Sequential use of TNF-alpha inhibitors in Crohn’s disease & Ulcerative Colitis.

**Background:**
NICE guidance recommends certain TNF-alpha inhibitors and vedolizumab (α4β7 integrin inhibitor) as biologic treatment options in the management of Crohn's Disease (CD) and Ulcerative colitis (UC). However, guidance is lacking on the sequential use of TNF-alpha inhibitors in those who experience intolerance or failure on these agents, the number of prior treatments (biologic or conventional) that may be tried before vedolizumab is used, the off-label use of biologic agents, and the use of biologics for prophylaxis of recurrence in the post-surgery setting. This review considers the evidence available to address these areas of uncertainty, to clarify the commissioning position of CCGs and use of biologics in CD and UC across Lancashire.

**Crohn’s disease recommendations:**

**CD Recommendation 1:** In CD patients who experience intolerance, secondary failure or primary failure with a first TNF-alpha inhibitor used in line with NICE, treatment with a second NICE TA187-approved TNF-alpha inhibitor may be tried. i.e. Red colour classification for infliximab and adalimumab as 1st and 2nd line biologics in Crohns Disease

There is consistent evidence that a second TNF-alpha inhibitor can induce and maintain clinical response and remission in many patients who experience inadequate control or intolerance on their first TNF-alpha inhibitor. Response and remission rates with a second TNF-alpha inhibitor are highest in those who discontinue their first TNF-alpha inhibitor due to intolerance or loss of response, compared with those who discontinue due to lack of an adequate initial response.

**CD Recommendation 2:** Use of a third TNF-alpha inhibitor in CD patients who have experienced treatment failure or intolerance to a second TNF-alpha inhibitor is not recommended i.e. Black Colour Classification. Vedolizumab may be used as a 3rd line biologic if clinically indicated i.e. Red Colour Classification

Infliximab and adalimumab are the only TNF-alpha inhibitors that are licensed currently for use in CD in the UK. Vedolizumab is recommended by NICE for use specifically following failure of TNF-alpha inhibitor therapy. Evidence in support of use of a third TNF-alpha inhibitor is insufficient to justify the use of a third, unlicensed TNF-alpha inhibitor ahead of vedolizumab.

**CD Recommendation 3:** Certolizumab and ustekinumab are not currently licensed for use in CD and are not recommended for use at this time. i.e. Black Colour Classification

Following failure or intolerance to conventional therapy, CD Recommendation 1 (above) extends the potential CD biologic pathway to include sequential use of two licensed TNF-alpha inhibitors and a further licensed biologic agent. Whilst there is evidence of efficacy from trials and retrospective observational studies of certolizumab and ustekinumab, this evidence is insufficient to support their off-label use ahead of licensed and NICE-recommended agents, or following exhaustion of licensed and NICE-recommended agents.
CD Recommendation 4: Routine use of biologic agents to prevent recurrence of CD following surgery is not recommended. In patients at high risk of recurrence (e.g. more than one resection, or penetrating or fistulising disease), prophylaxis with thiopurine should be considered where appropriate. A TNF-alpha inhibitor may be considered in these high risk patients upon recurrence, or if thiopurine treatment is not tolerated. i.e. Black Colour Classification

Limited evidence supports the efficacy of TNF-alpha inhibitors for post-surgery prophylaxis; however, in one of the largest trials available in this setting, patients at high risk of recurrence who were treated with immediate TNF-alpha inhibitor (adalimumab) post-surgery did not have a lower risk of endoscopic recurrence at 18 months compared with high-risk patients who were treated initially with thiopurines and stepped-up to adalimumab if there were signs of recurrence on endoscopy at 6 months. Given this and their significantly greater costs, routine use of TNF-alpha inhibitors ahead of conventional treatments cannot be supported at this time.

Ulcerative colitis recommendations:

UC Recommendation 1: In UC patients who experience intolerance, secondary failure or primary failure with infliximab as their first TNF-alpha inhibitor in line with NICE TA329, adalimumab should be used in preference to alternative TNF-alpha inhibitors where it is available.

Infliximab or golimumab may be used as a 2nd line biologic in UC ONLY where patients have had adalimumab 1st line.

Published evidence for use of a second TNF-alpha inhibitor in UC is limited to use of adalimumab following infliximab and there is an absence of quality data to support the use of golimumab and infliximab as second-line TNF-alpha inhibitors in UC. However, local data suggests that there is a significant cohort of patients within the Lancashire Health Economy with Ulcerative Colitis who are currently being treated with adalimumab 1st line. Additionally, due to differences in interpretation of NICE guidance, there is local experience of infliximab and golimumab being used as a 2nd line biologic after treatment with adalimumab. Therefore in recognition of local specialist experience and to allow this patient cohort equal access to the same number of biologic treatments as other patients with Ulcerative Colitis it is recommended that infliximab and golimumab are available as 2nd line biologic treatment options after failure of adalimumab in Ulcerative Colitis.

Vedolizumab is recommended by NICE for use specifically following failure of TNF-alpha inhibitor therapy. As per the LMMG agreed pathway vedolizumab is also available as a 2nd line biologic treatment option.

UC Recommendation 2: Use of a third TNF-alpha inhibitor in UC patients who have experienced treatment failure or intolerance to a second TNF-alpha inhibitor is not recommended. i.e. Black Colour Classification. Vedolizumab may be used as a 3rd line biologic if clinically indicated i.e. Red Colour Classification

There is little evidence in support of use of a third TNF-alpha inhibitor in UC, and none to justify use of a third TNF-alpha inhibitor ahead of NICE-recommended vedolizumab.

UC Recommendation 3: Certolizumab and ustekinumab are not currently licensed for use in UC and are not recommended for use in UC. i.e. Black Colour Classification

There is a lack of evidence for use of certolizumab and ustekinumab in UC, which precludes their off-label use ahead of licensed and NICE-recommended agents, or following exhaustion of
licensed and NICE-recommended agents.

**UC Recommendation 4: Use of biologic agents to prevent recurrence of UC following surgery is not recommended. i.e. Black Colour Classification**

There is a lack of evidence for TNF-alpha inhibitors or other biologic agents to support their use in the prevention of recurrence following surgery for UC.

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**Background and context**

NICE Clinical Guidelines CG152 on the management of Crohn’s disease (CD) [1] and CG166 on the management of ulcerative colitis (UC) [2] outline how drug treatment with the aim of achieving remission should normally begin with conventional immunosuppressive agents (e.g. 5- aminosalicylate, thiopurines) and/or corticosteroid, depending on severity of the presentation or exacerbation. Non-corticosteroid conventional treatments may be considered for maintenance of remission, including, where necessary, after surgery for CD [1].

NICE Technology Appraisals TA 187 and TA 329 recommend the use of TNF-alpha inhibitors as first-line biologic treatment options in the medical management of patients with severe CD (infliximab or adalimumab) and moderate to severe UC (infliximab or adalimumab or golimumab) only when response to conventional treatment is inadequate or when conventional treatments are contraindicated or not tolerated, as outlined in Figures 1 and 2 on page X [3,4]. Infliximab is also recommended for short term use in acute severe exacerbations of UC under specific circumstances [5]. Vedolizumab, an α4β7 integrin inhibitor, is recommended in NICE TA 352 as an option in severely active CD in patients who have had an inadequate response to or are intolerant of TNF-alpha inhibitor treatment, and in NICE TA 342 as an option in moderate to severely active UC in patients who have had an inadequate response to or are intolerant of conventional or TNF-alpha inhibitor treatment [6, 7].

Each of the above TNF-alpha inhibitors is recommended as a first-line biologic treatment option, with the choice between each agent been based on individual patient factors; if more than one agent is suitable, the least expensive agent (taking into account administration and dosing costs) should be used. Treatment should continue until failure (including the need for surgery) occurs or for up to 12 months, whichever is shorter, and treatment beyond this should continue only if there is clear evidence of response. In patients who achieve stable remission, a trial withdrawal should be considered, and people who experience relapse after treatment is stopped should have the option to start treatment again [3,4].

The literature reports that around a third of patients with CD or UC fail to respond to their initial TNF-alpha inhibitors (primary failure) and a further third or more of patients experience a loss of response (secondary failure) or discontinue treatment due to intolerance [8]. Whilst existing NICE guidance recommends certain biological agents as treatment options, guidance is lacking on the subsequent use of TNF-alpha inhibitors in those who experience intolerance or failure on these agents [3,4] the number of prior treatments (biologic or conventional) that should be tried before vedolizumab is used [6,7], the off-label use of biologic agents, and the use of biologics for prophylaxis of recurrence in the post-surgery setting. This review considers the evidence available to address these areas of uncertainty, to clarify the commissioning position of CCGs and use of biologics in CD and UC across Lancashire.
Structured literature searches of PubMed and the Cochrane Library were conducted to identify published systematic reviews, trials, or other studies of the use of TNF-alpha inhibitors or other biologic agents following prior treatment failure in CD or UC (see Appendix). Key published studies are summarised in Table 1 (page Y) and below under general headings relating to second-line use of TNF-alpha inhibitors, third-line use of TNF-alpha inhibitors, use of other biologic and unlicensed agents, and use of biologics for post-surgery prophylaxis.

**Response to a second-line TNF-alpha inhibitor:**

Evidence of response and safety with use of a second TNF-alpha inhibitor is based on a recently published systematic review that specifically addressed the use of a second TNF-alpha inhibitor in UC and CD patients who had withdrawn from first TNF-alpha inhibitor treatment. This considered studies of infliximab, adalimumab or certolizumab (not licensed for use in CD or UC in the UK – see below), of which 46 were included in the review and analyses [8]. In addition, a large Swiss registry study provides information on the durability of response and treatment duration with second and subsequent TNF-alpha inhibitors [9].

**Crohn's disease efficacy:**

The systematic review identified 37 studies related to use of a second TNF-alpha inhibitor in CD, of which only four were double-blind RCTs; the remainder were a mix of retrospective observational studies, case series and single-arm trials. Thirty-two studies reported outcomes following a switch from infliximab to adalimumab, four following a switch from infliximab to certolizumab, and one following a switch from adalimumab to infliximab [8].

Across all studies involving a switch from infliximab, irrespective of the reason for withdrawal of infliximab, the second TNF-alpha inhibitor induced clinical remission in 43% and a response in 63% of CD patients. However, the efficacy of the second TNF-alpha inhibitor was significantly influenced by the reason for withdrawal of the first TNF-alpha inhibitor (infliximab). In those who withdrew from infliximab due to intolerance, remission was achieved in 61%; however, in those who withdrew from infliximab due to secondary failure, remission was lower at 45% and in those who withdrew from infliximab due to primary failure, remission was lowest at 30%. Response rates followed the same pattern [8].

The single study exploring outcomes following a switch from adalimumab to infliximab was based on a historical cohort of 15 CD patients. None of seven patients with primary failure on adalimumab achieved remission or partial response with infliximab treatment when assessed at 4 weeks. All five patients with secondary failure on adalimumab achieved a response, one of which achieved remission. All three patients withdrawing from adalimumab due to intolerance achieved response with infliximab, of which two achieved remission [8].

Few studies considered response based on type or severity of CD. In patients with luminal disease, remission rates were 34% after primary failure, 41% after secondary failure and 78% after intolerance to the first TNF-alpha inhibitor. In fistulising disease, remission after primary failure was 36% and after secondary failure was 45%; no studies provided remission rates following withdrawal of the first TNF-alpha inhibitor due to intolerance [8].

Across studies providing data, remission rates were generally higher when assessed after medium (9-40 weeks) to long term (41-52 weeks) use, rather than after short-term (4-8 weeks) use, suggesting response to the second agent may be delayed [8]. The Swiss registry study,
which included data on 347 CD patients using TNF-alpha inhibitors, observed that duration of treatment (used as a proxy for efficacy and tolerance) reduced with each subsequent line of therapy (median duration of first-line TNF-alpha inhibitor treatment 25 months vs. 13 months for second-line, and 11 months for third-line) [9].

Ulcerative colitis efficacy:

The systematic review identified eight studies in UC patients, only one of which was a double-blind RCT; the remainder were a mix of retrospective observational studies, case series and single-arm trials. All studies explored outcomes following a switch from infliximab to adalimumab; no studies were identified that specifically explored a switch to golimumab or infliximab, although it should be noted that golimumab studies were not specifically targeted. In most studies secondary failure and intolerance were more common than primary failure as the reason for withdrawal of the first TNF-alpha inhibitor [8].

Data were too sparse and heterogeneous to allow exploration of outcomes by reasons for withdrawal of the first TNF-alpha inhibitor, or for effects in different types and severities of UC; however, the second TNF-alpha inhibitor (adalimumab) induced overall remission rates ranging from 0% to 50% across six studies, and overall response rates ranging from 23% to 92% across seven studies providing these data [8]. The Swiss registry study, which included data on 129 UC patients using TNF-alpha inhibitors, observed that duration of treatment (a proxy for efficacy durability and tolerance) was reduced with the second-line agent, but for third-line treatment was similar to the first-line treatment duration (median duration of first-line TNF-alpha inhibitor treatment 14 months vs. 4 months for second-line, and 15 months for third-line) [9].

The key clinical trials of golimumab in UC were conducted in patients who were TNF-alpha inhibitor naïve [10], and the structured literature searches, which included golimumab in the search terms, did not identify any evidence specific to the use of golimumab following prior TNF-alpha inhibitor therapy.

Safety data:

In CD, the incidence of adverse events ranged from 0% to 81%, most of which were of low intensity. Serious adverse events were reported in 0–21% of patients that received a second TNF-alpha inhibitor, and were most frequently gastrointestinal disorders and infections. Seven deaths were reported, of which two were possibly related to TNF-alpha inhibitor therapy. Two cases of demyelinating disease were reported. Withdrawal of the second TNF-alpha inhibitor due to adverse events was reported in up to 20% of CD patients [8].

In UC patients, adverse events ranged from 20% to 39%, and serious adverse events ranged from 0% to 7%. Withdrawal of the second TNF-alpha inhibitor due to adverse events was reported in up to 48% of UC patients [8].

Response to a third-line TNF-alpha inhibitor:

The structured literature search identified two retrospective studies reporting outcomes with use of a third TNF-alpha inhibitor [11,12], and a published systematic review that included only these two studies [13]. No prospective clinical trials measuring response to a third TNF-alpha inhibitor were identified.

Of the 129 patients observed across both studies, 123 had CD and only 6 had UC. Adalimumab and certolizumab (not licensed for use in CD or UC in the UK) were the third-line TNF-alpha inhibitors, depending on the prior treatment sequencing. Intolerance and secondary failure were more common than primary failure as the reason for withdrawal of both the first and second-line
TNF-alpha inhibitors across both studies [11,12].

Response to the third TNF-alpha inhibitor ranged from 51% to 75%, and was dependent on the length of follow-up; response at six weeks was a significant predictor of response at 20 weeks in one study [11]. Remission was achieved in 22% to 36% of patients. As observed in the Swiss Registry study [9], the durability of response decreased with each subsequent TNF-alpha inhibitor treatment. The probability of remaining on the third TNF-alpha inhibitor at 6 months was 68-69% in both studies (see Table 1).

One of the studies observed 24% of patients to experience adverse events with the third TNF-alpha inhibitor, which were mainly inflammatory skin disorders, and 15% discontinued treatment due to adverse events. Serious adverse events were experienced by 7%, including two deaths [11]. The second study provides limited safety data, but notes no significant serious infections leading to hospitalisation occurred and two patients discontinued treatment due to intolerance [12].

**Response to other biologics and unlicensed treatments following TNF-alpha inhibitor treatment:**

**Vedolizumab:**

NICE TA 352 recommends vedolizumab as a treatment option in patients with moderately to severely active CD only if a prior TNF-alpha inhibitor has failed (i.e. primary or secondary failure) or a TNF-alpha inhibitor cannot be tolerated or is contra-indications [7]. Key trials of vedolizumab in CD include GEMINI 2, which enrolled patients who had failed on either conventional or TNF-alpha inhibitor treatment [14], and GEMINI 3, in which the primary endpoint was assessed specifically in the 76% of patients enrolled in the trial who had previously failed on TNF-alpha inhibitor therapy [15]. In GEMINI 2, vedolizumab was superior to placebo for the primary endpoint of the proportion of patients in clinical remission at week 6 (14.5% vs. 6.8%; p=0.02), but failed to demonstrate superiority over placebo for the co-primary endpoint of the proportion of patients with an enhanced response (decrease in CDAI score of 100+) [14]. Clinical remission was maintained at 52 weeks in 39.0% responders who were randomised to vedolizumab every 8 weeks and in 21.6% who were randomised to placebo (p<0.001) [14]. In GEMINI 3, vedolizumab failed to achieve superiority over placebo for the primary end point of the proportion of patients in clinical remission at 6 weeks; however, in an exploratory analysis (being that the primary endpoint was not met), a higher proportion of patients who had failed on prior TNF-alpha inhibitor achieved clinical remission with vedolizumab than with placebo when assessed at 10 weeks (26.6% vs. 12.1%; nominal p=0.001) [15]. Of note, the majority of patients in whom TNF-alpha inhibitor had failed in GEMINI 3 had prior experience with two or more TNF-alpha inhibitors. Serious adverse events occurred in 24% on vedolizumab recipients and 15% on placebo in GEMINI 2 [14], but in less than 1% of patients enrolled in GEMINI 3 [15].

NICE TA 342 recommends vedolizumab as a treatment option in patients with moderately to severely active UC who have had an inadequate response with, or lost response to, or were intolerant to either conventional therapy or a TNF-alpha inhibitor [6]. Key trial data supporting the use of vedolizumab in UC patients is available from the GEMINI 1 study, in which 48% of the enrolled patients had received prior TNF-alpha inhibitor treatment, with which most had experienced primary or secondary failure [16]. A significantly greater proportion of all enrolled patients treated with vedolizumab achieved clinical response at 6 weeks compared with placebo (47.1% vs. 25.5%, p<0.001, which was also observed in the subgroup of patients with prior TNF-alpha inhibitor failure (39.0% vs. 20.6%; p=0.01), although it is unclear how many prior TNF-alpha
As the GEMINI studies compared vedolizumab against placebo, there are no direct comparative data for vedolizumab against TNF-alpha inhibitors (or other biologic agents) in CD or UC patients with prior failure on TNF-alpha inhibitors. The manufacturer of vedolizumab had presented in its submission to NICE a network meta-analysis of currently available data from CD patients who had experienced failure with prior TNF-alpha inhibitors; however NICE conclude this was not reliable [7]. In UC patients, an indirect comparison of vedolizumab and adalimumab was possible, but subject to considerable uncertainty. There were no suitable trial data available to compare vedolizumab against infliximab or golimumab in patients who had experienced treatment failure on prior TNF-alpha inhibitors [6].

**Ustekinumab:**

Ustekinumab is an interleukin-12 and -23 inhibitor, which is currently licensed in the EU as a subcutaneous injection for the treatment of plaque psoriasis and psoriatic arthritis. The manufacturer has recently submitted a license extension request for use in CD in the EU based on the UNITI trial program [17].

Results of the UNITI-1 induction trial in patients who are refractory to TNF-alpha inhibitor therapy are not yet available. However, in a published randomised, double-blind trial, intravenous ustekinumab was compared against placebo as induction therapy in 526 CD patients who had experienced treatment failure with one (50.8%) or more (48.9%) TNF-alpha inhibitors, mainly as a result of secondary failure and intolerance [18]. Significantly more patients randomised to induction therapy with ustekinumab 6mg/kg achieved the primary endpoint of a clinical response at week 6 compared with placebo (39.7% vs. 23.5%; p=0.005), but there was no difference between ustekinumab and placebo for the secondary endpoint of clinical remission at week 6. At week 8, patients entered a maintenance treatment phase, and those who had received ustekinumab induction were re-randomised to ustekinumab 90mg by subcutaneous injection or placebo. In those patients who had responded to ustekinumab induction, 41.7% who received ustekinumab 90 mg in the maintenance phase were in clinical remission at week 22 compared with 27.4% of patients receiving placebo (p=0.03). In those who failed to achieve response to ustekinumab induction therapy, there was no significant difference in clinical response rates for ustekinumab maintenance therapy or placebo at 22 weeks. Serious adverse event rates during induction and maintenance phases were similar for ustekinumab and placebo [18].

Retrospective observational studies (available only as abstracts) of use of subcutaneous ustekinumab have also been published, and report clinical response (or benefit) in 65% to 74% of CD patients who had experienced failure on prior TNF-alpha inhibitor therapy; however, these are small studies that use variable definitions of response [19,20]. Data on ustekinumab in UC are lacking.

**Certolizumab:**

Certolizumab is a TNF-alpha inhibitor that is licensed in the EU for use in rheumatoid arthritis, axial spondyloarthritis and psoriatic arthritis, but not for treatment of CD or UC. The European Medicines Agency declined a marketing authorisation for use in CD as it considered there was a lack of clinically relevant improvement in response and remission with certolizumab compared with placebo across all patients enrolled in the key phase 3 induction trial [21].

The systematic review of use of a second TNF-alpha inhibitor in UC and CD patients who had
Evidence for use of certolizumab in UC is lacking.

**Biologics for post-operative prevention of recurrence:**

NICE CG152 on the management of CD [1] discusses the use of conventional treatments (5-ASA, or the thiopurines azathioprine or mercaptopurine) for maintaining remission following surgery. It recommends consideration of azathioprine or mercaptopurine for maintenance of remission post-surgery in those with adverse prognostic risk factors for recurrence, such as those with more than one resection, or those with fistulising or penetrating disease. Biologic therapies for maintaining remission following surgery for CD are not discussed [1]. NICE CG166 does not discuss prophylaxis following surgery for UC [2].

A 2014 systematic review of prophylactic treatments in post-operative CD concluded that evidence for thiopurines is heterogenous and insufficient to support their routine use in this setting [22]. It also noted that evidence for TNF-alpha inhibitors as prophylaxis against recurrence following surgery is limited to few clinical trials involving low numbers of patients [22]. One published randomised controlled trial of a TNF-alpha inhibitor in this setting was identified. This compared infliximab against placebo in 24 patients post ileal resection. Infliximab reduced the risk of endoscopic recurrence at 12 months to 9% compared with 84% in the placebo group; however, there was no significant reduction in clinical remission. Several other study-types were also identified in which infliximab reduced recurrence compared with conventional therapies, and an observational study of adalimumab noted lower recurrence rates when compared with external controls [22]. Since then, a NICE Evidence Update to CG152 identified a recently published randomised controlled trial that compared adalimumab 40mg/kg every two weeks (n=16) against azathioprine 2mg/kg daily (n=17) or mesalazine 3g daily (n=18) in CD patients who had undergone ileal or ileocolonic resection within the previous four weeks [23]. Clinical recurrence at 2 years, defined as mild symptoms or worse, occurred in two people (13%) in the adalimumab group compared with 11 people (65%) in the azathioprine group (odds ratio [OR] =0.078, 95% CI 0.013 to 0.464), and nine people (50%) in the mesalazine group (OR=0.143, 95% CI 0.025 to 0.8169). Recurrence defined by CDAI score of more than 200 occurred in 1 (6%), 12 (71%), and 9 (50%) patients, respectively. The authors noted that larger trials are needed to assess the use of TNF-alpha inhibitors in preventing recurrence of CD after surgery [23].

The effect of different approaches to post-surgery prophylaxis has been assessed in a recent trial (POCER) and review articles [22, 24, 25]. Of 174 patients enrolled in the POCER trial, 83% were defined as high risk for recurrence (smokers, those with penetrating disease, or two or more resections) and received daily thiopurine or, if fortnightly adalimumab following regular induction if intolerant to thiopurine; the low risk remainder received no initial drug therapy. All patients (high or low risk) were then randomised to colonoscopy at 6 months (active care) or no colonoscopy (standard care). Those who had endoscopic evidence of recurrence at 6 months stepped-up treatment to either daily thiopurine, fortnightly adalimumab with thiopurine, or weekly adalimumab. Across all patients (high or low risk for recurrence) active care significantly reduced the primary endpoint of endoscopic recurrence at 18 months compared with standard care (49% vs. 67%; p=0.03), but not clinical recurrence. At 6 months significantly more high risk patients treated with...
immediate adalimumab had no endoscopic recurrence compared with those treated initially with thiopurine (94% vs. 62%; p=0.02); however, there was no difference in the primary endpoint of endoscopic recurrence at 18 months in patients on thiopurine who stepped up to receive adalimumab at 6 months based on endoscopy and those who received immediate adalimumab. The POCER authors conclude that prophylactic treatment according to clinical risk of recurrence, with early colonoscopy and treatment step-up for recurrence, is better than conventional drug therapy alone for prevention of post-operative Crohn’s disease recurrence. In addition, they concluded that selective immune suppression, adjusted for early recurrence, rather than routine use, leads to disease control in most patients [22,24,25].

No evidence for other biologic agents was identified, and no evidence specific to UC was identified.

Summary of recommendations and rationale:

Crohn’s disease:

CD Recommendation 1: Infliximab and adalimumab as 2nd line biologics in Crohns Disease RED.

In CD patients who experience intolerance, secondary failure or primary failure with a first TNF-alpha inhibitor used in line with NICE, treatment with a second NICE TA187-approved TNF-alpha inhibitor may be tried.

Rationale:

When medical treatment fails to control symptoms, surgical treatment is considered [1]. It is unclear whether or not TNF-alpha inhibitors ultimately reduce the need for surgery or simply delay the need for surgery; however, there is clear evidence that TNF-alpha inhibitors can induce clinical response and remission in patients who have failed on conventional treatments [3]. Although most of the evidence for use of a second TNF-alpha inhibitor is retrospective and observational, this is consistent with the findings of the few prospective RCTs that are available, and collectively provides a large body of evidence that demonstrates a second TNF-alpha inhibitor can induce and maintain clinical response and remission in many patients who experience inadequate control or intolerance on their first TNF-alpha inhibitor [8]. As CD Recommendation 3 (below) precludes use TNF-alpha inhibitors that are not licensed for CD in the UK, CD Recommendation 1 is restricted to those TNF-alpha inhibitors that are licensed for use in CD in the UK and are recommended as treatment options in current NICE guidance.

Points to note:

- Response and remission rates with a second TNF-alpha inhibitor are highest in those who discontinue their first TNF-alpha inhibitor due to intolerance or loss of response, compared with those who discontinue due to lack of an adequate initial response [8].
- The vast majority of evidence supporting a switch to a second TNF-alpha inhibitor relates to a switch from infliximab to adalimumab.
- Vedolizumab is recommended by NICE as a treatment option in CD patients who fail or are unable to take TNF-alpha inhibitors [7], and should be available as such. Based on a
crude comparison of the available data, clinical response and remission rates with a second TNF-alpha inhibitor [8] do not appear to be inferior to those achieved with vedolizumab [14,15]. As the majority of patients enrolled in the vedolizumab clinical trials had prior experience of two or more TNF-alpha inhibitors, the permitted use of a second TNF-alpha inhibitor is compatible with the requirements of the NICE recommendation for vedolizumab and represents a rational approach to the local use of biologic agents.

CD Recommendation 2:

Use of a third TNF-alpha inhibitor in CD patients who have experienced treatment failure or intolerance to a second TNF-alpha inhibitor is not recommended. i.e. Black Colour Classification. Vedolizumab may be used as a 3rd line biologic if clinically indicated i.e. Red Colour Classification

Rationale:

Evidence in support of use of a third TNF-alpha inhibitor is very limited, being based on few retrospective studies [13]. Although providing some evidence of benefit, a large registry study demonstrates that durability of response is diminished with each subsequent TNF-alpha inhibitor that is used. Vedolizumab, which is in a different class of biologic agent, is licensed for CD in the UK and is recommended by NICE as a treatment option specifically in CD patients who experience prior TNF-alpha inhibitor failure (i.e. primary or secondary failure) or in whom a TNF-alpha inhibitor cannot be tolerated or is contra-indicated. This is based on data from clinical trials, in which the majority of enrolled patients had prior experience of two or more TNF-alpha inhibitors. Currently, infliximab and adalimumab are the only TNF-alpha inhibitors that are licensed for use in CD in the UK, and there is insufficient evidence to justify the use of a third, unlicensed TNF-alpha inhibitor ahead of vedolizumab.

CD Recommendation 3: Black

Certolizumab and ustekinumab are not currently licensed for use in CD and are not recommended for use at this time.

Rationale:

Following failure or intolerance to conventional therapy, CD Recommendation 1 (above) extends the potential CD biologic pathway to include sequential use of two licensed TNF-alpha inhibitors and a further licensed biologic agent. Whilst there is evidence of efficacy from trials and retrospective observational studies of certolizumab and ustekinumab, this evidence is insufficient to support their off-label use ahead of licensed and NICE-recommended agents, or following exhaustion of licensed and NICE-recommended agents.

CD Recommendation 4: Black

Routine use of biologic agents to prevent recurrence of CD following surgery is not recommended. In patients at high risk of recurrence (e.g. more than one resection, or penetrating or fistulising disease), prophylaxis with thiopurine should be considered where appropriate. A TNF-alpha inhibitor may be considered in these high risk patients upon recurrence, or if thiopurine treatment is not tolerated. i.e. Red Colour Classification
Rationale:

NICE CG 152 recommends that consideration is given to the use of azathioprine or mercaptopurine for maintenance of remission post-surgery in those with adverse prognostic risk factors for recurrence, such as those with more than one resection, or those with fistulising or penetrating disease [1]. Evidence from a limited number of trials and studies, involving small patient numbers, suggest TNF-alpha inhibitors are effective for prevention of recurrence following surgery, and may be more effective than thiopurines [22,25]. However, the POCER trial indicates that prophylactic treatment should be guided by clinical risk of recurrence; early colonoscopy and treatment step-up for recurrence is better than conventional drug therapy alone for prevention of post-operative CD recurrence. Patients at high risk of recurrence who were treated with immediate TNF-alpha inhibitor (adalimumab) post-surgery did not have a lower risk of endoscopic recurrence at 18 months compared with high-risk patients who were treated initially with thiopurines and stepped-up to adalimumab if there were signs of recurrence on endoscopy at 6 months [24,25]. Given this, and their significantly higher costs compared with thiopurines, the cost effectiveness of routine use of TNF-alpha inhibitors in patients at high risk for recurrence is highly uncertain [25]. The suggested approach to maintenance of remission post-surgery in high risk patients as outlined in NICE CG152 [1] is therefore supported, with further recognition that a TNF-alpha inhibitor may be considered in those high risk patients upon recurrence, or if thiopurine treatment is not tolerated.

Ulcerative colitis:

UC Recommendation 1:

In UC patients who experience intolerance, secondary failure or primary failure with infliximab as their first TNF-alpha inhibitor in line with NICE TA329, adalimumab should be used in preference to alternative TNF-alpha inhibitors where it is available.

Infliximab or golimumab may be used as a 2nd line biologic in UC ONLY where patients have had adalimumab 1st line.

Rationale:

When medical treatment fails to control symptoms, surgical treatment may be necessary [2,3]. It is unclear whether or not TNF-alpha inhibitors reduce the need for surgery or simply delay the need for surgery; however, there is clear evidence that TNF-alpha inhibitors can induce clinical response and remission in patients who have failed on conventional treatments [4].

Published evidence for use of a second TNF-alpha inhibitor in UC is limited to use of adalimumab following infliximab and there is an absence of quality data to support the use of golimumab and infliximab as second-line TNF-alpha inhibitors in UC. However, local data suggests that there is a significant cohort of patients within the Lancashire Health Economy with Ulcerative Colitis who are currently being treated with adalimumab 1st line. Additionally, due to differences in interpretation of NICE guidance, there is local experience of infliximab and golimumab being used as a 2nd line biologic after treatment with adalimumab. Therefore in recognition of local specialist experience and to allow this patient cohort equal access to the same number of biologic treatments as other patients with Ulcerative Colitis it is recommended that infliximab and golimumab are available as 2nd line biologic treatment options after failure of adalimumab in Ulcerative Colitis.
Points to note:

- Response and remission rates with a second TNF-alpha inhibitor are highest in those who discontinue their first TNF-alpha inhibitor due to intolerance or loss of response, compared with those who discontinue due to lack of an adequate initial response [8].
- Vedolizumab is recommended by NICE as a treatment option in UC patients who fail or are unable to take conventional or TNF-alpha inhibitors [6], and should be available as such. Almost half of the patients enrolled in the UC vedolizumab clinical trials had prior experience with TNF-alpha inhibitors, although it is unclear how many had experience with two or more. The permitted use of a second TNF-alpha inhibitor would not be incompatible with the requirements of the NICE recommendation for vedolizumab and represents a rational approach to the local use of biologic agents.

UC Recommendation 2:

Use of a third TNF-alpha inhibitor in UC patients who have experienced treatment failure or intolerance to a second TNF-alpha inhibitor is not recommended i.e. Black colour classification. Vedolizumab may be used as a 3rd line biologic if clinically indicated i.e. Red Colour Classification

Rationale:
There is little evidence in support of use of a third TNF-alpha inhibitor in UC [8,13], and none to support use of a third TNF-alpha inhibitor ahead of vedolizumab, which is recommended by NICE as a treatment option in patients who experience prior TNF-alpha inhibitor failure (i.e. primary or secondary failure) or in whom a TNF-alpha inhibitor cannot be tolerated or is contra-indicated.

UC Recommendation 3: Black

Certolizumab and ustekinumab are not currently licensed for use in UC and are not recommended for use in UC.

Rationale:
Following failure or intolerance to conventional therapy, UC Recommendation 1 (above) potentially extends the UC biologic pathway to include sequential use of two licensed TNF-alpha inhibitors and a further licensed biologic agent. There is a lack of evidence for use of certolizumab and ustekinumab in UC, which precludes their off-label use ahead of licensed and NICE-recommended agents, or following exhaustion of licensed and NICE-recommended agents.

UC Recommendation 4: Black

Use of biologic agents to prevent recurrence of UC following surgery is not recommended.

Rationale:
NICE CG 166 refers generally to use of aminosalicylates and thiopurines for maintenance of remission in UC, but does not make any specific recommendations for the use of any treatments for prevention of recurrence following surgical intervention [2]. In the absence of evidence for TNF-alpha inhibitors or other biologic agents in the prevention of recurrence following surgery, their use cannot be supported.
Commissioning considerations:

Comparative unit costs:

Example annual acquisition costs of biosimilars licensed for use in either CD or UC are presented in Table 2, based on BNF list prices [26]. These exclude the confidential discount on the list price of vedolizumab agreed in NICE TA 342 [6] and TA 352 [7]. Adalimumab and golimumab are administered subcutaneously, but infliximab and vedolizumab would attract additional resource use and costs associated with their intravenous infusion.

For reference, the annual acquisition costs of conventional treatments (5-ASA, azathioprine and mercaptopurine) range from approximately £87 to £1,702 [27].

Table 2. Example annual acquisition costs of biologics licensed for use in either CD or UC

<table>
<thead>
<tr>
<th>Drug</th>
<th>Regimen</th>
<th>Cost per patient per year (ex VAT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab 100mg vial</td>
<td>5 mg/kg intravenously at weeks 0, 2 and 6 weeks, then every 8 weeks</td>
<td>1st Year: £12,085 - £13,428*</td>
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<tr>
<td></td>
<td></td>
<td>Subsequent years: £10,574 - £11,749*</td>
</tr>
<tr>
<td>Adalimumab 40mg pre-filled injection device</td>
<td>80mg subcutaneously then 40mg every 2 weeks</td>
<td>1st Year: £10,564</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Subsequent years: £9,156</td>
</tr>
<tr>
<td>Golimumab 50mg pre-filled injection device</td>
<td>Patients &lt; 80kg: Initial dose 200mg, then 100mg at week 2, then 50mg every 4 weeks thereafter, subcutaneously</td>
<td>1st Year: £13,733</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Subsequent years: £9,919</td>
</tr>
<tr>
<td></td>
<td>Patients ≥80kg: Initial dose 200mg, then 100mg at week 2, then 100mg every 4 weeks thereafter subcutaneously</td>
<td></td>
</tr>
<tr>
<td>Vedolizumab 300mg vial</td>
<td>300mg intravenously at weeks 0, 2 and 6 weeks, then every 8 weeks</td>
<td>1st Year: £16,400†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Subsequent years: £14,350†</td>
</tr>
</tbody>
</table>

Costs based on BNF list prices Dec 2015 [26]
*C Costs based on 70kg adult, assuming vial wastage, and reflect range of costs of Remicade® brand and available biosimilar products
¶ Assumes 100mg presentation will be provided at same cost as 50mg presentation, as per NICE TA329
† Stated cost reflects list price. Vedolizumab is recommended in NICE TA342 and TA 352 under a patient access scheme, which provides a confidential discount on this list price [6,7]
This table does not imply therapeutic equivalence of drugs or doses. See respective Summaries of Product Characteristics for full dosing details

Anticipated budget impact:

The proposed recommendations would potentially extend the CD and UC biologic pathways to include an additional licensed TNF-alpha inhibitor before the use of vedolizumab, and in the CD biologic pathway would also potentially include a TNF-alpha inhibitor as post-surgery prophylaxis in patients at high risk of recurrence in whom thiopurines are ineffective or not tolerated (although, it is possible that switching between TNF-alpha inhibitors and continued treatment following surgery has been done previously in practice).

Estimating the net budget impact of these recommendations is complicated. A published survey of 50 gastroenterologists in the UK reports that among UC patients failing infliximab or adalimumab as a first-line TNF-alpha inhibitor, around 50% would be switched to the other as a second-line TNF-alpha inhibitor and in the remaining 50% surgery would be pursued as a treatment option. Among CD patients failing infliximab, these clinicians estimated that around
70% would be switched to adalimumab as a second-line TNF-alpha inhibitor and in the remaining 30% surgery would be pursued as a treatment option. For adalimumab failures, around 50% would be switched to infliximab as a second-line TNF-alpha inhibitor and 50% would pursue surgery [28].

The NICE costing report for vedolizumab in TA 352 [29] estimates that 40% of CD patients have moderate or severe disease, of which 50% experience treatment failure or intolerance following conventional treatment and are potentially eligible for TNF-alpha inhibitor treatment (infliximab or adalimumab). Of these, TNF-alpha inhibitor treatment is estimated to be ineffective in 41% and not tolerated in 5%. These estimates would reflect the proportion of CD patients potentially eligible for a second TNF-alpha inhibitor.

Depending on which TNF-alpha inhibitor is used first-line, the acquisition costs of the second TNF-alpha inhibitor could range between £10,500 and £12,000 if used for the whole of the first year. However, these are unlikely to be significantly different to the acquisition costs of vedolizumab under the confidential discount on its list price. On average, a second TNF-alpha inhibitor may induce remission in 43% of patients who failed on their first TNF-alpha inhibitor [8], which would potentially prevent or delay use of vedolizumab in these patients. The differential impact on downstream resource use and costs (up and beyond surgery) is unclear but, crudely, clinical response and remission rates with use of a second TNF-alpha inhibitor compare favourably with those observed with vedolizumab [14,15]. On balance, the net budget impact of the use of a second TNF-alpha inhibitor is difficult to estimate but is not anticipated to be substantial.

Similar reasoning may be applied to the recommendation in the UC biologic pathway. Figures with which to estimate the use and budget impact of TNF-alpha inhibitor as post-surgery prophylaxis in CD are lacking.

References


### Table 1: Summary of key evidence identified in structured literature searches

<table>
<thead>
<tr>
<th>Ref</th>
<th>Study type</th>
<th>Therapy switching</th>
<th>Efficacy outcomes</th>
<th>Safety outcomes</th>
<th>Quality of evidence</th>
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</table>
| [8] | Systematic review and meta-analysis. Search dates up to October 2014:  
- 37 CD studies  
- 8 UC studies  
- (1 pouchitis study- not further discussed) | CD studies comprised:  
- 32 studies switching IFX→ADA,  
- 4 studies IFX→CZP  
- 1 studies ADA→IFX.  
UC studies comprised:  
- 8 studies switching IFX→ADA | CD outcomes:  
Overall remission after primary failure: 30%  
Overall response rate after primary failure: 53%  
Overall remission after secondary failure: 45%  
Overall response after secondary failure: 52%  
Overall remission after intolerance: 61%  
Overall response after intolerance: 72% | CD outcomes:  
Adverse event rate for 2nd treatment ranged from 0% to 81%  
Serious adverse event rate 0% to 21%  
Discontinuation rate due to adverse events <20% | Mixed study types, including prospective trials, retrospective cohort studies, case series. Only 5/45 were categorised as double-blind RCTs. Significant heterogeneity present in pooled analyses, due to different study types. Different definitins of remission and response used in studies. However, evidence of benefit for use of 2nd TNF-alpha inhibitor treatment consistent across prospective and retrospective studies |
|     |            |                   |                   |                |                     |
| [11,12,13] | Systematic review. Search dates up to January 2014:  
- 1 CD study (n=66)  
- 1 IBD study (CD n=57; UC n=6) | CD study [11]:  
1st line: IFX(n=63); ADA (n=1); CTZ (n=3)  
2nd line: ADA (n=39); CTZ (n=24); IFX (n=4)  
3rd line: CTZ (n=40); ADA (n=27); IFX (n=0)  
IBD study [12]:  
IFX→ADA→CTZ (n=54)  
IFX→CTZ→ADA (n=5)  
ADA→CTZ→IFX? (n=2)  
ADA→IFX?→CTZ (n=2)  
Remainder? | CD study [11]:  
Response (defined by HBI or clinician judgement) to 3rd drug was observed in 61% of patients at week 6 and in 51% at week 20. A 6-week response predicted 20-week response. Remission (defined by HBI<4) achieved in 22%. Median follow-up to discontinuation of 3rd treatment 6 months (vs.18 and 4 months for 1st and 2nd treatment durations). Probabilities of remaining on 3rd treatment at 3, 6 and 9 months were 68%, 58% and 45%. | CD study [11]:  
Adverse event rate for 3rd treatment: 24% (mainly inflammatory skin disorders)  
Serious adverse event rate: 7% (including 2 deaths)  
Discontinuation rate for 3rd treatment due to adverse events 15%. | Retrospective cohort studies in limited numbers of patients. Small subgroups require cautious interpretation. |
Remission (defined by HBI<4) achieved in 36.2%. Mean duration of 3rd treatment 13.2 months (vs. 21.5 and 17.4 months for 1st and 2nd treatment). Probabilities of remaining on 3rd treatment at 6, 12, 24 and 36 months were 0.69, 0.55, 0.37 and 0.25. Infections leading to hospitalisation and no reactivation of TB. Discontinuation for 3rd treatment due to intolerance in 2 patients.

Other biologics following TNF-alpha inhibitor failure: Vedolizumab

**[14]** Phase 3 trial, randomised, double-blind placebo-controlled study in CD (n=1115): Induction phase (n=568) & Maintenance phase in those who responded in induction phase

Assessed vedolizumab against placebo in patients with prior failure on conventional or TNF-alpha inhibitor treatment

Induction phase:
- Primary endpoint- Clinical remission (CDAI score <150) at 6 weeks: Vedolizumab 14.5% vs. Placebo 6.8%; p=0.02
- Co-primary endpoint- Clinical response (100+ point decrease in CDAI score): Vedolizumab 31.4% vs. Placebo 25.7%; p=NS

Maintenance phase:
- Clinical remission at 52 weeks in those who responded to induction: Vedolizumab every 8 weeks 39.0% vs. Placebo 21.6%; p<0.001

Serious adverse event rates: Vedolizumab 24.4% vs. Placebo 15.3%

Infections: Vedolizumab 44.1% vs. Placebo 40.2%

Serious infections: Vedolizumab 5.5% vs. Placebo 3.0%

Induction phase was double-blind RCT, allocation was likely to be concealed, ITT analyses

**[15]** Phase 3 trial, randomised, double-blind placebo-controlled study in CD (n=416):

Assessed vedolizumab against placebo in patients with prior TNF-alpha inhibitor failure (76%) or conventional treatment (24%)

Induction phase:
- Primary endpoint in patients with prior TNF-alpha inhibitor failure – Clinical remission (CDAI score <150) at 6 weeks: Vedolizumab 15.2% vs. Placebo 12.1%; p=NS
- Exploratory analysis - Clinical remission (CDAI score <150) at 10 weeks: Vedolizumab 26.6% vs. Placebo 12.1%; nominal p=0.001
- Exploratory analysis - Clinical response (100+ point decrease in CDAI score) at 6 weeks: Vedolizumab 39.2% vs. Placebo 22.3%; nominal p=0.001

Serious adverse event rates: Vedolizumab <1% vs. Placebo <1%

Discontinuation due to adverse events: Vedolizumab 2% vs. Placebo 4%

Short term induction trial. Double-blind RCT, allocation was likely to be concealed, ITT analyses

**[16]** Phase 3 trial, randomised, double-blind placebo-controlled study in UC (n=895):

Assessed vedolizumab against placebo in patients with prior TNF-alpha inhibitor failure (48%) or conventional treatment (52%)

Induction phase:
- Primary endpoint – all patients – Clinical response (defined by Mayo clinic scores) at 6 weeks: Vedolizumab 47.1% vs. Placebo 25.5%; p<0.001
- Primary endpoint – patients with prior TNF-alpha inhibitor failure – Clinical response at 6 weeks: Vedolizumab 39.0% vs. Placebo 20.6%; p=0.001

Serious adverse event rates: Vedolizumab 12.4% vs. Placebo 13.5%

Serious infections: Vedolizumab 1.9% vs. Placebo 2.9%

Short term induction trial. Double-blind RCT, allocation was likely to be concealed, ITT analyses

Maintenance phase involved enriched population of known responders
<table>
<thead>
<tr>
<th>Maintenance phase:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical remission (defined by Mayo clinic score) at 52 weeks in all patients who responded to induction:</td>
</tr>
<tr>
<td>Vedolizumab every 8 weeks 41.8% vs. Placebo 15.9%; p&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other biologics following TNF-alpha inhibitor withdrawal: Ustekinumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 2b, randomised, double-blind placebo-controlled study in CD:</td>
</tr>
<tr>
<td>Induction phase (n=526) &amp; Maintenance phase in those who responded in induction phase (n=364)</td>
</tr>
<tr>
<td>Assessed IV ustekinumab induction (1mg/kg, 3mg/kg, or 6mg/kg) against placebo in patients with prior failure on one (50.8%) or more (48.9%) TNF-alpha inhibitor treatment.</td>
</tr>
<tr>
<td>Assessed SC ustekinumab 90mg maintenance treatment against placebo</td>
</tr>
<tr>
<td>Induction phase: Primary endpoint – Clinical response (100+ point decrease in CDAI score) at 6 weeks: Ustekinumab 6mg/kg 39.7% vs. Placebo 23.5%; p=0.005</td>
</tr>
<tr>
<td>Secondary endpoint – Clinical remission at 6 weeks: Ustekinumab 6mg/kg 12.2% vs. Placebo 10.6%; p=NS</td>
</tr>
<tr>
<td>Maintenance phase: Clinical remission (CDAI score &lt;150) at 22 weeks in all patients who responded to induction: Ustekinumab 41.7% vs. Placebo 27.4%; p=0.03</td>
</tr>
</tbody>
</table>

CD=Crohn’s disease; CDAI=Crohn’s disease activity index; HBI=Harvey-Bradshw Index; ITT=intention-to-treat; IV=intravenous; NS=not statistically significant; RCT=Randomised controlled trial; UC=Ulcerative colitis

Induction phase: Serious adverse event rates: Ustekinumab 6mg/kg 6.9% vs. Placebo 8.3%

Maintenance phase: Serious adverse event rates: Ustekinumab 12.5% vs. Placebo 16.4%

Short term induction trial. Double-blind RCT, allocation was likely to be concealed, ITT analyses Maintenance phase involved enriched population of known responders
Appendix: Structured search and results

PubMed searched 16/11 2015: (ulcerative colitis OR (Crohn's disease OR Crohns)) AND (anti-tfn OR tnf alpha inhibitors OR biologics OR adalimumab OR infliximab OR golimumab OR vedolizumab) AND (second line OR third line OR fourth line OR prior failure OR treatment experienced OR intolerance OR intolerant OR relapse OR relapsed OR refractory OR switch); limited to English Language, Human studies.

<table>
<thead>
<tr>
<th>Possible Inclusion/Exclusion</th>
<th># Hits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Search results</td>
<td>1,086</td>
</tr>
<tr>
<td>Excluded – not clearly relevant based on title/abstract</td>
<td>(1,015)</td>
</tr>
<tr>
<td>Possible: UC</td>
<td>12</td>
</tr>
<tr>
<td>Possible: Crohn's</td>
<td>48</td>
</tr>
<tr>
<td>Possible: UC and Crohn's /IBD</td>
<td>11</td>
</tr>
</tbody>
</table>

Cochrane Library searched 16/11/2015: ((anti-TNF) OR (TNF-alpha inhibitors) OR adalimumab OR infliximab OR golimumab OR vedolizumab) AND ((ulcerative colitis) OR Crohn's OR crohns); limited to systematic reviews or systematic review protocols.