CSCN Hot Topics – What's New in the Treatment of Myasthenia Gravis?

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Introduction

The overall goal of this session is to look at recent published evidence regarding the treatment of myasthenia gravis and attempt to answer the question:

"What do you do when conventional myasthenia treatments fail?"

Specific objectives of the session are:

1. To review results of the recently published Myasthenia Gravis Thymectomy (MGTx) trial.
2. To discuss the role (if any) of thymectomy in practice.
3. To review the evidence supporting the use of Rituximab for Myasthenia Gravis.

These notes will not provide any additional information to what is covered in the power-point presentation.

What is failure of conventional treatment?

For the purpose of this session, "failure of conventional treatment" will be defined as failure of or intolerance to steroids, intravenous immunoglobulin (IVIG), and plasma exchange (PLEX).

Usually patients with myasthenia gravis (MG) who are worsening despite these treatments will not respond sufficiently to increasing doses of pyridostigmine. In my experience they will usually also not respond to azathioprine (Imuran) and mycophenylate mofetil (Cellcept), which are best considered as steroid-sparing agents; they allow you to reduce the dose or stop prednisone *in an otherwise stable patient*.

My definition of "failure of conventional treatment" resembles the definition of refractory MG given in the recent international consensus guidelines for the management of MG: "unchanged or worse after corticosteroids and at least 2 other immunosuppressant agents…with persistent symptoms or side effects that limit functioning" (Sanders 2016). The difference is that I have specified failure of IVIG and PLEX as these treatments are easily available and commonly used in Canada and, as above, more likely to be of benefit than azathioprine or mycophenylate.

Failure of conventional treatment does <u>not</u> imply that the patient is in myasthenic crisis (with a risk of respiratory failure). It could simply refer to an office patient who is not responding well or sufficiently to conventional treatment; as the treating neurologist seeing this patient in your clinic, what else can you do?

Failure of conventional treatment also does not necessarily imply that the person has generalized MG. Severe ptosis or diplopia unresponsive to treatment can be a significant problem as well.

The rationale for thymectomy in Myasthenia Gravis

A full review of the evidence for a role of the thymus in MG is beyond the scope of this session. The main arguments supporting this idea are:

1. The presence of myoid cells expressing Ach receptor in the thymus.
2. Removal of the thymus removes a "reservoir" of antibody-secreting B-cells.
3. Removal of the thymus may correct other disturbances of immune regulation (such as an abnormal proportion of T-cell subsets in the thymus).
4. Abnormally high levels of thymopoietin have been demonstrated in MG patients.

For more detail refer a comprehensive review of this topic (Cavalcante 2011).

Prior clinical evidence supporting the use of thymectomy

It has been known since Blalock performed the first thymectomy for a MG patient that some patients do appear to get better after thymectomy. An American Academy of Neurology practice parameter published in 2000 found positive associations in most case series between thymectomy and MG remission/ improvement, but conflicting associations when controlling for confounding variables (Gronseth 2000). The use of thymectomy by neurologists has been variable. A survey published in 1990 found that 53 of 56 neurologists believed thymectomy "should be done in selected generalized patients" (Lanska 1990), but there was no agreement about who those selected patients should be; only younger patients (24/53), disabling MG (21/53), patients unresponsive to AChE inhibitors (14/53), or disease of recent onset (12/53).

This uncertainty is reflected in published reviews of MG:

"There is now a broad consensus that patients with generalized myasthenia gravis who are between the ages of puberty and about 60 years should have surgical thymectomy"

Drachmann NEJM 1994

"Thymectomy is currently done early in young-onset, AChR antibody-positive patients with generalised myasthenia gravis as a therapeutic option"

Vincent Lancet 2001; 357: 2122.

"Thymectomy is recommended for most patients…"

Sanders and Howard in Bradley 2004

"Thymectomy is performed as an option to potentially avoid or minimize the dose or duration of immunotherapy, or if patients fail to respond to an initial trial of immunotherapy or have intolerable side-effects from that therapy"

Sanders Neurology 2016; 87: 419.

Finally, a Cochrane review published in 2013 concluded that there were no high quality studies (i.e. randomized controlled trials) on which to base treatment decisions (Cea 2013).

The Myasthenia Gravis Thymectomy (MGTx) trial (Wolfe 2016)

This trial published last year attempted to resolve the issue of whether or not thymectomy was of benefit for MG patients by answering two questions:

Question 1: Does extended trans-sternal thymectomy (ETTX) combined with prednisone result in a *greater improvement in myasthenic weakness*, compared to prednisone alone?

Question 2: Does ETTX combined with prednisone result in a *lower total dose of prednisone*, thus decreasing the likelihood of concurrent and long-term toxic effects, compared to prednisone alone?

The trial was NINDS funded and enrolled acetylcholine receptor antibody positive patients between the ages of 18 and 65 with generalized MG. The disease duration had to have been 5 years or less. Patients randomized to thymectomy had ETTX performed within 30 days of randomization. All patients (thymectomy and control) were treated with prednisone at a dose of 100 mg given on alternating days. Weakness due to MG was evaluated by a blinded examiner using the Quantitative Myasthenia Gravis (QMG) score (Barohn 1998). The QMG scale (Appendix 1) evaluates 13 items each graded from 0 (normal) to 3 (severe weakness), resulting in a maximum total score of 39 (higher numbers thus reflecting more severe disease).

Patients could receive IVIG or PLEX only if they were judged to be unstable. Azathioprine could be administered only if there had been no improvement by 1-year post-randomization.

Tapering of prednisone was begun when two criteria were met:

1. Patients had to meet “minimal-manifestation status”, meaning that they had no symptoms or functional limitations from myasthenia gravis, but may have had some weakness on examination of some muscles.
2. Their QMG score was less than 14 and improved by 1 point compared to randomization.

A total of 6958 patients were screened for the study, of whom 231 met eligibility criteria and 126 were randomized over 6 years. Patients were followed for 5 years but 3 year data was presented in the published report. The dual primary outcomes of improvement in the time-weighted QMG score and reduction in the time-weighted prednisone dose were both positive; the difference in mean QMG score was 2.85 points, and average prednisone dose decreased from 60 to 44mg. A variety of secondary outcomes also favored the thymectomy group including rate of hospitalization for MG exacerbations (9 vs 37%), days in hospital (8.4 vs 19.2), azathioprine use (17 vs 48%), and side effects.

What is the relevance of the MGTx trial results for clinical practice?

The first point to understand about this trial is that a highly selected group of patients were studied. They had to be anti-acetylcholine receptor antibody positive and had to have generalized myasthenia with disease onset within the past 5 years. Patients older than 65 were excluded. As stated above, only 231 of 6958 screened patients were deemed eligible for the trial. The second point to understand is that azathioprine and other adjuvant, steroid-sparing treatments were probably under-utilized compared to standard clinical practice. Many neurologists would either begin azathioprine with prednisone, or initiate it within 3-6 months of prednisone once it became clear that prednisone could not be tapered quickly. Finally, this study used exclusively the trans-sternal approach to thymectomy. The rationale was that this technique ensures the removal of the greatest possible amount of thymic tissue (which in adults is usually not contained in a single discrete gland, but can be spread throughout the mediastinum). In practice many neurologists, surgeons, and patients might favor the less-invasive supraclavicular/endoscopic approach in clinical practice, and it is not known if the trial results can be extrapolated to this technique.

Allowing for these limitations, the trial results confirm the long-held belief that thymectomy clearly has some benefit. On average patients treated with thymectomy in the trial had less weakness, were taking a lower dose of prednisone, were less likely to require hospitalization, and had fewer side effects. Thymectomy thus represents a viable treatment option. It is not a cure and we do not know if the benefits persist over a longer time period. It is not a standard treatment that every patient with MG, or even every patient with generalized MG, should undergo.

Thymectomy can benefit patients with generalized MG by improving weakness and reducing required doses of prednisone. It is a viable treatment option for a patient who is failing or intolerant of steroids, intravenous immunoglobulin (IVIG), and plasma exchange (PLEX). It is not a treatment for myasthenic *crisis*.

What is Rituximab?

Rituximab is a chimeric monoclonal antibody to the CD20 receptor on B lymphocytes. It results in the depletion of B-cells but not B-cell precursors or mature plasma cells. Patients usually receive weekly infusions for 1-4 weeks, and the effect on B-cells typically lasts for 12 months. Clinical response may take 4-6 weeks to become apparent. Rituximab was developed for use in lymphoma and has been most often used for the treatment of rheumatoid arthritis.

Although results of a randomized controlled trial of Rituximab in MG have not yet been published there is anecdotal evidence of significant benefit. In particular, there are reports (including several presented at prior CNSF congresses) that MG patients who are anti-MuSK antibody positive may have a strong response to Rituximab. A number of other targeted immunotherapies for MG are also in development. The rest of this session will look at the available evidence for the use of Rituximab in MG.

What is the evidence for the use of Rituximab in MG?

There have been at least 15 case series published describing the use of Rituximab in MG. Each

series has included from 2 to 20 MG patients, the vast majority of whom were positive for either anti-acetylcholine receptor or anti-MuSK antibodies. Patients were typically (but not always) responding poorly to other treatments. There was significant variability both within and between case series in terms of the induction doses used and whether maintenance doses were given.

Outcomes were most often reported as improvement in MGFA (Myasthenia Gravis Foundation of America) scores. The MGFA score categorizes MG patients into 5 states: 1=ocular, 2=mild generalized, 3=moderate generalized, 4=severe generalized, and 5=intubation (see appendix 2). A patient who received Rituximab and had changed from a score of 4 to 3 by the time of the last follow-up would be considered to have improved. Some case series simply reported whether improvement occurred, without referencing the MGFA score.

In the 5 largest case series reported to date (Collongues 2012; Diaz-Manera 2012; Nowack 2011; Blum 2011; Maddison 2011) a total of 69 of 75 MG patients were reported to have improved with Rituximab. Many patients were able to reduce their dose of prednisone or immunosuppression or both, as shown in the table:

STUDY*	TYPE	TOTAL PATIENTS (AChR/MuSK)	FOLLOW-UP	OUTCOME
Collongues 2012	Retrospective Multicenter	20 (12/4)	26 +/- 13 months	20 Improved MGFA** scores 11 off prednisone
Diaz-Manera 2012	Retrospective	17 (11/6)	31 (4-60) months	16 Improved MGFA scores Prednisone reduced Immunosuppression withdrawn in MuSK+
Nowak 2011	Retrospective	14 (6/8)	NR	14 (or 12?) Improved symptoms All reduced prednisone (8 off) 3/5 off immunosuppression
Blum 2011	Retrospective	14 (11/3)	14 (4-47) months	11 Improved (no details) 12 reduced immunosuppression (none off)
Maddison 2011	Retrospective Multicenter	10 (7/3)	12-48 months	8 Improved MGFA scores

A “meta-analysis” published in 2015 looked at all case series with at least two seropositive MG patients and reported that 83.9% of patients improved with Rituximab treatment, including 88.8% of MuSK antibody positive patients and 80.4% of acetylcholine receptor antibody positive patients (Iorio 2015). It should be kept in mind that this was not a true meta-analysis of randomized controlled clinical trials comparing odds ratios of a positive outcome with Rituximab treatment versus placebo. Rather, it simply combined (added up) all of the reported case series of

MG patients treated with Rituximab and reported on the presence or absence of clinical improvement (either physician impression of symptom improvement or a change in MGFA scale score). There was no real attempt to assess study quality or publication bias, so it represents more of a systematic review with pooled data, and not a true meta-analysis. Adverse effects were only reported in 7 of the 168 treated patients included. Four patients had an infection (1 each of herpes zoster, giardiasis, bronchitis, and pneumonia), two patients had prolonged B-cell depletion and one developed heart failure.

MuSK Positive Patients

There have been multiple reports of anti-MuSK antibody positive MG patients having an excellent response to Rituximab. The case series of Diaz-Manera et al cited above provided further details:

	MuSK antibody positive	**AChR antibody positive**
Status at follow-up	4/6 remission 2/6 minimal manifestation	10/11 improved
Required re-infusion	0/6	6/11
Immunosuppressants withdrawn	4/4	3/9
Average reduction in prednisone dose	49 to 6.5 mg/day	30.5 to 17.2 mg/day
Change in ab titres	6/6 reduced	5/11 reduced 5/11 increased

Rituximab Protocols

There is considerable variability both within and between case series in terms of how Rituximab is used. The most commonly used protocol for induction of treatment was 375 mg/m^2 given weekly for 4 weeks. Other protocols used 1 g weekly (without estimation of body surface area) for 2 weeks, or 500 mg weekly for 1-4 weeks. Maintenance therapy was not given in every patient. When used the protocols varied considerably: 375 mg/m^2 monthly for 2 months; 375 mg/m^2 every 3 months; 375 mg/m^2 every 6 months; or 1 g as needed. As stated above there is some evidence that anti-MuSK antibody positive patients are less likely to require re-infusion. There is published evidence showing that the effect of Rituximab on CD20+ lymphocytes usually lasts up to 1 year (Roll 2006). It seems prudent to watch for clinical deterioration in Rituximab treated MG patients after 9-12 months and be prepared to repeat treatment, particularly in the non-MuSK positive group. There is at least one reported case of prolonged B-

cell depletion in a MG patient; patients continuing to receive other immunosuppressant medication may be at higher risk (Yi 2013).

In Canada Rituximab will nearly always be given in a hospital setting. It is likely that protocols exist at individual hospitals for its use, given that it has been used more extensively in other diseases such as lymphoma and rheumatoid arthritis. Neurologists should contact their local hospital's infusion centre and/or rheumatology colleagues for further information. No standard exists for pre-treatment investigations but it seems prudent to consider a complete blood count (some authors recommend counts of lymphocyte sub-populations as well) and immunoglobulin levels (SPEP). There are no standard recommendations regarding testing for infectious exposure (HIV, Hepatitis, Varicella, etc…).

How should Rituximab be used in clinical practice?

The evidence supporting the use of Rituximab for MG comes exclusively from small case series. There is a real risk of publication bias (non-reporting of patients responding poorly to treatment). Published reports concern primarily refractory patients, and we do not know if the results with earlier use or in milder patients would differ. It appears to be well tolerated but the total number of treated patients is small and the follow-up short (publication bias is again a risk).

Allowing for these factors, the results across the published case series have been consistently positive. Rituximab appears to be a good option in patients failing conventional treatment. Earlier use should be considered in MuSK + patients given the strong results in this sub-group; although patient numbers are smaller there is also scientific support for a stronger response, given that anti-MuSK antibodies are of the IgG4 type that does not activate complement (Verschuuren 2013). Finally, one could argue on the basis of published reports that Rituximab should also be considered in certain patients likely to require long-term prednisone and azathioprine, in whom the side effect profile of Rituximab may be preferable to the combination of prednisone and azathioprine.

It should be noted, however, that no recommendation regarding the use of Rituximab was made as part of the recent international consensus statement on MG treatment: "evidence of efficacy is building, but…formal consensus could not be reached" (Sanders 2016).

Rituximab is a viable treatment option for a patient who is failing or intolerant of steroids, intravenous immunoglobulin (IVIG), and plasma exchange (PLEX). Anti-MuSK antibody positive patients may benefit to an even greater degree. Neurologists should watch for worsening 9-12 months after treatment.

The Future

There are a large number of phase II and III trials in MG that are either ongoing or awaiting publication of their results. This includes a small, prospective, open-label, phase I/II study of Rituximab that has been completed (NCT00619671) and a second prospective, open label, phase II study of Rituximab that has been completed and looked at both inflammatory myopathy and MG patients (NCT00774462).

Many trials are testing novel monoclonal antibodies and other targeted therapies:

AGENT	Mechanism of Action	Phase	ClinicalTrials.gov number
Bortezomib	Proteosome inhibition Depletes plasma cells	II	NCT02102594
Eculizumab*	Binds C5 and blocks complement cascade	III	NCT01997229 ("Regain")
Belimumab	Inhibits B-cell activating factor	II	NCT01480596**
Rozanolixizumab (UCB-7665)	Anti-FcRn receptor (intracellular Ig trafficking)	II	NCT03052751
CFZ 533	Anti-CD40	II	NCT02565576
ARGX-113	Anti-IgG	II	NCT02965573
CV-MG01	Vaccine?	II	NCT02609022
CK-2017357	Troponin Activator	II	NCT01268280

*Phase II results published (Howard Muscle Nerve 2013)
**Results show mean change QMG -4.21 vs. -2.37

Conclusions

1. Some patients with MG will fail and/or be intolerant to steroids, IVIG, and plasma exchange.

2. Both thymectomy and Rituximab appear to be well tolerated and could be treatment options for these patients

3. We should be testing for antibodies in most patients

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Appendix 1 – QMG Score

***Table 1** The quantitative myasthenia gravis score*

Test item	None	Mild	Moderate	Severe
Grade	0	1	2	3
Ptosis (upward gaze), s	61	11–60	1–10	Spontaneous
Diplopia (lateral gaze), R or L, s	61	11–60	1–10	Spontaneous
Eyelid closure	Normal	Complete, some resistance	Complete, no resistance	Incomplete
Dysarthria with counting 1–50	None	30–49	10–29	9 or less
Swallowing 4 oz water	Normal	Mild cough, throat clearing	Severe cough/choking	Unable
Vital capacity, % predicted	≥80	65–79	50–64	<50
Right arm held outstretched at 90 deg, s	240	90–239	10–89	0–9
Left arm held outstretched at 90 deg, s	240	90–239	10–89	0–9
Right hand grip, kgW, man/woman	≥45/≥30	15–44/10–29	5–4/5–9	0–4/0–4
Left hand grip, kgW, man/woman	≥35/≥25	15–34/10–24	5–4/5–9	0–4/0–4
Head lift 45 deg supine, s	120	30–119	1–29	0
Right leg held outstretched at 45 deg supine, s	100	31–99	1–30	0
Left leg held outstretched at 45 deg supine, s	100	31–99	1–30	0

(Table from Bedlack 2005)

As one example, a patient with ptosis at rest and diplopia provoked by sustained horizontal gaze for 5 seconds would score 5. If they were treated and their diplopia resolved but they still had ptosis brought out by 40 seconds of sustained upgaze, their score would have decreased to 1.

In a 6 month study patients rated as improved by neurologists had an average decrease in QMG score of 2.3 points, those rated as unchanged decreased by 0.7 points, and those who worsened had an average increase in score of 1.7 (Bedlack 2005). Similar results were obtained if improvement was defined as either the neurologist's subjective impression or improvement in muscle strength testing.

Appendix 2 - MGFA Clinical Classification

Class I: Any ocular muscle weakness; may have weakness of eye closure. All other muscle strength is normal.

Class II: Mild weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.

> IIa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
>
> IIb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.

Class III: Moderate weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.

> IIIa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
>
> IIIb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.

Class IV: Severe weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.

> IVa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
>
> IVb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.

Class V: Defined as intubation, with or without mechanical ventilation, except when employed during routine postoperative management. The use of a feeding tube without intubation places the patient in class IVb.