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Tofacitinib for the treatment of moderately to severely active ulcerative colitis: a systematic review, network meta-analysis and economic evaluation

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ABSTRACT

Background and aims In the UK, treatments for patients with moderately to severely active ulcerative colitis who have an inadequate response to conventional therapies comprise four biological therapies—the tumour necrosis factor inhibitor (TNFi) agents adalimumab, golimumab and infliximab and the anti-integrin vedolizumab—and an orally administered small molecule therapy, tofacitinib. However, there have been few head-to-head studies of these therapies. This study aimed to compare the clinical and cost-effectiveness of tofacitinib with biological therapies.

Methods A systematic literature review was conducted to identify all relevant randomised controlled trial (RCT) evidence. Clinical response, clinical remission and serious infection rates were synthesised using network meta-analysis (NMA). The results were used to compare the cost-effectiveness of tofacitinib and biologics with conventional therapy, using a Markov model, which incorporated lifetime costs and consequences of treatment from a UK National Health Service perspective. Analyses were conducted separately for TNFi-naïve and TNFi-exposed populations.

Results Seventeen RCTs were used in the NMAs. There were no statistically significant differences among biological therapies and tofacitinib for either TNFi-naïve or TNFi-exposed patients. In TNFi-naïve patients, all therapies were more efficacious than placebo. In TNFi-exposed patients, only tofacitinib was significantly more efficacious than placebo as induction therapy, and only tofacitinib and vedolizumab were significantly more efficacious than placebo as maintenance therapies. There were no significant differences in serious infection rates among therapies. The incremental cost-effectiveness ratios for tofacitinib versus conventional therapy were £21 338 and £22 816 per quality-adjusted life year (QALY) in the TNFi-naïve and TNFi-exposed populations, respectively. TNFi therapies were dominated or extendedly dominated in both populations. Compared with vedolizumab, tofacitinib was associated with a similar number of QALYs, at a lower cost.

Conclusion Tofacitinib is an efficacious treatment for moderately to severely active ulcerative colitis and is likely to be a cost-effective use of NHS resources.

Summary

What is already known about this subject?

- In the UK, there are currently five treatment options for patients with ulcerative colitis who have an inadequate response to conventional therapies: the parenteral biological therapies adalimumab, golimumab, infliximab and vedolizumab and an orally administered small molecule therapy, tofacitinib. To date, there has been no direct comparison of tofacitinib and any biological therapy for ulcerative colitis, and there are few head-to-head studies among the biological therapies.

What are the new findings?

- A network meta-analysis based on a comprehensive systematic literature review found that there were no statistically significant differences among biological therapies and tofacitinib, either for patients naïve to tumour necrosis factor inhibitor (TNFi) therapy or for TNFi-exposed patients. However, in the TNFi-exposed group, only tofacitinib was associated with statistically significantly greater efficacy than placebo as an induction therapy, and only tofacitinib and vedolizumab were significantly more efficacious than placebo as maintenance therapies. There were no statistically significant differences in the incidence of serious infections among therapies.
- Cost-effectiveness modelling, from the UK National Health Service perspective, found that, compared with biological therapies, tofacitinib was likely to be the most cost-effective therapy at current National Institute for Health and Care Excellence (NICE) willingness-to-pay threshold of £30 000 per quality-adjusted life year (QALY). Compared with vedolizumab, tofacitinib was associated with a similar number of QALYs, at a lower cost.

INTRODUCTION

Ulcerative colitis is a lifelong inflammatory disorder of the colon characterised by intermittent flares of symptoms (relapses) between variable periods of remission. Ulcerative

Summary

How might it impact on clinical practice in the foreseeable future?

- This analysis provides a comparison of biological therapies and tofacitinib for the treatment of ulcerative colitis, with specific regard to TNFi-naïve and TNFi-exposed subgroups and shows that for both subgroups tofacitinib is likely to be a cost-effective therapy for the treatment of moderately to severely active ulcerative colitis.

colitis may present at any age, but most commonly affects adults in the second-to-fourth decades of life,[1–3] resulting in disability in patients' most economically productive years. The physical symptoms of ulcerative colitis are debilitating,[3 4] and the disease has a high negative impact on patients' quality of life, social and psychological well-being and daily functioning.[5–8]

The primary goals of treatment for ulcerative colitis are to induce remission rapidly, maintain remission once achieved and prevent complications.[3 9] In the UK,[10] treatment options for patients with an inadequate response to conventional therapies comprise four biological therapies—the tumour necrosis factor inhibitor (TNFi) agents adalimumab, golimumab and infliximab[4] and the anti-integrin therapy vedolizumab[11]—and an orally administered small molecule therapy, tofacitinib.[12]

Tofacitinib has a novel mode of action for the treatment of ulcerative colitis: inhibition of the Janus kinase family.[13] Acting intracellularly, tofacitinib can modulate the response of multiple cytokines implicated in the pathogenesis of ulcerative colitis.[12] As a small molecule, tofacitinib is likely to avoid the immunogenicity seen with large proteins such as biological therapies.[14] To date, however, there has been no direct comparison of tofacitinib and any biological therapy for ulcerative colitis. The aim of this study is therefore to compare the clinical and cost-effectiveness of tofacitinib with licensed biological therapies for the treatment of moderately to severely active ulcerative colitis from a UK perspective.

Where data exist from randomised controlled trials (RCTs) with the same comparators, these can be combined using meta-analysis, a statistical procedure that integrates the results of several independent studies.[15] Network meta-analysis (NMA) combines both direct and indirect evidence allowing for the comparison of multiple treatments simultaneously, including those that have not been compared in an RCT.[16] NMAs are typically based on the results of comprehensive systematic literature reviews, to ensure that all relevant RCT evidence is captured. In addition to providing estimates of the comparative efficacy of interventions, NMA results often inform cost-effectiveness analysis, providing a comparable set of efficacy inputs for the comparators of interest.[17]

Cost-effectiveness analysis is a means of comparing interventions in terms of cost per unit of effectiveness.[18] In the UK, effectiveness is usually measured as quality-adjusted life years (QALYs).[18 19] Interventions with a cost per QALY (incremental cost-effectiveness ratio (ICER)) of under £30 000 are generally considered acceptable value for money to the NHS by the National Institute of Health and Care Excellence (NICE) and the Scottish Medicines Consortium.[18 19]

METHODS

Systematic literature review

A systematic literature review was conducted to identify evidence to support the clinical effectiveness and safety of tofacitinib and recommended biologics used to treat moderately to severely active ulcerative colitis. Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) reporting guidelines were followed throughout.[20]

Information sources and search strategy

Searches of Medline, Embase, the Cochrane Library and supplementary sources were initially run on 16 November 2017 as described in online supplementary file and updated on 10 April 2019. Search strings, designed to capture all relevant evidence, combined terms related to ulcerative colitis, specific therapies and RCTs. Search results were screened in a double-blinded manner by two reviewers according to prespecified inclusion/exclusion criteria (see online supplementary file).

Patient population

Adult patients with moderately to severely active ulcerative colitis, with or without prior exposure to TNFi therapies.

Interventions

Eligible studies were limited to RCTs of adalimumab, golimumab, infliximab, tofacitinib, vedolizumab and biosimilars of biologics at European Medicines Agency licensed doses. Different doses and/or dosing regimens were treated as unique comparators.

Comparators

Studies involving any of the above interventions, thiopurines, aminosalicylates, corticosteroids or placebo as comparators were included.

Outcomes

For RCTs to be included in the NMA, they were required to have information for either an induction (6–10 weeks) and/or a maintenance (approximately 1 year) time point for either efficacy outcomes (clinical response and/or clinical remission) or serious infections.

Data extraction and critical appraisal

For studies meeting the above criteria, study design details, patient demographics, treatment details and relevant outcomes were extracted for the overall intention-to-treat (ITT) population and for TNFi-naïve and TNFi-exposed subgroups. The methodological quality of included studies was assessed using the NICE concise critical appraisal checklist (see online supplementary file).[21]

The potential risk of bias was determined by assessing heterogeneity of treatment and outcome characteristics as well as study and patient characteristics.

Network meta-analysis (NMA)

Analysis methods

Study results were combined by means of a Bayesian NMA.[22] Analyses were conducted separately for the TNFi-naïve and TNFi-exposed networks. NMA methods are described in detail in the supplementary file.

All analyses were implemented in WinBUGS (V.1.4),[23 24] using vague, non-informative priors. Clinical response and clinical remission (hereafter response and remission) analyses used a multinomial model with probit link, which treats the outcomes as ordered categorical data with three mutually exclusive categories: no response, response and remission. The serious infection analysis used a binomial model with logit link (ie, the serious infection outcome was binary, either yes or no, for each patient). Results were generated using both fixed and random effects models and compared for goodness of fit to the data.

NMA sensitivity analyses

Sensitivity analyses were performed to test alternatives to the population inclusion criteria and assumptions. First, response and remission rates for tofacitinib were based on centrally read endoscopic subscores from the OCTAVE trials. Second, outcomes were based on the overall ITT populations of the included trials. Third, data were used only for patients with prior TNFi failure, rather than prior TNFi exposure.

Cost-effectiveness analysis

Target population and subgroups

Informed by the results of the NMA, an economic evaluation was conducted to compare the cost-effectiveness of tofacitinib and biologics with conventional therapy. In line with the NMA, and because prior exposure to biologic treatment is likely to be a significant treatment effect modifier, the base-case analysis considered TNFi-naïve and TNFi-exposed populations separately. The hypothetical cohort of patients was 59% male and had a mean age of 41 years and a mean weight of 74 kg.[25]

Model structure and key features

A Markov model, designed in Excel 2016 (Microsoft, Redmond, Washington, USA), was used to compare lifetime costs and consequences of treatment with tofacitinib, biologics and conventional therapy. The analysis took a UK National Health Service (NHS) perspective and measured benefits in terms of QALYs. In accordance with the NICE reference case, future costs and benefits were discounted at 3.5% per annum.[18]

A schematic diagram illustrating the structure of the economic model is shown in figure 1. The model expanded on previous economic evaluations[26] and updated assumptions, where possible, with contemporary UK evidence.

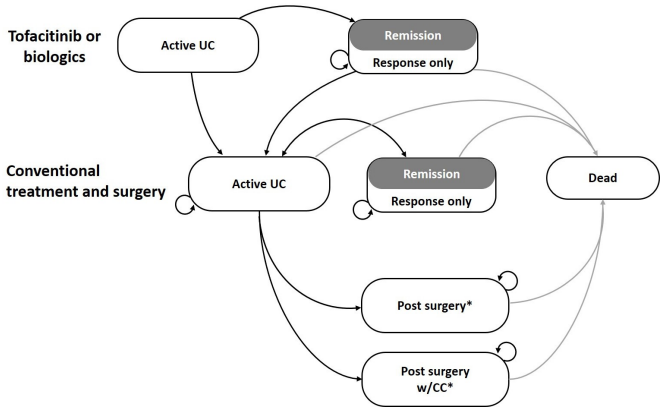

Figure 1 Schematic of cost-effectiveness model. *Patients transition to the postsurgery states following either emergency or elective colectomy. CC, colectomy complications; UC, ulcerative colitis.

Model structure

The model consisted of nine health states defined by type of treatment (biological or tofacitinib; non-biological; surgery) and level of disease control (active ulcerative colitis, response-without-remission and remission). Patients were initially treated with 8 weeks of induction therapy with a TNFi (adalimumab, golimumab or infliximab), vedolizumab or tofacitinib. Patients who responded to treatment were separated into remission and response-without-remission groups, based on outcomes defined in the NMA. Patients experiencing neither response nor remission were still considered to have moderately to severely active ulcerative colitis.

The distribution of patients between no-response, response-without-remission and remission groups at week 8 was based on the NMA results. Non-responders were assumed to remain with active ulcerative colitis and discontinue treatment with their induction therapy, transitioning to receive conventional therapy instead. Patients achieving response or remission in the induction phase entered the maintenance phase of the model and continued to receive the same treatment until loss of response, acute exacerbation event requiring emergency colectomy or death (all-cause mortality was calculated from UK life tables[27]). The maintenance phase NMA results determined the proportion of patients achieving remission or losing response. Those losing response transitioned to conventional therapy. During conventional therapy, patients who did not respond or lost response to conventional therapy were assumed to remain in the active ulcerative colitis state. A proportion of these patients were assumed to be offered elective colectomy. The analysis also considered perioperative and long-term complications from emergency and elective colectomy. For simplification, no additional or alternative treatments were offered; therefore, the remaining non-responders continued to receive conventional therapy. The risk of serious infections in the model was based on the results of the safety NMA.

Health state utility values were taken from a UK study by Woehl *et al*.[28] The HRQoL impact associated with serious

infection was modelled by applying a utility multiplier (0.9858), representing a reduction in the base utility.[29 30] The health state utility values were adjusted over time to control for patient physical and mental functions due to age and comorbidities.[31]

Cost and healthcare resource use inputs included drug acquisition, administration costs and costs associated with adverse events and conventional therapy; all costs were for the year 2016/2017 and are detailed in online supplementary file.

Sensitivity analysis

All model inputs were tested using appropriate deterministic and probabilistic sensitivity analysis. A list of all parameter distributions included in the probabilistic sensitivity analysis is presented in online supplementary file.

In addition, scenario analyses explored the impact of dose escalations in maintenance for tofacitinib and biologics for some patients, using an alternative source for utility weights,[32] or including acute exacerbations from different health states. Furthermore, two scenarios were explored based on the NMA sensitivity analyses using centrally read endoscopic subscores from the tofacitinib trials or ITT data. Finally, the impact of using 5-year and 10-year time horizons was explored.

RESULTS

Literature search results

PRISMA flow diagrams of the number of studies included and excluded at each stage are presented in figure 2. In total, 22 RCTs were included in the review, of which 17 RCTs, described in 14 publications, were used in the NMA (see online supplementary file).[11 25 33–44]

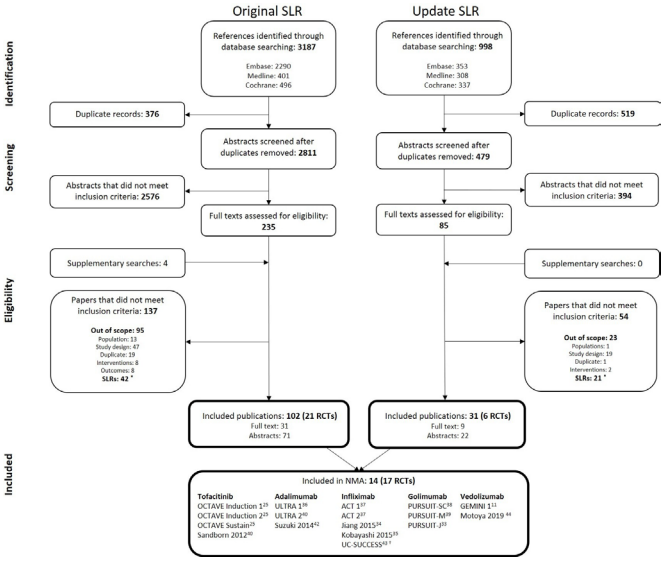

Figure 2 PRISMA flow diagram showing included and excluded studies. *SLRs were used for bibliography checks and then excluded. †UC-SUCCESS compared infliximab with azathioprine. This study was included in the safety NMA but excluded from the efficacy analysis due to differences in outcome definition and time point of evaluation. NMA, network meta-analysis; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review.

Study characteristics

All studies were conducted in patients with moderately to severely active ulcerative colitis. Seven studies, including the tofacitinib and vedolizumab phase III trials, also included patients who had an inadequate response or intolerance to prior TNFi therapies.[11 25 40 41 44] In 17 of 22 studies, clinical response was defined as a reduction in the Mayo score of ≥3 points and a decrease of ≥30% from the baseline score, with a decrease of ≥1 point on the rectal bleeding subscale or an absolute rectal bleeding score of 0 or 1 and clinical remission was defined as a total Mayo score of ≤2 points, with no individual subscore exceeding 1 point. All included RCTs were double-blind, with the exception of Armuzzi 2004.[45] Where stated, all were phase III, except for Suzuki 2014[42] and PURSUIT-SC,[38] which were described as phase II/III and Sandborn 2012,[41] which was a phase II trial. The only patient characteristic that was notably different across the evidence network was prior TNFi exposure. Study design and patient characteristics of studies included in the review are presented in online supplementary file, along with a rationale for its inclusion or exclusion from the NMAs. No RCT evidence was identified for golimumab or infliximab in patients with prior TNFi exposure.

Risk of bias across studies

Across the trials, baseline characteristics between treatment arms were broadly similar. In most of the included studies, approximately half of participants had extensive colitis or pancolitis. Baseline total Mayo scores in induction phase trials were largely consistent. Overall, mean disease duration across the studies was 7.4 years (range, 4.3–10.9 years).

Network meta-analysis (NMA)

Evidence network

Networks of published evidence for the induction phase and maintenance phase NMAs for both TNFi-naïve and TNFi-exposed subgroups are shown in online supplementary file. The TNFi-naïve analysis included all comparators in the systematic review. However, for the TNFi-exposed analysis, evidence was only available for tofacitinib, adalimumab and vedolizumab. All studies were connected to the network through a common direct comparison with placebo. In addition, three studies compared different doses or treatment regimens for tofacitinib (5 mg or 10 mg), vedolizumab (every 8 weeks or every 4 weeks) and golimumab (50 mg or 100 mg).[11 25 39] For the sensitivity analysis using outcomes from the ITT population, only trials of tofacitinib and vedolizumab were deemed sufficiently similar in terms of their case mix of prior TNFi-exposure to synthesise. The evidence network for the analysis of induction phase serious infections was identical to that for efficacy outcomes, with the addition of a link between infliximab and azathioprine (see online supplementary file).[43]

Table 1 Induction and maintenance phase NMA INF 5 mg/kg

		Comparator vs PBO		
		OR, median (95%CrI)		
Analysis	**Comparator**	**Clinical response**	**Clinical remission**	**SUCRA* (%)**
Induction phase	TNFi-naïve subgroup			
	PBO			0.8
	TOF 10 mg BID	**2.66 (1.56 to 4.76)**	**2.99 (1.67 to 5.45)**	62.1
	INF 5 mg/kg	**3.78 (2.46 to 6.1)**	**4.28 (2.73 to 6.91)**	90.7
	ADA 160/80/40 mg†	**1.75 (1.07 to 2.82)**	**1.9 (1.09 to 3.21)**	28.4
	GOL 200/100 mg‡	**2.4 (1.11 to 5.31)**	**2.69 (1.13 to 6)**	53.7
	VED 300 mg§	**2.74 (1.4 to 5.36)**	**3.08 (1.48 to 6.09)**	64.2
	TNFi-exposed subgroup			
	PBO			17.3
	TOF 10 mg BID	**4.28 (1.27 to 18.59)**	**5.61 (1.36 to 24.53)**	92.9
	ADA 160/80/40 mg†	1.43 (0.11 to 13.16)	1.57 (0.05 to 17.65)	42.4
	VED 300 mg§	1.55 (0.27 to 7.24)	1.74 (0.17 to 10.01)	47.4
Maintenance phase	TNFi-naïve subgroup			
	PBO			9.2
	TOF 5 mg BID	4.58 (0.42 to 78.74)	4.71 (0.39 to 65.66)	68.2
	TOF 10 mg BID	6.03 (0.56 to 117.98)	6.14 (0.53 to 94.07)	78.0
	INF 5 mg/kg	2.27 (0.17 to 30.23)	2.34 (0.15 to 27.67)	42.0
	ADA 40 mg Q2W	1.82 (0.32 to 10.32)	1.86 (0.29 to 10.28)	32.5
	GOL 50 mg	2.31 (0.26 to 27.57)	2.38 (0.23 to 25.65)	42.4
	GOL 100 mg	3.07 (0.65 to 23.21)	3.17 (0.63 to 21.72)	55.5
	VED 300 mg Q8W	3.78 (0.63, 23.84)	3.89 (0.61 to 22.29)	62.7
	VED 300 mg Q4W	3.55 (0.35 to 44.46)	3.66 (0.32 to 38.93)	59.4
	TNFi-exposed subgroup			
	PBO			0.8
	TOF 5 mg BID	**4.53 (2.1 to 22.23)**	**4.7 (2.12 to 26.64)**	47.8
	TOF 10 mg BID	**8.66 (3.87 to 65.79)**	**8.98 (3.91 to 80.19)**	87.1
	ADA 40 mg Q2W	2.97 (0.86 to 17.51)	3.07 (0.86 to 20.36)	33.4
	VED 300 mg Q8W	**6.51 (2.45 to 46.58)**	**6.78 (2.49 to 56.15)**	69.6
	VED 300 mg Q4W	**5.74 (1.91 to 41.39)**	**5.97 (1.94 to 49.09)**	61.3

Bold font indicates a significant result, shown by CrIs which exclude the null value.
*SUCRA is a numeric assessment of the overall ranking of treatments. SUCRA values for each treatment range from 0% to 100%. The higher the SUCRA value, the higher the likelihood that a therapy is the most efficacious or one of the most efficacious treatment; however, SUCRA values are not probabilities of a therapy being the most efficacious.
†160 mg at week 0, 80 mg at week 2, 40 mg at weeks 4 and 6.
‡200 mg at week 0, 100 mg at week 2.
§At weeks 0 and 2.
ADA, adalimumab;BID, twice daily; CrI, credible interval; GOL, golimumab; INF, infliximab;NMA, network meta-analysis; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks; SUCRA, surface under cumulative ranking curve; TNFi, tumour necrosis factor inhibitor; TOF, tofacitinib; VED, vedolizumab.

NMA results

Based on model fit (see online supplementary file), random effect models were used for all analyses, with the exception of the TNFi-exposed maintenance NMA, for which the fixed effect model showed a better fit. The results of the induction and maintenance phase NMAs are shown in table 1 as ORs of achieving a treatment effect (response or remission) versus placebo and as surface under cumulative ranking curve values. For patients naïve to TNFi therapy, all treatments had statistically significantly greater efficacy than placebo as induction therapy; none of the maintenance phase results were statistically significant due to wide credible intervals. For TNFi-exposed patients, tofacitinib as an induction therapy was associated with statistically significantly greater efficacy than placebo, and both tofacitinib and vedolizumab were significantly more efficacious than placebo as maintenance therapies. Results of the NMA sensitivity analyses were consistent with the

base case (see online supplementary file). There were no statistically significant differences among therapies in the NMA of serious infections (see online supplementary file).

Cost-effectiveness analysis results

Base-case analysis

Key inputs to the economic evaluation are presented in table 2 and results of the base case analysis are presented in table 3. For TNFi-naïve patients, tofacitinib was predicted to provide an additional 0.544 QALYs compared with conventional treatment, at an additional lifetime cost of £11 615; therefore, the ICER for tofacitinib compared with conventional treatment was £21 338 per QALY. In the incremental cost-effectiveness analysis, tofacitinib dominated infliximab, that is, patients treated with tofacitinib are predicted to gain more QALYs than those receiving infliximab, at a reduced cost to the healthcare system. Adalimumab and golimumab were extendedly dominated, meaning that a mixed strategy of conventional therapy and tofacitinib would provide more QALYs overall, at a lower cost.[46]

In the TNFi-exposed subgroup, the ICER for tofacitinib compared with conventional treatment was £22 816 per QALY. Tofacitinib dominated infliximab, providing more QALYs at a lower cost. As in the TNFi-naïve analysis, adalimumab and golimumab were extendedly dominated.

Following the NMA results, the cost-effectiveness showed near-equivalence in the QALYs between vedolizumab and tofacitinib in both subgroups. Vedolizumab generated higher total costs than tofacitinib: £8730 and £4981 higher over a patient lifetime in the TNFi-naïve and TNFi-exposed populations, respectively.

Sensitivity analyses

Deterministic sensitivity analysis results for tofacitinib versus conventional therapy showed that the model results were robust. In only two cases did the ICER exceed £30 000 per QALY: when the rates of response and remission for tofacitinib were set to their lower 95% credible interval limit from the NMA for induction in TNFi-exposed patients and in maintenance for TNFi-naïve patients (see online supplementary file). Results were also sensitive to the costs associated with conventional therapy and treating serious infections, but the effects on the ICERs had no impact on base-case conclusions. Results similar to the base-case were seen for deterministic sensitivity analyses comparing tofacitinib with biological therapies (not shown). Probabilistic sensitivity analysis showed that tofacitinib was more likely than the biological therapies to be the most cost-effective therapy at a willingness-to-pay threshold of £30 000 per QALY (54% probability in TNFi-naïve patients, 46% in TNFi-exposed patients).

Scenario analysis

Most scenarios tested had little impact on the ICERs for tofacitinib versus conventional therapy (see online supplementary file). Using the ITT population values instead of modelling by TNFi-exposure subgroup showed tofacitinib to dominate vedolizumab and to have an ICER of £20 038 per QALY gained versus conventional therapy. The only analyses that generated ICERs above £30 000 per QALY were the use of alternative health state utility values and a scenario in which 50% of patients were assumed to require a higher dose of maintenance therapy (in both scenarios, tofacitinib still dominated vedolizumab in both the TNFi-naïve and TNFi-exposed populations).

DISCUSSION

This study explored the comparative effectiveness, safety and cost-effectiveness of tofacitinib against conventional treatment and the biological therapies currently available in the NHS for the treatment of ulcerative colitis. A comprehensive review of the literature identified 22 studies, of which 17 presented comparable evidence for5 therapies, including levels of clinical response, clinical remission and serious infections.

The methods for the evidence review and NMA followed international guidelines for best practices.[20 22 47] The selection of studies and outcomes for the efficacy and safety comparisons was part of a systematic process that carefully assessed the bias introduced when combining evidence from different sources. Studies with TNFi-naïve and TNFi-exposed populations were analysed separately to ensure comparability. Furthermore, the reported data of three trials[36 37 42] were adjusted to match those from five studies[11 25 33 39 44] in which patients achieving a response were rerandomised after the induction phase. It was not possible to adjust the studies for differences in placebo response rates, which have been shown to vary over time (Jairath *et al* demonstrated a consistent increase in placebo response and remission rates from 1987 to 2007, with constant rates from 2008 onward).[48] However, it is expected that such an adjustment would likely move the NMA results in favour of tofacitinib.

Most studies shared placebo as the common comparator in the meta-analysis. The relatively sparse networks and the use of a random-effects model lead to wide credible intervals, particularly for the maintenance phase analyses. Overall, sensitivity analysis suggested that the NMA results were robust.

Results of our NMA are similar to those of other recently published NMAs of the same comparators, despite some noteworthy differences in terms of design. Bonovas *et al*[49] and Trigo-Vicente *et al*[50] focused only on TNFi-naïve patients, whereas Singh *et al*[51] evaluated comparative induction phase efficacy in both TNFi-naïve and TNFi-exposed groups separately. All three NMAs used the stricter 'remission' outcome from the OCTAVE trials[25] rather than 'clinical remission', an outcome more comparable to other RCTs. This resulted in biased estimates of effect for tofacitinib, notably leading to it being ranked lower than golimumab as induction therapy.

Table 2 Model parameters

Parameter			Mean value		Source
Clinical outcomes—probabilities			*Clinical response (%)*	*Clinical remission (%)*	
TNFi-naive	Induction	Placebo	36.2	10.5	NMA of RCTs
		Tofacitinib 10 mg BID	60.1	26.0	
		Infliximab 5 mg/kg	68.2	33.5	
		Adalimumab 160/80/40 mg	49.8	18.3	
		Golimumab 200/100 mg	57.6	24.0	
		Vedolizumab 300 mg	60.8	26.5	
	Maintenance	Placebo	31.1	20.2	
		Tofacitinib 5 mg two times a dayBID	67.1	54.1	
		Tofacitinib 10 mg two times a dayBID	72.8	60.6	
		Infliximab 5 mg/kg	50.4	37.1	
		Adalimumab 40 mg Q2W	45.0	32.1	
		Golimumab 50 mg	51.2	37.9	
		Golimumab 100 mg	58.4	45.0	
		Vedolizumab 300 mg Q8W	62.6	49.2	
		Vedolizumab 300 mg Q4W	61.3	47.9	
TNFi-exposed	Induction	Placebo	25.4	4.7	
		Tofacitinib 10 mg two times a dayBID	59.1	21.5	
		Adalimumab 160/80/40 mg*	32.6	7.1	
		Vedolizumab 300 mg	34.4	7.8	
	Maintenance	Placebo	19.8	12.0	
		Tofacitinib 5 mg two times a dayBID	47.7	35.1	
		Tofacitinib 10 mg two times a day	61.4	48.6	
		Adalimumab 40 mg Q2W*	38.6	27.0	
		Vedolizumab 300 mg Q8W	55.1	42.2	
		Vedolizumab 300 mg Q4W	52.4	39.5	
Adverse events			*Probability (%)*	*Cost/utility reduction*	
Serious infection	Serious infection risk				
		Placebo	0.90		NMA of RCTs
		Tofacitinib 10 mg BIDtwo times a day	3.83		
		Infliximab 10 mg/kg	0.37		
		Adalimumab 160/80/40 mg	0.93		
		Golimumab 200/100 mg	0.11		
		Vedolizumab 300 mg†	0.19		
	Cost of serious infection			£2539	NHS reference costs[59]
	Serious infection utility reduction multiplier			0.9858	Diamantopoulos 2014[29]

Continued

Table 2 Continued

Parameter		Mean value		Source
Colectomy	Elective colectomy rate	0.06		Misra 2016[52]
	Emergency colectomy rate	0.02		
	Risk of perioperative mortality	2.84		Archer 2016,[26] Tappenden 2016[60] and RCP audit 2014[61]
	Risk of perioperative elective surgery complications	31.67		RCP audit 2014[61]
	Risk of perioperative emergency surgery complications	34.70		
	Risk of long-term complications	1.46		Ferrante 2008[62]
	Cost of colectomy operation without complications		£6091	NHS reference costs[59]
	Cost of colectomy operation with complications		£7295	NHS reference costs[59]
	Postsurgery complication utility reduction multiplier		0.7889	Kosmas 2015[63]
Health state inputs		*Utility*	*Annual cost*	
Active ulcerative colitis		0.41	£5944	Woehl 2008[28] cited in Archer 2016,[26] Tsai 2008[64] and NHS reference costs[59]
Response-no-remission		0.76	£4350	
Remission		0.87	£1236	
Postcolectomy without long-term complications		0.71	£629	
Postcolectomy with long-term complications		0.56	£10 202	
Drug costs, per 8 week cycle		*Induction*	*Maintenance*	
Conventional therapy		£55	£55	SmPC; MIMS[65]
Tofacitinib 5 mg BID		£2760	£1380	
Tofacitinib 10 mg BID		£2760	£2760	
Adalimumab 160/80/40 mg		£2534	£1267	
Golimumab 200/100/50 mg		£3052	£1526	
Infliximab 10 mg/kg		£4742	£1581	
Vedolizumab 300 mg Q8W		£6150	£2050	
Vedolizumab300 mg Q4W		£6150	£4100	

*In the absence of evidence for golimumab or infliximab in the TNFi-exposed population, a class-effect was assumed and adalimumab values were used.
BID, twice daily; MIMS, Monthly Index of Medical Specialties; NHS, National Health Service; NMA, network meta-analysis; RCP, Royal College of Physicians; RCT, randomised controlled trial; SmPC, summary of product characteristics.

The biggest differences between NMAs relate to the handling of maintenance phase outcomes. Bonovas *et al* performed no indirect comparisons on maintenance phase outcomes, citing differences in study design as a source of bias. Singh *et al* evaluated maintenance phase efficacy, but only by combining outcomes from studies with the same design and disregarding prior TNFi exposure. Trigo-Vicente *et al* synthesised all maintenance phase outcomes for TNFi-naïve patients regardless of differences in design. Across these NMAs, tofacitinib and vedolizumab perform among the best as maintenance therapies, but the relative rank of TNFi therapies differs.

We focused on the outcomes of response and remission because they were needed to inform the cost-effectiveness analysis. Mucosal healing is another important and clinically relevant outcome in ulcerative colitis, which is well reported in the included RCTs. We performed a similar set of NMAs on the proportion of patients achieving mucosal healing and the results were similar to those for response and remission. The rank order of therapies in both TNFi-exposure subgroups in induction and maintenance phases is consistent across the outcomes. These results are available on request.

The presented NMA estimates were used in a cost-effectiveness analysis. The structure of the cost-effectiveness model expanded on previous economic evaluations[26] and updated the assumptions, where possible, with contemporary evidence. In addition to the new data on clinical efficacy, this analysis also considered serious infections. For colectomy, evidence from a large, UK, retrospective population-based study was used.[52] Regarding the health state utilities, a further strength of the economic analysis is the use of an age-dependent and gender-dependent adjustment, reflecting the natural decline of patients'

Table 3 Base-case lifetime cost-effectiveness analysis

	Total		Incremental vs conventional therapy			Fully incremental		
Strategy	**QALYs**	**Costs (£)**	**QALYs**	**Costs (£)**	**ICER**	**QALYs**	**Costs (£)**	**ICER**
TNFi-naïve subgroup								
Conventional	8.991	£132 349	N/A	N/A	N/A	N/A	N/A	–
Adalimumab	9.191	£138 534	0.200	£6185	£30 982			Extendedly dominated
Golimumab	9.286	£141 360	0.294	£9012	£30 602			Extendedly dominated
Infliximab	9.346	£145 660	0.355	£13 311	£37 495			Dominated
Vedolizumab	9.462	£152 694	0.471	£20 345	£43 205			Dominated
Tofacitinib	9.536	£143 963	0.544	£11 615	£21 388	0.544	£11 615	£21 338
TNFi-exposed subgroup								
Conventional	8.903	£132 712	N/A	N/A	N/A	N/A	N/A	–
Adalimumab	9.051	£137 035	0.148	£4324	£29 284			Extendedly dominated
Infliximab	9.051	£140 661	0.148*	£7949	£53 831			Dominated
Golimumab	9.051	£138 088	0.148*	£5376	£36 403			Extendedly dominated
Vedolizumab	9.146	£145 380	0.242	£12 668	£52 275			Dominated
Tofacitinib	9.240	£140 399	0.337	£7687	£22 816	0.337	£7132	£22 816
Scenario analysis: Overall ITT population†								
Conventional	8.948	£132 508	N/A	N/A	N/A	N/A	N/A	–
Vedolizumab	9.301	£147 822	0.352	£15 314	£43 485			Dominated
Tofacitinib	9.397	£141 500	0.449	£8991	£20 038	0.449	£8991	£20 038

*In the absence of evidence for golimumab or infliximab in the TNFi-exposed population, a class-effect was assumed and adalimumab values were used.
†NMA results are presented in the supplement.
ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; NA, not applicable; QALY, quality-adjusted life year; TNFi, tumour necrosis factor inhibitor; TOF, tofacitinib.

physical and mental functions due to age and other comorbidities.[31]

The QALYs generated in our cost-effectiveness model (9–10 QALYs across all comparators) were comparable to but lower than those in Archer *et al.* (11 QALYs).[26] Conversely, the total costs were higher (£130 000 to £155 000) than in Archer *et al.* (£75 000 to £100 000).[26] The difference in QALYs is attributed to the age-adjustment and gender-adjustment of the utility values used in this study. The difference in costs is caused by the higher resource use frequency, in particular hospitalisation, while in the active ulcerative colitis health state.

The conceptualisation and programming of the economic model followed international standards for best-practice research methods.[47 53 54] The assumptions on the model structure, clinical evidence, utility, resource use and cost inputs were reviewed by UK clinicians and independent health economists. The authors have made the working version of the model available to the journal for further scrutiny.

The cost-effectiveness model showed an overall improvement in QALYs for patients on tofacitinib or biological therapy against conventional treatment. When synthesised with relevant costs of treatment, downstream complications and colectomy, the analysis showed a cost-effectiveness of £20 000 to £25 000 per QALY for tofacitinib versus conventional therapy in both TNFi-naïve and TNFi-exposed populations. In the comparison with the biological therapy strategies, the combination of higher QALYs, lower health state costs, lower treatment acquisition and administration costs led to tofacitinib dominating or extendedly dominating its comparators.

One limitation of the economic model was the definition of transition probabilities between response, remission and active disease. Because of the way trial data were often reported, it was not always possible to derive transition probabilities for maintaining response or remission, conditional on the induction response levels. To resolve this, a direct association between the maintenance phase response levels (1 year data) and the treatment duration in the model was assumed. This approach introduced a strong correlation between maintenance phase response and discontinuation but had the advantage of directly translating the trial evidence to the economic model structure and avoided further assumptions and data manipulation from model calibration techniques. Internal and external validation of the predicted patient proportions with response and remission suggested that the model accurately reflected the NMA results and was within the range of clinical experts' expectations for treatment persistence in clinical practice. Nevertheless, it is noted that further research is required to identify the reasons for treatment discontinuation and in parallel to accurately derive estimates of long-term drug persistence rates.

Moreover, due to lack of data, other inputs of the model required assumptions to complete the analysis: the mix of drugs in conventional treatment, used alone or concomitantly with biologics or tofacitinib; the cost of complications and the type of events caused by serious infections. Several scenario analyses and one-way sensitivity analyses were conducted to test the importance of those assumptions, and they were not found to be major drivers of the cost-effectiveness results.

Notwithstanding its limitations, the results of this study are relevant and applicable to clinical practice in England and Wales. The comparative effectiveness and safety covered all likely treatments. The cost-effectiveness analysis used recent drug list prices for all comparators, including biosimilars where appropriate. The study outcomes were based on Mayo scores, also used to identify treatment response and continuation in clinical practice. Furthermore, most of the evidence for unit costs, resource use as well as the disease utility weights were obtained from UK sources.

Since this research was undertaken, three RCTs have completed. The VISIBLE 1 study compared vedolizumab administered intravenously or subcutaneously with placebo over a 52-week maintenance period.[55] Effects for both administration methods were similar to those observed in the maintenance phase of GEMINI 1.[11] The phase III UNIFI trial compared two dosing regimens of ustekinumab with placebo over a 6 week induction period followed by a 44-week maintenance period.[56 57] Preliminary effect sizes for ustekinumab compared with placebo in the ITT populations are similar to those for tofacitinib and vedolizumab in induction and lower in maintenance. A 52-week head-to-head comparison of vedolizumab and adalimumab is also anticipated but has not yet reported results.[58] Future reviews and NMAs should build on the work presented here by incorporating this new evidence.

CONCLUSION

Tofacitinib is an efficacious treatment for moderately to severely active ulcerative colitis and is likely to be a cost-effective use of NHS resources.

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REFERENCES

1. Molodecky NA, Soon IS, Rabi DM, *et al*. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on Systematic review. *Gastroenterology* 2012;142:e42; quiz e30:46–54.
2. Ng SC, Shi HY, Hamidi N, *et al*. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *Lancet* 2018;390:2769–78.
3. Ungaro R, Mehandru S, Allen PB, *et al*. Ulcerative colitis. *Lancet* 2017;389:1756–70.
4. Danese S, Fiocchi C. Ulcerative colitis. *N Engl J Med* 2011;365:1713–25.
5. Yarlas A, Rubin DT, Panés J, *et al*. Burden of ulcerative colitis on functioning and well-being: a systematic literature review of the SF-36® health survey. *J Crohns Colitis* 2018;12:600–9.
6. Rubin DT, Dubinsky MC, Panaccione R, *et al*. The impact of ulcerative colitis on patients' lives compared to other chronic diseases: a patient survey. *Dig Dis Sci* 2010;55:1044–52.
7. Ghosh S, Mitchell R. Impact of inflammatory bowel disease on quality of life: results of the European Federation of Crohn's and ulcerative colitis Associations (EFCCA) patient survey. *J Crohns Colitis* 2007;1:10–20.
8. Vaizey CJ, Gibson PR, Black CM, *et al*. Disease status, patient quality of life and healthcare resource use for ulcerative colitis in the UK: an observational study. *Frontline Gastroenterol* 2014;5:183–9.
9. Magro F, Gionchetti P, Eliakim R, *et al*. Third European evidence-based consensus on diagnosis and management of ulcerative colitis. Part 1: definitions, diagnosis, extra-intestinal manifestations, pregnancy, cancer surveillance, surgery, and ileo-anal pouch disorders. *J Crohns Colitis* 2017;11:649–70.
10. National Institute for Health and Care Excellence. NICE pathway: inducing remission in people with ulcerative colitis 2018updated 18 January 2018. Available: https://pathways.nice.org.uk/pathways/ulcerative-colitis#path=view%3A/pathways/ulcerative-colitis/inducing-remission-in-people-with-ulcerative-colitis.xml&content=view-index [Accessed 1 Mar 2018].
11. Feagan BG, Rutgeerts P, Sands BE, *et al*. Vedolizumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2013;369:699–710.
12. Danese S, Grisham M, Hodge J, *et al*. JAK inhibition using tofacitinib for inflammatory bowel disease treatment: a hub for multiple inflammatory cytokines. *Am J Physiol Gastrointest Liver Physiol* 2016;310:G155–G162.
13. Hodge JA, Kawabata TT, Krishnaswami S, *et al*. The mechanism of action of tofacitinib - an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis. *Clin Exp Rheumatol* 2016;34:318–28.
14. Boland BS, Sandborn WJ, Chang JT. Update on Janus kinase antagonists in inflammatory bowel disease. *Gastroenterol Clin North Am* 2014;43:603–17.
15. Egger M, Smith GD, Phillips AN. Meta-analysis: principles and procedures. *BMJ* 1997;315:1533–7.
16. Li T, Puhan MA, Vedula SS, *et al*. Network meta-analysis-highly attractive but more methodological research is needed. *BMC Med* 2011;9.
17. Thorlund K, Zafari Z, Druyts E, *et al*. The impact of incorporating Bayesian network meta-analysis in cost-effectiveness analysis - a case study of pharmacotherapies for moderate to severe COPD. *Cost Eff Resour Alloc* 2014;12.
18. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013 London: National Institute for health and care excellence, 2013. Available: https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781 [Accessed 8 Mar 2017].
19. Scottish Medicines Consortium. A guide to quality adjusted life years (QALYs), 2018. Available: https://www.scottishmedicines.org.uk/media/2839/guide-to-qalys.pdf [Accessed 10 Jan 2019].
20. Hutton B, Salanti G, Caldwell DM, *et al*. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med* 2015;162:777–84.
21. National Institute for Health and Care Excellence. Single technology appraisal: User guide for company evidence submission template, 2015. Available: https://www.nice.org.uk/process/pmg24/resources/single-technology-appraisal-user-guide-for-company-evidence-submission-template-pdf-72286715419333 [Accessed 8 Mar 2017].
22. Dias S, Sutton AJ, Ades AE, *et al*. Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. *Med Decis Making* 2013;33:607–17.
23. Stephenson M, Fleetwood K, Yellowlees A. Alternatives to Winbugs for network Meta–Analysis. *Value in Health* 2015;18.
24. MRC Biostatistics Unit. WinBUGS. Available: https://www.mrc-bsu.cam.ac.uk/software/bugs/the-bugs-project-winbugs/ [Accessed 9 Jan 2019].
25. Sandborn WJ, Su C, Sands BE, *et al*. Tofacitinib as induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2017;376:1723–36.
26. Archer R, Tappenden P, Ren S, *et al*. Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy (including a review of TA140 and TA262): clinical effectiveness systematic review and economic model. *Health Technol Assess* 2016;20:1–326.
27. Office for National Statistics. National life tables: England; release September 2017, 2017. Available: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesenglandreferencetables [Accessed 11 Mar 2018].
28. Woehl AH, McEwanP. The relation between disease activity, quality of life and health utility in patients with ulcerative colitis. *Gut* 2008;57(Suppl 1).
29. Diamantopoulos A, Finckh A, Huizinga T, *et al*. Tocilizumab in the treatment of rheumatoid arthritis: a cost-effectiveness analysis in the UK. *Pharmacoeconomics* 2014;32:775–87.
30. Sisk JE, Moskowitz AJ, Whang W, *et al*. Cost-effectiveness of vaccination against pneumococcal bacteremia among elderly people. *JAMA* 1997;278:1333–9.
31. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. *Value Health* 2010;13:509–18.
32. Swinburn P, Elwick H, Bean K, *et al*. The impact of surgery on health related quality of life in ulcerative colitis. *Gut* 2012;61.
33. Hibi T, Imai Y, Senoo A, *et al*. Efficacy and safety of golimumab 52-week maintenance therapy in Japanese patients with moderate to severely active ulcerative colitis: a phase 3, double-blind, randomized, placebo-controlled study-(PURSUIT-J study). *J Gastroenterol* 2017;52:1101–11.
34. Jiang X-L, Cui H-F, Gao J, *et al*. Low-dose infliximab for induction and maintenance treatment in Chinese patients with moderate to severe active ulcerative colitis. *J Clin Gastroenterol* 2015;49:582–8.
35. Kobayashi T, Suzuki Y, Motoya S, *et al*. First Trough level of infliximab at week 2 predicts future outcomes of induction therapy in ulcerative colitis-results from a multicenter prospective randomized controlled trial and its post hoc analysis. *J Gastroenterol* 2016;51:241–51.
36. Reinisch W, Sandborn WJ, Hommes DW, *et al*. Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial. *Gut* 2011;60:780–7.
37. Rutgeerts P, Sandborn WJ, Feagan BG, *et al*. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2005;353:2462–76.
38. Sandborn WJ, Feagan BG, Marano C, *et al*. Subcutaneous golimumab induces clinical response and remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology* 2014;146:quiz e14-5:85–95.
39. Sandborn WJ, Feagan BG, Marano C, *et al*. Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis. *Gastroenterology* 2014;146:96–109.
40. Sandborn WJ, van Assche G, Reinisch W, *et al*. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology* 2012;142:e1-3:257–65.
41. Sandborn WJ, Ghosh S, Panes J, *et al*. Tofacitinib, an oral Janus kinase inhibitor, in active ulcerative colitis. *N Engl J Med* 2012;367:616–24.

42. Suzuki Y, Motoya S, Hanai H, *et al*. Efficacy and safety of adalimumab in Japanese patients with moderately to severely active ulcerative colitis. *J Gastroenterol* 2014;49:283–94.
43. Panaccione R, Ghosh S, Middleton S, *et al*. Combination therapy with infliximab and azathioprine is superior to monotherapy with either agent in ulcerative colitis. *Gastroenterology* 2014;146:392–400.
44. Motoya S, Watanabe K, Ogata H, *et al*. Vedolizumab in Japanese patients with ulcerative colitis: a phase 3, randomized, double-blind, placebo-controlled study. *PLoS One* 2019;14:e0212989.
45. Armuzzi A, De Pascalis B, Lupascu A, *et al*. Infliximab in the treatment of steroid-dependent ulcerative colitis. *Eur Rev Med Pharmacol Sci* 2004;8:231–3.
46. Cantor SB. Cost-effectiveness analysis, extended dominance, and ethics: a quantitative assessment. *Med Decis Making* 1994;14:259–65.
47. Hoaglin DC, Hawkins N, Jansen JP, *et al*. Conducting indirect-treatment-comparison and network-meta-analysis studies: report of the ISPOR Task Force on indirect treatment comparisons good research practices: Part 2. *Value Health* 2011;14:429–37.
48. Jairath V, Zou GY, Parker CE, *et al*. Placebo response and remission rates in randomised trials of induction and maintenance therapy for ulcerative colitis. *Cochrane Database Syst Rev* 2017;9.
49. Bonovas S, Lytras T, Nikolopoulos G, *et al*. Systematic review with network meta-analysis: comparative assessment of tofacitinib and biological therapies for moderate-to-severe ulcerative colitis. *Aliment Pharmacol Ther* 2018;47:454–65.
50. Trigo-Vicente C, Gimeno-Ballester V, García-López S, *et al*. Systematic review and network meta-analysis of treatment for moderate-to-severe ulcerative colitis. *Int J Clin Pharm* 2018;40:1411–9.
51. Singh S, Fumery M, Sandborn WJ, *et al*. Systematic review with network meta-analysis: first- and second-line pharmacotherapy for moderate-severe ulcerative colitis. *Aliment Pharmacol Ther* 2018;47:162–75.
52. Misra R, Askari A, Faiz O, *et al*. Colectomy rates for ulcerative colitis differ between ethnic groups: results from a 15-year nationwide cohort study. *Can J Gastroenterol Hepatol* 2016;2016:1–7.
53. Husereau D, Drummond M, Petrou S, *et al*. Consolidated health economic evaluation reporting standards (cheers) statement. *Int J Technol Assess Health Care* 2013;29:117–22.
54. Roberts M, Russell LB, Paltiel AD, *et al*. Conceptualizing a model: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--2. *Value Health* 2012;15:804–11.
55. Takeda. *Study shows investigational subcutaneous formulation of ENTYVIO® (vedolizumab) achieves and maintains clinical remission and mucosal healing in moderately to severely active ulcerative colitis*, 2018.
56. Janssen. *New phase 3 data show single dose of STELARA® (ustekinumab) induces clinical remission and response in adults with moderate to severe ulcerative colitis*, 2018.
57. Sandborn WJ, Sands BE, Panaccione R, *et al*. OP37 efficacy and safety of ustekinumab as maintenance therapy in ulcerative colitis: week 44 results from UNIFI. *Journal of Crohn's and Colitis* 2019;13(Supplement_1):S025–S026.
58. Takeda. An efficacy and safety study of Vedolizumab intravenous (IV) compared to adalimumab subcutaneous (Sc) in participants with ulcerative colitis, 2018. Available: https://ClinicalTrials.gov/show/NCT02497469 [Accessed 26 Sept].
59. Department of Health. *NHS reference costs*, 2016–17.
60. Tappenden P, Ren S, Archer R, *et al*. A model-based economic evaluation of biologic and Non-Biologic options for the treatment of adults with Moderately-to-Severely active ulcerative colitis after the failure of conventional therapy. *Pharmacoeconomics* 2016;34:1023–38.
61. Royal College of Physicians. National clinical audit of biological therapies - UK inflammatory bowel disease (IBD) audit, 2014. Available: https://data.gov.uk/dataset/uk-inflammatory-bowel-disease-ibd-audit-round-4-2012-2014
62. Ferrante M, Declerck S, De Hertogh G, *et al*. Outcome after proctocolectomy with ileal pouch-anal anastomosis for ulcerative colitis. *Inflamm Bowel Dis* 2008;14:20–8.
63. Kosmas CE, Kerr C, Marsh SE, *et al*. Health related quality of life (Hrqol) in patients who have undergone colectomy for ulcerative colitis: impacts of complications post-surgery. *Value Health* 2015;18.
64. Tsai HH, Punekar YS, Morris J, *et al*. A model of the long-term cost effectiveness of scheduled maintenance treatment with infliximab for moderate-to-severe ulcerative colitis. *Aliment Pharmacol Ther* 2008;28:1230–9.
65. Monthly Index of Medical Specialties. *Monthly index of medical specialties*, 2018.