Northern Treatment Advisory Group

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Biologic drugs for treatment-refractory moderately to severely active ulcerative colitis

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Summary

- Ulcerative colitis (UC) is the most common inflammatory disease of the bowel. There are estimated to be around 240 people per 100,000 with UC in the UK, with around 10 new cases diagnosed per 100,000 population per annum. Studies have suggested that almost 10% of patients with UC experience chronic continuous disease activity.
- Four biologic drugs are licensed for the treatment of ulcerative colitis that does not respond to or cannot be treated with standard therapies: three tumour necrosis factor inhibitors (TNFi), adalimumab, golimumab and infliximab, and; the novel $\alpha 4\,\beta 7$-integrin binding T-helper lymphocyte adhesion inhibitor, vedolizumab.
- A NICE appraisal of adalimumab, golimumab and infliximab for moderate to severely active UC is currently underway. The Appraisal Consultation Document does not recommend TNFi treatment for adults with treatment-refractory moderately to severely active ulcerative colitis. NICE summarised all relevant studies and conducted a network meta-analysis to inform cost effectiveness modelling. For those patients for whom it was an option, colectomy dominated all of the treatments under evaluation and conventional therapy. For patients for whom colectomy is not an option, adalimumab was likely to be the most cost-effective option, but the base-case incremental cost-effectiveness ratio was considerably above the level considered to represent cost-effective use of NHS resources. NICE acknowledged several shortcomings in the evidence base and areas of uncertainty which may be pertinent to local decision making.
- An independent systematic review and meta-analysis combined the key TNFi trials with data from the one published trial of vedolizumab. The results suggested that infliximab may be more effective at inducing clinical response and mucosal healing than adalimumab. None of the other indirect comparisons reached statistical significance. There was no signal to suggest that vedolizumab might have advantages over the TNF inhibitors. No conclusions about relative efficacy of the four biologic therapies for maintenance of response and/or remission could be drawn.
- Safety issues identified in the adalimumab, golimumab and infliximab trials were consistent with those previously identified for TNFi drugs and set out in Summaries of Product Characteristics. In the vedolizumab trial, adverse events were reported to be similar across treatment groups, with no important differences between placebo groups and vedolizumab-treated groups. Other integrin inhibitors have been associated with increased risk of progressive multifocal leukoencephalopathy.
- If 10% of patients with ulcerative colitis experience chronic continuous disease activity, there could be approximately 775 patients in the North East and North Cumbria who might be considered for treatment with biologic drugs. The proportion of those patients who have moderately to severely active disease that cannot be controlled by optimising conventional therapy and the proportion of those whom colectomy might not be a reasonable treatment option is not known. Treating all 775 patients were treated with adalimumab could cost approximately £3.5 million.

Introduction[1]

Ulcerative colitis is the most common inflammatory disease of the bowel. There are estimated to be around 240 people per 100,000 with UC in the UK, with around 10 new cases diagnosed per 100,000 population per annum. Peak incidence occurs between 15 and 25 years of age. UC is a lifelong disease which typically has a relapsing-remitting pattern. Approximately 50% of people with UC will experience a relapse at least once a year. Inflammation, which may be accompanied by ulceration of the mucosa, usually starts in the rectum and can extend to include the whole of the colon (pancolitis). Symptoms of active disease or relapse include abdominal pain, bloody diarrhoea and urgency. Extensive disease and prolonged symptoms can cause fatigue, weight loss and anaemia. A minority of sufferers experience extra-intestinal manifestations, such as arthritis, uveitis and pyoderma gangrenosum. UC can be classified by both extent and severity. Several different UC scoring systems have been developed for use in clinical practice and research. NICE Clinical Guideline 166 Ulcerative colitis: management in adults, children and young people (June 2013) adopted the Trulove and Witts' severity index for adults and the Paediatric Ulcerative Colitis Activity Index (PUCAI) for children and young people. Roughly 80% of adult cases are classed as mild (fewer than 4 bowel movements per day) to moderate (between 4 and 6 bowel movements per day without marked systemic illness). Severe active colitis (more than 6 bowel movements per day plus marked systemic illness) is a potentially life-threatening emergency.

Recommended treatment for UC is summarised in NICE CG 166 (June 2013) and the linked NICE pathway.[1] Aminosalicylates (topical and oral), corticosteroids (topical, oral and intravenous), tacrolimus*, ciclosporin* and infliximab are all options for inducing remission, with specific drugs, routes and doses recommended depending upon the disease characteristics and severity. Aminosalicylates (topical and oral) are the mainstay of maintenance treatment. Azathioprine* or mercaptopurine* are recommended for maintenance following acute severe episodes, when there are frequent exacerbations and when remission is not maintained by aminosalicylates. Methotrexate[1] is not included in NICE CG 166, but may also be considered for maintenance of remission where alternatives are ineffective or unsuitable in clinical practice (although good quality evidence of efficacy is lacking). The effectiveness of drugs used to maintain remission may decline with prolonged use. A proportion of patients develop "steroid-dependent UC" in which disease relapses when corticosteroid doses are reduced.

There is no universally agreed pathway for management of patients with treatment-refractory moderately to severely active UC.[2] Sub-optimal use of currently available treatments and lack of adherence have been identified as important causes of apparently refractory UC.[3] Management focuses on confirming disease activity, exclusion of alternative diagnoses, attention to adherence and appropriate escalation of established therapies.[3] Treatments may be influenced by the severity

[1] None of these drugs (Azathioprine, ciclosporin, mercaptopurine, methotrexate and tacrolimus) are currently licensed for treatment of ulcerative colitis.

of symptoms, the extent and location of inflammation, clinical advice and individual patient choice.

Surgery is considered to be largely curative of the gastrointestinal features of UC and to eliminate the risk of colorectal cancer. Among appropriately selected patients, surgery is associated with sustained improvements in quality of life.[3] Surgery is, however, also associated with considerable risks and potential long-term adverse effects. There are two principal routes to surgery in UC. Surgery may be urgently required in patients with acute severe UC when disease does not respond to intravenous steroids, ciclosporin and/or infliximab, or where life-threatening complications (such as perforation) arise or may be imminent. A larger proportion of patients may opt for surgery due to chronic sub-acute disease or repeated exacerbations despite optimal management. People with UC are at increased risk of colorectal cancer and surgery may also be considered to prevent cancer in patients in whom polyps or dysplasia is detected during endoscopic surveillance and for patients who are at very high risk due to prolonged extensive disease.

The advantages and disadvantages of extended trials of medical therapy in patients not responding well to standard treatments and for whom colorectal surgery is an option are not well established. There are data to suggest that delaying surgery in acute severe UC may increase the risks of complications and reduce the chances of satisfactory outcomes.[4] Those patients who do not respond to additional medical therapy may be at greatest risk of any adverse effects on surgical outcome associated with delay. The effects of delay on surgical outcome among patients who may be candidates for elective surgery have not been directly studied, however.

Four biological drugs are licensed for the treatment of ulcerative colitis, three tumour necrosis factor inhibitors (TNFi), adalimumab, golimumab and infliximab, and the novel $\alpha 4\,\beta 7$-integrin binding T-helper lymphocyte adhesion inhibitor, vedolizumab. Infliximab has been licensed for adults with moderately to severely active UC who have had an inadequate response to or are unable to take conventional therapy (specifically including corticosteroids, 6-mercaptopurine and azathioprine) since 2006. The marketing authorisations for adalimumab and golimumab were extended to include the same patient group in 2012 and 2013. Vedolizumab was approved in the EU in June 2014 for treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNFi.[5]

Infliximab is also licensed for treatment of UC in children and adolescents (>6 years). Three of the agents are also licensed for treatment of Crohn's disease (adalimumab and golimumab for both adults and children $\geq$ 6 years, vedolizumab for adults only).[5]

Both infliximab and vedolizumab are given as intravenous infusions. Adalimumab and golimumab are given as sub-cutaneous injections from pre-filled syringes.

NICE guidance

NICE have published advice on the role of biological agents in UC on three separate occasions. Two further appraisals are in development.

NICE TA 140 (2008) dealt with the use of infliximab for sub-acute UC, defined as disease that would normally be managed in an outpatient setting and that does not require hospitalisation or the consideration of urgent surgical intervention. Infliximab is not recommended for the treatment of sub-acute manifestations of moderately to severely active ulcerative colitis.[6]

NICE TA 163 (2008) recommends an induction course of three infusions of infliximab for the treatment of acute exacerbations of severe active UC **only** when ciclosporin is contraindicated or clinically inappropriate. Maintenance treatment with infliximab is **not** recommended.[7]

NICE Clinical Guideline 166: Ulcerative Colitis (June 2013) explicitly acknowledges that more data are needed to determine the relative advantages and disadvantages of different treatment options for patients with treatment-refractory sub-acute moderately to severely active UC. The guideline poses the following specific research question: "What are the benefits, risks and cost effectiveness of methotrexate, ciclosporin, tacrolimus, adalimumab and infliximab compared with each other and with placebo for induction of remission for people with sub-acute ulcerative colitis that is refractory to systemic corticosteroids?"[1]

NICE ID695 is a multiple technology appraisal of adalimumab, golimumab and infliximab for [sub-acute] moderate to severely active UC currently underway.[2] The scope includes a review of TA 140. The Appraisal Consultation Document does not recommend TNFi treatment for ulcerative colitis in either children with severely active UC or adults with moderately to severely active UC that has responded inadequately to conventional therapy including corticosteroids and mercaptopurine or azathioprine, or who are intolerant to or have medical contraindications for such therapies.[2]

NICE ID691 is a single technology appraisal of vedolizumab for moderate to severely active UC (anticipated publication date: June 2015). The scope of the appraisal is almost identical to ID695.[8]

Findings from NICE ID695: Infliximab, adalimumab and golimumab for the second line treatment of moderately to severely active ulcerative colitis (including review of TA140 and TA262)[2]

The NICE Assessment Group summarised all relevant studies and conducted a network meta-analysis (NMA) to inform cost effectiveness modelling. The Assessment Group analysis synthesised the results of nine randomised controlled trials of licensed doses of TNFi in adults selected from a total of 9,683 citations retrieved from the initial search, plus two open-label follow-up studies. Six of these with appropriate designs and endpoints, plus an additional study for sensitivity analysis, were included in the NMA that informed the cost effectiveness modelling. Additional data provided by manufacturers on transition between no response, response and remission during maintenance trials was also included in the NMA.

Overall, the trials showed that patients treated with adalimumab, golimumab or infliximab were more likely to achieve clinical response and remission at induction and maintenance time points than patients who received placebo. The NMA results confirmed that all treatments were associated with significant beneficial effects relative to placebo during the induction phase. Infliximab was associated with the highest probability of moving from no response to response and no response to remission at this stage. For patients classified as responders after induction, treatment effects during maintenance were not significantly different from placebo. For patients classified as in remission after induction, the results of the NMA analysis of maintenance treatment varied with the interval studied (8-32 weeks or 32-52 weeks). Other than adalimumab at 32-52 weeks, none of the treatment effects during maintenance were significantly different from placebo.

Probabilities derived from the NMA were fed into a cost-effectiveness model. For those patients for whom it was an option, colectomy dominated all of the treatments under evaluation and conventional therapy – i.e. all medical options are expected to produce fewer quality adjusted life years (QALYs) at greater cost over a patient's remaining lifetime than colectomy. For patients for whom colectomy is not an option, the Assessment Group determined that adalimumab was likely to be the most cost-effective of the treatments considered, but the base-case incremental cost-effectiveness ratio (ICER) for adalimumab compared with conventional therapy was over £50,000 per QALY gained. The Appraisal Committee considered and noted several factors, including:

- *Limitations of conventional therapy (including adverse effects, e.g. prolonged use of corticosteroids).*
- *Surgery not being an acceptable option for some patients*
- *Likely preference of many patients for delay in surgery (e.g. to allow completion of studies).*
- *Lack of clear criteria for stopping TNF inhibitor treatment if only a slight response is achieved.*
- *Lack of clinically relevant subgroups for which there is evidence of differential effectiveness.*
- *Lack of specific groups of people for whom TNF inhibitor treatment is particularly cost effective.*
- *Higher rates of surgery in practice than assumed in NICE cost-effectiveness modelling.*
- *Greater cost of surgery in practice than assumed (accounted for in sensitivity modelling).*

The Appraisal Committee also acknowledged several shortcomings in the evidence base and areas of uncertainty, including:

- *No direct comparisons between biological agents have been published*
- *Lack of adequate definition of inadequate response/intolerance to conventional therapy in trial protocols.*
- *Lack of criteria for minimum dose/duration of previous conventional therapy in trial protocols.*

- *In no study had all participants previously trialled corticosteroids plus either azathioprine or mercaptopurine (as required in EMA marketing authorisations).*
- *Optimal duration of TNFi therapy not known. Maintenance of remission following withdrawal unclear. Safety and efficacy of re-administration following interruption not fully established. No RCT evidence for efficacy and safety of second biologic intervention in patients who are non-responders or who are intolerant of a first biologic treatment.*
- *There is insufficient data to determine whether the treatment effect will be maintained beyond 54 weeks or whether the treatment effect will be maintained in patients whose disease responded if they stop anti-TNF-alpha therapy.*
- *NICE Assessment Group cost effectiveness model assumes that patients whose disease responds or remits during TNFi therapy will continue receiving treatment until benefit is lost. Other scenarios were not explored due to a lack of robust evidence to guide stopping rules for TNFi therapy.*
- *Very limited data on outcomes of hospital admission – data suggests that outcomes may be more favourable for adalimumab and infliximab-treated patients than for those treated with placebo.*
- *Sparse data on surgical intervention – with potential inconclusive benefit for intervention-treated patients compared with placebo-treated patients.*
- *No trials reporting whether surgical outcomes were elective or emergency.*
- *Results of cost effectiveness analysis **highly sensitive** to utility values used, specifically the difference between the utility values for patients having medical treatment and those having surgery.*
- *Limitations of data on quality of life among patients who have undergone colectomy.*

Other points to note include:

- *Potential impact of surgery on fertility not included in cost effectiveness modelling or considered in detail by Appraisal Committee, as the main comparator for the TNF inhibitors was considered to be conventional medical therapy.*
- *Impact of surgery on younger patients not fully assessed.*
- *The possible impact on cost-effectiveness of newly licensed biosimilar versions of infliximab was not included in the models. NHS prices are not available.*
- *Lack of direct concordance between Mayo Clinical Scores used to determine eligibility for trials and to define response and remission and UK recommended clinical scoring system (Trulove and DeWitts). Few patients with "moderate-to-severe" UC as defined by the Mayo score are likely to have severe UC as defined in the UK (requires systemic features, including pyrexia, pulse > 90bpm and erythrocyte sedimentation rate >30 mm/hour). Two elements of the four component Mayo score may be at least partially subjective and influenced by inter-rater variability (endoscopic findings and*

physician's global assessment). Possible for patient to be classed as responder on basis of change in subjective components alone.

Clinical evidence – comparison with vedolizumab

An additional independent Bayesian network meta-analysis which combined the key TNFi trials included in the NICE Assessment Group report with data from the one published phase III randomised controlled trial of vedolizumab has recently been published.[9]

Eight phase III randomised placebo-controlled trials with similar designs were included in the meta-analysis.[10-16] Although inclusion and exclusion criteria, endpoints studied and trial procedures were very similar, there were some important differences between trials that limited comparative analysis. Most importantly, the randomised arms of trials of maintenance therapy with golimumab or vedolizumab only included patients who had achieved a response during induction, whereas in trials of adalimumab and infliximab patients continued into the maintenance phase in the treatment arms to which they were assigned before induction. As a result, only data from the induction phases of the trials was included in the network meta-analysis. Maintenance phase results were summarised using frequentist fixed-effects models instead.

All eight studies enrolled patients with moderately to severely active UC, defined according to the Mayo Clinical Score. In all studies patients had previously received conventional therapy (principally aminosalicylates). Details of specific therapies varied and, with the exception of the vedolizumab study, trial procedures did not generally specify requirements (dose, duration, etc.) or define terms such as intolerance or inadequacy of response. Trials only required patients to "fail" treatment with one or more conventional therapy; in no single trial had all participants previously trialled corticosteroids plus either azathioprine or mercaptopurine. Patients previously treated with a TNF inhibitor were excluded from most studies but allowed to participate in one adalimumab trial and the trial of vedolizumab (approximately 40% prior TNFi exposure in both studies). Only data on TNFi-naïve patients was included in the network meta-analysis. This may make the results more relevant to UK practice – as TNF inhibitors are unlikely to be routinely commissioned for treatment-refractory moderate-to-severely active UC at present.

The NMA suggested that infliximab is more effective at inducing clinical response and mucosal healing than adalimumab. None of the other indirect comparisons reached statistical significance. There was no signal to suggest that vedolizumab might have advantages over the TNF inhibitors. No conclusions about relative efficacy of the four biological therapies for maintenance of response and/or remission could be drawn.

Clinical evidence – vedolizumab

One phase III randomised placebo-controlled clinical trial of vedolizumab for the treatment of UC has been published in full.[15] Participants were aged 18-80 years with a Mayo Clinic score of 6 to 12 (see table 1 below), a sigmoidoscopy subscore of at least 2 and disease that extended 15cm or more from the anal verge and unsuccessful previous treatment. Unsuccessful previous treatment was defined as inadequate response, loss of response or intolerance to at least one of three prior treatment options (corticosteroids, immunosuppressants [azathioprine or

mercaptopurine], or TNF inhibitors) over the previous 5-year period. The dose and duration of each treatment option required to meet the trial definition of inadequate response or loss of response were clearly set out. However, the extent, severity or duration of persistent disease required for treatment to be considered unsuccessful was not defined. Mesalazine, corticosteroids (up to 30mg prednisone or equivalent) and stable doses of immunosuppressants could be continued during the trial (except in the USA where immunosuppressants were discontinued at week 6, i.e. before commencement of maintenance phase). Any rectal therapy with corticosteroids or mesalazine was discontinued two weeks before screening. This may be linked to the low numbers of screened patients who were excluded due to insufficient disease activity (95/1406).

Exclusion criteria were similar to other trials of biologic agents in moderate to severe UC and included: exposure to vedolizumab, natalizumab, efalizumab or rituximab; toxic megacolon; abdominal abcess; symptomatic colonic stricture; stoma; history of colectomy; increased risk of infectious complications; clinically meaningful laboratory abnormalities; colonic dysplasia or adenomas, and; malignant neoplasm.

895 out of 1406 screened patients entered the initial 6-week induction phase. 374 of these were randomised to receive intravenous vedolizumab 300mg or placebo on days 1 and 15. Randomisation was stratified by concomitant use (or non-use) of corticosteroids and prior TNF inhibitor use (or non-use).

The remaining 521 patients formed an additional open-label cohort treated with vedolizumab 300mg on days 1 and 15 in order to fulfil sample size requirements for the 46-week maintenance phase (total trial duration = 52 weeks). Patients from either cohort with a defined clinical response (Mayo score less than baseline by ≥ 3 points and by $\geq 30\%$ + decrease in rectal bleeding score or ≥ 1 point or score ≤ 1) at week 6 were randomised to one of three maintenance treatment arms: vedolizumab 300mg iv every 8 weeks (licensed standard dose); vedolizumab 300mg every 4 weeks (licensed for dose intensification if response declines or following interruption of therapy), or; placebo. Randomisation was stratified by three factors: concomitant use or non-use of corticosteroids; concomitant use of non-use of immunosuppressants, and; prior use or non-use of TNFi.

The primary outcome for the induction phase was clinical response at week 6. Secondary outcomes included clinical remission (Mayo score ≤ 2 with no individual subscore > 1) and mucosal healing (endoscopic subscore of 0 or 1). The primary outcome for the maintenance phase was clinical remission at week 52. Secondary outcomes included durable clinical response (clinical response at both weeks 6 and 52), durable clinical remission and corticosteroid-free remission at week 52 in patients receiving corticosteroids at baseline.

Placebo and active treatment groups in both the induction and maintenance phases of the study were reasonably well balanced. 28.5% of participants were not taking either corticosteroids or immunosuppressants at baseline.

Results for the induction phase, with the difference between placebo and active treatment groups adjusted for stratification factors, are shown in table 1 below.

Table 1

[redacted]	Proportion with outcome		
	Placebo (n = 149)	Vedolizumab (n = 225)	Adjusted Difference (95% CI)
Response	25.5	47.1	21.7 (11.6 - 31.7)
Remission	5.4	16.9	11.5 (4.7- 18.3)
Mucosal Healing	24.8	40.9	16.1 (6.4 - 25.9)

Response = Mayo score less than baseline by ≥3 points and by ≥30% + decrease in rectal bleeding score or ≥1 point or score ≤1

Remission = Mayo score ≤2 with no individual subscore > 1

The Mayo score has four domains, each with four states from "normal", with a score of zero, to "severe", with a score of four points. Hence total scores range from zero to twelve. Scores less than 2 indicate remission (or "normal" condition), scores from two to five indicate mild disease and scores of six or more define moderate to severe disease. The domains (or subscores) are: stool frequency (range = normal to five or more per day); rectal bleeding (no blood to only blood passing); endoscopic findings (normal to severe), and; physician's global assessment (normal to severe).

Results for the maintenance phase (8-weekly standard licensed dose) are shown in table 2 below.

Table 2

[redacted]	Proportion with outcome		
	Placebo (n = 126)	Vedolizumab (n = 122)	Adjusted Difference (95% CI)
Remission at 52 weeks	15.9	41.8	26.1 (14.9 – 37.2)
Response at both 6 & 52 weeks	23.8	56.6	32.8 (20.8 – 44.7)
Remission at both 6 & 52 weeks	8.7	20.5	11.8 (3.1 – 20.5)
Mucosal healing at 52 weeks	19.8	51.6	32.0 (20.3 – 43.8)
Steroid-free remission at 52 weeks	13.9	31.4	17.6 (3.9 – 31.3)

Clinical evidence – simplified summary of trial results

Table 3 shows placebo-subtracted response and remission rates for licensed dose regimens taken from the key trials of biologic agents for ulcerative colitis. The table should be interpreted with caution; potentially important information (including tests

for statistical significance and confidence intervals) has been omitted and several simplifying assumptions have been made.

Trials differed in duration of induction and maintenance phases, previous drug exposure of participants (including whether previous exposure to TNF inhibitors was permitted), selection of primary endpoint (response or remission at set time-points) and several other details. For trials of vedolizumab and golimumab, induction-phase responders to the trial drugs were re-randomised to active treatment or placebo for maintenance phase comparisons (excluding induction phase non-responders and those assigned to placebo from primary analysis). In trials of adalimumab and infliximab, patients continued into the maintenance phases in the treatment arms to which they were assigned before induction.

Table 3

	DIFFERENCE BETWEEN ACTIVE AND PLACEBO GROUPS (% POINTS) [Number Needed to Treat for one extra person to achieve outcome in square brackets]					
OUTCOME	INFLIXIMAB	INFLIXIMAB	ADALIMUMAB (TNFi NAÏVE)	GOLIMUMAB	VEDOLIZUMAB	VEDOLIZUMAB (TNFi NAÏVE)
Response (6 or 8 weeks)	32.2 [4]	35.2 [3]	20.7 [5]	51 [2]	21.6 [5]	18.4 [6]
Remission (6 or 8 weeks)	23.9 [5]	28.2 [4]	10.3 [10]	17.8 [6]	11.5 [9]	
Response (30, 52, 54 or 60 weeks)	25.7 [4]	21.1 [5]	12.6 [8]	49.7 [3]	32.8 [4]	
Remission (30, 52, 54 or 60 weeks)	18.2 [6]	15.0 [7]	9.6 [11]	27.8 [4]	25.9 [4]	31.9 [4]

Safety

Safety issues identified in the adalimumab, golimumab and infliximab trials were consistent with those previously identified for TNFi drugs and set out in Summaries of Product Characteristics.[2,5]

All patients who received vedolizumab were included in the safety analysis. This included non-responders to induction therapy (excluded from efficacy analysis) who were treated with vedolizumab every four weeks up to week 52.[15]

Adverse events were reported to be similar across treatment groups, with no important differences between placebo groups and vedolizumab-treated groups. Similar proportions of participants in placebo (13.5%) and vedolizumab (12.4%) groups experienced serious adverse events. Headache, ulcerative colitis, nasopharyngitis, upper respiratory tract infection, arthralgia, nausea, abdominal

pain, anaemia, fatigue and cough were all reported by more than 5% of vedolizumab treated participants. The proportions of participants receiving placebo reporting these events were similar.

Vedolizumab is a novel agent which shares some properties with the $\alpha 4\,\beta 1$-integrin antagonist natalizumab which has been linked to substantially increased risks of progressive multifocal leukoencephalopathy (PML) and immune reconstitution inflammatory syndrome – both serious and potentially fatal adverse events.[5] Natalizumab is licensed in the USA for treatment of Crohn's disease. Trial participants exposed to vedolizumab underwent active surveillance for PML over 52 weeks. No cases of PML were reported.

Cost analysis

NICE estimate that around 50% of people with ulcerative colitis will have at least one relapse per year, that about 80% of these are mild to moderate and about 20% are severe. Studies have suggested that almost 10% of patients with UC experience chronic continuous disease activity.[3] This would equate to approximately 775 patients across the NTAG footprint. There are no reliable estimates of the proportion of those people who will experience moderate to severe relapses that do not respond adequately to optimal conventional therapy or the proportion for whom colectomy may not be a reasonable option. Data from Clinical Commissioning Groups in the North of England suggest that approximately 1 person per 2,000 patients with ulcerative colitis per year may be considered for treatment with TNFi via the individual funding route at present.

NICE estimate that average costs of treatment for moderately to severely active UC with the TNF inhibitors (based on 8 weeks of induction therapy followed by 26 weeks of maintenance therapy) are as follows:

Adalimumab [Humira®, AbbVie] = £4,622

Golimumab [Simponi®, MSD] = £9,554 for patients with a body weight less than 80 kg and £14,530 for patients with a body weight of 80 kg or more

Infliximab [Remicade®, MSD] = £10,509 (excluding administration costs & assuming the patient weights 77 kg)

It would, therefore, cost approximately £3.5 million to treat 775 patients with adalimumab, the most cost-effective TNFi identified via the NICE appraisal process.

Purchase prices may vary due to locally negotiated procurement discounts in some localities.

Two biosimilar versions of infliximab (Inflectra®, Hospira and Remsima®, Celltrion) have marketing authorisation in the UK for the same indications as Remicade®. There are currently no published or approved UK list prices for these products. There is currently no UK list price for vedolizumab.

Patient impact

Patients with UC that is poorly controlled despite optimum use of standard therapies and who are reluctant to or determined not to undergo surgery despite clinical advice currently have few options other than to tolerate their symptoms, the adverse effects of medication (possibly including long-term effects of exposure to corticosteroids), the increased risks of colorectal cancer and the regular endoscopic surveillance that this entails.

Points to consider

- Adalimumab, golimumab, infliximab and vedolizumab have been shown to be effective treatments for treatment-refractory moderately to severely active ulcerative colitis. NNTs for induction and maintenance of remission (up to 52 weeks) among selected patients enrolled in trials range from 4 to 11.
- NICE have considered the cost-effectiveness of treatment with the TNF inhibitors, adalimumab, golimumab and infliximab. For patients for whom colectomy is not an option, adalimumab is likely to be the most cost-effective option, but the base-case incremental cost-effectiveness ratio is considerably above the level considered to represent cost-effective use of NHS resources.
- NICE acknowledged several shortcomings in the evidence base and areas of uncertainty which may be pertinent to local decision making. In particular, the results of the cost-effectiveness analysis were found to be highly sensitive to the utility values used. These values were associated with considerable uncertainty.
- An independent systematic review and meta-analysis has compared vedolizumab with the TNF inhibitors. The results suggest that infliximab may be more effective at inducing clinical response and mucosal healing than adalimumab. None of the other indirect comparisons reached statistical significance. There was no signal to suggest that vedolizumab might have advantages over the TNF inhibitors. No conclusions about relative efficacy of the four biologic therapies for maintenance of response and/or remission could be drawn.
- Safety issues identified in the adalimumab, golimumab and infliximab trials were consistent with those previously identified for TNFi drugs and set out in Summaries of Product Characteristics. In the vedolizumab trial, adverse events were reported to be similar across treatment groups, with no important differences between placebo groups and vedolizumab-treated groups. Natalizuamb, another integrin inhibitor used for treatment of inflammatory bowel disease, has been associated with an increased risk of progressive multifocal leukoencephalopathy.
- If 10% of patients with ulcerative colitis experience chronic continuous disease activity, there could be approximately 775 patients in the North East and North Cumbria who might be considered for treatment with biologic drugs. The proportion of those patients who have moderately to severely active disease that cannot be controlled by optimising conventional therapy and the proportion of those whom colectomy might not be a reasonable treatment option is not known. Treating all 775 patients were treated with adalimumab could cost approximately £3.5 million.

Author's declaration.

One member of the lead author's extended family has long-standing ulcerative colitis and has experienced relapses which have sometimes proved difficult to control despite conventional therapy. No other interests to declare.

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