Biologic Therapy in Inflammatory Bowel Disease

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SUMMARY

In luminal Crohn's disease with moderate to severe inflammatory activity, infliximab and adalimumab can be used in the case of treatment failure with conventional therapies, such as systemic steroids and immunosuppressive therapy or if this treatment is not tolerated.

Further treatment strategy depends on the primary response to induction therapy

Effect of maintenance therapy should be evaluated clinically and paraclinically at least every 26-52 weeks, and maybe supplemented by endoscopy or MRI scan

Decision of treatment discontinuation is based on disease manifestation, treatment response and paraclinical parameters

In fistulising Crohn's disease, treatment with infliximab or adalimumab can be initiated in simple fistula with rectal inflammation or complex fistula when the initial treatment has insufficient effect.

Further treatment strategy depends on the primary response to induction therapy

Maintenance therapy is often necessary in complex fistulas

Treatment efficacy and possible discontinuation of treatment is evaluated at least every 26-52 weeks – if possibly with diagnostic imaging

In acute severe ulcerative colitis, treatment with infliximab can be used in patients with partial response after 3-5 days of treatment with a high-dose systemic steroid and when surgical treatment is not preferred or required.

Further treatment strategy depends on the response to the first drug administration and colectomy should always be considered as an option

Effect of subsequent initiated maintenance therapy should be evaluated at least every 26-52 weeks on the basis of symptoms, clinical markers, paraclinical parameters and possibly by endoscopy

In chronic active ulcerative colitis, infliximab and adalimumab can be used in the case of treatment with immunosuppressive therapy fails and if surgery is not preferred.

Further treatment strategy depends on the response to induction therapy

Treatment efficacy is assessed by symptoms, clinical markers, paraclinical parameters and possibly by endoscopy

Effect of maintenance therapy should be evaluated at least every 26-52 weeks

During treatment with biologic drugs focus should be on possible complications, such as infections, infusion or injection reactions and dermatological side effects.

An overview of levels of evidence and recommendations is presented I table 4.

LIMITATION OF THE SUBJECT

This guideline covers the treatment of adult patients with biologic drugs for which randomised studies have documented efficacy in Crohn's disease or ulcerative colitis (evidence 1A and 1B). The guideline is not limited to the two anti-TNF-alfa antibodies (infliximab and adalimumab), for which Crohn's disease or ulcerative colitis are approved indications in the EU. The included drugs are the following:

Infliximab (Remicade ®) (1-3) is approved in the EU for the treatment of moderate to severe active Crohn's disease, fistulising Crohn's disease and moderate to severe active ulcerative colitis.

Adalimumab (Humira ®) (4-6) is approved in the EU for the treatment of moderate to severe active Crohn's disease and moderate to severe active ulcerative colitis.

Certolizumab pegol (Cimzia ®) (7, 8) is approved in the U.S. and Switzerland for the treatment of moderate to severe active Crohn's disease.

Natalizumab (Tysabri ®) (9) is approved in the U.S. for the treatment of moderate to severe active Crohn's disease.

INTRODUCTION

Biologic drugs are produced in living organisms using biotechnology. The drugs are characterised only by the method of manufacture and not by a common mechanism of action or a common target organ. Biologic drugs are mainly monoclonal antibodies or

antibody fragments that bind to immunological mediators and receptors.

Treatment guidelines have been developed on the basis of European (ECCO and BSG) (10-12), U.S. (AGA) (13) and Danish (DSGH) (14, 15) guidelines, international consensus reports (16, 17) and recent systematic reviews and meta-analyses for the treatment of Crohn's disease and ulcerative colitis with biologic drugs (18, 19). This guideline is consistent with the treatment algorithm developed by Rådet for Anvendelse af Dyr Sygehusmedicin (RADS) (www.regioner.dk/sundhed/medicin).

There are no direct comparative studies on the effect of one biologic drug to another, or of one biologic drug to glucocorticoids in chronic inflammatory bowel disease. It is therefore unclear whether one biologic drug is more effective than another or whether biologic drugs generally are more effective than glucocorticoids. The price of biologic drugs is more than 100 times higher than that of glucocorticoids, and because the drugs do not have documented improved clinical efficacy, biologic therapy should not be the first choice of standard treatment.

DEFINITIONS

The assessment of disease activity in Crohn's disease is based on a global clinical assessment, but it can be graduated according to the Harvey-Bradshaw Index (20) and generally follows the ECCO guidelines (21). In clinical practice, disease activity is divided as follows:

Mild activity: Changes in stool habits and abdominal pain, but the patient can eat and drink, <10 % weight loss and no fever, dehydration, palpable mass in the abdomen, abdominal tenderness or symptoms of stenosis.

Moderate activity: Treatment of mild disease is ineffective and/or there is intermittent vomiting or weight loss > 10 % or tender abdominal mass.

Severe activity: Persistent symptoms despite intensive treatment - there is often significant weight loss and symptoms of bowel obstruction or abscedation.

In ulcerative colitis, disease activity is assessed by the Simple Clinical Colitis Activity Index (SCCAI) or the Mayo Score (22). Disease activity can also be graded according to Truelove and Witt's criteria as mild, moderate or severe. Acute severe ulcerative colitis is defined as severe ulcerative colitis requiring hospitalization. See table 1.

METHODS

Literature searches were ended on March 31, 2012. The searches were performed in PubMed, http://www.ncbi.nlm.nih.gov/pubmed/, with the use of the MeSH terms "Crohn's disease", "Colitis, ulcerative", "Biological Therapy", with and without the use of Filters, including Randomized controlled trial and Practice guideline. Reference lists of identified reviews and guidelines were searched for additional relevant studies.

	Mild	*Moderate*	*Severe*
Number of bloody stools/day	< 4	4-5 *if*	≥6 *and*
Pulse rate per minute	<90	< 90	≥90 *or*
Temperature	normal	normal	fever *or*
Haemoglobin	normal	decreased	decreased (<75 % below reference) *or*
Acute phase response (C-reactive protein)	normal	increased	increased

Table 1. Assessment of disease activity in ulcerative colitis

GENERAL CONDITIONS

PREPARATION BEFORE TREATMENT

See DSGH guidelines for screening, prophylaxis and critical information prior to treatment with anti-TNF-α (23).

COMBINATION OF BIOLOGIC DRUGS WITH OTHER IMMUNOSUPPRESSANTS

The value of the combination of an anti-TNF-α antibody and an immunosuppressive drug was tested in a randomised, controlled trial in Crohn's disease (SONIC) (24). There was a significantly higher remission rate for the combination of infliximab and azathioprine compared to treatment with infliximab alone. Combination therapy may therefore be generally recommended. The very rare, hepatosplenic T-cell lymphoma in young men receiving anti-TNF-α antibody therapy (25) and progressive multifocal leukoencephalopathy (PML) in patients receiving natalizumab (26) is almost exclusively observed in patients receiving combination therapy with immunosuppressants. It is therefore considered contraindicated to combine natalizumab treatment with immunosuppressants, and the use of combination treatment with an anti-TNF-α antibody and immunosuppressants in young men should be considered carefully.

Preparation overview and treatment cascade can be seen in table 2 and 3 respectively.

Preparation name	Generic name	Administration	Induction dose	Maintenance dose	Other doses
Remicade®	infliximab	intravenous	5 mg/kg at week 0, 2, 6	5 mg/kg every 8 weeks	10 mg/kg every 8 weeks or 5 mg/kg every 4-6 weeks
Humira®	adalimumab	subcutaneous	160 mg at week 0, 80 mg at week 2	40 mg every 2 weeks	40 mg every week
Cimzia®	certolizumab pegol	subcutaneous	400 mg at week 0, 2, 4	400 mg every 4 weeks	
Tysabri®	natalizumab	intravenous	300 mg at week 0	300 mg every 4 weeks	

Table 2. Preparation overview

	1. Choice	2. Choice
Luminal Crohn's disease	infliximab or adalimumab	
Fistulising Crohn's disease	infliximab	adalimumab
Ulcerative Colitis	infliximab or adalimumab*	

** For the treatment of acute severe ulcerative colitis, infliximab is the first choice*

Table 3. Treatment cascade

TREATMENT MANUAL

LUMINAL CROHN'S DISEASE

When to start treatment

Biologic therapy can be initiated in moderate to severe inflammatory active disease in the case of treatment failure with conventional therapy with systemic corticosteroids and immunosuppressants (azathioprine 1.5 to 2.5 mg/kg/day, 6-mercaptopurine 0.75 to 1.5 mg/kg/day, methotrexate 25 mg/week orally or subcutaneously) or if this treatment is not tolerated (14-16). This step-up treatment strategy is generally recommended rather than a top-down treatment. The primary top-down treatment is hardly cost-effective and may cause sensitisation. Episodic treatment and treatment with single infusions should be avoided.

Further treatment strategy, including discontinuation

In complete primary response after induction therapy, reassess the need for continued maintenance therapy or discontinuation of the biologic therapy.

In partial primary response to induction treatment, maintenance treatment may be considered. Treatment escalation may be necessary (shortening of the interval, increasing the dose).

In non-response (no effect or worsening of symptoms) to induction or maintenance treatment, the treatment should be discontinued or possibly switched to another biologic drug.

Monitoring

Treatment efficacy is assessed by symptoms, clinical markers (Harvey-Bradshaw Index) and paraclinical parameters (C-reactive protein/F-calprotectin).

Treatment duration

Effect of maintenance therapy is evaluated clinically and paraclinically every 26-52 weeks, if possible supplemented with endoscopy or MRI scanning (27). Treatment should be continued if signs of disease activity are observed. If the disease is inactive, treatment can be stopped and disease activity reassessed after 8 weeks. If the disease is still inactive, the patient can discontinue the biologic therapy. In the case of relapse after discontinuation of maintenance therapy, the therapy can be re-initiated.

FISTULISING CROHN'S DISEASE

When to start treatment

Biologic therapy can be initiated in simple fistulas with rectal inflammation or complex fistulas, where the initial treatment (abscess drainage, seton drain , antibiotics and immunosuppressive therapy: azathioprine 1.5-2.5 mg/kg/day, 6-mercaptopurine 0.75-1.5 mg/kg/day, methotrexate 25 mg/week orally or subcutaneously) is not sufficient (28-31).

Further treatment strategy, including discontinuation

In complete primary response (closure of fistula or decreased secretion) after induction therapy, the need for continued maintenance therapy or discontinuation of the biologic therapy is evaluated.

In partial primary response to induction treatment, maintenance treatment may be considered. Treatment escalation may be necessary (shortening of the interval, increasing the dose).

Primary non-response of induction treatment does not exclude a long-term effect. If there is not any effect by maintenance treatment, the treatment should be discontinued.

Monitoring

The status of the fistulas is assessed every 26-52 weeks, possibly by diagnostic imaging. In the case of fistula recurrence, the patient must be revaluated for possible surgical intervention, combined surgical and medical treatment or re-initiation of maintenance therapy.

Treatment duration

Complete healing of the fistula(s) after induction therapy is rarely seen. Patients with complex fistulas often need long-term treatment. Treatment may be continued if there is complete or partial response.

ACUTE SEVERE ULCERATIVE COLITIS

When to start treatment

In acute severe ulcerative colitis, if only a partial response after 3-5 full days of treatment with a high dose of systemic corticosteroid is observed, treatment with infliximab or ciclosporin can be initiated if surgical treatment is not preferred (32, 33).

Further treatment strategy, including discontinuation

If a complete response is observed after a few days, induction therapy is continued and may be followed by maintenance therapy on an individual basis, possibly determined by endoscopic evaluation. Treatment with 5-ASA and immunosuppressants (azathioprine, 6-mercaptopurine) is continued or initiated. Prednisolone is tapered off.

For a partial response/ non-response, patients should be offered surgery.

Monitoring

Treatment efficacy is assessed on the basis of symptoms, clinical indices (Mayo/SCCAI) and paraclinical parameters (CRP/F-calprotectin). Endoscopic evaluation is advised on an individual basis.

Treatment duration

Effect of maintenance therapy should be assessed (clinical and paraclinical) every 26-52 weeks. With continuing signs of disease activity, patients should be offered surgery. If the disease is inactive, treatment can be stopped and disease activity reassessed after 8 weeks. If the disease is still inactive, the patient can discontinue biologic therapy. In the case of relapse after discontinuation, maintenance therapy may be re-initiated or surgery may be considered.

CHRONIC ACTIVE ULCERATIVE COLITIS

When to start treatment

Biologic therapy can be initiated in chronic active ulcerative colitis that is not brought into remission or relapses during the tapering of steroids, which cannot be brought or kept in remission with immunosuppressive therapy (azathioprine, 6-mercaptopurine), and where surgery is not preferred.

Further treatment strategy, including discontinuation

If a complete response is observed after induction therapy, the need for continued treatment is evaluated to determine the need for maintenance therapy or discontinuation of the biologic therapy.

For an incomplete/missing response or worsening, the biologic therapy is discontinued and surgery is offered.

Monitoring

Treatment efficacy is assessed on the basis of symptoms, clinical indices (SCCAI / Mayo) and paraclinical parameters (C-reactive protein, F-calprotectin). Endoscopic evaluation is advised on an individual basis.

Treatment duration

Effect of maintenance therapy should be assessed at least every 26-52 weeks (clinical and paraclinical). In the case of relapse after discontinuation of maintenance therapy, it may be re-initiated or surgery may be offered.

MONITORING

General

- Indication
- Treatment, name of drug, start date
- Other medical treatment
- Weight

Disease activity

- Crohn's disease: Harvey-Bradshaw Index (HBI)
- Ulcerative Colitis: Simple Clinical Colitis Activity Index (SCCAI) or Mayo score
- Quality of life (e.g., Short Health Scale by Hjortswang)

Biochemical activity markers

- C-reactive protein
- F-calprotectin

Assessment of treatment response, including measuring drug concentrations and antibodies

In approximately one third of patients receiving a biologic drug, the effect of the therapy decreases and dose escalation or shortening the intervals between drug administrations must be done. In the loss of a treatment response, the effect can be achieved in 25-35 % of cases by switching to another biologic drug. The presence of antibodies to adalimumab or infliximab may correlate with reduced efficacy and for infliximab, the risk of infusion reactions. Furthermore, the low trough levels of infliximab have also been shown to correlate with reduced efficacy. At present, it is not completely clear whether measurements of antibody and drug trough levels can be used to determine further treatment strategies.

COMPLICATIONS

INFECTIONS

Serious infections such as sepsis, pneumonia, opportunistic infections, tuberculosis (TB) and abscesses have been reported during treatment with anti-TNF-α, some with fatal outcomes (32, 34). Special attention should be paid to patients with chronic or recurrent infections. In early studies, serious infections appeared more frequently at higher doses of infliximab (10 mg/kg versus 5 mg/kg) (28), but in long-term studies, no dose relationship was found. In the TREAT registration for Crohn's disease, the risk of serious infections seems to be related to disease activity and the use of glucocorticoids. In some studies,up to 33 % of patients experience infection during infliximab treatment versus 25 % on placebo. Temporary or permanent discontinuation of anti-TNF-α therapy is recommended if the patient develops a serious infection and appropriate antibiotic treatment should be initiated. During treatment with anti-TNF-α, close monitoring and a diagnostic investigation on the suspicion of a complicating infection is advised. Patients with Crohn's disease and acute suppurative fistulas must not initiate/continue treatment with anti-TNF-α before the infection is treated and possible abscesses are excluded/treated.

Generally, there are no large studies that describe how long an interruption of anti-TNF-α treatment after an infection should last. The time interval will depend on the type and severity of the infection. In most cases, when the patient can resume treatment with anti-TNF-α will be based on a case-to-case evaluation.

The risk of opportunistic infections is mainly observed in patients receiving combination therapy with immunosuppressants (EL 3b, RG C) and malnutrition (EL 4, RG D). Concomitant illness and old age seem to pose a risk of infectious complications (EL 5, RG D).

An overview of opportunistic infections and relevant actions can be seen in table 5.

INFUSIONS AND INJECTION REACTIONS

Due to intravenous administration, infliximab may cause both acute (0-24 hours after administration) and late (> 24 hours to 14 days) infusion reactions. The frequency of infusion reactions is significantly higher in episodic than with continuous infliximab treatment and lower in infliximab in combination with other immunosuppressive drugs (37-40) (EL 1b, RG A). The infusion reactions of infliximab can be divided into three categories:

Acute severe immune-mediated (anaphylactoid) infusion reactions occur rarely (less than 1 %). Symptoms include shortness of breath, chest tightness, hypotension, tachycardia, flushing of the face, back pain, blurred consciousness, nausea and vomiting. The treatment is immediate interruption of the infusion (but keep intravenous access) and treatment of anaphylactic shock. Patients should not receive infliximab after an anaphylactoid infusion reaction.

Acute mild/moderate infusion (non-immune-mediated) response occurs in approximately 5 % of patients, depending on the infusion rate. Symptoms include itching, flushing of the face and palpitations. The treatment is to stop the infusion, administer antihistamine and paracetamol, and re-start the infusion after 30 minutes by slow titration of the infusion rate in accordance with a scheme (initially 10 ml/hour for 15 minutes increased by 10 ml/hour every 15 minutes to a total of 40 ml/hour). The next three infliximab administrations involve premedication with steroids and possibly antihistamine.

Late infusion reaction (24 hours-14 days), a serum sickness-like disease, is observed in 1-3 % of patients. Symptoms may include muscle and joint pain, oedema, fever, headache/sore throat, itching, and flu-like symptoms. The treatment is usually short (few weeks) and includes oral corticosteroids supplemented with antihistamine/paracetamol. Biologic therapy should not usually be continued after a delayed infusion reaction.

In > 10 % of cases, adalimumab caused a local reaction at the injection site, while urticaria and infections were observed in 1-10 %.

DERMATOLOGICAL SIDE EFFECTS

Approximately 20 % of patients treated with anti-TNF-α agents develop dermatological manifestations as a result of the treatment (41). These may be eczematous, psoriasiforme or infectious. Most are mild, but in severe cases a dermatologist must be involved in the diagnosis and treatment. In the most severe cases, the anti-TNF-α therapy must be discontinued (42).

In connection with the injection of adalimumab, localised redness, itching and pain can develop, but this is rarely the result of an allergic reaction. It may be treated with local steroid treatment if it does not disappear by itself in case the biologic therapy is continued (43). Severe cutaneous infections occur in up to 2 % (43). In addition to viral infections, folliculitis fungal infections are observed. The key is to distinguish an infection from the pure eczematous and psoriasiforme manifestations and obtain a dermatological assessment with a low threshold. Eczema can be seen anywhere on the body, and local steroid treatment is effective in most cases (44).

Psoriasiforme elements are well defined, often pustular and without the characteristics of psoriasis plaques. The exanthema is primarily localised to the hands and feet like palmoplantar pustulosis and at the hairline and in the scalp (45). The reaction seems to be a class effect, which disappears at the end of treatment but often recurs upon the resumption or switch to another biologic drug (43, 44). Local treatment with steroids is less effective (43).

SPECIAL SITUATIONS

BIOLOGIC DRUGS WITHOUT EUROPEAN APPROVED INDICATION IN INFLAMMATORY BOWEL DISEASES

The efficacy of natalizumab in the treatment of Crohn's disease has been described in several RCTs and summarised in a Cochrane review (46). Pooled data from four studies have shown that natalizumab is effective for the induction of response and remission in patients with moderate to severe Crohn's disease (300 mg, or 3-4 mg/kg) (EL 1a, RG A). In the decision regarding the use of natalizumab in patients with failure of other biologic drug, the risk of progressive multifocal leukoencephalopathy (PML) must be considered. The risk of PML among natalizumab-treated patients is approximately 1-2/1000 patients per year (47) (EL 4, RG C).

PREMEDICATION PRIOR TO INFUSION OF INFLIXIMAB

Evidence for the use of premedication with corticosteroids, antihistamines and/or paracetamol to prevent infusion reactions is scarce. In a study of 355 patients with rheumatoid arthritis who were randomised to placebo or bethametason 30 minutes prior to infusions of infliximab, no difference was found in the number of infusion reactions (48). After the randomisation of 80 patients with Crohn's disease to hydrocortisone or placebo treatment, a lower incidence of infusion reactions was observed in the hydrocortisone group (15 % vs. 24 %), but the difference was not statistically significant (49). A prospective open-label study investigated the effect of antihistamine given at week 6 and week 14 and found no difference in the incidence of infusion reactions (50). The studies compare mainly patients who were initiated on or maintained the anti-TNF-α treatment. Studies that address the effect of premedication when treatment with anti-TNF-α is resumed after a temporary discontinuation is needed (51). In conclusion, the efficacy of premedication is not clearly documented in newly initiated infliximab treatments, while there is larger evidence for treating patients with steroids and antihistamine, if a previous infusion reaction was observed.

POSTOPERATIVE PROPHYLAXIS OF CROHN'S DISEASE

Only one study has assessed the effect of postoperative prophylaxis with biologic therapy. Twenty-four patients, who had undergone ileocolonic resection, were randomised to infliximab or placebo within 4 weeks after surgery, with a treatment duration of 52 weeks. The primary endpoint (endoscopic recurrence at 1 year) was significantly lower among infliximab-treated patients than in the placebo group: 9.1 % versus 84.6 %. There was no significant difference between the numbers of patients in clinical remission (52).

POUCHITIS

Construction of an ileal-pouch-anal anastomosis (IPAA) may be complicated by inflammation in the pouch (pouchitis). The incidence is 20-60 % 5 years after surgery, and a small proportion (5-10 %) develops chronic pouchitis (53). There are no clinically controlled, randomised studies that have evaluated the effect of biologic drugs on possible complications after construction of IPAA. In contrast, several retrospective studies that illustrate the efficacy of infliximab in refractory pouchitis, usually defined as symptoms despite more than 4 weeks of antibiotic therapy, have been published. In several of the series, patients with Crohn's-like complications are also included. After treatment with infliximab at 5 mg/kg of body weight at week 0, 2 and 6 followed by maintenance therapy every 8 weeks in a Belgian study of 28 patients (82 % received concomitant immunosuppressive therapy), a short-term effect (partial or complete response) of 88 % after 10 weeks was observed. Long-term efficacy after a median follow up of 20 months was 56 %. Five patients had an ileostomy (54). A Spanish study of 33 patients with fewer patients receiving immunosuppressive therapy (54 %) obtained similar results: 84 % had a response (21 % complete, 63 % partial) assessed after 8 weeks, 56 % had a partial or complete response after 52 weeks.

EXTRAINTESTINAL MANIFESTATIONS

Extraintestinal manifestations (EIMs) occur in 20-45 % of patients with IBD and contribute to significant morbidity. The most common EIMs consist of peripheral arthropathy and arthritis, axial arthropathy, skin manifestations such as erythema nodosum and pyoderma gangrenosum and eye diseases such as episcleritis, iridocyclitis and uveitis. In addition, a variety of rare EIMs can be observed. In relation to treatment, there are primarily data from retrospective case series, data from prospective open series and only a few results from RCTs on the effect of EIM (including TNF-α therapy). In some RCTs, patients without IBD were included. The effect of anti-TNF-α on EIM has been observed in both EIM running parallel to intestinal disease activity (peripheral arthropathy, erythema nodosum, episcleritis) and in EIM -independent of disease activity (axial arthropathy, uveitis). A decrease of EIMs in 79 % of the treated patients was observed in an open-label study on adalimumab in patients with Crohn's disease (55). In a controlled study of infliximab (compared to standard therapy) among patients with IBD and spondylarthropathy, infliximab-treated patients had rapid and sustained relief of symptoms (56). A placebo-controlled RCT has also shown the effect of infliximab on pyoderma gangrenosum (57).

REFERENCES

1. Stack WA, Mann SD, Roy AJ et al. Randomised controlled trial of CDP571 antibody to tumour necrosis factor-alpha in Crohn's disease. Lancet 1997; 349:521-524.
2. Targan SR, Hanauer SB, Van Deventer SJ et al. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. N Engl J Med 1997; 337:1029-1035.
3. Behm BW, Bickston SJ. Tumor necrosis factor-alpha antibody for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev 2008;CD006893.
4. Colombel JF, Sandborn WJ, Rutgeerts P et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. Gastroenterology 2007; 132:52-65.
5. Hanauer SB, Sandborn WJ, Rutgeerts P et al. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. Gastroenterology 2006; 130:323-333.
6. Sandborn WJ, Hanauer SB, Rutgeerts P et al. Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. Gut 2007; 56:1232-1239.
7. Sandborn WJ, Feagan BG, Stoinov S et al. Certolizumab pegol for the treatment of Crohn's disease. N Engl J Med 2007; 357:228-238.
8. Sheridan C. Cimzia's setback paves way for other TNF inhibitors in Crohn's disease. Nat Biotechnol 2007; 25:487-488.
9. MacDonald JK, McDonald JW. Natalizumab for induction of remission in Crohn's disease. Cochrane Database Syst Rev 2007;CD006097.
10. Dignass A, Van AG, 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.
11. Travis SP, Stange EF, Lemann M et al. European evidence-based Consensus on the management of ulcerative colitis: Current management. J Crohns Colitis 2008; 2:24-62.
12. 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; 142:63-70.
13. Kornbluth A, Sachar DB. Ulcerative colitis practice guidelines in adults: American College Of Gastroenterology, Practice Parameters Committee. Am J Gastroenterol 2010; 105:501-523.
14. Dahlerup JF, Hvas CL, Jacobsen BA et al. Diagnostik og behandling af fistulerende Crohns sygdom. Dansk Gastroenterologisk Selskab 2011.
15. Christensen LA, Kjeldsen J, Knudsen T et al. Behandling af akut svær colitis ulcerosa. Dansk Gastroenterologisk Selskab 2011.
16. Lichtenstein GR, Hanauer SB, Sandborn WJ. Management of Crohn's disease in adults. Am J Gastroenterol 2009; 104:465-483.
17. 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.
18. Talley NJ, Abreu MT, Achkar JP et al. An evidence-based systematic review on medical therapies for inflammatory bowel disease. Am J Gastroenterol 2011; 106 Suppl 1:S2-25.
19. Ford AC, Sandborn WJ, Khan KJ et al. Efficacy of biological therapies in inflammatory bowel disease: systematic review and meta-analysis. Am J Gastroenterol 2011; 106:644-59, quiz.
20. Harvey RF, Bradshaw JM. A simple index of Crohn's-disease activity. Lancet 1980; 1:514.
21. van Assche G, Dignass AU, Reinisch W et al. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Definitions and diagnosis. Journal of Crohn's and Colitis 2010; 4:7-27.

22. Stange EF, Travis SP, Vermeire S et al. European evidence-based Consensus on the diagnosis and management of ulcerative colitis: Definitions and diagnosis. J Crohns Colitis 2008; 2:1-23.
23. Belard E, Dahlerup JF, Gerstoft J et al. Retningslinjer for screening, profylakse og information før behandling med anti-TNF-alfa. Dansk Gastroenterologisk Selskab 2011.
24. 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.
25. Mackey AC, Green L, Liang LC et al. Hepatosplenic T cell lymphoma associated with infliximab use in young patients treated for inflammatory bowel disease. J Pediatr Gastroenterol Nutr 2007; 44:265-267.
26. van Assche G, Van Ranst M, Sciot R et al. Progressive multifocal leukoencephalopathy after natalizumab therapy for Crohn's disease. N Engl J Med 2005; 353:362-368.
27. Mowat C, Cole A, Windsor A et al. Guidelines for the management of inflammatory bowel disease in adults. Gut 2011; 60:571-607.
28. Present DH, Rutgeerts P, Targan S et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. N Engl J Med 1999; 340:1398-1405.
29. Sands BE, Anderson FH, Bernstein CN et al. Infliximab maintenance therapy for fistulizing Crohn's disease. N Engl J Med 2004; 350:876-885.
30. Behm BW, Bickston SJ. Tumor necrosis factor-alpha antibody for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev 2008;CD006893.
31. Colombel JF, Schwartz DA, Sandborn WJ et al. Adalimumab for the treatment of fistulas in patients with Crohn's disease. Gut 2009; 58:940-948.
32. Biancone L, Michetti P, Travis S et al. European evidence-based Consensus on the management of ulcerative colitis: Special situations. J Crohns Colitis 2008; 2:63-92.
33. Reinisch W, Van AG, Befrits R et al. Recommendations for the treatment of ulcerative colitis with infliximab: a gastroenterology expert group consensus. J Crohns Colitis 2012; 6:248-258.
34. van Assche G, Dignass AU, Reinisch W et al. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Special situations. Journal of Crohn's and Colitis 2010; 4:63-101.
35. Shale MJ. The implications of anti-tumour necrosis factor therapy for viral infection in patients with inflammatory bowel disease. Br Med Bull 2009; 92:61-77.
36. Rahier JF, Ben-Horin S, Chowers Y et al. European evidence-based Consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. J Crohns Colitis 2009; 3:47-91.
37. Cheifetz A, Smedley M, Martin S et al. The incidence and management of infusion reactions to infliximab: a large center experience. Am J Gastroenterol 2003; 98:1315-1324.
38. Miehsler W, Novacek G, Wenzl H et al. A decade of infliximab: The Austrian evidence based consensus on the safe use of infliximab in inflammatory bowel disease. J Crohns Colitis 2010; 4:221-256.
39. Breynaert C, Ferrante M, Fidder H et al. Tolerability of shortened infliximab infusion times in patients with inflammatory bowel diseases: a single-center cohort study. Am J Gastroenterol 2011; 106:778-785.
40. Cassinotti A, Travis S. Incidence and clinical significance of immunogenicity to infliximab in Crohn's disease: a critical systematic review. Inflamm Bowel Dis 2009; 15:1264-1275.
41. Fidder H, Schnitzler F, Ferrante M et al. Long-term safety of infliximab for the treatment of inflammatory bowel disease: a single-centre cohort study. Gut 2009; 58:501-508.
42. Shmidt E, Wetter DA, Ferguson SB et al. Psoriasis and palmoplantar pustulosis associated with tumor necrosis factor-alpha inhibitors: The Mayo Clinic experience, 1998 to 2010. J Am Acad Dermatol 2011.
43. Kerbleski JF, Gottlieb AB. Dermatological complications and safety of anti-TNF treatments. Gut 2009; 58:1033-1039.
44. Rahier JF, Buche S, Peyrin-Biroulet L et al. Severe skin lesions cause patients with inflammatory bowel disease to discontinue anti-tumor necrosis factor therapy. Clin Gastroenterol Hepatol 2010; 8:1048-1055.
45. Cullen G, Kroshinsky D, Cheifetz AS et al. Psoriasis associated with anti-tumour necrosis factor therapy in inflammatory bowel disease: a new series and a review of 120 cases from the literature. Aliment Pharmacol Ther 2011; 34:1318-1327.
46. MacDonald JK, McDonald JW. Natalizumab for induction of remission in Crohn's disease. Cochrane Database Syst Rev 2007;CD006097.
47. Tavazzi E, Ferrante P, Khalili K. Progressive multifocal leukoencephalopathy: an unexpected complication of modern therapeutic monoclonal antibody therapies. Clin Microbiol Infect 2011; 17:1776-1780.
48. Sany J, Kaiser MJ, Jorgensen C et al. Study of the tolerance of infliximab infusions with or without betamethasone premedication in patients with active rheumatoid arthritis. Ann Rheum Dis 2005; 64:1647-1649.
49. Farrell RJ, Alsahli M, Jeen YT et al. Intravenous hydrocortisone premedication reduces antibodies to infliximab in Crohn's disease: a randomized controlled trial. Gastroenterology 2003; 124:917-924.
50. Wasserman MJ, Weber DA, Guthrie JA et al. Infusion-related reactions to infliximab in patients with rheumatoid arthritis in a clinical practice setting: relationship to dose, antihistamine pretreatment, and infusion number. J Rheumatol 2004; 31:1912-1917.
51. Lecluse LL, Piskin G, Mekkes JR et al. Review and expert opinion on prevention and treatment of infliximab-related infusion reactions. Br J Dermatol 2008; 159:527-536.
52. Regueiro M, Schraut W, Baidoo L et al. Infliximab prevents Crohn's disease recurrence after ileal resection. Gastroenterology 2009; 136:441-450.
53. Crohn BB, Ginzburg L, Oppenheimer GD. Regional ileitis. A pathological and clinical entity. JAMA 1932; 99:1323-1329.
54. Ferrante M, D'Haens G, Dewit O et al. Efficacy of infliximab in refractory pouchitis and Crohn's disease-related complications of the pouch: a Belgian case series. Inflamm Bowel Dis 2010; 16:243-249.
55. 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.
56. Generini S, Giacomelli R, Fedi R et al. Infliximab in spondyloarthropathy associated with Crohn's disease: an open study on the efficacy of inducing and maintaining remission of musculoskeletal and gut manifestations. Ann Rheum Dis 2004; 63:1664-1669.
57. Brooklyn TN, Dunnill MG, Shetty A et al. Infliximab for the treatment of pyoderma gangrenosum: a randomised, double blind, placebo controlled trial. Gut 2006; 55:505-509.

LEVEL OF EVIDENCE AND GRADE OF RECOMMENDATIONS

ASSESSMENT OF THE LEVEL OF EVIDENCE (1-5) AND GRADE OF RECOMMENDATIONS (A-D) FOLLOWS THE CENTRE FOR EVIDENCE BASED MEDICINE, UNIVERSITY OF OXFORD.

	Level of Evidence	Grade of Recommendation
Remission rate is higher with combination of biologic therapy and immunosuppressants	Ib	B
Serious but rare side effects are mainly observed in combination therapy	IV	
Biologic therapy has efficacy in moderate to severe active luminal Crohn's disease, where there is no effect of conventional treatment	Ib	A
Maintenance therapy may be given when effect of induction therapy is observed	Ia	A
Treatment efficacy is assessed on the basis of clinical and laboratory markers	IIb	B
In Crohn's disease, biologic therapy is initiated in simple fistula with rectal inflammation or in complex fistulas where there is no effect of conventional treatment	Ia	A
Treatment with infliximab can be initiated in acute severe ulcerative colitis if there is a partial response after 3-5 days of treatment with high-dose systemic steroid and where surgery is not preferred	Ib	B
Biologic therapy can be used in ulcerative colitis with chronic activity despite conventional therapy and where surgery is not preferred	Ib	B
Opportunistic infections occur most frequently during combination therapy of biologic therapy and immunosuppressants	IIIb	
Infusion reactions occurred more frequently during episodic treatment with biologic therapy	IIb	
Infusion reaction is less often observed with concomitant immunosuppressive therapy	IIb	
Dermatological manifestations are observed in up to 20 % of the treated patients	IIb	
Premedication with steroids or paracetamol in newly started biologic therapy has not been proven to have a preventive effect against infusion reactions	IIb	B
In Crohn's disease, postoperative prophylaxis with biologic therapy reduces endoscopic but not clinical recurrence rate	IIb	B
Biologic therapy may ameliorate chronic pouchitis	IV	D
Extraintestinal manifestations, including pyoderma gangrenosum, are improved by biologic therapy	IIb	C

Table 4. Level of Evidence and Grade of Recommendations

OPPORTUNISTIC INFECTIONS

HCV	Acute HCV infection has not been described in patients receiving biologic therapy, and the importance of continued treatment is unknown.
HBV	Reactivation of HBV has been reported in association with biologic therapy (35, 36). Status of HBV infection/prior vaccination must be assessed (HBsAg, anti-HBs Ab, anti-HBc Ab) in all IBD patients prior to the use of biologic therapy. If an HBV infection is detected, HBeAg, anti-HBe Ab and HBV DNA should be measured to determine a treatment strategy. In the case of positive HBsAg, regardless of the grade of viraemia, prophylactic therapy with antiviral agents should be provided if biologic therapy is considered (EL 4, RG C).
HIV	Acute HIV infection during biologic therapy is not observed. It is, however, recommended that acute HIV is treated according to guidelines and possible temporary discontinuation with the biologic drug should be considered if the patient does not respond to the administered HIV treatment. Biologic therapy is not contraindicated in HIV-positive patients with a normal immune response (CD4 level) (EL 4, RG D).
CMV	Latent or subclinical CMV is not a contraindication to biologic therapy (EL 2). In acute CMV and concomitant severe colitis, treatment with antiviral medications while pausing the biologic drug until recovery in colonic inflammation is advised. Systemic CMV infection requires withdrawal of biologic medications (EL 2, RG B).
HSV	Initiation of biologic therapy is not recommended during an active HSV infection. Antiviral treatment and temporary discontinuation of the biologic drug is recommended during active HSV (EL 4, RG C).
VZV	Infection with VZV during biologic therapy requires antiviral therapy (EL 1, RG B) and simultaneous temporary discontinuation of the biologic drugs (EL5, RGD). Resumption of biologic therapy can be initiated when vesicles or fever are absent (EL 5, RG D).
EBV	In severe cases of EBV infection during biologic therapy, antiviral therapy and cessation of the biologic drug is recommended (EL4, RG D). In EBV-related lymphoma, biologic therapy should be permanently discontinued.
HPV	In cases of extensive cutaneous warts or condyloma, discontinuation of biologic drugs is recommended (EL 5, RG D), while previous HPV infection or mild current HPV infection does not necessarily demand discontinuing the biologic therapy (EL2a, RG B).
JC	The JC virus itself is not related to the biologic therapy. In cases of reactivated JC virus and the development of progressive multifocal leukoencephalopathy, biologic therapy must be stopped immediately.
Influenza	Risk of influenza during biologic therapy seems to be increased (EL 4), but the efficacy of and need for antiviral treatment of influenza is unknown. Early antiviral treatment may reduce the development of complications of influenza (EL 5, RG D).
TB	Latent TB must be excluded before the start of biologic therapy. With TB infection, the anti-TB treatment is initiated and the biologic drug should be discontinued. Biologic therapy can be resumed 2 months after initiation of anti-TB treatment, if still indicated (EL 4, RG D).
Bacterial infection	In general, temporary discontinuation of biologic therapy is recommended during an active infection (EL 5, RG D).

Table 5. Opportunistic infections