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Myasthenia Gravis: Reducing Outcome Measures Variability in Clinical Trials

Lew Fredane, MD - June is 'Myasthenia Gravis Awareness' month and a great opportunity to raise awareness of this rare autoimmune disease that, like many other rare diseases, is often unknown by the general public. Over the past decades, Myasthenia Gravis (MG) clinical trials have made remarkable progress in shining a light on this debilitating disease.

In this article we will be discussing some of the history of this disease and the efforts made to develop treatments as we have continued to understand Myasthenia Gravis and its underlying mechanisms better over time. In addition, we will examine some of the aspects of clinical development that may significantly generate outcome variability in the clinical trials needed to prove efficacy of the treatments and the measures used to reduce such outcome variability.

Myasthenia Gravis – managing unpredictability one step at the time

Myasthenia Gravis (MG) is a rare, neuromuscular, autoimmune disease which causes muscle weakness and fatigue. Prevalence rates have increased worldwide over the past 50 years not due to increased incidence but due to greater awareness of MG and improvements in diagnosis. The current prevalence is estimated to range between 150 to 200 cases per million (Dresser et al, 2021).

Communication between the nerves and the muscles they activate relies of the release of acetylcholine (ACh) from the nerve terminal and being picked up by the acetylcholine receptors (AChRs) on the target muscle fibers, leading to contraction of those muscle fibers. In MG, disruption of these processes occurs when autoantibodies directed against the AChR block the binding of ACh to the receptor thereby preventing the AChR from causing the muscle fiber to contract.

Although MG can affect people of all ages, it is commonly observed in women younger than 40 and in men older than 60. Symptoms vary greatly from person to person and impact the ability to perform daily tasks. These can include:

- Oculomotor symptoms, namely double vision and droopy eyelids, appear within the first two years in two thirds of the patients
- One sixth of the patients will develop oropharyngeal symptoms causing difficulties in swallowing and chewing or talking

- Arm/Leg muscle weakness develops in 10% of the MG patients
- Symptom expression fluctuates throughout the day, with patients feeling worsening muscle weakness and fatigue as the day progresses

Furthermore, the severity of the symptoms fluctuates over time with patients going through periods of exacerbation and remission during the course of the disease. The unpredictability of the disorder is marked by the variable degree and combination of ocular, bulbar, limb, and respiratory symptoms from one person to another.

Clinical trials in MG – What does history tell us?

Clinical trials have, throughout the years, generated invaluable knowledge about MG and effective treatment options that can significantly improve patients' lives. It was not until the 20th century that MG was treated as a unique disorder and that the first treatments that managed MG symptoms started being discovered (Nguyen-Cao et al., 2019).

Early clinical trials focused on the efficacy of acetylcholinesterase inhibitors and immunosuppressive agents to manage MG symptoms. However, these were limited to a short-term effect on symptoms and did not address the underlying autoimmune pathology of the disease.

In the last 50 years, the industry has observed a growing number of clinical trials in MG and considerable progress in the treatment options available for patients.

With a better understanding of the disease mechanisms, new target treatment options emerged in the 20th century. The discovery of monoclonal antibodies targeting specific immune processes was a significant discovery as they offer different mechanisms of action based on specific antibody target (Song et al., 2022).

Challenges in MG clinical trials

Important lessons were taken from this accelerated progress in clinical trials (Benatar et al., 2012). These include:

- Participant recruitment was slower and difficult to complete, resulting in smaller sample sizes than expected in the beginning of the trial
- Study duration was often inadequate. They were either too long, with patient retention throughout the trial being challenging or too short for significantly visible treatment effect (such as steroid-sparing effects of immune suppressive agents).
- Lack of sensitive outcome measures to precisely capture significant treatment effects
- Lack of standardization in the performance of outcome measures, a major source of

variability in clinical trial data

- Due to the fluctuating nature of the disease, symptoms are usually more evident to the patient than to the clinician.

It is therefore important to prioritize study participants' responses about the symptom expression and its impact on quality of life as an outcome measure in clinical trials.support.

4 Methods for reducing outcome variability in MG clinical trials

Overcoming these challenges is crucial to ensuring success of MG clinical trials and securing the successful development of new therapies for patients. Sponsors can enhance the quality and reliability of MG trial data using several methods:

- Standardize the administration of outcome measures

For many years, the 'Quantitative Myasthenia Gravis score' (QMG) was the main outcome measure for MG clinical trials. With more emphasis being placed on incorporating patient-reported outcomes in drug development, the 'MG-Activities of Daily Living Scale' (MG-ADL) became the primary or key secondary efficacy endpoint for many subsequent Phase 2 and 3 studies.

Variability in the administration of outcome measure administration may cause confusion amongst site staff and sponsors and can ultimately lead trials to measure disease symptoms differently (Guptill et al., 2023). As an example, the assessment of 'Vision' items in the QMG may differ from site to site and has changed significantly throughout the years. Simultaneously, the accuracy of spirometry assessment is highly dependent on the administration of the task and in the device model selected for each trial.

It is then crucial to carefully standardize outcome measures performance (by the scale administrator and the study participant) in the trial environment for accurate, reliable endpoint results.

- Standardize your rater training strategy

High intra- and inter-rater variability often impacts the quality of study endpoints. In outcome measures such as the QMG and MG-ADL, where often the Minimal Clinically Important Change Score (MCID) is small (2 / 3 points), any additional variability introduced by lack of detailed training can be detrimental to data quality and jeopardize signal detection. With Signant Health's Rater Training & Qualification program, Sponsors can increase data accuracy and consistency in administration and scoring across raters and sites. It is also no small point that emphasis is placed on having the same rater for the same participant at every visit during a study.

- Incorporate data analysis and interpretation

It is important to be vigilant and monitor how data is captured throughout the duration of a trial. Signant Health's Blinded Data Analytics is a statistical data monitoring model of blinded data that identifies and remediates data quality concerns which may impact the study endpoint(s). With Blinded Data Analytics it is possible to identify in a timely manner during the conduct of the study and from the beginning unexpected variability in data points related to erratic changes in scores across visits, outlying changes in important outcomes measures such as the QMG and the MG-ADL or time of assessments (crucial in MG patients as they get more fatigued as the day progresses).

- Use electronic clinician ratings

Often MG outcome measures selected for MG clinical trials have complex scoring systems, including the capture of raw scores and corresponding assigned grades and composite scores (such as the 'Myasthenia Gravis Composite' scale). These can be a source of frustration for site raters. Clinician-reported outcomes (ClinROs) that use paper scales are susceptible to human error and missing data. Electronic Clinical Outcome Assessments (eCOA) greatly reduce scale administration errors, improve data accuracy (by including the option of audio/video data collection) and data reliability as well as eliminating errors that occur as a result of data transfer from paper scale copies. Please check out Signant Health's Electronic Clinician Ratings options catered to the unique needs of sponsors and regulators.

If you want to take the next step in advancing MG drug research and are interested in better understanding Signant's extensive experience in MG clinical trials, please contact our team.

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