Evidence for infliximab dose intensification (5mg/kg every 4-6 weeks) for the maintenance treatment of Ulcerative Colitis in patients who have lost response

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Background
The National Institute for Health and Care Excellence (NICE) guidance on the treatment of moderately to severely active ulcerative colitis (UC) after the failure of conventional therapy (TA329) recommend infliximab 5mg/kg given as an intravenous infusion followed by additional 5mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter.

Commissioning groups are being asked to fund requests for infliximab dose intensification (i.e. reducing intervals to 4-6 weeks at a 5mg/kg dose) for patients with UC that have lost response. It is unclear how long patients should remain on the escalated regimens and what patients are likely to benefit. The manufacturers (Merck Sharp & Dohme Limited), state that the safety and efficacy of re-administration of infliximab other than every 8 weeks has not been established. Therefore this review aims to answer the following question:

Key question
- What is the evidence for a reduced dosing interval (5mg/kg every 4-6 weeks) for the maintenance treatment of ulcerative colitis in patients who have lost response to standard infliximab maintenance therapy?

Summary
Infliximab is licenced for the management of ulcerative colitis at a dose of 5mg/kg every 8 weeks after an initial induction period.

The NICE clinical guideline on the management of ulcerative colitis does not address dose escalation of biologics. U.S. ulcerative colitis practice guidelines state some patients with an initial response to infliximab at a dose of 5mg/kg in whom the benefit is attenuated after multiple doses may benefit from dose escalation, or shortening dosing intervals, or both. They do not specify how dose intensification may be achieved.

A systematic search of the literature was carried out using both Medline and Embase databases. No randomised controlled trials (RCTs) were found addressing shortening the dosage interval of infliximab or a comparison between shortening dosage intervals versus changing to an alternative biologic. However, five retrospective observational studies investigating outcomes after infliximab intensification in patients with UC were identified. These studies were mainly on a small scale and range from 33 patients to the largest, which involved 144 patients. The duration of follow up for these studies ranged from a mean time of 13.6 to 38 months.

Dose intensification was found to be a common strategy to lost/attenuated infliximab response, with 37-70% of patients requiring intensification. All five studies included two types of dose intensification strategies: a proportion of patients received infliximab 5mg/kg every 4 or 6 weeks whilst others received a higher dose of 10mg/kg every 8 weeks. Dose intensification in the studies was always carried out according to clinical response, and not according to infliximab drug levels or antibody levels. Three out of the five studies demonstrated positive outcomes associated with dose intensification in patients with UC who had a loss of response during maintenance treatment. This enabled patients to have both short term rapid recovery responses (leading to a reduction in relative risk of colectomy) and also long term responses such as clinical remission and avoidance of colectomy. The remaining two studies showed that despite dose intensification, lower clinical remission rates, discontinuation for loss of response and higher colectomy rates were still seen. One of these studies reported that the cumulative risk of colectomy was not found to be significantly different between the escalated and non-escalated groups. The largest study (n=144) demonstrated that whilst dose intensification is effective in some patients, it can also be associated with poorer outcomes; although arguably these patients are likely to have a poorer prognosis. Rapid clinical response to dose intensification was found to be a possible predictor of better outcomes.

Results were generally given for the whole cohort of patients receiving either of the dose escalation regimens. However, the two studies which had a sub-group analyses on the two dose escalation regimens, found similar response rates. It was suggested, however, that as patients in the interval shortening groups were overall
more likely to return to a standard infliximab regimen, shortening the interval to 4-6 weeks could result in higher rates of de-escalation (de-escalation to standard dosing ranged from approximately 6-13 months), and hence this strategy may be more cost-effective than doubling the dose.  

Overall, there is limited evidence supporting the use of infliximab dose intensification in UC patients who have lost response to the standard 5mg/kg every 8 weeks maintenance treatment. All of the studies are small, retrospective studies and lack control comparisons, which limits the validity of the data due to selection bias. There is a lack of standard methods to evaluate relapse and response rates and some rely on clinical observation which can be subjective. Some of the studies showed that patients who had initial response to the intensified dose, later lost efficacy or were associated with a poorer outcome. Others lack detail and it is difficult to know how long patients continued to receive the intensified dose and the continued response rate at the end of follow-up.

In summary, there is limited data from published studies reporting a regain in clinical response after infliximab dose escalation in patients with UC. The results suggest that infliximab dose intensification could be considered before switching to another drug in patients who have lost response to infliximab during maintenance therapy. However, more robust adequately designed prospective studies with a control group are needed to draw firm conclusions.

**Published guidance**

UK National guidance on the management of ulcerative colitis, (NICE CG1661, NICE TA3293, British Society of Gastroenterologists and European Crohn’s and Colitis organisation), do not address the issue of infliximab dose intensification / shortening dosage intervals in patients with UC.

However, the American College of Gastroenterology Ulcerative Colitis Practice Guidelines state that, although not studied in a controlled manner, some patients with an initial response to infliximab at a dose of 5mg/kg in whom the benefit is attenuated after multiple doses may benefit from shortening dosing intervals or dose escalation, or both. They do not specify how dose intensification may be achieved.

**Published data**

*What is the evidence for reduced dosing interval (5mg/kg every 4-6 weeks) for the maintenance treatment of ulcerative colitis in patients who have lost response to standard infliximab maintenance therapy?*

There are no published randomised controlled trials that have evaluated the evidence for a reduced infliximab dosing interval (5mg/kg every 4-6 weeks) in patients with UC.

However, five relevant retrospective observational studies were identified from our systematic search of the literature. The studies were fairly small with the largest study including only 144 patients. They investigated the outcomes of infliximab dose intensification in UC patients with a secondary loss of response as well as comparing outcomes between intensified and non-intensified infliximab treatment.

The most recent evidence for infliximab dose intensification is from Taxonera et al which is an uncontrolled, open-label, retrospective analysis of 79 UC patients. The study aimed to assess the short term response to infliximab dose escalation in patients with severe UC who had lost response to the drug. Long term infliximab failure-free survival and colectomy-free survival rates were also assessed.

The short-term primary end-point was clinical response, defined as a 3-point decrease in the partial Mayo score or a decrease of ≥50% in the partial Mayo score and a final partial Mayo score of ≤2, with a drop in the rectal bleeding subscore of at least 1 point, or an absolute rectal bleeding score of 0 or 1. The long-term co-primary endpoints were the proportion of patients without infliximab failure at each study visit including the last follow-up visit and the need for colectomy. At baseline, 43% of patients were receiving corticosteroids and 77% were receiving an immunosuppressant. In 49 patients dose escalation was performed by decreasing the dosage interval (5mg/kg every 4 or 6 weeks), whilst in 30 patients, infliximab dose escalation was performed by increasing the dose to 10mg/kg every 8 weeks. Dose intensification was carried out according to clinical response, and not according to infliximab drug levels or antibody levels.

The following results were reported for the whole cohort of patients:
• At week 12, 68.4% of patients achieved a short-term clinical response, and 51.9% of patients entered clinical remission (defined as a partial Mayo score of 0 or 1). The mean partial Mayo score was 5.6 at baseline and reduced to 2.3 at week 12 (p<0.0001).

• At a median of 15 months (range 8-26 months) after the first dose escalation, 46 of 79 patients (58.2%) maintained sustained clinical benefit, whilst 33 patients experienced treatment failure (complete loss of response (n=26) or adverse effects (n=7)).

• None of the patients needed a colectomy before week 12. During a median follow-up of 24 months, 9 of 79 patients (11.4%) needed colectomy. The median time to colectomy was 9 months. Seven of the colectomies occurred among the 25 short-term non-responders and only 2 of 54 patients who achieved short-term clinical response required colectomy during the follow-up (p = 0.005). Of the 13 patients who received infliximab as in-patients in hospital, three underwent colectomy at weeks 36, 42, and 130, respectively.

• The safety analysis included data from 83 patients exposed to high doses of infliximab for a total of 1175 months and reported 18 adverse events per 100 patients/years of therapy; 6 of these adverse events were considered serious.

Among the 28 patients who received 5mg/kg every 6 weeks, 18 (64%) required a second dose escalation (mainly to 5mg/kg every 4 weeks or to 10 mg/kg every 8 weeks). Median time to the second escalation was 5 months. After a median of 6 months of dose escalation, 12 of 79 patients (24%) were able to return to the standard infliximab regimen (5mg/kg every 8 weeks). Further sub-analysis of the data showed a trend towards a reduced response rate (63%) in the short-term in those receiving infliximab 5mg/kg every 6 weeks compared to 10mg/kg every 8 weeks (p=0.09), although this was not statistically significant. It was concluded that there were no differences between doubling the dose and halving the interval as escalation strategies.

This cohort study reports the outcomes of infliximab dose escalation in UC patients with a loss of response. Approximately 70% of patients achieved response after dose escalation, with a colectomy rate of 11% in the whole study population. Achieving short-term clinical response after infliximab dose escalation was the only significant predictor of better outcomes in the long term. Among the cohort of patients achieving short-term response, 3 of 4 maintained sustained clinical benefits and only 4% needed colectomy. Conversely in the cohort of short-term non-responders, only 1 of 4 patients had sustained clinical benefits and 28% needed colectomy. For patients who had short-term response, there was an 86% reduction in the relative risk of colectomy. The authors concluded that these marked differences can help decide the best therapeutic strategy in UC patients. For UC patients who have lost response to infliximab during maintenance, infliximab dose escalation can be considered before switching to another drug.

Cesarini et al7 (2014) conducted a retrospective multicentre study (n= 41) in Europe to investigate infliximab dose optimisation in UC patients with secondary loss of response and to compare safety and efficacy outcomes in subjects treated with dose increase or interval shortening. Fifteen subjects were treated by doubling the dose (DD group) to 10 mg/kg every 8 weeks and 26 were treated by interval shortening (IS group) to every 4–6 weeks. Optimisation strategy was chosen on a clinical basis, according to the clinician’s judgement.

The primary outcome was rapid clinical response, defined as a decrease of at least 30% from baseline in the clinical Mayo subscore, with no partial score exceeding 2, assessed at the next time of infliximab administration. Secondary outcomes were rapid clinical remission (defined as a global Mayo Score <1), clinical remission (defined as Mayo subscore ≤1), clinical response (defined as a decrease of 3 points of partial Mayo score and of at least 30% from baseline), and colectomy rate at week 52 following infliximab dose intensification. Adverse events due to dose intensification were also evaluated and compared.

• In the whole study population, rapid clinical response was achieved in 90.2% of patients and rapid clinical remission in 46.3%.

• In the DD group (n=15), 86.7% of patients had rapid clinical response and 66.7% had rapid clinical remission, compared to 92.3% and 34.6% in the IS group (n=26), respectively.

• At week 52, 68.3% maintained clinical remission, but 9.8% under-went colectomy. In the DD group 53.3% of patients were in remission and 20% underwent colectomy, compared to 76.9% and 3.8% in the IS group.
Dose optimisation was considered generally safe. Five of 41 subjects (12.1%) developed adverse events: allergic reaction to infliximab (n = 3), psoriasis-like skin rash (n = 1), and pericarditis (n = 1). One patient developed pneumonia soon after he had developed an allergic reaction to infliximab.

A total of 21 patients were able to return to the standard regimen (5mg/kg every 8 weeks) after a mean period of 13.6 months (range 4.7–37.6 months) of dose escalation; 4 of these were in the DD group and 17 in the IS group (p=0.008). Eleven subjects (28%) required a second dose optimisation (mean time: 7.09 months, range 1–18 months), and were able to return to the standard regimen after both optimisations, except for one patient who underwent colectomy.

Overall, dose optimisation of infliximab was found to be effective to restore clinical response or remission and to prevent colectomy in UC patients with secondary loss of response. No significant difference was found between the DD and IS groups for all outcomes (p = 0.14 for remission, p = 0.25 for colectomy). Subjects who achieved rapid clinical response had significantly higher chance of avoiding colectomy than patients who did not (p = 0.002 at week 52). As patients in the IS group were overall more likely to return to a standard regimen with infliximab (p = 0.01), it is suggested shortening the interval to 4–6 weeks may result in higher rates of de-escalation, and that this strategy may be more cost-effective than doubling the dose.

Yamada et al (2014) conducted a retrospective study (n=33) assessing the long-term efficacy of infliximab dose intensification in patients with refractory UC in a hospital in Japan. Refractory UC was defined as steroid-resistant, steroid dependant, or refractory to immunosuppressive therapies (such as tacrolimus and azathioprine). Infliximab intensification was defined as a dose escalation (up to 10 mg/kg) and/or shorter intervals between infusions (every 4–6 weeks). The long term efficacy of infliximab treatment was determined by evaluating the remission maintenance rate, the colectomy–free rate and mucosal healing rates. Colectomy rates were compared in patients who did or did not achieve mucosal healing.

All patients received infliximab induction treatment; two patients experienced adverse events requiring discontinuation of infliximab. Scheduled maintenance treatment followed, and of the 24 responders, seven patients (29.2%) maintained clinical remission, whereas 17 patients (70.8%) experienced a relapse of UC and required infliximab intensification.

The results were as follows:

- After dose intensification, 16 patients (94.1%) achieved and maintained clinical remission, whereas 1 patient (5.9%) required tacrolimus owing to failure of infliximab intensification.
- The remission maintenance rates at 6, 12, 24 and 36 months after infliximab initiation in the 24 responders who received infliximab maintenance treatment were 100%, 100%, 92.3% and 90% respectively.
- The cumulative remission maintenance rate of the 24 responders to infliximab maintenance treatment including infliximab intensification was estimated to be 90.9% at 63 months.
- Of the 33 patients who received infliximab treatment, 6 (18.2%) underwent colectomy during follow-up, including 4 patients who did not respond to infliximab induction treatment and 2 who were found to have colon cancer during scheduled infliximab maintenance treatment. The colectomy free rate at 3, 6, 12, and 36 months after infliximab use were 92.9%, 88.5%, 82.6% and 64.3% respectively.
- 17 of the 24 responders had colonic examinations at a median 10.0 months. A total of 13 of the 17 patients achieved mucosal healing; six were receiving infliximab intensification therapy. Rates of mucosal healing 6, 12, 24 and 36 months after infliximab initiation were 87.5%, 80.0%, 78.6% and 81.3%, respectively. None of the patients who showed mucosal healing underwent colectomy, whereas two of the four patients (50%) who did not show mucosal healing underwent colectomy for colon cancer.

The findings showed that infliximab intensification can maintain clinical improvement in patients with refractory UC, over a median follow-up of 1.5 years. The authors found that 70.8% of the initial responders to infliximab required infliximab intensification and that 87.5% maintained clinical remission. Additionally, all UC patients who received infliximab intensification therapy avoided colectomy, with a cumulative colectomy-free rate in the 33 infliximab treated patients calculated to be 64.8% at 63 months.
Fernández-Salazar et al. (2015) conducted a retrospective analysis of 10 hospitals with 144 patients whom had a response to infliximab induction. The aim was to establish the frequency and form of intensification for UC in clinical practice, as well as predictors and to compare outcomes between intensified and non-intensified treatment. Predictive variables for intensification were analysed and outcome, loss of response to infliximab and colectomy rates were compared between intensified and non-intensified therapy.

Follow-up was 38 months and duration of infliximab therapy, 24 months. The results were as follows:

- A total of 37% of patients received intensified therapy. The criteria for infliximab intensification varied at each site and further explanation with regards to this was not given. Thirty-six patients had shortened intervals and received 5mg/kg every 6 weeks following 9.5 months (IQR 5-16) after induction, seven patients received 10mg/kg every 8 weeks following 9 months (IQR 4-20) from induction, and ten patients required double intensification (10mg/kg every 6 weeks), with the first intensification occurring at 6 months (IQR 4-9) after induction. Therefore, the intensification rate was 2.3 per 100 patients monthly.

- Steroid reintroduction (35% vs. 18%; p = 0.018), infliximab discontinuation for loss of response (30.4% vs. 10.1%; p = 0.002) and colectomy rates (22% vs. 6.4%; p = 0.013) were higher with infliximab intensification versus standard therapy. Adverse event rates were similar (14.3% vs. 20.5%, p=NS).

- Therapy de-intensification was attempted for 14 patients, and this was sustained in 9. All 9 patients on de-intensified therapy had a lower loss-of-response rate (0% vs. 38.6%; p = 0.024) and colectomy rate (0% vs. 28.9%; p = 0.087), the latter without statistical significance, as compared to patients who remained on intensified therapy. The reason for de-intensification was not a studied variable, but was considered in the study as mostly due to infliximab response recovery.

- Use of thiopurine immunosuppressants before infliximab, clinical remission after infliximab induction and thiopurine immunosuppressant therapy concurrent with infliximab were factors predictive of infliximab intensification. Time of immunosuppressant therapy introduction for co-treatment was the only variable independently predicting intensification.

Overall, the study concludes that infliximab intensification is common. In this case it was associated with poorer outcomes; these patients arguably have a poorer prognosis, however. Whilst the study includes a larger number of patients across 10 different sites with data collection over 10 years, the fact that the criteria for therapy intensification was omitted detracts from the study’s robustness and creates a major limitation of the data.

Rostholder et al. (2012) carried out a retrospective observational study to examine the prevalence of, and outcomes after, infliximab therapy escalation in patients with moderate-severe UC receiving maintenance treatment (n=56). Escalation was defined as either an increase in maintenance infliximab to 10mg/kg at least every 8 weeks or 5mg/kg every 4-6 weeks. The primary outcome was clinical remission at 12 months (defined as the absence of symptoms of active UC e.g. no diarrhoea, rectal bleeding or abdominal pain). The secondary outcome was cumulative rate of colectomy during the follow up period. An intention to treat analysis was used for efficacy outcomes.

Infliximab therapy escalation was required in 54% patients (due to relapse in symptoms), after an average of 6 maintenance infusions. The baseline demographic and clinical characteristics of patients in both escalation and non-escalation groups at inception were similar (data not provided). Patients who required dose escalation had a longer mean duration of UC at initiation of infliximab than those who did not require escalation (10.4 years vs. 6 years, P = 0.03 by t-test). No other individual demographic or clinical factor was significantly associated with the need for dose escalation in this cohort. Patients who required dose escalation received a mean total number of 12 infusions, and had 34 months of follow-up.

Clinical remission was noted in 36% at 12 months in the entire cohort. Patients on dose escalation had a remission rate of 19% at 12 months, compared with 56% in the non-escalation group. Neither concomitant therapy with azathioprine or mercaptopurine, pre-treatment CRP or ESR levels, or drop in CRP were significantly associated with the probability of clinical remission at 12 months. Patients who required infliximab escalation were less likely to be in clinical remission at 12 months (OR 0.2, 95% CI 0.1–0.6, P = 0.01) when compared with those who did not require escalation. Overall, 27% of all patients with moderate UC who received maintenance infliximab therapy required a colectomy during follow-up; 33% in the escalation group.
and 21% in the non-escalation group which was not a statistically significant difference. The mean time to colectomy was 17 months in the whole cohort.

It was concluded that a significant proportion of patients with UC treated with maintenance infliximab required therapy escalation over time. Patients receiving dose escalation had lower remission rates and higher colectomy rates.

Details of search strategy:

A. Search of relevant guidance
   - NICE, British Society of Gastroenterologists Guidelines, European Crohn’s and Colitis Organisation (ECCO), American College of Gastroenterology and Cochrane.

B. Literature search of Medline and Embase
   - EMTREE terms: ("INFLIXIMAB/ AND ""ULCERATIVE COLITIS") AND ("DRUG TREATMENT FAILURE"/ OR "TREATMENT FAILURE") AND ("DRUG DOSE INCREASE"/ OR "DRUG DOSE INTENSIFICATION"/ OR "DRUG DOSE ESCALATION")

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1. NICE clinical guideline on the management of ulcerative colitis (June 2013) https://www.nice.org.uk/guidance/cg166/resources/ulcerative-colitis-management-35109695126725
3. NICE technology appraisal guidance on infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy (25 February 2015) https://www.nice.org.uk/guidance/ta329