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Cost-effectiveness Analysis of Subcutaneous Infliximab for Inflammatory Bowel Diseases in Sequential Biologic Treatment

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Background: Inflammatory bowel disease (IBD) guidelines recommend tumor necrosis factor-α inhibitors (TNFis) for patients who have not responded to conventional therapy, and vedolizumab in case of inadequate response to conventional therapy and/or TNFis. Recent studies have shown that vedolizumab may also be effective in the earlier treatment lines. Therefore, we conducted cost-effectiveness analyses to determine the optimal treatment sequence in patients with IBD.

Methods: A Markov model with a 10-year time horizon compared the cost-effectiveness of different biologic treatment sequences in patients with moderate to severe ulcerative colitis (UC) and Crohn's disease (CD) from the UK and French perspectives. Subcutaneous formulations of infliximab, vedolizumab, and adalimumab were evaluated. Comparative effectiveness was based on a network meta-analysis of clinical trials and real-world evidence. Costs included pharmacotherapy, surgery, adverse events, and disease management.

Results: The results indicated that treatment sequences starting with infliximab were less costly and more effective than those starting with vedolizumab for patients with UC in the United Kingdom and France, and patients with just CD in France. For patients with CD in the United Kingdom, treatment sequences starting with infliximab resulted in better health outcomes with incremental cost-effectiveness ratios (ICERs) near the threshold.

Conclusions: Based on the ICERs, treatment sequences starting with infliximab are the dominant option for patients with UC in the United Kingdom, and patients with UC and CD in France. In UK patients with CD, ICERs were near the assumed "willingness to pay" threshold. These results reinforce the UK's National Institute for Health and Care Excellence recommendations for using infliximab prior to using vedolizumab in biologics-naïve patients.

Lay Summary

A Markov model compared the cost-effectiveness of biologic treatment sequences in patients with moderate to severe inflammatory bowel diseases from a European perspective. The results indicated that treatment sequences starting with infliximab are the dominant option than those starting with vedolizumab.

Key Words: infliximab, inflammatory bowel disease, cost-effectiveness

Introduction

Inflammatory bowel disease (IBD) refers to a group of chronic inflammatory disorders predominantly affecting the gastrointestinal tract. The most common phenotypes of IBD are Crohn's disease (CD)[1] and ulcerative colitis (UC).[2]

Treatment goals in IBD include achievement of clinical response as an immediate target, clinical remission as an intermediate target, and endoscopic healing and normalized health-related quality of life (HRQoL) as long-term targets.[3]

Tumor necrosis factor-α inhibitors (TNFis), such as infliximab and adalimumab, were the first class of biologics approved for the treatment of patients with IBD and are highly effective against luminal and extraintestinal manifestations of the disease.[4–6] Anti-integrin agents (eg, vedolizumab) are the second class of biologics to have been proven effective in IBD.[7] Surgery is often necessary for patients who do not achieve satisfactory disease control with medical agents. The majority of patients undergo surgical procedures during the course of the disease.[8]

A biosimilar of infliximab with a new subcutaneous formulation, was developed to address the unmet needs of patients with CD or UC .[9] The subcutaneous formulation of infliximab has the potential to change the way patients manage their condition on a day-to-day basis, offering them a greater choice

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Key Message

- The objective of this study is to determine the optimal treatment sequence in the treatment of IBD using TNFis. This is important because there are only a few biologics available for treatment.
- This study concludes that in patients with moderate to severe IBD, starting biologics treatment with infliximab is more cost-effective than treatment starting with vedolizumab.
- Countries aim to utilize health care resources in cost-effective way would benefit from this study by applying treatment sequences that would yield better health outcomes.

and convenience in the long term. Furthermore, the option to self-administer infliximab will lessen the demand on health care systems by reducing the time patients spend in hospitals, keeping patients out of clinics, and providing clinicians with additional time to spend with other patients.[10] Noninferiority was demonstrated between the subcutaneous and intravenous formulations of infliximab in terms of pharmacokinetics.[11]

Guidelines for UC recommend treatment escalation with thiopurines, TNFi therapy, and vedolizumab or tofacitinib for patients receiving high-dose mesalazine maintenance therapy who become corticosteroid-dependent or refractory.[12] In case of TNFi treatment failure, second-line therapy with vedolizumab or tofacitinib should be considered.[12] Recently, ustekinumab (interleukin 12/23 inhibitor) and ozanimod (sphingosine-1-phosphate receptor inhibitor) have been approved for the treatment of UC, and ustekinumab is already used in many countries.[12,13] Treatment guidelines for CD recommend TNFis for patients who have not responded to conventional therapy (eg, steroids and/or thiopurines); vedolizumab and ustekinumab are recommended for patients who have had an inadequate response to conventional therapy and/or TNFis.[14] The use of TNFis early in the disease course (in the first 2 years) may be more effective than using it at later stages and could be particularly beneficial in patients with poor prognostic factors, such as those with fistulizing perianal disease.[14]

In the TNFi-naïve population, vedolizumab was not cost-effective compared with TNFis[15]; thus, the UK's National Institute for Health and Care Excellence (NICE) recommends using vedolizumab only if TNFis are contraindicated. However, recent studies have shown that vedolizumab may also be effective in earlier lines of therapy.[16]

Few prior analyses have attempted to establish optimal treatment patterns for IBD. Scott et al[16] compared treatment sequences including infliximab, adalimumab, and vedolizumab and found that treatment sequences starting with vedolizumab were dominant over those starting with adalimumab and that they were not cost-effective in comparison with treatment sequences starting with infliximab. However, Scott et al[16] assumed a time horizon of 1 year, which is not long enough to evaluate the effectiveness and cost of a treatment sequence. Additionally, the effectiveness of infliximab was assumed to be the same in the first and subsequent lines of treatment, which is not appropriate considering that biologics are more effective in biologics-naïve patients.[17]

Providing effective pharmacological treatments and prolonging their effects are critical in the management of IBD because there are fewer treatment options than in other immune-related diseases, such as rheumatoid arthritis. The limited treatment options underscore the importance of exploring the most cost-effective sequence of biologics for IBD. Here, we conducted a cost-effectiveness analysis to determine the optimal treatment sequence in patients with moderately to severely active UC and CD.

Materials and Methods

Scope of Health-Economic Analysis

A model-based cost-effectiveness analysis was conducted to compare the cost-effectiveness of different biologic treatment sequences in patients with moderate to severe IBD. Three biologics were evaluated in this analysis: adalimumab, infliximab, and vedolizumab. Up to 3 lines of biologic treatment could be incorporated into 1 treatment sequence. Surgery was included as a final treatment option after failure of biologic treatments (last line of treatment).

Our model explored 4 competing treatment sequences, which are illustrated in Figure 1. Sequences 1 and 2 included tw2o lines of biologic treatment, and sequences 3 and 4 included 3 lines of biologic treatment. In sequence 1, patients received infliximab first and were switched to vedolizumab when treatment failure occurred. In sequence 2, patients received vedolizumab first and were switched to infliximab when treatment failure occurred. In sequence 3, patients received infliximab first and were switched to adalimumab and then vedolizumab when treatment failure occurred. In sequence 4, patients received vedolizumab first and were switched to infliximab and then adalimumab when treatment failure occurred. If all potential biologic therapies in sequences 1 to 4 failed, patients received surgery.

The health-economic analysis was undertaken from the perspective of the United Kingdom's and French health care systems over 10 years. Health outcomes considered in the model were quality-adjusted life-years (QALYs), total life-years (LYs), LYs in remission, and LYs in response. Cost outcomes included in the analysis were pharmacotherapy, surgery, disease management, including treatment of surgery

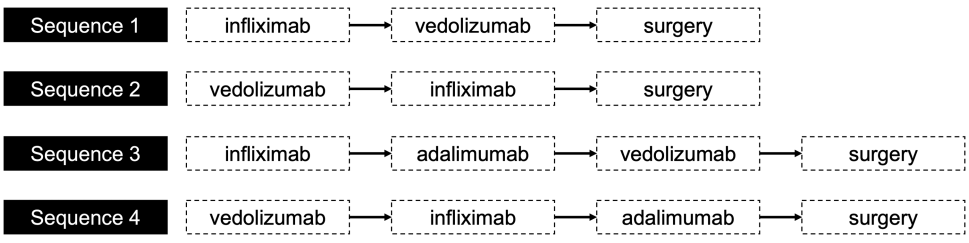

Figure 1. Schematic to illustrate the competing treatment sequences used in the Markov Model.

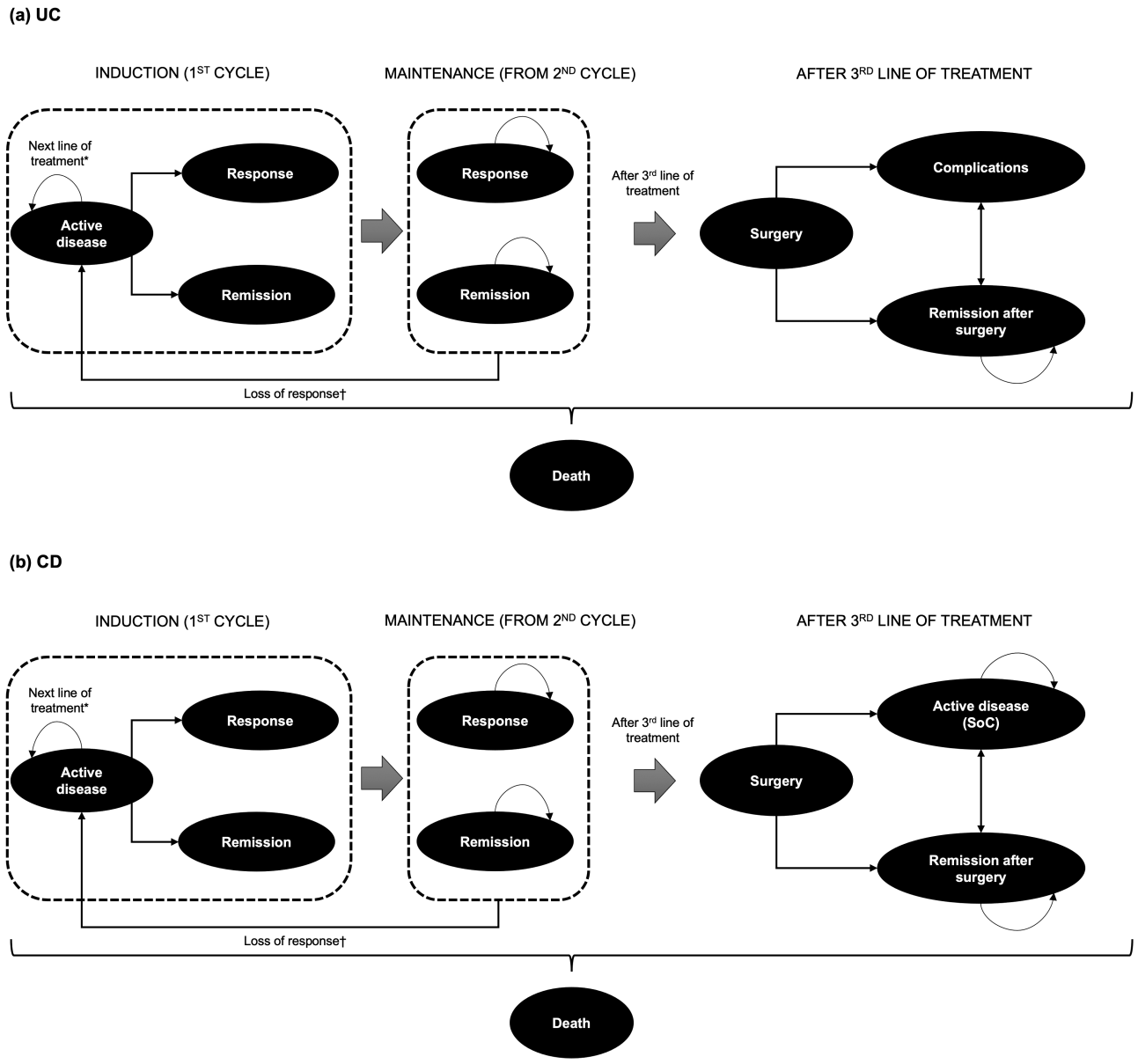

Figure 2. Structure of the Markov model used for economic evaluation of (A) patients with ulcerative colitis and (B) Crohn's disease. *Denotes up to 3 lines of treatment used in case of lack of response. †Denotes starting next line of treatment.

complications, and adverse events. Based on the health and cost outcomes, incremental cost-effectiveness ratio (ICER) per QALYs gained was investigated. To assess the cost-effectiveness of a treatment sequence, a "willingness to pay" (WTP) threshold of £30,000 was assumed for patients in the United Kingdom. Although no official WTP threshold exists in France, we used international thresholds as a reference and defined a hypothetical ICER below €50,000 as being cost-effective (the same WTP threshold is frequently used in cost-effectiveness analyses performed in Western Europe).[18] Costs and outcomes were discounted at a rate of 3.5% per annum.[19] Costs were valued at 2021 prices. Half-cycle correction was made throughout the simulations.

Model Structure

A Markov model with a cycle length of 8 weeks was used for the economic evaluation. The model structure (Figure 2) was developed based on a review of previous models and clinical input of experts.[20–22]

All patients began in the "active disease" health state and received one of the analyzed drugs. After the first cycle (induction treatment), patients could achieve remission (UC, total Mayo score of ≤2 points, with no individual subscore >1; CD, Crohn's Disease Activity Index [CDAI] score of <150 points)[23,24] or response (UC, total Mayo score reduction by ≥30% or score of ≥3 points, with a decrease in rectal bleeding subscore of ≥1 or a rectal bleeding subscore of 0/1; CD, CDAI score reduction by ≥100 points)[23,24] and moved to the "remission" or "response" health state, respectively. These patients continued treatment in the maintenance phase. Patients who did not achieve a response or remission stayed in the "active disease" state and started the next line of treatment in a base-case scenario.

In several previous clinical studies,[5,25] patients continued to receive the study drug after the induction phase even if

they had not achieved a response. To account for this, we performed a scenario analysis (scenario 1) that assumed no treatment discontinuation in the first year for the first and subsequent lines of treatment. In this scenario, patients who did not achieve remission or response in the first cycle stayed in the "active disease" state and did not proceed to the next line of treatment. Only after 1 year of treatment, patients who did not achieve a response moved to the next line of treatment. Patients in the "response" or "remission" state were able to stay in their current state or moved to the "active disease" state in case of drug discontinuation due to any reason after the first cycle or after the first year.

Patients failing the last line of biologic treatment could undergo surgery and moved to the "surgery" state. Based on data from clinical practice, the model assumed that all patients received surgery following the last line of biologic treatment. After surgery, patients with UC moved to the "remission after surgery" or "complications" state. As surgery for UC involves removal of the colon, it is usually considered curative, but major complications may occur during and after surgery. If patients with UC in the "surgery" or "remission after surgery" state developed complications, they moved to the "complications" state. It was assumed that the complications resolved within 1 cycle and that these patients then moved to the "remission after surgery" state. In patients with CD, patients moved to the "remission after surgery" if surgery was successful and in case of surgery failure, patients moved to the "active disease (standard of care [SoC])" state where patients received SoC treatment until death. Patients could also transit to the "active disease (SoC)" state in case of disease recurrence after complication-free surgery.

"Death" is an absorbing state and patients could move to this state from all other states.

Base case

1. First cycle of treatment: Patients who did not achieve remission or response in the first cycle moved to the next line of treatment in the second cycle. Patients were assigned to the "remission" or "response" state based on inputs from the induction treatment.
2. Second to seventh cycle of treatment: Patients were assigned to the "remission" or "response" state based on inputs from the maintenance treatment.
3. Eighth cycle of treatment and onwards: Proportion of patients between remission (maintenance) and response (maintenance) was based on persistence data from real-world studies. Patients were assigned to the "remission" or "response" state based on inputs from the maintenance treatment.
4. Patients who did not maintain remission or response moved to the next line of treatment.

Model Inputs

Baseline Characteristics

Patients included in this analysis were individuals with a diagnosis of moderately to severely active IBD. Baseline characteristics of patients with UC were derived from the economic evaluation study.[20] In the patients with UC, the average age was 40 years, average body weight was 77 kg, and 43% of individuals were female.[20] Baseline characteristics of patients with CD were derived from the GEMINI II study, a pivotal study of vedolizumab in patients with CD.[7] In the patients with CD, the average age was 36 years, average weight was 70 kg, and 53% of individuals were female.[7]

Clinical Efficacy

Probabilities of remission and response, for both induction and maintenance treatment, were sourced from Lohan et al[26] (for UC) and Singh et al[35] (for CD). Lohan et al[26] conducted a network meta-analysis to assess efficacy differences between treatments including infliximab, adalimumab, and vedolizumab. Singh et al[35] conducted a systematic review and network meta-analysis of biologic therapies including infliximab, adalimumab, and vedolizumab in the treatment of moderate to severe CD. Probabilities were calculated based on probabilities of remission and response for placebo and odds ratios (ORs) for biologic treatments vs placebo.

The probabilities for the treatments were calculated using this formula:

$$P_{Trt} = \frac{P_{Plc} * OR_{Trt\ vs\ Plc}}{1 - P_{Plc} + P_{Plc} * OR_{Trt\ vs\ Plc}}$$

where,

- P_{Trt} is the probability (of remission or response) for treatment
- P_{Plc} is the probability (of remission or response) for placebo (infliximab, adalimumab, or vedolizumab)
- $OR_{Trt\ vs\ Plc}$ is the OR for the biologic treatment in comparison to placebo.

In their analysis, Lohan et al[26] presented comparative efficacy and safety data for first-line treatment in UC for all biologic drugs and data for the subsequent line of treatments for all biologic drugs except infliximab. Therefore, the OR for infliximab in the subsequent lines was assumed to be the same as the lowest of the OR values reported for adalimumab and vedolizumab. As Singh et al[35] did not include probabilities for placebo in their publication, these were calculated using the methodology described by Miller.[42] There were a number of missing values for maintenance treatment; missing ORs were calculated as ratios of other OR values. The efficacy data for infliximab in subsequent lines were also missing. Therefore, the lowest OR value reported for adalimumab and vedolizumab in the subsequent lines of treatment was used as a proxy.

Discontinuation of Treatment

Long-term discontinuation was based on data from 3 real-world studies assessing the persistence of biologic treatments.[27–29] The results of Chen et al's study[27] were used as a source of persistence data for infliximab and adalimumab in the first line of treatment. Helwig et al's studies[28,29] were used as a data source for vedolizumab in the first line of treatment and all biologic treatments in the subsequent lines. Because persistence at year 1 in the base case was based on the 1-year maintenance data from clinical studies, long-term persistence rate was recalculated using real-world studies with 1 year as the starting point. The adjusted persistence was used to calculate treatment discontinuations per cycle.

Outcome After Surgery

Surgery was the last line of therapy included in our analysis. As surgery for UC involves removing the colon, it was assumed that remission was permanent. Considering the extent of the surgery, complications may occur. The probability of complications after surgery was sourced from Lohan et al,[26] and the probability of complications recurrence in the long term was calculated based on Peyrin-Biroulet et al's study.[30] Our analysis assumed that the treatment of surgical complications lasted for 1 cycle (8 weeks), after which patients moved to the "remission after surgery" state. Surgery for CD may temporarily resolve the disease. The probability of disease remission after surgery was the sum of probabilities of moving from "surgery" state to "remission" state and to "postsurgery remission" state from a Markov model using data from a population-based cohort.[36] The probability of disease recurrence per cycle was calculated based on Blackhouse et al.[37]

Safety

Serious infection was considered an adverse event in this study. Probabilities of serious infections in UC were based on the network meta-analysis by Lohan et al.[26] Probabilities of serious infections in CD were based on clinical trial results for each treatment.[7,38,39] It was assumed that the probability of serious infection did not differ between treatment lines and that serious infections resolved within 1 cycle.

Mortality

General mortality was sourced from national life tables from the United Kingdom and France.[43,44] Previous studies found no differences in mortality between patients with UC in the United Kingdom and the general population.[31,32] However, mortalities of patients with CD in both countries and patients with UC in France have been shown to be higher than in the general population.[31–33,40]

In addition to the mortality associated with age and disease type, in UC, surgery state was associated with additional perioperative mortality.[26] In CD, it was assumed that the increased mortality due to surgery was already included in the standardized mortality ratio. Other than the perioperative mortality in patients with UC, no specific health state or treatment type was considered as mortality in patients with UC and CD.

Utility

Health state utilities were based on Tappenden et al[20] for UC and Lindsay et al[41] for CD. Values for the "response", "active disease", and "complications after surgery" health states in UC were calculated based on the respective utility and disutility values. Utility for the "surgery" health state was assumed to be the same as that for "active disease." Disutility due to serious infection was sourced from Worbes-Cerezo et al.[34] Serious infection was the only adverse event included.

Resources and Costs

Pharmacotherapy with biologics cost

Dosing of biologic treatments was based on the Summary of Product Characteristics (SmPC) for each drug.[9,45,46] Treatment dosage was different for the first cycle (induction) and subsequent (maintenance) cycles of treatment. Because administration costs of intravenous formulations account for a high proportion of pharmacotherapy costs, subcutaneous formulations were assumed for all drugs to reduce bias due to differences in administration costs between subcutaneous and intravenous formulations. Notably, although we assessed subcutaneous formulations of infliximab and vedolizumab, according to the SmPC the first 2 injections should be intravenous.[9,46] This was included in the analysis by assuming 2 intravenous injections during the induction phase of infliximab and vedolizumab treatment. The unit drug costs for each treatment were taken from the British National Formulary, data source published by NICE for the United Kingdom,[47] and Base des Médicaments et Informations Tarifaires (BdM IT), data source published by l'Assurance Maladie for France.[48] For drugs with an intravenous formulation such as infliximab and vedolizumab in the induction phase, the administration cost from Soini et al[49] was applied. No administration cost was assumed for subcutaneous drugs such as infliximab and vedolizumab in the maintenance phase and adalimumab.

Standard of care cost

Standard of care treatment was considered for CD only in case of surgery failure or disease recurrence after surgery. Treatments used in the SoC for CD and their dosing were based on data from the vedolizumab submission to NICE.[15] The unit drug costs for each treatment were taken from the British National Formulary for the United Kingdom and BdM IT for France.[47,48] If multiple products were available for the same drug, the lowest price per dose was included in analysis. From the perspective of the public payer, opting for the least expensive product is the expected approach. Moreover, looking at the efficacy data, more patients were expected to stay in the "active disease (SoC)" health state for treatment sequences starting with vedolizumab; thus, this assumption may be considered conservative. No additional administration costs were assumed for SoC.

Health state costs

Health state costs for UC were calculated based on the resource use reported in the study of long-term cost-effectiveness of infliximab.[22] The unit costs of each procedure were derived from the national schedule of National Health Service (NHS) costs for the United Kingdom and previous studies for France.[50–52] Health state costs for CD were calculated based on Bodger et al[53] for the United Kingdom and Jaisson-Hot et al[54] for France.

Bodger et al[53] described a cost-effectiveness analysis of biologic therapy for CD in the United Kingdom; 8-week costs were derived for the "full response", "partial response", and "nonresponse" states. In our analysis, the value for the "remission" health state was based on that for "full response", the cost for "response" was based on that for "partial response", and the cost for "active disease" was based on that for "nonresponse." As costs in Bodger et al[53] were derived for the year 2006/2007, we used inflation data from the Office of National Statistics[55] to adjust the costs to the year 2021. Jaisson-Hot et al[54] presented a lifetime cost-utility analysis for CD in France. Health state costs of 2 months' care were derived and applied to the analysis. In our study, the cost for the "remission" state was based on that for "remission not following surgery", the cost for "response" was based on that

Table 1. Input parameters and data sources used in the Markov model for ulcerative colitis.

Parameters	Value	Data Source
Patients' characteristics		
Age, years	40	Tappenden 2016[20]
Females, %	43	Tappenden 2016[20]
Weight, kg	77	Tappenden 2016[20]
Transition probabilities (per cycle)		
Treatment efficacy		
First-line treatment		
Induction phase		
Remission		
Infliximab	0.3343	Calculation based on Lohan 2019[26]
Adalimumab	0.1823	Calculation based on Lohan 2019[26]
Vedolizumab	0.2654	Calculation based on Lohan 2019[26]
Response		
Infliximab	0.3477	Calculation based on Lohan 2019[26]
Adalimumab	0.3160	Calculation based on Lohan 2019[26]
Vedolizumab	0.3431	Calculation based on Lohan 2019[26]
Maintenance phase		
Remission		
Infliximab	0.3720	Calculation based on Lohan 2019[26]
Adalimumab	0.3201	Calculation based on Lohan 2019[26]
Vedolizumab	0.4961	Calculation based on Lohan 2019[26]
Response		
Infliximab	0.1341	Calculation based on Lohan 2019[26]
Adalimumab	0.1309	Calculation based on Lohan 2019[26]
Vedolizumab	0.1343	Calculation based on Lohan 2019[26]
Subsequent lines		
Induction phase		
Remission		
Infliximab	0.0719	Assumption: to be same as least efficacious drug
Adalimumab	0.0719	Calculation based on Lohan 2019[26]
Vedolizumab	0.0790	Calculation based on Lohan 2019[26]
Response		
Infliximab	0.2556	Assumption: to be same as least efficacious drug
Adalimumab	0.2556	Calculation based on Lohan 2019[26]
Vedolizumab	0.2664	Calculation based on Lohan 2019[26]
Maintenance phase		
Remission		
Infliximab	0.2951	Assumption: to be same as least efficacious drug
Adalimumab	0.2951	Calculation based on Lohan 2019[26]
Vedolizumab	0.4804	Calculation based on Lohan 2019[26]
Response		
Infliximab	0.1279	Assumption: to be same as least efficacious drug
Adalimumab	0.1279	Calculation based on Lohan 2019[26]
Vedolizumab	0.1361	Calculation based on Lohan 2019[26]
Discontinuation of treatment from real-world evidence		
First-line treatment		
Infliximab	0.0396	Calculation based on Chen 2019[27]
Adalimumab	0.0658	Calculation based on Chen 2019[27]
Vedolizumab	0.0387	Calculation based on Helwig 2021[28]
Subsequent lines		
Infliximab	0.0490	Calculation based on Helwig 2020[29]
Adalimumab	0.0446	Calculation based on Helwig 2020[29]

Table 1. Continued

Parameters	Value	Data Source
Vedolizumab	0.0401	Calculation based on Helwig 2020[29]
Outcomes after surgery		
Remission	0.6833	Calculation based on Lohan 2019[26]
Complications	0.3167	Lohan 2019[26]
Probability of complications recurrence	0.0150	Calculation based on Peyrin-Biroulet 2016[30]
Safety		
Serious infection probabilities (per cycle)		
Infliximab	0.0037	Calculation based on Lohan 2019[26]
Adalimumab	0.0093	Calculation based on Lohan 2019[26]
Vedolizumab	0.0019	Calculation based on Lohan 2019[26]
Mortality		
Standardized mortality ratio—UK	1.0000	King 2020,[31] Selinger 2012[32]
Standardized mortality ratio—France	1.1000	Jess 2007[33]
Perioperative mortality	0.0284	Lohan 2019[26]
Utility		
Active disease	0.41	Tappenden 2016[20]
Remission	0.87	Tappenden 2016[20]
Response	0.76	Tappenden 2016[20]
Surgery	0.41	Tappenden 2016[20]
Remission after surgery	0.71	Tappenden 2016[20]
Complications after surgery	0.54	Tappenden 2016[20]
Disutility		
Serious infections	0.07	Worbes-Cerezo 2019[34]

for "drug responsive moderate to severe disease", and the cost for "active disease" was based on that for "drug-refractory moderate to severe disease." Medication costs were excluded from the total cost for each state to avoid overestimating the medication cost.

Surgery cost

The cost of surgery in our analysis was based on the national schedule of NHS costs[50] for the United Kingdom and Lawton et al's study[56] for France. The cost of surgery in the United Kingdom was based on the currency codes FD02A and FD02B for UC and FD02C and FD02D for CD (Supplementary Table 1). The weighted average cost was calculated using the total cost and the number of activities for each currency code. Lawton et al[56] evaluated the annual direct costs of patients with IBD treated with TNFi therapy. The mean annual cost of surgery reported from 7 patients who underwent surgery over a timeframe of 1 year was €4972. The total number of surgeries included in the analysis was 7, which means that each patient underwent 1 surgery in 1 year; thus, the mean annual cost of surgery presented in the paper is assumed to be equal to the mean unit cost of surgery.

Adverse event cost

Serious infections were considered adverse events in the present study. The cost of treating serious infection was based on Lohan et al's study[26] for the United Kingdom and Badia et al's study[57] for France. Lohan et al considered the weighted average cost of treatment of 6 types of infection: sepsis, tuberculosis, pneumonia, skin and soft tissue infection, bone and joint infection, and urinary tract infection.[26] The currency codes used in our analysis were based on Lohan et al's supplementary data, but the activity and the total cost data were sourced from the national schedule of NHS costs (Supplementary Table 2).[50] Badia et al[57] studied the burden of surgical site infection (SSI) in terms of cost and HRQoL. The authors found that in France, the cost per patient was higher by €17,434 in those who developed an SSI than in those who did not.[57]

The resource use and cost are presented in Supplementary Table 3. All costs were adjusted to the year 2021 based on each country's Consumer Price Index.[55,58]

The model parameters and their data sources are presented in Table 1 and Table 2.[7,20,26–41]

Sensitivity Analyses

To accommodate the uncertainty of the model inputs and to test the robustness of the model output, deterministic sensitivity analysis (DSA), probabilistic sensitivity analysis (PSA), and scenario analyses were conducted.

Deterministic sensitivity analysis

The DSA aims to assess the sensitivity of the results of a cost-effectiveness model to predefined changes in input parameters. Here, we conducted a DSA with 1-way sensitivity analysis. The influence of each individual parameter was examined using plausible ranges of values from the literature, with the minimum and maximum values based on 95% confidence intervals wherever available or by varying the estimates by ± 20%. Sensitivity analysis results for each input were ranked from most sensitive to least sensitive and plotted on a tornado diagram. The tornado charts were not produced if the base-case results were dominant.

Table 2. Input Parameters and Data Sources used in the Markov Model for Crohn's Disease.

Parameters	Value	Data Source
Patients' characteristics		
Age, years	36.1	Sandborn 2013[7]
Females, %	53	Sandborn 2013[7]
Weight, kg	69.8	Sandborn 2013[7]
Transition probabilities (per cycle)		
Treatment efficacy		
First-line treatment		
Induction phase		
Remission		
Infliximab	0.5454	Calculations based on Singh 2018[35]
Adalimumab	0.4359	Calculations based on Singh 2018[35]
Vedolizumab	0.3536	Calculations based on Singh 2018[35]
Response		
Infliximab	0.3480	Calculations based on Singh 2018[35]
Adalimumab	0.0291	Calculations based on Singh 2018[35]
Vedolizumab	0.0424	Calculations based on Singh 2018[35]
Maintenance phase		
Remission		
Infliximab	0.4649	Calculations based on Singh 2018[35]
Adalimumab	0.5731	Calculations based on Singh 2018[35]
Vedolizumab	0.4134	Calculations based on Singh 2018[35]
Response		
Infliximab	0.4029	Calculations based on Singh 2018[35]
Adalimumab	0.0470	Calculations based on Singh 2018[35]
Vedolizumab	0.0639	Calculations based on Singh 2018[35]
Subsequent lines		
Induction phase		
Remission		
Infliximab	0.1160	Assumption: to be same as least efficacious drug
Adalimumab	0.2344	Calculations based on Singh 2018[35]
Vedolizumab	0.1160	Calculations based on Singh 2018[35]
Response		
Infliximab	0.2077	Assumption: to be same as least efficacious drug
Adalimumab	0.1591	Calculations based on Singh 2018[35]
Vedolizumab	0.2077	Calculations based on Singh 2018[35]
Maintenance phase		
Remission		
Infliximab	0.1389	Assumption: to be same as least efficacious drug
Adalimumab	0.3367	Calculations based on Singh 2018[35]
Vedolizumab	0.1389	Calculations based on Singh 2018[35]
Response		
Infliximab	0.2519	Assumption: to be same as least efficacious drug
Adalimumab	0.2032	Calculations based on Singh 2018[35]
Vedolizumab	0.2519	Calculations based on Singh 2018[35]
Discontinuation of treatment from real-world evidence		
First-line treatment		
Infliximab	0.0326	Calculation based on Chen 2019[27]
Adalimumab	0.0637	Calculation based on Chen 2019[27]
Vedolizumab	0.0387	Calculation based on Helwig 2021[28]
Subsequent lines		
Infliximab	0.0490	Calculation based on Helwig 2020[29]
Adalimumab	0.0446	Calculation based on Helwig 2020[29]

Table 2. Continued

Parameters	Value	Data Source
Vedolizumab	0.0401	Calculation based on Helwig 2020[29]
Outcomes after surgery		
Remission	0.5268	Silverstein 1999[36]
Probability of active disease after surgery	0.4732	Calculations based on Silverstein 1999[36]
Probability of disease recurrence	0.0350	Blackhouse 2012[37]
Safety		
Serious infection probabilities (per cycle)		
Infliximab	0.0063	Calculations based on Hanauer 2002[38]
Adalimumab	0.0042	Calculations based on Colombel 2007[39]
Vedolizumab	0.0087	Calculations based on Sandborn 2013[7]
Mortality		
Standardized mortality ratio—UK	1.2600	King 2020[31]
Standardized mortality ratio—France	1.3900	Duricova 2010[40]
Perioperative mortality	0.0000	Assumption (included in SMR)
Utility		
Active disease	0.4	Lindsay 2008[41]
Remission	0.83	Lindsay 2008[41]
Response	0.55	Lindsay 2008[41]
Surgery	0.4	Assumption: same as utility for active disease
Remission after surgery	0.67	Lindsay 2008[41]
Active disease (SoC)	0.4	Assumption: same as utility for active disease
Disutility		
Serious infections	0.07	Worbes-Cerezo 2019[34]

Abbreviations: SMR, standardized mortality ratio; SoC, standard of care.

Probabilistic sensitivity analysis

In the PSA, the key parameters were varied according to their statistical distributions and are presented in Supplementary Table 4 for UC and in Supplementary Table 5 for CD. One thousand iterations with different sets of input values were performed and drawn randomly from prespecified statistical distributions (normal distribution for patient characteristics, beta distribution for probabilities and utilities, log-normal distribution for ORs, and gamma distribution for costs). The parameters for each distribution were calculated based on the base-case value and minimum value from the DSA.

Scenario analyses

As the clinical trials used as a source of efficacy data in our analysis had different study designs, we included 2 additional scenarios in the model to reflect the clinical practice (Figure 3).

Scenario 1

1. First to seventh cycle of treatment: Patients were assessed for remission and response based on maintenance treatment data from clinical studies. The values reported after 1 year were recalculated to reflect values per cycle. It was assumed that all patients continued treatment for the first 7 cycles. Patients who did not achieve remission or response after the 7 cycles moved to the next line of treatment.
2. Eighth cycle of treatment and onwards: For patients who maintained remission or response, same persistence data as base case from real-world studies were applied. Patients who did not maintain remission or response moved to the next line of treatment.

Scenario 2

- First cycle of treatment: Patients were assessed for remission and response based on induction treatment data from clinical studies. Patients who did not achieve remission or response moved to the next line of treatment.
- Second cycle of treatment and onwards: For patients who maintained remission or response, persistence data from real-world studies were applied. For scenario 2, no adjustments were deemed necessary, and persistence in the last year was taken directly from the publications. Patients who did not maintain remission or response moved to the next line of treatment.

Results

Base-Case Analysis

The results of the base-case analysis of patients with moderate to severe UC and CD in the United Kingdom and France are summarized in Table 3. Over a 10-year time horizon,

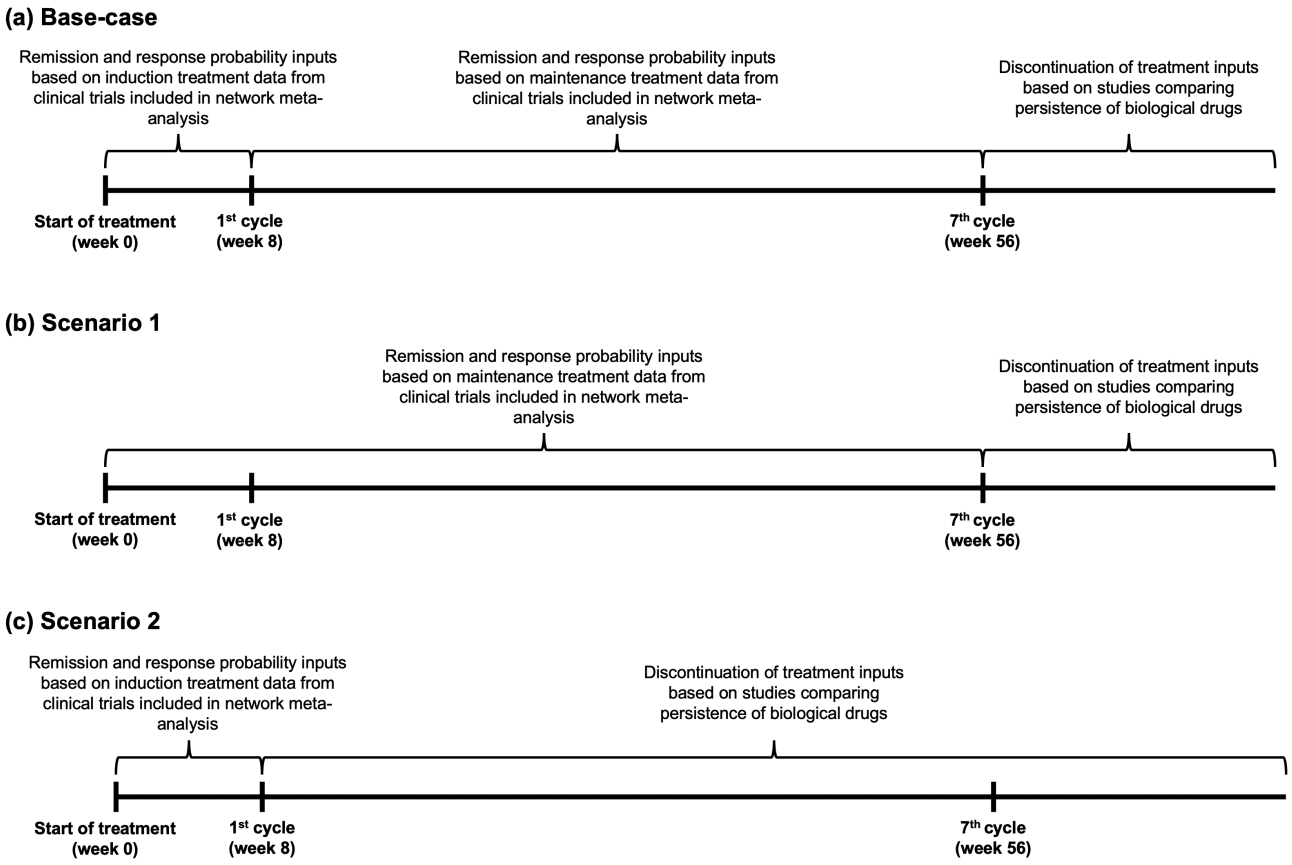

Figure 3. Schematic to illustrate the scenario analysis for (A) base case, (B) scenario 1, and (C) scenario 2.

patients on treatment sequences starting with infliximab were expected to gain more QALYs than patients on treatment sequences starting with vedolizumab in both UC and CD in both countries. The incremental QALY gain associated with sequences starting with infliximab vs sequences starting with vedolizumab ranged from 0.4875 to 0.5522 in patients with CD. The analysis also showed that treatment sequences starting with infliximab were dominant (ie, more effective and less costly) over treatment sequences starting with vedolizumab in both the United Kingdom and France, except for patients with CD in the United Kingdom. In UK patients with CD, treatment sequences starting with infliximab were more costly but also more effective. The incremental cost per QALY gained with the infliximab → vedolizumab → surgery treatment sequence compared with vedolizumab → infliximab → surgery for UK patients with CD was £31,349. The incremental cost per QALY gained with the infliximab → adalimumab → vedolizumab → surgery treatment sequence compared with vedolizumab → infliximab → adalimumab → surgery was £30,464. Assuming a WTP threshold of £30,000 per QALY gained, treatment sequences starting with infliximab were not cost-effective in comparison with treatment sequences starting with vedolizumab in UK patients with CD; however, the ICER was very close to the threshold value.

The incremental gain in life-years in remission with the infliximab → vedolizumab → surgery treatment sequence compared with vedolizumab → infliximab → surgery for patients with UC was 0.0994 (UK) and 0.0998 (France); for patients with CD, it was 1.0719 (UK) and 1.0755 (France). The incremental gain in life-years in remission with the infliximab → adalimumab → vedolizumab → surgery treatment sequence compared with vedolizumab → infliximab → adalimumab → surgery for patients with UC was 0.0843 (for UK) and 0.0847 (France); for patients with CD, it was 0.9527 (UK) and 0.9564 (France).

Sensitivity Analyses

Deterministic sensitivity analyses

In comparisons where treatment sequences starting with infliximab were dominant, treatment sequences starting with infliximab remained dominant in most of the DSAs (Supplementary Tables 6-11). In the DSA for CD in the United Kingdom, where the results of the comparisons were near the £30,000 WTP threshold, results were not heavily impacted by changes to most parameters. The ICER was generally close to the base-case value. Supplementary Figure 1 illustrates the results of 1-way sensitivity analyses in comparisons where the results of base-case analyses were not dominant; the 20 most influential parameters are shown. The results were most sensitive to changes in the utility values and package price of subcutaneous infliximab.

Probabilistic sensitivity analysis

Assuming a WTP threshold of £30,000 per QALY gained in the United Kingdom, infliximab → vedolizumab → surgery was cost-effective in comparison with vedolizumab → infliximab → surgery in 61.0% and 43.3% of simulations for UC and CD, respectively. Infliximab → adalimumab →

Table 3. Results of the base-case analysis of patients with moderate to severe UC and CD in the United Kingdom and France.

Sequence	Ulcerative Colitis					Crohn's Disease				
	Cost	QALY	Incremental Costs*	Incremental QALYs*	ICER	Cost	QALY	Incremental Costs*	Incremental QALYs*	ICER
UK										
Sequence 1: infliximab → vedolizumab → surgery	£59,605.74	6.0266	–£1767.01	0.0241	Dominant	£72,166.04	4.8202	£17,243.49	0.5500	£31,349.42
Sequence 2: vedolizumab → infliximab → surgery	£61,372.74	6.0025	–	–	–	£54,922.55	4.2702	–	–	–
Sequence 3: infliximab → adalimumab → vedolizumab → surgery	£58,367.32	6.0627	–£6580.01	0.0211	Dominant	£77,849.41	4.9715	£14,850.32	0.4875	£30,463.88
Sequence 4: vedolizumab → infliximab → adalimumab → surgery	£64,947.32	6.0416	–	–	–	£62,999.09	4.4841	–	–	–
France										
Sequence 1: infliximab → vedolizumab → surgery	€41,778.44	6.0515	–€3099.32	0.0242	Dominant	€116,980.61	4.8396	–€6181.45	0.5522	Dominant
Sequence 2: vedolizumab → infliximab → surgery	€44,877.76	6.0273	–	–	–	€123,162.06	4.2873	–	–	–
Sequence 3: infliximab → adalimumab → vedolizumab → surgery	€41,778.16	6.0879	–€6922.34	0.0212	Dominant	€118,123.44	4.9916	–€6686.41	0.4896	Dominant
Sequence 4: vedolizumab → infliximab → adalimumab → surgery	€48,700.49	6.0666	–	–	–	€124,809.85	4.5021	–	–	–

*Incremental costs, incremental QALYs of sequence 1 compared with sequence 2, and sequence 3 compared with sequence 4.
Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

vedolizumab → surgery in UK patients was cost-effective in comparison with vedolizumab → infliximab → adalimumab → surgery in 78.2% and 45.2% of simulations for UC and CD, respectively. Assuming a WTP threshold of €50,000 per QALY gained in France, infliximab → vedolizumab → surgery was cost-effective in comparison with vedolizumab → infliximab → surgery in 71.0% and 100.0% of simulations for UC and CD, respectively. Infliximab → adalimumab → vedolizumab → surgery in patients in France was cost-effective in comparison with vedolizumab → infliximab → adalimumab → surgery in 82.4% and 99.9% of simulations for UC and CD, respectively.

Infliximab → vedolizumab → surgery was dominant over vedolizumab → infliximab → surgery in 26.1%, 26.5%, and 96.2% of simulations in UK patients with CD, patients with UC in France, and patients with CD in France, respectively. Infliximab → adalimumab → vedolizumab → surgery dominated over vedolizumab → infliximab → adalimumab → surgery in 36.1%, 41.8%, and 95.6% of simulations in UK patients with CD, patients with UC in France, and patients with CD in France, respectively.

Incremental cost-effectiveness plane and cost-effectiveness acceptability curve are presented in Supplementary Figure 2 and Supplementary Figure 3, respectively.

Scenario analyses

In scenario 1, efficacy inputs were derived from maintenance treatment data for the first 7 cycles and persistency data based on real-world evidence for subsequent cycles. The results of the cost-effectiveness analysis for scenario 1 are presented in Table 4.

For the United Kingdom, the dominant results in UC remained dominant. In CD, the incremental costs of infliximab → vedolizumab → surgery vs vedolizumab → infliximab → surgery decreased, but the ICER increased slightly, likely because the decrease in the ratio of incremental QALYs was larger than the decrease in the ratio of incremental costs. In contrast to the base-case analysis results, the comparison of infliximab → adalimumab → vedolizumab → surgery vs vedolizumab → infliximab → adalimumab → surgery became dominant because the cost of the former sequence has changed from more expensive to less expensive than the cost of the latter sequence.

For France, all the dominant results remained dominant. All the treatment sequences starting with infliximab dominated over treatment sequences starting with vedolizumab.

In scenario 2, efficacy inputs were derived from induction treatment data for the first cycle of treatment and persistency data based on real-world evidence for subsequent cycles. The results of the cost-effectiveness analysis for scenario 2 are presented in Table 4.

For the United Kingdom, dominant results in UC remained dominant. In CD, the incremental costs of treatment sequences starting with infliximab vs treatment sequences starting with vedolizumab decreased; the ICER also decreased. Incremental QALYs forming the denominator of the ICER decreased, but ICER values decreased because the decrease in the ratio of incremental QALYs was smaller than the decrease in the ratio of incremental costs.

For France, all the dominant results remained dominant. All the treatment sequences starting with infliximab dominated over treatment sequences starting with vedolizumab.

Discussion

Effective management of IBD with TNFis is critical because pharmacological treatment options are limited. Results of the cost-effectiveness analysis have shown that treatment sequences starting with infliximab are dominant over treatment sequences starting with vedolizumab for UC in the United Kingdom and for UC and CD in France. In the cost-effectiveness analysis for CD in the United Kingdom, treatment sequences starting with infliximab gave better results in terms of health outcomes but were not cost-effective assuming a WTP threshold of £30,000 per QALY gained. This could be due to low remission rate and low response rate for vedolizumab in the first line of treatment, which resulted in a shorter treatment span and lower costs. Patients who did not achieve a response or remission in the first cycle were assumed to move to the next line of treatment in the base case; consequently, patients starting treatment with vedolizumab underwent surgery earlier. In this model, there were either no treatment costs or minimal costs applied for SoC-treated patients after surgery, which lowered the overall therapy cost. Nevertheless, ICER results were close to the assumed WTP threshold (£31,349 for the comparison of infliximab → vedolizumab → surgery vs vedolizumab → infliximab → surgery; and £30,464 for the comparison of infliximab → adalimumab → vedolizumab → surgery vs vedolizumab → infliximab → adalimumab → surgery).

In France, the difference between the list price and the transaction price is insignificant; although in the United Kingdom, the transaction price according to the NHS framework agreement may reflect significant discounts from the list price. Although transaction price is unknown in the public domain, the price differences between vedolizumab and TNFis are expected to be higher than the differences shown in the list price. Therefore, the cost-effectiveness of treatment sequences starting with infliximab is expected to be greater. Sensitivity analysis results confirmed the conclusions from the base-case analysis in the majority of cases.

The previous economic analysis assessing treatment sequences in UC used a 1-year time horizon, which may be too short to evaluate their cost-effectiveness.[16] Additionally, it was assumed that the efficacy of infliximab in the subsequent lines of treatment was the same as that in the first line.[16] Based on clinical data for other biologic drugs, this assumption is unlikely to be true. In our analysis, we assumed that the efficacy of infliximab in the subsequent lines was the same as that of the least efficacious drug (adalimumab or vedolizumab), which is a more sensible approach. We found 2 previous analyses that assessed treatment sequences with infliximab and vedolizumab in CD.[59,60] However, both studies compared treatment sequences with a different number of treatment lines, making comparisons with the current analysis difficult. It was expected and confirmed by the results of our analysis that treatment sequences with a larger number of treatment lines lead to better health outcomes.

Our analysis has several limitations. There was no head-to-head trial comparing the efficacy of the different treatment options evaluated in the study. Thus, a network meta-analysis of clinical trials and real-world studies were used to estimate efficacy values, which is a commonly used and accepted approach. There were no data for infliximab in the second-line treatment, so assumptions had to be made concerning its efficacy in the subsequent lines.

Table 4. Results of the Cost-Effectiveness Analysis for Scenarios 1 and 2.

Sequence	Ulcerative Colitis					Crohn's Disease				
	Cost	QALY	Incremen-tal Costs*	Incremen-tal QALYs*	ICER	Cost	QALY	Incremental Costs*	Incremen-tal QALYs*	ICER
UK—Scenario 1										
Sequence 1: infliximab → vedolizumab → surgery	£85,552.52	5.8787	–£216.54	0.0361	Dominant	£85,396.21	4.7167	£4148.11	0.1266	£32,764.29
Sequence 2: vedolizumab → infliximab → surgery	£85,769.06	5.8426	–	–	–	£81,248.10	4.5901	–	–	–
Sequence 3: infliximab → adalimumab → vedolizumab → surgery	£96,697.29	5.8071	–£2811.20	0.0079	Dominant	£94,841.15	4.9377	–£461.16	0.1027	Dominant
Sequence 4: vedolizumab → infliximab → adalimumab → surgery	£99,508.49	5.7991	–	–	–	£95,302.31	4.8349	–	–	–
UK—Scenario 2										
Sequence 1: infliximab → vedolizumab → surgery	£60,655.80	5.9446	–£1300.24	0.0345	Dominant	£67,015.14	4.6686	£9778.32	0.3157	£30,972.00
Sequence 2: vedolizumab → infliximab → surgery	£61,956.03	5.9101	–	–	–	£57,236.82	4.3528	–	–	–
Sequence 3: infliximab → adalimumab → vedolizumab → surgery	£67,933.79	5.9662	–£1754.83	0.0333	Dominant	£73,549.97	4.8384	£8438.56	0.2863	£29,471.24
Sequence 4: vedolizumab → infliximab → adalimumab → surgery	£69,688.62	5.9329	–	–	–	£65,111.41	4.5520	–	–	–
France—Scenario 1										
Sequence 1: infliximab → vedolizumab → surgery	€62,001.92	5.9041	–€1245.32	0.0365	Dominant	€130,031.20	4.7364	–€7474.48	0.1272	Dominant
Sequence 2: vedolizumab → infliximab → surgery	€63,247.24	5.8677	–	–	–	€137,505.68	4.6092	–	–	–
Sequence 3: infliximab → adalimumab → vedolizumab → surgery	€72,378.89	5.8325	–€3159.43	0.0083	Dominant	€132,805.70	4.9586	–€10,373.58	0.1031	Dominant
Sequence 4: vedolizumab → infliximab → adalimumab → surgery	€75,538.32	5.8242	–	–	–	€143,179.27	4.8556	–	–	–
France—Scenario 2										
Sequence 1: infliximab → vedolizumab → surgery	€42,357.65	5.9692	–€2684.12	0.0346	Dominant	€119,295.09	4.6870	–€4220.13	0.3169	Dominant
Sequence 2: vedolizumab → infliximab → surgery	€45,041.77	5.9347	–	–	–	€123,515.22	4.3702	–	–	–
Sequence 3: infliximab → adalimumab → vedolizumab → surgery	€48,993.25	5.9910	–€3026.18	0.0334	Dominant	€120,599.01	4.8577	–€4585.73	0.2875	Dominant
Sequence 4: vedolizumab → infliximab → adalimumab → surgery	€52,019.43	5.9576	–	–	–	€125,184.73	4.5702	–	–	–

*Incremental costs, incremental QALYs of sequence 1 compared with sequence 2, and sequence 3 compared with sequence 4.
Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

Although our study did not compare all possible treatment sequences that may result from the 3 pharmacological agents and surgery, the selected sequences were confirmed by clinicians based on the most clinically relevant and meaningful sequences and scenarios. One of the comparisons (infliximab → vedolizumab → surgery vs vedolizumab → adalimumab → surgery) is less common in CD than in UC. In addition, there are frequent cases of infliximab → surgery → adalimumab only in CD. These sequences were not considered by the model.

The cycle length of our model was 8 weeks, and adverse events (serious infections) were assumed to last 8 weeks with a disutility of 0.07 attached. Because it is difficult to estimate the length of serious infections, and only a small number of cases of serious infections may last up to 8 weeks, this may not accurately reflect the level of utility. Applying disutility for a full cycle may underestimate QALY. However, the assumption of no disutility for serious infections only changed the base-case ICER result marginally (0.18% for CD model, domination in UC model).

Surgery and aftercare form a large part of CD treatment cost, and patients may undergo more than 1 surgery to treat the disease.[61] This analysis focused on biologic treatments, so only the impact of biologic treatment on delayed need for surgery was included. Additionally, only the cost of surgery itself was included (the after-procedure costs were not). Because patients treated with infliximab first tend to receive surgery later than patients treated with vedolizumab first, not including the after-procedure costs can be considered a conservative assumption.

Conclusion

Our study suggests that in patients with moderate to severe IBD, treatment sequences starting with infliximab lead to greater improvements in health outcomes than treatment sequences starting with vedolizumab. Comparing the incremental cost per QALY gained, treatment sequences starting with infliximab are the better option for UK patients with UC and for patients with UC and CD in France. In UK patients with CD, the ICER values were close to the assumed WTP threshold. These results reinforce the NICE recommendation of using infliximab earlier than vedolizumab in biologic-naïve patients.

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Conflicts of Interest

Y.B. declares fees from AbbVie, Amgen, Biogaran, Biogen, Boehringer Ingelheim, Celltrion, Ferring, Fresenius Kabi, Gilead, Hospira, Janssen, Lilly, Mayoli Spindler, Merck, MSD, Norgine, Pfizer, Roche, Sandoz, Sanofi, Shire, Takeda, UCB. R.A. declares the following paid or unpaid consultancies, or sources of honoraria payments, which could potentially be viewed as a conflict of interest: AbbVie, Amgen, Arena Pharmaceuticals, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Celltrion Healthcare, Dr Falk Pharma, Ferring, Fresenius Kabi, Galapagos, Gilead, GlaxoSmithKline, InDex Pharmaceuticals, Janssen-Cilag, Kliniksa Pharmaceuticals, MSD Sharp & Dohme, Novartis, Pandion Therapeutics, Pfizer, Roche Pharma, Samsung Bioepsis, Stelic Institute, Sterna Biologicals, Takeda Pharma, Tillotts Pharma AG. V.G. is an employee of Creativ-Ceutical. D.C. is an employee of Celltrion Healthcare United Kingdom Ltd. M.G. reports no conflict of interest. M.Y.J., S.W.Y., T.S.K., and D.B. are employees of Celltrion Healthcare Co., Ltd.

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