Treatment of inflammatory bowel disease: medical and surgical aspects
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Citation for published version (APA):

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GENERAL INTRODUCTION
& OUTLINE OF THESIS

Parts have been published in:
Infliximab for the treatment of ulcerative colitis  Expert Review on Gastroenterology and Hepatology 2009
Surgical options in Crohn’s disease Gut and Liver 2011; 174:60-67
GENERAL INTRODUCTION

Inflammatory bowel diseases (IBD) are chronic, idiopathic inflammatory diseases of the gastrointestinal tract. The two main diagnoses in IBD are Crohn’s disease (CD) and ulcerative colitis (UC), leaving a rest category that is referred to as ‘IBD-unspecified’. In Europe, incidence rates vary from 0.7 to 9.8 cases per 100,000 person years for CD and from 1.5 to 20.3 cases per 100,000 person years for UC. Lower incidences are found in Southern Europe compared to Northern Europe. In the Netherlands, prevalence of IBD is estimated at 90,000. Yearly, approximately 1000 new CD patients and 1500 new UC patients are diagnosed.

Parallels in CD and UC are a peak age-of-onset in the 2nd or 3rd decade, an aetiology that is thought to be multifactorial (Figure 1), and both diseases are characterized by relapses alternating with periods of remission. Treatment of both CD and UC has a twofold primary goal: patients who suffer from an exacerbation need remission-induction therapy and once remission is regained, patients need maintenance therapy to prevent further relapses. Secondarily, adverse effects of medication, avoiding complications and ensuring an acceptable quality of life (QOL) are important aims of therapy.

Clinically, endoscopically and immunologically several factors discriminate CD from UC. Subsequently, therapy also differs for the two disease categories.

**FIGURE 1: THE EXACT ETIOLOGY OF IBD IS UNKNOWN, BUT MULTIPLE FACTORS HAVE BEEN UNRAVELLED THAT CONTRIBUTE TO THE DEVELOPMENT OF THE DISEASES**

Characteristics of Crohn’s disease

CD disease activity can occur in the entire gastrointestinal tract and is endoscopically characterised by transmural inflammation and a skip lesions pattern. Disease behaviour can be inflammatory, obstructive or perforating. The disease is classified according to the Montreal classification that characterizes the disease in the categories age, location and disease behaviour. The disease behaviour of CD, which can be penetrating, stricturing or...
inflammatory, changes with longer follow-up periods (Figure 2)\textsuperscript{11}. Typical complaints of CD are abdominal pain in the lower right quadrant, persistent diarrhoea, fever with or without anorexia and nausea and vomiting as signs of obstruction. Immunologically, T-helper type 1 and 17 cells and their cytokines, particularly tumor necrosis factor (TNF)-α, have shown to play an important role in the development of CD\textsuperscript{12}. The exact immunological mechanisms remain to be sorted out.

**FIGURE 2: CUMULATIVE RATE OF REMAINING FREE OF INTESTINAL PENETRATING OR STRICTURING COMPLICATIONS IN ILEAL (LEFT) AND COLONIC (RIGHT) CD, REPRODUCED WITH PERMISSION\textsuperscript{11}**.

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**Therapeutic options for CD**

**Medical**

CD is most commonly treated following a step-up approach. Therapy is started with the least toxic but also least potent drugs first, to be intensified with stronger medication if necessary. Mild to moderate disease is treated with budesonide or a short course of steroids to induce remission. To keep remission, azathioprine, 6 mercaptopurine or methotrexate are started as maintenance agents. If patients have relapses despite these agents, biologicals such as infliximab (IFX) or adalimumab (ADA) are indicated\textsuperscript{8}.

Biological therapy has been developed in the early nineties when the role of the proinflammatory cytokine TNF-α in the immune response of IBD was discovered. This led to the development of monoclonal antibodies targeting the cytokine\textsuperscript{13}. Now, two decades further, it has been shown that IFX and ADA have profoundly improved the management of luminal and fistulising CD\textsuperscript{14-17}, although some patients have a primary non response, others show loss of response or develop adverse reactions. Another disadvantage is the high cost associated with biologicals\textsuperscript{18,19}. Currently, novel biologic agents are being developed, not all as successful as IFX and ADA\textsuperscript{20}. 
Surgical
The recurrent character of CD requires a therapy that is aimed at preservation of bowel. This is why treatment of the disease is primarily medical. However, it is estimated that more than two thirds of patients with CD will need surgery at least once. This need for intestinal resection has remained stable over the past 25 years, despite improvements in medical therapy.

Indications for surgery are treatment of complications such as abdominal abscesses, perforations, bleeding and perianal abscesses. Electively, surgery is applied for obstructive disease, medical refractory disease and abdominal or perianal fistulas.

Since disease activity is confined solely to the terminal ileum in 30-35% of all CD patients, an ileocolic resection is by far the most performed surgical resection. Many studies have shown that an ileocolic resection can be performed safely and preferably laparoscopically, with complication rates requiring reoperation varying between 0 and 8.3%. Furthermore, with the current availability of potent immunosuppressive drugs, a low recurrence is seen nowadays. The optimal postoperative medical management to prevent recurrence has however not been defined yet.

Disadvantages of surgery are the risk of complications and the recurrent character of CD in the entire intestine, which never makes surgery curative.

Characteristics of ulcerative colitis
Patients with UC typically present with a history of bloody diarrhoea, abdominal cramping and fatigue. Endoscopically, UC diffusely affects the superficial mucosa of the colon. Disease activity is confined to the colon, and almost always involves the rectum. From there it may extend continuously upwards. Patients can therefore be classified as having proctitis (disease limited to the rectum), left-sided colitis (disease activity extending to proximal but not beyond the splenic flexure), or pancolitis (with disease activity extending from the rectum proximally to the caecum). Immunologically, T-helper type 2 cells and their cytokines, particularly interleukin (IL)-4, are thought to play an important role in the development of UC. Since cytokine production within the appendix has been proposed to trigger an immunological cascade in the colorectum, the appendix is suggested to be a potential priming site in the development of UC.

Therapeutic options for UC
Medical
Also for UC, the current recommended treatment algorithm is the step-up approach. Generally, mild to moderate disease is treated with mesalazine, topically or orally (depending on the extension of the colitis). Systemic or topical corticosteroids can be added if symptoms of active colitis do not respond rapidly to treatment with mesalazine. Severe UC should be treated with intravenous corticosteroids during hospital admission. Last options to prevent surgical treatments are cyclosporine or IFX. The latter was approved for treatment of UC in 2006.
Surgical

Colitis refractory to all medical management is treated surgically, mostly by means of a subtotal colectomy in the acute setting and restorative proctocolectomy with ileal J-pouch anastomosis electively. Since UC is confined to the large intestine, this will cure the disease. If surgery can be done in an elective setting, a proctocolectomy with ileal pouch anal anastomosis (IPAA) will be performed with or without temporary defunctioning loop ileostomy. This is decided by the surgeon depending on the risks for an anastomotic leakage, like use of steroids and nutritional status. Operation rates vary in the literature from 7.5% after 5 years to 24% after 10 years. Restorative proctocolectomy with pouch construction may be complicated by the development of anastomotic leakage requiring reoperation and later by pouchitis, high stool frequency, faecal incontinence and reduced fecundity. It is as yet unknown whether preoperative medical rescue therapies such as IFX negatively influence the postoperative complication rates; there are contradicting publications regarding this issue.

AIM OF THE THESIS

In this thesis several aspects of medical and surgical treatment options for patients with Crohn’s disease (CD) and ulcerative colitis (UC) are highlighted. The aim of part I was to evaluate efficacy and safety of biologic agents. Purpose of Part II was to critically appraise aspects of the surgical management of inflammatory bowel disease (IBD). Finally, Part III concerns the question whether - in case of recurrent ileocecal CD - biologic agents or surgery should be applied.

OUTLINE OF THE THESIS

Biological therapy for inflammatory bowel disease: efficacy and safety (part I)

Most evidence available regarding the efficacy and safety of biological therapies for IBD are derived from randomized clinical trials. Daily-practice data are scarce. The aims of chapter 1 and chapter 2 were to assess efficacy and safety of infliximab (IFX) (chapter 1) and adalimumab (ADA) (chapter 2) in two large consecutive unselected cohorts of patient with CD.

Regarding the safety of anti-TNF therapy, aim of chapter 3 was to investigate a clinical observation whether anti-TNF treatment is a risk factor for the occurrence of free perforation in CD.

In the literature there are contradictory publications with regard to the role of anti-TNF therapy as a risk factor for increased complications after proctocolectomy with IPAA procedure in UC patients. Aim of chapter 4 was to compare complication rates of patients who underwent restorative proctocolecomy with IPAA with and without preoperative IFX therapy.
Surgical therapy for inflammatory bowel disease: efficacy, safety and new techniques (part II)

Patients with isolated ileocecal CD refractory to medical therapy are best treated by means of an ileocolic resection. Data suggest that this is a safe and effective therapy. Aim of **chapter 5** was to assess short- and long-term outcomes of a consecutive cohort of CD patients who underwent ileocolic resection in the last decade in our center.

A laparoscopic ileocolic resection has been shown to be superior compared with open surgery with regard to short-term outcome. Whether laparoscopy also offers advantages with regard to long-term outcomes is as yet unknown. **Chapter 6** and **chapter 7** present data of two studies in which the long-term outcomes after laparoscopically assisted and open ileocolic resection were compared.

A new development in the minimal invasive approach of abdominal surgery is ‘Natural Orifice Transluminal Endoscopic Surgery (NOTES)’. In this light, we investigated a new technique to minimize abdominal wall damage during ileocolic resection, using a colonoscope to extracorporate the resected specimen transcolonically. The results of a series of ten patients operated this way are described in **chapter 8**.

There is evidence that an appendectomy in medical history protects against development of UC. Whether an appendectomy also affects the disease course of patients with UC remains unknown. In **chapter 9**, a systematic review of studies investigating the effect of appendectomy on the disease course in patients with UC is presented.

Medical or surgical therapy for Crohn’s disease (part III)

Steroid refractory ileocecal CD can be treated both medically (with biologic agents) and surgically. It is not known which treatment strategy generates the best quality of life and is most cost-effective. **Chapter 10** provides an overview of the available evidence concerning the different medical and surgical treatment options for ileocecal CD. In **chapter 11**, a randomized controlled multi-center trial is proposed to determine whether IFX therapy or an ileocolic resection is to be preferred in case of steroid refractory recurrent ileocecal disease.
### Reference List


14 General introduction & outline of thesis


