Diagnosis and treatment of inflammatory bowel disease in children
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Introduction
Introduction

In this thesis, several important clinical aspects of pediatric and adolescent inflammatory bowel disease (IBD; Crohn's disease, ulcerative colitis and indeterminate colitis) will be discussed. Why a separate thesis on IBD in childhood, as innumerable reviews, articles, and books have been written about many aspects of these chronic gastrointestinal disorders? Are diagnosis and treatment of IBD really different in children compared to in adults? Are we not performing similar endoscopic procedures to diagnose disease? And are we not using the same drugs as the "adult" gastroenterologists do for their patients? Though tempting, a simple reply to these three questions cannot be given. Children are not just small adults. In most children, the onset of disease comes around the time of puberty, an especially vulnerable period, characterized by linear growth, pubertal development and psychosocial changes. Thus, the disease has a potential for long-term impact on physical growth and psychosocial development. Diagnosis and treatment should be tailored to the needs of small patients and aimed at remission of disease activity, as well as conservation of growth and pubertal development. The unique diagnostic and therapeutic features of pediatric onset of inflammatory bowel disease are listed in Table 1, and will be discussed below. To be able to understand the etiology and origin of these specific issues in young patients with IBD, more clinical pediatric research is needed. This introduction will identify the paucity of pediatric trials, as well as provide insights into the specific problems that are encountered when one is engaged in pediatric clinical research. Using this approach, the stage will be set for the six clinical studies in children with IBD that are presented in this thesis. These studies will complement the small body of literature on the diagnosis and treatment of children with inflammatory bowel disease. A review of the "best available" evidence on treatment of children and adults is presented at the end.
History

The first report of ulcerative colitis has been ascribed to Sir Samuel Wilks, a physician and pathologist who lived in London from 1824 to 1911. He described the postmortem of a young girl who had died under controversial circumstances in 1859. The girl had suffered from “dysentery” for 3 weeks, but the cause of her death was said to be a result of ingestion of a poison that was supposed to induce abortion. In fact, "the morbid appearances in the intestines of Miss Banks" presented a classic description of severe ulcerative colitis\(^1\).

As early as 1828, Abercrombie described a girl of 13 years with ileocecal inflammatory thickening with skip lesions\(^2\). More cases of the disease that was later named Crohn's disease were reported in 1913 by Dalziel, who described 3 patients, one of whom was a 10 year old boy, who had suffered from intestinal obstruction as a result of transmural inflammation in the jejunal, ileal and colonic areas\(^3\). Twenty years later, the same disease was described by Dr Burrill B. Crohn as regional enteritis, and was reported to affect mainly young adults\(^4\).

Epidemiology

More than 70 years after the description by Crohn and colleagues, it is common knowledge that Crohn’s disease may present before the age of 20 years in 25-30% of the patients\(^5\). Ulcerative colitis can be seen in very young children, whereas Crohn’s disease is extremely rare below two years of age\(^6,7\). For both Crohn’s disease and ulcerative colitis, there is a peak of onset between 15 and 25 years of life\(^8\). Epidemiology of IBD has been studied widely in adults, showing incidence and prevalence rates that vary considerably. For Crohn's disease, incidence (per 100,000 population, per year) in adults is reported to be 0.7 to 15, and prevalence ranges from 6 to 104 per 100,000 inhabitants per year\(^9\). For ulcerative colitis, incidence per year is 0.5 to 15, and prevalence ranges from 37 to 121 per 100,000 in adults. In a prospective study during the
years 1991-1995 in the Netherlands, incidence for CD in adults was found to be 6.9 per 100,000 per year, while it was 10 for UC\textsuperscript{10}. Part of the variation must be due to differences in disease definition, recognition, and coding, but there is little doubt that disease incidence varies with geographic area. In the USA as well as in Europe, IBD seems to be more common in northern than in southern areas\textsuperscript{11,12}.

In the pediatric age group, several small epidemiological studies have been published over the last 10 years. Both retrospective and prospective studies were performed in Sweden\textsuperscript{13-15}, Denmark\textsuperscript{16}, Scotland\textsuperscript{17,18}, Wales\textsuperscript{19,20}, and the United Kingdom\textsuperscript{21}. These studies show incidence rates of 0.2 to 5.9 per 100,000 per year in children (aged ≤ 16 years) for Crohn's disease, and 0.5 to 3.2 for ulcerative colitis. Prevalence of Crohn's disease is reported as 6 to 16 per 100,000 per year, and 3.4 to 9.2 for ulcerative colitis.

In the Netherlands, pediatric IBD patients have been included prospectively in a national registry since 1998, and incidence has been found to be 7.2 per 100,000 children (aged ≤ 17 years) per year\textsuperscript{22}.

In Europe as well as in the USA, the need to collect prospectively and share patient data in regional, national or nationwide pediatric IBD databases is well recognized, and as a result, epidemiological information on pediatric IBD is now rapidly expanding. A database that is used to characterize disease on a prospective basis is an absolute necessity for investigators studying genetics, drug therapy, health outcomes, and the socioeconomic impact of these diseases. In addition to these clinical aspects, a large and well-organized database greatly enhances the value of human material (specimens), enabling research on the genetics, etiology and pathophysiology of early onset IBD.
Clinical presentation

There are certain features that are unique to pediatric IBD as compared to adult onset-disease (Table 1). One feature is growth failure, which is present at diagnosis in 10-40% of affected children\textsuperscript{23}. Less obvious, but nevertheless clinically important, are the differences in clinical presentation: abdominal pain is the most frequent symptom in children with IBD, whereas adults tend to present most often with rectal bleeding (in ulcerative colitis) or diarrhea (in Crohn's disease)(Table 2). Furthermore, the impact of a chronic and debilitating disease on the psychosocial development of a child or adolescent and her/his family should not be underestimated.

Future collection of epidemiological information on disease expression at presentation, characteristics during the course of disease, potential predisposing factors, extraintestinal manifestations, treatment course, surgery, and outcome may generate additional knowledge about the differences between early-onset and adult-onset inflammatory bowel disease. Most probably, research on the young patient with new-onset disease (and no co-morbidity) will provide us with more clues on the etiology of inflammatory bowel disease.

Diagnosis

As might be expected from differences in epidemiology, clinical presentation, and differential diagnosis, the diagnostic evaluation of a child with symptoms suggestive of IBD demands a somewhat different approach than that in adults. The endoscopic and radiological procedures performed in children do not differ from those used in adults, but the anxiety experienced by young patients, and the need to control pain, discomfort and excess movement often necessitate the use of anesthesia and the participation of an anesthesiologist\textsuperscript{24-26}. 
Table 1. Unique features of IBD with onset in childhood or adolescence

**Diagnosis**

- Growth failure and delayed sexual maturation, especially in Crohn's disease\(^{13,23}\)
- Increased morbidity rate in Crohn's disease in the younger children (<10 years)\(^7\)
- Increased morbidity rate in moderate to severe ulcerative colitis in children and adolescents\(^5\)
- Ulcerative colitis: more extensive disease at diagnosis in children (versus adults)\(^{16}\)
- Incidence of CD and UC lower than in adults
- Positive family history (30%) more often in children than in adults (13-18%)\(^{64}\)
- Increased risk of colonic carcinoma in prolonged colitis\(^{65-69}\)

**Treatment**

- **Goals:** induce remission, prolong periods of remission, stop or delay progression of disease, minimize disease- and therapy-related complications, avoid unnecessary corticosteroid exposure, ensure normal growth and development, encourage compliance, improve quality of life and allow for normal participation in school and activities
- In new-onset disease: less interference of anti-inflammatory treatment by complications (i.e. strictures) of disease; ideal subgroup to study treatment efficacy
- Enteral nutrition is (option for) primary treatment of Crohn's disease\(^{60,70}\)
- Longitudinal growth failure indicates insufficient treatment (and insufficient nutrition)\(^{71}\)
- Most medical treatment is not "evidence based": no pharmacokinetic trials, lack of randomized controlled trials, lack of placebo-controlled trials
- Specific problems with treatment compliance during childhood and adolescence (puberty)
- Risk of serious varicella, and EBV infection during immunosuppressive treatment\(^{72}\)
- Life-long duration of (immunosuppressive or immunomodulatory) treatment, therefore specific consideration to long-term effects and outcome

**Etiology**

- New onset disease with less co-morbidity; ideal subgroup for research on etiology
**Table 2.** Clinical presentation of IBD in children versus adults

<table>
<thead>
<tr>
<th>Clinical findings</th>
<th>Children</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ulcerative colitis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>71 %</td>
<td>33-53 %</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>67 %</td>
<td>37-80 %</td>
</tr>
<tr>
<td>Rectal bleeding</td>
<td>52 %</td>
<td>80-90 %</td>
</tr>
<tr>
<td>Weight loss</td>
<td>39 %</td>
<td>43 %</td>
</tr>
<tr>
<td>Fever</td>
<td>12 %</td>
<td>27 %</td>
</tr>
<tr>
<td>Growth failure</td>
<td>6 %</td>
<td>-</td>
</tr>
<tr>
<td>Arthritis/arthralgia</td>
<td>16 %</td>
<td>13 %</td>
</tr>
<tr>
<td><strong>Crohn's disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>62-95 %</td>
<td>60 %</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>66-77 %</td>
<td>60-100 %</td>
</tr>
<tr>
<td>Rectal bleeding</td>
<td>80-92 %</td>
<td>20 %</td>
</tr>
<tr>
<td>Weight loss</td>
<td>22-83 %</td>
<td>34 %</td>
</tr>
<tr>
<td>Fever</td>
<td>14-60 %</td>
<td>26-51 %</td>
</tr>
<tr>
<td>Growth failure</td>
<td>30-33 %</td>
<td>-</td>
</tr>
<tr>
<td>Arthritis/arthralgia</td>
<td>15-25 %</td>
<td>4-7 %</td>
</tr>
</tbody>
</table>

Adopted from Shashidar, Integlia, and Grand 2000\(^\text{73}\), with permission

The diagnostic approach in children has been summarized in a consensus publication in the Netherlands\(^\text{27}\), and is currently being addressed across Europe. Table 3 summarizes the diagnostic approach as published in the original consensus, updated with some additional suggestions in *italics*. As in adults, a diagnosis of inflammatory bowel disease is made on the basis of clinical presentation, endoscopic and histological features, and radiological abnormalities.
Table 3. Summary of Dutch consensus on diagnosis of pediatric IBD\textsuperscript{27} (\textit{and suggested additions})

1. History
Abdominal pain, stool pattern, tenesmus, anorexia, vomiting, fever, malaise, weight loss, sense of well-being, secondary amenorrhea, daily activity, school absence, family history, extraintestinal manifestations (vision, mouth sores, rash, joint pain, back pain), depression, insomnia, smoking

2. Physical examination
General impression, vital signs, anthropometry, abdomen, extraintestinal (eyes, mouth, edema, rash, clubbing, erythema nodosum, pyoderma gangrenosum, arthralgia, arthritis, jaundice), perianal (tags, fissures, fistula, abscess), rectal examination

3. Exclude infectious etiologies
Stool culture (Salmonella, Shigella, Yersinia, Campylobacter, E. coli, Clostridium diff \textit{and toxin A and B}), if appropriate: amoebae, parasites, CMV, TBC

4. Markers of inflammation, \textit{serologic markers}
Hemoglobin, hematocrit, indices, WBC count, platelet count, ESR, CRP, albumin, fecal alpha-1 antitrypsin, ASCA (\textit{anti-Saccharomyces Cerevisiae antibody}) and p-ANCA (perinuclear anti-neutrophil cytoplasmic antibody)

5. Bone age, \textit{bone mineralisation}
Hand/wrist X-ray, DEXA scan of lumbar spine and femur

6. If malnutrition:
Vitamin A and E, serum iron, ferritin, iron binding capacity, zinc, vitamin B\textsubscript{12}, folate

7. If signs of extraintestinal manifestations:
Bilirubin, AST, ALT, AlkPhos, GGT, amylase
If appropriate, consultation of ophthalmologist

8. If growth retardation:
IGF-1, IGF BP-3, T4 (free), TSH (at least once)
If bone age > 9 year (girls) or > 11 year (boys): LH, FSH, E2 or testosterone

9. Endoscopy, \textit{assisted by anesthesiologist}
Ileocolonoscopy plus biopsies, and \textit{upper endoscopy plus biopsies}

10. If Crohn's disease: small bowel follow-through and abdominal ultrasound

DEXA scan, Dual Energy X-ray Absorptiometry.

Use of serologic markers, such as ASCA (\textit{anti-Saccharomyces Cerevisiae} antibody) and p-ANCA (perinuclear anti-neutrophil cytoplasmic antibody) was not yet widely available in 1994, when the consensus text was written. In pediatric as well as in adult gastroenterological practice, the markers are of little help in the diagnosis since their sensitivity is so low\textsuperscript{28,29}. Some studies in adult
patients have shown that markers may yield additional information on the distinction between ulcerative colitis and Crohn's disease\textsuperscript{30}, or even help predict a response to anti-TNF treatment\textsuperscript{31}. Therefore, serologic markers are suggested as an addition to the consensus.

Another addition to the consensus is the assessment of bone mineralization by Dual Energy X-ray Absorptiometry (DEXA-scan). Up to 15\% of children with inflammatory bowel disease may have decreased bone mineral density, and this may progress as a result of corticosteroid treatment\textsuperscript{32,33}.

The key challenge in the care of pediatric IBD is the necessity to establish a correct and complete diagnosis, preferably before any treatment is started. A complete diagnosis should include the endoscopic and histological extent of disease in the gastrointestinal tract. Endoscopic and histological features may change as a result of treatment, or during the course of disease, while the choice of treatment modality depends on the location, extent and severity of disease. Consequently, the 1996 Dutch consensus encompasses a complete colonoscopy, including ileoscopy and multiple biopsies from ileum and all segments of the colon in children, suspected of having IBD. This approach may seem overly aggressive. However, complete characterization of involved intestine at diagnosis aids in planning therapy and predicting outcome.

Many physicians choose to start the diagnostic program by performing only proctosigmoidoscopy. Indeed, proctosigmoidoscopy can be performed without anesthesia, is relatively easy, and does not need complete bowel preparation. However, these practical advantages of proctosigmoidoscopy may not outweigh the theoretical preference of a complete colonoscopy; This been questioned in the study described in Chapter 1.1. In this section, the accuracy of a histological diagnosis based on only rectal and sigmoid biopsies is compared to the assessment of a complete set of biopsies from ileum and all segments of the colon. As Crohn's disease may also present in the upper intestinal tract at the time of diagnosis\textsuperscript{28}, we suggest adding upper endoscopy to the diagnostic work-up.

Endoscopy and histology are of key importance in the diagnosis of IBD, but also in the assessment of disease activity during the course of treatment.
Specifically, disease may be in remission clinically, while there is no endoscopic or mucosal healing. In fact, in children with IBD, clinical and endoscopic remission do not correlate very well, as was demonstrated in a pediatric trial of mesalazine and prednisolone in 20 children with active ulcerative colitis\(^{34}\). The study showed complete remission of clinical disease activity by 8 weeks in 85% of patients, complete endoscopic remission in 40%, but histological remission occurred in only 15% of the patients. Subsequently, endoscopic and/or histological disease activity has rarely been used as an outcome variable or endpoint in pediatric clinical trials. In children, enteral nutrition can induce significant histological healing in children with Crohn’s disease\(^{35-37}\).

In adults with Crohn’s disease, treatment with anti-tumor necrosis-\(\alpha\) antibody (anti-TNF, infliximab) was shown to induce endoscopic\(^{38}\) as well as histological healing\(^{39}\). In children, the effects of anti-TNF on histological disease activity have been assessed in the first pediatric multicenter trial of anti-TNF in severe treatment-resistant Crohn’s disease.

This novel study is presented in Chapter 1.2.

**Treatment**

Medical treatment of children with Crohn’s disease or ulcerative colitis is mostly based on evidence from studies in adult IBD patients. Dosages are extrapolated from adult dosages and adjusted according to body weight or body surface area. In addition, duration of treatment is mostly determined by empirics and from experience gained in adults.

The current medical and nutritional treatment for pediatric IBD are summarized in Table 4, with treatment options that have been studied in randomized controlled trials in children marked in the shaded areas, thereby illustrating the scarcity of adequate therapeutic trials in pediatric IBD.
## Table 4. Medical or nutritional treatment options for pediatric IBD

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Ulcerative colitis</th>
<th>Indication in:</th>
<th>Crohn's disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enteral nutrition</td>
<td>no evidence</td>
<td>Induction of remission and maintenance</td>
<td></td>
</tr>
<tr>
<td>Salicylates</td>
<td>Maintenance of remission</td>
<td>Maintenance: no advantage over placebo</td>
<td></td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>Induction of remission in mild-moderate disease</td>
<td>Induction of remission in mild-moderate colitis</td>
<td></td>
</tr>
<tr>
<td>Mesalazine</td>
<td>Maintenance of remission</td>
<td>Induction of remission in mild-moderate disease</td>
<td>Controversial in induction of remission or maintenance</td>
</tr>
<tr>
<td>Steroids</td>
<td>Induction of remission in moderate-severe disease</td>
<td>Induction of remission in moderate-severe disease</td>
<td>Maintenance: no indication</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>Maintenance: no indication</td>
<td>Maintenance: no indication</td>
<td></td>
</tr>
<tr>
<td>Budesonide</td>
<td>enema: Induction of remission in mild-moderate distal disease</td>
<td>oral: Induction of remission in moderate disease in (ileo)cecal or ascending colon</td>
<td></td>
</tr>
<tr>
<td>Antibiotics</td>
<td>no indication</td>
<td>Fistulous disease: induction of remission and maintenance</td>
<td></td>
</tr>
<tr>
<td>Metronidazole and/or</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunomodulators</td>
<td>Maintenance</td>
<td>Initial treatment (combined with steroids)</td>
<td>Maintenance</td>
</tr>
<tr>
<td>Azathioprine/6-MP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Rescue therapy in severe, active disease unresponsive to steroids.</td>
<td>not effective</td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>too little data</td>
<td>Induction of remission and maintenance (if azathioprine or 6-MP unsuccessful or not tolerated)</td>
<td></td>
</tr>
<tr>
<td>Biological response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>modifier</td>
<td>Encouraging data in adults and children, no controlled trials</td>
<td>Induction of remission in severe, refractory disease</td>
<td></td>
</tr>
<tr>
<td>anti-TNF α (Infliximab)</td>
<td></td>
<td>Maintenance treatment</td>
<td>Fistulouss disease</td>
</tr>
</tbody>
</table>

| evidence from randomized controlled trials in children |
| some pediatric evidence, but mostly adult trials |
In Crohn's disease, nutritional therapy has proven to be effective in inducing and maintaining remission, while promoting linear growth in children. Conventional treatment 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 general, "milder" agents have been used to treat milder disease activity, while more potent drugs (with more side effects) have been reserved for more active or severe disease. Whether or not this approach is optimal (although customary) remains unstudied. Furthermore, many clinicians now recommend a dual drug approach, with maintenance medications being started simultaneously with therapy for acute or active disease. In Crohn's disease, methotrexate may serve as an alternative to azathioprine or 6-MP, if these drugs are not tolerated or are ineffective. Cyclosporine may serve as "rescue therapy" in severe ulcerative colitis, but will only postpone surgery. A novel strategy to treat Crohn's disease is offered by infliximab, a monoclonal antibody to the pro-inflammatory cytokine tumor necrosis factor (TNF)-α. This biologic agent has now been evaluated in several open-label non-controlled studies of children and adolescents with severe, treatment-resistant Crohn's disease, and in one study of pediatric ulcerative colitis.

As of this writing, April 2002, an OVID Medline search (1966-April 2002) on treatment trials in pediatric IBD that are randomized and/or controlled, or even non-controlled, will disappointingly reveal just 46 studies, of which only 22 are truly pediatric (Table 5).
Table 5. OVID-Medline search for (randomized) controlled drug trials in children with IBD (1966-April 2002)

<table>
<thead>
<tr>
<th>search #</th>
<th>enteral nutrition</th>
<th>5-ASA or SASP</th>
<th>Prednisolone</th>
<th>Budesonide</th>
<th>Antibiotics: metronidazole or ciprofloxin</th>
<th>AZA or 6-MP</th>
<th>Cyclosporine</th>
<th>MTX</th>
<th>IFX</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>keyword</td>
<td>9188</td>
<td>3968</td>
<td>453913</td>
<td>1854</td>
<td>376422</td>
<td>15746</td>
<td>22028</td>
<td>21742</td>
</tr>
<tr>
<td>2</td>
<td>exp. Inflammatory Bowel Diseases/ or ibd.mp. or exp Crohn Disease/ 29205</td>
<td>296</td>
<td>2067</td>
<td>2320</td>
<td>138</td>
<td>1000</td>
<td>810</td>
<td>266</td>
<td>104</td>
</tr>
<tr>
<td>3</td>
<td>combine 1 and 2</td>
<td>41</td>
<td>345</td>
<td>320</td>
<td>38</td>
<td>86</td>
<td>83</td>
<td>29</td>
<td>19</td>
</tr>
<tr>
<td>4</td>
<td>limit 3 to CT or CCT or RCT</td>
<td>17</td>
<td>87</td>
<td>110</td>
<td>13</td>
<td>22</td>
<td>33</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>limit 4 to all child &lt;0 to 18 years&gt;</td>
<td>9</td>
<td>16</td>
<td>29</td>
<td>0</td>
<td>8</td>
<td>12</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>common keyword</td>
<td>9</td>
<td>37,74-81</td>
<td>252,83</td>
<td>6**75,77,79,84-86</td>
<td>0</td>
<td>187</td>
<td>3**78,88</td>
<td>4***76,78,79,88</td>
</tr>
</tbody>
</table>

Total of 22 pediatric drug trials that are (non)controlled, or randomized controlled

* 4 trials were also selected in the search for prednisolone
** 4 trials were also selected in the search for enteral nutrition; 1 trial was selected in the search for cyclosporine
*** 2 trials were also selected in the search for AZA/6-MP, and 1 trial was also selected in the search for prednisolone

5-ASA, 5-aminosalicylic acid; SASP, sulfasalazine; AZA, azathioprine; 6-MP, 6-mercaptopurine; MTX, methotrexate; IFX, infliximab (anti-TNF, anti-tumor necrosis factor-α; CT, clinical trial; CCT, controlled clinical trial; RCT, randomized clinical trial.
More careful searching by hand, and inclusion of studies published only as abstract, has yielded additional "pediatric evidence". For reference, all pediatric studies on IBD treatment have been reviewed and important adult studies have been summarized at the end of this thesis, in Chapter 3.3.

Pediatric drug trials

The limited availability of clinical trials is not unique for medications used in pediatric IBD, but for all childhood disorders. Interestingly, in vaccination trials that were the first human research experiments to be documented in the 1900s, the research subjects were children. In these initial trials, Edward Jenner first tested smallpox vaccines on his firstborn son and on neighborhood children\(^{48}\), while the first human who was subjected to an antidote to rabies by Louis Pasteur was a child\(^{49}\). Only after consultation with two medical colleagues and when the death of the child "appeared inevitable", did Pasteur decide to test his potential therapy in his young patient\(^{50}\).

Throughout history, the question of whether children should be included in (or excluded from) clinical trials has been a controversial subject. An unfortunate example is the budesonide pharmacokinetic study, described in Chapter 2.1, that raised such controversy during its review by one Ethics Committee in 1996 that after a year of deliberation it was decided by the investigators to conduct the study in Sweden, where regulations more realistically favored research on therapeutics in children.

Budesonide is a substrate for cytochrome P450 (CYP) 3A4, a drug-metabolizing enzyme that appears to have the same activity in children 9 to 14 years old as in adults\(^{51}\). The low systemic bioavailability of budesonide is the result of rapid inactivation of 90% of this new corticosteroid drug in the liver. In the study presented in Chapter 2.1, both adults and children were included, thereby providing an excellent opportunity to evaluate the systemic exposure of oral budesonide in children and adults with active Crohn's disease. The results
of this trial illustrate once more why we should not think of children as small adults.

The three basic ethical principles that underlie all human subject research, as identified in the 1979 Belmont Report are 1. respect for persons, 2. beneficence and 3. justice. Regarding the involvement of children in research, the principle of respect for persons (limit involvement of children because children are unable to choose for themselves) and the principle of justice (encourage involvement because in many cases children have to be involved in research in order to derive the benefit of that research or experimental treatment) are in conflict with one another. This dilemma has led to the longstanding exclusion "for ethical reasons" of minors in clinical trials. As a result, most drugs that are used to treat children are either not licensed for use in children or are prescribed outside the terms of their product license (off label prescription). Evaluations in the USA demonstrated that little had changed between 1973 (78% of drugs without pediatric labeling), and 1994 (71% of drugs without pediatric labeling). In Europe, a recent survey in five pediatric hospital wards in the United Kingdom, Sweden, Germany, Italy, and The Netherlands showed that approximately two thirds of the medications for inpatient use had not been studied in children.

The absence of pediatric testing and labeling poses significant risks for children. Inadequate dosing information exposes pediatric patients to the risk of adverse reactions that could be avoided if such information were provided in product labeling. It may also expose pediatric patients to ineffective treatment through underdosing, or may deny pediatric patients the ability to benefit from therapeutic advances because physicians choose to prescribe existing, less effective medications in the face of insufficient pediatric information about a new medication. The failure to produce drugs in dosage forms that can be used by young children (e.g. liquids or chewable tablets) can also deny them access to important medications. It is very disconcerting that even for a first-line drug such as mesalazine, prescribed to virtually every child with Crohn's disease or ulcerative colitis, there is no published pediatric dosing information. Mesalazine (5-aminosalicylic acid) is believed to act topically through the luminal side of the
intestine, and systemic availability may affect tolerability\textsuperscript{57}. Studies in adult IBD patients have shown that high dosages (up to 4 g/day) may be most effective\textsuperscript{58}, and that the different preparations of mesalazine are responsible for the variation in clinical results\textsuperscript{57}. Absorption, urinary and fecal excretion may all be different in children. In order to get more precise dosing information, a pharmacokinetic study of mesalazine in children with Crohn's colitis and ulcerative colitis needs to be performed.

The growing concern over these severe limitations has led to several regulatory actions over the last 5 years. In the USA, a federal law, the "Better Pharmaceuticals for Children Act" was introduced in 1997, as part of the Food and Drug Administration Modernization Act (FDAMA). This law, also named the \textit{pediatric exclusivity provision}, provided six months additional exclusivity (or patent protection) to manufacturers in return for conducting pediatric studies (requested by the FDA). Although these voluntary measures have been effective in generating studies on many drugs and in providing useful new information in product labeling, a final "Pediatric Rule" became effective in 1999\textsuperscript{59}. Under this rule, pharmaceutical companies were \textit{mandated} by the government to perform a pediatric assessment of every new drug (except when a waiver is granted), and of marketed drugs that are used in a substantial number of pediatric patients. This assessment was to consist of "adequate studies to characterize the safety and effectiveness of a drug or biological product for the claimed indications in all relevant subpopulations". In January 2002, not long after the "Pediatric rule" was adopted, the financial incentives of the \textit{pediatric exclusivity provision} were reauthorized, under the new "Best Pharmaceuticals for Children Act". At the present time, a two-year suspension of the older mandate has been issued by the FDA, during which it will be assessed if this new law "takes care of the problem". It should be noted that the current US president has indicated disagreement with the FDA position - clearly not a "child friendly" position.

In Europe, new guidelines for Good Clinical Practice (GCP) were established in 1997, allowing for non-therapeutic research in children under specific conditions\textsuperscript{60,61}(Table 6). These updated rules were incorporated in the WMO
law (Wet Medisch-Wetenschappelijk Onderzoek met Mensen)\textsuperscript{62}, that was introduced in 1999 in the Netherlands. This law regulates medical research in humans, thereby protecting subjects involved in research studies.

**Table 6.** European Guidelines for GCP for therapeutic research in pediatric patients

- Informed consent (permission) from the parents
- Assent from older children (≥ 12 year old)
- Investigator, parents and older child is informed about every possible risk, discomfort or side effect of the study drug
- The research is conducted by investigators who are scientifically qualified, and supervised by a clinically competent medical person
- If appropriate, the research will be conducted in 5 separate age groups
- If appropriate, research on long-term effects and outcome will be conducted
- Whenever possible, population pharmacokinetics will be applied
- Type of study is preferably controlled and randomized
- Parameters of effectiveness are appropriate for the pediatric age group
- Every possible safety measure has to be taken by the investigator
- Psychological or physical discomfort, painful or invasive measures is to be minimized
- Volume and frequency of blood samples is minimized
- Whenever possible, non-invasive specimens (urine, stool, saliva) are collected
Following these important changes, it seems that there is already some improvement in pediatric labeling. In 1999, the US Food and Drug Administration (FDA) estimated that about 40% of the drugs approved every year were adequately tested or labeled for treating youngsters\(^\text{63}\). The exclusivity incentives have produced new pediatric information on labels for 29 drugs in the past 3.5 years, and more than 400 pediatric trials are underway, as reported by a spokesman for the Pharmaceutical Research and Manufacturers of America (PhRMA) (quote from the New York Times, March 18 2002). In fact, the multicenter study of the anti-TNF antibody (infliximab), described in Chapter 2.3 is a direct result of the changing regulations in the USA. The timing of this American-European pediatric study is unique, as it was initiated "only" 4 years after the first controlled trial in adult Crohn's disease patients. This trial provided the opportunity for children with severe and treatment resistant Crohn's disease to benefit from a new and potent therapy. The experience gained from this trial led to the treatment with infliximab of an exceptional patient with metastatic Crohn's disease, described in Chapter 3.2.

In conclusion, there is reason for optimism, as some of the major impediments (financial, legal) for pediatric studies have been eliminated. In the USA, it has become easier to perform pharmacokinetic research in pediatric patients, as this will provide the necessary data for labeling purposes. Nonetheless, some problems specific to pediatric research will remain (listed in Table 7), and to perform a good quality clinical trial in children will never be an easy task. All of these problems have indeed been encountered during the design, planning, and enrollment in the multicenter randomized controlled trial of budesonide versus prednisolone in children with Crohn's disease, presented in Chapter 3.1. The trial is the first pediatric European multicenter drug trial in Crohn's disease, and has been a combined effort of 32 investigators in 8 countries. In this study, "real" pediatric evidence of the efficacy and safety of a relatively new corticosteroid, oral budesonide, is presented. In addition, the study is the first to demonstrate important differences between adults and children in regard to steroid-responsiveness as well as glucocorticosteroid side effects.
Table 7. Problems encountered in research involving pediatric patients

Patients or disease
Low incidence of disease, necessitating multicenter approach
Non-homogeneous presentation of disease
Unwillingness to participate (extra visits, invasive procedures, anxiety)
Non-compliance of patients and/or parents

Physicians
Lack of motivation as a result of insufficient time, insufficient scientific (or monetary) reward, insufficient support from research, nursing or administrative staff, fear of losing own patients

General
Overload of ethical, regulatory, administrative considerations (when preparing protocol and seeking approval)
Conflict minimal risk-potential benefit
Healthy pediatric volunteers are not allowed by IRB guidelines
Ethical problems with use of placebo
Lack of (or insufficient) financing (multicenter, multinational trials)
If sponsored by pharmaceutical company: potential conflicts of interest
Outline of this thesis and specific aims

The aim of this thesis is to provide new insights concerning the two most important clinical aspects of inflammatory bowel disease (IBD) in children: diagnosis and treatment. Special consideration will be given to histology, pharmacokinetics and drug treatment of children with IBD.

Part 1 aims to further delineate the histological diagnosis of children with Crohn's disease, ulcerative colitis or indeterminate colitis. For this purpose, a retrospective study on the accuracy of rectal and sigmoid biopsies in the diagnosis of pediatric IBD was performed, as presented in Chapter 1.1. In addition, in Chapter 1.2, the aim is to assess the changes in histology before and after therapy. The focus was an evaluation of histological improvement after treatment with anti-tumor necrosis factor α (anti-TNF, infliximab) in children with severe Crohn's disease.

Part 2 aims to expand knowledge of pharmacokinetics of the drugs that are used in children with IBD. The ultimate goal of these studies is to provide pediatric dosing information on these treatments. For this purpose, two different medications have been studied: a new glucocorticosteroid (budesonide) and a novel biologic agent (anti-TNFα). In Chapter 2.1, we set out to investigate the pharmacokinetics of oral budesonide in children with Crohn's disease. In Chapter 2.2 we investigated the pharmacokinetics and report the first safety and efficacy results of anti-TNF α in children with severe Crohn's disease.

Part 3 aims to add to the (little) knowledge that is available from pediatric clinical trials on the treatment of children with IBD. To this extent, we investigated the efficacy and safety of budesonide versus prednisolone in children with Crohn’s disease. This pediatric randomized controlled multicenter trial is presented in Chapter 3.1. In Chapter 3.2, a new indication for treatment with anti-TNFα is described, the case being a child with metastatic Crohn’s disease. In Chapter 3.3, our aim is
to review all the currently available evidence on treatment of IBD in children, and present this against the background of what is already known from trials in adults. Finally, treatment algorithms that correspond to the present state-of-the-art treatment of pediatric inflammatory bowel disease are presented. These algorithms may serve as a guide in the complex medical care of children with Crohn's disease or ulcerative colitis.
References


Introduction


62. WMO, Wet Medisch-Wetenschappelijk Onderzoek met Mensen. http://www.parnassia.nl/research/wmo.html 1999 Ref Type: Electronic Citation


