Cost-effectiveness analysis of infliximab, adalimumab, golimumab, vedolizumab and tofacitinib for moderate to severe ulcerative colitis in Spain

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ABSTRACT

Objective Despite the biological drugs, the treatment of moderate to severe ulcerative colitis is still a challenge, particularly in resource-limited settings. The aim of this study was to assess the efficiency of biological drugs and tofacitinib for moderate to severe ulcerative colitis in the Spanish context.

Methods A Markov model was built to simulate the progression of moderate to severe ulcerative colitis in a cohort of patients. The model used a time horizon of 10 years. The perspective chosen was the National Health Service, with a discount rate of 3%, and a threshold of €30,000/quality adjusted life-year (QALY). It carried out a one-way sensitivity analysis and probabilistic sensitivity analysis.

Results The comparison of infliximab with adalimumab and golimumab estimated an incremental cost-effectiveness ratio (ICER) of €43,928.07/QALY and €31,340.69/QALY, with a difference of –0.43 and –0.82 QALY, respectively. Vedolizumab vs infliximab achieved an ICER of €122,890.19/QALY with a gain of 0.46 QALY. The comparison of infliximab with tofacitinib yielded an estimated ICER of €270,503.19/QALY, with a slight gain in QALY (0.16). The one-way sensitivity analysis showed a robust study.

Conclusion For a threshold of €30,000/QALY, adalimumab was the most cost-effective treatment versus infliximab for moderate to severe ulcerative colitis in Spain.

WHAT IS KNOWN AND OBJECTIVE

Ulcerative colitis (UC) and Crohn's disease are both regarded as inflammatory bowel diseases. They share remarkable similarities in both pathogenesis and clinical manifestations. UC is a chronic inflammatory disease that affects mucosa of the rectum and colon. It is characterised by alternating flare-ups and remissions. Both aetiology and pathogenesis of UC remain unclear.

Incidence and prevalence of UC is high, and they are increasing worldwide. While UC appears to be decreasing in Europe and North America, in some areas of developing countries in Asia, South America and the Middle East, prevalence is rising.¹

UC is associated with a high morbidity and reduces the quality of life and the productivity of workers. The standard treatments for moderate to severe UC are steroids, thiopurines and biological drugs (infliximab, adalimumab, golimumab and vedolizumab).² Moreover, tofacitinib, a new oral molecule, has recently been labelled. This drug is a JAK1/JAK3 inhibitor.^{3,4} Surgery is considered as the last option

Key messages

What is already known on this subject?

- Moderate to severe ulcerative colitis is a chronic and disabling disease, which has a high impact on health-related quality of life for patients. In addition, this disease generates an elevated burden of disease.
- The duration of clinical trials of these drugs are usually short (1 year) for a lifelong disease.
- Because of limited resources, cost-effectiveness analysis is necessary as a complement to efficacy and safety studies.

What does this study add?

- The results of this work could be transferable to other public-financed systems.
- This study includes biological drugs, a biosimilar of infliximab and the new small oral molecule tofacitinib.
- Cost-effectiveness analysis assesses the efficiency of treatments, and whether they are useful as a tool for formulary placement.

although it is considered the only curative therapy. It can lead to postoperative complications, remaining the abnormal bowel function.

Therapy for moderate to severe UC generates high cost. The effects of the high budget impact influences in contexts with limited resources. Cost-effectiveness analysis (CEA) provide helpful information about the therapeutic management of the disease. Concretely, there are some of these studies which studied the efficiency of different drugs for UC. Previously, we published another article including infliximab, adalimumab, golimumab and vedolizumab in Spain.⁵ In this case, we added to the study tofacitinib to position the different available drugs according to their efficiency.

In Spain and some countries of Europe all of these treatments are dispensed at the hospital pharmacy. Because of that, clinical pharmacists play an important role in the management of these drugs, the right route of administration, the adherence and minimising the risk of adverse events, trying to provide the best treatment alternative for the greatest number of patients.

METHODS

Cost-effectiveness analysis: Markov model design and perspective analysis

A seven-health state-transitions Markov model was constructed for each therapeutic alternative. The

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model was developed from the Spanish National Healthcare System perspective. A time horizon of 10 years was chosen to balance the short-term evidence from the CT, and the late term events. A threshold limit of €30,000/quality-adjusted life year (QALY) was adopted according to the literature's recommendations.⁶ A discount rate of 3% was applied to costs and outcomes.

Treatment strategies and effectiveness

We evaluated the biological treatments and tofacitinib on moderate to severe UC. The dose and frequency of administration used for the different drugs were based on their pivotal trials and summary of product characteristics (SmPC)^{7–17} (see online supplementary table S1).

The drugs' efficacy data were provided by a fixed-model network meta-analysis.¹⁸ Efficacy outcomes were clinical remission, clinical response and mucosal healing for induction therapy, and clinical remission, mucosal healing and sustained clinical remission for maintenance therapy. Fourteen studies were included in this work and tofacitinib and other drugs in the investigational phase such as ozanimod and etrolizumab were added. In the CEA, all treatments were compared with infliximab biosimilar as a reference.

Costs' estimation

Drug acquisition costs were estimated based on the posology described in CT and the SmPC. Estimate of the drug acquisition cost was obtained from Spanish National Healthcare System prices, without discount or other agreements. Direct costs of treatment bearing on the administration, the monitoring, the adverse effects and the follow-up time were included. These costs were obtained from the Spanish region of Aragón Healthcare System's analytical accounting.¹⁹ These costs were updated according to the gross domestic product values. Costs associated with the different states, healthcare resource consumption, surgery and its complications were considered. Table 1 details the cost estimations. All costs were calculated in euros (€) and were updated to 2018.

Quality of life

The utility values were obtained from the literature.^{20–22} Their figures were elicited by applying the standardised questionnaire *EuroQol-5D*²² and by the *Time-Trade-Off*²¹ method. Disutilities due to serious adverse events were calculated by relative risk (RR), using infliximab as reference. See table 2.

Markov model

A Markov-based decision model was developed to analyse the efficiency and long-term impact of the different treatment options (figure 1). The Markov model was constructed using TreeAge Pro Suite 2014 (Tree-Age Software, Inc., Boston, MA, USA). We calculated the incremental cost-effectiveness ratio (ICER) of each therapy. The equation for the ICER is as follows:

$$ICER = \frac{(Costs_{study\ drug} - Costs_{comparator\ drug})}{(QALY_{study\ drug} - QALY_{comparator\ drug})}$$

The Markov model over 10 years with cycle times of 8 weeks was computed. A mid-cycle correction was carried out. It was assumed a cohort of patients with active disease (Mayo score ≥ 6) at the time of entry into the model. After starting the treatment, the patients could move to the remission or the response state, depending on their response and remission rates. From week 56, the probability of permanence in those states were calculated from their sustained remission or sustained response rates.

The patients remained in the active colitis state if they did not come to either the remission or the response states. Likewise, the patients came back to the active colitis state if the treatment lost its efficacy. In this case, they could stay in the active colitis state or go through the surgery state. The surgery rates were obtained from the literature.²³ Patients who opted for surgery could either reach remission, or experience post-surgical complications, or die. Mortality rate was considered similar to that of the general population.²⁴ The transition rates are shown in (online supplementary table S2).

Sensitivity analysis

A one-way sensitivity analysis (SA) was done to evaluate the influence of single variables in the ICER. The selected variables were age at disease onset,¹¹ weight,¹¹ discount rate, drugs acquisition costs, utility values and the maintenance of clinical response and remission RR. They were modified by $\pm 20\%$. We also considered the impact of a commercial discount of tofacitinib, because it is the most recently authorised molecule for moderate to severe UC. A probabilistic sensitivity analysis (PSA) of 1000 iterations of Monte Carlo simulations was carried out. The selected distributions are noted in the (online supplementary table S2). The results of the PSA were plotted in the incremental cost-effectiveness plane and cost-effectiveness acceptability curve.

RESULTS

Cost-effectiveness analysis: base-case analysis

The results of the Markov simulation for the different scenarios are shown in table 3. In the base-case scenario, infliximab was associated with 6.28 QALYs and €91 604. Among the therapeutic options, adalimumab was the most cost-effective treatment compared with infliximab for the threshold of €30,000/QALY.

Sensitivity analyses

One-way sensitivity analysis

The onset of disease did not influence the ICER. For the defined threshold, adalimumab was cost-effective for those patients whose weight was higher than 76.6 Kg. The efficiency of golimumab depended on the weight and the dose used. As the discount rate increases, the ICER decreases. In relation to commercial discounts, they would be more than 35,36% to render tofacitinib as a cost-effective treatment. Although adalimumab and golimumab were the alternatives with lower cost, they were less effective than the others. Vedolizumab was not cost-effective, despite the discounts.

The variation in the utility in response and in active disease stages influenced the ICER in a similar way. An increasing value of utility decreased the cost-effectiveness of all alternatives. For utility in the remission state, a higher value produced a decrease in the ICERs. The variation of RR of response and remission had almost no influence on the ICER. For all the drugs, as the value of RR of response and remission increased, the ICER decreased.

Probabilistic sensitivity analysis

With a willingness to pay €30,000/QALY, adalimumab was cost-effective in 64% of the iterations, infliximab in 29.1%, golimumab in 7.1%, vedolizumab in 0.5% and tofacitinib in 0%. See figures 2 and 3.

DISCUSSION

Based on our base-case analysis, adalimumab would be the most efficient alternative for the target population. One point worth

Table 1 Cost estimations

Drug acquisition cost*									
Drug	Commentary	Unit cost (€)	Cost first year (€)†	Cost following years (€)†	Ref				
Adalimumab 40 mg	Cost of one syringe of Humira 40 mg	494.61	14 830	12 860	19				
Golimumab 50 mg	Cost of one syringe of Simponi 50 mg	1074.55	18 267	12 895	19				
Golimumab 100 mg	Cost of one syringe of Simponi 100 mg	2149.11			19				
Infliximab 100 mg	Cost of one phial of Inflectra 100 mg	423.04	11 845	9624	19				
Vedolizumab 300 mg	Cost of one phial of Entyvio 300 mg	3334.29	26 674	21 673	19				
Tofacitinib 5 mg	Cost of one table Xeljanz 5 mg	14.16	20 680	20 680	19				
Follow-up costs (units/ 8 weeks' cycle)‡									
Health state	Biochemical profile	Day hospital	Endoscopy	Emergency endoscopy	Specialist	Surgery costs	Surgery complication	Ref	
Active colitis	1	0.05	0.31	0.12	1	0	0	19	
Induction	1	0	1	0	2	0	0	19	
Remission	0.5	0.05	0.03	0	0.31	0	0	19	
Response	0.6	0.05	0.08	0.04	0.69	0	0	19	
Surgery	0	0	0	0	0	1	0	2021	
Surgery complication	0.5	0.02	0.1	0.1	0.27	0	1	2021	
Surgery remission	0.23	0	0.19	0.08	0.23	0	0	2021	
Follow-up costs values (unit costs obtained from the Aragon Public Hospitals accounting system 2018)									
PSA distribution §									
Biochemical profile	Baseline value mean (SD)	Ref							
	125.81 (1)	GAMMA ($\alpha=15$ 8280.16; $\lambda=125.81$)							
Day hospital	112.83 (1)	GAMMA ($\alpha=12$ 7300.61; $\lambda=112.83$)							
Endoscopy	307.08 (1)	GAMMA ($\alpha=94$ 2980.13; $\lambda=307.08$)							
Emergency endoscopy	307.08 (1)	GAMMA ($\alpha=94$ 2980.13; $\lambda=307.08$)							
Hospitalisation	6508 (7.02)	GAMMA ($\alpha=0.86$; $\lambda=1.32e^{04}$)							
Specialist	49.95 (1)	GAMMA ($\alpha=24940.50$; $\lambda=49.95$)							
Surgery	10 290 (6543)	GAMMA ($\alpha=2.47$; $\lambda=2.40e^{06}$)							
Surgery complication	7968.53 (11.83)	GAMMA ($\alpha=0.45$; $\lambda=5.69e^{06}$)							
Adverse events, costs 2018¶									
PSA distribution §									
Adverse events, costs 2018¶	Baseline value mean (SD)	Ref							
Appendicitis	3923.64 (2,539.08)	GAMMA ($\alpha=2.39$; $\lambda=6.09e^{04}$)							
Gastroenteritis	2596.2 (2,264.76)	GAMMA ($\alpha=1.31$; $\lambda=5.06e^{04}$)							
Infusion reaction	3316.68 (4,331.88)	GAMMA ($\alpha=0.59$; $\lambda=1.77e^{04}$)							
Pancreatitis	3335 (2,375)	GAMMA ($\alpha=1.97$; $\lambda=5.91e^{04}$)							
Sinusitis	2334.96 (2,289)	GAMMA ($\alpha=1.04$; $\lambda=4.45e^{04}$)							
Serious infection	4218 (5,570)	GAMMA ($\alpha=0.57$; $\lambda=1.36e^{04}$)							

*Regimen treatments are shown in table 1.

†It is considered the weight of 76.2 Kg.

‡Units of resources consumed in one cycle, length of 8 weeks.

\$PSA distribution parameters used in the model.

††Severe and serious adverse events were included depending on their frequency of appearance based on their SnPC.

PSA, Probabilistic sensitivity analysis; Ref, Reference.

Table 2 Utilities and disutilities

	Basal	Minimum	Maximum	Distribution	Ref
Utilities					
Active disease	0.41	0.33	0.5	—	21
Response	0.76	0.61	0.91	—	21
Remission	0.87	0.70	1	—	21
Surgery	0.68	—	—	BETA ($\alpha=83.77$; $\beta=39.42$)	20 35
Surgery complication	0.49	—	—	BETA ($\alpha=56.91$; $\beta=59.23$)	20 35
Surgery remission	0.68	—	—	BETA ($\alpha=83.77$; $\beta=39.42$)	20 35
Disutilities for adverse events					
		Mean (SD)		Ref	
Infliximab		−0.1		18	
RR golimumab vs infliximab		1.23 (1.54)		18	
RR adalimumab vs infliximab		1.35 (1.33)		18	
RR vedolizumab vs infliximab		1.46 (1.61)		18	
RR tofacitinib vs infliximab		0.96 (1.57)		18	

Ref, Reference; RR, Relative risk; SD, Standard deviation

noting here is the place of adalimumab and golimumab in the cost-effectiveness plane. Both drugs are located near the cost-effectiveness acceptability frontier, in the south-west region of the cost-effectiveness plane. This means that they are less effective but with lower global costs. This situation creates a dilemma: should cost be saved by using a less effective drug or should the more effective but costlier drug be used? In these cases, based on net monetary benefit, whose value for both of them is greater than zero, they would be considered as a cost-effective drug for the selected threshold.

In our previous work,⁵ adalimumab and golimumab were placed in the same region of the cost-effectiveness plane. As a difference, this time we included tofacitinib and a biosimilar of infliximab. Tofacitinib and golimumab resulted as dominated therapeutic options. The inclusion of infliximab biosimilar resulted in the extended dominance of adalimumab and infliximab vs golimumab formed by the efficiency frontier.

Drug acquisition costs is one of the variables which influences the most. In Europe, all of these kind of drugs are approved for all the countries, and in every case it is decided if they will be commercialised. Prices are different among European countries and because of that, big differences in the prices of the same drug could make a cost-effective drug from the same defined threshold.²⁵ Tofacitinib, despite being not cost-effective for a willingness to pay €30000/QALY, has some advantages. It has a

different mechanism of action from other therapeutics options, and it is for oral intake, which could be preferable for some patients.

A lesser drug acquisition cost of adalimumab or golimumab resulted in a lower ICER. Although this should be considered with caution, because adalimumab and golimumab, although lower cost, were less effective than the other alternatives. In a simulated scenario in which the biosimilar of adalimumab is introduced, the efficiency of adalimumab, which resulted as the most cost-effective drug, would be higher.

Age-related UC onset has negligible influence in ICER. This may be because we did not consider the indirect costs of loss of labour productivity.

The variation of RR on remission had almost no influence because the utility of response and remission were considered to have the same value, and the variable of response was included in the remission one.

In the past 3 years, another two CEA for moderate-to-severe UC were published. In both of them, vedolizumab was the most cost-effective of the compared therapeutic options in a lifetime horizon. One of them was carried out for the UK,²⁶ but their results are not comparable to ours, because the cost for the biological drugs were calculated for a shorter period of 3 years. Wu et al²⁷ studied treatment for China and the UK population. We examined the results for the UK because of the similarity

Figure 1 Markov model.

Table 3 Results of cost-effectiveness analysis

	Cost (€)	QALY	Incremental cost (€)	Incremental efficacy (QALY)	ICER (€/QALY)
Infliximab	91 604	6.28	0	0	0
Adalimumab	72 671	5.85	−18,933	−0.43	43 928.07
Golimumab	66 030	5.46	−25,574	−0.82	31 340.69
Vedolizumab	147 642	6.74	56 038	0.46	122 890.35
Tofacitinib	134 073	6.44	42 469	0.16	270 503.19

.ICER, Incremental cost-effectiveness ratio; QALY, Quality of life-adjusted years.

with our population. This study neither is comparable to ours, because they analysed sequences of different treatments. In our study, the time horizon was 10 years, because available data of efficacy was proven in a small sample size and making a long-term extrapolation on that small data reduced the reliability of the result. The cost of vedolizumab and tofacitinib, which are the drugs with the higher cost, had a high impact on the ICER in both the study of Wu et al²⁷ and ours. In contrast, the CEA of Wilson et al²⁶ did not consider this parameter in the SA.

The chronic and progressive course of the disease has been shown to increase disability, and cause a loss of patients' HRQL and the ability to work.²⁸ Apart from loss of HRQL, this produces both direct and indirect costs for the health systems and employees, which increase with the severity of the disease.²⁹ There are some publications which estimate the loss of HRQL and the economic impact.^{30–33} However, these data could be changed because the use of biological drugs in this stage of the disease implied a reduction in hospitalisations and surgical treatments,³³ which suggests a decrease in the associated costs of complications from hospitalisation and surgery. Additionally, the use of these treatments in moderate to severe UC can be proved to potentially bring improvement in the HRQL of these patients in the short term.³⁴

This study has several limitations. In the absence of direct comparisons, the data was provided from a fixed-model network meta-analysis.¹⁸ This analysis was for the anti-TNF naïve population. There are many patients who fail first-line therapy. Because of that, it would be very interesting to boast data in the second and/or third line of treatment, and to assess the efficiency of the drugs in those scenarios. However, feasible data for pre-treated patients are currently limited (infliximab and golimumab trials included just naïve patients). This study excluded indirect costs which are thought to be an impact on budgets. Short temporal discontinuation of treatment or intensification had been ignored in this study. This is usual practice in the management of these drugs that is not based on robust evidence.

This CEA, which includes the last molecules for the treatment of moderate to severe UC, such as tofacitinib and vedolizumab, could be useful for the positioning of the different drugs for this pathology, depending on their efficiency. It also could serve as a decision-making tool for the selection of treatments. However, every treatment should be individualised for each patient, considering the safest and the most efficient treatment in each case, based on the best evidence and according to patients' preferences.

WHAT IS NEW AND CONCLUSION

For a willingness to pay €30,000/QALY, neither of the drugs is cost-effective. Adalimumab and golimumab are the most efficient drugs, although their efficacy is lower than that obtained for the remaining therapeutic options.

A box of commercialised tofacitinib should have a price of €532.81 to be cost-effective for that willingness to pay in Spain. All of these drugs for the CU are authorised in Europe through the centralised procedure, but the acquisition cost of each medicine depends on the decision-makers of every country. It also depends on the differences in healthcare systems and reimbursement policies between countries.

Figure 2 Cost-effectiveness analysis

CE Acceptability Curve

Figure 3 Cost-effectiveness acceptability curve.

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