), Unchanged (U), Worse (W).

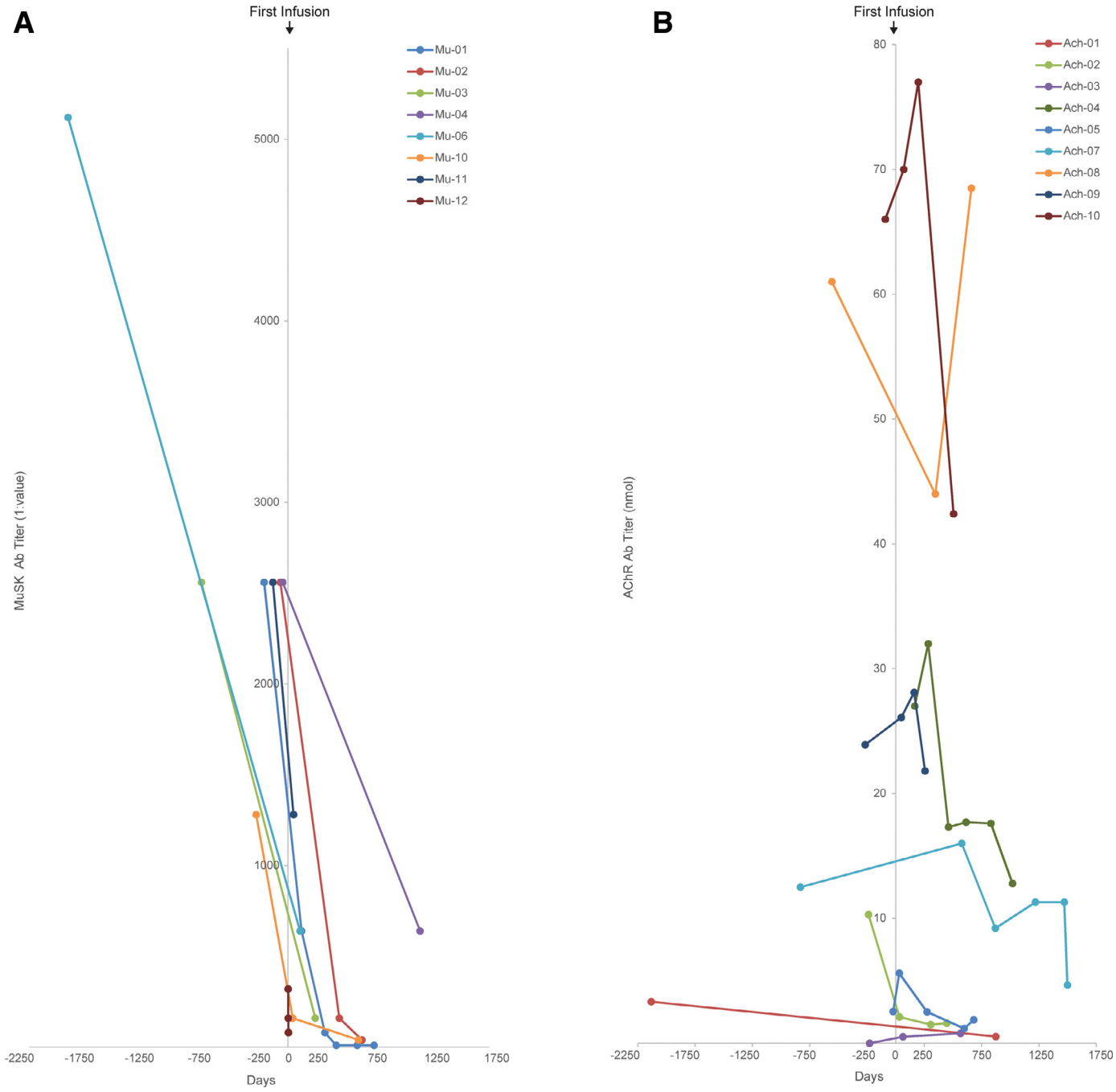

Fig. 3. *Change in antibody titers over time*. The available changes in titers are shown for both anti-MuSK+ **(A)** and anti-AChR+ **(B)** patients.

nonetheless a uniform goal of treatment was to successfully reduce the prednisone dose to the lowest level possible to minimize the risk of side effects, adverse effects, and MG flare.

The average daily prednisone dose for the entire patient cohort was statistically significantly decreased from an average of 19.9 to 10.2 mg/day (Fig. 2A). Subgroup analysis showed the daily prednisone dose was also significantly decreased from 19.6 to 10.0 mg in the anti-AChR+ patients and from 20.5 to 9.2 mg in the anti-MuSK+ group. In the double seronegative group, half the patients were able to decrease the steroid dose, but this reduction did not reach statistical significance, and the small size of the group does not allow for meaningful statistical conclusions. This suggests that treatment with rituximab was similarly effective in reducing prednisone in patients with either anti-AChR+ or anti-MuSK+ myasthenia gravis.

A total of 24 patients were on prednisone prior to treatment with rituximab (Table 1, Fig. 2B). Across all serotypes 20 of 24 patients decreased the prednisone dose, including 6 of 24 patients who tapered off completely. It was completely tapered off in 6 out of 24 patients. Subgroups analysis indicates that it was discontinued in 5 of 11 anti-MuSK+ and 1 of 10 anti-AChR+ patients. All double seronegative

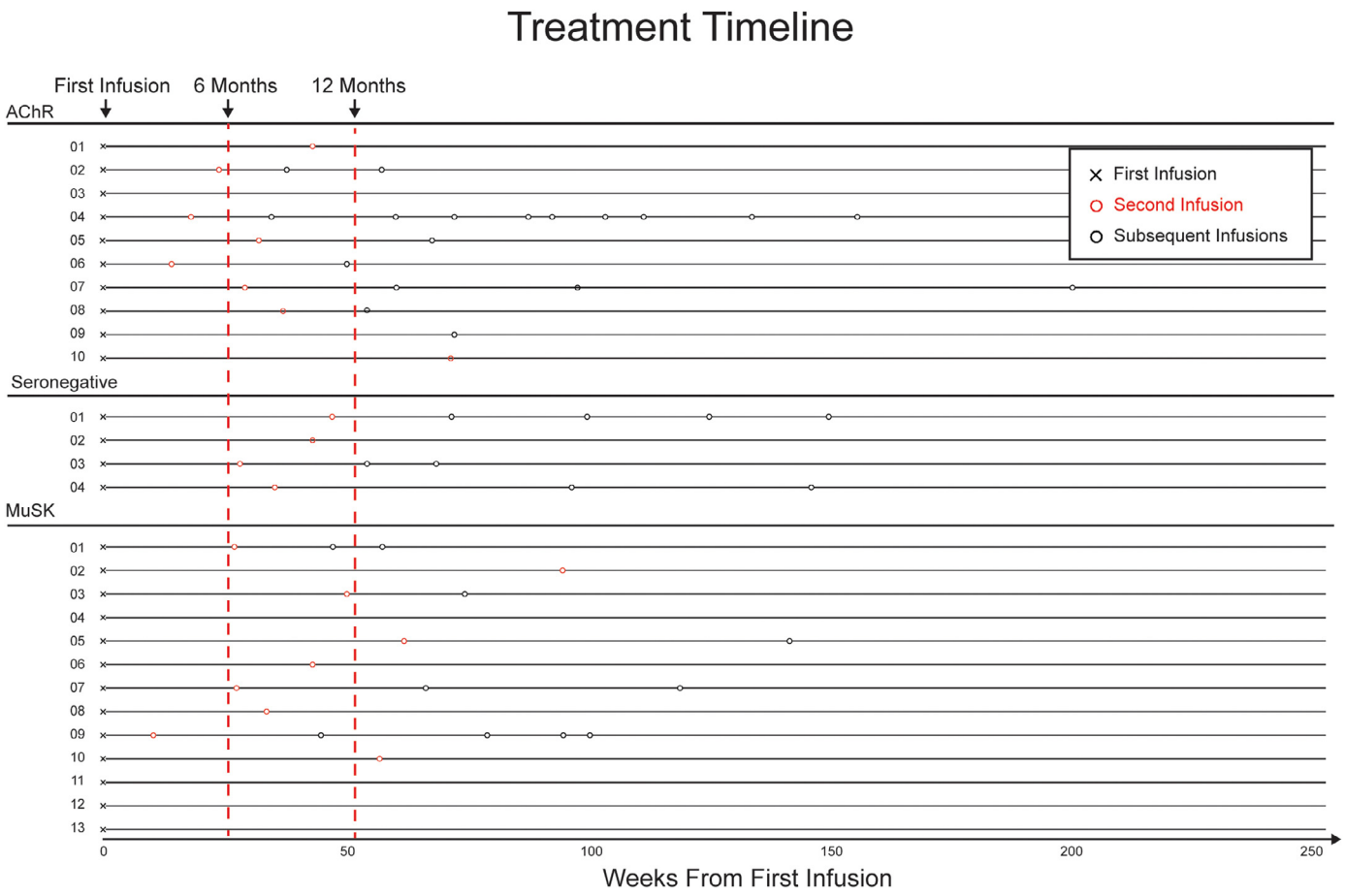

Fig. 4. *Time line for infusions*. The first infusion occurs at time zero (X). Subsequent infusions are marked as well (O). The first re-infusion (second infusion) is marked with red (O).

patients who were on prednisone (3/4) continued it; two of the three were able to decrease the steroid dose.

3.2.3. Improvement in the MGFA PIS

The MGFA PIS was determined for all the patients based on their last clinic visit (Table 1, MGFA PIS "Current" heading). Minimal manifestation or better was achieved in 15 out of 27 patients, 9 of 13 anti-MuSK+ and 4 of 10 anti-AChR+ patients. No patients were worse (W).

Subgroup analysis demonstrated all the complete stable remission cases were in the anti-MuSK+ group, while improvement (I) was seen in all groups (Fig. 2C). Unchanged status (U) was seen rarely in the anti-AChR+ (1/10) and double seronegative groups (1/10), and not in the anti-MuSK+ group. Overall, all groups benefited, however rituximab appeared especially efficacious in the anti-MuSK+ subgroup.

3.3. Change in antibody titers

Available AChR and MuSK antibody titers prior to initiation of rituximab treatment and the most recent titer post treatment are shown (Fig. 3). In some instances, the pre-treatment MuSK titers were reported as antibodies being "present or not", in which case we were not able to compare to pre-treatment titers but generally had samples of post-treatment titers over time. A striking reduction in the MuSK antibody titers is seen uniformly in the anti-MuSK+ group. MuSK titers responded especially well to treatment with rituximab. AChR titers also decreased following rituximab treatment, but it appeared that the response was slower compared to MuSK titers.

3.4. Timing of rituximab re-dosing

After the first cycle of rituximab therapy, patients were re-dosed if needed before 6 months (4/27), between 6 and 12 months (13/27), and after 12 months (5/27) (Fig. 4). The maximum number of courses received by a single patient in our cohort was 12 doses (AChR-04). Two patients each received 6 cycles of treatment. Five patients had not been re-dosed for the period that the study spanned.

3.5. Adverse effects

Serious adverse effects included one anti-AChR+ patient who developed neutropenia after her sixth course, which responded to filgrastim. Another anti-AChR+ patient experienced diverticulitis and one anti-MuSK+ patient developed osteomyelitis while being treated. Minor infusion

reactions, which responded to anti-histamines and reduction in the infusion rate were not uncommon.

4. Discussion

This is a retrospective study of a cohort of 27 patients with myasthenia gravis treated with rituximab, many of which had their oral steroid-sparing agent stopped upon initiation of rituximab therapy. We include patients with anti-AChR+, anti-MuSK+, and double seronegative MG. The majority of our patients were female, and we had approximately equal numbers for patients with anti-AChR+ and anti-MuSK+ MG.

We were able to stop oral steroid-sparing agents in all patients who were on them. The effect of tapering mycophenolate mofetil in patients with stable myasthenia gravis was recently investigated [26]. Although it was shown to be possible to taper the dose, the rapidity with which the dose was reduced was associated with worsening symptoms, but not with development of myasthenic crisis. Our data shows that it can be stopped at the time of initiation of rituximab therapy or tapered thereafter without associated long-term consequences.

The data also shows the effectiveness of rituximab in the treatment of myasthenia across seropositive subtypes. Minimal manifestation or better MGFA PIS was achieved in 13 of 23 anti-AChR+ or anti-MuSK+ patients. In addition, most patients were also able to significantly decrease their daily prednisone dose. No patients were worse.

Antibody titer changes over time show a distinct trend. A striking reduction in the MuSK antibody titer was seen following treatment compared to a slow decline in the AChR antibody titers. This differential decrease possibly reflects the way the antigenic response is maintained in both groups, due to the prolonged presence of anti-AChR+ memory cells [27].

One of the limitations of our study is that data was ascertained from patient records in a retrospective manner. Another is the limited numbers of double seronegative patients. The lack of uniformity in the treatment strategies is another drawback of this retrospective study. The rationale for stopping the agent was uniformly to minimize the cumulative adverse risks of prolonged immunosuppressive therapy while maintaining or improving MG control. As successive patients demonstrated stable or improved MG control with rituximab, our practice shifted to abrupt cessation of the oral steroid sparing agent upon initiation of rituximab.

Our data indicates that rituximab is an effective therapy for myasthenia gravis and that it allows for the immediate cessation of oral steroid-sparing therapy. It is effective in both anti-AChR+ and anti-MuSK+ patients, however it appears to be particularly effective in the latter group. Our report adds to the growing evidence that rituximab is a powerful therapeutic option for those suffering from antibody positive myasthenia gravis.

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References

[1] Drachman DB. Myasthenia gravis. N Engl J Med 1994;330:1797–810. doi:10.1056/NEJM199406233302507.

[2] Lindstrom JM, Seybold ME, Lennon VA, Whittingham S, Duane DD. Antibody to acetylcholine receptor in myasthenia gravis. Prevalence, clinical correlates, and diagnostic value. Neurology 1976;26:1054–9. doi:10.1212/wnl.51.4.933-a.

[3] Hoch W, McConville J, Helms S, Newsom-Davis J, Melms A, Vincent A. Auto-antibodies to the receptor tyrosine kinase MuSK in patients with myasthenia gravis without acetylcholine receptor antibodies. Nat Med 2001;7:365–8. doi:10.1038/85520.

[4] Scuderi F, Marino M, Colonna L, Mannella F, Evoli A, Provenzano C, et al. Anti-p110 autoantibodies identify a subtype of "seronegative" myasthenia gravis with prominent oculobulbar involvement. Lab Investig J Tech Methods Pathol 2002;82:1139–46. doi:10.1097/01.lab.0000028144.48023.9b.

[5] Guptill JT, Sanders DB, Evoli A. Anti-MuSK antibody myasthenia gravis: clinical findings and response to treatment in two large cohorts. Muscle Nerve 2011;44:36–40. doi:10.1002/mus.22006.

[6] McConville J, Farrugia ME, Beeson D, Kishore U, Metcalfe R, Newsom-Davis J, et al. Detection and characterization of MuSK antibodies in seronegative myasthenia gravis. Ann Neurol 2004;55:580–4. doi:10.1002/ana.20061.

[7] Higuchi O, Hamuro J, Motomura M, Yamanashi Y. Autoantibodies to low-density lipoprotein receptor-related protein 4 in myasthenia gravis. Ann Neurol 2011;69:418–22. doi:10.1002/ana.22312.

[8] Pevzner A, Schoser B, Peters K, Cosma N-C, Karakatsani A, Schalke B, et al. Anti-LRP4 autoantibodies in AChR- and MuSK-antibody-negative myasthenia gravis. J Neurol 2012;259:427–35. doi:10.1007/s00415-011-6194-7.

[9] Zhang B, Tzartos JS, Belimezi M, Ragheb S, Bealmear B, Lewis RA, et al. Autoantibodies to lipoprotein-related protein 4 in patients with double-seronegative myasthenia gravis. Arch Neurol 2012;69:445–51. doi:10.1001/archneurol.2011.2393.

[10] Gasperi C, Melms A, Schoser B, Zhang Y, Meltoranta J, Risson V, et al. Anti-agrin autoantibodies in myasthenia gravis. Neurology 2014;82:1976–83. doi:10.1212/WNL.0000000000000478.

[11] Zhang B, Shen C, Bealmear B, Ragheb S, Xiong W-C, Lewis RA, et al. Autoantibodies to agrin in myasthenia gravis patients. PLOS ONE 2014;9:e91816. doi:10.1371/journal.pone.0091816.

[12] Guptill JT, Soni M, Meriggioli MN. Current treatment, emerging translational therapies, and new therapeutic targets for autoimmune myasthenia gravis. Neurotherapeutics 2016;13:118–31. doi:10.1007/s13311-015-0398-y.

[13] Huijbers MG, Zhang W, Klooster R, Niks EH, Friese MB, Straasheijm KR, et al. MuSK IgG4 autoantibodies cause myasthenia gravis by inhibiting binding between MuSK and Lrp4. Proc Natl Acad Sci USA 2013;110:20783–8. doi:10.1073/pnas.1313944110.

[14] Verschuuren JJGM, Huijbers MG, Plomp JJ, Niks EH, Molenaar PC, Martinez-Martinez P, et al. Pathophysiology of myasthenia gravis with antibodies to the acetylcholine receptor, muscle-specific kinase and low-density lipoprotein receptor-related protein 4. Autoimmun Rev 2013;12:918–23. doi:10.1016/j.autrev.2013.03.001.

[15] Pascuzzi RM, Coslett H, Johns TR. Long-term corticosteriod treatment of myasthenia gravis: report of 116 Patients. Ann Neurol 1984;15:291–8. doi:10.1002/ana.410150316.

[16] Pescovitz MD. Rituximab, an Anti-CD20 Monoclonal Antibody: history and Mechanism of Action. Am J Transpl 2006;6:859–66. doi:10.1111/j.1600-6143.2006.01288.x.

[17] Tandan R, Hehir MK, Waheed W, Howard DB. Rituximab treatment of myasthenia gravis: a systematic review: rituximab in myasthenia gravis. Muscle Nerve 2017;56:185–96. doi:10.1002/mus.25597.

[18] Baek WS, Bashey A, Sheean GL. Complete remission induced by rituximab in refractory, seronegative, muscle-specific, kinase-positive myasthenia gravis. J Neurol Neurosurg Psychiatry 2007;78 771–771. doi:10.1136/jnnp.2006.093567.

[19] Díaz-Manera J, Martínez-Hernández E, Querol L, Klooster R, Rojas-García R, Suárez-Calvet X, et al. Long-lasting treatment effect of rituximab in MuSK myasthenia. Neurology 2012;78:189–93. doi:10.1212/WNL.0b013e3182407982.

[20] Blum S, Gillis D, Brown H, Boyle R, Henderson R, Heyworth-Smith D, et al. Use and monitoring of low dose rituximab in myasthenia gravis. J Neurol Neurosurg Psychiatry 2011;82:659–63. doi:10.1136/jnnp.2010.220475.

[21] Nowak RJ, DiCapua DB, Zebardast N, Goldstein JM. Response of patients with refractory myasthenia gravis to rituximab: a retrospective study. Ther Adv Neurol Disord 2011;4:259–66. doi:10.1177/1756285611411503.

[22] Yi JS, DeCroos EC, Sanders DB, Weinhold KJ, Guptill JT. Prolonged B-cell depletion in MuSK myasthenia gravis following rituximab treatment. Muscle Nerve 2013;48:992–3. doi:10.1002/mus.24063.

[23] Zaja F, Russo D, Fuga G, Perella G, Baccarani M. Rituximab for myasthenia gravis developing after bone marrow transplant. Neurology 2000;55:1062–3. doi:10.1212/WNL.55.7.1062-a.

[24] Wylam ME, Anderson PM, Kuntz NL, Rodriguez V. Successful treatment of refractory myasthenia gravis using rituximab: a pediatric case report. J Pediatr 2003;143:674–7. doi:10.1067/S0022-3476(03)00300-7.

[25] Beecher G, Anderson D, Siddiqi ZA. Rituximab in refractory myasthenia gravis: extended prospective study results. Muscle Nerve 2018;58:452–5. doi:10.1002/mus.26156.

[26] Hobson-Webb LD, Hehir M, Crum B, Visser A, Sanders D, Burns TM. Can mycophenolate mofetil be tapered safely in myasthenia gravis? A retrospective, multicenter analysis: use of MMF in MG. Muscle Nerve 2015;52:211–15. doi:10.1002/mus.24694.

[27] Yi JS, Guptill JT, Stathopoulos P, Nowak RJ, O'Connor KC. B cells in the pathophysiology of myasthenia gravis. Muscle Nerve 2018;57:172–84. doi:10.1002/mus.25973.