Recommendations on the use of anti-TNFs in adults with Inflammatory Bowel Disease

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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
   - *Bressler B, Marshall JK, Bernstein CN, et al. Clinical practice guidelines for the medical management of non-hospitalized ulcerative colitis: the Toronto Consensus. Gastroenterology 2015; 148:1035–1057*

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
   - *Dignass A, Van Assche G, Lindsay JO, et al. The second European evidence-based consensus on the diagnosis and management of Crohn's disease: current management. J Crohns Colitis. 2010;4:28–62*
   - *Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance inflix¬imab for Crohn's disease: the ACCENT I randomised trial. Lancet. 2002;359:1541–1549*
   - *Terdiman JP, Gruss CB, Heidelbaugh JJ, et al. American Gastroenterologi¬cal Association Institute guideline on the use of thiopurines, methotrexate, and anti-TNF-alpha biologic drugs for the induction and maintenance of remission in inflammatory Crohn's disease. Gastroenterology. 2013;145:1459–1463*
2. Before commencing anti-TNFs active IBD must be confirmed with raised acute phase reactants, faecal calprotectin, endoscopy, appropriate imaging studies and/or histology. The exact combination depends on the disease type and location
3. Patients with active infection should not receive anti-TNFs until this has been treated. Abscess collections must be drained prior to initiation. Patients need to be evaluated for latent tuberculosis, hepatitis B, and HIV before anti-TNFs are initiated. Patients who have received live vaccines should not receive biological therapy for 3 months.
   - *D'Haens GR, Panaccione R, Higgins PD, et al. The London Position Statement of the World Congress of Gastroenterology onBiological 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 2011;106:199–212*
4. Anti–TNF-α monotherapy is more effective than thiopurine monotherapy in inducing remission in patients with moderate to severe luminal CD and can be used as 1st line therapy in selected cases where corticosteroids or thiopurines are contraindicated or when a rapid therapeutic response is required. This is due to the delayed effect of thiopurines/methotrexate.
   - *Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. N Engl J Med. 2010; 362:1383–1395*
   - *Terdiman JP, Gruss CB, Heidelbaugh JJ, et al. American*

Gastroenterologi¬cal Association Institute guideline on the use of thiopurines, methotrexate, and anti-TNF-alpha biologic drugs for the induction and maintenance of remission in inflammatory Crohn's disease. Gastroenterology. 2013;145:1459–1463

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
   - *Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. N Engl J Med. 2010; 362:1383–1395*
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.
   - Lofberg R, Louis EV, Reinisch W, et al. Adalimumab produces clinical remission and reduces extraintestinal manifestations in Crohn's disease: results from CARE. Inflamm Bowel Dis. 2012;18:1–9.
   - Ho GT, Mowat A, Potts L, et al. Efficacy and complications of adali¬mumab treatment for medically-refractory Crohn's disease: analysis of nationwide experience in Scotland (2004–2008). Aliment Pharmacol Ther. 2009;29:527–534
   - Panaccione R, Loftus EV Jr, Binion D, et al. Efficacy and safety of adalimumab in Canadian patients with moderate to severe Crohn's disease: results of the Adalimumab in Canadian Subjects with Moderate to Severe Crohn's Disease (ACCESS) trial. Can J Gastroenterol. 2011;25:419–425

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
   - *Dignass A, Van Assche G, Lindsay JO, et al. The second European evidence-based consensus on the diagnosis and management of Crohn's disease: current management. J Crohns Colitis. 2010;4:28–62*
   - *Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance inflix¬imab for Crohn's disease: the ACCENT I randomised trial. Lancet. 2002;359:1541–1549*
   - *Terdiman JP, Gruss CB, Heidelbaugh JJ, et al. American Gastroenterologi¬cal Association Institute guideline on the use of thiopurines, methotrexate, and anti-TNF-alpha biologic drugs for the induction and maintenance of remission in inflammatory Crohn's disease. Gastroenterology. 2013;145:1459–1463*
2. Either the combination of an anti–TNF and a thiopurine or anti–TNFs alone can used to maintain remission of luminal CD induced by anti-TNF therapy. Combination therapy is more effective than anti-TNF monotherapy
   - *Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. N Engl J Med. 2010; 362:1383–1395*
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
   - *Van Assche G, Vermeire S, Ballet V, et al. Switch to adalimumab in patients with Crohn's disease controlled by maintenance infliximab: prospective randomised SWITCH trial. Gut 2012; 61:229*
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.
   - *Regueiro M, Siemanowski B, Kip KE, Plevy S. Infliximab dose intensification in Crohn's disease. Inflamm Bowel Dis. 2007;13:1093–1099*
   - *Kopylov U, Mantzaris GJ, Katsanos KH, et al. The efficacy of shortening the dosing interval to once every six weeks in Crohn's patients losing response to maintenance dose of infliximab. Aliment Pharmacol Ther. 2011;33:349–357*
   - *Schnitzler F, Fidder H, Ferrante M, et al. Long-term outcome of treatment with infliximab in 614 patients with Crohn's disease: results from a single-centre cohort. Gut 2009; 58: 492–500*
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
   - *Sandborn WJ, Rutgeerts P, Enns R, et al. Adalimumab induction therapy for Crohn disease previously treated with infliximab: a randomized trial. Ann Intern Med 2007; 146: 829–838*

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
   - *Louis E, Mary JY, Vernier-Massouille G, et al. Maintenance of remission among patients with Crohn's disease on antimetabolite therapy after infliximab therapy is stopped. Gastroenterology 2012; 142:63*
   - *Dignass A, Van Assche G, Lindsay JO, et al. The second European evidence-based consensus on the diagnosis and management of Crohn's disease: current management. J Crohns Colitis. 2010;4:28–62*
   - *D'Haens GR, Panaccione R, Higgins PD, et al. 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 2011;106:199–212*

1c. Fistulising CD

1. Anti-TNFs are 1st line therapy in patients with fistulizing 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
   - *Dignass A, Van Assche G, Lindsay JO, et al. The second European evidence-based consensus on the diagnosis and management of Crohn's disease: current management. J Crohns Colitis. 2010;4:28–62*
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
   - *Sands BE, Anderson FH, Bernstein CN, et al. Infliximab maintenance therapy for fistulising Crohn's disease. N Engl J Med. 2004;350:876–885*
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
   - *Sands BE, Anderson FH, Bernstein CN, et al. Infliximab maintenance therapy for fistulising Crohn's disease. N Engl J Med. 2004;350:876–885*
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.
   - *Domènech E, Hinojosa J, Nos P, et al. Clinical evolution of luminal and perianal Crohn's disease after inducing remission with infliximab: how long should patients be treated? Aliment Pharmacol Ther 2005;22:1107–1113*

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

2.a 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
   - *Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med 2005;353:2462–2476*
   - *Reinisch W, Sandborn WJ, Hommes DW, et al. Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial. Gut 2011;60:780–787*
   - *Sandborn WJ, van Assche G, Reinisch W, et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology 2012;142:257–265*
   - *Sandborn WJ, Feagan BG, Marano C, et al. Subcutaneous golimumab induces clinical response and remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology 2014;146:85–95*
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
   - *Panaccione R, Ghosh S, Middleton S, et al. Combination therapy with infliximab and azathioprine is superior to monotherapy with either agent in ulcerative colitis. Gastroenterology 2014;146:392–400*
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
   - *Panaccione R, Ghosh S, Middleton S, et al. Combination therapy with infliximab and azathioprine is superior to monotherapy with either agent in ulcerative colitis. Gastroenterology 2014;146:392–4003*
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
   - *Bressler B, Marshall JK, Bernstein CN, et al. Clinical practice guidelines for the medical management of non-hospitalized ulcerative colitis: the Toronto Consensus. Gastroenterology 2015;148:1035–1057*
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
   - *Bressler B, Marshall JK, Bernstein CN, et al. Clinical practice guidelines for the medical management of non-hospitalized ulcerative colitis: the Toronto Consensus. Gastroenterology 2015;148:1035–1057*

2.b Maintaining remission.

1. 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
   - *Bressler B, Marshall JK, Bernstein CN, et al. Clinical practice guidelines for the medical management of non-hospitalized ulcerative colitis: the Toronto Consensus. Gastroenterology 2015;148:1035–1057*
2. Anti-TNFs should be given as long term, regular scheduled maintenance therapy to maintain anti-TNF induced remission
   - *Dignass A, Lindsay JO, Sturm A, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 2: current management. J Crohns Colitis 2012;6:991–1030*
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
   - *Bressler B, Marshall JK, Bernstein CN, et al. Clinical practice guidelines for the medical management of non-hospitalized ulcerative colitis: the Toronto Consensus. Gastroenterology 2015;148:1035–1057*
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
   - *Dignass A, Lindsay JO, Sturm A, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 2: current management. J Crohns Colitis 2012;6:991–1030*

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.
   - *Dignass A, Lindsay JO, Sturm A, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 2: current management. J Crohns Colitis 2012;6:991–1030*
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
   - *Dignass A, Lindsay JO, Sturm A, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 2: current management. J Crohns Colitis 2012;6:991–1030*

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.
   - *ECCO Consensus on reproduction and pregnancy in inflammatory bowel disease. Journal of Crohn's and Colitis, 2015:1–18 doi:10.1093/ecco-jcc/jju006*
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
   - *ECCO Consensus on reproduction and pregnancy in inflammatory bowel disease. Journal of Crohn's and Colitis, 2015:1–18 doi:10.1093/ecco-jcc/jju006*
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
   - *ECCO Consensus on reproduction and pregnancy in inflammatory bowel disease. Journal of Crohn's and Colitis, 2015:1–18 doi:10.1093/ecco-jcc/jju006*

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 receiving an anti-TNF. It is mandatory that Hepatitis serology is measured prior to initiating anti-TNFs
iv. In addition the European Crohn's and Colitis Organisation recommends the following additional screening for opportunistic infections before initiating immunosuppressive agents:
   - Varicella zoster virus (VZV) serology in patients without a reliable history of VZV immunisation
   - Hepatitis C virus serology
   - Epstein–Barr virus serology
   - Human immunodeficiency virus (HIV) serology
   - *Rahier JF, Magro F, Abreu C, et al. Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. Journal of Crohn's and Colitis 2014 8, 443–468*