Studies on inflammatory bowel disease and functional gastrointestinal disorders in children and adults
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Citation for published version (APA):

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APPENDICES

Summary, discussion and future perspectives
Functional gastrointestinal disorders

In part I different aspects of functional gastrointestinal disorders (FGIDs) are discussed. FGIDs encompass a spectrum of disorders characterized by chronic gastrointestinal symptoms in the absence of an evident organic etiology.

Functional gastrointestinal disorders: Abdominal pain-related functional gastrointestinal disorders

The prevalence of FGIDs in adults is high and consequently, the financial burden to society of FGIDs in adults is significant. Although FGIDs are also common in children and adolescents, their associated costs were largely unknown. In chapter 2, we investigated the annual costs of three common abdominal pain-related FGIDs (irritable bowel syndrome [IBS], functional abdominal pain [FAP] and functional abdominal pain syndrome [FAPS]). We showed that the annual costs per patient of these disorders were approximately €2500, of which more than one-half consists of inpatient and outpatient healthcare use. Although these results may not have direct implications for patients who suffer from abdominal pain, these data may prove to be very useful for grant applications for future research. Furthermore, insight in the large financial consequences of pediatric abdominal pain-related FGIDs may motivate health insurance providers to reimburse effective but costly treatments such as hypnotherapy.

In FGIDs, the magnitude and determinants of the placebo response are important for clinical trial design and clinical practice. Meta-analyses in adults have shown that the proportion of patients with FGIDs responding to placebo is high, with an average placebo response rate in irritable bowel syndrome (IBS) of 36.0% to 42.6%. Furthermore, various determinants of the placebo response were identified, including the duration of treatment. A systematic review of the magnitude and determinants of the placebo response in children with abdominal pain-related FGIDs was not available. In chapter 3, we performed a systematic review and meta-regression analysis of placebo-controlled trials in children with abdominal pain-related FGIDs, aiming to study the magnitude and determinants of the placebo response in these studies. We have shown that approximately 41% of children with abdominal pain-related FGIDs improve with placebo. The country where the trial was performed, and whether the randomization schedule was adequately described were significantly correlated with the magnitude of the placebo response. Similarly to chapter 2, while these data may not have direct implications for the patient, they are useful for the conduct of future clinical trials.

Functional gastrointestinal disorders: functional constipation

Functional constipation, another common FGID in children, was the subject of chapters 4 and 5. In chapter 4, an overview was provided of current and future pharmacological treatment options for pediatric functional constipation. We concluded that despite the widespread use of laxatives in children with constipation, there is a paucity of evidence to
support this practice. Furthermore, we showed that no strong conclusions can be drawn with respect to which laxative to prefer over the other. In chapter 5 we performed a randomized, double blind, head-to-head study of two polyethylene glycol-based laxatives (Transipeg® and Forlax®), which are the first-line laxatives in children with functional constipation. Although non-inferiority criteria were not met, the results indicate that both agents are similarly effective and safe for long-term use in children with functional constipation.

Despite the fact that there are various pharmacological treatment options for pediatric functional constipation, the long-term outcome is often disappointing. For example, in chapter 5, after 52 weeks of treatment, success was achieved in only one-half of participants. Furthermore, it has been shown that many children with functional constipation continue to experience symptoms beyond puberty. Thus, there is the need for alternative, effective treatment options.

Since the review in chapter 4 has been published, results from only one randomized controlled trial (RCT) that aimed to investigate the efficacy of a new class of drug in pediatric constipation have been published. This study evaluated the efficacy of prucalopride compared to placebo. Although results from adult studies and an open-label pilot study in children were promising, the results from the RCT in children were downright disappointing, with not even a trend towards higher response rates in constipated children randomized to prucalopride.

These results make one wonder, why does prucalopride work in adults, but not in children? We hypothesized that behavior might play a more important role in the development and maintenance of constipation in children compared to adults. While pharmacological treatment may soften the stool and stimulate peristalsis in order to facilitate easy evacuation, dysfunctional defecation dynamics and excessive stool withholding, which are found in many children with constipation, may require an additional/alternative approach. However, results from studies that aimed to improve defecation dynamics or constipation-related behavior have also been disappointing. Hopefully, results from ongoing studies regarding new pharmacological agents that have been shown to be effective in adults with constipation (e.g. lubiprostone [NCT02042183] and linaclotide [NCT02559570]), are more effective in children with constipation as well.

**Inflammatory bowel diseases**

Part II of this thesis discusses inflammatory bowel diseases (IBDs). These diseases, Crohn’s disease and ulcerative colitis, are characterized by gastrointestinal inflammation resulting in diarrhea, abdominal pain and weight loss.
Inflammatory bowel diseases: Therapeutic drug monitoring

The therapeutic anti-tumor necrosis factor (TNF) antibodies infliximab, adalimumab and golimumab are effective in patients with IBD. Nevertheless, many patients do not respond to anti-TNF-antibodies, or gradually lose response over time\(^{26,36,37}\), which is shown in adults to be related to low serum drug concentrations and anti-drug-antibodies\(^{38-45}\). Pediatric data were lacking. In chapter 6, we investigated the relationship between infliximab serum levels and anti-infliximab-antibodies in children receiving infliximab as maintenance therapy for IBD. We demonstrated that infliximab concentrations are related to disease activity. These data provide a rationale for the use of therapeutic drug monitoring in pediatric IBD.

Since drug concentrations are related to disease activity, therapeutic drug monitoring (comprising measurement of levels of drug and anti-drug-antibodies and adjusting treatment accordingly) has been recommended\(^{46}\). However, these strategies were based solely on the measurement of levels of drug and anti-drug-antibodies at trough (i.e. immediately prior to administration of the next dose). Since a point-of-care test for levels of drug and anti-drug-antibodies is not readily available, the results of testing are only available after the next dose has been administered, potentially causing a delay in dose adjustments. Therefore, in chapter 7 we investigated the relationship between intermediate serum infliximab concentration and infliximab trough concentration in adult Crohn’s disease patients in remission. We have shown that intermediate infliximab concentrations correlate excellently with infliximab concentration at trough. Thus, we concluded that determination of intermediate infliximab concentrations can accelerate therapeutic drug monitoring in Crohn’s disease patients in clinical remission.

Therapeutic drug monitoring appears to be a promising strategy in anti-TNF treatment for IBD. However, results from the first two prospective controlled trials that were published on this subject were disappointing, with no difference with respect to the primary outcome between patients randomized to therapeutic drug monitoring and patients that received conventional, symptom-based care\(^{47,48}\). A potential explanation may be that therapeutic drug monitoring algorithms in these trials were suboptimal. We hypothesize that therapeutic drug monitoring based on pharmacokinetic modeling, an approach that has been used for many years to ensure proper exposure to drugs with a narrow therapeutic window (such as vancomycin), improves the outcome of IBD treatment with anti-TNF antibodies. To date, multiple pharmacokinetic models of anti-TNF agents have been published. The models incorporate albumin, body weight, and anti-drug-antibody status as predictors of anti-TNF drug concentration. We are currently conducting a randomized controlled trial that aims to compare a therapeutic drug monitoring algorithm based on a Bayesian pharmacokinetic model with conventional dosing in IBD patients in clinical remission receiving infliximab maintenance treatment (NCT02453776).
Inflammatory bowel diseases: Treatment strategies

In Crohn’s disease, the optimal treatment strategy is subject of ongoing research. Conventionally, patients are treated in a step-up fashion, which comprises initial treatment with topical or systemic corticosteroids, followed by treatment intensification if the initial therapy fails. It has been shown that early combined immunosuppression (consisting of the combination of an immunomodulator and an anti-TNF agent) is more effective than conventional management on the short-term. However, long-term outcomes were unknown. In chapter 8, we investigated the long-term outcome of patients who participated in a trial in which patients with newly diagnosed Crohn’s disease were randomized to either early combined immunosuppression or conventional management. We found that early combined immunosuppression was associated with a lower relapse rate and a lower use of anti-TNF and corticosteroid treatment during long-term follow-up. However, no benefit was shown with respect to rates of clinical remission, endoscopic remission, hospitalization, surgery, rescue treatment or development of new fistulas.

Considering the lower relapse rate and lower use of anti-TNF agents and corticosteroids, early combined immunosuppression appears to be an attractive treatment strategy. However, considering the associated costs and risks (such as infections) and the potential risk of overtreatment of patients with a potentially ‘benign’ disease course, a one-size-fits-all top-down approach should perhaps not be recommended as an universal treatment strategy for Crohn’s disease. There is a need for reliable predictors to identify patients at risk for a severe course of disease in whom combined immunosuppression should be initiated early.

In chapter 9, we investigated patterns of anti-TNF use and associated outcomes in IBD patients using a database of over 4 million insured persons in the Netherlands. We found that discontinuation of anti-TNF therapy often occurs earlier than previously was reported. Anti-TNF discontinuation occurs earlier in patients with ulcerative colitis compared to patients with Crohn’s disease, in patients receiving infliximab compared to those receiving adalimumab, and in patients receiving non-intensified anti-TNF treatment. Furthermore, corticosteroid use was significantly higher in ulcerative colitis patients than in Crohn’s disease patients, and in patients receiving adalimumab compared to patients receiving infliximab. These results provide insight in real-life use of anti-TNF agents, while previous reports concern analyses of clinical trials and tertiary care cohorts, which may not provide reliable estimates of real-life drug use.

Inflammatory bowel diseases: Disease monitoring

When symptoms are used as endpoints in clinical trials, patient reported outcome measures, defined as any report of the status of a patient’s health condition that comes directly from the patient without interpretation of the patient’s response by a clinician or anyone else, are probably the way to go, as they measure what is most important for the patient. However, the development of patient reported outcome measure is a lengthy process involving patient concept elicitation interviews, expert interviews, item generation, content validity testing,
patient cognitive interviews and quantitative validation. Currently, no true patient reported outcome measure is available for Crohn’s disease. For the meantime, as shown in chapter 10, the Bristol Stool Form Scale and a visual analogue scale for abdominal pain appear to be useful instruments to monitor patients with Crohn’s disease. Future studies are however required to validate the responsiveness and construct validity of these instruments in an independent cohort before their routine use can be recommended.

Chapters 11 and 12 were based on the observation that children with IBD often report no symptoms despite biochemical signs of ongoing inflammation. In chapter 11, we investigated the relation between IBD symptoms and biochemical markers of disease activity in children. A strong discrepancy was found between clinical symptoms and the biomarkers of inflammation fecal calprotectin and CRP in children with IBD. It appears that only a small proportion of the variation in symptoms can be explained by variation in inflammation. In chapter 12, we investigated whether biochemical markers of inflammation in asymptomatic pediatric IBD patients are predictive of the risk of relapse. We found that levels of fecal calprotectin and CRP are predictive of the risk of a symptomatic relapse in children and adolescents with IBD.

Based on these results and on previous studies, it appears that the goal of treating IBD may best be separated into control of symptoms on one hand and control of inflammation on the other hand. While reducing patients’ symptoms and restoring their quality of life is an obvious goal of treatment, asymptomatic patients may still have (severe) ongoing inflammation which can affect the long-term outcome.

The optimal way to assess inflammation in IBD patients is a subject of research. While mucosal remission or mucosal healing (often defined as the complete resolution of macroscopic signs of inflammation on endoscopy) is often advocated as the holy grail of treating IBD, histologic remission is emerging as a goal beyond mucosal healing. It has been shown that patients with mucosal healing often have ongoing inflammation on microscopic evaluation of endoscopic biopsy samples, which is predictive of long-term outcome. If attainable, complete resolution of inflammation on a cellular level (as evidenced by histologic remission) is an intuitive and logical target of therapy for IBD. However, monitoring patients through regular endoscopies with histological assessment of biopsy samples may not be feasible in daily practice. Another limitation of routine histologic assessment is the issue of sampling of biopsies: the detection of residual inflammation remains confined to the area that is biopsied. Alternatively, complete resolution of inflammation may be assessed using biomarkers. A potential advantage of biomarkers over histologic assessment of remission is that biomarkers of inflammation may reflect the total amount of inflammation in the gut, thus overcoming the issue of sampling. In support of this hypothesis, levels of the inflammatory biomarker fecal calprotectin were shown to predict the medium-term outcome more accurately than histologic disease activity in a cohort of adult IBD patients in clinical and mucosal remission. Based on this observation, one could hypothesize that biochemical remission is the holy grail of treating IBD.
Irritable bowel syndrome-type symptoms in inflammatory bowel disease

Part III of this thesis is focused on persisting gastrointestinal symptoms in patients with IBD in remission. This is often interpreted as the coexistence of an FGID and an IBD. Because patients with persisting gastrointestinal symptoms usually fulfill diagnostic criteria for IBS, these symptoms are often referred to as IBS-type symptoms. Approximately one third of adult patients with IBD in remission suffer from IBS-type symptoms. The prevalence of IBS-type symptoms in children with IBD was unknown. Therefore, in chapter 14, we investigated the prevalence of IBS-type symptoms in a cohort of pediatric IBD patients. We found that the prevalence of IBS-type symptoms was much lower than reported in adults. This difference may be related to the relatively short duration of disease in children. It has been suggested that a long disease duration may result in more structural changes in the colon, thereby predisposing to the development of IBS-type symptoms. Indeed, in a study by Simren et al., duration of the disease tended to be longer in inflammatory bowel disease patients with IBS-type symptoms. Other studies, as well as our study, however, did not find such an association.

The cause of IBS-type symptoms remains to be elucidated. It has been hypothesized that IBS-type symptoms in IBD reflect mild, ongoing inflammation. To test this hypothesis, we investigated in chapter 14 whether IBS-type symptoms were correlated to biomarkers of inflammation. In this study in children with IBD, IBS-type symptoms were unrelated to biomarkers of gastrointestinal inflammation. Furthermore, in chapter 15, we evaluated the prevalence of IBS-type symptoms in adults IBD patients who were in remission as determined using biomarkers of inflammation. We found that IBS-type symptoms are common in IBD patients without evidence of ongoing inflammation.

Despite the high prevalence of IBS-type symptoms in IBD, little is known about how it should be treated. We hypothesized that IBS-type symptoms reflect “true IBS”. Consequently, we expected that IBD patients with IBS-type symptoms and IBS patients respond similarly to treatment. Various effective treatment options are available for patients with IBS, such as fibers, probiotics, antidepressants and psychological interventions (of which hypnotherapy is among the most effective). The efficacy of these treatment options in IBD patients with IBS-type symptoms has never been thoroughly investigated. Therefore, in chapter 16, we conducted a randomized, controlled trial to compare the efficacy of hypnotherapy with standard IBS management in the treatment of IBS-type symptoms in patients with IBD in remission. At the end of treatment and after 6 months of follow-up, no difference between groups was found with respect to symptom severity and quality of life. Although the primary endpoint was met in only a small proportion of patients in both groups, rates of adequate relief indicate that both treatments appear to be valuable treatment options for IBS-type symptoms in IBD.

The results of chapters 14 and 15 do not support the hypothesis that IBS-type symptoms
reflect ongoing inflammation. On the other hand, results from chapter 16 suggest that IBS-type symptoms may not reflect “true IBS” either, considering that hypnotherapy, a very effective treatment in “true IBS”, appears to be less effective in IBS-type symptoms. In recent years, insight into the pathophysiology of IBS has increased substantially. Several factors have been found to be associated with IBS, including genetic polymorphisms, changes in gut microbiome, bile acid malabsorption, changes in enteric nerves and alterations of serotonin transporter \(^{571}\). Whether these factors also contribute to IBS-type symptoms in IBD patients in remission is largely unknown. The increasing insight in the pathophysiology of IBS may guide future studies to increase our understanding of IBS-type symptoms in IBD.