Targeted Immune Modulators for Ulcerative Colitis: Final Policy Recommendations

October 16, 2020

Policy Recommendations

Introduction

The following policy recommendations reflect the main themes and points made during the Policy Roundtable discussion at the September 24, 2020 CTAF public meeting on the use of targeted immune modulators (TIMs) for the treatment of ulcerative colitis (UC). At the meeting, ICER presented the findings of its revised report on these treatments and the CTAF voting council deliberated on key questions related to their comparative clinical effectiveness, potential other benefits and contextual considerations, and long-term value for money at current prices. Following the votes, ICER convened a Policy Roundtable of two patients, two clinical experts, two payers, and two representatives from a pharmaceutical manufacturer to discuss how best to apply the evidence and votes to real-world practice and policy. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants.

A recording of the conversation can be accessed here, and a recording of the voting portion of the meeting can be accessed here. More information on Policy Roundtable participants, including conflict of interest disclosures, can be found in the appendix of this document. ICER's report on these treatments, which includes the same policy recommendations, can be found here.

The roundtable discussion was facilitated by Dr. Steven Pearson, MD, MSc, President of ICER. The main themes and recommendations from the discussion are organized by audience and summarized below.

Clinicians, Payers, Manufacturers, and Patient Groups

The significantly lower prices seen for infliximab and its biosimilars speaks to the important potential for improved value with broader availability and uptake of biosimilar treatment options. All stakeholders should collaborate to ensure that TIM biosimilars have an increasing and comprehensive role in the UC treatment landscape.

The biosimilar market is a $2.8 billion annualized business with health care savings now estimated at $5.6 billion per year. A recent analysis by Bernstein analyst Ronny Gal estimated that biosimilar versions of infliximab accounted for 42% of the savings as the price for the brand-name biologic dropped about 48%. Although the resulting net price for infliximab and its biosimilars did not reach traditional cost-effectiveness thresholds in the ICER analysis, their cost effectiveness was far superior to that of other treatment options. Roundtable participants emphasized the benefit of having biosimilars to infliximab available in the UC treatment armamentarium and expressed frustration that other biosimilars are FDA-approved (e.g., adalimumab) but not yet available on the

US market. In addition, it was noted that the Affordable Care Act (ACA), which provided the regulatory pathway for biosimilar agents, is under threat. Clinicians, payers, manufacturers, and patient groups should collaborate to develop an approach for broader biosimilar access, including a contingency plan in the event the ACA is overturned.

Manufacturers and Payers

The "bundled rebate" approach, in which rebates are provided at the drug level across all of its possible indications, should be abolished and replaced with an indication- and value-based pricing approach.

Several TIMs in this review carry indications for multiple inflammatory conditions. Manufacturers have historically been able to negotiate on a "bundled" basis, offering a single price and rebate across all indications. Our cost-effectiveness analyses indicated that the pricing of all TIMs (with the possible exception of infliximab biosimilars) was far out of alignment with the benefits delivered. Abolishing the bundled rebate approach and replacing it with pricing that is tied to the value brought by a given TIM for each indication, would allow payers to relax certain step therapy requirements and increase patient access to all TIMs.

Payers

Insurance coverage should be structured to prevent situations in which patients are forced to choose a treatment approach on the basis of cost.

Patient input on the Roundtable indicated a variety of views on and experiences with surgical colectomy. Some also suggested that, due to copayment and coinsurance structures, some reluctant patients might nevertheless opt for colectomy as a "cheaper" option if they are having difficulty paying for their medications. Payers should take particular pains to ensure that benefit structures are sufficiently flexible so that patients wishing to avoid a colectomy have other options at their disposal.

Specialty society guidelines and drug labels should be monitored for changes, with coverage policy adjusted accordingly.

Findings from our review and discussion at the Roundtable noted several instances in which payer coverage policy has not matched changes in clinical guidelines or in the drug label. For example, vedolizumab's label changed in 2019 to remove the requirement for an initial trial of TNF inhibitors. Despite this change, payer coverage policies have generally continued to require use of a TNF inhibitor before vedolizumab can be given. Payers should routinely monitor guidelines and label changes just as they would for new clinical evidence and modify coverage policy accordingly.

Because there are no clear biomarkers or predictors of the success for any given treatment in UC, it is not unreasonable to consider prior authorization criteria in order to manage the costs of expensive medications and negotiate prices for TIMs priced beyond a fair range. However, prior authorization criteria should be based on clinical evidence, specialty society guidelines, and input from clinical experts and patient groups. The process for authorization should be clear and efficient for providers.

Options for specific elements of coverage criteria within insurance coverage policy are discussed below.

Patient Eligibility Criteria

- **Diagnosis**: Because a diagnosis of UC is made based on clinical symptoms and endoscopic investigation, physician attestation is sufficient for diagnosis.
- **Patient population:** Patients eligible for TIMs include those with moderate-to-severe UC whose disease has had an inadequate response to conventional systemic therapy. Patient eligibility criteria should be flexible given that clinical trials used tools (e.g., Mayo Score for disease severity) that are not routinely used in clinical practice. Relying on physician attestation of the level of disease severity is the most common approach taken by insurers. Inadequate response to conventional systemic therapy is the facet of clinical criteria that insurers may choose to define by specifying particular types of systemic therapies, number of attempts, or duration. This approach is reasonable as long as there is a valid citation or reference for the specifications given. Measurement of therapy "failure" in clinical trials is based on the Mayo Score, but as noted, this should not be used as a criterion within insurance coverage.
- **Exclusions**: UC patients with mild disease and those without a prior trial of conventional systemic agents are not eligible for TIM therapy.

Step Therapy

Given the lack of biomarkers and other predictors of TIM treatment success in UC, it is not unreasonable to use step therapy in this case to manage the costs of treatment. Step therapy among agents for UC appears to meet criteria for reasonable step therapy:

- Use of the first-step therapy reduces overall health care spending, not just drug spending.
- The first-step therapy is clinically appropriate for all or nearly all patients and does not pose a greater risk of any significant side effect or harm.
- Patients will have a reasonable chance to meet their clinical goals with first-step therapy.
- Failure of the first-step drug and the resulting delay in beginning the second-step agent will not lead to long-term harm for patients.

For step therapy to be reasonable, it must ensure that patients are not required to retry a first-line drug with which they have previously had adverse side effects or an inadequate response at a reasonable dose and duration. In addition, the exception process must be rapid, transparent, and *administratively competent*; electronic systems for exceptions should be employed whenever possible to minimize time and paperwork burdens for patients and providers. Similarly, any cost savings realized from step therapy protocols (e.g., originator to biosimilar switch) should be returned to the patient as efficiently as possible, using electronic systems as feasible.

Required Switching

- **Required switching of TIM therapy for patients who are stable on current treatment should be limited to switches to another medication with the same mechanism of action or from an originator to a biosimilar agent.** Given the availability of multiple classes of TIMs for UC and the benefits that sustained remission provide to patients, requiring a switch to another class for a patient who is currently responding to treatment raises a risk that the patient could have new significant side effects or insufficient response, either of which renders this kind of switch unreasonable. Required switches should be within-class only (e.g., between TNF inhibitors) or from an originator to a biosimilar product (e.g., infliximab). Even for required switches within the same class, if the switch requires the patient to adopt a different route of administration, e.g., IV infusion instead of subcutaneous injection, there should be provisions to allow for exceptions if a patient's living or caregiver situation makes the switch infeasible. In addition, as with step therapy, any switching policy must ensure that patients are not required to switch to a drug that they have used before at a reasonable dose and duration with inadequate response and/or significant side effects, including earlier use under a different payer. We note that switching policies can be deeply resented by patients and clinicians and should only be contemplated if coordinated efforts are also made to educate providers and patients; the success of Kaiser Permanente's initiative to switch patients from the originator infliximab to a biosimilar is an example of such a comprehensive approach.

Provider Qualification Restrictions

- **TIM therapy should be prescribed and managed by gastroenterologists with specific training and expertise in UC.** Several stakeholders have noted gaps in clinical practice when the care of UC patients is managed by those without specific training and expertise, including overuse of steroids to manage recurrence of symptoms.

Patient Advocacy Organizations

Patient advocacy organizations should be an active voice in noting the potentially negative effects of TIM pricing on patient access.

Patient Roundtable participants recognized the challenges posed by TIM pricing (and payer response to this) on patients' ability to access the drug they need at the time they need it. Patient groups can represent a strong voice for pricing moderation to align more closely with clinical value, increased use of and access to biosimilars, and other efforts to modulate the pricing-access tension.

Specialty Societies

Consensus guidelines should be developed across the major gastroenterology societies, in collaboration with patient groups, to ensure a common voice for UC treatment guidance.

Several Roundtable participants noted that, unlike other specialties such as cardiology, the major gastroenterology societies (the AGA and the ACG) maintain separate guidelines. Development of common consensus guidelines, with direct input from patient groups, would allow payers to more closely align coverage policy. Such guidelines should involve clinical experts who are free from significant financial or other conflicts of interest to ensure their patient-centricity.

Regulators

Given the maturity and longstanding use of several of the TIMs of focus in this review, the FDA should require the inclusion of active control arms in Phase III clinical trials of UC treatments.

As noted in this review, only one of the 19 RCTs in the available evidence base featured a head-to-head comparison between TIMs. This is despite the longstanding availability of several of these TIMs on the US market. Clinical trials of new agents for other chronic inflammatory conditions such as rheumatoid arthritis and psoriasis now routinely feature an active comparator, including some of the same TIMs featured in this review (e.g., adalimumab). There is no obvious reason why the same approach cannot be taken in UC.

Researchers

The research community should make a strong commitment to generate real-world evidence that can fill in the gaps from available RCTs and allow for comprehensive comparisons of TIMs.

Our review noted several gaps in evidence that RWE may be positioned to fill, such as ongoing monitoring of the safety of newer TIMs as well as information on clinical benefits observed in populations without RCT evidence but with clear real-world experience (e.g., infliximab in biologic-experienced patients). In addition, there is limited understanding of the trajectory of disease and relative effectiveness of TIMs in African American, Asian, and LatinX population. The Crohn's and Colitis Foundation's IBD Plexus initiative is a nationwide registry of over 16,000 patients with UC and Crohn's disease, and research is already underway to gain a better understanding of how IBD affects minority populations, the quality of IBD care, and better understanding of disease severity in pediatric populations. This should be supplemented with other efforts to fill in data gaps both in IBD Plexus and other large data networks such as PCORNet and the Sentinel Research Network.

Further clinical study should be conducted to ascertain the optimal sequencing of TIM therapy in UC.

Clinical experts on the roundtable noted that there are currently no available tools with which to predict response to specific UC treatments, and there is no current evidence that involves robust comparisons of different sequences of TIM therapy. Future clinical study could compare clinical benefit and safety for sequences involving within-class switching versus switching outside of class, for example, or long-term outcomes when the same agent is used for both induction and maintenance in comparison to a switch after induction.

Appendix

Appendix Tables 1 through 3 contain conflict of interest (COI) disclosures for all participants at the CTAF public meeting on September 24, 2020.

Table A1. ICER Staff and Consultants and COI Disclosures

Name	Organization	Disclosures
Lisa Bloudek, PharmD, MS	Senior Research Scientist, University of Washington	*
Pamela Bradt, MD, MPH	Chief Scientific Officer, ICER	*
Josh J. Carlson, PhD, MPH	Associate Professor, Department of Pharmacy, University of Washington	*
Rick Chapman, PhD, MS	Director of Health Economics, ICER	*
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Rajshree Pandey, PhD, MPH	Research Lead, Evidence Synthesis, ICER	*
Steven D. Pearson, MD, MSc	President, ICER	*

*No relevant conflicts of interest to disclose, defined as more than $10,000 in health care company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers.

Table A2. Policy Roundtable Participants and COI Disclosures

Name	Organization	Disclosures
Thomas Brownlie, PhD, MS	Senior Director, US Payer Policy, Pfizer	Full-time employee of Pfizer.
Deborah Gan, MBA	Leader, US Payer Marketing, Primary Care, Merck	Full-time employee of Merck.
Patrick Gleason, PharmD	Assistant Vice President, Health Outcomes, Prime Therapeutics	Full-time employee of Prime Therapeutics.
Bruce Sands, MD, MS	Professor of Medicine and Chief, Division of Gastroenterology, Mount Sinai	Dr. Sands has consulted for AbbVie, Janssen, Pfizer, and Takeda.
Siddharth Singh, MD	Assistant Professor of Medicine, UC San Diego School of Medicine; Gastroenterologist, UC San Diego Health	Dr. Singh has received research grants from AbbVie, and consulting fees from AbbVie, Takeda, Pfizer, AMAG Pharmaceuticals.
Megan Starshak	Patient Advocate	No conflicts of interest to disclose.
Fernando Velayos, MD	Director, Inflammatory Bowel Disease Program, Kaiser Permanente Northern California	Dr. Velayos' spouse has received honoraria in consulting fees.
Laura Wingate	Senior Vice President, Education, Support, and Advocacy, Crohn's & Colitis Foundation	No conflicts of interest to disclose.

Table A3. CTAF Panel Member Participants and COI Disclosures

Name	Organization	Disclosures
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Felicia Cohn, PhD	Bioethics Director, Kaiser Permanente, Orange County	*
Rena K. Fox, MD	Professor of Medicine, UCSF	*
Paul Heidenreich, MD, MS (Chair)	Professor and Vice-Chair for Quality, Clinical Affairs, and Analytics, Stanford University	*
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*No relevant conflicts of interest to disclose, defined as more than $10,000 in health care company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers.