



Practical guidelines for the treatment of inflammatory bowel disease

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Abstract

In recent years, great progress has been made regarding the treatment of inflammatory bowel disease (IBD), particularly in the field of biological therapies. Nevertheless, the ultimate treatment is not in sight. With the development of new medication, it has become clear that we need a new understanding of IBD. Therapy needs to fit the different subtypes of IBD; e.g. mild disease in comparison to severe chronic active disease or Crohn's disease with or without fistulation or stenosis. The following article gives a practical overview of actual treatments for IBD. The intention of this article is not to provide a complete review of all new scientific developments, but to give a practical guideline for therapy of IBD.

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Key words: Inflammatory bowel disease; Ulcerative colitis; Crohn's disease; Immunomodulators; Anti-tumor necrosis factor

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INTRODUCTION

Crohn's disease and ulcerative colitis are both defined as inflammatory bowel diseases (IBD), characterized by a chronic inflammation of the gut mucosa. The clinical course of both diseases can differ from a mild form, in which the patient reaches long-term remission without taking permanent medication, to a chronic active form,

in which remission is only reached by permanently taking immunosuppressives and/or biologics or by taking them for a long period of time. Patients are not only burdened by the most common symptoms of IBDs; e.g. diarrhea, bowel pain, fever and complications such as fistulation, stenosis and abscesses in Crohn's disease and megacolon in ulcerative colitis, but are also burdened by the side-effects of the therapeutics, which the patients take to achieve a normal quality of life. Therefore, it is a great responsibility for a physician to consider treatment for an individual patient.

Recent discussions in the field of IBD are concerned with recommendations for a step-down or step-up therapy. A step-down therapy means using the most effective biologic or immunosuppressive treatment on the market, even without prior use of therapeutics such as steroids, in order to reach an effective remission as soon as possible. A step-up therapy means using a "classical" treatment by, for example, starting with aminosalicylates and ending up with an immunosuppressive and/or biological. Even if using a common step-up therapy treatment, the decision about which drug to use should be based on the individual patient, considering the clinical course and diagnosed complications according to current treatment guidelines.

This article provides a short overview of IBD and practical guidelines for the actual treatment of IBD (Figures 1 and 2). It is recognized that there is still an urgent medical need for improvement in the treatment in IBD and that treatments may not be sufficient for all patients, although great progress has been made in therapeutic approaches in the last decades (especially regarding biological therapeutics). The current guidelines for IBD therapy are distinguished by the course, place and severity of the clinical disease^[1-7]. In Crohn's disease, a mild active form, a moderate or severe active form or a severe chronically active form can be differentiated. Patients can also be defined as steroid-dependent or steroid-refractory. The endoscopic and clinical pattern, the segments of the body that are involved (e.g. only small colon or small and large colon and/or stomach), the complications (such as fistulation and/or stenosis) as well as the duration of the inflammation and the response (or loss of response) to steroids are taken into account in the evaluation. In ulcerative colitis, differentiation is easier because inflammation only involves the large colon, starting from the rectum to the caecum. Therefore, treatment is determined by the clinical disease course and the involved segments of the colon, such as left-sided disease or pancolitis, as well as the response to steroids

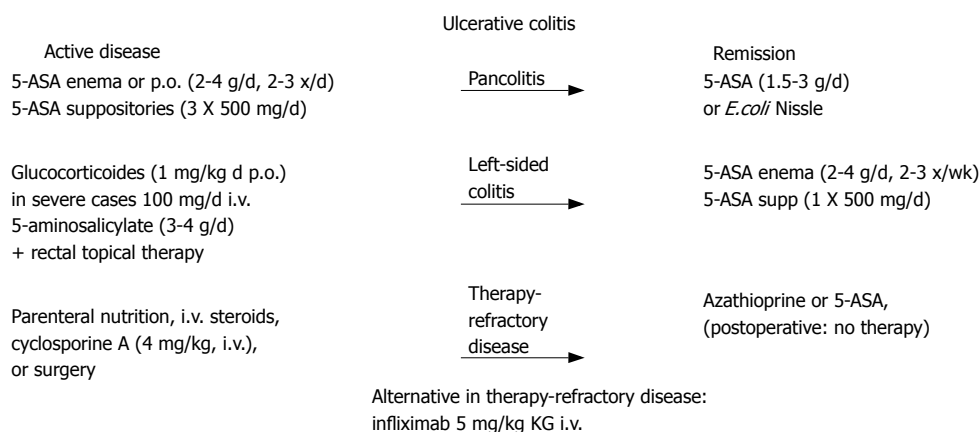


Figure 1 Short overview of the treatment regime of ulcerative colitis.

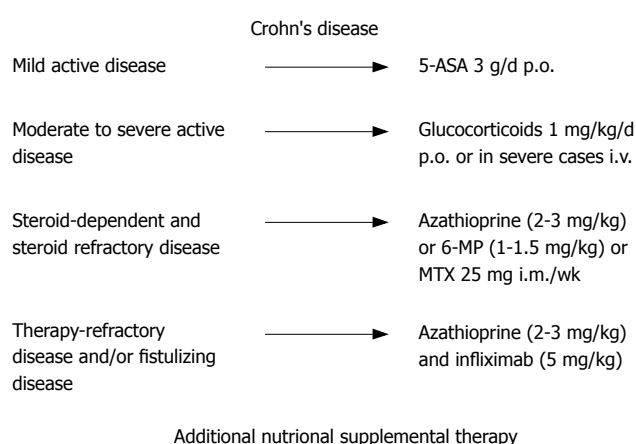


Figure 2 Short overview of treatment regimen in Crohn's disease.

(steroid-dependent or steroid-refractory). In the following paragraphs the treatment of IBD will be discussed according to use of different therapeutic drugs.

5-Aminosalicylates (5-ASA)

5-ASA are bowel-specific drugs that are metabolized in the gut where the predominant actions occur. As a derivative of salicylic acid, 5-ASA is also an antioxidant that traps free radicals, which are potentially damaging by-products of metabolism. In the radical induction theory of ulcerative colitis, 5-ASA functions as a free radical trap as well as an anti-inflammatory drug. 5-ASA is considered to be the active moiety of sulphasalazine, which metabolizes to it. Oral and/or topical 5-ASA is recommended for mild to moderate ulcerative colitis to induce and maintain remission. The dosage of 5-ASA should be no less than 3 g/d. In practice, most patients do not like a topical treatment, but in left-sided disease, an enema with 4 g of 5-ASA 2 times per day or suppositories with 500 mg 5-ASA 3 times per day are most effective. Sometimes it is helpful for the patient to use the enema only in the evening and the suppositories in the morning. In Crohn's disease, aminosaliclates should also be used in initial therapy for mild disease, although discussion about efficacy has increased recently. In contrast to ulcerative colitis, the use of aminosaliclates for the maintenance of remission is not

recommended for Crohn's disease because clinical studies have not shown success in remission maintenance^[8,9]. 5-ASA is a standard treatment for ulcerative colitis, but not for Crohn's disease. In the last few years, new formulations have been on the market with varying clinical value. In some special cases; e.g. patients with an ileostoma, a formulation that sets metabolites free prior to the large bowel may be helpful. In patients with IBD and arthritis, sulphasalazine rather than 5-ASA formulations seems to be more effective regarding arthritis. In most patients, the side-effects are not very severe with headache as one of the most common side-effects. However, in some cases nephritis, pancreatitis and hair loss have been reported, which suggests regular monitoring of renal and liver enzymes at least once in three months.

Antibiotics

Antibiotics (e.g. metronidazole) play only a minor role in the additional treatment of fistulizing disease^[10]. Although metronidazole (for up to 3 mo in a dosage of 400 mg 2 times per day) is often used in post-operative management after an ileocecal resection or fistula/abscess operation for Crohn's disease, this therapy is not based on study evidence. A side-effect of long-term treatment with metronidazole is polyneuropathy and monitoring is, therefore, required. Antibiotics are also used in the conservative treatment of small abscesses. Understanding the role of microbiota and antibiotics in IBD may become important in the future, but currently clinical studies have not provided support for this concern.

Corticosteroids

In patients with moderate to severe Crohn's disease or ulcerative colitis, corticosteroids are effective for the induction of clinical response and remission^[11-16]. Dosages from 40-60 mg/d or 1 mg/kg per day orally are effective for the induction of remission. After the induction of remission, the steroid dose should be tapered (10 mg/wk until 40 mg; 5 mg/wk until 20 mg, followed by a tapering of 2.5 mg/wk). In severe disease, the application of parenteral glucocorticoids as soon as possible is useful for an anti-inflammatory response. Before the initiation of steroid treatment, the presence of an abscess should be excluded. In patients who have been on glucocorticoids

for more than one month, an ACTH (Adrenocorticotrophic hormone)-Test should be performed before beginning tapering of the steroid. The ACTH-test can detect deficient cortisol production in the body. If there is a deficiency, hydrocortisone should be used as a substitute.

Budesonide

The benefits of glucocorticoid therapy should be carefully balanced against possible side-effects. Budesonide can reduce typical steroid side effects by a 90% first-pass metabolism in the liver and erythrocytes. Due to a special structural formulation, budesonide achieves the best anti-inflammatory effect in ileocecal inflammation^[17-20]. Therefore, it is useful in therapy for Crohn's disease with ileocecal inflammation only. However, neither budesonide nor any other glucocorticosteroid should be used for a maintenance therapy due to the side-effects (e.g. Cushing-syndrome, osteoporosis or cardiomyopathy^[21,22]). All patients treated with corticosteroids should additionally receive vitamin D and calcium substitution to avoid bone loss.

Immunosuppressives

The clinical course of 36% of IBD patients is defined as steroid-refractory and in 20% as steroid-dependent^[23]. Immunomodulators are, therefore, recommended for the treatment of chronic active IBD. Studies have shown an efficacy for immunosuppressives that is similar to azathioprine and its metabolite, 6-mercaptopurine (6-MP; 2-3 mg/kg per day, resp. 1-1.5 mg/kg per day), in the long-term use of chronic active disease. Immunomodulators have been shown to be efficient for the control of inflammation and remission maintenance. Only limited data exists on the efficacy of immunosuppressants in fistulizing Crohn's disease and the prevention of post-operative recurrence^[24-30]. Evidence-based data is missing on the post-operative use of azathioprine and many IBD referral centers are using azathioprine for the prevention of post-operative recurrence. Prior to an initiation of treatment with azathioprine or 6-MP, patients should be thiopurine methyltransferase (TPMT) genotype assessed in order to detect for a homozygous deficiency in TPMT in an effort to avert AZA or 6-MP-induced potential adverse events. All patients on azathioprine or 6-MP should be monitored weekly in the first month and after that once a month regarding their white blood count and liver enzymes because a myelosuppression or an elevation of liver enzymes subsequent to the use of azathioprine or 6-MP can occur. In such cases, the dosage of azathioprine or 6-MP should be reduced or paused until lab values are normal. In patients with gastrointestinal side-effects after the intake of azathioprine, a change to 6-MP should be considered.

Methotrexate and cyclosporine

Methotrexate is another immunomodulatory agent that is used in long-term treatment of IBD. The dosage for induction of remission in chronic active disease is 25 mg i.m. per week for 16 wk, followed by a maintenance treatment of 15 mg i.m. per week. In contrast to azathioprine and 6-MP, the data on use of methotrexate

is rather scarce^[31-33]. Cyclosporine is reserved for the treatment of severe steroid-refractory ulcerative colitis only. Intravenous cyclosporine (2-4 mg/kg) was able to prevent a decided colectomy in two of three patients with severe ulcerative colitis. Due to its toxicity, use should be considered carefully; i.e. it should be used only in very severe active disease cases to avoid a colectomy. In Crohn's disease, cyclosporine has been shown to be effective only in fistulizing, but not luminal disease^[34-37].

Tacrolimus

Only very inadequate data is available for tacrolimus. Improvement of fistula drainage, but not closure was demonstrated in a randomized, placebo-controlled trial with tacrolimus^[38,39].

Infliximab

Biological therapies, especially anti-TNF agents, play a pivotal role in the treatment of chronic active IBD and fistulizing disease^[40-43]. The first anti-TNF agent on the market, infliximab, is a chimeric IgG1 mouse/human monoclonal antibody. Randomised, placebo-controlled trials (ACCENT I and II) demonstrated the efficacy of infliximab (5 mg/kg, i.v.) in the induction of clinical response and remission in patients with active Crohn's disease. In fistulizing disease, complete fistula closure of at least 50% of the fistulas could be seen in 55% of the patients after three infusions of infliximab at wk 0, 2 and 6 (ACCENT II). Given on a regular basis in intervals of 8-12 wk (5 mg/kg i.v.), infliximab is able to maintain remission^[44-50].

In ulcerative colitis, the recently completed ACT I and ACT II randomised, placebo-controlled trials demonstrated the efficacy of infliximab treatment in induction of remission and mucosal healing in 61.2% of the infliximab treated patients *versus* 32.4% of placebo treated patients^[51,52].

Contraindications and side-effects should be taken into consideration carefully prior to infliximab therapy^[53]. Due to immunogenicity, infliximab can lead to the formation of human anti-chimeric antibodies (HACA) in 30% to 75% of the patients. Additional administration of immunosuppressants; e.g. azathioprine and/or pretreatment with intravenous prednisolone, can reduce the risks of HACA formation. The main reported side-effect is an infusion reaction, which can occur as an acute allergic/anaphylactic reaction or a delayed hypersensitivity reaction. In clinical trials, observations have included infections, drug-induced lupus, cardiac failure, non-Hodgkin's lymphoma and, in post-marketing surveillance, tuberculosis, pneumonia, histoplasmosis, listeriosis and aspergillosis. To avoid a potential tuberculosis reactivation, a purified protein derivative (PPD) skin test and a chest-X-ray should be performed prior to infliximab treatment^[54-67]. Patients with perianal or enterocutaneous fistulizing Crohn's disease should be treated first with infliximab. The effect of infliximab is not as effective on entero-enteral or recto-vaginal fistulas. Patients with steroid-refractory or chronic active Crohn's disease or ulcerative colitis who do not respond to immunosuppressive therapy alone should also be treated with infliximab. The recommended

treatment regimen is an induction scheme with three infusions (5 mg/kg i.v.) at 0, 2 and 6 wk, followed by a maintenance treatment of infliximab every 8 wk (5 mg/kg i.v.). Additionally, immunosuppressive therapy with azathioprine, for example, is recommended. HACA testing is not recommended routinely for every patient on infliximab, but it is recommended if there is a delayed hypersensitivity reaction or if the last infliximab infusion was more than 12 wk previous.

Adalimumab

Other TNF agents also showed efficacy in Crohn's disease. The human IgG1 antibody adalimumab, which is a therapeutic agent used for rheumatoid arthritis, was effective in open-label experience. A placebo-controlled, randomised trial was also conducted. One advantage, in comparison to infliximab, might be the completely human structure of the antibody, which leads to better tolerance and a subcutaneous route of administration. Data on adverse reactions in Crohn's disease patients are still not available, but adalimumab is well-tolerated in patients with rheumatoid arthritis^[68-71].

CDP-870

Certolizumab pegol (CDP-870), which is a polyethylene-glycolated Fab-fragment of the anti-tumour necrosis factor, has been shown to be effective in the treatment of Crohn's disease in a recent published, randomised, placebo-controlled trial. At week ten, 52.8% of the certolizumab (400 mg) treated patients showed a clinical response versus 30.1% in the placebo treated group (the high placebo response was seen in a large patient subgroup with low C-reactive protein levels; this might have been due to statistical separation between treatment and placebo group^[72]). The antibody was well tolerated. Ongoing trials, however, are necessary to establish efficacy in Crohn's disease.

CDP-571

CDP-571, which is a humanized IgG4 monoclonal antibody against tumour necrosis factor alpha, initially showed an induction of clinical response in controlled trials, but failed in a phase III trial which was discontinued^[73].

Onercept and eterncept

Onercept, which is a recombinant human p55 soluble receptor to TNF, and also eterncept, which is a recombinant human p75 soluble receptor to TNF, failed in a phase II trial with Crohn's disease and both trials were discontinued^[74-76].

Natalizumab

Adhesion molecule inhibiting agents, such as natalizumab, which is a humanized IgG4 antibody, demonstrated a clinical response in a clinical trial in Crohn's disease, but all trials had to be stopped immediately after cases of progressive multifocal leucoencephalopathy in patients receiving natalizumab for multiple sclerosis were reported^[77-79].

The antisense oligonucleotide of the adhesion

molecule ICAM-1 (anti-ICAM-1) was ineffective in Crohn's disease^[80].

A hopeful, novel approach for the treatment of Crohn's disease is an anti-IL-12/IL-23p40 antibody that proved effective for induction of response and remission in a phase II study^[81].

β -Interferon

The use of β -Interferon, which has been investigated in a small pilot study in ulcerative colitis with a subcutaneous administration, seems to be effective, but larger, randomised, placebo-controlled studies need to be performed to clarify the clinical efficacy^[82].

In conclusion, the only biological therapeutic today, which has been proven effective in IBD and is available on the market is infliximab. The market release of new TNF agents might happen in the near future.

Probiotics

A different group of therapeutic agents for therapy of IBD are probiotics. The use of probiotics has been advocated in colonic inflammatory disease for a long time. Only recently, two controlled trials demonstrated that *E. coli* nissle is as effective as 5-ASA for remission maintenance in ulcerative colitis^[83,84]. For remission maintenance and pouchitis, studies demonstrated the benefit of probiotics^[85,86]. Due to a better understanding of the molecular events and the pathophysiological processes of this disease, it is hoped that more probiotic agents will be developed in the near future.

5-ASA

A short, practical guideline would be incomplete without discussing IBD and pregnancy. 5-ASA is not harmful during pregnancy and there is very little placental transport. 5-ASA should be avoided during breast feeding because there are no studies on 5-ASA use during breast feeding^[87]. Acute disease or a flare up of IBD can be treated throughout an entire pregnancy with steroids. Glucocorticoids pass the placental barrier, but there has been no significant evidence of teratogenesis. There have been some observations of cleft lip and palate associated with the intake of steroids. In general, no increase in fetal complications have been found with use of 5-ASA compared to the general population^[88].

Azathioprine or 6-mercaptopurine

The use of azathioprine or 6-mercaptopurine should not be completed during pregnancy. Extensive experience with use of these substances during pregnancy exists with other autoimmune diseases and patients who received renal transplants. No teratogenic effects in humans have been reported so far. However, it is very important to discuss all the data and possible complications with the patient and it is essential that the decision to take the drug should be made by the patient^[89].

Methotrexate is contraindicated during pregnancy as it is mutagenic and teratogenic^[90]. Cyclosporine is not teratogenic, but due to its side-effects, it needs to be considered very carefully and should only be used to avoid a colectomy^[91]. Infliximab should not be given as

maintenance therapy during pregnancy. In very severe disease, it can be considered as an emergency therapy^[92]. Nutrition has not been discussed in this article so far. However, the balance of trace elements and vitamins is essential for successful therapy. Vitamin B12 and folic acid, for example, should be monitored in Crohn's disease patients with ileal inflammation to avoid a deficiency syndrome, which can lead to severe anemia. Also ferritin should be monitored and, if necessary, substituted orally or intravenously to avoid severe iron deficiency anemia. In severe cases of iron deficiency anemia, erythropoietin (10000IE s.c. 3 times per week) plus iron i.v. (62.5 mg in 250 mL NaCl) is effective^[93]. In severe ulcerative colitis or Crohn's disease, patients profit from short term parenteral or additional high calorie nutrition^[94].

All above treatment regimens attempt to avoid complications and inflammation in IBD. However, all conservative therapy sometimes fails or is not effective enough. Examples might be therapy for refractory ulcerative colitis, which can only be successfully treated by an operation (e.g. a colectomy with an ileoanal pouch anastomosis), non-inflammatory stricture in Crohn's disease or severe fistulizing disease, in which a protective ileostoma can be very useful for supporting conservative treatment. In such cases, close collaboration with an experienced IBD surgeon is essential.

It can be summarized that although a number of new biological agents have been developed in the last decades for the treatment of IBD, there is still a great need for new pharmacotherapeutics, particularly for chronic refractory disease patients with multiple complications.

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