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Therapeutic sequencing in inflammatory bowel disease: Determining the optimal position of vedolizumab for long-term Crohn's disease control using real-world evidence

Edouard Louis[1] | Michal Litkiewicz[2] | Christian Agboton[3] | Alessandro Armuzzi[4,5]

[1]Department of Gastroenterology, University Hospital CHU of Liège, Liège, Belgium

[2]Modeling and Simulation, Evidera (a part of Thermo Fisher Scientific), London, UK

[3]Takeda, Cambridge, Massachusetts, USA

[4]IBD Center, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy

[5]Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy

Correspondence
Christian Agboton, Takeda Pharmaceuticals Inc., 125 Binney Street, Cambridge, MA 02142, USA.
Email: Christian.Agboton@takeda.com

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Abstract

Background: Several biologics are available for the treatment of moderate to severe Crohn's disease, but data to optimize their use are scarce. Vedolizumab (VDZ) is a gut-selective anti-lymphocyte trafficking monoclonal antibody that was approved in 2014 for the treatment of moderate to severe Crohn's disease. Based on real-world evidence, a model was developed to examine the effect of VDZ's position in the treatment sequence on clinical outcomes.

Objective: The aim of this study was to develop a model using real-world data to investigate how the positioning of VDZ in a sequence of biologic therapies for CD affects clinical effectiveness outcomes of quality-adjusted life-years (QALYS), patient-reported disease activity, and surgery rates.

Methods: A semi-Markov sequential model was developed to identify the optimal position of VDZ in a treatment sequence that included corticosteroids (CS), two biologics, and best supportive care (BSC). Using real-world data, three sequences were compared: VDZ as first (position), second, and last biologic (with anti-tumor necrosis factor alpha agents adalimumab (ADA) and infliximab (IFX) and the anti-interleukin-12 and -23 agent ustekinumab (UST) as alternative biologic treatments). Published real-world evidence informed model inputs. Vedolizumab sequences were compared and ranked based on QALYS, patient-reported outcomes from Crohn's disease activity index scores, or proportion of patients undergoing surgery by the 10-year time horizon for model simulation. Sensitivity analyses were used to evaluate the impact of model input uncertainty.

Results: Vedolizumab as the first biologic was the optimal position for this treatment according to all criteria, including yielding the highest QALYs (5.09) versus VDZ in second (4.97) and third (4.96) biologic sequence positions in sequences containing CS, anti-TNFα (aggregated data), UST, and BSC; 1780/2000 (89%) probabilistic simulations. In sequences containing ADA, VDZ, and UST biologics,

ADA and VDZ in the first-line biologic position yielded QALYs of 5.09 versus 5.07, respectively. Adalimumab as the first biologic was best for clinical remission.

Conclusions: This simulation model using real-world evidence indicates that positioning VDZ or ADA as the first biologic is likely to lead to improved long-term patient outcomes when compared to administering these treatments later or starting with IFX monotherapy.

KEYWORDS
biologics, Crohn's disease, IBD, Markov model, real-world, sequencing, therapy, vedolizumab

INTRODUCTION

Treatment choice for Crohn's disease (CD) should be based on the patient's best chance of response and safety considerations, but also with a view to altering the disease course (i.e., disease modification) to achieve disease control for as long as possible.[1–4] Disease modification may be best achieved by early biologic therapy.[1,5–7] Rather than waiting for conventional therapies to fail, recent American Gastroenterological Association guidelines suggest that patients should be treated with biologic therapy early in the disease course.[5] Choosing the correct initial biologic treatment and knowing which treatment to switch to and when if the initial biologic therapy is unsuccessful, are important decisions for the physician.[8]

Over a 5-year period, the majority of patients with CD initiating treatment with anti-tumor necrosis factor alpha (TNFα) agents will lose response.[9] With this in mind, a treatment strategy allowing disease control for as long as possible by optimizing the sequence of newly available therapies is advisable.

Vedolizumab is a humanized monoclonal anti-$\alpha_4\beta_7$ integrin antibody, the only gut-selective anti-lymphocyte trafficking drug approved to treat patients with moderate-severe CD.[10,11] Clinical trial data and real-world evidence have shown that using anti-TNFα agents after VDZ does not impact their clinical effectiveness, whereas VDZ is likely to be more effective if initiated before anti-TNFα treatment.[12–14] This asymmetric relationship could form the basis of a rationale for using VDZ at the start of a sequence of therapies designed to provide long-term disease control and ultimately disease modification. However, there are limited data available to inform optimal CD treatment decisions involving biologic therapies such as VDZ.[15,16]

The aim of this study was to develop a model with real-world data to investigate how the positioning of VDZ in a sequence of biologic therapies for CD affects patient outcomes. To compare the various sequences, the disease was simplified by defining important disease states for treatment decision making. Owing to its importance in CD management, corticosteroid (CS) therapy was included in the treatment sequence.

Using a semi-Markov chain, a quantitative evaluation of patient outcomes was obtained and the parameters to which these outcomes were sensitive were explored using probabilistic and deterministic sensitivity analyses. Finally, average "patient trajectories" were plotted over time to answer the question "Is there a sequence using VDZ that maximizes the likelihood of disease control over a 10-year timeframe?"

Key summary

Summarize the established knowledge on this subject

- There are limited comparative data available to assist clinicians in optimizing the sequencing of biologic therapies for treating patients with moderate to severe Crohn's disease.
- We developed a model to investigate how the positioning of vedolizumab (VDZ) in a sequence of biologic therapies for Crohn's disease affects patient outcomes.

What are the significant and/or new findings of this study?

- A semi-Markov model was developed using real-world data to find the optimal position for VDZ in a treatment sequence that also comprised corticosteroids (CS), two other biologics (from a choice of infliximab (IFX), adalimumab (ADA), or ustekinumab (UST)), and best supportive care (BSC). Sequences were ranked based on clinical effectiveness outcomes of quality-adjusted life-years (QALYS), patient-reported disease activity, and surgery rates.
- VDZ in the first biologic position was optimal versus other positions according to all outcomes criteria tested in the model.

METHODS

Relevant CD outcomes for all treatments included in the model were based on real-world outcome publications identified from the literature. A systematic literature review (10 January 2014 to 22 June

2017) and then a targeted literature review (19 July 2020) were used to identify potential model input sources (for publications search strategy and Population, Interventions, Comparisons, Outcomes, and Study Design eligibility criteria see Supplementary Information, Methods 1 and Table S1). The transition probabilities between states were determined by clinical data obtained from the literature.

The semi-Markov model

Markov modeling facilitates decision making by simulating transitions of a patient cohort between discrete health states (e.g., in their most simplistic form: "Health," "Sick," or "Dead") over time, according to a set of probabilities. A semi-Markov model is an extension of the classic Markov model that allows transition probabilities (e.g., probability of death) to change over time (e.g., as the cohort ages). To make the model relevant for CD, relationships between health states were mapped, including identifying the direction of patient movement between health states. A semi-Markov sequential model was developed to identify the optimal position for VDZ in different sequences of therapies for CD to maximize benefit (Figure 1).

Disease modeling was designed to be as close as possible to the sequence of events observed during treatment of CD in real-world clinical practice. Clinical response to induction (Week 4 for ADA, Week 6 for IFX, Week 12 for UST, Week 14 for VDZ) was included, with a decision to continue therapy for maintenance or to change

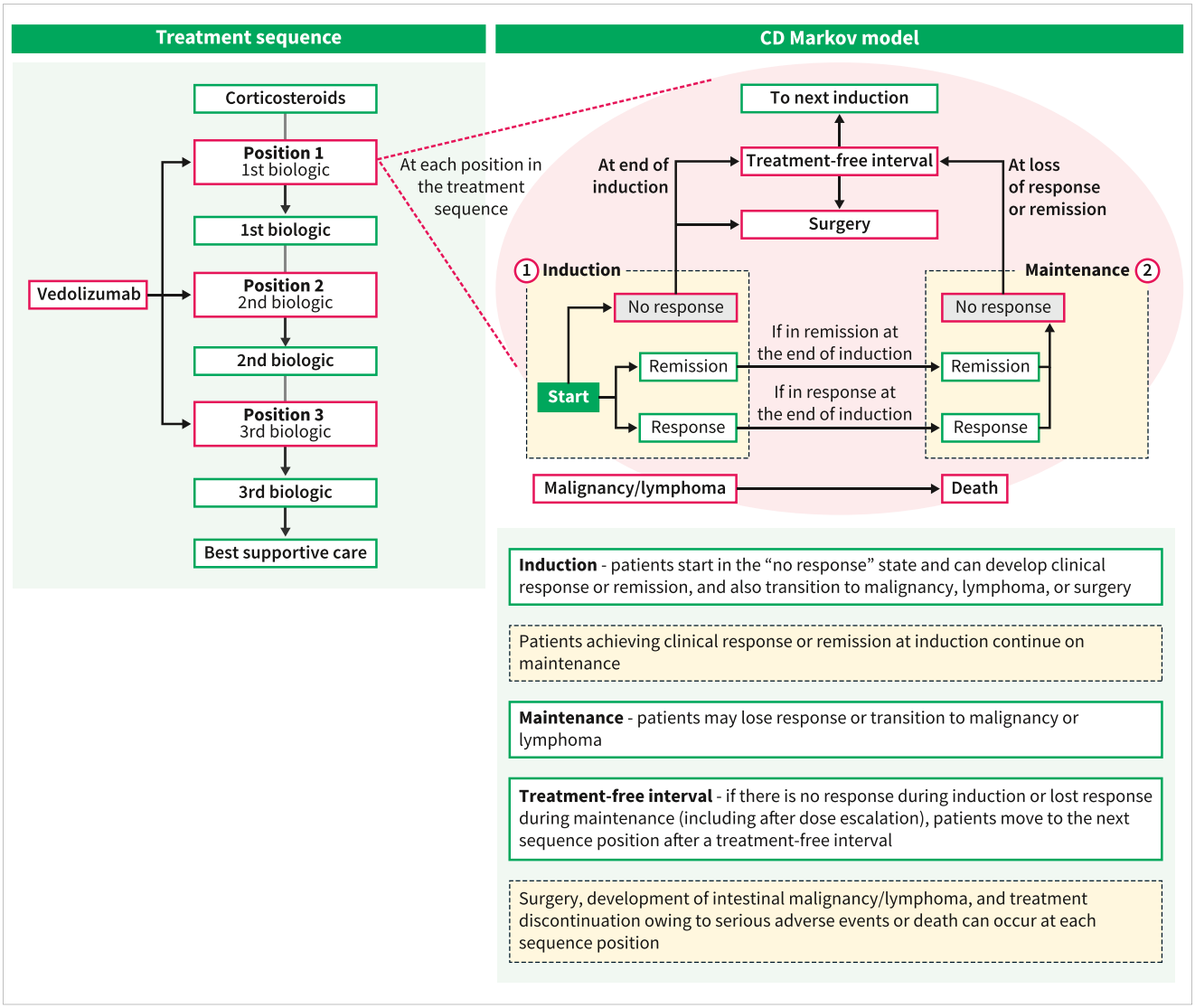

FIGURE 1 Semi-Markov sequential model developed to identify the optimal position for vedolizumab (VDZ) in a sequence of therapies for CD. Patient-related model input data included age, sex, presence/absence of ileal disease, and prior anti-TNFα treatment (naive or experienced). Three different treatment sequences were compared: position 1, with VDZ as the first biologic; position 2, with VDZ as the second biologic; and position 3, with VDZ as the third biologic. The other biologics in the treatment sequence were 2 anti-TNFα agents (infliximab (IFX) and adalimumab (ADA)), and ustekinumab (UST) as an alternative biologic. CD, Crohn's disease; TNFα, tumor necrosis factor alpha.

therapies upon a lack of clinical response to induction therapy. Data from the targeted literature review allowed selection of clinical responses for each treatment. Input values for the probability of clinical remission during induction, risk of disease flare in remission and response during maintenance, treatment discontinuation owing to adverse events (AEs) and lack/loss of response and rates of surgery, malignancies, and deaths are shown in Supplementary Tables S2–S6.

Disease states included in the model were states of clinical response or clinical remission at induction (or not). Patients in clinical response or remission could lose response during maintenance (including after dose escalation) and be moved to the next position of the sequence after a 4-week treatment-free interval. Induction with a new therapy was started when secondary loss of response occurred. Surgery, development of intestinal malignancy/lymphoma, and serious AEs (SAEs) or death could occur at each sequence position (see Supplementary Information, Methods).

The base sequences of therapies for CD included in the model were CS, followed by an anti-TNFα (IFX or ADA), UST, and best supportive care (BSC). In this sequence, different VDZ positioning strategies were considered (Figure 1): VDZ as the first biologic (before anti-TNFα treatments and UST), as the second biologic (after an anti-TNFα treatment and before UST), and as the third biologic (after an anti-TNFα treatment and UST).

In most sequential health economic models, the main outcome is quality-adjusted life-years (QALYs).[17,18] QALYs are relevant for economic analyses but less familiar to clinicians. In this model, the QALYs were therefore complemented with patient-reported outcomes (PROs) 2/3 and the risk of surgery over the years of medical treatment. PRO2 and PRO3 (recommended PROs for CD symptoms derived from CD activity index [CDAI] subscores) were used. PRO2 is the sum of loose stool frequency (SF) and abdominal pain (AP), and PRO3 is a 3-item composite of SF, AP, and wellbeing score.[4,19,20] Response outcomes based on CDAI scores were converted to PRO2 and PRO3 using published algorithms.[19] PRO scores for individual model states were weighted by the time spent in each state to obtain an average PRO.

The different VDZ strategies were compared over 10 years in terms of total accrued QALYs, mean PRO2 and PRO3, and the proportion of patients undergoing surgery. Sequences were ranked based on QALYs, PRO2/3, or the proportion of patients undergoing surgery by the end of 10 years for model simulation. See Supplementary Information Methods and Table S7 for details on model assumptions and calculation of disutility owing to SAEs.

Average patient trajectories (remission and response) were plotted and assessed visually over time. This showed the cumulative effect that small differences in treatment outcomes could have over a 10-year treatment period.

The model was programmed in R.[21] Calculations were implemented using custom code while the package ggplot2[22] was used to generate result plots.

Probabilistic and deterministic sensitivity analyses explored the impact of parameter uncertainty on the model outcomes. In the probabilistic sensitivity analyses, all uncertain parameters were sampled simultaneously from their probability distributions in 2000 iterations, and the proportion of simulations for which each VDZ strategy was optimal was calculated. In the deterministic sensitivity analyses, parameters or groups of parameters were individually varied to the maximum and minimum 95% confidence interval (CI) values, and the impact on differences between strategies was assessed. If 95% CIs were not reported in the sources, they were calculated from the available data, such as standard errors or standard deviations and sample sizes. An additional sensitivity analysis was performed to set the discount rate at 0% so that future outcomes were valued the same as current outcomes.

RESULTS

The model included adult patients diagnosed with moderate-severe CD (average age: 42.5 years; female: 59.1%; Table 1).

Optimal positioning of vedolizumab: Treatment sequences containing adalimumab/infliximab and ustekinumab

Infliximab was separated from ADA in sequences to provide a more granular approach. Outcomes of QALYs, PRO2/3, and surgery rate

TABLE 1 Model base case settings.

Characteristic	Value
Time horizon, years	10
Age, mean, years	42.5
Female, %	59.1
Evaluated sequences	VDZ in CS-IFX-UST; VDZ in CS-ADA-UST; VDZ in CS-TNF-UST[a]
Half-cycle correction[b]	Yes
Cycle length	1 week
Discount rate for outcomes, %[c]	3.5
Surgery included	Yes
Malignancies included	Yes
Disutility owing to SAEs included	No

Abbreviations: ADA, adalimumab; CS, corticosteroids; IFX, infliximab; QALY, quality-adjusted life-year; SAE, serious adverse event; TNF, anti-tumor necrosis factor alpha agent; UST, ustekinumab; VDZ, vedolizumab.

[a]TNF as an average of IFX and ADA.

[b]In economic models that use Markov-type processes, it is recommended that a half-cycle correction be built into the analysis to account for the fact that events and transitions can occur at any point during the cycle, not necessarily at the start or end of each cycle.

[c]The applied discount rates on QALYS are based on the National Institute for Health and Care Excellence technology appraisal guidance (https://www.nice.org.uk/process/PMG9/chapter/Foreword).

over 10 years were compared when VDZ was positioned at different points in the following treatment sequences: CS, IFX, UST, BSC; CS, ADA, UST, BSC (Table 2). The sequence with ADA as the first-line biologic after CS therapy was superior to that with IFX as the first-line biologic (QALYs of 5.09 vs. 4.84, respectively).

When examining the sequence containing IFX, VDZ achieved better scores in the first biologic position in terms of QALYs, PROs, and surgery rates versus the second and third biologic positions (Table 2). Depending on assumptions, ADA as the first biologic could lead to superior outcomes compared with VDZ as the first-line biologic (QALYs of 5.09 vs. 5.07, respectively). However, surgery rates did not change between these two sequences (Table 2).

Optimal positioning of vedolizumab: Treatment sequences with anti-TNFα agents (aggregated data) and ustekinumab

Results for anti-TNFα sequences were calculated as an average of results with sequences containing ADA and IFX. Outcomes such as QALYs, PRO2/3, and surgery rate over 10 years were compared when VDZ was at different positions in the sequence of therapies (first-, second-, or third-line biologic) in the following treatment sequence: CS, anti-TNFα, UST, BSC (Table 3). Using QALYs as the ranking criterion, first-line VDZ was the optimal position, yielding 5.09 QALYs (Table 3) and incremental QALYs of 0.12 and 0.11 versus the second- and third-line strategies, respectively. Vedolizumab as the first biologic also achieved better scores in terms of PROs and surgery rates versus VDZ in the second and third biologic positions. The cumulative surgery risk over 10 years evolved from 28.9% to 32.1% with VDZ as the first biologic versus the last biologic. Having VDZ in the last position (after UST) or before UST in the sequence did not lead to different outcomes (Table 3). Adding disutility owing to SAEs to the model had no effect on outcomes.

Sensitivity analyses

Early positioning of VDZ in the treatment sequence as the first biologic was the optimal strategy in the majority of probabilistic sensitivity analysis iterations (Figure 2). In 1780/2000 (89%) iterations, VDZ positioned as the first biologic yielded the highest QALYs

TABLE 2 Optimal positioning of vedolizumab (VDZ) in the treatment sequences containing anti-TNFα agents infliximab (IFX) or adalimumab (ADA): 10-year time horizon (base case).

VDZ position	Treatment sequence	QALYs	Mean PRO2	Mean PRO3	Patients receiving surgery, %
With IFX					
First biologic	CS-**VDZ**-IFX-UST-BSC	5.11	16.0	24.5	28.9
Second biologic	CS-IFX-**VDZ**-UST-BSC	4.84	17.4	26.6	31.9
Third biologic	CS-IFX-UST-**VDZ**-BSC	4.84	17.4	26.6	32.1
With ADA					
First biologic	CS-**VDZ**-ADA-UST-BSC	5.07	16.5	25.1	27.8
Second biologic	CS-ADA-**VDZ**-UST-BSC	5.09	16.3	24.8	27.8
Third biologic	CS-ADA-UST-**VDZ**-BSC	5.08	16.3	24.8	28.0

Note: PRO2 includes Crohn's disease activity index subscores of abdominal pain and stool frequency; a value of ≤8 is considered as clinical remission. PRO3 includes PRO2 items and general wellbeing; a value of ≤13 is considered as clinical remission.

Abbreviations: ADA, adalimumab; BSC, best supportive care; CS, corticosteroids; IFX, infliximab; PRO, patient-reported outcome; QALY, quality-adjusted life-year; TNFα, tumor necrosis factor alpha; UST, ustekinumab; VDZ, vedolizumab.

TABLE 3 Optimal positioning of vedolizumab (VDZ) in the treatment sequence containing anti-tumor necrosis factor alpha agent (TNF) (aggregated data for adalimumab (ADA) and infliximab (IFX)) and ustekinumab (UST): 10-year time horizon (base case).

VDZ position	Time on VDZ, years	Treatment sequence	QALYs	Mean PRO2	Mean PRO3	Patients receiving surgery, %
First biologic	3.1	CS-**VDZ**-TNF-UST-BSC	5.09	16.25	24.8	28.35
Second biologic	1.7	CS-TNF-**VDZ**-UST-BSC	4.97	16.85	25.7	29.85
Third biologic	1.6	CS-TNF-UST-**VDZ**-BSC	4.96	16.85	25.7	30.05

Note: PRO2 includes Crohn's disease activity index subscores of abdominal pain and stool frequency; a value of ≤8 is considered as clinical remission. PRO3 includes PRO2 items and general wellbeing; a value of ≤13 is considered as clinical remission.

Abbreviations: BSC, best supportive care; CS, corticosteroids; PRO, patient-reported outcome; QALY, quality-adjusted life-year; TNF, anti-tumor necrosis factor alpha agent; UST, ustekinumab; VDZ, vedolizumab.

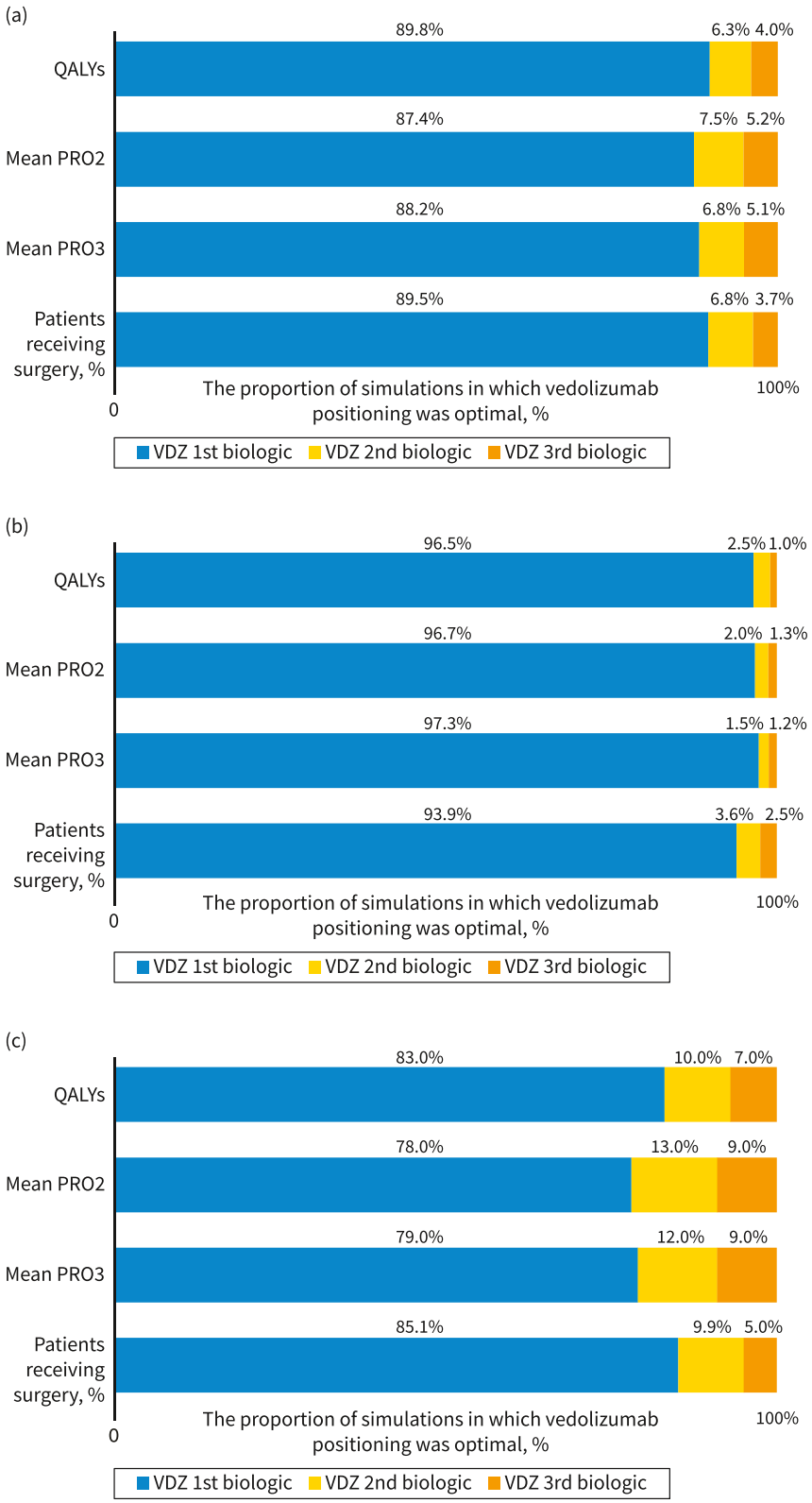

FIGURE 2 Probabilistic sensitivity analysis results. The probabilistic sensitivity analysis assessed the probability of each vedolizumab (VDZ) position in a sequence being optimal by simultaneously varying the uncertain model parameters. Graphs show the proportion of model simulations in which each vedolizumab positioning strategy was optimal for the following treatment sequences: (a) corticosteroids (CS), anti-TNFα, ustekinumab (UST), best supportive care (BSC); (b) CS, infliximab (IFX), UST, BSC; and (c) CS, adalimumab (ADA), UST, BSC. PRO2 includes CDAI subscores of abdominal pain (AP) and stool frequency (SF); a value of ≤8 is considered as clinical remission. PRO3 includes PRO2 items and general wellbeing; a value of ≤13 is considered as clinical remission. CDAI, Crohn's disease activity index; PRO, patient reported outcome; QALY, quality-adjusted life-year; TNFα, tumor necrosis factor alpha; VDZ, vedolizumab.

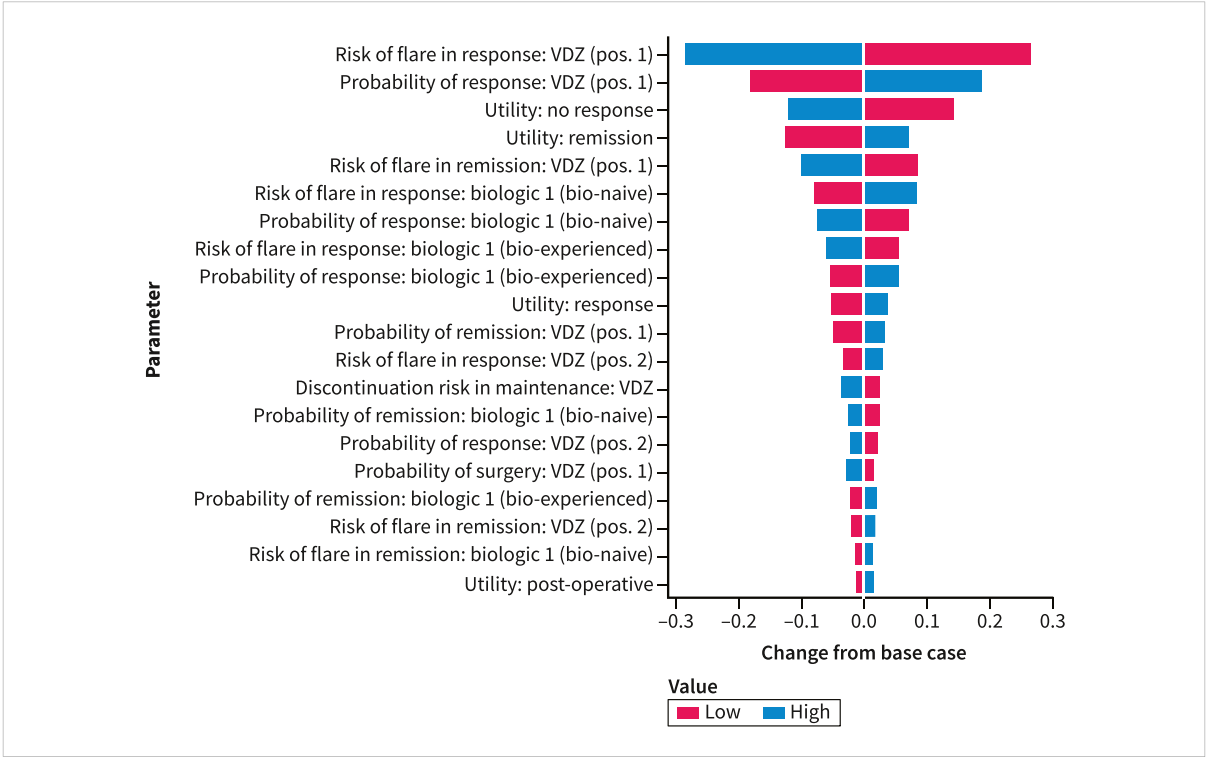

FIGURE 3 Deterministic sensitivity analysis results. Illustration of parameter sensitivity of the incremental QALYs between the following vedolizumab strategies: corticosteroids (CS), vedolizumab, infliximab (IFX), ustekinumab (UST), best supportive care (BSC); CS, IFX, vedolizumab, UST, BSC. Incremental QALYs in the base case were normalized to 0; horizontal bar plots show the deviation from the base case incremental QALYs. Pos., position; QALY, quality-adjusted life-year; VDZ, vedolizumab.

compared with VDZ in other sequence positions. The results were similar to sequences including ADA or IFX separately.

Deterministic sensitivity analysis results illustrate the model's sensitivity to specific parameters (Figure 3). Parameter sensitivity of the incremental QALYs between IFX-containing sequences showed that the most impactful parameters were risk of flare in response (VDZ as the first biologic), probability of response (VDZ as the first biologic), and utilities in the no response and remission health states. Results for equivalent sequences containing ADA (Supplementary Figure S1) show that the two most common impactful parameters were risk of flare in response and the probability of response with VDZ in the earlier of two positions in the treatment sequence. Other parameters in the ranking varied. Results for the sensitivity analysis with the discount rate set at 0% are shown in Supplementary Table S8. The ranking of treatment sequences according to all outcome types remained unchanged relative to the base case analysis. Although, without discounting, the absolute values of accumulated QALYs and PROs increased for all sequences, the differences between sequences remained similar to the base case analysis.

Patient remission and response analysis

Trajectories for patient remission and response across different positions of VDZ in the treatment sequences showed the biggest divergence early on, mostly corresponding to the proportion of patients responding during induction with VDZ, after which the difference between the curves representing the different treatment sequences remained relatively constant at 1 year to 5 years (Figure 4).

DISCUSSION

To our knowledge, this is the first study using Markov modeling with real-world evidence on patient outcomes to identify the optimal position for VDZ in CD treatment sequences. Instead of limiting the outputs to QALYs, we also aimed to define clinically relevant outcomes such as PRO2/3 and risk of surgery. Our data show that altering the sequence of biologic treatment can significantly alter the duration of treatment effectiveness. Both ADA and VDZ yielded the best outcomes in the model when positioned as the first biologic treatment; ADA was superior to VDZ in this position. In the case of VDZ, being positioned later in the sequence, after anti-TNFα agents, may considerably shorten the mean duration of response or remission achieved, consistent with evidence from clinical trials and real-world settings.[12–14]

This study also employed an innovative approach of using "average patient trajectories." The height of the early peak in response seen in the model mostly corresponds to the proportion of

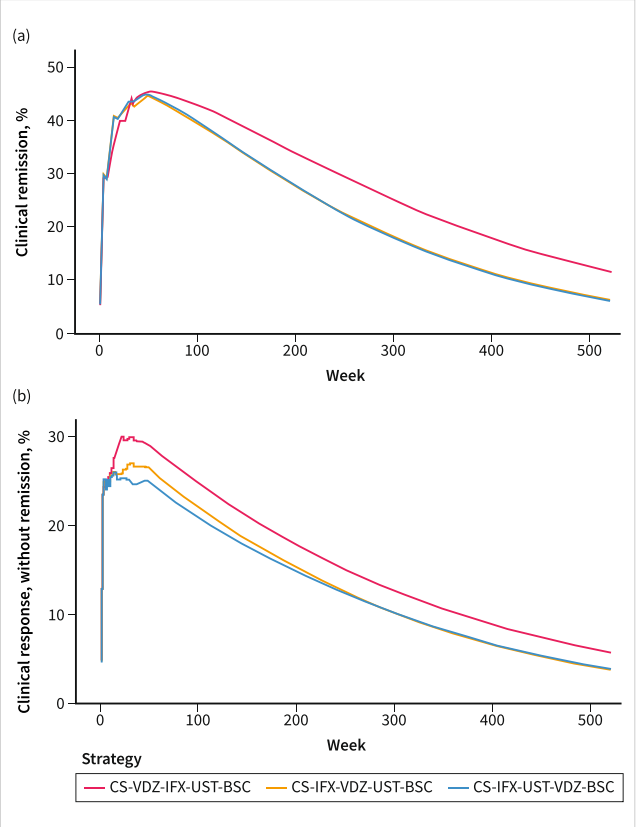

FIGURE 4 Trajectories for patient (a) remission and (b) response. BSC, best supportive care; CS, corticosteroids; IFX, infliximab; UST, ustekinumab; VDZ, vedolizumab.

patients responding to induction with their first biologic treatment, suggesting that the most important factor is treatment choice in the first year of therapy. The absolute difference in the proportion of patients in response or remission is similar after 5 years to after 1 year, which further highlights the importance of early treatment choices. The rate of surgery after 10 years derived from the model is consistent with epidemiology data on surgery rates in patients with CD; although there will be some variation between countries, 50% have been reported to require surgery within 10 years of diagnosis, and the annual incidence of hospital admissions was ~20%,[23] representing an external validation of the model.

In CD, the evidence clearly shows the impact of disease duration on the effectiveness of therapy.[24] The sequence with ADA as the first anti-TNFα treatment yielded positive outcomes, which were slightly superior to those with VDZ as the first biologic (depending on the model inputs). When comparing average patient trajectories, no difference between the two treatments could be observed in terms of discontinuation rates to account for this. Owing to ADA's shorter induction time, clinical responses following ADA treatment were evaluated earlier than following treatment with VDZ. The combination of earlier evaluation and marginally better clinical responses compared with VDZ may explain the model behavior. The probability of achieving clinical remission in biologic-naive patients was slightly higher with ADA versus VDZ, and there was also a lower risk of flare with ADA versus VDZ. The relationship was reversed in biologic-experienced patients, where there was a higher risk of flare with ADA compared with VDZ; this had the effect of accentuating the difference between sequences with ADA as first versus second or third biologic. Sequences starting with IFX had worse outcomes than those starting with ADA; the immunogenicity of IFX is a likely factor contributing to the poorer outcomes reported in real-world data.

In clinical practice, ~30% of biologics are prescribed alongside CS.[25–27] To test the sensitivity of the model, we simulated off-label use of VDZ before treatment with CS (Supplementary Table S9). This approach yielded the best outcomes and indicated that the model can integrate the role of co-medications in the treatment sequence; negative effects of CS were the predominant parameters in the model.

An analytical model allows for a better understanding of the dynamics of patient treatment responses. The reliance on real-world evidence may be questioned, but in patients with CD, treatments are rarely (if ever) used as they are in clinical trials.[28] Examples include VDZ co-treatment with CS for induction in clinical practice (the combination of VDZ and CS at induction yielded better results vs. the overall VDZ group in GEMINI 2[17,29]) and also three-dose VDZ induction used in clinical practice[11] versus two-dose induction in clinical trials. Thus, an advantage of real-world evidence over clinical trial data is better external validity: results are applicable to real-life situations where concomitant medications, drug optimization, and medical algorithms for switching from one treatment to another might differ.

Recently, Scott et al proposed a Markov model using inputs from pivotal clinical trials. Considering that the induction period of VDZ was shorter in GEMINI 2 compared with real-life settings, and that the model was limited to 1 year, the benefit of 0.016–0.020 QALYs appears to be relatively limited.[18] The preference for VDZ as the first biologic in the sequence could be mainly attributed to the high response rates after induction. Interestingly, this was also the case in the open-label induction phase of the VISIBLE 2 study when both two-dose and three-dose responders were accounted for (82.6% of patients achieved a clinical response after two or three VDZ IV infusions).[30] Varying the time horizon in our model did not change the overall sequence hierarchy, but rates of surgery were >50% when the treatment period was >15 years, which corresponds to most reported surgery rates in patients with CD.[31]

This study has some important limitations, firstly related to the source data used to construct the model. Real-world data has inherent limitations versus clinical trial data, including inconsistent evaluation of patients and potential for confounding risk factors and selection/publication bias. Treatment optimization, including dose escalation and combination with immunomodulators, is more likely to occur in real-world practice versus clinical trials; this might be expected to increase the external validity of the model to the real-world treatment landscape. This situation arguably favors the other biologics rather than VDZ, as VDZ is comparatively less optimized

versus other biologics and tends to follow label dosing in real-world practice.[32] Another limitation is that position-specific effectiveness data were not available for all interventions at the time of model development (e.g., UST as first biologic). The effectiveness of VDZ (as second vs. third biologic), IFX (as first vs. second biologic), and UST (as second vs. third biologic) was assumed to be the same. Recent comparisons of VDZ and UST in the second or third position showed similar levels of effectiveness.[33–35] In contrast, position-specific effectiveness data were available for ADA as first versus second biologic treatment, and VDZ as first biologic administered to biologic-naive patients. Considering treatment outcomes for monotherapy rather than combination therapy is an additional limitation, particularly in relation to anti-TNFα agents IFX and ADA; these and VDZ are often combined with CS at induction (bridging therapy) or maintenance.[13]

The model allows for disease recurrence in patients who were in clinical remission; however, there was an assumption that the risks of loss of response and remission were the same (owing to the lack of disaggregated data available on these two health states) and assumes a constant rate of response/remission loss during maintenance for patients who achieved response/remission at induction. Data on the average duration of treatment were used to inform the model on transition times between response/remission and loss of response/remission. The model also assumes that all patients are comparable at baseline without considering pertinent clinical information such as patient antecedents, biological markers, and existing disease complications.

Quality-adjusted life-years synthesize information about both health-related quality of life and life duration; however, PRO measures were not intended for integration over time or to be combined with life duration, so only average scores could be calculated. Patient-reported outcome scores could not be calculated for some model health states such as post surgery. Consequently, PROs should be viewed as a complement to QALYs rather than a substitute.

In reality, each patient requires personalized therapy. However, the model offers a basis for understanding the average impact of each sequence of therapies on long-term outcomes, such as surgery. Although modeling implies simplification of reality, we took great care to evaluate each input that could have affected clinical decision making.

CONCLUSION

This modeling study using real-world data indicated that ADA and VDZ both yield the best results when positioned as the first biologic treatment in patients with CD, across most assessment criteria including clinical outcomes. Adding disutility owing to SAEs did not affect these results. Average patient trajectories were mostly influenced by the treatment sequence within the first 5 years of therapy. These data provide further support for the use of VDZ early in biologic treatment sequences to optimize long-term treatment outcomes for patients.

AUTHOR CONTRIBUTIONS

Michal Litkiewicz and Christian Agboton contributed to the conception and design of the study, and acquisition of the data. All authors contributed to the analysis and interpretation of the data, drafted the article or critically revised it for intellectual content, and provided final approval of the version submitted for publication.

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CONFLICT OF INTEREST STATEMENT

E.L. reports educational and research grants from AbbVie, Fresenius Kabi, Janssen, Pfizer, and Takeda; speaker fees from AbbVie, Bristol Myers Squibb, Celgene, Dr Falk, Ferring, Galapagos, Janssen, Pfizer, and Takeda; serving on advisory boards for AbbVie, Arena, Bristol Myers Squibb, Celgene, Eli Lilly, Ferring, Gilead-Galapagos, Janssen, Pfizer, and Takeda; and reports consultancy for AbbVie. M.L. is an employee of Evidera, part of Thermo Fisher Scientific, which received funding from Takeda. C.A. is an employee of Takeda and holds stock/stock options in Takeda. A.A. reports consulting/advisory board fees from AbbVie, Allergan, Amgen, Arena, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Celltrion, Eli Lilly, Ferring, Galapagos, Gilead, Janssen, MSD, Mylan, Pfizer, Protagonist Therapeutics, Roche, Samsung Bioepis, Sandoz, and Takeda; speaker fees from AbbVie, Amgen, Arena, Biogen, Bristol Myers Squibb, Eli Lilly, Ferring, Galapagos, Gilead, Janssen, MSD, Novartis, Pfizer, Roche, Samsung Bioepis, Sandoz, Takeda, and TiGenix; and research support from Biogen, MSD, Pfizer, Takeda.

DATA AVAILABILITY STATEMENT

The datasets, including the redacted study protocol, redacted statistical analysis plan and individual participants' data supporting the results reported in this article, will be made available within 3 months from initial request to researchers who provide a methodologically sound proposal. The data will be provided after its de-identification, in compliance with applicable privacy laws, data protection and requirements for consent and anonymization.

ORCID

Christian Agboton https://orcid.org/0000-0002-1178-2429

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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