PIPC Partnership to Improve Patient Care

August 18, 2021

Dr. Steven D. Pearson
President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Dear Dr. Pearson,

The Partnership to Improve Patient Care (PIPC) appreciates this opportunity to comment on the Institute for Clinical and Economic Review's (ICER) draft evidence report regarding treatments for Myasthenia Gravis (MG). MG is a rare disease characterized by the fluctuating and weakness of patients' muscle systems that can greatly impair quality of life. Currently there is no cure for MG and there are very few available treatments. MG can present very differently in different patients, and it can often be difficult to find a treatment regimen that works for each patient. For this reason, availability of and choice between multiple treatments is very valuable to MG patients and physicians. With this in mind, we ask ICER to consider the following comments.

ICER's Model is Overly Simplified and Does Not Accurately Capture the Patient Experience with MG

ICER's model is too simplistic and does not capture the full spectrum of health improvements that matter to patients. The model has just three health states excluding death. These are improved MG on treatment, unimproved MG on treatment and unimproved MG off treatment. Using these broad health states limits the sensitivity of the model and does not allow the model to capture incremental improvements in health that matter to patients.

The model also excludes reference to a key aspect of the burden of MG, myasthenic crises. Myasthenic crises refer to a rapid deterioration in neuromuscular function with respiratory compromise due to ventilator muscle insufficiency or weakness of upper airway musculature or both. Regularity and severity of crises make a difference to patient quality of life, and this should have been included as a component of the model.

Typically, models developed to evaluate interventions in MG include frequency of myasthenic crisis as a key component in the model[1,2,3] usually as a transitioning health state or at a minimum as a disutility. Many have also included mortality associated with myasthenic crisis into their model structure.

ICER's Model Does not Accurately Capture Patient Heterogeneity

[1] Chicaiza-Becerra LA, Garcia-Molina M, Gamboa O, Castañeda-Orjuela C. The cost-effectiveness of open or thoracoscopic thymectomy compared to medical treatment in managing Myasthenia gravis without thymomas. Revista de Salud Pública. 2012 Apr;14(2):260-70.
[2] Heatwole C, Johnson N, Holloway R, Noyes K. Plasma exchange vs. intravenous immunoglobulin for myasthenia gravis crisis: an acute hospital cost comparison study. Journal of clinical neuromuscular disease. 2011 Dec;13(2):85.
[3] Canadian Agency for Drugs and Technologies in Health. CADTH Drug Reimbursement Review: Pharmacoeconomic Report on Eculizumab (Soliris). https://www.ncbi.nlm.nih.gov/books/NBK567510/. Published 2021

MG is a highly heterogeneous condition that affects patients in a host of different ways. Clinical presentations vary substantially, both for anti-AChR positive and negative MG, and accurate diagnosis and selection of effective treatment depends on recognition of less typical as well as classic disease phenotypes. Accumulating evidence suggests that clinical MG subgroups might respond differently to treatment.[4] Despite this evidence in the research literature, ICER ran only two base case analyses: "refractory" anti-AChR antibody positive gMG and patients with gMG.

It has been suggested that heterogeneity on the autoantibody level may be associated with genetic heterogeneity and clinical phenotypes with different treatment responses.[5] As a result, any interpretation of the relative effectiveness of new treatments for MG must be applied to treatments while reflecting this heterogeneity. To ignore this fact risks payers deciding to reduce or delay access to effective treatments for those who could benefit in an effort to prevent these therapies from being made available to all patients.[6]

This is an especially important element when evaluating treatments for MG, as the burden of a disease falls more acutely on Black women, a typically underserved population. Black women typically present with MG at younger ages and may have a more severe disease course than other patient groups.[7,8] If patient heterogeneity is not captured by the study, payers referencing the study may choose to restrict coverage and exacerbate this existing health inequity.

The Model Does Not Accurately Represent Hospitalization Costs

The cost of patients experiencing MG-related hospitalizations was derived from a 2017 study.[9] The study provides estimates of hospitalization cost in the period 2003-2013, while also concluding that costs of MG inpatient care rose 13-fold from 2003 to 2013. Based on this, it is reasonable to assume that the cost of MG inpatient care may have risen at a similar rate between then and now. Yet ICER has inflated cost estimates from this study by applying an inflation rate of 3%. This is very likely to be inaccurate, and we would suggest ICER look to a more recent study or claims data to derive a more accurate input for hospitalization cost.

ICER also does not use a unit cost for an MG-related emergency visit, instead using a mean cost for an emergency room (ER) visit in the US, obtained from the Healthcare Cost and Utilization Project

[4] Meriggioli MN, Sanders DB. Autoimmune myasthenia gravis: emerging clinical and biological heterogeneity. The Lancet Neurology. 2009 May 1;8(5):475-90.
[5] Pal J, Rozsa C, Komoly S, Illes Z. Clinical and biological heterogeneity of autoimmune myasthenia gravis. Journal of neuroimmunology. 2011 Feb 1;231(1-2):43-54.
[6] Basu A, Grieve R, Pritchard D, Stevens W. One size does not always fit all in value assessment. Am J Manag Care. 2019 Nov 1;25(11):540-2.
[7] Bubuioc AM, Kudebayeva A, Turuspekova S, Lisnic V, Leone MA. The epidemiology of myasthenia gravis. Journal of Medicine and Life. 2021 Jan;14(1):7.
[8] Alshekhlee AM, Miles JD, Katirji B, Preston DC, Kaminski HJ. Incidence and mortality rates of myasthenia gravis and myasthenic crisis in US hospitals. Neurology. 2009 May 5;72(18):1548-54.
[9] Omorodion JO, Pines JM, Kaminski HJ. Inpatient cost analysis for treatment of myasthenia gravis. Muscle Nerve. 2017;56(6):1114-1118

(HCUP). This produced a figure of $563. HCUP data are net hospital costs, not costs to the healthcare system. A more realistic estimate from the literature is $1,390.[10]

It should also be noted that there is significant heterogeneity for ER visit costs. The mean cost is much higher for people with severe health conditions than it is for visits for minor ailments among people who are not disabled or with a chronic condition. Unfortunately, overwhelming the ER has become a last line of defense for the uninsured, which means it sees many minor ailments from the generally healthy population. Most ER visits are for prescriptions or for basic care. A recent study suggests a little over 1% of attendees at the emergency room require 'immediate and urgent' attention. Less than 30% were in urgent need of care. If an MG patient visits an emergency room for a crisis, then it is for an urgent visit, not for a prescription, so using a mean cost for an ER visit is likely a very poor proxy for the cost to healthcare systems for an MG crisis.

ICER's Model Relies on the Discriminatory Quality-Adjusted Life Year

In recent years, there has been a widespread questioning of several the assumptions on which traditional cost-effectiveness analysis is built.[11]

The quality-adjusted life year (QALY) is known to discriminate by undervaluing the lives of people with disabilities and chronic illnesses, like MG.[12] Despite the known discriminatory implications of the QALY, ICER continues to use the metric. We believe this is inappropriate and would encourage ICER to identify and use alternative methods that do not discriminate.

The argument has also been made that we need to reassess the assumption that every unit of health gain – measured here in health-related quality of life - is equal in value.[13] In other words, a single unit of health generates the same utility whether that health is accrued to someone with considerable disease burden, or to someone with minimal disease burden.[14] In fact, several health technology assessment systems in Europe have backed away from direct use of strict cost-per-QALY estimates for this very reason, and incorporate the role of severity adjacent to the results to make a more context-relevant case for, or against, a new technology.[15,16]

A system of evaluation that treats therapeutic innovations for highly disabling diseases as of similar relative value for unit of health gain in less severe conditions - and for patients who have minimal

[10] Chang CF. Visitors to hospital emergency rooms: Who, why, and how much do they cost. The Methodist Le Bonheur Center for Healthcare Economics: Research Brief. 2015 Jul:1-6.
[11] Beresniak A, Medina-Lara A, Auray JP, De Wever A, Praet JC, Tarricone R, Torbica A, Dupont D, Lamure M, Duru G. Validation of the underlying assumptions of the quality-adjusted life-years outcome: results from the ECHOUTCOME European project. Pharmacoeconomics. 2015 Jan 1;33(1):61-9.
[12] https://ncd.gov/sites/default/files/NCD_Quality_Adjusted_Life_Report_508.pdf
[13] Sund B, Svensson M. Estimating a constant WTP for a QALY—a mission impossible? The European Journal of Health Economics. 2018 Jul;19(6):871-80.
[14] MacKillop E, Sheard S. Quantifying life: understanding the history of quality-adjusted life-years (QALYs). Social Science & Medicine. 2018 Aug 1;211:359-66.
[15] Barra, M. and K. Rand-Hendriksen, *A missing cornerstone in the Norwegian Priority Commission's weighting scheme–Sub-treatment balancedness is a necessary property for priority setting criteria.* Nordic Journal of Health Economics, 2016. **4**(2): p. pp. 8-23.
[16] Swedish Parliamentary Priorities Commission, *Priorities in health care: ethics, economy, implementation*. 1995, Stockholm: Swedish Government.

disease burden - is thought by many to be inherently unfair and unrealistic. Multiple studies[17] have made this case.[18,19] We would encourage ICER to explore these newer, more comprehensive approaches to modeling versus continuing to rely on traditional cost-effectiveness analyses.

Conclusion

ICER's model does not paint a full picture of the value of these treatments to the patient or society. It does not capture patient heterogeneity and omits outcomes that matter to patients and fails to capture accurate costs and burden of the disease. We urge ICER to make appropriate revisions to its model and to clearly communicate these limitations in its final report so that payers are not tempted to create one-size-fits-all coverage restrictions for new MG treatments.

Sincerely,

Tony Coelho
Chairman
Partnership to Improve Patient Care

[17] Shiroiwa, T., et al., *WTP for a QALY and health states: More money for severe health states?* Cost Effectiveness and Resource Allocation, 2013. **11**(1): p. 22.
[18] Lancsar, E., et al., *Deriving distributional weights for QALYs through discrete choice experiments.* Journal of health economics, 2011. **30**(2): p. 466-478
[19] Richardson, J., A. Iezzi, and A. Maxwell, *How important is severity for the evaluation of health services: new evidence using the relative social willingness to pay instrument.* The European Journal of Health Economics, 2017. **18**(6): p. 671-683.