Clinical and Health Outcomes Associated With Different Treatment Sequences for Moderate-to-Severe Ulcerative Colitis

EE331

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Introduction

- Several advanced treatments (ATs) are approved for moderate to severe ulcerative colitis (UC), including anti-tumor necrosis factor (TNF) agents (infliximab [INF], adalimumab [ADA]), the anti-integrin a4b7 vedolizumab (VED), the anti-interleukin 12/23 ustekinumab (USK), Janus kinase inhibitors (tofacitinib [TOF] and upadacitinib [UPA]), and the selective oral sphingosine 1-phosphate receptor modulator ozanimod (OZA)
- While some of these treatments are indicated only for use after TNF failure, many can be used as the first AT option. However, access policies often require patients to fail ≥1 ATs before moving to another
- Given the availability of multiple treatment classes, we evaluated the positioning of OZA in the current access treatment pathway varying its position to determine the impact on disease control and treatment switching

Objective: This study quantified the total costs accrued per line of treatment (first line [1L], second line [2L], and third line [3L]), of the entire treatment sequence and the health benefits (time on treatment, endoscopic improvement, mucosal healing, corticosteroid-free remission, and symptomatic remission) of treatment sequences with OZA as a pre- or post-biologic therapy option

Methods

Model overview

- A simplified cost and outcomes calculator was developed using a decision tree model structure to track clinical and cost outcomes through 3 lines of AT (1L, 2L, and 3L) followed by best supportive care, including treatment with corticosteroids (CSs) or immunomodulators
- The model compared current lines of therapy where OZA is available only as 2L or 3L or as part of a basket with TOF and/or USK versus OZA being added to current 1L TNF inhibitor (TNFi) basket of INF and ADA or replacing the 1L biologics basket of INF, ADA, VED, and/or USK
  - **Sequence 1.** 1L: OZA; 2L: ADA, INF, VED; 3L: TOF, USK
  - **Sequence 2.** 1L: OZA; 2L: ADA, INF, VED, USK; 3L: TOF, USK
  - **Sequence 3.** 1L: INF, ADA, OZA; 2L: VED, USK; 3L: TOF
  - **Sequence 4.** 1L: OZA; 2L: ADA, INF, VED, USK; 3L: TOF
- The model predicted
  - Average time on each treatment line (ToT)
  - Clinical outcomes: response, remission, relapse, endoscopic improvement (EI), mucosal healing (MH), CS-free remission (CSR), and symptomatic remission (SR)
  - Total treatment-related costs of disease management and drug costs
  - Incremental outcomes (cost per ToT)
- Clinical inputs for OZA were based on the True North clinical trial and validated with open-label extension data and matching-adjusted indirect comparison, stratified by TNFi exposure. Cost inputs were derived from published literature and national databases
- The list of sequences included in the model was derived from treatment guidelines, clinical opinions, real-world evidence on treatment use in 1L-3L, and data availability. Sequences were compared pairwise (**Table 1**)

Table 1. Basketed treatment sequences[a]

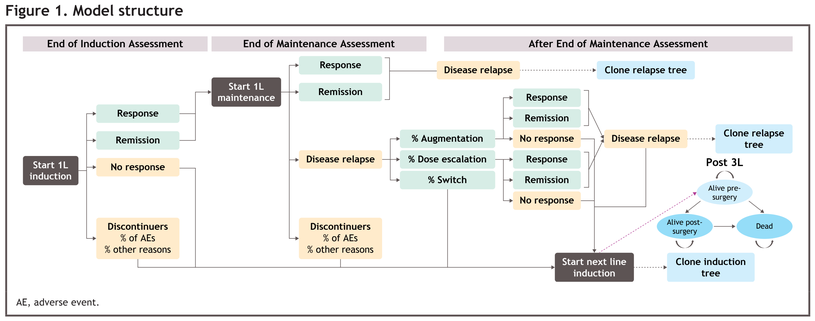
Sequence 1		Sequence 2		Sequence 3		Sequence 4	
Current	Proposed	Current	Proposed	Current	Proposed	Current	Proposed
1L: ADA (34%), INF (38%), VED (28%)	1L: OZA only	1L: ADA (32%), INF (36%), VED (26%), USK (6%)	1L: OZA only	1L: INF (47%), ADA (53%)	1L: INF (33%), ADA (37%), OZA (30%)[b]	1L: INF (34%), ADA (38%), VED (28%)	1L: OZA only
2L: OZA only	2L: ADA (34%), INF (38%), VED (28%)	2L: OZA only	2L: ADA (32%), INF (36%), VED (26%), USK (6%)	2L: VED (65%), USK (35%)	2L: VED (65%), USK (35%)	2L: USK only	2L: ADA (32%), INF (36%), VED (26%), USK (6%)
3L: TOF (12%), USK (88%)	3L: TOF (12%), USK (88%)	3L: TOF (12%), USK (88%)	3L: TOF (12%), USK (88%)	3L: TOF (50%), OZA (50%)	3L: TOF only	3L: TOF (50%), OZA (50%)	3L: TOF only

Note: Percentages denote US-based market shares associated with each treatment within a basket. Market shares across lines of treatment were obtained from a treatment pattern study conducted by Bristol Myers Squibb (data on file).
[a]Patients continued on 1L treatment until they experienced a relapse that led to flare management, treatment augmentation, escalation, or switching. Patients without response or discontinuing 1L treatment were moved to 2L treatment. The occurrence of a second relapse was assumed to result in treatment switch. The patient pathway for 2L and 3L were driven by the type of treatment received in prior lines.
[b]Based on the percentage of patients expected to develop anti-TNF antibodies.

Model structure

- The cohort started the induction phase with the induction duration being treatment specific (**Figure 1**)
- Patients achieving response and remission at the end of the induction period continued on the maintenance period. Patients without response or discontinuing moved to next line of treatment (2L)
- In the maintenance phase, patients achieving response or remission continued on treatment until relapse, leading to flare management and consequent treatment augmentation (with CSs or immunomodulators), escalation, or switching
- The average time to relapse was extrapolated (log-normal) using loss of response observed in the True North trial and applied to all comparators
- The occurrence of a second relapse, for patients who experienced augmentation or escalation, was assumed to lead to treatment switch
- The patient pathway of 2L and 3L followed what has been described above for 1L, with the type of treatment received in prior lines driving 2L-3L effectiveness
- After cycling through all lines of treatment, patients received best supportive care until they received a colectomy. Following colectomy, a Markov model was used to track patients through the following health states: alive pre-surgery, alive post-surgery, and dead
- Time to death and time to colectomy were modeled based on a constant risk of colectomy (for patients not in response or remission) and a general population mortality rate, increased by UC disease-specific mortality

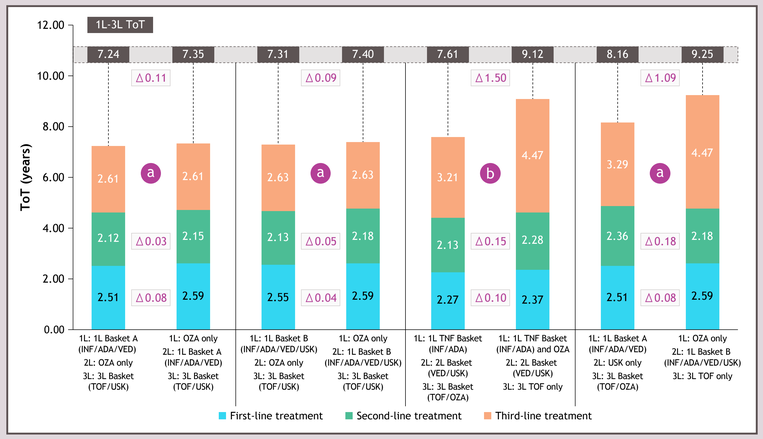
Figure 1. Model structure



AE, adverse event.

Positioning OZA as 1L or 2L was associated with improved time on treatment

Figure 2. Time on treatment by scenario

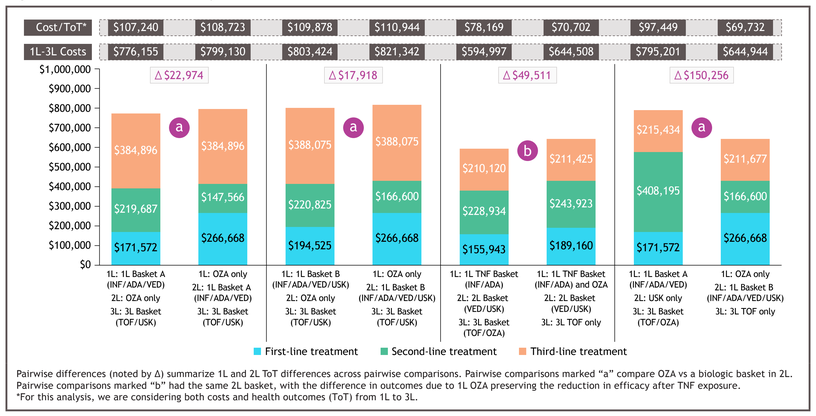


Pairwise differences (noted by Δ) summarize 1L and 2L ToT differences across pairwise comparisons. Pairwise comparisons marked "a" compare OZA vs a biologic basket in 2L. Pairwise comparisons marked "b" had the same 2L basket, with the difference in outcomes due to 1L OZA preserving the reduction in efficacy after TNF exposure.

Results

- Among all sequences tested, OZA replacing or displacing 1L TNF +/− other biologics basket was associated with higher ToT
  - Addition of ozanimod to 1L TNFi basket accrued the highest ToT (9.25), increasing 1L ToT by 0.1 years, MH rates by 8%, SR by 4%, CSR by 5%, and similar EI rates
  - The increase in ToT mainly arose due to OZA performing well in 1L, as well as TOF alone achieving better clinical outcomes than TOF/OZA mix in 3L
- Replacing current 1L biologics with ozanimod extended 1L ToT by 0.04-0.08 years and increased MH rates by 24-26%, SR by 16%, and CSR by 12%; however, EI rates remained the same
- For 2L outcomes, sequences with OZA mostly led to higher ToT (2.18-2.28) than comparator sequences (marked "a" in **Figure 2**)
- Sequences with OZA replacing 1L and retaining the 2L basket (marked "b" in **Figure 2**) were associated with better outcomes when OZA was added to 1L along with the 1L TNF basket, since OZA preserved the reduction in efficacy after TNF exposure
- The highest costs are observed in the sequences with the 1L biologics basket, including USK and OZA starting sequences
- Compared to later-line use of OZA, 1L OZA was associated with a lower or similar total cost per ToT (difference of ~$27,717 to $1483) (**Table 2**, **Figure 2**, and **Figure 3**)

Figure 3. Cost of treatment by scenario



Pairwise differences (noted by Δ) summarize 1L and 2L ToT differences across pairwise comparisons. Pairwise comparisons marked "a" compare OZA vs a biologic basket in 2L. Pairwise comparisons marked "b" had the same 2L basket, with the difference in outcomes due to 1L OZA preserving the reduction in efficacy after TNF exposure.
*For this analysis, we are considering both costs and health outcomes (ToT) from 1L to 3L.

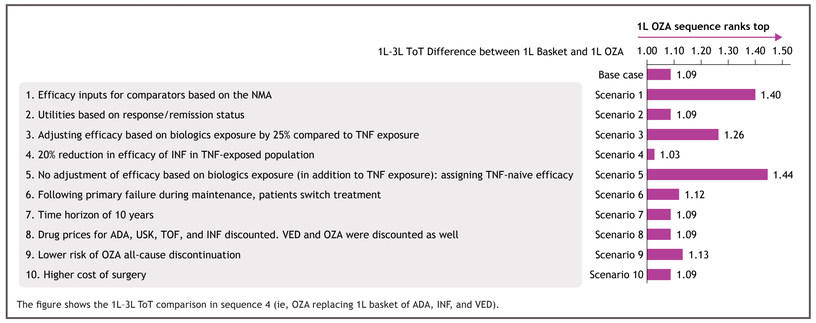
Table 2. Summary of clinical outcomes

	Proportions of patients achieving clinical outcomes							
	Sequence 1		Sequence 2		Sequence 3		Sequence 4	
	Current	Proposed	Current	Proposed	Current	Proposed	Current	Proposed
Outcomes	1L: ADA, INF, VED 2L: OZA only 3L: TOF, USK	1L: OZA only 2L: ADA, INF, VED 3L: TOF, USK	1L: ADA, INF, VED, USK 2L: OZA only 3L: TOF, USK	1L: OZA only 2L: INF, ADA, VED, USK 3L: TOF, USK	1L: INF, ADA 2L: VED, USK 3L: TOF, OZA	1L: INF, ADA, OZA 2L: VED, USK 3L: TOF only	1L: INF, ADA, VED 2L: USK only 3L: TOF, OZA	1L: OZA only 2L: INF, ADA, VED, USK 3L: TOF only
Endoscopic improvement								
1L	0.64	0.57	0.63	0.57	0.64	0.62	0.64	0.57
2L	0.36	0.60	0.37	0.59	0.56	0.55	0.52	0.59
3L	0.53	0.53	0.52	0.52	0.45	0.55	0.46	0.55
Mucosal healing								
1L	0.06	0.32	0.08	0.32	0.03	0.11	0.06	0.32
2L	0.18	0.03	0.18	0.04	0.07	0.09	0.19	0.04
3L	0.17	0.17	0.17	0.17	0.08	0.00	0.09	0.00
Symptomatic remission								
1L	0.44	0.60	0.44	0.60	0.46	0.50	0.44	0.60
2L	0.51	0.39	0.52	0.39	0.34	0.35	0.44	0.39
3L	0.43	0.43	0.44	0.44	0.45	0.41	0.46	0.41
CS-free remission								
1L	0.20	0.32	0.20	0.32	0.17	0.22	0.20	0.32
2L	0.20	0.18	0.20	0.18	0.21	0.31	0.15	0.18
3L	0.16	0.16	0.16	0.16	0.19	0.20	0.20	0.20

Sensitivity and scenario analyses

- One-way deterministic sensitivity analysis was performed separately for each of the sequences. The key model drivers were the drug costs of USK and OZA in the maintenance phase, the average time to relapse, and response rates
- Across most of the scenario analyses conducted (**Figure 4**), 1L-3L ToT were impacted, but there was minimal to no impact on the ranking, with 1L OZA sequence accruing higher ToT in all scenarios.
  - The scenarios where the 2L-3L effectiveness was reduced after other biologics exposure (VED, OZA, USK) by 25% (Scenario 3) or by 0% (Scenario 5) increased the overall ToT by 1.26 and 1.44 respectively; this had limited impact on the ranking
  - Using efficacy inputs for comparators based on the network meta-analysis (NMA) (Scenario 1) led to 1L OZA sequence ranking among the top with Δ1.40 ToT compared to 1L basket consisting of ADA, INF, and VED

Figure 4. Sensitivity analysis



The figure shows the 1L-3L ToT comparison in sequence 4 (ie, OZA replacing 1L basket of ADA, INF, and VED).

Limitations

- Cost inputs to the model were derived from published literature and national databases, and may not reflect all actual costs
- The sequences in the model were derived from treatment guidelines, clinical opinions, real-world evidence on treatment use, and data availability. The sequences may not be followed in all clinical situations
- Clinical inputs were based on clinical trial data and may not be generalizable to a real-world population
- The model assumed progression through lines of treatment, extrapolated time to relapse, and assumed that second relapses resulted in treatment switch, which may not be generalizable to all patients

Conclusions

- Primarily driven by OZA efficacy and safety, positioning OZA as either 1L or 2L therapy was associated with improved time on treatment in 1L and 2L and better clinical outcomes versus most of the AT baskets considered, with minimal impact on costs
- These findings are consistent with previous research demonstrating the efficacy of OZA in patients who were biologic-naive and biologic-exposed[1,2]

References

1. Sandborn WJ et al. *N Engl J Med*. 2021;385:1280-1291.
2. Siegmund B et al. ECCO Annual Congress. 2022. Abstract No. DOP43.

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Disclosures

- **DP and MC:** employees and/or shareholders of Bristol Myers Squibb.
- **SB and AA:** employees of Evidera, a company that received fees from Bristol Myers Squibb for the conduct of this research.

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