Summary, general discussion and recommendations for future research
Summary

The onset of inflammatory bowel disease (IBD; Crohn's disease, ulcerative colitis, and indeterminate colitis) occurs in childhood in 25-30% of all patients. The available epidemiological studies in children show incidence rates of 0.2 to 5.9 per 100,000 children (aged ≤ 16 years) per year in for Crohn's disease, and 0.5 to 3.2 for ulcerative colitis. A recent epidemiological study in the Netherlands suggests a higher incidence of 7.2 patients per 100,000 children (aged ≤ 17 years) per year. These patients have a life-long disease ahead, with remissions and unexpected exacerbations, leading to symptoms that often cause embarrassment and isolation; they will chronically need immunosuppressive medication, will sometimes be submitted to invasive diagnostic procedures, surgery or nutritional intervention. A thesis on how to cope with all this might have been more useful. In contrast, the studies presented in this thesis deal with diagnosis and medical treatment of children with inflammatory bowel disease. A correct diagnosis is essential for coping with any disease and is needed to guide choice of treatment; successful medical treatment will add to the patient's physical and mental well being. Children are not small adults, and therefore children with IBD need a different diagnostic and therapeutic approach compared to the approach used in adult patients. The lack of pediatric clinical studies however often necessitates extrapolation from adult literature.

In this thesis, 6 clinical studies are presented that will contribute to the existing evidence on how to diagnose and treat children with inflammatory bowel disease.

In Chapter 1.1, an important diagnostic issue is discussed; namely which endoscopic procedure is the most accurate in children suspected of inflammatory bowel disease. Specifically, this study focused on the histological diagnosis based on biopsies from the rectum, sigmoid, colon and/or ileum. In 42 children with a known diagnosis of IBD, mucosal biopsies taken from the rectum and sigmoid were re-assessed by a blinded pathologist. These children
all had undergone a total colonoscopy and sometimes also an ileoscopy at the time of presentation. Using this approach, the accuracy of a diagnosis based on biopsies from rectum and sigmoid was compared to the accuracy of a histological diagnosis based on biopsies from all segments of the colon (and in some cases ileum). The results of this retrospective analysis clearly demonstrated the superiority of a total (ileo)colonoscopy, with a diagnostic accuracy in (ileo)colonic biopsies of 0.7619, while diagnostic accuracy of rectosigmoid histology was 0.4524.

In Chapter 1.2, the importance of endoscopy and histology in the follow-up of medical treatment is discussed. The endoscopic and histological disease activity was assessed in 7 children with refractory, steroid-dependent Crohn's disease, before and 4 weeks after a single infusion of infliximab (a monoclonal anti-tumor necrosis factor antibody). Endoscopic lesion severity by means of a visual analog score (ranging from 0-10) decreased significantly as a result of treatment: mean values (±SE) were 8 (±1) before treatment and 3.5 (±1) after 4 weeks. Histological scores (range 0-16) showed a similar trend, median values decreasing from 12 to 6 points. The correlation between clinical disease activity scores and endoscopy score was moderate; correlation between clinical activity scores and histology scores was poor.

In Chapter 2.1, the first pediatric pharmacokinetic data of budesonide capsules are presented. Budesonide, a potent steroid with low systemic availability is known to effectively induce remission while adrenal suppression is less than suppression during prednisolone treatment in adults with active Crohn's disease. In 8 children and 6 adults with mild to moderately active Crohn's disease, systemic exposure, peak plasma concentration, bioavailability and suppression of plasma cortisol were determined. After a single infusion of 0.5 mg budesonide, patients received 9 mg oral budesonide capsules daily for 7 days. Systemic exposure and cortisol suppression were slightly, but not significantly higher in children than in adults. No clinically important side effects were identified during this study.
In Chapter 2.2, a multicenter pharmacokinetic study is presented on the pharmacokinetics, preliminary efficacy, and safety of infliximab, a monoclonal antibody to tumor-necrosis-factor (anti-TNF), in children with refractory Crohn's disease. Patients were randomized to receive a single infusion of 1 mg/kg, 5 mg/kg or 10 mg/kg of infliximab. The pharmacokinetic profile was similar to that in adults. Serum infliximab concentrations were detectable through week 8 in the 5 mg/kg group. During the trial, all 21 patients achieved a clinical response (defined as improvement from baseline of ≥ 10 points on the Pediatric Crohn's Disease Activity Index (PCDAI) at any point) and 10 of the 21 (48%) achieved clinical remission (defined as PCDAI < 10).

Chapter 3.1 reports the results of a multicenter, randomized, controlled trial on the efficacy and safety of budesonide versus prednisolone in children with active Crohn's disease in the ileum, cecum and/or ascending colon. In this study, 46 children were randomized to receive oral treatment with either budesonide (9 mg daily for 8 weeks, followed by 6 mg daily for 4 weeks) or prednisolone (1 mg/kg/day for 4 weeks, followed by 8 weeks of tapering down to 2.5 mg daily at week 12). At the primary endpoint of 8 weeks, 55% of patients in the budesonide group and 71% of patients receiving prednisolone were in clinical remission (as defined by a Crohn's Disease Activity Index of 150 or less). This difference was not statistically significant. Glucocorticosteroid (GCS) side effects, in particular moon face and acne, occurred significantly less in the patients receiving budesonide. In addition, morning plasma cortisol remained at a significantly higher level during budesonide treatment, as compared to levels in the prednisolone group. These results demonstrate that budesonide is effective in the treatment of active Crohn's disease in children, while GCS side effects and adrenal suppression is significantly less than during prednisolone treatment.

Chapter 3.2 is the report on a rare case of metastatic Crohn's disease that was successfully treated with infliximab. A 9 year-old boy presented with painless swelling and redness of his penis and scrotum, while no gastrointestinal
complaints were observed. On examination a small anal fissure was found. Histopathology of a scrotal skin biopsy revealed granulomatous lesions, and after exclusion of other granulomatous disorders, a diagnosis of metastatic Crohn's disease was made. Remarkably, none of the endoscopic investigations (upper endoscopy and ileocolonoscopy), nor histology of any of the mucosal biopsies had shown inflammatory changes. After failure of several immunosuppressive medications, infliximab treatment was started (in combination with azathioprine), almost 2 years after the initial presentation. Swelling and redness was reduced within weeks, and treatment was continued for over a year. To date, no gastrointestinal complaints exist.

Chapter 3.3 is an extensive review of the existing literature on the medical treatment of childhood IBD. In addition, the most important evidence based data from drug trials in adults are discussed. Indications, dosage, and recommended investigations are provided for all the available treatments. Logarithms are presented that suggest how to integrate all the available evidence into treatment regimens in children with Crohn's disease, Crohn's disease with fistulae, or ulcerative colitis. In Crohn's disease, nutritional therapy has proven to be effective in inducing and maintaining remission, while promoting linear growth in children. Mean remission rates after enteral nutrition or steroids are similar, approximately 85%, as described in a recent meta-analysis of 7 pediatric clinical trials. Conventional medical treatment of IBD consists of aminosalicylates and corticosteroids, while the early introduction of immunosuppressives (such as azathioprine or 6-mercaptopurine (6-MP)) is advocated as maintenance treatment in Crohn's disease. Methotrexate can be used in Crohn’s disease, when azathioprine is ineffective or not tolerated. In severe ulcerative colitis, cyclosporine may be an effective, but temporary rescue therapy. More potent immunomodulatory treatment such as infliximab is generally reserved for patients with severe, treatment resistant Crohn's disease.
Discussion

The 6 clinical studies presented in this thesis provide new data on how to diagnose and treat children with inflammatory bowel disease. A diagnosis of IBD depends heavily on endoscopy and histology, and a complete ileocolonoscopy with multiple biopsies yield more accurate information than do biopsies taken during rectosigmoidoscopy. Histological features such as the distribution pattern of the inflammatory changes are important in distinguishing Crohn’s disease from ulcerative colitis. Distribution and presence of focal abnormalities provide an additional dimension that can only be achieved by assessing multiple biopsies from the ileum and multiple segments of the colon. An accurate diagnostic procedure is of key importance in pediatric IBD because distribution pattern and type of disease will guide the medical, nutritional or surgical treatment. In addition, but beyond the scope of this thesis, it is becoming increasingly important to rigorously phenotype patients in order to have a solid basis for the future molecular classification of inflammatory bowel disease with childhood onset.

To evaluate the effect of treatment, endoscopic and/or histological remission might be more valuable than clinical remission in terms of duration of remission and subsequent course of the disease. As was previously demonstrated in children receiving nutritional treatment, a single infusion of infliximab results in endoscopic and histological improvement of the inflammatory changes in the colon of children with treatment-resistant Crohn’s disease. The poor correlation between clinical disease activity and histological disease activity is not surprising, taking into account the patchy nature of the disease, and the problems encountered when comparing biopsy specimens taken supposedly from the same region at two timepoints. Presently, we do not know the clinical significance of histological healing. One could hypothesize that histological remission may be accomplished more easily in children with new-onset disease. Another hypothesis is that clinical remission will last longer once histological remission is achieved. One preliminary study has shown that duration of response is indeed longer in children with new-onset disease, as
compared to children with longstanding Crohn’s disease. It has also been suggested that histological healing may even prevent cancer in ulcerative colitis. Taken together, histological disease activity provides an important outcome variable that to date has been used insufficiently in clinical trials. In common practice, it is mostly clinical disease activity that will guide treatment decisions. The question of whether careful assessment of histology during or after any drug treatment will ultimately help us in the clinical management of Crohn’s disease in children is unclear. Assessment of endoscopic and histological disease activity during and after treatment is not feasible in the routine care of pediatric patients. Repeated performance of invasive procedures such as endoscopies can not always be justified in children, for both ethical and economic reasons. A non-invasive test that correlates highly with disease activity at the mucosal level is therefore needed.

The pharmacokinetic studies in this thesis exemplify again why “children are not little adults”. Looking at budesonide, bioavailability and cortisol suppression is similar in children and adults with Crohn’s disease. As a consequence, the dosage regimen of budesonide capsules should be the identical in children and adults, and a daily dose of 9 mg was chosen for the multicenter randomized pediatric trial discussed below. Without the pediatric pharmacokinetic data, dosage would have been adjusted to bodyweight, resulting in undertreatment. As in budesonide, the pharmacokinetic data of infliximab are every similar in children and adults. For this potent biological treatment, a single dose of 5 mg/kg per infusion seems to be well tolerated and safe in pediatric, as well as in adult patients. Again, the results of this study permit the design and performance of further pediatric clinical studies with infliximab.

The multinational randomized trial of budesonide versus prednisolone in children with active Crohn’s disease is unique, as it is the first European pediatric IBD randomized drug trial. The results are important as they provide “real evidence” on efficacy and side effects of budesonide and prednisolone. While remission rates are not significantly different in the two treatment groups, children in the budesonide group have significantly less side effects and less adrenal suppression. Short term treatment with budesonide may therefore
serve as an alternative to prednisolone in children with either new-onset moderately active Crohn's disease or in patients who have experienced steroid toxicity. The glucocorticosteroid side effects of long-term budesonide treatment, such as bone demineralization and growth failure have not been studied yet. However, with the early instigation of immunosuppressive maintenance treatment (such as azathioprine or 6-mercaptopurine), and the availability of infliximab, chronic steroid use may become increasingly rare in children. Contrary to the conventional step-up strategy (starting with less potent and less toxic medication or with nutritional treatment), a top-down approach, starting with infliximab in combination with azathioprine, 6-mercaptopurine or methotrexate, may alter the course of disease more effectively. This hypothesis needs to be tested, and children with new-onset disease are the ideal study population for this trial.

If nutritional treatment is effective, this is obviously the best thing to do: it induces mucosal healing, while no side effects are experienced. In this scenario, nutritional treatment is the first step in a step-up strategy. In contrast, stepping up that starts with conventional steroids does not induce mucosal healing, may result in chronicity, while side effects are serious and often irreversible. Evidence is mounting that with the early introduction of 6-mercaptopurine, steroid sparing is accomplished in most children with Crohn's disease. In cases where nutritional treatment is not effective, the top-down approach starting with infliximab may help to avoid steroid treatment. At present, there is no evidence of a disease modifying effect of infliximab, and there are no long-term outcome data of treatment with the new biological drugs. Therefore, extreme care should be taken, especially in children who have life-long disease and treatment ahead.
Recommendations for future research

On diagnosis and treatment of IBD in children, several areas of future research can be identified:

Diagnostic approach

As endoscopy and histology rightfully deserves to be the gold standard in the diagnosis of inflammatory bowel disease, an alternative and less invasive approach seems unfeasible at first presentation. However, in patients already fully diagnosed, clinical symptoms may be insufficiently informative, while assessment and/or location of disease activity is needed to guide further treatment. In this situation, MR- or CT based virtual colonoscopy may obviate the need for colonoscopy. This technique needs to be validated in children with inflammatory bowel disease. On the other hand, assessment of treatment results on an endoscopic and histological level may provide information on prognosis of the course of disease. The relation between endoscopic or histological remission and duration of remission needs to be determined. Histological remission needs to be clearly defined, and should be used as an endpoint in clinical drug trials.

Database

For retrospective and prospective analysis of large populations, pediatric IBD databases are essential. Uniform criteria for diagnosis, and a protocol for complete and strict collection of data need to be generated. Data to be collected should consist of type and location of disease, presence or absence of extraintestinal manifestations, fistulae or strictures, disease behavior, use of medication (and its effect and side effects), as well as data on quality of life and social implications of chronic disease. This will ultimately yield reliable information on incidence of pediatric IBD, but will also generate knowledge on disease prognosis. This knowledge will guide clinicians in the physical, psychological en social care of children and adolescent with IBD. Both regional and national databases, or even better a European database would greatly aid
in identifying, selecting and following up various pediatric IBD groups. In addition, the search for genes associated with early-onset IBD can only be completed using a large enough pediatric cohort. This will have to involve a large international database, with active cooperation and sharing of data among investigators.

**Drug trials**

Children with Crohn's disease or ulcerative colitis should be able to benefit (in the context of a clinical study) from new therapeutic agents, targeted at TNFα (infliximab, and humanized anti-TNFα antibody CDP571), at interferon (IFN)-γ, at interleukin (IL)-12, at transcription factor NFκB (antisense oligonucleotide to NFκB p65), or at intercellular adhesion molecules (antisense oligonucleotide to ICAM-1), or agents directed against integrins (anti-α4 integrin and anti-α4β7 integrin), inhibiting leukocyte recruitment. These therapies may be more effective in children with new-onset disease than in adults with longstanding disease. For these pilot studies, not only patients with refractory disease, but preferably children with new-onset disease should be included. In this context, the use a placebo group will have to be re-considered. In addition, carefully designed and well conducted trials should investigate the efficacy and safety of short-term treatment, as well as maintenance treatment with biologic therapies. One of the aims should be to investigate whether initial biologic treatment (for instance infliximab, anti-TNF) used in a top-down approach can positively modify disease behavior in children. All patients receiving biological treatment should be followed lifelong for possible outcomes such as cancer, or other unknown long-term effects.
References


