A Sum Score to Define Therapy-Refractory Myasthenia Gravis: A German Consensus

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ABSTRACT

BACKGROUND AND PURPOSE: In 2017, eculizumab has been approved for treatment-refractory generalised myasthenia gravis (TRgMG). The German Myasthenia Foundation has published a consensus statement on the use of eculizumab, with a recent update. However, a treatment-refractory state is still ill-defined and the term warrants further clarification. We aimed at developing a sum score to operationalise the definition of a TRgMG status, which is easy- to-handle in clinical decision making.

METHODS: We established a structured consensus process according to the Delphi consensus methodology, with 12 members of the medical advisory board of the German Myasthenia Foundation. Accordingly, 4 consensus rounds were accomplished. Additionally, a literature survey covering the years 2004-2020 was done and relevant information offered to the consensus group. Consensus criteria were predefined. In the consensus process the relative importance of scoring items were to be consented, with a sum score of 20 and above indicating a TRgMG status.

RESULTS: The sum score considers the categories disease severity, inefficiency of antecedent therapies, cessation of therapies due to side effects, and long term stay on the intensive care unit. Categories were specified by a total of 13 scoring items. Eventually, the Delphi process developed an unanimous scoring consensus.

CONCLUSION: We suggest a sum score to define treatment refractory state in generalised myasthenia gravis. Beyond clarifying the indication of eculizumab, this easy-to-handle score facilitates clinical decision making and offers new inclusion criteria for clinical studies that explore new therapeutic perspectives in myasthenia gravis treatment.

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Introduction

The German Myasthenia gravis Foundation (Deutsche Myasthenie Gesellschaft, DMG) has certified 'Integrated Myasthenia Centres' throughout Germany to ensure quality standards for the care of patients suffering from myasthenia gravis (MG). In turn,

the heads of those centres constitute the Medical Advisory Board of the DMG. The board has met on a regular basis in an effort to set best practice standards in myasthenia diagnostics and therapy in Germany.

Beyond the well-established Myasthenia Gravis Foundation of America (MGFA) classification system, regulatory authorities have coined the term treatment-refractory generalised myasthenia gravis (TRgMG) to describe the indication for treatment with eculizumab as labelled in the EU since August 2017. However, the term treatment-refractory is still ill-defined in the context of MG, and several medical and economic uncertainties emerged how and when to use eculizumab in clinical routine.

Previous discussions led to a consensus describing 4 main categories of items considered essential for the definition of TRgMG: (i) a certain severity of disease as a prerequisite, (ii) the inefficiency of previous therapies, (iii) adverse specific side effects that caused physicians to discontinue therapies and (iv) clinical deterioration of the patient's status requiring exacerbation therapies such as plasma exchange, intravenous immunoglobulins (IVIg), or prolonged intensive-care unit (ICU) treatment.[1]

We believed that the use of a sum score provides a robust and reproducible way to assess a possible treatment-refractory state of myasthenia. To this end, a structured consensus process was undertaken to develop an easy-to-use clinical sum score.

Material and Methods

This work conforms to the ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals. Our study did not require an ethical board approval because it did not fit the criteria of a clinical trial, nor report on specific patient data. We established a stepwise Delphi consensus that took place between May 9th and June 28th, 2020. Differing from the classical Delphi process, the participants knew each other from the medical advisory board of the DMG.

Scoring items were extracted from the revised consensus statement and antecedent discussions of the medical advisory board on the use of eculizumab.[1] The score items refrain from including therapies that define a treatment refractory state for itself, for example, chronically repetitive IVIG use or eculizumab.

In a first step participants were asked to play around with those scoring items that covered qualitative criteria (i-iv, see introduction), and to figure out scores for fictive cases. As predefined, a sum score of 20 and above should indicate a treatment refractory state. The outpoint of 20 was chosen to keep numbers in a range well reasonable for figuring out scores in fictive and real clinical situations. Excluding decimal steps, the cut-off of 20 was chosen to allow not only binary decisions but weighing scores for the 13 items. In the first round, scoring suggestions were sent back to the moderator (MS). Participants were informed about the whole Delphi consensus process, scores deviating more than 2 points from the median were commented on and sent back by the moderator to the participants who were asked to reconsider their scoring proposal (2nd round). Systematic review and commentary were given again by the moderator, along with results of a literature review (see below). Participants had the chance to read the renewed commentaries of the moderator, the literature survey, and to adjust their scoring, accordingly (3rd round). Lastly, a fourth round was held as a virtual meeting on June 25th, 2020, and scorings were openly discussed. As predefined, a >75% match of scorings was regarded a consensus. Finally, participants had the chance to re-consider their score suggestions and sent it to the moderator immediately after the panel discussion.

Literature Survey

In 2013, the phase 2 trial investigating eculizumab in MG treatment has defined the scenario of TRgMG.[2] Accordingly, searching strategy in PubMed followed 2 time windows, one before and one after the study publication that is from 2004 to 2013 and from 2014 to 06/2020, respectively. Search terms were 'refractory AND myasthenia', 'score AND myasthenia', 'consensus AND myasthenia'. The abstracts were scanned for definitional procedures and sum scores to define and determine clinical states. In doubt, full length paper was scanned for valuable information according to the scope of this paper.

HITS IN PUBMED, TOTAL NUMBER (& PER YEAR), SEARCHED ON JUNE 11TH, 2020	2004–2013	2014-06/2020
Refractory AND myasthenia	79 (8)	140 (22)
Score myasthenia	218 (22)	293 (45)
Consensus AND myasthenia	24 (2)	32 (5)

Results

Literature survey and development of score items

Until 2010, the term treatment refractory relates to treatment failure of conventional immunosuppressant drugs, for example, azathioprine, ciclosporin A or mycophenolate mofetil. In this context, several publications deal with the discovery of Muscle specific kinase antibody (MuSK) positive MG. Rapidly it was recognised that MuSK positive MG is frequently refractory to conventional immunosuppressants, and in some instances,

MuSK positive MG and treatment refractory were used in a somewhat synonymous way in early publications. Other risk factors for a treatment refractory state are presence of thymoma, and female sex.[3,4] Rituximab, IVIg and plasmapheresis have been reported to be effective in overcoming treatment refractory condition in those patients. Having the recording bias in mind, and the aforementioned treatment options in our hands, a treatment refractory state will affect much less than a proportion of 10% to 15% of myasthenia patients as reported earlier.[3] Although these reports do not state on a more general definition of a treatment refractory state, an algorithm is proposed to define a therapy refractory state, with conventional immunosuppressants and steroid therapy as the main prerequisites.[3] We can assume that failure to respond to conventional immunosuppressant therapy puts an essential piece to the puzzle in defining TRgMG.

In more recent publications a sufficiently long treatment, such as a minimum of 12 months for azathioprine and mycophenolate mofetil, is a prerequisite to define inefficient treatment.[1,4]

Although these reports deal with patients with substantial clinical deficits, a cut-off to define treatment refractory is missing. Even an ocular myasthenia gravis can have an refractory course. However, bulbopharyngeal symptoms and respiratory failure are the symptoms most often mentioned to underscore disease severity. Regarding the Myasthenia Gravis – Activity of Daily Living score (MG ADL), cut-offs of 6, 8, or 10 have been used to define 'severe myasthenia' in clinical studies. Similarly, neglecting points from ocular symptoms to a variable extent, a Quantitative Myasthenia gravis Score (QMG) of 8 or 10 as well as a current MGFA status of III and above have been used to define a 'severe myasthenia gravis' in clinical trials. Data from the eculizumab trials allowed the comparison of QMG and MG-ADL to measure disease severity. Whereas MG-ADL gives a sensitive estimate on therapy response, one time point measure of disease severity may be inferior to QMG.[5] However, QMG is often time-consuming for clinical routine. Although the MGFA has been dedicated to classify disease severity but not reflect the present disease status, we agreed that the current status according to the MGFA classification system gave an easy-to-use measure for the designated scoring system.

With a limited number of therapeutic options in our hands, any side effects that urge to stop treatment narrows our treatment repertoire and therefore may contribute to a treatment-refractory state. Although quite obvious, evidence to support this assumption is scarce, and we expect new evidence from registries as recently initialised in Germany. The use of IVIg, plasma exchange, or immunoadsorption are therapeutic options in the situation of myasthenic exacerbation and crisis, respectively, which may in turn stem from a treatment refractory situation.[6] Finally, the myasthenic crisis requires treatment on the ICU. While we discussed an ICU stay as an ambiguous sign of severe and therapy-refractory myasthenia, which could be caused by diseases other than the myasthenia itself, a prolonged stay on the ICU was regarded as a more unequivocal sign of severe and treatment refractory myasthenia.

Interestingly, the use of rituximab has changed over time. In the earlier reports it was used only to overcome a treatment refractory state.[7] Although evidence from a controlled clinical trial is still missing, accumulating evidence make rituximab a first-line therapy especially in MuSK positive MG, and may be used systematically in early MG patients.[8,9] Although still controversial, these data suggest that rituximab treatment should be tried before a patient is considered treatment-refractory, and, with even greater certainty, failure to respond to rituximab will contribute to a treatment refractory state. However, it is conceivable that a (failure of) rituximab treatment is not always required to define a therapy-refractory state.

As expected, refractory patients have more outpatient visits and inpatients stays, as well as worse MG-Quality of Life ratings, with substantial overlap between responders and treatment refractory patients.[10] At the end, results regarding economic burden parameters as well as subjective estimations on burden of disease were not included in the items.

Previous studies and definitions of treatment refractory states have been recently reviewed.[4] Qualitative criteria are converging in more recent publications, with some variations.[4] All those clinical studies do predefine treatment refractory but do not investigate a quantitative cut-off. Additionally, criteria showed a substantial overlap between responders and refractory patient groups.

All in all, converging qualitative criteria have been developed in a number of reports, which make a contribution but do not separate a TRgMG from responders. As a logical consequence, a combination of criteria may be superior, and it is expected that a sum score will better balance the relative importance of the individual items contributing to a refractory state.

The search on 'myasthenia AND score' did not reveal reports that suggest scores in the context of TRgMG.

Since early recommendations to measure the clinical status in myasthenia consensus papers focussed on treatment algorithms.[11] PubMed search did not reveal any consensus statement on the development and validation of new clinical scoring systems.

Finally, the selected items for scoring were suggested to the board members for evaluation (Table 1). Structured Delphi process was initiated as detailed above. Most interestingly, the predefined criteria of consensus, a $<75\%$ match of scoring values, were already reached after the second round. Exposing the results of the literature survey did not essentially change scoring. Discussion in the open round (4th round) revealed that the items 'MGFA IV or V' and 'ICU stay longer than 42 days' (Table 1) are not completely disjunctive and independent: MGFA V may implicate that the patient is presently on ICU, and, vice versa, a patient staying longer than 42 days on ICU will very likely be classified as MGFA V. In addition, myasthenia may manifest with crisis necessitating ICU therapy. A substantial delay in recognising of the diagnosis may result in a prolonged ICU stay but does not mean a treatment refractory state. In that particular situation those items may overscore. Therefore the contribution of both items to the sum score was limited to 15 points (Table 1).

Finally, the scoring sheet was consented as follows:

Table 1. Sum score to define treatment refractory myasthenia.

SCORE CATEGORY	SCORE ITEM	SCORING
Present MGFA score	MGFA III	5
	MGFA IV or V[1]	10
Inefficacy of treatment (failure to reach a MGFA II status)	Azathioprine, at least for 12 months	5
	Mycophenolate, at least for 12 months	5
	All other conventional immunosuppressants, at least for 12 months[2]	5
	Rituximab, cumulative dosage at least 2 g and at least for 3 months	8
	Steroids: prednisolone 1 mg/kg body weight for 8 weeks, or equivalent	5
	Plasma exchange or immunoadsorption, 5 sessions at least	8
Treatment cessation due to side effects	Azathioprine	3
	Mycophenolate	4
	Rituximab	5
	Others[2]	4
ICU stay	Longer than 42 days[1]	10
1 If both apply resulting points are reduced to 15!		
2 May apply only once irrespective of the number of substances tried		
Sum score	Scoring of at least 20 defines treatment refractory	

Discussion

The introduction of immunosuppressive treatment meant a breakthrough in MG therapy. However, a significant proportion of patients still does not respond sufficiently or do not respond at all. MuSK-positive patients have often experienced failure of conventional immunosuppressants that can be overcome by rituximab. Rituximab has been successfully used in acetylcholine receptor antibody-positive (AChR+) and antibody negative forms of MG as well. Eculizumab was successfully tested for AChR+ generalised MG and has been approved for AChR+ TRgMG in 2017. This approval revealed a need to define treatment refractory state to allow a meaningful sequence of myasthenia therapies.

The medical advisory board of the German Myasthenia Society has commented on the use of eculizumab in myasthenia, with an update in May, 2020.[1] Similarly, a recently published review aimed at summarising the information and differential therapies for therapy-refractory myasthenia.[4]

We opted for the development of a sum score to facilitate clinical decision making in putative treatment refractory situations and new emerging therapies for myasthenic syndromes currently studied in clinical trials support the need for such guidelines.

Within the experts group of the medical advisory board, there was immediate and broad consensus on most of the identified items of the sum score. At variance from the classical Delphi process, the experts knew each other. However the board unifies in a unique fashion the expertise of the leading heads of myasthenia centres of Germany.

Although not explicitly stated in the score, 'other immunosuppressive therapies' relate to the use of methotrexate, cyclosporine, tacrolimus, or cyclophosphamide. Although these drugs are generally thought effective as steroid-sparing agents, they are not ranked as first-or second-line immunosuppressant drugs in most German myasthenia centres. Their use is therefore rare. Any use of those drugs will add to the sum score but only once even when several of them have been used before.

One of the essential discussion points was the relative importance of rituximab in the spectrum of myasthenia treatment. From the historical point of view, rituximab was primarily used to treat myasthenia refractory to conventional immunosuppressants. Beyond MuSK positive MG, the use of rituximab pushed the borders of what may be considered as treatment refractory. Therefore, the failure to respond to rituximab treatment is suggested as a prerequisite to consider a myasthenia gravis patient treatment refractory. On the contrary, without or licensing rituximab treatment, others considered rituximab not mandatory or feasible in severe myasthenia beforehand of eculizumab.

Finally, the sum score provides a solution for the dispute that gives a weighted importance to the previous rituximab treatment. It may reveal clinical situations where the course of the MG is considered severe but not refractory (yet) independent of rituximab use.

The trial design of the pivotal eculizumab study required a long term treatment with immunosuppressants as inclusion criteria. However, from a clinical point of view, eculizumab treatment is regarded particularly valuable in the ICU setting, when patients fail to be weaned from artificial ventilation or tube feeding. In that situation, there is certainly no time to wait 12 months for that therapeutic option. Accordingly, there is a need to define treatment refractory state with bypassing such long treatment attempts. Accordingly, the sum score gives extra attention to a long lasting ICU stay for longer than 6 weeks but refrains on defining that condition as the only prerequisite for a treatment refractory state. Therefore, the combination of MGFA V status and ICU stay was restricted to 15 points, and other items must add before a minimum of 20 points will suggest a refractory situation. For similar reasons, we have refrained from including score items that define a therapy-refractory state for themselves, for example intermittent or chronically repeated IVIG use as well as eculizumab.

This score was developed with an entirely empirical approach based on the clinical expertise of the participants. Still, this hypothesis is to be validated in clinical practice comparing the score to what is judged treatment-refractory from a clinical point of view. The prompt consensus in the first round of the Delphi process suggested a common perception of what is regarded treatment refractory. Additionally, we made an effort to make items as robust as possible in the interest of interrater variability (eg, not 'long ICU stay' but 'ICU stay longer than 42 days'). The performance of the score for this point has to be validated as well. Finally, it would be helpful to determine the specificity and sensitivity of the score compared to a gold standard. However, as the literature review demonstrates, neither does such a gold standard nor a validated rating system for treatment-refractory myasthenia exist.

As a methodological limitation, with the advent of new therapies, the clinical judgement of treatment refractory may be subject to change shifting the gold standard that compares to the score.

In summary, we propose the sum score as a suitable and unifying way to describe a baseline in clinical trials to characterise myasthenic patients with different pretreatments. The definition of treatment refractory state is not restricted to the use or non-use of certain drugs. Moreover, the sum score might be also used in clinical routine to support decision making in escalating medical treatment of MG patients. However, new treatment options will further shift and change the boundaries of a treatment-refractory state and ultimately require a modification of the sum score presented.

Author Contributions

M.S. came up with the idea of developing a sum score, predefined the items, intiated and moderated the Delphi processus, performed the literature survey, and wrote the first draft of the manuscript. All authors took part in the Delphi process, discussed the score items and contributed to the manuscript. M.S. and A.M. designed the study and finalized the manucript.

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