

## Evidence Review for Prescribing Clinical Network

**Treatment:** Continuation of dose escalation and switching of Biologics (Infliximab and Adalimumab) in secondary failure of Crohn's Disease

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**Topic Submitted by:** Surrey IBD network

**Date:** December 2014

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### Summary page

Infliximab and Adalimumab are licensed and are used by local gastroenterologists to treat Crohn's Disease. Currently there is no commissioned pathway for patients who lose response to these treatments. The PCN are asked to consider commissioning

- Gastroenterologists to switch patients to other NICE approved biologic after secondary failure (loss of response to 1<sup>st</sup> line biologic) but not dose escalate before switch, OR
- Gastroenterologists to dose escalate (Infliximab (5mg/kg) 4-6 weekly, 10mg/kg (3 doses) OR Adalimumab weekly) for 12 weeks to recapture response (already commissioned). At 12 weeks the patient should be revert back to standard dosing (8 weekly Infliximab and bi weekly Adalimumab). If disease flares then switch to other biologic
- Gastroenterologists to dose escalate (Infliximab (5mg/kg) 4-6 weekly, 10mg/kg (3 doses) OR Adalimumab weekly) AND if the patient responds to treatment (in line with pre-defined criteria), at 12 weeks the dose will revert back to standard dosing. If the disease flares the patient will be able to continue with the dose escalation (following an MDT discussion) and then switch to the other NICE approved biologic if the escalated dose does not control disease.

How strong is the evidence for claimed efficacy? **There is published British guidance intended to guide clinicians in the UK (post NICE). The guidance makes reference and compliments the European Crohn's & Colitis Organisation (ECCO) guidelines and the NICE guidance (TA187 May 2010)**

Potential advantages: **There is no cure for Crohn's Disease, optimising the current available treatments will delay or avoid surgery for these patients**

Is there a clear place in therapy / treatment pathway? **Proposed treatment pathway at the foot of this review**

Is monitoring for efficacy required? **Monitoring by specialist in secondary care**

Is monitoring for toxicity required? **Monitoring by specialist in secondary care**

Is dose titration required? **Not required**

Traffic light status (ie who will prescribe the drug and any restrictions required)? **RED**

Role of the specialist (if applicable)? **Monitor patient's response to treatment (clinical, biochemical and endoscopic) and communicate outcomes to commissioners so that continued funding can be agreed.**

Role of GP (if applicable)? **Be aware of side effects, potential complications and report to specialist**

Financial implications?

**Costs of standard dosing (local discounts may apply)**

- **Infliximab (5mg/kg) induction plus 8 weekly dosing (1<sup>st</sup> year costs)** £12k - £16k/year inclusive of VAT. A day case infusion tariff (estimated £400-500) would also be charged for each administration of infliximab.
  - **Subsequent years (8 weekly dosing)** - £9k to £12k (inclusive of VAT)
- **Adalimumab induction (accelerated schedule) plus bi-weekly dosing (1<sup>st</sup> year costs)** - £11k
  - **Subsequent years (bi weekly dosing)** – £9155.64/year

**Cost of dose escalation:** Currently commissioned for 12 weeks and then back to standard dosing above

- **Infliximab 6 weekly dosing (5mg/kg)** - £3k to £4k (2 x 6 weekly doses). A day case infusion tariff (estimated £400-500) would also be charged for each administration of infliximab.
- **Infliximab 4 weekly dosing (5mg/kg)** – £4.5k to £6k (3 x 4 weekly doses) A day case infusion tariff (estimated £400-500) would also be charged for each administration of infliximab.
- **Infliximab 10mg/kg (3 doses)** - £6k A day case infusion tariff (estimated £400-500) would also be charged for each administration of infliximab.
- **Adalimumab weekly dosing** - £4,225.68/12 weeks

**Continued (on-going) dose escalation**

- **Infliximab 6 weekly dosing (weight based)** - £13k to £17.5k/year inclusive of VAT A day case infusion tariff (estimated £400-500) would also be charged for each administration of infliximab.
- **Infliximab 4 weekly dosing (5mg/kg)** – £18k to £24k/year inclusive of VAT A day case infusion tariff (estimated £400-500) would also be charged for each administration of infliximab.
- **Adalimumab (40mg) weekly dosing** - £18,590/year

**Cost of switching**

- **See costs above for costs of both treatments in comparison.**

Other issues: **Infliximab off patent in February 2015. Biosimilar will be available soon after. The cost of infliximab may be reduced but the infusion tariff will still be charged.**

National Guidance available: NICE TA187 (May 2010). **Switching of biologic treatment was not discussed. Dose escalation was noted and accepted that local arrangements would have an impact on relative costs**

**VERSION CONTROL SHEET**

| Version | Date          | Author      | Status | Comment  |
|---------|---------------|-------------|--------|--|
| V1      | October 2014  | Clare Johns |        | Evidence and treatment pathway discussed and amended by local gastroenterology consultants |
| V2      | December 2014 | Clare Johns |        |  |

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**1. Purpose of the Review**

Both of these biologic treatments are licensed and are used by local gastroenterologists to treat Crohn's Disease but patients lose response (secondary failure) to these treatments and currently there is no commissioned pathway for these patients to switch to the other NICE approved biologic treatment

**2. Appropriateness**

**2.1 The problem:** Switching of biologic treatment was not discussed when NICE published TA187 (May 2010) Dose escalation was noted and accepted that local arrangements would have an impact on relative costs NICE TA187 (May 2010)

**Current status for funding:**

Biologic Naïve patients or new episode of care: Funding for either Adalimumab or Infliximab for an initial treatment period (Adalimumab – 3 months/ Infliximab 3 induction doses). Following induction a clinical update is required.

**Dose Escalation: Current process**

Patients can be dose escalated as follows:

- Adalimumab weekly OR
- Infliximab 10mg/kg (3 doses) OR
- Decrease dose interval to 6 weekly or 4 weekly

Funding is for 12 weeks in total (to recapture response) and then patients are expected to return to normal dosing (bi weekly for Adalimumab for 8 weekly for Infliximab)

**Comments: Currently 5mg/kg 4-6 weekly is outside of the product license for Infliximab in adults (only children). Increasing the dose to 10mg/kg is noted in the ACCENT trial which is quoted in the Infliximab license.**

Local clinicians were asked the reasons for their choosing to decrease dose interval, usually to 6 weeks over the escalation to 10mg/kg for up to 3 doses. Clinicians at the gastroenterology network responded that patients usually respond well and then present with loss of response after 5 or 6 weeks and struggle for 2-3 weeks before next infusion so decreasing dose interval seems more logical. They considered that both should be options as occasionally they do need to increase the initial response and use 10mg/kg.

**Switching biologic treatment: Current process**

- Where a patient has an allergic reaction (at any time) to the initial treatment choice OR
- Where a patient has not responded to induction treatment (Objective response to treatment should be provided via blueteq (continuation form) after 3 months for Adalimumab and after 2 or 3 doses of infliximab (PRIMARY FAILURE)

**Definition:** [www.emedicine.medscape.com](http://www.emedicine.medscape.com)

Crohn disease is an idiopathic, chronic inflammatory process of the gastrointestinal tract that can affect any part of the tract from the mouth to the anus. Individuals with this condition often experience periods of symptomatic relapse and remission

## Signs and symptoms

The characteristic presentation in Crohn disease is abdominal pain and diarrhea, which may be complicated by intestinal fistulization or obstruction. Unpredictable flares and remissions characterize the long-term course.

Other signs and symptoms in Crohn disease may include the following:

- Rectal bleeding
- Fever
- Weight loss, anorexia
- Nausea, vomiting
- Malnutrition, vitamin deficiencies
- Generalized fatigability
- Bone loss
- Psychosocial issues (eg, depression, anxiety, and coping difficulty); pediatric patients may also experience psychological issues regarding quality of life and body image
- Growth failure in pediatric patients: May precede gastrointestinal symptoms by years

## Diagnosis

Examination for Crohn disease includes the following:

- Vital signs: Normal, but possible presence of tachycardia in anemic or dehydrated patients; possible chronic intermittent fever
- Gastrointestinal: May vary from normal to those of an acute abdomen; assess for rectal sphincter tone, gross rectal mucosa abnormalities, presence of hematochezia
- Genitourinary: May include presence of skin tags, fistulae, ulcers, abscesses, and scarring in perianal region; nephrolithiasis, hydronephrosis, and enterovesical fistulae
- Musculoskeletal: Possible arthritis and arthralgia, particularly in large joints<sup>[7]</sup>
- Dermatologic: May show pallor or jaundice, mucocutaneous or aphthous ulcers, erythema nodosum, and pyoderma gangrenosum
- Ophthalmologic: May reveal episcleritis; possible uveitis
- Growth delay: Decreased growth velocity (eg, height), pubertal delay
- Hematologic: Hypercoagulable state

**Laboratory Tests:** Although laboratory results for Crohn disease are nonspecific and are of value principally for facilitating disease management, they may also be used as surrogate markers for inflammation and nutritional status and to screen for deficiencies of vitamins and minerals.

**Imaging studies:** Radiography, barium contrast, CT scans, MRI pelvis, abdominal imaging, nuclear imaging

**Procedures:** Endoscopy, Colonoscopy, ileocolonoscopy, small bowel enteroscopy

## 2.2 The Intervention: [www.medicines.org.uk](http://www.medicines.org.uk)

### Infliximab

Infliximab (Remicade, Schering-Plough Ltd) is a tumour necrosis factor alpha (TNF- $\alpha$ ) inhibitor and has a UK marketing authorisation as follows:

Adult Crohn's disease:

Remicade is indicated for:

- treatment of moderately to severely active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies.
- treatment of fistulising, active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with conventional treatment (including antibiotics, drainage and immunosuppressive therapy).

**Adalimumab**

Adalimumab (Humira Abbott Laboratories) is a recombinant human monoclonal antibody.

Crohn's disease

Humira is indicated for treatment of moderately to severely active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies.

**How do they work?**

TNF is a cytokine that is released from T lymphocytes; it mediates inflammation and modulates the cellular immune response.

Infliximab is a chimeric human-murine monoclonal antibody that binds with high affinity to TNF- $\alpha$  and inhibits its functional activity.

Adalimumab is a recombinant human monoclonal antibody that binds specifically to tumour necrosis factor alpha (TNF- $\alpha$ ), blocking interaction with its cell-surface receptors and thereby limiting the promotion of inflammatory pathways.

**Care setting:** Infliximab is given by intravenous infusion in the outpatient setting  
Adalimumab is given by subcutaneous injection and is available via homecare

**Frequency:**

**Infliximab:**

**Moderately to severely active Crohn's disease**

5 mg/kg given as an intravenous infusion followed by an additional 5 mg/kg infusion 2 weeks after the first infusion. If a patient does not respond after 2 doses, no additional treatment with infliximab should be given. Available data do not support further infliximab treatment, in patients not responding within 6 weeks of the initial infusion.

In responding patients, the alternative strategies for continued treatment are:

- Maintenance: Additional infusion of 5 mg/kg at 6 weeks after the initial dose, followed by infusions every 8 weeks or
- Re-administration: Infusion of 5 mg/kg if signs and symptoms of the disease recur.

Although comparative data are lacking, limited data in patients who initially responded to 5 mg/kg but who lost response indicate that some patients may regain response with dose escalation. Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit after dose adjustment.

**Fistulising, active Crohn's disease**

5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg infusions at 2 and 6 weeks after the first infusion. If a patient does not respond after 3 doses, no additional treatment with infliximab should be given.

- In responding patients, the alternative strategies for continued treatment are: Maintenance: Additional infusions of 5 mg/kg every 8 weeks or
- Re-administration: Infusion of 5 mg/kg if signs and symptoms of the disease recur followed by infusions of 5 mg/kg every 8 weeks

Although comparative data are lacking, limited data in patients who initially responded to 5 mg/kg but who lost response indicate that some patients may regain response with dose escalation (see section 5.1). Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit after dose adjustment.

In Crohn's disease, experience with re-administration if signs and symptoms of disease recur is limited and comparative data on the benefit/risk of the alternative strategies for continued treatment are lacking.

**Adalimumab:** The recommended Humira induction dose regimen for adult patients with moderately to severely active Crohn's disease is 80 mg at Week 0 followed by 40 mg at Week 2. In case there is a need for a more rapid response to therapy, the regimen 160 mg at Week 0 (dose can be administered as four injections in one day or as two injections per day for two consecutive days), 80 mg at Week 2, can be used with the awareness that the risk for adverse events is higher during induction.

After induction treatment, the recommended dose is 40 mg every other week via subcutaneous injection. Alternatively, if a patient has stopped Humira and signs and symptoms of disease recur, Humira may be re-administered. There is little experience from re-administration after more than 8 weeks since the previous dose.

During maintenance treatment, corticosteroids may be tapered in accordance with clinical practice guidelines.

Some patients who experience decrease in their response may benefit from an increase in dosing frequency to 40 mg Humira every week.

Some patients who have not responded by Week 4 may benefit from continued maintenance therapy through Week 12. Continued therapy should be carefully reconsidered in a patient not responding within this time period.

### **2.3 Alternative treatments:**

Corticosteroid treatment, 5-aminosalicylate (5-ASA) treatment, antibiotics and immunosuppressive treatment

## **3. Effectiveness**

**3.1 Expected benefits:** Commission care to optimise available therapies for patients with severe presentation of Crohn's Disease

### **3.2 Review of evidence (See Appendix 1. for Search Strategy and Summary of Results)**

[www.nice.org.uk](http://www.nice.org.uk)

TA187 – May 2010

## **1. Guidance**

- 1.1.** Infliximab and adalimumab, within their licensed indications, are recommended as treatment options for adults with severe active Crohn's disease (see 1.6) whose disease has not responded to conventional therapy (including immunosuppressive and/or corticosteroid treatments), or who are intolerant of or have contraindications to conventional therapy. Infliximab or adalimumab should be given as a planned course of treatment until treatment failure (including the need for surgery), or until 12 months after the start of treatment, whichever is

shorter. People should then have their disease reassessed (see 1.4) to determine whether ongoing treatment is still clinically appropriate.

- 1.2. Treatment as described in 1.1 should normally be started with the less expensive drug (taking into account drug administration costs, required dose and product price per dose). This may need to be varied for individual patients because of differences in the method of administration and treatment schedules.
- 1.3. Infliximab, within its licensed indication, is recommended as a treatment option for people with active fistulising Crohn's disease whose disease has not responded to conventional therapy (including antibiotics, drainage and immunosuppressive treatments), or who are intolerant of or have contraindications to conventional therapy. Infliximab should be given as a planned course of treatment until treatment failure (including the need for surgery) or until 12 months after the start of treatment, whichever is shorter. People should then have their disease reassessed (see 1.4) to determine whether ongoing treatment is still clinically appropriate.
- 1.4. Treatment with infliximab or adalimumab (see 1.1 and 1.3) should only be continued if there is clear evidence of ongoing active disease as determined by clinical symptoms, biological markers and investigation, including endoscopy if necessary. Specialists should discuss the risks and benefits of continued treatment with patients and consider a trial withdrawal from treatment for all patients who are in stable clinical remission. People who continue treatment with infliximab or adalimumab should have their disease reassessed at least every 12 months to determine whether ongoing treatment is still clinically appropriate. People whose disease relapses after treatment is stopped should have the option to start treatment again.
- 1.5. Infliximab, within its licensed indication, is recommended for the treatment of people aged 6–17 years with severe active Crohn's disease whose disease has not responded to conventional therapy (including corticosteroids, immunomodulators and primary nutrition therapy), or who are intolerant of or have contraindications to conventional therapy. The need to continue treatment should be reviewed at least every 12 months.
- 1.6. For the purposes of this guidance, severe active Crohn's disease is defined as very poor general health and one or more symptoms such as weight loss, fever, severe abdominal pain and usually frequent (3–4 or more) diarrhoeal stools daily. People with severe active Crohn's disease may or may not develop new fistulae or have extra-intestinal manifestations of the disease. This clinical definition normally, but not exclusively, corresponds to a Crohn's Disease Activity Index (CDAI) score of 300 or more, or a Harvey-Bradshaw score of 8 to 9 or above.
- 1.7. When using the CDAI and Harvey-Bradshaw Index, healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect the scores and make any adjustments they consider appropriate.
- 1.8. Treatment with infliximab or adalimumab should only be started and reviewed by clinicians with experience of TNF inhibitors and of managing Crohn's disease

[www.bsg.org.uk](http://www.bsg.org.uk)

British Society of Gastroenterology Guidelines

**Guidelines for the management of inflammatory bowel disease in adults Craig Mowat et al (Gut 2011;60:571-607.doi:10.1136/gut.2010.224154)**

Practical guidance in the use of anti-TNF therapies in induction and maintenance strategies

**For IFX**, the dosing regimen is as follows:

- A dose of 5 mg/kg IFX is used with loading doses at 0, 2 and 6 weeks:
- If no evidence of initial response after two doses (primary non-responders), reconsider overall medical and surgical management of patient. Switch to ADA or dose intensification to 10 mg/kg can be considered but with caution as data supporting these strategies are not strong (EL4, grade C).
- If there is evidence of initial response, scheduled maintenance therapy will usually be appropriate. This is given initially at 8-weekly intervals (EL1b, RG B). Where response is lost, a valid initial strategy is to decrease infusion interval (initially to 6 weeks; no more frequent than 4-weekly) or to dose intensify by a single dose of 10 mg/kg or to switch to ADA (EL4, RG C).

**For ADA**, the induction regimen can be 80mg/40mg sc on successive weeks, or 160mg/80mg (EL1b, grade B). The 80mg/40mg loading regimen is associated with a high requirement for subsequent dose escalation (EL4 grade C).

The alternative of 160mg/80mg may be more effective in patients who have lost response /intolerant to IFX (EL2 grade C)

- Maintenance therapy is 40mg every other week
- If response is lost, then escalate to 40mg every week
- If response is regained, it may then be possible to decrease dosing back to 40mg every other week (EL5 RG D)

[www.ecco-ibd.eu](http://www.ecco-ibd.eu)

**The second European evidence-based consensus on the diagnosis and management of Crohn's disease: Current management (ECCO guidelines) A. Dignass et al Journal of Crohn's and Colitis (2010) 4, 28–62**

#### **ECCO Statement 5J (new)**

Loss of response to anti-TNF therapy should lead to re-evaluation of disease activity, exclusion of complications and discussion of surgical options with the patient [EL5, RG D]. For active disease, reduction in interval between doses, or dose escalation are appropriate strategies before switching to another agent [EL5 RG D]. Switching is an effective strategy [EL1b, RG A], but reduces future therapeutic options. For intolerance, especially if severe, switching to an alternative anti-TNF agent is appropriate. Response to a third anti-TNF therapy occurs in some patients and may be an appropriate option [EL3 RG C], although surgical options should also be considered and discussed. Primary lack of response may be determined within 12 weeks and an alternative anti-TNF agent tried for active disease [EL3, RG C].

**D'Haens GR et al (2011) The London Position Statement of the World Congress of Gastroenterology on Biological Therapy for IBD With the European Crohn's and Colitis Organization: When to start, when to stop, which drug to choose, and how to predict response? Am J Gastroenterol; 106:199-212**

This position statement of the World Congress of Gastroenterology published in 2011 states the following :



- Secondary non-response affects 30-40% of patients during the first year of anti-TNF therapy. It may be due to disease-related factors or drug-related factors, including the development of neutralising antibodies, altered clearance, or possibly biological escape mechanisms.
- A diminished or suboptimal response to infliximab may be managed by shortening the interval between dosing or increasing the dose to 10mg/kg
- Patients who continue to have a diminished or loss of response after increasing the dose may benefit from switching to a different anti-TNF agent
- Patients losing response to one anti-TNF have a lower chance of responding to a second anti-TNF agent

### **Additional evidence**

#### **For Switching**

**Lichtiger S et al (2010) The CHOICE trial: adalimumab demonstrates safety, fistula healing, improved quality of life and increased work productivity in patients with Crohn's disease who failed prior infliximab therapy. *Alimentary Pharmacology and Therapeutics*; 32:1228-1239**

The CHOICE trial was an open-label, single-arm Phase IIIb study evaluating the safety and efficacy of adalimumab in adult patients with moderate-to-severe CD who had failed to respond to, or had lost response to infliximab. The focus was on safety, fistula healing, quality of life, and work productivity. This study has been described in more detail as it was the largest uncontrolled study identified from the literature search (n=673). Following a minimum washout period of 8 weeks following the last infusion of infliximab, all patients received open-label treatment with adalimumab 160mg at week 0 and 80mg at week 2, followed by 40mg maintenance every other week (this could be increased to once weekly at the investigator's discretion).

The majority of patients (83%) had initially responded to infliximab but had stopped treatment due to adverse events or loss of response; 17% were primary non-responders. The mean age of participants was 41 years, 59% were female and 91% were white. Baseline characteristics were similar between the groups, except primary non-responders had a greater disease duration (15.9 vs. 13.4 years; p=0.015). Around 40% were receiving other treatments for CD (corticosteroids, aminosalicylates, and/or immunosuppressants) during the study. At least one draining cutaneous fistula was present in 13% at baseline. The main outcomes reported were as follows:

- Complete fistula healing was achieved in 34 of 88 patients (39%) with this complication at baseline
- Serious adverse events (majority GI in nature) were experienced in 13.1% (63.2 events per 100 patient-years)
- 3% (10.1 events per 100 patient-years) suffered from serious infections (mainly abscesses)
- Improvements in quality of life and work productivity were seen and sustained from week 4 to 24 for all patients (including primary non-responders)

**Adalimumab for Crohn's disease after infliximab treatment failure: a systematic review Da et al *Eur J Gastroenterol Hepatol*. 2013 Aug; 25(8):885-91**

The tumor necrosis factor inhibitors infliximab and adalimumab are effective treatments for Crohn's disease (CD); however, some patients treated with infliximab experience a loss of efficacy. There is a lack of high-quality evidence available on whether adalimumab is an effective treatment for patients who

have failed infliximab treatment. A systematic review was carried out to examine the efficacy and safety of adalimumab for the treatment of CD in patients who have failed infliximab treatment. PubMed, Google Scholar, and the Cochrane Library were searched using the terms 'adalimumab AND infliximab AND Crohn's'. Randomized-controlled trials and cohort studies were included if they involved patients treated with adalimumab after failing infliximab. Outcomes were response and remission rates, adverse event (AE) rate, and the rate of discontinuations because of AEs. Ten studies (one randomized-controlled trial and nine cohort studies) involving 1009 patients were included. Luminal disease remission rates ranged from 12 to 67% during induction and 29 to 72% during maintenance therapy. Fistulizing disease remission rates ranged from 5 to 50% during induction and 27 to 68% during maintenance therapy. Luminal disease response rates ranged from 29 to 83% during induction and 31 to 59% during maintenance therapy. Fistulizing disease response rates ranged from 15 to 44% during induction and 41 to 56% during maintenance therapy. The overall AE rate ranged from 13 to 69%. Most AEs were mild to moderate in severity. The rate of discontinuation because of AEs ranged from 0 to 14%. The findings reported in the current literature support adalimumab as an efficacious and safe treatment for CD in patients who have failed infliximab treatment

**Effectiveness of infliximab after adalimumab failure in Crohn's disease María Chaparro et al. *World J Gastroenterol* 2012 October 7; 18(37): 5219-5224**

**Abstract**

**AIM:** To evaluate the effectiveness of infliximab as a second-line therapy in Crohn's disease patients after adalimumab failure.

**METHODS:** A historical cohort study in a community based gastroenterology practice evaluated Crohn's disease patients treated with infliximab (induction plus maintenance) after adalimumab failure. Patients were identified using a large Spanish database (ENEIDA).

**RESULTS:** We included 15 Crohn's disease patients who received infliximab after adalimumab failure. Five patients discontinued adalimumab due to loss of response, 3 due to adverse events and 7 due to partial response. After infliximab therapy was started, all patients who had interrupted adalimumab due to loss of efficacy regained response. All patients who discontinued adalimumab due to adverse events responded to infliximab and maintained this response; one of these patients had an uneventful course on infliximab, but

2 developed adverse events. None of the 7 patients who interrupted adalimumab due to partial response reached remission with infliximab.

**CONCLUSION:** Switching from adalimumab to infliximab may be useful in patients who develop adverse effects or loss of response, however, the benefit of infliximab in primary non responders was not established.

**Comments on trial: Treatment study, no comparator arm. 5 patients who lost response to adalimumab. What conclusion can we draw from these 5 patients?**

**Efficacy of Infliximab as second-line Biologic in Crohn's Disease E Russo et al Reference: Sandborn WJ. *Ann Intern Med.* June 19;2007;146(12):829-38 10.1136/gutjnl-2014-307263.331**

**Comments on case series: Abstract only: 14 of the 28 patients had secondary loss of response to Adalimumab and were initiated on Infliximab. 12 of the 14 patients re-captured response. 11 of those patients were still on treatment at publication**

**Efficacy of switching to infliximab in Crohn's disease patients with loss of response to adalimumab H. Peeters et al Poster presentations: Clinical: Therapy & observation (2014) taken from ECCO (European Crohn's and Colitis Organisation Inflammatory Bowel Diseases website)**

In case of loss of response to adalimumab (ADA), switching to infliximab (IFX) is routinely done in patients with Crohn's disease (CD). Nevertheless, data on the efficacy of this strategy are scarce.

**Methods:** A prospective, observational, multicenter study was performed to evaluate the efficacy of IFX after loss of response to ADA in CD. Loss of response to ADA was defined as CDAI  $\geq$  220 in combination with CRP  $\geq$  5 mg/L or endoscopic or radiological evidence of disease activity and after at least 4 weeks of weekly injections of ADA. The primary efficacy variable was clinical remission at week 10 (CDAI  $\leq$  150). Other efficacy variables were clinical response and strong clinical response (respectively 70 and 100 point drop in CDAI) at week 10.

Clinical remission and response were also evaluated after 26 and 52 weeks. Therapy adjustments and safety data were recorded. Ethics committee approval was obtained.

**Results:** 22 CD patients were included at 11 BIRD centers (Belgian IBD Research and Development Group). Mean age was 36 years (19-69 y), M/F ratio was 5/17, mean disease duration was 7.3 years (1-33 y) and mean duration of ADA therapy was 24 months (6-60m). In 2 patients no CDAI score was recorded at week 10. At week 10 10/20 patients (50%) were in clinical remission. Clinical response and strong clinical response was seen in respectively 12/20 (60%) and 10/20 (50%) patients. At week 26 the clinical remission rate was 5/16 (31%), clinical response 11/16 (69%) and strong clinical response 6/16 (38%). The mean CDAI dropped from 289 (226-413) at baseline to 172 (0-371) at week 10 and 163 (0-399) at week 26. The mean CRP level dropped from 70 mg/L at baseline to 26 mg/L at week 10 and 29 mg/L at week 26. Ten patients needed IFX therapy optimization (interval shortening), 6 patients needed an intermittent course of steroids. In 2 patients immunomodulator therapy was changed. In none of the patients IFX therapy was ceased during the first 26 weeks. There were no infusion reactions. Data on sustained remission and response at week 52 are still being collected.

**Conclusions:** Switching from adalimumab to infliximab can be useful in patients with loss of response to adalimumab. Predictive factors of remission and response are currently under investigation.

## For Dose Escalation

### Dose escalation with infliximab

One RCT (ACCENT trial – discussed in the IBD guidance above) and five single-arm cohort studies reported the frequency and the results of infliximab dose escalation:

In ACCENT I, patients received induction therapy with infliximab (5mg/kg) at baseline and were then randomised to receive maintenance therapy with placebo (episodic treatment), scheduled infliximab 5mg/kg, or scheduled infliximab 10mg/kg, at weeks 2 and 6 and every 8 weeks thereafter. The patients who responded to treatment but worsened at any point of the study were crossed over to receive active episodic re-treatment with infliximab (5mg/kg, 10mg/kg, and 15mg/kg for the patients who were assigned to episodic treatment, scheduled infliximab 5 mg/kg, and scheduled infliximab 10 mg/kg respectively). Worsening was defined by an increase of 70 points or more in Crohn's Disease Activity Index (CDAI) from the qualifying score, with a CDAI of at least 175; an increase in CDAI of 35% or more from the baseline; the introduction of a new treatment; or an increased dose of an existing treatment of active disease.

During 54 weeks of follow-up:

- Rates of crossover to an episodic treatment with a higher dose were 46%, 30%, and 26% for the patients in episodic treatment, 5mg/kg scheduled treatment, and 10mg/kg scheduled treatment groups respectively.
- In all three groups, the largest numbers of cross-overs occurred at week 14.

- 90% of patients in 5mg/kg scheduled treatment and approximately 80% of patients in 10mg/kg scheduled treatment who were treated with higher doses of infliximab, re-established response.

Regueiro et al 67 followed 108 patients who received at least 8 infliximab doses in a period of up to 30 months to determine the proportion of patients who needed an increase in dose, a reduction in interval, or both and found that:

- 42% of patients had a lapse in infliximab therapy, which was defined as a period > 6 months between any two infliximab infusions.
- By the end of the study, 30.9% of the patients needed an interval decrease, 51.8% needed a dose increase, and 54.3% required both.

This study showed no statistically significant relationship between dose escalation and prior use of infliximab, loss of response to treatment, or use of concomitant immunosuppressive therapy.

In an observational study, Menachem et al reported the results of increasing the infliximab dose in 12 patients who lost response to treatment with a lower dose of infliximab. All the patients showed an initial response to induction therapy with infliximab 5mg/kg but had a disease flare-up under regular maintenance treatment (mean of 5.3 infusions). After relapse, the patients were treated with infliximab 10mg/kg (mean 3.3 infusions/patient). A reduction in the Harvey-Bradshaw activity index score represented clinical benefit; after dose escalation, this score decreased from 13.5 to 8.8 (p = 0.03).

In Schnitzler et al.'s cohort study, 614 patients with CD who were on infliximab were followed for a median of 55 months. Of this group, 34.7% of patients received episodic treatment, 29.8% started with episodic treatment and then switched to maintenance, and 35.5% received scheduled treatment from the start. During the study, 19.7% patients needed a decrease in interval, 26.3% needed an increase in dose, and 3.8% required both. Among those patients who received dose escalations, 21.6% stopped infliximab as a result of loss of response.

Chaparro et al, in a retrospective observational study, reported the effects of infliximab dose escalation in 33 patients with CD who lost response to induction therapy with three doses of infliximab 5mg/kg. Patients were treated with infliximab 10mg/kg every 8 weeks or infliximab 5mg/kg every 4 weeks. The mean follow-up was 40 weeks. After the first intensification dose, 83% of patients responded, and at the end of follow-up (after last intensification dose), 65% of patients were still responding to treatment.

Plevy et al studied 181 patients treated with at least 8 infusions of infliximab, to assess the dose escalation rate and associated factors. The proportion of patients who required dose escalation was 47.5% in the first year and 65.5% at two years.

No harms or serious adverse events that were attributable to dose escalation were reported in these studies.

## **Dose escalation with Adalimumab**

[Journal of Crohn's and Colitis Volume 7, Issue 2 \(2012\)](#)

**Adalimumab dose escalation and dose de-escalation success rate and predictors in a large national cohort of Crohn's patients Filip Baert et al (Belgian sponsored by Abbott Belgian)**  
**Adalimumab dose escalation and dose de-escalation success rate and predictors in a large national cohort of Crohn's patients, 2013-03-01Z, Volume 7, Issue 2, Pages 154-160,**

## Abstract

Adalimumab is efficacious in inducing and maintaining remission in Crohn's disease but dose escalation is needed in 30–40% after 1 year. Attempts for dose de-escalation have not been studied. This study aimed to assess the need for, predictors, and outcome of dose escalation and de-escalation in a large cohort of adalimumab treated Crohn's patients.

## Background and aims

Adalimumab is efficacious in inducing and maintaining remission in Crohn's disease but dose escalation is needed in 30–40% after 1 year. Attempts for dose de-escalation have not been studied. This study aimed to assess the need for, predictors, and outcome of dose escalation and de-escalation in a large cohort of adalimumab treated Crohn's patients.

## Methods

All consecutive patients treated with open label adalimumab for active Crohn's disease from the participating centres were included in this cohort study. A detailed retrospective chart review was performed to look for possible factors predicting outcome.

## Results

Eighty four percent of 720 patients had a primary response and were followed up for a median of 14 months. Thirty four percent needed escalation after a median of 7 months (0–55 months). Multivariate predictors for dose escalation were the following: prior anti-TNF use ( $p < 0.0001$ ), no concomitant azathioprine or  $< 3$  m ( $p < 0.02$ ) and abnormal CRP at start ( $p < 0.05$ ). Dose escalation re-induced response for at least 6 months in 67%. Only abnormal CRP at start correlated with failure of dose escalation ( $p = 0.02$ ). Dose de-escalation was attempted in 54% and was successful in 63%. After a median follow-up of 14 m adalimumab was discontinued in 29% of patients.

## Conclusion

In this study real life nationwide cohort of Crohn's patients treated with adalimumab dose escalation was needed in 34% and was successful in 67%. Dose de-escalation was attempted in 54% and was successful in 63%. Overall 71% of patients maintained long term response on adalimumab

## Discussion from authors

In this large nationwide real life series of Crohn's patients treated with adalimumab we observed a need for dose escalation in 34% after a median follow up of 14 months. Prior anti-TNF use, abnormal CRP at start and no concomitant immunomodulator treatment (or given for less than 3 months before starting adalimumab) were predicting loss of response on the conventional bi-weekly dosing.

This nationwide cohort comprises a mix of high volume referral centres and regional centres. The high proportion of previous anti-TNF failures may account for the 34% dose escalation. This is in line with all the other series showing a good response to adalimumab in second line therapy but with a greater need for dose escalation.

However dose escalation was equally successful in first line treated patients compared to those with prior anti-TNF use. The need for dose escalation occurs gradually over time with a median time to dose escalation of 7 months.

An interesting new finding of this study is the fact that patients without immunomodulator co-treatment needed dose escalation more frequently. Although it has been demonstrated clearly that secondary loss of response is at least partly due to immunogenicity in infliximab treated patients, data for adalimumab is still scarce. Abstracts recently presented from other series report similarly beneficial effects for immunomodulator co-treatment. One study showed a lower loss of response rate and the other a lower need for dose escalation with concomitant immunomodulator treatment.

In rheumatology it has been clearly demonstrated that anti-adalimumab antibodies occur more frequently in patients without concomitant immunomodulators and they correlate with loss of response as was observed with infliximab in the Sonic trial.

It should also be noted that the proportion of patients on concomitant immunomodulators in this cohort gradually diminished over time. This reflects probably the practice of stopping co-treatment upon achieving complete remission.

An abnormal CRP level only at start of the adalimumab treatment correlated with the need for dose escalation and with failure of dose escalation. However measurements of CRP at the time of dose escalation and dose de-escalation were not predictive of response to treatment adjustments.

Although a clinical response to anti-TNF treatment has usually been associated with elevated CRP, it was the contrary in the recently published CARE trial reporting on a prospective open label treatment with adalimumab suggesting together with our current data that a higher inflammatory burden may require higher dosage of anti-TNF.

In addition a bias in treatment change cannot be excluded as in this retrospective cohort; in contrast to randomised controlled trials investigators were not blinded for the CRP values but may have on the contrary be guided by the CRP levels in their evaluation and treatment decisions.

Other factors such as perianal disease, high volume centres and university centres were only predictive for need for dose escalation at univariant level most likely reflecting a more refractory patient population. Somewhat contradictory is that fact that a high induction dose scheme was also borderline, significant at univariate analysis for a higher need for dose escalation. We think that this result is biased. Only in a small minority was the lower induction dose used. This is likely to be the case in patients with milder Crohn's activity.

This is the first series, to our knowledge, reporting on dose de-escalation. In this retrospective study de-escalation was not done per protocol. However, it was successful in half of the patients. This is in line with dose optimisation with infliximab where in routine practise the dosing interval can often be increased again upon re-inducing response by shortening the interval. We found no factors predicting the success of de-escalation but this may be due to the small subgroups.

Almost all patients were started on a high dose induction regimen (160 mg–80 mg, 40 mg 2QW) provided by the company as negotiated by the Belgian reimbursement authorities. This may explain the high primary response rate in this cohort along with the open label real life treatment situation and with the arbitrary definition of primary response in this study. However this high primary response rate is in line with other reported open label single centre and multi centre series.

Primary response was higher in anti-TNF naïve patients compared to patients with prior infliximab treatment reflecting a more refractory disease for the latter patients. Patients in academic centres had a lower response rate compared to patients in nonacademic centres.

This analysis was no longer significant when corrected for primary versus secondary TNF treatment suggesting that more patients in academic centres were started on adalimumab as a second TNF treatment.

Limitations of this study include its retrospective and non-interventional nature. All patients in this study were treated in a standard fashion according to the Belgian reimbursement criteria and to the discretion of the physicians and the patients. Therefore investigator or centre bias as to when dose escalation or dose de-escalation was decided or to when concomitant immunomodulators were needed is an intrinsic risk. Therefore although no strict prospective treatment algorithms were used in this study we believe that this report closely reflects the real life situation and adds information to the randomised controlled trials conducted with adalimumab particularly on dose de-escalation.

In summary in this real life nationwide cohort of Crohn's patients treated with adalimumab dose escalation was needed in a third of patients and was successful in two thirds. Abnormal CRP at start is predictor for need of dose escalation and failure of dose escalation. However if dose escalation was successful, dose de-escalation was successful in 60%.

## 4. Summary of Key Points for Consideration

### 4.1 National guidance:

- NICE guidance is available (TA187) above but switching biologics or dose escalation was not considered at the time (May 2010)
- European Crohn's and Colitis Organisation Inflammatory Bowel Diseases Crohn's Disease Guidelines: Current Management (2010)
- British Society of Gastroenterology Guidelines (Guidelines for the management of inflammatory bowel disease in adults Craig Mowat et al (Gut 2011;60:571-607.doi:10.1136/gut.2010.224154)
- The Surrey collaborative IFR panel has approved 2 dose escalation IFRs in the last 6 months, where response to treatment has been re-captured with dose escalation. Following the 12 weeks commissioned course of treatment the patients had been returned back to standard dosing and the disease has re-flared so continuation of dose escalation was approved at IFR panel

### 4.2 Efficacy

### 4.3 Potential Benefits over existing therapy

There is no cure for Crohn's Disease, optimising the current available treatments will delay surgery for these patients

### 4.4 Potential disadvantages

Infliximab will incur a day case tariff every 8 weeks for each patient (adalimumab can be given via homecare and self-administered. These costs could likely be offset against the frequent outpatient and inpatient attendances currently required for patients with severe active Crohn's Disease who have had secondary failure to 1<sup>st</sup> line biologic treatment

### 4.5 Budgetary Impact

#### Costs of standard dosing (local discounts may apply)

- **Infliximab (5mg/kg) induction plus 8 weekly dosing (1<sup>st</sup> year costs)** £12k - £16k/year inclusive of VAT. A day case infusion tariff (estimated £400-500) would also be charged for each administration of infliximab.
  - **Subsequent years (8 weekly dosing)** - £9k to £12k (inclusive of VAT)
- **Adalimumab induction (accelerated schedule) plus bi-weekly dosing (1<sup>st</sup> year costs)** - £11k
  - **Subsequent years (bi weekly dosing)** – £9155.64/year

**Cost of dose escalation:** Currently commissioned for 12 weeks and then back to standard dosing above

- **Infliximab 6 weekly dosing (5mg/kg)** - £3k to £4k (2 x 6 weekly doses). A day case infusion tariff (estimated £400-500) would also be charged for each administration of infliximab.
- **Infliximab 4 weekly dosing (5mg/kg)** – £4.5k to £6k (3 x 4 weekly doses) A day case infusion tariff (estimated £400-500) would also be charged for each administration of infliximab.
- **Infliximab 10mg/kg (3 doses)** - £6k A day case infusion tariff (estimated £400-500) would also be charged for each administration of infliximab.
- **Adalimumab weekly dosing** - £4,225.68/12 weeks

#### **Continued (on-going) dose escalation**

- **Infliximab 6 weekly dosing (weight based)** - £13k to £17.5k/year inclusive of VAT A day case infusion tariff (estimated £400-500) would also be charged for each administration of infliximab.
- **Infliximab 4 weekly dosing (5mg/kg)** – £18k to £24k/year inclusive of VAT A day case infusion tariff (estimated £400-500) would also be charged for each administration of infliximab.
- **Adalimumab (40mg) weekly dosing** - £18,590/year

## Cost of switching

- See costs above for costs of both treatments in comparison.

### 4.5.2 Precedent setting:

**South West London** – Fund in line with NICE. Do not allow switching in Secondary Failure and dose escalates for 12 weeks only, if required.

**South East London** – Developing IBD pathway at the moment. Not available currently but I have requested it f

**South Warwickshire CCG** – Commissioning Policy: (December 2013)

- Infliximab 5mg/kg every 6 weeks is approved as an alternative to infliximab 10mg/kg every 8 weeks in patient who initially responded to 5mg/kg every 8 weeks but lost response. Any dose increase must be agreed at MDT meeting

## 5. Conclusions and Recommendations

- Gastroenterologists to switch patients to other NICE approved biologic after secondary failure (loss of response to 1<sup>st</sup> line biologic) but not dose escalate before switch, OR
- Gastroenterologists to dose escalate (Infliximab (5mg/kg) 4-6 weekly, 10mg/kg (3 doses) OR Adalimumab weekly) for 12 weeks to recapture response (already commissioned). At 12 weeks the patient should be revert back to standard dosing (8 weekly Infliximab and bi weekly Adalimumab). If disease flares then switch to other biologic
- Gastroenterologists to dose escalate (Infliximab (5mg/kg) 4-6 weekly, 10mg/kg (3 doses) OR Adalimumab weekly) AND if the patient responds to treatment (in line with pre-defined criteria), at 12 weeks the dose will revert back to standard dosing. If the disease flares the patient will be able to continue with the dose escalation (following an MDT discussion) and then switch to the other NICE approved biologic if the escalated dose does not control disease.

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