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ORIGINAL RESEARCH ARTICLE

Cost-Effectiveness Analysis of Crohn's Disease Treatment with Vedolizumab and Ustekinumab After Failure of Tumor Necrosis Factor-α Antagonist

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Abstract

Objective The aim was to evaluate the cost-effectiveness of Crohn's disease (CD) treatment with vedolizumab and ustekinumab after failure of therapy with tumor necrosis factor-α antagonists (anti-TNFs).

Methods The Markov model incorporated the lifetime horizon, synthesis-based estimates of biologics' efficacy in relation to anti-TNF exposure, and administration of biologics reflecting clinical practice (e.g., sequence of biologics, retreatment, 12-month treatment). The utilities, non-medical costs and indirect costs were derived from a study of 200 adult patients with CD, while the healthcare costs were from a study of 1393 adults with CD who used biologics in Poland. The quality-adjusted life years (QALYs) and costs (the societal perspective) were discounted with the annual rates of 3.5 and 5%, respectively.

Results The addition of vedolizumab (ustekinumab) to the sequence of available anti-TNFs (after first-line infliximab or after second-line adalimumab) led to a gain of 0.364 (0.349) QALYs at an additional cost of €5600.24 (€6593.82). The incremental cost-effectiveness ratios (ICERs) were €15,369 [95% confidence interval (CI) 7496–61,354] and €18,878 (95% CI 9213–85,045) per QALY gained with vedolizumab and ustekinumab, respectively. Sensitivity analyses revealed a high impact on the ICERs of the relapse rate after discontinuation of biologic treatment. The highest value of vedolizumab/ustekinumab was estimated after the failure of therapies with both anti-TNFs.

Conclusions CD treatment with ustekinumab or vedolizumab after failure of anti-TNF therapy appears to be cost-effective at a threshold of €31,500. The replacement of the second-line anti-TNF with ustekinumab/vedolizumab and the course of the disease after discontinuation of biologics are influential drivers of the cost-effectiveness.

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Key points

Ustekinumab and vedolizumab are effective treatments of Crohn's disease (CD) with uncertain pharmacoeconomic value after failure of therapy with tumor necrosis factor-α antagonists (anti-TNFs).

Ustekinumab and vedolizumab treatment after failure of anti-TNF therapy appears to be cost-effective from the societal perspective

Sensitivity analyses revealed that the conclusion was influenced by the course of the disease (e.g., relapse rate) among patients who failed or had contraindications to therapy with infliximab and adalimumab. The highest economic value of ustekinumab or vedolizumab was estimated after failure of therapies with both anti-TNFs

1 Introduction

Crohn's disease (CD) is a chronic and recurrent inflammatory bowel disease, which is often associated with parenteral symptoms (up to 40% of patients) and related immune disorders. It is not possible to cure the disease, but proper treatment can significantly reduce the symptoms and lead to long-term remission. Aminosalicylates, glucocorticoids, immunomodulatory drugs and antibiotics are used to treat active CD (standard treatments). The use of biologic drugs is recommended mainly among patients who cannot use the standard treatments because of intolerance, no response or contraindications. The tumor necrosis factor-α antagonists (anti-TNFs), namely, infliximab and adalimumab, have been the mainstay of biologic treatment of CD [1]. Recently, new biologic agents, namely, vedolizumab and ustekinumab, were approved for the treatment of CD in Europe. Vedolizumab is a second-generation monoclonal antibody directed against the intestinal tissue-specific α4β7 integrin. Ustekinumab is a monoclonal antibody directed against the p40 subunit of interleukins 12 and 23. Those biologics are usually positioned after failure of therapy with anti-TNF because of a different mechanism of action, possibly lower efficacy and/or a possibly higher cost [2].

Only three cost-effectiveness studies of vedolizumab in the treatment of CD [3–5] and no study of ustekinumab have been published [see the Electronic Supplementary Material (ESM), Supplementary Table 1]. However, the appraisals of the manufacturers' economic evaluations of those biologics are available [6, 7]. The limitations of the published studies make them of little use in terms of obtaining plausible conclusions for the population of patients who failed therapy with anti-TNFs. For example, the clinical data indicated a difference in efficacy between anti-TNF–naive and anti-TNF–failure patients [2, 8], but the studies did not address this issue [4, 5]. Additionally, Erim et al. [3] assumed continuation of anti-TNF treatment despite no response, which cannot be applied to all patients after failure of anti-TNF therapy in real-world practice. The failure of anti-TNF therapy is usually defined as no response, loss of response or intolerance of anti-TNF, and there are usually no contraindications to use another anti-TNF. Moreover, in clinical practice, patients can be treated several times with the same agent (retreatment) [6]. The inclusion of vedolizumab or ustekinumab in the treatment of CD will result in its use among patients who cannot use anti-TNFs because of failure of therapy, those who would have another treatment with the same anti-TNF, and those who would start another anti-TNF in the absence of ustekinumab or vedolizumab. Therefore, the research problem is not limited to a comparison between no biologic treatment and the treatment with vedolizumab or ustekinumab.

Authorities in some countries (e.g., Poland, UK) have introduced a limitation of treatment duration because of the lack of long-term data and/or other reasons. Despite the limit, retreatment is usually allowed [9]. There has been no economic evaluation that would incorporate both aspects of CD treatment (the limitation of treatment duration and retreatment) [6]. Bodger et al. [10] incorporated anti-TNF treatment durations of 12 and 24 months, but did not consider the possibility of retreatment and a different course of the disease after discontinuation of biologic treatment. Available evidence indicates that the risk of relapse after discontinuation of biologic treatment of CD is very high [11, 12]. The failure to capture the progressive and chronic nature of CD was indicated as the major limitation of the economic models for biologic treatment [6].

CD constitutes a significant burden for the patient and society [13]. The indirect costs are relevant in an economic evaluation adopting a societal perspective, and inclusion of indirect cost is often advocated [14]. Poor data on indirect costs were indicated as one of the major challenges in the cost-effectiveness analysis of biologic treatment of CD [15].

Therefore, our aim was to evaluate the cost-effectiveness of CD treatment with vedolizumab and ustekinumab after failure of anti-TNF therapy from the societal perspective, using a model incorporating the efficacy of biologics in relation to previous exposure to anti-TNF, indirect costs and treatment reflecting clinical practice (sequence of

biologic agents, retreatment allowed, maximum treatment duration of 12 months, maintenance treatment among responders to induction only, and utilization of drugs during induction treatment according to product characteristics).

2 Methods

The population included adult patients with moderate to severe CD, not adequately treated with standard treatments. The cohort of patients was observed from the start of the first biologic treatment to death (lifetime horizon). Up to three lines of biologic treatments were considered, and each treatment could not last longer than 12 months. Retreatment with the same agent was allowed among patients who were successfully treated previously, that is, patients after either elective discontinuation or completion of the 12-month treatment period. Three competitive treatment strategies were considered: (1) second-line adalimumab after failure of therapy with infliximab in the first line (status quo); (2) adalimumab or vedolizumab in the second line after failure of therapy with infliximab, and each of the second-line treatments after another one in the third line; and (3) adalimumab or ustekinumab in the second line after failure of therapy with infliximab, and each of the second-line treatments after another one in the third line. A standard dosage regimen was used for all biologics [16]. It was assumed that some patients could not start a subsequent line of the biologic treatment; therefore, they were subjected to intensified standard treatments (including surgery). To distinguish patients excluded from the subsequent line of biologic treatment from those after successful biologic treatment, the standard CD treatments used in both groups were named best supportive care (BSC) and standard of care, respectively. In a base-case analysis, it was assumed that one-third of the patients did not receive the last line of biologic treatment and two-thirds of the patients received vedolizumab or ustekinumab in the second line of the new strategies. The remaining patients could use the treatment or BSC in the third line, after failure of therapy with second-line anti-TNF (see the ESM, Supplementary Figure 1).

The Markov model incorporated synthesis-based estimates of the efficacy of biologics (details in Sect. 2.3) and patient-level data on costs and utilities obtained from recent studies from Poland: a survey among 200 adult patients [13] and an analysis of resource utilization among 1393 adult patients treated with biologics who were identified from the national database [17]. The setting of this study was the same as the country of the cost data (Poland). The health outcomes and costs were discounted at an annual rate of 3.5 and 5%, respectively [18].

2.1 Decision Model

Health states differing by the severity of CD symptoms, response to treatment, and type of treatment were included in the model (Fig. 1). The disease course of clinical remission (CR), response to treatment without remission (R), non-response (NR), and surgery (S) states was simulated with 4-week cycles. The cycle length was based on dosing intervals of the biologics, duration of the biologic treatment in clinical practice, and available information on transition probabilities (Sect. 2.2). The induction (three cycles) and maintenance phases of biologic treatment were included. Patients entered the model in the NR state of the "biologic treatment" module and faced movement to subsequent health states. Overall, the model included 384 states for each strategy and was implemented in Microsoft Excel (Microsoft Corporation, Redmond, WA). The main parameters of the model are presented in Table 1.

2.2 Natural Course of the Disease

The baseline matrix of transition probabilities between the states was derived from the study by Silverstein et al. [34]. The original eight-state matrix [34] was reduced to health states included in the model, using a previously described method [35] (i.e., weighting the combined states using the total time spent in those states, which preserves the course of the disease observed in the original study [34]). The medical and post-surgery remission states were combined into the CR state; the "mild" and "drug-responsive" states into the R state; and the "drug-dependent" and "drug-refractory" states into the NR state; the surgery state was unchanged [10]. A meta-analysis of observational studies revealed that the cumulative risk of relapse was 38, 40, and 49% at 6, 12, and >24 months, respectively, after elective discontinuation of biologic treatment [11]. Compared to prediction of the baseline matrix, the relapse rate was significantly higher during the first 6 months (38 vs. 4.9%), but slightly lower between 6 and 12 months after discontinuation (3.2 vs. 5.7%). Hence, an increased relapse rate was assumed during the first 6 months after elective discontinuation of biologic treatment (e.g., due to therapeutic success) or completion of the 12-month treatment period. Among patients who discontinued biologic treatment due to failure, a more severe course of the disease was assumed, which included: (1) a higher increase in the relapse rate compared with the rate after elective discontinuation [12] and (2) an increase in the relapse rate without time limit. The relapse rates derived from studies by Gisbert et al. [11] and Casanova et al. [12] were used to adjust the baseline matrix of transition probabilities.

The efficacy of biologics for induction treatment was used to embed patients to health states during the second

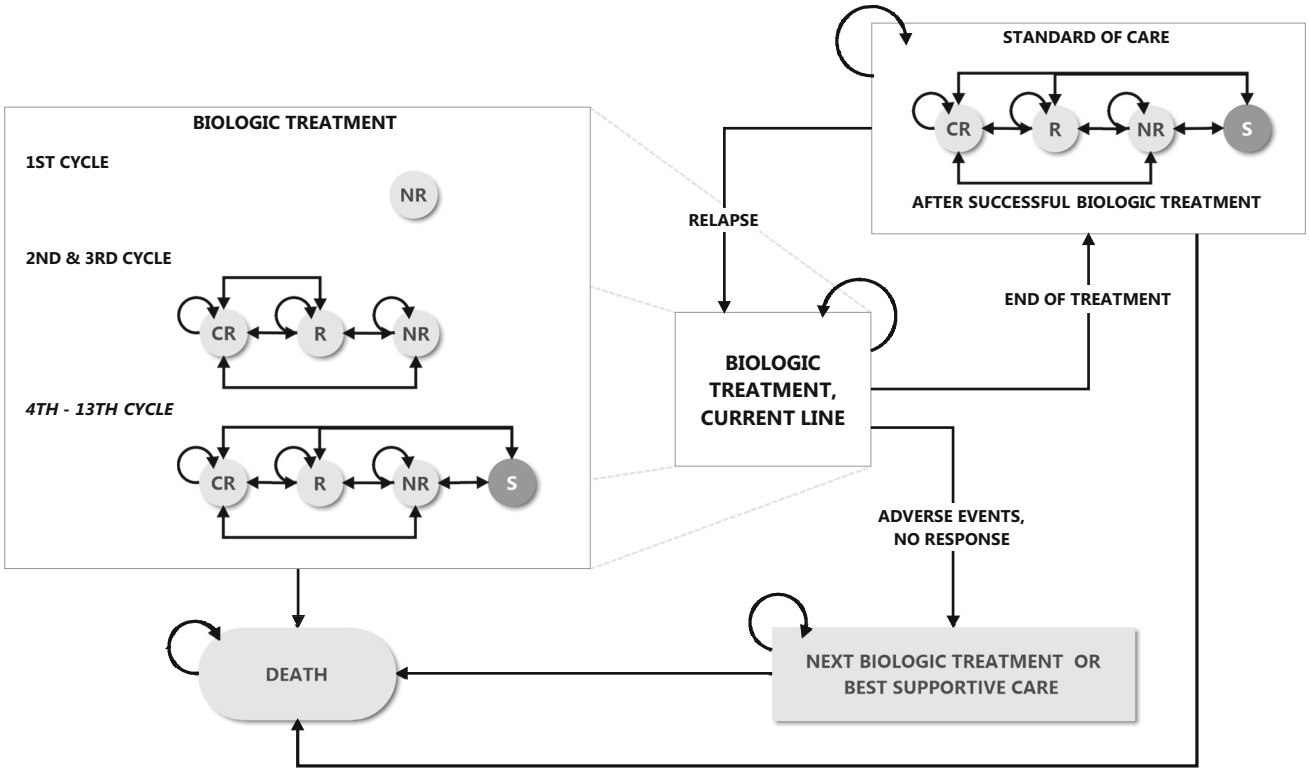

Fig. 1 Markov model diagram. "CR" indicates clinical remission, "R" response without remission (mild, moderate or severe Crohn's disease), "NR" non-response (moderate or severe Crohn's disease) and "S" any surgery for Crohn's disease (criterion for discontinuation of biologics in some cases). "Best supportive care" was defined as an intensified standard of care (standard treatments and surgery) among patients who had failed or had contraindications to therapy with all available biologics (the module included the response rate observed in the placebo arm of the clinical trials). The "standard of care" module included 7 groups of presented states, allowing the time since the last dose of a biologic agent to be accounted for. "End of treatment" included elective discontinuation due to therapeutic success and completion of the 12-month treatment period. "Relapse" was defined as progression to the NR state. No surgery was assumed during induction treatment with biologics (first 3 cycles of the biologic treatment). Biologics were used in the NR state only during induction treatment

cycle of the module "biologic treatment." To incorporate the effect of maintenance treatment with biologics, the baseline matrix was adjusted with the odds ratio of remission maintenance during biologic treatment in comparison with placebo, as described previously [35] (see the ESM, Supplementary Table 2).

The state-dependent risk of death derived from a study by Silverstein et al. [34] was used to simulate CD-related mortality. Data on the average probability of death among the general population of Poland [36] were used to obtain the mortality not related to CD.

In sensitivity analyses, the alternative data source of state-dependent mortality and baseline matrix of transition probabilities was tested (Odes et al. [37]).

2.3 Efficacy

The efficacy of biologics was obtained from published meta-analyses or results of the meta-analyses of studies identified in recent systematic reviews [8, 21, 38]. For the latter, random-effect models for relative effects and variance-stabilization models for absolute effects were used. The efficacy of vedolizumab and ustekinumab was assessed among patients who failed therapy with anti-TNF. Separate efficacy determinants were used for induction and maintenance treatment (Table 1). To reflect clinical practice, the probability of response induction with those drugs was evaluated in the longest follow-up available (10 weeks for vedolizumab and 8 weeks for ustekinumab) [22–24]. The efficacy of anti-TNFs was assumed to be independent of the previous exposure to other biologics. The efficacy of BSC was based on the meta-analyses of the response rate among patients who failed therapy with anti-TNF from the control arms of the trials [22–24]. Discontinuation due to adverse events was included, but the rate of adverse events not leading to treatment cessation was not. The rate of discontinuation for biologics other than infliximab was assessed in comparison with infliximab. The odds ratio of discontinuation during ustekinumab treatment was calculated using the indirect comparison of studies [19, 23, 24, 26–28] (see the ESM, Supplementary Table 3).

Table 1 Main input parameters

	Value	Source
Clinical input (subpopulation)		
Probability of response induction: infliximab and adalimumab (anti-TNF naive)	0.684	Meta-analysis [19, 20]; NMA [21]
Probability of response induction: placebo (anti-TNF failure)	0.210	Meta-analysis [22–24]; assigned to BSC
OR of response induction vs. placebo (anti-TNF failure)		
Vedolizumab	2.67	[22]
Ustekinumab	2.75	Meta-analysis [23, 24]
OR of remission maintenance vs. placebo		
Infliximab/adalimumab (anti-TNF naive)	2.80/5.10	NMA [21]
Vedolizumab (anti-TNF failure)	2.60	[25]
Ustekinumab (anti-TNF failure)	1.96	Meta-analysis [23, 24]
Discontinuation due to adverse events		
Infliximab: cumulative rate	0.076	Meta-analysis [19, 26]
OR, infliximab vs. adalimumab/vedolizumab	5.56/4.17	NMA [21];
OR, infliximab vs. ustekinumab	2.51	[19, 26–28] vs. [23, 24]
Share of CD in remission among responders		
Infliximab/adalimumab (anti-TNF naive)	0.485/0.615	Meta-analysis [19, 20], [29, 30]
BSC (anti-TNF failure)	0.456	Meta-analysis [22–24]
Vedolizumab (anti-TNF failure)	0.568	[22]
Ustekinumab (anti-TNF failure)	0.503	Meta-analysis [23, 24]
Share of mild CD among responders without remission	0.724	[20]
IRR of surgery: during vs. after biologic treatment	0.26	Analysis of 1393 patients[b]
Share of surgeries that result in biologic treatment discontinuation	0.407	Analysis of 1393 patients[b]
Relapse rate after biologics discontinuation	0.0707 per cycle	[11]
HR of relapse: failure vs. elective discontinuation	1.23	[12]
Probability of retreatment success	0.92	[11]
Utilities		
CR state (clinical remission)	0.908	[13]
R state (response without CD in remission)	0.822	[13]
NR state (non-response)	0.727	[13]
S state (surgery)	0.878	[13]
Multiplicator of state's utility for aging of the cohort	0.76–1.00	[31]
Cost inputs		
Net price of vedolizumab, 300 mg vial[a]	€1872.37	Without VAT, margins [32]
Net price of ustekinumab, 130 or 90 mg vial[a]	€2362.80	Without VAT, margins [32]
Cost of 1 mg of infliximab/adalimumab (NFZ)	€2.64/€9.73	With VAT, margins [33]
Administration of infliximab or vedolizumab (NFZ)	€156.46	Per each administration[b]
Administration of adalimumab or ustekinumab (NFZ)	€119.28	Every 4 to 12 weeks[b]
Diagnostic procedures during biologic treatment (NFZ)	€52.42 per cycle	Analysis of 1393 patients[b]
Healthcare costs, per cycle		
During biologic treatment: NFZ/patients	€79.49/€7.31	Analysis of 1393 patients[b]
After treatment, standard of care: NFZ/patients	€113.61/€7.93	Analysis of 1393 patients[b]
After treatment, BSC: NFZ/patients	€144.70/€8.03	Analysis of 1393 patients[b]
Surgery and care after procedure: NFZ/patients	€1,170.06/€10.07	Analysis of 1393 patients[b]
Non-medical costs (patients)[c]/indirect costs[d], per cycle		
CR state (clinical remission)	€12.62/€167.96	[13]
R state (response without CD in remission)	€23.28/€349.66	[13]
NR state (non-response)	€29.59/€421.94	[13]

Table 1 continued

	Value	Source
S state (surgery)	€22.00/€751.21	[13]

Anti-TNF tumor necrosis factor-α antagonist, *BSC* best supportive care, *CD* Crohn's disease, *HR* hazard ratio, *IRR* incidence rate ratio, *NFZ* Narodowy Fundusz Zdrowia (Polish National Health Fund), *NMA* network meta-analyses, *OR* odds ratio, *VAT* value added tax

[a]Multiplied by 1.134 to obtain the cost of vial from the NFZ perspective

[b]A retrospective analysis of 1393 adults with CD who used biologics in Poland (see Electronic Supplementary Material for the details)

[c]Special diet, transportation to the medical facility, etc

[d]Absenteeism, presenteeism among patients at productivity age, loss of productivity at unpaid job (if not compensated by caregivers), and informal care; among patients aged ≥ 65 years, the values were reduced by 80–90% (see Electronic Supplementary Material, Supplementary Table 6)

2.4 Utilities

The health outcomes were assessed in terms of the quality-adjusted life years (QALYs). The model was informed with the state-dependent utilities from a cross-sectional study of 200 adult patients with CD from Poland [13]. The information regarding patients with any surgery for CD in a month preceding participation in the study (five patients) was used to obtain the utility of the surgery state. The published sources of utilities (see the ESM, Supplementary Table 4) were tested in sensitivity analyses.

The size of the study by Holko et al. [13] was insufficient to assess the impact of age on the utilities. Hence, the age-dependent utilities of the general population of Poland [31] were incorporated to adjust the state-dependent utilities for the cohort aging. The biologics differ by route of administration, but the process utility was not included in the model. No significant difference in the process utility of subcutaneous and intravenous biologics has been reported recently [39].

2.5 Costs

The costs were assessed from the societal perspective. The healthcare, direct non-medical costs and indirect costs were included and presented in Euros [€1 = 4.27 Polish zloty (PLN) = US$1.13 = 0.88 British pounds (GBP); average in 2017). Older cost data were inflated to 2017 using the overall consumer price index [40] and converted to Euros using the average exchange rate in the 2017 [41].

The direct non-medical costs (e.g., special diet, transportation to a medical facility) and indirect costs (absenteeism, presenteeism, loss of productivity at unpaid job if not compensated by caregivers and informal care) in relation to the health state were calculated using patient-level data from study by Holko et al. [13]. Currently, vedolizumab and ustekinumab (90 mg) are not available in Poland. The maximum reimbursement prices of vedolizumab and ustekinumab in Slovakia [32] (a Central and Eastern European country with the list prices of those biologics available) were adjusted for the difference in taxes and margins between Slovakia and Poland and used in the model. The average reimbursement costs of infliximab and adalimumab in Poland in the first half of 2017 were included [33]. The costs of administration and diagnostic procedures during biologic treatment were based on medical resources identified in a retrospective analysis of 1393 patients with CD (the description of the cost analysis among patients identified from a database by Holko et al. [17] is presented in the ESM). The data were used to obtain other CD-related healthcare costs, namely, the cost of immunomodulatory drugs (azathioprine, cyclosporine, mercaptopurine, methotrexate), aminosalicylates, systemic glucocorticoids, antibiotics, and all medical services of hospital and ambulatory care. The cost of adverse events was not assessed directly, but was included in overall healthcare costs. However, due to the lack of detailed information on CD severity among participants, the healthcare costs were assessed in relation to biologic treatment, that is, during treatment (12,508 patient-years) and after biologic treatment among patients exposed to biologics for more than 100 days (11,771 patient-years). The healthcare cost of BSC was based on the post-treatment data among patients exposed to biologics for 100 days or less (most likely non-responders; 3843 patient-years). The cost of the surgery state was based on 1043 procedures (678 patients).

2.6 Cost-Effectiveness Analysis

The primary endpoint was the incremental cost-effectiveness ratio (ICER) calculated as the ratio of the difference in total costs and in QALYs between the new strategies with ustekinumab or vedolizumab and status quo. The ICERs were compared with the threshold of three times the gross domestic product per capita in Poland (€31,500 or PLN134,514) [18].

The "threshold price" informs about the maximal price of a drug at which using it is still cost-effective with a given threshold. To enhance generalizability and limit the

impact of assumptions on the prices of ustekinumab and vedolizumab on the conclusions, the "threshold prices" of those drugs were presented as a function of the threshold and price of the biosimilar infliximab [42]. The method of calculation of the "threshold price" from the formula of incremental net monetary benefit is presented in Supplementary Table 5 (see the ESM).

Reporting of the study was done in adherence with the Consolidated Health Economic Evaluation Reporting Standards [43] and Polish guidelines [18].

2.7 Sensitivity Analyses

One- and multi-way deterministic sensitivity analyses (DSA) were performed for all parameters. Based on their results, the extreme scenario analyses were constructed for each group of parameters. Additionally, the alternative source or assumption was tested.

The probabilistic sensitivity analysis, based on 1000 sets of randomly drawn input parameters, was carried out for calculating the confidence intervals (CIs) around the base-case results, using a nonparametric approach and to generate a cost-effectiveness acceptability curve.

All parameters of the model with CI and probability distribution are presented in Supplementary Table 6 (see the ESM). The model was available for review.

3 Results

3.1 Model Validation

The model predictions were validated with data from clinical trials and a study on 1393 patients using anti-TNFs in Poland (see the ESM, Supplementary Table 7). The model predicted survival on anti-TNF treatment that was quite similar to the one observed among 1393 patients treated with biologics in Poland. However, in the real-world, more patients discontinued treatment during the induction phase, but fewer patients discontinued treatment right after completion of this phase in comparison with model predictions (Supplementary Figure 2). This resulted in some differences in the average use of biologics (e.g., 6.2 of administrations of infliximab in the model vs. 5.5 of those in the real-world). Around 47.6% of patients starting infliximab and 44.3% of those starting adalimumab received retreatment or subsequent-line biologic treatment during the 2 years from the start of the therapy in the model. The corresponding values in the real-world were similar: 48.1 and 39.5%, respectively.

The 12-month remission rate for BSC among responders (23%) calculated with the model's inputs was similar to the results of the placebo arm of the study for ustekinumab (26%) [23], but higher than the results of the study for vedolizumab (13%) [25]. Additionally, the model was validated by the authors via hand searching of the model's code and formulas, extreme value testing for all input parameters, tracking of patients through the model, testing of the submodules, and implementation of alternative input data.

3.2 Base-Case Analysis

The strategy with vedolizumab treatment led to a gain of 0.364 QALYs (95% CI 0.066–0.649) at an additional cost of €5600.24 (95% CI 2003.40–10,600.94) per patient compared with status quo. The corresponding values for ustekinumab were 0.349 (95% CI 0.060–0.610) and €6593.82 (95% CI 2680.09–12,204.19), respectively. The ICERs were €15,369 (95% CI 7496–61,354) and €18,878 (95% CI 9213–85,045) per QALY gained with vedolizumab and ustekinumab (Table 2). The probability of vedolizumab or ustekinumab treatment being cost-effective with the threshold of €31,500 was 84.6 and 72.4%, respectively (Fig. 2). The new strategy was cost-effective compared with status quo if the net price of vedolizumab or ustekinumab did not exceed €3494.41 and €3681.13, respectively. The threshold prices followed the functions:

$$\text{Price}_{\text{vedolizumab,300mg}} = (0.000432 \times \text{Threshold} + 1.405) \times \text{Price}_{\text{infliximab,100mg}}$$

$$\text{Price}_{\text{ustekinumab,130 or 90mg}} = (0.000449 \times \text{Threshold} + 1.680) \times \text{Price}_{\text{infliximab,100mg}}$$

The treatments resulted in similar outcomes, but the point estimates indicated that vedolizumab dominated ustekinumab, with slightly better health outcomes (0.015 QALY gained, 95% CI −0.430 to 0.527), slightly lower cost (−€993.58, 95% CI −7770.39 to 5711.26), and a probability of being cost-effective of 61.2% compared with ustekinumab.

3.3 Sensitivity Analyses

The value of vedolizumab and ustekinumab depended on the share of anti-TNF that was replaced by those treatments in the second line. The ICER increased when the larger number of patients was treated with vedolizumab or ustekinumab instead of the second-line anti-TNF (Fig. 3). Both treatments had an ICER above the threshold if a higher relapse rate after discontinuation of biologics or the 1-year limitation of treatment duration was excluded. The strategy with vedolizumab or ustekinumab treatment was cost-effective compared with status quo [in a time horizon longer than 16.7 and 19.2 years, respectively (see the ESM, Supplementary Figure 3)] and if the relapse rate after

Table 2 Results of base-case analysis

	Status quo	New strategy with vedolizumab	New strategy with ustekinumab
Health outcomes			
Life years	16.316	16.597	16.584
Life years with CD in remission	8.749	9.514	9.468
QALYs	13.258	13.623	13.608
Costs (economic perspective)			
All biologic agents (NFZ); incl. ustekinumab or vedolizumab	€14,744.17	€22,210.41; incl. €6784.85	€23,397.90; incl. €7901.22
Administration and diagnostic procedures during biologic treatment (NFZ)	€3602.24	€4469.20	€4216.21
Healthcare after (i.e., "standard of care") and during biologic treatment (NFZ)	€15,183.84	€18,645.69	€18,589.90
"Best supportive care" (NFZ)	€8002.52	€3419.03	€3472.63
All above healthcare costs (NFZ)	€41,532.77	€48,744.34	€49,676.64
All healthcare costs (patients)	€1415.94	€1430.05	€1429.06
Non-medical direct costs (patients)	€3315.96	€3220.34	€3223.66
Indirect costs (society)	€45,696.17	€44,166.35	€44,225.30
Total cost from the societal perspective	€91,960.84	€97,561.08	€98,554.66
Cost-effectiveness			
ICER vs. status quo (per QALY gained)	Reference	€15,369	€18,878
ICER, ascending (per QALY gained)	Reference	€15,369	Dominated

CD Crohn's disease, *ICER* incremental cost-effectiveness ratio, *incl.* including, *NFZ* Narodowy Fundusz Zdrowia (Polish National Health Fund), *QALY* quality-adjusted life year

discontinuation of biologics increased by at least 2.6- and 3.7-fold, respectively, compared with the prediction of the baseline matrix. The exclusion of retreatment, BSC cost, surgery cost, and change of the prices, healthcare costs, utilities, indirect costs, or state-dependent mortality rates resulted in a significant change of ICERs, but did not change the conclusions (Fig. 4). The DSA of other parameters did not cause a change of ICERs of more than $\pm 5\%$.

4 Discussion

The study suggests that CD treatment with ustekinumab and vedolizumab after failure of therapy with anti-TNF is cost-effective. The relapse rate after discontinuation of biologic treatment and replacement of the second-line anti-TNF (i.e., treatment of similar effectiveness but less costly) were influential drivers of the cost-effectiveness. The conclusion regarding the cost-effectiveness of vedolizumab was more robust to the changes of its place in the sequence than that of ustekinumab. This suggests that vedolizumab should be used before ustekinumab in CD treatment. However, the data on the efficacy of ustekinumab after failure of vedolizumab therapy are not available [38]. Therefore, the hypothesis requires further research and was not tested in our study. The high relapse rate after anti-TNF discontinuation is well documented. It seems that a higher relapse rate after elective discontinuation occurs mainly during the first 6 months, and patients who discontinued biologic treatment because of failure of therapy with anti-TNFs have a higher relapse rate than those who discontinued the treatment for other reasons [11, 12]. However, long-term outcomes among patients who failed therapy with anti-TNFs are lacking. The available data did not exceed a period of around 100 months and considered only relapse rates among patients who failed therapy with anti-TNFs due to adverse events [12].

The choice of the time horizon highly influenced the results. However, due to the chronic character of the disease and long-term effects of biologic treatment, using a shorter time horizon than a lifetime will likely result in biased estimates of ICERs [10].

The strengths of the study include patient-level data on cost and utilities (a more accurate assessment of state-dependent values than using aggregate data) and a positive validation of the model predictions with real-world data of 1393 patients with CD from Poland. Even though we made every effort to reflect treatment patterns in clinical practice, it was necessary to make some assumptions. Those limitations are as follows: (1) Infliximab and adalimumab were considered as the only anti-TNFs, according to current

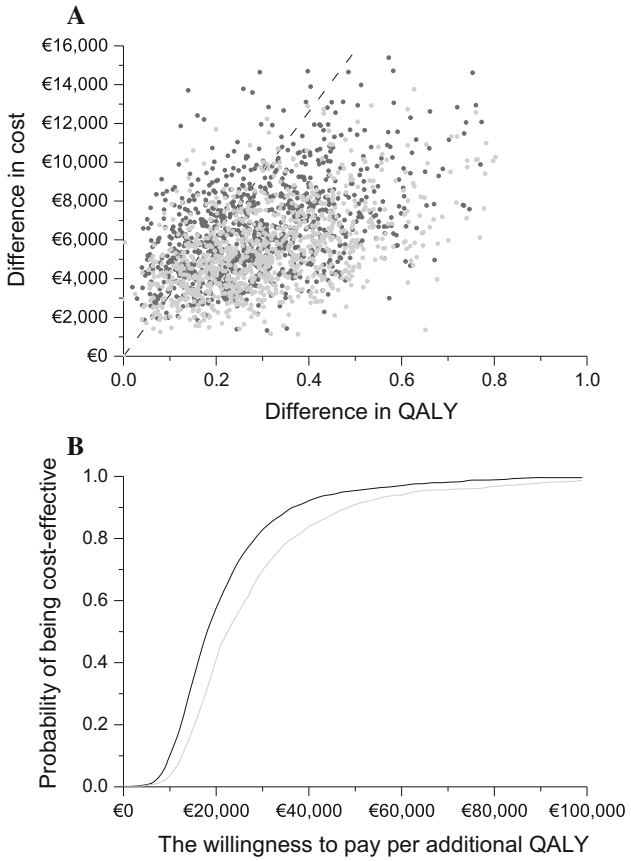

Fig. 2 Results of probabilistic sensitivity analysis: the scatter plot (**a**) and the cost-effectiveness acceptability curves (**b**). The gray circles and grey line indicate the results of a new strategy with vedolizumab compared with status quo; the black circles and black line indicate a new strategy with ustekinumab compared with status quo. The dashed line on the scatter plot indicates the threshold of €31,500 per QALY gained. *QALY* quality-adjusted life year

practice in Poland (e.g., certolizumab was excluded because it is not registered for CD treatment in Europe). (2) Dose intensification of adalimumab was excluded as it is rarely used in Poland. (3) The prices of ustekinumab and vedolizumab were forecast using the list prices of those biologics from other countries, and the potential agreement between manufacturers and the payer which reduce the treatment cost was not included. Those aspects can have a high impact on the cost comparison between vedolizumab and ustekinumab. We found that the difference in costs and QALYs between vedolizumab and ustekinumab was non-significant, but the difference in costs can be quite different when other sources of prices of those biologics are used (see the ESM, Supplementary Table 8). (4) There are potential differences in the characteristics of the patient population of studies that were used to inform the model (e.g., state-dependent utilities assessed in a wider population of patients with CD than the study population [13]). (5) Additional health benefits and cost savings resulting from the treatments among patients with fistulizing CD were not included (up to one-fourth of patients in clinical trials). (6) The healthcare cost of BSC was based on the data among patients who were most likely non-responders to biologic treatment, judging from the total duration of biologic treatment (i.e., shorter than the duration of induction treatment), but the non-response was not confirmed by clinical data (see the ESM). (7) The efficacy of adalimumab after failure of infliximab treatment was the same as the efficacy among anti-TNF–naive patients (conflicting evidence on the impact is available). (8) Potential savings in the healthcare cost resulting from the treatments were omitted, because separate healthcare costs among patients in remission, patients responding to biologic treatment, and non-responding patients were not available (the healthcare costs were assessed in relation to biologic treatment only, i.e., during or after biologic treatment, irrespective of the disease severity). (9) The efficacy data are limited due to no head-to-head trials being available, the different characteristics of the patients included in available trials, and the different design of the trials included in indirect comparisons [6, 7, 21]. Specifically, the different designs of clinical trials of maintenance treatment limited the results of indirect comparisons. However, we found little impact of the relative efficacy during maintenance treatment on the ICERs (Fig. 4).

The model structure was based on the study by Bodger et al. [10] and followed the structure of other models for biologic treatment [6]. The modifications introduced in this study (i.e., retreatment, higher relapse rate after treatment discontinuation, subsequent lines of biologics) allowed us to overcome some limitations of the previous models using a similar structure and to capture the progressive and chronic nature of CD [6]. The model also allowed us to track whether the remission was induced by surgery, and, in some cases, patients with post-surgery remission were excluded from the biologic treatment according to clinical practice. However, the impact of surgery on the incidence of future surgeries or the long-term quality of life was not analyzed [6].

Two cost-effectiveness analyses using cost data from nine European countries indicated that vedolizumab treatment after failure of both infliximab and adalimumab therapies resulted in a 5-year ICER ranging from €87,214 to €363,232 per QALY gained, depending on the CD patient group and setting [4, 5]. However, the studies did not include retreatment with the same biologic agent, indirect costs, a high relapse rate after anti-TNFs discontinuation, and efficacy of vedolizumab in relation to previous exposure to anti-TNFs. The ICER for vedolizumab was estimated at €326,824 per QALY gained using our model with similar assumptions (vedolizumab in the third line only, no retreatment, no indirect costs, 5-year time

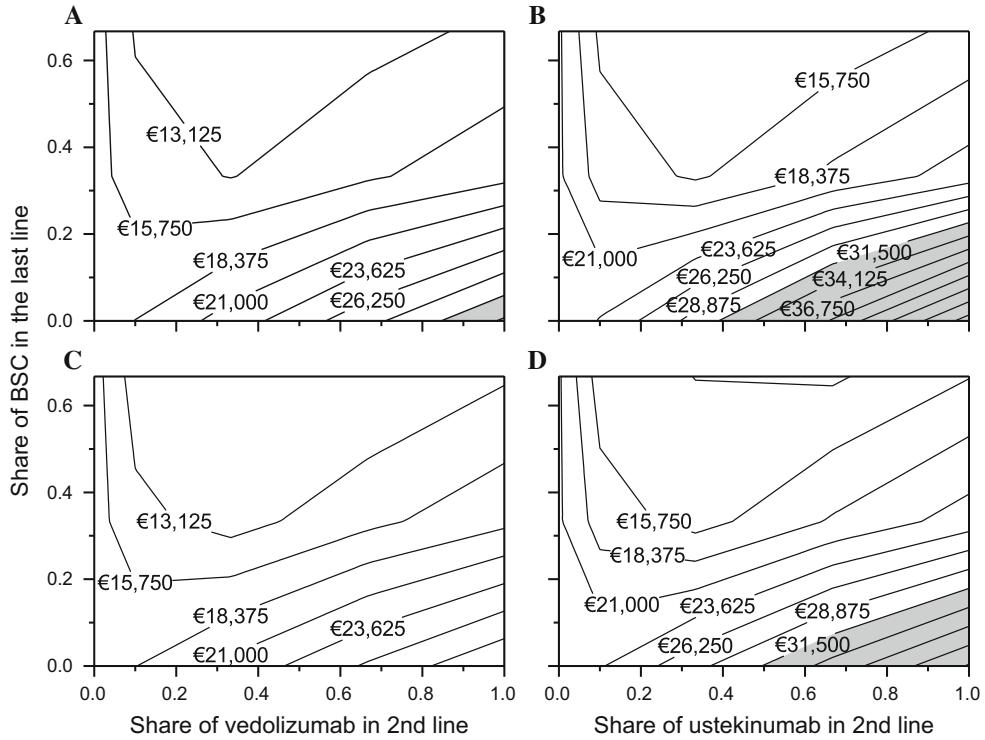

Fig. 3 Incremental cost-effectiveness ratios in relation to the position of ustekinumab and vedolizumab in the sequence of biologic treatments of Crohn's disease. Incremental cost-effectiveness ratios are presented in relation to (1) the share of best supportive care (BSC) in the last line (third line for the new strategy; second line for status quo; the BSC of status quo was replaced in part or full by vedolizumab or ustekinumab in the new strategy); (2) first-line treatment (**a**, **b** infliximab; **c**, **d** adalimumab); and (3) the share of vedolizumab (**a**, **c**) or ustekinumab (**b**, **d**) in the second line of the new strategy (the remaining patients were using the treatment or BSC in the third line, after failure of therapy with the second-line tumor necrosis factor-α antagonist). The gray filled area indicates a incremental cost-effectiveness ratio above the threshold of €31,500 per quality-adjusted life year gained

horizon, BSC after all biologics only, no increase in the relapse rate after discontinuation of biologics). Hodgson et al. [6] calculated an ICER of above £100,000 per QALY gained with ustekinumab and vedolizumab treatment after failure of anti-TNF therapy in comparison with conventional care. Rafia et al. [7] presented a lifetime ICER of £21,620 per QALY gained for vedolizumab in a similar population. The difference in baseline transition probabilities, cost data, and no increase in relapse rate after discontinuation of biologic treatment in those studies were presumably the main reasons for the discrepancies with our findings. By excluding the increase in the relapse rate after biologic treatment and the indirect costs only, the ICER for ustekinumab and vedolizumab was estimated at around £100,000 per QALY gained using our model. The cross-validation with the study by Hodgson et al. [6] (see the ESM, Supplementary Table 9) revealed that the point difference in health outcomes between ustekinumab and vedolizumab depended on the time point from clinical trials selected for the assessment of efficacy of induction treatment. Using clinical data from 6 weeks of the clinical trial by Hodgson et al. [6] indicated slightly better health outcomes with ustekinumab (difference in QALY of 0.03); using data from a longer follow-up, we obtained slightly better health outcomes with vedolizumab (difference in QALY of 0.015). However, the difference was not significant in both cases (less than 11 quality-adjusted days during lifetime).

Erim et al. [3] showed that using vedolizumab as the rescue treatment among patients who failed adalimumab treatment was more effective and less costly than the continuation of adalimumab with or without its dose intensification. Our study indicated the highest value of vedolizumab treatment after failure of both anti-TNF therapies, but cost savings were not observed. However, Erim et al. [3] used a lower cost of vedolizumab compared with adalimumab than that in our study (vedolizumab to adalimumab unit cost ratio of 3.6 and 5, respectively). This difference and the assumption on the continuation of treatment among non-responders (cost incurred with no effect) were presumably the main reasons for the discrepancies with our findings.

The majority of countries do not restrict the period of biologic treatment [9], while other countries may show poor adherence to the 1-year restriction [6]. However, in Poland the 1-year limitation is observed in clinical practice (see the

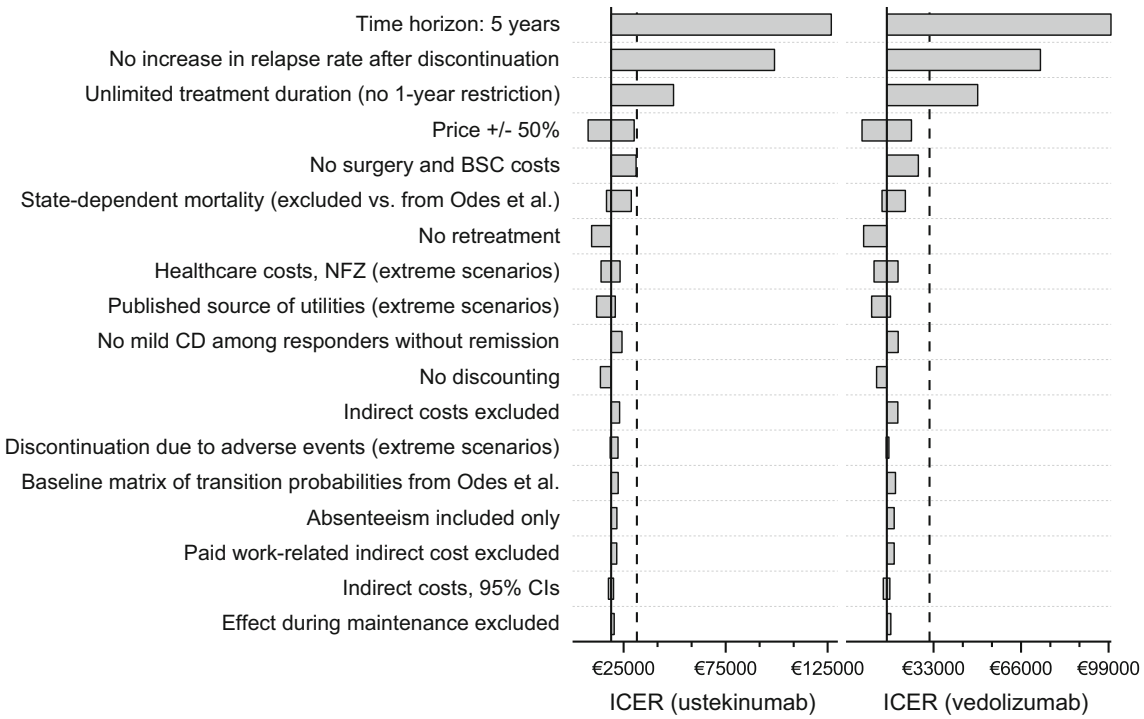

Fig. 4 Tornado diagram for deterministic sensitivity analyses. The dashed line indicates the threshold of €31,500 per quality-adjusted life year gained. *BCS* best supportive care (intensified standard of care that included standard treatments and surgery), *CD* Crohn's disease, *CI* confidence interval, *ICER* incremental cost-effectiveness ratio, *NFZ* Narodowy Fundusz Zdrowia (Polish National Health Fund)

ESM, Supplementary Figure 2). Therefore, the results of our study cannot be completely generalized to all settings. However, the "threshold prices" as a function of the threshold and price of a well-known drug used in the similar indication across markets as a reference were provided. Nevertheless, our approach to enhance generalizability did not consider all possible differences between settings. The results were still not adjusted for the difference in medical services valuation or treatment patterns. On the other hand, the study provides implications for the future assessment of biologics for the treatment of CD in any healthcare system. First, it revealed that the exclusion of retreatment and replacement of a second-line anti-TNF improves the ICERs for vedolizumab and ustekinumab. Hence, any decision regarding treatments among patients who fail therapy with anti-TNF should consider other anti-TNF as an alternative treatment. Secondly, long-term data on the health outcomes and healthcare cost of BSC is essential to explicitly assess the economic value of ustekinumab and vedolizumab in the treatment of patients with CD after anti-TNF therapy failure.

5 Conclusions

CD treatment with ustekinumab or vedolizumab after failure of anti-TNF therapy appears to be cost-effective at a threshold of €31,500. The replacement of the second-line anti-TNF with ustekinumab or vedolizumab and the course of the disease after discontinuation of biologics are influential drivers of the cost-effectiveness.

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Author Contributions PH: the concept and design of the study; methodology; data management, acquisition, analysis, validation, visualization, and interpretation; and manuscript drafting. PK: the concept and design of the study; and validation and interpretation of data. AP: the concept and design of the study, and project administration.

Compliance with Ethical Standards

Conflict of Interest: Przemysław Holko, Paweł Kawalec, and Andrzej Pilc declare no conflict of interest.

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Data Availability Statement All input data of the model are presented in the manuscript or the supplementary file. The model is available from the corresponding author upon reasonable request.

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