A LOOK AT **TARGETED IMMUNE MODULATORS FOR ULCERATIVE COLITIS**

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Summary

WHAT IS ULCERATIVE COLITIS?

Ulcerative colitis (UC) is a chronic 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). The disease is typically diagnosed between age 15 and 35 and causes long-lasting inflammation and ulcers in the digestive tract. Symptoms may include frequent diarrhea, sometimes with blood or pus, abdominal and/or rectal pain, weight loss, and fatigue. When the disease affects children, it can have a detrimental impact on growth, nutritional status, and psychosocial development. It is estimated that approximately 900,000 individuals in the United States have UC; the economic burden of UC is significant, ranging between $15-32 billion per year, including lost productivity at work and/or school.

TREATMENT OPTIONS

The goal of UC treatment is to reduce the disease's key symptoms (known as clinical "response") or effect a complete remission of the symptoms during a short-term (6-14 week) "induction" phase of treatment. Maintenance of the clinical response or remission via long-term "maintenance" therapy may occur at a lower dose than required for initial response. In patients with mild disease, local or topical use of aminosalicylates may induce and maintain remission. Once symptoms become moderate-to-severe, however, the use of corticosteroids and other systemic immune-modulating therapies is typically warranted. For patients whose disease does not adequately respond to systemic therapies, a number of targeted immune modulators (TIMs) are available for use.

We assessed the comparative clinical effectiveness and value of TIMs for the treatment of moderate-to-severe ulcerative colitis, including:

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

KEY REPORT FINDINGS

- All agents in this review had evidence demonstrating their superiority to placebo.
- The evidence was quite limited in helping to distinguish among the different TIMs but in the one head-to-head trial available, supported by network meta-analysis, vedolizumab was found to produce greater rates of clinical response and remission over adalimumab, the market leader, in both patients who had used TIMs previously ("biologic-experienced") as well as those who did not ("biologic-naïve").
- All the other TIMs were found to produce net health benefits at least comparable to adalimumab, with no clear differences among them.

KEY POLICY RECOMMENDATIONS

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

Clinical Analyses

How strong is the evidence that these therapies improve outcomes in patients with ulcerative colitis?

ICER EVIDENCE RATINGS

TIM	Comparator	Rating
Infliximab	Infliximab biosimilars	C
Infliximab	Placebo	A*
Golimumab	Placebo	A*
Tofacitinib	Placebo	B+†
All other TIMs	Placebo	A
Vedolizumab	Adalimumab	B+
Ustekinumab	Adalimumab	C+
Infliximab	Adalimumab	C+*
Tofacitinib	Adalimumab	P/I†
Vedolizumab	Golimumab	C+*
All other TIM Comparisons	–	I

*Biologic-naïve only.
†Biologic-experienced only.

- Our evidence ratings were based on a combined evaluation of the clinical benefits and potential harms of TIMs across the induction and maintenance periods within both the biologic-naïve and biologic-experienced populations.

- We rated infliximab-dyyb and infliximab-abda, the two biosimilars to infliximab, as comparable ("C") to the originator product. This rating is based on the Food and Drug Administration's (FDA) determination that the biosimilars are therapeutically equivalent in UC.

- TIMs were rated "A" (superior) to placebo with the exception of tofactinib (B+), given uncertainty around recent safety warnings regarding thrombosis and mortality.

Clinical Analyses (continued)

KEY CLINICAL BENEFITS STUDIED IN CLINICAL TRIALS

How effective are these therapies?

TIMs generally showed higher rates of clinical response and remission compared to placebo in trials; key comparisons between TIMs can be found below.

Clinical Response and Remission between TIMs (based on NMA results)

TIM	Comparator	Phase	Biologic-Naïve	Biologic-Experienced
Vedolizumab	Adalimumab*	Induction	⬆	⬆
		Maintenance	⬆	–
Ustekinumab	Adalimumab	Induction	–	⬆
		Maintenance	–	–
Infliximab	Adalimumab	Induction	⬆	N/A
		Maintenance	–	N/A
Tofacitinib	Adalimumab	Induction	N/A	⬆
		Maintenance	N/A	–
Vedolizumab	Golimumab	Induction	–	N/A
		Maintenance	⬆	N/A

*Based on results from NMA. Results from the head-to-head trial showed that compared to adalimumab, vedolizumab had significantly higher rates of response during induction in both populations and significantly higher rates of remission during maintenance in the biologic-naive population.

⬆ showed a benefit

– showed no difference

N/A comparison not evaluated due to lack of data for infliximab and golimumab in the biologic-experienced population; use tofacitinib is no longer feasible in a biologic-naïve population based on an FDA-enforced label change.

Clinical Analyses (continued)

HARMS

Severe and serious adverse events were rare during the induction and maintenance phases across all trials. There was no indication of increased rates of serious infections, tuberculosis, and mortality for any of the agents in available RCTs. Data from observational studies suggest somewhat higher rates of serious infection for certain TIMs vs. conventional therapy, but there were no consistent differences between older TIMs, and long-term data are lacking for the newer TIMs.

SOURCES OF UNCERTAINTY

Lack of head-to-head trials: Only one of the 19 RCTs was a head-to-head trial, so our comparisons between TIMs were largely informed by findings from NMAs.

Limitations of NMA: Our NMAs were limited by differences in study design, populations, and outcomes and sparse networks of evidence for the biologic-experienced population.

Limited evidence on treatment algorithm: There is currently very limited information to understand the optimal sequence of treatment. Some insight can be gleaned from assessing results for the biologic-naïve and biologic-experienced populations, but the definition of "experienced" varied across trials.

Limited long-term safety data on new therapies: There are limited to no long-term safety data on newer UC therapies, such as tofacitinib, ustekinumab, and vedolizumab. Limited data on children and adolescents: A substantial proportion of UC cases are diagnosed in children and adolescents. There is no available comparative evidence for this population.

Economic Analyses

LONG-TERM COST-EFFECTIVENESS

Do these treatments meet established thresholds for long-term cost-effectiveness?

Incremental Cost-Effectiveness Ratios for TIMs compared to conventional treatment:

	Biologic Naïve Population		Biologic Experienced Population	
Treatment	Cost Per QALY Gained	Cost Per evLYG	Cost Per QALY Gained	Cost Per evLYG
Adalimumab	$1,870,000	$1,847,000	$1,885,000	$1,878,000
Golimumab	$1,455,000	$1,432,000	–	–
Infliximab	$212,000	$209,000	–	–
Infliximab-dyyb	$186,000	$184,000	–	–
Infliximab-abda	$195,000	$193,000	–	–
Ustekinumab	$1,163,000	$1,155,000	$1,252,000	$1,239,000
Vedolizumab	$887,000	$880,000	$902,000	$895,000
Conventional Treatment	Reference	Reference	Reference	Reference
Tofacitinib	–	–	$495,000	$489,000

Economic Analyses (continued)

HEALTH-BENEFIT PRICE BENCHMARKS

What is a fair price for these therapies based on its value to patients and the health care system?

Annual Cost-Effectiveness Threshold Prices per Maintenance Year for TIMs for the Treatment of UC in the Biologic-Naïve Population

	Annual WAC	Annual Estimated Net Price	Annual Price at $100,000 Threshold	Annual Price at $150,000 Threshold	Discount from WAC to Reach Threshold Prices	Price within or below range?
Adalimumab	$72,400	$46,900	$5,800	$6,900	90%-92%	NO
Golimumab	$75,300	$42,300	$6,300	$7,600	90%-92%	NO
Infliximab	$27,900	$14,600	$8,800	$10,900	61%-68%	NO
Infliximab-dyyb	$22,600	$13,500	$8,800	$10,900	52%-61%	NO
Infliximab-abda	$18,000	$13,900	$8,800	$10,900	40%-51%	NO
Ustekinumab	$150,400	$91,600	$12,900	$16,600	89%-91%	NO
Vedolizumab	$43,800	$44,200	$9,500	$11,700	73%-78%	NO

ICER's recommended health-benefit price benchmark (HBPB) for these TIMs in the biologic-naïve population ranges from $5,800-$16,600 per year, which would require between a 40%-92% discount off the treatment's current list price.

Economic Analyses (continued)

Annual Cost-Effectiveness Threshold Prices per Maintenance Year for TIMs for the Treatment of UC in the Biologic-Experienced Population

	Annual WAC	Annual Estimated Net Price	Annual Price at $100,000 Threshold	Annual Price at $150,000 Threshold	Discount from WAC to Reach Threshold Prices	Price within or below range?
Adalimumab	$72,400	$46,900	$5,700	$6,800	91%-92%	NO
Tofacitinib	$57,200	$35,500	$12,600	$15,300	73%-78%	NO
Ustekinumab	$150,400	$91,600	$8,100	$11,800	92%-95%	NO
Vedolizumab	$43,800	$44,200	$8,900	$11,100	75%-80%	NO

For TIMs in the biologic-experienced population, the HBPB ranges from $5,700-$15,300.

ICER's recommended health-benefit price benchmark (HBPB) for these TIMs in the biologic-naïve population ranges from $5,700-$15,300 per year, which would require between a 73%-95% discount off the treatment's current list price.

The HBPB is a price range suggesting the highest US price a manufacturer should charge for a treatment, based on the amount of improvement in overall health patients receive from that treatment, when a higher price would cause disproportionately greater losses in health among other patients in the health system due to rising overall costs of health care and health insurance. In short, it is the top price range at which a health system can reward innovation and better health for patients without doing more harm than good.

Economic Analyses (continued)

POTENTIAL SHORT-TERM BUDGET IMPACT

How many patients can be treated before crossing ICER's $819 million budget impact threshold?

At the current price of ustekinumab, the newest TIM approved to treat UC, approximately 21% of eligible patients could be treated in a given year without crossing the ICER budget impact threshold of $819 million at the WAC price. We did not include the other therapies modeled above in this potential budget impact analysis given their established presence on the market for UC.

Voting Results

The CTAF deliberated on key questions raised by ICER's report at a public meeting on September 24, 2020. The results of the votes are presented below. More detail on the voting results is provided in the full report.

These voting questions are focused on adults with moderate-to-severe UC.

CLINICAL EVIDENCE

- A majority of panelists found that the evidence was adequate to demonstrate a net health benefit of vedolizumab when compared to adalimumab.
- All panelists found that the evidence was inadequate to demonstrate a net health benefit of ustekinumab when compared to adalimumab.
- A majority of panelists found the evidence not adequate to distinguish the net health benefit among tofacitinib, ustekinumab, and vedolizumab.

LONG-TERM VALUE FOR MONEY

- Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering all other benefits, disadvantages, and contextual considerations, a majority of CTAF panelists at the public meeting voted that the current pricing of infliximab and its biosimilars represented an **intermediate long-term value for money** when used to treat ulcerative colitis. Consistent with ICER's methodology, the CTAF did not vote on long-term value for money of the other TIMs because, at their current prices and for this indication, they all far exceed commonly cited thresholds for cost-effectiveness.

OTHER BENEFITS AND CONTEXTUAL CONSIDERATIONS

- A majority of panelists found that when compared to conventional therapy, treating patients with TIMs will significantly reduce caregiver or broader family burden.
- A majority of panelists found that when compared to conventional therapy, treating patients with TIMs offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.
- A majority of panelists found that when compared to conventional therapy, treating patients with TIMs will have a significant impact on improving patients' ability to return to work and / or their overall productivity.
- In assessing the long-term value for money of TIMs, a majority of panelists believed it was important to consider that these interventions are intended for the care of individuals with a condition of particularly high severity in terms of impact and quality of life and a high lifetime burden of illness.
- In assessing the long-term value for money of TIMs, a majority of panelists believed that compared to conventional therapy, there is significant uncertainty about the long-term risk of serious side effects of these interventions.
- In assessing the long-term value for money of TIMs, a majority of panelists believed that compared to conventional therapy, there is significant uncertainty about the magnitude of durability of the long-term benefits of these interventions.

Policy Recommendations

For 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

For Patient Advocacy Organizations

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

For Payers

- Insurance coverage should be structured to prevent situations in which patients are forced to choose a treatment approach on the basis of cost.
- Specialty society guidelines and drug labels should be monitored for changes, with coverage policy adjusted accordingly.
- 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.

For 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.

For 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.

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

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent nonprofit research institute that produces reports analyzing the evidence on the effectiveness and value of drugs and other medical services. ICER's reports include evidence-based calculations of prices for new drugs that accurately reflect the degree of improvement expected in long-term patient outcomes, while also highlighting price levels that might contribute to unaffordable short-term cost growth for the overall health care system.

ICER's reports incorporate extensive input from all stakeholders and are the subject of public hearings through three core programs: the California Technology Assessment Forum (CTAF), the Midwest Comparative Effectiveness Public Advisory Council (Midwest CEPAC) and the New England Comparative Effectiveness Public Advisory Council (New England CEPAC). These independent panels review ICER's reports at public meetings to deliberate on the evidence and develop recommendations for how patients, clinicians, insurers, and policymakers can improve the quality and value of health care.

For more information about ICER, please visit ICER's website (www.icer-review.org).