PATIENTS RISING NOW

July 29, 2020

Steven D. Pearson, MD, MSc, FRCP
President, Institute for Clinical and Economic Review
One State Street, Suite 1050
Boston, MA 02109 USA

RE: Draft Evidence Report "Targeted Immune Modulators for Ulcerative Colitis: Effectiveness and Value"

Dear Dr. Pearson:

Patients Rising Now advocates on behalf of patients with serious and chronic conditions and diseases for them to have access to vital therapies and services. Access to life improving treatments and services are essential for those people, and it spans affordability, insurance coverage and physical access. To support improved access, we are committed to engaging patients, caregivers, physicians, media, health policy experts, payers, providers and others to foster people-centered, discussions about the entire U.S. health care system. That is, our goal is a balanced dialogue that illuminates the truth about health care in a just and equitable way.

We appreciate the opportunity to provide our comments on ICER's May 23rd Draft Evidence Report "Targeted Immune Modulators for Ulcerative Colitis." Our specific people-focused comments about the draft report are organized below into sections about People-Centered Perspectives; Uncertainties; and Errors and Additional Points.

<u>People-Centered Perspectives</u>
Ulcerative Colitis (UC) is a serious, complicated autoimmune disease that is often thought of as only being a disorder affecting the lower gastrointestinal tract, but as the draft report indicates, UC can cause significant problems in other organs including the joints, the lungs, and the eyes.

Overall, it is great that the Targeted Immune Modulators (TIMs) provide clinical benefit for people with UC, e.g., "all TIMs were more likely to achieve response and remission compared to placebo,"[i] with low risks of serious adverse effects: "In placebo-controlled trials, the risk of severe or serious adverse events and serious infections was low and generally comparable between the treatment and placebo groups."[ii] Those clinical benefits also mean that people with UC can avoid the adverse effects of steroids.

The draft report does a respectable job of including people-centered information and perspectives in its description of UC, including the variety of ways UC affects different individuals: "As with many chronic diseases, the presentation of symptoms and disease course can vary substantially among patients. In some, the disease course may reflect periods of active disease and remission, while in others, the symptoms are persistent despite escalating medical therapy."[iii]

In the realm of patient-centeredness, we are concerned that the limited metrics used in the clinical trials have been validated for Crohn's Disease, but not for Ulcerative Colitis. While the

two conditions have similarities, they are clearly different entities with different arrays of symptoms and effects on patients' and caregivers' lives. And those metrics are mostly disease-oriented focusing on GI signs and symptoms, and not patient-oriented. This would be an appropriate area for further discussion in the draft report, such as how future research could help fill this gap, and perhaps, even for ICER to start closing that gap in collaboration with patient advocacy and related research groups with focus groups or surveys - as ICER has done in the past and indicated it will do more of in the future.[iv]

We appreciate the draft report's information and discussion about access restrictions from insurance plans. We particularly noted patient concerns about how some insurance requirements may mean patients having to "try" medicines they have already failed if they switch insurance plans – which can occur with a change of job or geographic location.[v] For example, the draft report notes, "The Crohn's and Colitis Foundation also mentioned insurance-mandated step therapy, in which patients are required to try agents other than the one they or their clinician prefer, even if the use of that medication is contraindicated. Clinical expert input indicated that continued use of aminosalicylates in patients who have been failed by such therapy and escalated to use of TIMs is a pervasive and low-value intervention."[vi] And similarly, "In some cases, patients must be failed by treatment with at least two TNF inhibitors before vedolizumab is considered, despite clinical evidence that they do not respond to this biologic class."[vii]

We continue to be concerned that ICER's reports and conclusions empower insurance company created step-therapy programs that are economically driven and may run counter to patient interests. While the draft report describes those access restrictions, it does not discuss how they are – or are not – supported by any clinical data. If such policies are not derived from clinical evidence, that indicates that they are primarily created for economic considerations, which can undermine patient-clinician shared decision making. In support of that disconnect, we note that there is a lack of consensus of coverage by different plans as described in Table 3.1,[viii] - and the restrictions on biosimilars being greater than the original biologic medicines similarly indicates that coverage policies are being made for economic reasons rather than rationale based on clinical benefit or to guide shared decision making.

On a related note, we think that ICER should discuss how copay assistance programs (including coupons) are not available to people on Medicare, and that a recent Federal rule enables private insurance plans to limit the benefits of those programs for people with private insurance.[ix]

Another patient perspective that the draft report does not cover adequately is how the route of administration for treatment options can affect patient access and costs. For example, medicines that can be self-administered (either orally or via subcutaneous injection) do not require travel to the doctor's office or additional payments for those visits etc. With the ongoing shortage of qualified clinicians in rural and other underserved areas – and the increase in telemedicine due to COVID-19 – the ability of patients to receive their care without additional physical access barriers is an important consideration of value to patients.

Therefore, patient and caregiver travel costs and burdens should be part of the draft report's discussion and calculations for its cost-effectiveness analysis. We recognize that differential requirements for patient travel could be considered under "Potential Other Benefits," which is

expected to be discussed at the meeting of ICER's CTAF group. But by not explicitly mentioning it in the draft report leaves it to others to insert this important consideration into the conversation. This is too important an issue to be left to chance because of how it can affect the individualization of patients' treatment plans.

While we applaud ICER for conducting more subgroup analyses – which should provide more insights for patients' and clinicians' shared decision making – the subgroup analysis presented lacks information about differences among racial/ethnic groups or by sex. If there is insufficient data or research to analyze, then that lack of information should be pointed out in ICER's reports since it is an important facet for illumination as it reveals an area that could be a priority for future research, such as confirming that colectomies are more common in women with UC.[x] We also note that the description of the "Geriatric Population" is problematic in that it does not specify an age range, and the term "geriatric," may be offensive and reflect an ageist bias.[xi] We suggest a better term might be "older," and that the age range be specified, e.g., over 50 or 60.

Uncertainties

There is significant lack of agreement among the clinical guidelines described in the draft report – as there are with insurance plan coverage requirements – and some of those differences can be very important for patients. For example, the draft report notes that "the AGA recommends the early use of biologics rather than step therapy with aminosalicylates, which may delay effective treatment in patients at high risk of complications, hospitalization, and colectomy."[xii] This guidance may run counter to health insurance prior authorization or fail-first policies, adding stress and uncertainty for both clinicians and patients. Similarly, "the ACG does acknowledge that the use of treatments with fewer systemic effects (i.e., oral budesonide or vedolizumab) is an emerging clinical practice."[xiii]

One of the ongoing, inherent problems with ICER's analytical methodology is the meta-analysis approach that attempts to draw conclusions about the relative utility of different treatments in the absence of direct comparisons in well-designed research. This severe weakness is exemplified in the draft report because its basic data sources are from "19 included trials in the adult population, one trial was a head-to-head trial comparing vedolizumab and adalimumab."[xiv] And of those 19, only "Eight RCTs [Randomized Controlled Trials] were included in our NMA [Network Meta-Analysis]" for the subgroup analysis of Biologic-Naïve Patients.[xv] And for the Biologic-Experienced Patients subgroup, the NMA is based on six trials, and there is "relatively smaller sample size of the biologic-experienced population included in these trials."[xvi] As the draft report itself notes, "Our comparisons were therefore driven almost exclusively by the conduct of NMAs …[and]… there is currently very limited information with which to ascertain the optimal sequence of treatment."[xvii] In other words, the analysis is based almost entirely on a single head-to-head trial of only two of the treatments under evaluation, while the remainder are single compound versus placebo trials, with the data from those separate publications reanalyzed in single metanalytical crucibles.

For the potential budget impact analysis in the draft report, our reading is that at the end of five years, all the patients will be using ustekinumab: "For the purposes of this analysis, we assumed that 20% of these patients would initiate ustekinumab in each of the five years, or 21,780 biologic-naïve patients per year and 17,820 biologic-experienced patients per year."[xviii] Is that

correct? If so, how does that in any way model real-world expectations or experience?

Also, what is ICER's policy and rationale in its potential budget impact analysis concerning already approved medicines that have new indications? We ask since ICER's potential budget impact analysis formula includes the number of newly approved medicines as a fundamental factor, but ustekinumab was approved in 2009, which means that is could be used off-label for people with UC since then.

Errors and Additional Points

- Concerning the makeup of the CTAF, (i.e., ICER's "independent committee of medical evidence experts") we note that it contains several medical doctors with experience in cardiology and oncology, but none with expertise in gastroenterology or immunology.
- The draft report notes that one of the medicines received a new warning on its label, but the report does not recognize the FDA's December 2019 approval of the extended release version for UC,[xix] which would be an easier dosing schedule for patients. Further, to put the warning information into a broader context, it should also be noted that the new warning has specific reference to patients with Rheumatoid Arthritis, but not UC, and that the anti-TNF treatment options also have black box warnings on the FDA approved labels.[xx]
- We are glad to see that concerning biosimilars ICER has matured its approach to this complicated area since its 2019 review for rheumatoid arthritis treatments. Specifically, the draft report on UC does not repeat the errors of the 2019 report that implied interchangeability was on the horizon, nor does it present a separate minimalistic section on biosimilar legal, regulatory, and market issues.
- Reference #6 is to 2014 document, not a 2020 document as referenced.
- In Table 5.8 and the accompanying text on page 74 the description of the study cited for determining the risk of colectomy is incomplete and misleading. First, the data is not from patient experiences from 1997-2004, but from 1970-2004; Second, there was significant sex difference in rates of colectomy at 10 years - 10.6% women v. 24.8% men; And third, all the patients were from a single county in the middle of Minnesota, which indicates a likely rather homogenous population.
- The draft NICE report cited on page 22 (Reference #42) has been released in final form.[xxi] Both the content of the section and the reference should be updated to reflect the findings and conclusions of the final report.
- We are concerned about a concluding sentence characterizing the quality of life data: "However, the WPAI-UC score of patients in the placebo group for all four domains worsened (increased) at the end of the maintenance phase."[xxii] Why is this "However," for the placebo group? Shouldn't this be "As might be expected," The use of the leading "However," as a connector from the previous sentence minimizes the importance of the preceding sentence's statement that "improvements achieved at the end of induction" that were "consistent through the end of maintenance." Are not the improvements with treatment MORE significant because of the worse results seen in people who received placebo?
- In the discussion of neutralizing antibodies on page 58, it should be noted that such antibodies are produced to biologic medicines, but not to small molecule treatments such as tofacitinib, which in mice has been shown to suppress such antibodies.[xxiii] Further, it should be noted that small molecule medicines exist in a different patent and regulatory environment, so that generic competition is generally faster and more certain than for

biosimilars, with also significantly greater price reductions.

Conclusions

Patients Rising Now is pleased that people with UC have access to new treatment options. However, we are concerned that access may be limited or barred by insurance plans and their agents through formulary design, cost-sharing structures, of prior authorization requirements, some of which are described in the draft report, and that ICER's conclusions may encourage such access restrictions, thus expanding administrative barriers for clinicians and patients.

We also believe that comprehensive evaluations containing people's perspectives must include the direct out of pocket costs and indirect costs related to patients' ability to work, and requirements for travel to receive treatment etc. Any analysis that is designed to ethically support society's best interests needs to encompass such real-world patient challenges and choices within the pluralistic U.S. health care system. That is, we believe the voices of people with serious health conditions must be a part of defining and assessing the value of treatment options.

Sincerely,

Terry Wilcox
Co-Founder & Executive Director, Patients Rising Now

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[i] Draft report p. 37
[ii] Draft report p. 58
[iii] Draft report p. 11-12
[iv] ICER, "2020-2023 Value Assessment Framework," January 31, 2020, p. 48
[v] While the draft report discusses coverage variability from different health plans, and different clinical guidelines, it would be very illuminating to understand the current landscape of actual treatments used by people with moderate to severe UC. That is, what percentage are using which medications – either alone of in combination? We realize that since many of the TIMs that UC patients might be using are also used by people with other autoimmune conditions – and possibly soon by people with COVID-19 – making such data collection difficult. But without knowing what patients are currently using makes it difficult to judge whether clinical guidelines are being followed or if patients are being under or over treated, and if so with what categories or types of medicines. Additionally, subgroup analysis of this type of information by both type of insurance and geographic location (which may be a proxy for access problems), would be very helpful.
[vi] Draft report p. 9
[vii] Draft report p. 14
[viii] Draft report, Table 3.1, p. 16
[ix] " CMS Finalizes Rule Expressly Permitting Copay Accumulator Programs," May 15, 2020, https://www.cov.com/en/news-and-insights/insights/2020/05/cms-finalizes-rule-expressly-permitting-copay-accumulator-programs
[x] Samuel S, Ingle SB, Dhillon S, et al. Cumulative incidence and risk factors for hospitalization and surgery in a population-based cohort of ulcerative colitis. Inflamm Bowel Dis. 2013;19(9):1858-1866.
[xi] https://www.dictionary.com/browse/geriatric
[xii] Draft Report p 20
[xiii] Draft Report p. 21
[xiv] Draft Report p. 27
[xv] Draft Report, p. 41
[xvi] Draft Report p. 47

[xvii] Draft Report p. 62
[xviii] Draft Report p 107
[xix] https://www.empr.com/home/news/xeljanz-xr-approved-for-ulcerative-colitis/
[xx] "FDA Drug Safety Communication: Drug labels for the Tumor Necrosis Factor-alpha (TNF-alpha;) blockers now include warnings about infection with Legionella and Listeria bacteria," September 7, 2011, https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-drug-labels-tumor-necrosis-factor-alpha-tnfa-blockers-now-include, and "Tumor necrosis factor inhibitors – state of knowledge," Arch Med Sci. 2014 Dec 22; 10(6): 1175–1185.https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4296073/
[xxi] https://www.nice.org.uk/guidance/TA633
[xxii] Draft Report p. 57
[xxiii] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4106678/