This document details the indications, use and side effects of anti-TNFs in the management of Inflammatory Bowel Disease (IBD). It is clear from this review that these are safe and highly efficient agents to control and maintain patients with IBD. They have dramatically reduced the complications of sepsis and surgery, and thereby reduced the expense involved in the management of IBD.

Definitions
1. Corticosteroid resistance: a lack of a symptomatic response despite a course of oral prednisone of 40 to 60 mg/day (or equivalent) for a minimum of 14 days
2. Corticosteroid dependence: the inability to withdraw (within 3 months of initiation) oral corticosteroid therapy without recurrence of symptoms, a symptomatic relapse within 3 months of stopping corticosteroid therapy, or the need for 2 or more courses of corticosteroid therapy within 1 year
3. Primary Biologic failure: inability of the patient to achieve corticosteroid-free remission despite dose optimization
4. Secondary Biologic failure: inability of the patient to maintain corticosteroid-free remission after achieving a symptomatic response

1. Anti-TNFs in CD

1a. Induction of remission in luminal Crohn’s disease (CD)

1. The anti-TNF-α biologics infliximab and adalimumab are indicated to induce remission in patients with moderate to severe luminal CD refractory to other therapies including corticosteroids, azathioprine, 6-mercaptopurine or methotrexate, as well as in patients who are corticosteroid dependent

References:
1. Long term regular scheduled anti–TNF therapy should be used to maintain anti-TNF induced remission in patients with luminal CD. The failure to follow a scheduled regimen may result in increased symptoms, flares and the need to escalate therapy or rotate to another agent.


2. Either the combination of an anti–TNF and a thiopurine or anti–TNF’s alone can used to maintain remission of luminal CD induced by anti-TNF therapy. Combination therapy is more effective than anti-TNF monotherapy.


3. Complete mucosal healing is increasingly used as a treatment goal and as a surrogate for disease activity. The use of faecal calprotectin and/or colonoscopy to monitor disease activity is recommended to guide therapy. The frequency of these investigations is at the discretion of the attending physician.

4. Patients with luminal CD who have achieved a sustained response with one anti-TNF should be maintained on that agent and not be switched to an alternative anti-TNF agent because of convenience or cost. Switching in this setting is associated with worse clinical outcomes.


5. In patients with CD who lose response to anti-TNF maintenance therapy (secondary biologic failure) the dose should be optimized after exclusion of other causes of recurrent symptoms. An alternative approach would be to measure drug and autoantibody levels.


6. Patients with CD who lose response to anti-TNF maintenance therapy (secondary biologic failure) and in whom dose optimisation is unsuccessful, can be switched to another anti-TNF


5. The combination of anti–TNF-α biologics and thiopurines is superior to either thiopurine monotherapy or anti-TNF monotherapy in inducing remission in patients who have moderate to severe luminal CD.


6. Patients with CD treated with anti-TNFs should be evaluated for response to anti-TNF induction therapy 8 to 12 weeks after initiation to determine the need to modify therapy.

7. Patients with CD who have a suboptimal response to anti-TNF induction therapy (primary biologic failure) should be evaluated to determine why they have not responded. Fibrostenotic stricture, co-infection (e.g. with Clostridium difficile) or cytomegalovirus) or symptoms caused by irritable bowel syndrome must be considered.

- KT Park, Crandall WV, Fridge J, et al Implementable strategies and exploratory considerations to reduce costs associated with anti-TNF therapy in inflammatory bowel disease. Inflamm Bowel Dis 2014;20:946-951

8. In patients with CD who have a suboptimal response to anti-TNF induction therapy (primary biologic failure) dose intensification or treatment with a 2nd anti-TNF agent can be considered.


1b. Maintenance of remission in luminal CD

1. Long term regular scheduled anti–TNF therapy should be used to maintain anti-TNF induced remission in patients with luminal CD. The failure to follow a scheduled regimen may result in increased symptoms, flares and the need to escalate therapy or rotate to another agent.


7. It is unclear if anti-TNFs can be stopped once patients are in prolonged, deep corticosteroid-free remission (clinical, endoscopic, radiologic and biochemical remission). There is insufficient data to specify a time point or criteria for discontinuation. Many patients will relapse and indefinite therapy may be required. This decision needs to be made by the attending physician


1c. Fistulising CD

1. Anti-TNFs are 1st line therapy in patients with fistulising perianal Crohn’s disease. A real danger however is the flaring of a current or latent associated abscess. Imaging or EUA is required to exclude an infective collection before initiation


2. In patients with fistulising CD who have a suboptimal response to anti-TNF induction (primary biologic failure) therapy, dose intensification can be considered

3. Long term regular scheduled anti–TNF therapy should be used to maintain anti-TNF induced remission in patients with fistulising CD


4. Either the combination of an anti–TNF and a thiopurine or anti–TNFs alone can used to maintain remission induced by anti-TNFs in patients with fistulising CD


5. In patients with fistulising CD who lose response to anti-TNF maintenance therapy (secondary biologic failure) the dose should be optimized before switching to another anti-TNF

6. Evidence suggests that anti-TNFs should be given indefinitely. Most patients will relapse on discontinuation.


2. Anti-TNF in moderate to severe Ulcerative Colitis (UC) in the outpatient setting

2a Inducing remission

1. The anti-TNFs infliximab, adalimumab or golimumab are indicated to induce remission in patients with moderate to severe UC refractory to other therapies, including mesalazine, corticosteroids, and immunomodulators. Anti-TNFs are also indicated in steroid dependent ulcerative colitis where there has been an inadequate response to other therapies, including mesalazine and immunomodulators


2. Anti–TNF–α monotherapy is more effective than thiopurine monotherapy in inducing remission in patients with moderate to severe UC and can be used as 1st line therapy in selected cases where corticosteroids or thiopurines are contraindicated or where a rapid therapeutic response is required. This is due to the delayed effect of thiopurines


3. The combination of anti–TNF–α biologics and thiopurines is superior to thiopurine monotherapy or anti-TNF monotherapy in inducing remission in patients with moderate to severe UC


4. Patients with UC treated with anti-TNFs should be evaluated for symptomatic response to anti-TNF induction therapy 8 to 12 weeks after initiation to determine the need to modify therapy


5. In patients with UC who have a suboptimal response to anti-TNF induction therapy (primary biologic failure) dose intensification should be considered before switching to an alternative anti-TNF

2. In patients responding to anti-TNFs, both maintaining remission with anti-TNF monotherapy or anti-TNFs in combination with azathioprine/6-mercaptopurine is appropriate. Combination therapy is more effective.


2. Anti-TNFs should be given as long term, regular scheduled maintenance therapy to maintain anti-TNF induced remission.


3. In patients with UC who lose response to anti-TNF maintenance therapy (secondary biologic failure) the dose should be optimized to recapture remission after exclusion of other causes of recurrent symptoms.


4. Patients with UC who lose response to anti-TNF maintenance therapy (secondary biologic failure) and in whom dose optimisation is unsuccessful, can be treated with another anti-TNF.

5. It is unclear if anti-TNFs can be stopped once patients are in prolonged, deep corticosteroid-free remission (clinical, endoscopic, radiologic and biochemical remission). There is insufficient data to specify a time point for discontinuation. Many patients will relapse and indefinite therapy may be required. This decision needs to be made by the attending physician.


3. Acute severe UC in the inpatient setting

1. Urgent salvage therapy with infliximab is an alternative to cyclosporine in patients with acute severe ulcerative colitis who have failed 3 to 5 days of intravenous corticosteroid therapy and in whom surgery is being considered. There is currently no data on the use of adalimumab or golimumab for this indication.


2. In acute severe colitis responding to intravenous steroids, intravenous cyclosporin or infliximab, azathioprine/6-mercaptopurine should be considered to maintain remission. However, in patients responding to infliximab continuing infliximab is appropriate. The prior failure of thiopurines favours maintenance with infliximab.


4. Pregnancy and anti-TNFs

1. Exposure to infliximab or adalimumab during pregnancy does not appear to confer an increased risk of adverse pregnancy outcomes.


2. Timing the last dose of anti-TNFs before delivery should be individualised depending on the mother’s disease activity and the risk of drug placental transfer. In patients with well controlled IBD, discontinuation of the anti-TNF can be considered during the 3rd trimester.


3. Detectable levels of anti-TNFs are present in the infant for up to 6 months post-delivery. As such live vaccines should not be administered during this time period. Vaccination with non-live vaccines is safe and these should be administered as for infants unexposed to anti-TNF agents in utero.


Additional issues for the use of anti-TNFs

Contraindications to the use of anti-TNFs are to be found in the package inserts. Special consideration needs to be given to:

i. Patients with active sepsis, congestive cardiac failure and a history of malignancy.

ii. Tuberculosis has a high mortality in patients receiving anti-TNFs and all individuals in whom such treatment is being considered should have a chest X-ray and a Mantoux test or IGRA.

iii. Hepatitis B virus infection may flare up in patients given to:

iv. Human immunodeficiency virus (HIV) serology