Targeted Immune Modulators for Ulcerative Colitis: Effectiveness and Value

Revised Background and Scope

November 4, 2019

Background

Ulcerative colitis (UC) is an autoimmune inflammatory bowel disease (IBD) that affects the mucosa, the innermost lining of the intestinal wall in the large bowel (i.e., the colon and rectum).[1] The disease causes long-lasting inflammation and ulcers in the digestive tract, and is typically marked by periods of remission and recurrence of symptoms. Symptoms may include frequent diarrhea, sometimes with blood or pus, abdominal and/or rectal pain, weight loss, and fatigue.[2] When the disease affects children, it can have a detrimental impact on growth, nutritional status, and psychosocial development.[3] It is estimated that approximately 900,000 individuals in the United States (US) have UC, 15-20% of whom are children.[4] Most individuals are diagnosed between the ages of 15 and 35.[5] The economic burden of UC is significant, ranging between an estimated $15-32 billion per year.[5]

UC is diagnosed based on the presence of symptoms with confirmation of disease via colonoscopy and biopsy. Other disease processes that may cause similar symptoms, such as infection and cancer, should be excluded.[6] The management of UC in adults is dependent on the severity of symptoms. In patients with mild disease, the use of rectal aminosalicylates may induce and maintain remission. Once symptoms have become moderate-to-severe, however, the use of budesonide or other corticosteroids as well as systemic immunomodulators such as azathioprine is warranted.[6] Those whose disease does not respond to or recurs despite systemic therapy are candidates for a number of targeted immune modulators (TIMs) to induce and/or maintain remission, including the tumor necrosis factor (TNF) inhibitors adalimumab (Humira®, AbbVie), golimumab (Simponi®, Janssen), and infliximab (Remicade®, Janssen), the $\alpha_4\beta_7$ integrin inhibitor vedolizumab (Entyvio®, Takeda), the Janus kinase (JAK) inhibitor tofacitinib (Xeljanz®, Pfizer), and the recently approved interleukin (IL)-12 and IL-23 inhibitor ustekinumab (Stelara®, Janssen). Elective colectomy (surgical removal of the colon) may be considered in patients whose disease does not respond to maximal medical management.[6] Recommended treatment options are more limited in children but do include most of the systemic therapies as well as infliximab.[4]

In addition to the above treatment approaches, vedolizumab, which is currently only available in intravenous (IV) form, is under review by the Food and Drug Administration (FDA) for subcutaneous

use. How the clinical and economic effects of the currently approved and proposed medications for UC compare is of interest to patients, clinicians, and payers alike.

Stakeholder Input

This revised scoping document was developed with input from diverse stakeholders, including patient organizations, clinicians, and manufacturers of the agents of focus in this review. This document incorporates feedback gathered during preliminary calls with stakeholders and open input submissions from the public. Revisions from the draft scoping document include the addition of other subgroups of interest and clarification around methods for our planned network meta-analyses (NMAs). ICER looks forward to continued engagement with stakeholders throughout the review to refine our understanding of the clinical effectiveness and value of TIMs for UC.

Patient organizations highlighted the need to include evidence on the impact of treatment sequencing on disease progression, as limited access to certain treatments may lead to worsening UC and put patients at higher risk for UC-related hospitalization or surgery. Patient organizations also emphasized the heterogeneity of the patient population and the importance of considering factors such as comorbidities, side effects, route of administration, and costs when choosing treatments. Additionally, patient organizations spoke of the extraintestinal manifestations, such as arthritic symptoms and psychological effects, that can further impact patients' quality of life in addition to their UC symptoms.

Report Aim

This project will evaluate the health and economic outcomes of TIMs for UC. The ICER Value Assessment Framework includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms—including those not typically captured in the clinical evidence such as innovation, public health effects, reduction in disparities, and unmet medical needs—are considered in the judgments about the clinical and economic value of the interventions.

Scope of Clinical Evidence Review

The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be abstracted from randomized controlled trials as well as high-quality systematic reviews; high-quality comparative cohort studies will be considered, particularly for long-term outcomes and uncommon adverse events. Our evidence review will include input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see

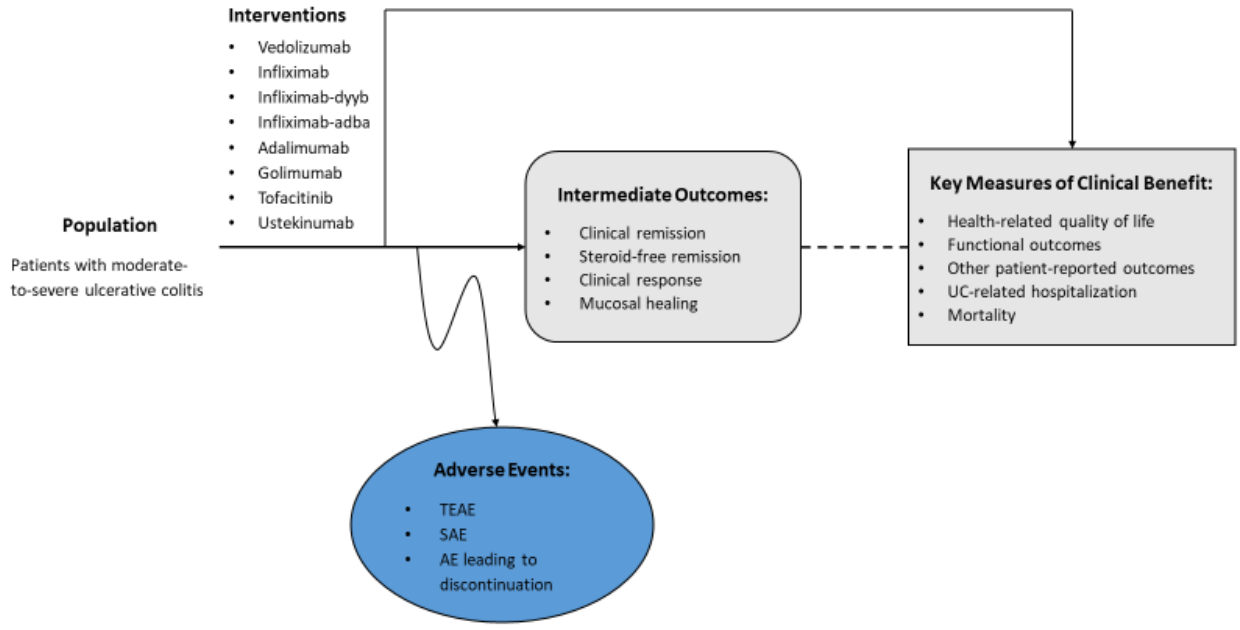
https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework-2/grey-literature-policy/).

All relevant evidence will be synthesized qualitatively or quantitatively. Wherever possible, we will seek out head-to-head studies of the interventions and comparators of interest. Data permitting, we will also consider the combined use of direct and indirect evidence in NMAs of selected outcomes. Given the likely constellation of data, NMA specifications stratified by experience with biologic therapy (i.e., naïve vs. experienced) and phase of treatment (i.e., induction vs. maintenance) will be considered. Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis will be provided in a research protocol published on the Open Science Framework website (https://osf.io/cwyn5/).

Analytic Framework

The general analytic framework for the assessment of TIMs for UC is depicted in Figure 1.

Figure 1. Analytic Framework: TIMs for UC



AE: adverse event, SAE: serious adverse event, TEAE: treatment-emergent adverse event, UC: ulcerative colitis

The diagram begins with the population of interest on the left. Actions, such as treatment, are depicted with solid arrows, which link the population to outcomes. For example, a treatment may be associated with specific health outcomes. Outcomes are listed in the shaded boxes; those within the rounded boxes are intermediate outcomes (e.g., changes in disease activity including clinical

remission, response, and mucosal healing), and those within the squared-off boxes are key measures of benefit (e.g., health-related quality of life). The key measures of benefit are linked to intermediate outcomes via a dashed line, as the relationship between these two types of outcomes may not always be validated. Curved arrows lead to the adverse events of treatment, which are listed within the blue ellipse.[7]

Populations

The population of focus for the review is adults with moderately-to-severely active UC, whose disease has either inadequate response or intolerance to conventional therapy, such as corticosteroids, azathioprine, or mercaptopurine.

Additionally, based on the availability of data, we intend to include evidence on children ages six to 17 years old with moderately-to-severely active UC.

Data permitting, we intend to examine subpopulations including but not limited to:

1) Patients who are naïve to biologic therapy
2) Patients who have previously used biologic therapy.

Other subgroups of interest may include age (e.g., ≥65), presence of extraintestinal manifestations, or other comorbidities, data permitting.

Interventions

The interventions of interest developed with input from clinicians and patient organizations include:

- Vedolizumab (Entyvio, Takeda), subcutaneous and IV formulations
- Infliximab (Remicade, Janssen)*
- Infliximab-dyyb (Inflectra®, Pfizer)*
- Infliximab-abda (Renflexis®, Merck)*
- Adalimumab (Humira, AbbVie)
- Golimumab (Simponi, Janssen)
- Tofacitinib (Xeljanz, Pfizer)
- Ustekinumab (Stelara, Janssen)

*Given the labelled indication, we intend to review evidence on the use of infliximab and its biosimilars in children. Evidence on off-label use of any other interventions of interest in children may be included, if available.

We intend to include all FDA-approved biosimilars of originator products that are currently available on the US market. Importantly, our focus will be on patient-centric data for UC only; information limited to pharmacodynamics, pharmacokinetics, or other laboratory parameters will not be

considered. We do not plan to include other FDA-approved biosimilars (e.g., biosimilars for adalimumab) as their entry to the US marketplace has been substantially delayed due to patent litigation.

Comparators

Based on data availability, we intend to compare the interventions of interest to ongoing background conventional therapy (i.e., placebo arms of clinical trials) and against each other.

Outcomes

The following outcomes of interest will be explored for evidence:

Efficacy

- Clinical remission
- Steroid-free remission
- Clinical response
- Mucosal healing
- Health-related quality of life
- Functional outcomes
- Other patient-reported outcomes
- Use of rescue medication
- UC-related hospitalization
- Surgery
- Mortality

Safety

- Serious adverse events
- Adverse events leading to discontinuation
- Treatment-emergent adverse events
    - Infections
    - Headache
    - Nausea
    - Fatigue
    - Pain
    - Pharyngitis
    - Respiratory
    - Autoimmune
    - Demyelinating disease
    - Injection reactions

- Development of neutralizing antibodies

Timing

Evidence on intervention effectiveness and harms will be derived from studies testing treatments with at least six weeks exposure duration.

Settings

All relevant settings will be considered, with a focus on outpatient settings as well as ambulatory and hospital-based settings.

Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits offered by the interventions to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These elements are listed in the table below.

Table 1. Potential Other Benefits and Contextual Considerations

Potential Other Benefits
This intervention offers reduced complexity that will significantly improve patient outcomes.
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.
This intervention will significantly reduce caregiver or broader family burden.
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.
This intervention will have a significant impact on improving return to work and/or overall productivity.
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.
Potential Other Contextual Considerations
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.
This intervention is the first to offer any improvement for patients with this condition.
Compared to "the comparator," there is significant uncertainty about the long-term risk of serious side effects of this intervention.
Compared to "the comparator," there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.

Scope of Comparative Value Analyses

As a complement to the evidence review, we will develop a simulation model to assess the lifetime cost-effectiveness of the treatments of interest relative to relevant comparator treatments. Treatments of interest include:

- Vedolizumab, subcutaneous and IV formulations
- Infliximab
- Infliximab-dyyb
- Infliximab-abda
- Adalimumab
- Golimumab
- Tofacitinib
- Ustekinumab

The model structure will be based in part on a literature review of prior published models of UC. The base-case analysis will take a health care system perspective (i.e., focus on direct medical care costs only). Data permitting, productivity losses will be considered in a separate analysis. The target population will consist of individuals with moderately-to-severely active UC, with either inadequate response or intolerance to conventional therapy, including corticosteroids, azathioprine, or mercaptopurine. Data permitting, we intend to examine subpopulations including but not limited to patients who are naïve and exposed to biologic therapy. We plan to include pediatric patients in the comparative value analysis if sufficient data allows for modeling in this population.

The model will likely consist of health states including active UC, response, remission, post-colectomy health states (with and without complications), and death. A cohort of patients will transition to response and remission health states during an induction phase. Following induction, patients achieving response or remission during the induction phase will enter a maintenance phase. Patients who do not achieve response or remission during the induction phase will discontinue treatment and transition to a subsequent treatment. Patients who do not achieve response or remission or who have lost response to all modelled biologic treatments will transition to conventional non-biologic therapy. Patients in the conventional therapy group will continue receiving conventional therapy irrespective of whether they achieve response or remission. Patients with active UC who are receiving conventional therapy will have a time-independent probability of undergoing colectomy. The model will use a lifetime time horizon in the base case. In addition, cost effectiveness will be estimated for shorter time horizons (e.g., five years). A discount rate of 3% per year will be applied to all costs and outcomes.

Key model inputs will include clinical probabilities, quality of life values, and health care costs. Probabilities, costs, and other inputs will differ to reflect varying effectiveness among interventions. Should data permit, findings from an NMA may be used to estimate treatment effectiveness.

Health outcomes and costs will be dependent on time spent in each health state, clinical events, adverse events, and direct medical costs. The health outcome of each intervention will be evaluated in terms of time in remission, remissions gained, colectomy procedures avoided, life years, equal value life years gained (evLYG), and quality-adjusted life years (QALYs) gained. Quality of life weights will be applied to each health state, including quality of life decrements due to disease flares, short-term and long-term complications associated with colectomy (e.g., pouchitis and infertility), and for serious adverse events associated with the interventions of interest. The model will include direct medical costs, including but not limited to costs related to drug administration, drug monitoring, condition-related care, hospitalizations, surgery, surgical complications, and serious adverse events. In addition, productivity losses and other indirect costs will be included in a separate analysis, data permitting. Relevant pairwise comparisons will be made among treatments, and results will be expressed in terms of the marginal cost per QALY gained, cost per evLYG, and cost per life year gained. Additional outcomes of interest may be included, such as cost per remission gained.

In separate analyses, we will explore the potential health system budgetary impact of treatment over a five-year time horizon, utilizing published or otherwise publicly available information on the potential population eligible for treatment and results from the simulation model for treatment costs and cost offsets. This budgetary impact analysis will indicate the relation between treatment prices and level of use for a given potential budget impact and will allow assessment of any need to manage the cost of such interventions.

More information on ICER's methods for estimating potential budget impact can be found at: http://icer-review.org/wp-content/uploads/2018/05/ICER-value-framework-v1-21-18.pdf.

Identification of Low-Value Services

As described in its Value Assessment Framework, ICER will now include in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create additional resources in health care budgets for higher-value innovative services (for more information, see https://icer-review.org/material/final-vaf-2017-2019/). These services are ones that would not be directly affected by TIMs for UC as these services will be captured in the economic model. Rather, we are seeking services used in the current management of UC beyond the potential offsets that arise from a new intervention. We heard from stakeholders that the repeated use of corticosteroids may qualify as a low-value service.

References

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