The myasthenia gravis (MG) content at this year’s American Academy of Neurology (AAN) meeting covered multiple aspects of MG management, including:

- MG types and their classification
- Available treatment options
- Resources to measure disease severity

This report covers select oral presentations and abstracts from the 2019 AAN meeting on the topic of MG and is in-line with areas of need identified by the CARE™ Needs Assessment on MG. Results from the needs assessment are found as a supplemental section at the end of this AAN report.

**CARE™ Faculty Perspectives:**

Dr. Vera Bril  
(Toronto General Hospital)

The content that follows is written in the language in which it was presented and is adapted from the abstracts of the AAN 2019 meeting.
In Period-1, patients received rozanolixizumab (n=21) or placebo (n=22). At D29, LSMean change from baseline in quantitative-MG (QMG) score (primary outcome) was −1.8 and −1.2 with rozanolixizumab and placebo, respectively (LSMean-difference −0.7, p=0.221). Reductions in MG-composite (MGC, −3.1 vs −1.2, LSMean-difference −1.8, p=0.089) and MG-activities of daily living (MG-ADL, −1.8 vs −0.4, LSMean-difference −1.4, p=0.036) scores were also observed. MG-ADL responder rate (≥3-point improvement) was 47.6% with rozanolixizumab versus 13.6% with placebo (p=0.017).

Improvements continued in Period-2: for patients continuing rozanolixizumab 7mg/kg, mean(SD) change from baseline scores 1-week post-final-dose (D50) were: QMG = −5.08 (3.64); MGC = −8.5 (4.6); MG-ADL = −3.90 (4.43); patients reallocated to rozanolixizumab also saw clinical improvements. Rapid total IgG and anti-AChR antibody titer reductions were seen, with mean reductions of −68% in patients continuing rozanolixizumab 7mg/kg.

During Period-1, 16/21 (76.2%) and 0/21 patients receiving rozanolixizumab and 16/22 (72.7%) and 2/22 (9.1%) taking placebo reported ≥1 TEAE and SAE, respectively. By D99, 36/43 (83.7%) rozanolixizumab-treated patients reported ≥1 TEAE, and 5/43 (11.6%) and 16/22 (72.7%) and 2/22 (9.1%) taking placebo reported ≥1 SAE; no deaths occurred. As expected, headache was more frequent (57.1%) versus placebo (13.6%) (Period-1); all were manageable and resolved with standard therapies. Per protocol, three rozanolixizumab-treated patients with headache withdrew.

Conclusions: Proof-of-concept was achieved based on clinically-meaningful improvements in MG outcomes and reductions in autoantibody titers, although difference versus placebo for the primary outcome was not statistically significant. The safety profile was consistent with other SC rozanolixizumab studies.

CARE™ Faculty Perspectives:

Anti-FcRn antibody therapy is a targeted therapy to reduce pathogenic antibodies in MG patients. This study of rozanolixizumab showed proof of concept in lowering serum IgG and anti-AChR antibody titres by about 70% and with this lowering, patients improved on several clinical scales: QM GS, MGC and MG-ADL. This subcutaneous once weekly therapy was also safe with the main adverse event being headaches.

Conclusions: Most MG patients who were doing well on IVIg maintained disease stability for another 12 weeks once transitioned to SCIg.

CARE™ Faculty Perspectives:

This open label study of 22 MG patients demonstrated that about 80% of MG patients being treated with IVIg can transition safely to SCIg without relapse for another 12 weeks once transitioned. This study provides evidence to transition MG patients to subcutaneous therapy with a good chance that they will remain clinically stable on this therapy.

ADDITIONAL ABSTRACTS OF INTEREST


Aditi Sharma, et al.

Results: Sixty-two (21%) out of 297 patients were classified as refractory, and a total of 496 patient encounters with MG crisis with ARF who ≥1 time(s) and ≥3 times was 74.2% versus 28.5% and 25.8% versus 2% in the refractory and non-refractory groups respectively (p-values <0.001, <0.001). Differences in healthcare utilization, use of rescue therapy and chronic IVIg/PLEX among other variables was observed, consistent with a higher financial burden in the refractory group.

Conclusions: Patients with refractory MG have key clinical characteristic differences including a greater burden of disease. Understanding disease burden from both a quality of life and financial perspective as well as further characterizing it remains a high priority as treatment paradigms emerge for patients with difficult to manage MG.

CARE™ Faculty Perspectives:

This retrospective chart review done on the Yale MG Clinic Registry from 2003-2018 showed that 21% of patients were classified as refractory. Of these, 65% were women with early-onset, more likely MuSK antibody positive, have had thymectomy, and had coexisting autoimmune disease. 41% had an MGFA class V and ½ had been hospitalized at least once.


Shuja Sheikh, et al.

Results: A total of 496 patient encounters with MG crisis with ARF who received treatment were identified (mean age 63.3 years ± 18.1, 47.6% of whom were male) of which 20.2% were treated with IVIG, 30.66% with PE and 4.2% with steroids. Of these 66 (13.3%) patients were in the age group 20-49 years, 125 (25.2%) in age group 50-79 years, and 54 (10.9%) over the age of 80 years. 80 years and older patients were more likely to develop ARF (23.7%) than patients aged 50-79 years (13.5%) and patients aged 20-49 years.
years (9.8%) (p-value < 0.05). 46.3% of 80 years and older patients were treated with IVIG compared to 30.3% patients aged 20–49 years and 32.8% patients aged 50–79 years (p=0.41. 50% of 80 years and older patients were treated with PE compared to 59.1% patients aged 20–49 years and 60.8% patients aged 50–79 years (p=0.77).

**Conclusions:** Elderly patients are more likely to develop acute respiratory failure with MG crisis as compared to younger patients. No significant difference in the use of IVIG vs PE for the treatment of MG crisis between different age groups suggesting that age does not influence the choice of therapeutic options.

### CARE™ Faculty Perspectives:

This study reviewed 496 patients with MG crisis in the NY State database, and found that there was no difference in the use of IVIg or PE for crisis patients and that there was no difference in usage across age groups, meaning that age does not influence the choice of therapeutic options in MG crisis.

**AAN 2019. P5.2-080. Changes in Concomitant Immunosuppressive Therapy Use During a Phase 3 Open-label Study of Eculizumab in Adults with Generalized Myasthenia Gravis: an Interim Analysis.**

Richard Nowak et al.

**Results:** Median eculizumab treatment duration from OLE baseline was 22.7 months (range, 1 day to 37.3 months; 227 patient-years’ exposure). At OLE baseline, 98.3% (115/117) of participants were receiving at least one IST. Thereafter, 67.5% (79/117) stopped or decreased the dose of an IST on 439 occasions in total, most commonly because of MG symptom improvement (46.2% [54/117] of participants on 256/439 occasions), and 53.8% (63/117) started or increased the dose of an IST on 189 occasions, most commonly because of MG symptom worsening (32.5% [38/117] of participants on 89/189 occasions).

**Conclusions:** In eculizumab-treated adults with gMG, a numerically larger proportion stopped or decreased the dose of a concomitant IST than started or increased the dose. MG symptom improvement and MG symptom worsening were the most common reasons for stopping/decreasing and starting/increasing IST, respectively.

### CARE™ Faculty Perspectives:

This long-term extension of the REGAIN trial enrolled 117 patients for a median treatment duration of about 23 months at the time of this analysis. About 54/117 patients were able to reduce their dose of concomitant immunosuppressive treatment (IST) or stop the treatment due to symptom improvement, but 38/117 patients had to start or increase their dose of IST due to symptom worsening. Another 25/117 patients decreased their dose or stopped IST due to other reasons. There may be some benefit to long-term treatment with this complement inhibitor.

**AAN 2019. P5.3-078. Zilucoplan, a Subcutaneously Self-Administered Peptide Inhibitor of Complement Component 5 [C5], for the Treatment of Generalized Myasthenia Gravis: Results of a Phase 2 Randomized, Double-Blind, Placebo-Controlled Trial and Open-Label Long-Term Extension.**

James F. Howard, Jr. et al.

**Results:** Forty-four patients were randomized 1:1:1 to placebo, zilucoplan 0.1 mg/kg, or zilucoplan 0.3 mg/kg subcutaneously (SC) daily over 12 weeks. Clinically meaningful and statistically significant improvements in the primary and key secondary efficacy endpoints were observed. Zilucoplan dosed at 0.3 mg/kg SC daily achieved a mean reduction from baseline of 6.0 points in the QMG score (placebo-corrected change: -2.8; p=0.05) and a mean reduction from baseline of 3.4 points in the MG-ADL score (placebo-corrected change: -2.3; p=0.04). Rescue therapy (intravenous immunoglobulin or plasma exchange) was required in 3/15 subjects in the placebo arm, 1/15 in the 0.1 mg/kg zilucoplan arm, and 0/14 in the 0.3 mg/kg zilucoplan arm. Zilucoplan was observed to have a favorable safety and tolerability profile, consistent with prior clinical trials. Long-term data from the OLE will also be presented.

**Conclusions:** These positive data support the potential therapeutic role of zilucoplan in gMG and its further evaluation in a registrational Phase 3 trial.

### CARE™ Faculty Perspectives:

Zilucoplan is a small peptide that binds to C5 and inhibits activation and therefore the formation and assembly of the membrane attack complex. This study enrolled 44 patients with QMGs of at least 12 points to placebo, low or high dose Zilucoplan. For 12 weeks. In the high dose group, the QMGS dropped by 6 points or 2.8 points more than placebo. Long-term benefits were observed. This therapy prevents destruction of the acetylcholine receptor but does not block other mechanisms responsible for weakness in MG.

**AAN 2019. P2.2-102. Comparison of the Quantitative Myasthenia Gravis (QMG) and Myasthenia Gravis Activities of Daily Living (MG-ADL) scores in the MGTX Randomized Trial.**

Tarrant McPherson, et al.

**Results:** Assuming normality for QMG appears adequate, but MG-ADL is better fit by a Poisson distribution. Treatment group and time were significant (p<0.05) in both models. The AR(1) parameter was similarly high for QMG (0.8448) and MG-ADL (0.7225). Visually the QMG model fits better overall and especially for TPP patients. The baseline correlation between the measures was 0.65 (TPP) and 0.53 (PA). The increasing multivariate relationship describing the observed correlation between the two measures and their means (HLT p<0.0001) and standard deviations (HLT p<0.0001) at each time point suggests the measures perform more similarly when the disease is less well controlled.

**Conclusions:** QMG and MG-ADL are clearly correlated and appear to perform similarly in measuring MG severity. The model curves and AR(1) coefficients are similar reflecting treatment modifications across study visits. Normality assumptions apply in modeling QMG, thereby facilitating statistical analyses and enabling a wider range of model assessments.

### CARE™ Faculty Perspectives:

This study showed that the QMG and MG-ADL are correlated and perform similarly in measuring MG severity, but normality assumptions apply in modeling QMG, but not MG-ADL, facilitating statistical analyses with QMG.
In Fall of 2018, CARE™ neuromuscular faculty led by Dr. Vera Bril (UHN), conducted a Needs Assessment on Myasthenia Gravis that was distributed to Canadian neuromuscular specialists. The purpose of this Needs Assessment was to gather feedback on the current state of MG management, while also identifying potential areas of need or gaps in knowledge.

The findings of this Needs Assessment are significant, suggesting that there is not currently consensus among healthcare practitioners in regards to Myasthenia Gravis management.

Responder feedback and areas of need are very aligned to content covered at AAN and touched on the previous pages of the AAN report.

Specific areas of need:

- Ill-defined patient subgroupings (i.e. refractory versus first line).
- Lack of agreement regarding superior diagnostic tools in the identification of MG-associated impairment.
- Low practitioner confidence in ability to manage MG (high referral levels).

What follows are results and CARE™ faculty perspectives and call to action as provided by Dr. Vera Bril (VB).

### 1. Who typically refers MG patients to you? (n=42)

<table>
<thead>
<tr>
<th>Group</th>
<th>Response Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>General practitioners</td>
<td>71%</td>
</tr>
<tr>
<td>Another neurologist</td>
<td>33%</td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>Top responses in “other”</td>
<td>45%</td>
</tr>
</tbody>
</table>

Note: total percentage exceeds 100% as responders selected more than 1 answer.

### 2a. Are there situations where you would refer one of the MG patients you are managing to a specialist in an academic centre? (n=41)

- Yes: 85%
- No: 15%

### 2b. If yes, please identify which MG patients you would refer and why. (n=35)

<table>
<thead>
<tr>
<th>Common Responses Included (in rank order):</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Refractory to treatment</td>
</tr>
<tr>
<td>• All patients because: “another practitioner’s expertise in MG”, “don’t see enough MG patients”, “already in a university hospital”</td>
</tr>
<tr>
<td>• Need second opinion/confirmation</td>
</tr>
<tr>
<td>• Most patients because of my limited experience</td>
</tr>
<tr>
<td>• For thymectomy</td>
</tr>
</tbody>
</table>

### 3. I define refractory MG patients as... (n=42)

<table>
<thead>
<tr>
<th>Definition</th>
<th>Response Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Those who fail 2 immunosuppressive therapies</td>
<td>55%</td>
</tr>
<tr>
<td>Those who fail 1 immunosuppressive therapy and require chronic IVIg or PLEX</td>
<td>50%</td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>Top responses in “other” (in rank order):</td>
<td>12%</td>
</tr>
<tr>
<td>• Unsure</td>
<td></td>
</tr>
<tr>
<td>• Those who fail IVIg/PLEX or can’t have them</td>
<td></td>
</tr>
<tr>
<td>• Disease does not stabilize with mexitonin + high dose prednisone + IVIg</td>
<td></td>
</tr>
</tbody>
</table>

Note: total percentage exceeds 100% as responders selected more than 1 answer.

### Perspectives:

Patients are referred primarily from GPs but many other specialists are also involved (Qtn 1 & 2a, 2b). Results from question 3 suggest that there is currently no standard definition for a refractory MG patient. This represents an opportunity to build a Canadian guidance or standard definition of refractory MG which could allow for more effective management, and timely considerations for moving to the next therapy.

- VB.

### 4. What percentage of your MG patients would you define as being refractory to conventional treatment? (n=37)

- <5%: 60%
- 6-10%: 16-25%
- 11-15%: 03
- 16-25%: 0
- 26-50%: 0

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**INSIGHTS FROM MG NEEDS ASSESSMENT**

**Definition**

- Those who fail 2 immunosuppressive therapies: 55%
- Those who fail 1 immunosuppressive therapy and require chronic IVIg or PLEX: 50%
- Other: 12%

**Common Responses Included**

- Refractory to treatment
- All patients because: “another practitioner’s expertise in MG”, “don’t see enough MG patients”, “already in a university hospital”
- Need second opinion/confirmation
- Most patients because of my limited experience
- For thymectomy
5. Is your treatment approach different for refractory MG patients who are anti-acetylcholine receptor antibody positive (AChR autoAb+ve) versus other MG patients? (Please explain) (n=36)

Common Responses Included (in rank order):
- “No”
- Not applicable (do not manage/refer on)
- If Ab+: thymectomy
- If MuSK+: no thymectomy, no mestinon, more likely to give rituximab

6. What is the standard test for assessing MG-associated impairment at your centre? (n=34)

<table>
<thead>
<tr>
<th>Test</th>
<th>Response Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>MG impairment index (MGII)</td>
<td>9%</td>
</tr>
<tr>
<td>MG composite assessment (MGC)</td>
<td>3%</td>
</tr>
<tr>
<td>Qualitative MG score (QMGS)</td>
<td>6%</td>
</tr>
<tr>
<td>MG activities of daily learning assessment (MG-ADL)</td>
<td>6%</td>
</tr>
</tbody>
</table>

Top responses in “other” (in rank order):
- Don’t have/use standard testing
- Clinical exam/clinical definition 82%

Perspectives: 60% of responders suggest that upwards of 25% of MG patients are refractory to treatment (Qtn 4). With regards to standardized testing - there is currently no standardized test for MG management. However, work is being done on approaches to testing MG. Dr. Carolina Barnett-Tapia (University of Toronto) and I are currently reviewing data to refine the MG impairment index (MGII). The intent is to have insights available to share with peers in the fall.

- VB

7. To what extent do you agree with the following statements on treatment selections: (n=42)

<table>
<thead>
<tr>
<th>Statement</th>
<th>Strongly Disagree</th>
<th>Disagree</th>
<th>Neutral</th>
<th>Agree</th>
<th>Strongly Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>7a. I understand the role of the complement system in MG.</td>
<td>19%</td>
<td>29%</td>
<td>36%</td>
<td>12%</td>
<td>4%</td>
</tr>
<tr>
<td>7b. I am comfortable treating patients with MG throughout the course of their disease.</td>
<td>19%</td>
<td>17%</td>
<td>12%</td>
<td>29%</td>
<td>23%</td>
</tr>
<tr>
<td>7c. I am comfortable managing patients with MG who are refractory to “standard” treatment (i.e. pyridostigmine, ISTs, etc.).</td>
<td>31%</td>
<td>17%</td>
<td>9%</td>
<td>36%</td>
<td>7%</td>
</tr>
<tr>
<td>7d. I am satisfied with the available MG treatment options.</td>
<td>2%</td>
<td>21%</td>
<td>44%</td>
<td>28%</td>
<td>5%</td>
</tr>
</tbody>
</table>

Perspectives: 84% of responders are neutral to, or identified as not understanding the role of the complement system in MG. This represents an area of opportunity. There are agents which affect the complement system that have demonstrated effectiveness in relapsed/refractory patients.

- VB

8. When treating MG, in which patients would you use IVIg vs. PLEX? (n=42)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Description of MG Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>8a. Short-term PLEX</td>
<td>• MG crisis • Pre-op, attack or flare • Acute exacerbation • Relapse • Contradiction or failure of IVIg</td>
</tr>
<tr>
<td>8b. Chronic PLEX</td>
<td>• Rarely use • Contradiction or failure of IVIg • Refractory/failure of therapies</td>
</tr>
<tr>
<td>8c. Short-term IVIg</td>
<td>• All with disabling symptoms • MG crisis • Post-op • Acute exacerbation • Pre-op, attack or flare • Relapse • Young MG • Swallowing/breathing problems</td>
</tr>
<tr>
<td>8d. Chronic IVIg</td>
<td>• Rarely use • Refractory/failure of therapies • IVIg or IST not working • If advised by a specialist</td>
</tr>
</tbody>
</table>

Concluding Thoughts

The AAN meeting and CARE™ MG Needs Assessment results convey a need for improved classification and diagnosis of Myasthenia Gravis, with a focus on patients who are refractory to treatment.

Delays in the identification and treatment of MG patients (as a result of frequent referral, unclear disease stratification and limited consensus on superior diagnostics) are leading to more frequent hospital stays, increased rescue therapy usage, and poorer patient outcomes – trends that are most pronounced in refractory patients.

Timely diagnosis and treatment of MG patients can only happen after HCP consensus on the standard of care for refractory MG patients is reached. This goal may only be achieved through improved communication in the form of annual meetings and other educational initiatives. Currently, forums of discussion for MG management are lacking, but physicians must be given regular updates on how to optimally refer MG patients, identify disease stage and measure MG associated impairment.

Call to action, assemble leading North American MG treaters in a working group at the upcoming AANEM (American Association of Neuromuscular & Electrodiagnostic Medicine), October 2019. The goal of this working group will be to review new data, consider approaches to MG treatment, and land on a treatment algorithm/guidance that can help direct future MG management in Canada.

UPCOMING - CNSF REPORT

CARE™ faculty attended and are also reviewing key abstracts/news from the annual Canadian Neurological Science Federation (CNSF) conference Montréal, June 16-19 2019. A report to follow with emphasis on a newer agent.
The CARE™ (Community. Academic. Research. Education) Faculty is a Pan-Canadian group of leaders in their field who gather, discuss and address gaps in knowledge, to develop education initiatives that frame news from a Canadian perspective.

The vision of the CARE™ Faculty is to share opinions and update Canadian specialists with news and developments from key conferences framed in a Canadian perspective.

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