NHS
Cambridgeshire and Peterborough
Clinical Commissioning Group

DOSE ESCALATION FOR PATIENT'S RECEIVING INFLIXIMAB INFUSIONS FOR INFLAMMATORY BOWEL DISEASE

ISSUE

This paper is for the approval of dose escalation for patient's receiving infliximab infusions for CCG commissioned indications within the product licence.

This paper does not include any dose escalation in relation to the prescribing of subcutaneous infliximab.

KEY POINTS

2.1	We currently commission infliximab infusions 8 weekly for Crohn's disease, ulcerative colitis (UC), rheumatoid conditions, and psoriasis in line with the relevant NICE TAs. For patients with Crohn's disease and Ulcerative colitis a dose escalation for 3 doses is also commissioned.
2.2	During the reconciliation process of High-Cost Drugs invoices it has been identified that a significant proportion of the patients with an indication of inflammatory bowel disease are receiving more frequent infusions than 8 weekly, and these charges have been challenged and not funded.
2.3	IFR's have been submitted for several patient's following these challenges and due to the high volume of requests, a business case is presented.
2.4	Following discussions at both Cambridge University Hospital NHS Foundation Trust and North West Anglia Foundation Trust it was proposed that the CCG agree to fund dose escalation as the evidence/ experience with use has progressed since the NICE Technology Appraisal was published.
2.5	A patient on standard 8 weekly infusions of infliximab will receive 8.75 doses in year 1 and on average 6.5 infusions each year thereafter. A patient on 6 weekly infusions will receive 10.5 doses in year 1 and 8.7 doses a year thereafter.
2.6	Likewise, there are a small number of patients that are on extended doses e.g., 10 weekly.
2.7	Looking at the infusions provided to patient's this year at our Trusts approximately a third of patients appear to be receiving more frequent infusions, particularly those with Crohn's disease.
2.8	Vedolizumab and Ustekinumab are both now additional options for treatment for patients with Crohn's disease and ulcerative colitis. However, these are significantly more expensive than intravenous infliximab (and associated tariff costs), including in comparison to costs associated with dose escalation.

2.9	Dose escalation is being requested for those patients that demonstrate a good response to infliximab infusion however the duration of effect is not maintained from the standard 8 weekly administration, requiring patients to need up to 6 weekly infusions. The frequency will vary between patients from 6 to 8 weekly dependent on individual response.

BACKGROUND INFORMATION

There is increasing evidence that patients respond to infliximab in differing ways and that a group of patients require infliximab to be administered more frequently than NICE guidance suggests. The guidance is now 10 years old and so best practice has moved on. It is unlikely that the guidance will be reviewed so clinicians have adopted differing methods of treating patients with increasing doses of infliximab.

Our neighbouring CCGs have allowed clinicians the ability to increase the dose where required to bring and maintain patients in remission thus reducing the need for more expensive drugs or surgery.

At present CPCGG request an IFR before escalating dosage is agreed. This is becoming an increasing administrative burden for the Exceptional Case panel and an administrative burden for clinicians. Where IFRs have been presented (6 since January 2020) all have been agreed.

EVIDENCE AND SAFETY

Relevant retrospective observational studies were identified. 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.

Evidence for infliximab dose intensification is available from Taxonera et al as 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 endpoint 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 coprimary 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.
- 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.
- 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).

Cesarini et al (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. Secondary outcomes were rapid clinical remission, clinical remission, clinical response 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).
- 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).

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 who 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.

Overall, the study concluded that infliximab intensification is common. However, in this case it was associated with poorer outcomes, but these patients had a poorer initial prognosis compared to other studies. 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 and reported outcomes.

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.

RECOMMENDATION

It is recommended to CPJPG and CCG Governing Body, that clinicians are supported to be able to choose dose frequency of intravenous infliximab based on patient response to the standard 8 weekly infusion frequency.

Infliximab (intravenous) biosimilar is a low-cost treatment for patients suffering from Ulcerative colitis and Crohn's disease. In escalating doses in patients who do not respond to the normal schedule, it enables clinicians to optimise patients without use of more expensive drugs or in extreme cases surgery with the lifelong cost of stoma treatments and patient inconvenience.

By offering this treatment without the need to fill out an IFR, it reduces the need for clinicians to spend considerable administrative time which could be better used in seeing and treating patients.

1. Taxonera C et al. Infliximab dose escalation as an effective strategy for managing secondary loss of response in ulcerative colitis. Digestive Diseases and Sciences 2015; 60 (10): 3075-3084
2. Cesarini M et al. Dose optimization is effective in ulcerative colitis patients losing response to infliximab: A collaborative multicentre retrospective study. Dig Liver Dis. 2014; 46(2): 135-139.
3. Yamada S et al. Long- term efficacy of infliximab for refractory ulcerative colitis: results from a single center experience. BMC Gastroenterology 2014;14 (80):1471-1480.
4. Fernández-Salazar L et al. Frequency, predictors and consequences of maintenance infliximab therapy intensification in ulcerative colitis. Rev Esp Enferm dig. 2015; 107 (9): 527-533.