Complications and optimalisation of Mesalazine and anti-TNF-alpha therapy in inflammatory bowel disease
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Introduction
General introduction and outline of this thesis

Inflammatory Bowel Disease (IBD) is a chronic inflammatory disease of the gut that is characterized by a heterogeneous presentation. It comprises both Crohn’s disease (CD) and Ulcerative Colitis (UC). IBD is characterized by relapsing symptoms as diarrhea, abdominal pain, fatigue and weight loss. The diagnosis is confirmed by a combination of clinical, endoscopical, histological and radiological findings. UC is a superficial mucosal inflammation that starts in the rectum and may affect the whole colon. Histologically, the inflammation is confined to the mucosal layer usually with a mixed cellular infiltrate without granulomas. As UC only affects the colon, CD can affect the whole gastrointestinal tract. The inflammation is not continuous but discontinuous. The disease location is most frequent in the colon in combination with the ileum (41%) but it can also be present in the terminal ileum (37%) or colon (22%) only. The upper gastrointestinal tract is affected in 10% of the cases. The ulcers can penetrate the perianal region leading to perianal abscesses or fistula. The inflammation is transmural, and can contain granuloma’s. Apart from the intestinal inflammation, IBD can also have extra intestinal manifestations in skin (10%), joints (22%) and eyes (4%).

The precise etiology of IBD is unknown, and there is no medical therapy that can cure IBD. Removal of the colon is a surgical option to cure UC. Current medical therapy (figure 1) is aiming to control the intestinal inflammation by inducing and maintaining remission. The treatment strategy for IBD is mainly based on the severity, distribution and pattern of disease. Figure 1 shows the rounded or range of reported clinical remission rates upon induction therapy.

![Figure 1: Clinical Remission upon induction therapy.](image-url)
Part I of this thesis focuses on mesalazine (5-Amino Salicylic Acid, [5-ASA]) which is the cornerstone of medical treatment of UC. They are highly effective for inducing and maintaining remission in UC at doses \( \geq 2 \) gram.\(^5\) 5-ASA is a relatively safe drug and has fewer side effects than the original sulfasalazine.\(^6\) Different dosages and enteral delivery formulations has been developed with no clear difference in efficacy.\(^7-9\) It is acknowledged, that once-daily dosing is likely to improve compliance; \( \geq 2g/\text{day} \) oral 5-ASA induces remission more effectively than lower doses [relative risk for failure to achieve remission at weeks 4 – 8 of 0.91, 95% confidence interval 0.85–0.98].\(^5\) Patients with moderate disease may benefit from the higher dose of 4.8 g/day.\(^3,8\)

Although the frequency of adverse events in clinical trials in UC and CD patients were comparable between 5-ASA and placebo, about 6.5% of patients using 5-ASA develop adverse effects.\(^10\) The most common adverse effects are nausea, vomiting, headache, abdominal pain, rash and diarrhea. Adverse effects can be classified into predictable (type A) and unpredictable (type B) reactions. Type B reactions are responsible for 10-15% of all drug side effects. In some forms of type B reactions, especially in case of immunologic/allergic reactions, mast cell associated (type-1) desensitization can be achieved. Desensitization is the procedure to induce tolerance to drugs responsible for hypersensitivity reactions using a slowly incremental dose of the drug. Effective desensitization is described for cytostatics, antibiotics and also for sulfasalazine.\(^11,12\) As the use of 5-ASA can be limited by the occurrence of adverse events, desensitization is of interest.\(^11,12\) A few case-reports reported successful desensitization for patients intolerant for 5-ASA. In these cases, patients had a variety of side-effects, e.g. urticaria, fever, exanthema, diarrhea and nausea, sometimes combined with eosinophilia.\(^13-18\)

We tried to desensitize UC patients with a demonstrated 5-ASA intolerance with a rapid desensitization protocol (Chapter 2). Other rare, but severe, adverse side-effects are hepatotoxicity, pancreatitis, pneumonitis, and interstitial nephritis.\(^19-22\) Patients with IBD are also at risk for hepatobiliary disease; IBD patients can develop primary sclerosing cholangitis (PSC) (2%), auto Immune Hepatitis (AIH) and several overlap syndromes. Therefore, the diagnosis can be challenging. Studies showed that patients with IBD may also develop acute or chronic hepatic injury as a result of drugs as 5-ASA.\(^23,24\) We describe a patient with therapy refractory UC who developed a 5-ASA luxated auto-immune hepatitis/PSC overlap syndrome (Chapter 3).

Nephrotoxicity is a rare idiosyncratic reaction to 5-ASA therapy. Nephrotoxicity associated with 5-ASA agents was first described in case reports and has since then been reported multiple times for both sulfasalazine and the more modern 5-ASA agents.\(^25,26\) Data from clinical trials suggest an annual risk of 0.26% and data from a questionnaire sent to gastroenterologists estimated an incidence of 1 case per 4000 patient years.\(^27,28\) The aim of Chapter 4 was to characterize the clinical features of this serious adverse event and then perform the first genome wide association study to identify genetic risk factors for the development of a drug-induced interstitial nephritis.

In Part II of these thesis we focus on agents against tumor necrosis factor alpha (TNF-alpha) in IBD. Anti-TNF-alpha such as Infliximab (IFX), Adalimumab (ADA) and Golimumab have proven to be effective in the treatment of IBD i.e. CD and UC as well as
in the treatment of rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and psoriasis. TNF-alpha antibodies are effective in inducing and maintaining remission of luminal and fistulizing CD and UC. These drugs are administered at fixed dose and intervals derived from dose finding studies for IFX and ADA. Observational studies showed that approximately 10% - 21% of the patients annually lose their response to these TNF-alpha antibodies partially due to formation of antibodies against the drug causing low drug trough levels. The production of antidrug antibodies is associated with infusion reactions and an accelerated antibody clearance resulting in lower anti-TNF-alpha antibody titers. Observational studies have demonstrated a relationship between IFX and ADA drug concentrations, the presence of antidrug antibodies and clinical outcome. Strategies to prevent developing antibodies to IFX and ADA are scheduled dosing to maintain stable trough drug levels and co-administration of an immunomodulator (e.g. thiopurines). In the case of loss of response with low drug titers without antibodies, increasing the dose or shortening of the dosing interval is effective. Whereas in cases of low drug titers due to anti-drug antibody formation, a switch to another anti-TNF-alpha is the preferable strategy. Therapeutic Drug and Immunogenicity Monitoring (TDIM) with early serial trough and antidrug antibody level measurements will probably optimize anti-TNF-alpha treatment. Therefore several studies are designed to dose IFX or ADA based on trough levels. Different assays are being used to measure drug and anti-drug antibody levels. The most commonly used assay types are the: enzyme-linked immunosorbent assay (ELISA) and radio-immunoassay (RIA) and a fluid phase mobility shift assay. Standardization of assays to measure IFX or ADA trough levels and anti-IFX or anti-ADA antibodies is lacking. Several confounding factors such as drug interference and background can influence the measurement of biological drugs and antibodies to these drugs. This may result in poor specificity, sensitivity and reproducibility. Our aim in Chapter 5 was to determine the correlation between academically developed assays (Leuven and Amsterdam) that were used in several studies to detect IFX drug levels and anti-IFX antibodies and a commercially available assay (further referred to as BMD ELISA). The population pharmacokinetics of IFX have been described earlier for patients with ankylosing spondylitis, rheumatoid arthritis and IBD. However these models were not used to predict serum trough levels or for dose optimizing of IFX. In this thesis we developed a pharmacokinetic (PK) model for IFX in IBD patients for dose-optimization (Chapter 6). TNF-alpha blocking agents are very expensive and currently constitute the majority of the costs of IBD therapy. IFX-biosimilars, for example CT-P13 (Inflectra/Remsima) and Flixabi (Biogen) are available now. These biosimilars are expected to have the same specificity and the same sequence as the original molecule IFX (Remicade), but are marketed at a much lower price than the first-generation anti-TNF-alpha blocking agents, which will allow treatment of these diseases to be more cost-effective. Furthermore (Chapter 7) we want to determine whether antibodies to IFX (ATI) always neutralize the anti-TNF-alpha drug and whether they show cross-reactivity towards other available anti-TNF-alpha biologicals or IFX biosimilar. As described before some patients treated with IFX or ADA develop ATI and this can result in loss of response. However,
currently we are unable to predict or differentiate which patients are at risk of developing these antibodies to IFX or ADA. One possible risk factor may be genetic predisposition. As immunogenicity to anti-TNF alpha plays a role in the loss of response to anti-TNF alpha therapy, our aim was to replicate known HLA regions and identify novel (non-HLA) genetic regions associated with the development of anti-drug antibodies in patients with IBD (Chapter 8). IFX is administered intravenously. This gives rise to certain disadvantages; patients need to visit the hospital for the treatment, gets punctured and acute and late-onset infusion reactions could result due to treatment. Additionally, substantial side effects are expected as TNF-alpha is an endogenous mediator and the patients receives IFX systemically causing systemic immunosuppression. Finally, ATI could develop leading to an increase in side effects or loss of response to IFX therapy. These disadvantages have a negative impact on health care cost and burden as well as patient-friendliness. A part of these disadvantages could be eliminated if IFX is administered orally, inducing a localized, anti-inflammatory effect. Studies have shown that tissue IFX concentration correlates with a better and sustained response in CD and that IFX exerts its effect at least partly by local anti-inflammatory and immunomodulatory effects in the bowel. The ColoPulse technology is a coating technology which consist of a pH-sensitive polymer in which a superdisintegrant is incorporated in the coating matrix. This coating was specifically developed to target the ileo-colonic region in humans and is characterized by fast and site-specific drug targeting. ColoPulse capsules and tablets target the ileo-colonic region in healthy subjects as well as CD patients (Chapter 9). Furthermore, we have shown that IFX compounded in ColoPulse tablets is feasible and stable. There is no published data on the efficacious dose of oral ileo-colonic-targeted IFX. In Chapter 10 we propose a protocol Towards Mucosal Application of IFX (TOMATE study). The objective of this protocol is to describe a study to treat patients with active ileo-colonic CD with orally administered ColoPulse IFX tablets instead of intravenously administrated IFX.

**Outline of this thesis**

**Part I: mesalazine**

In chapter 2 we describe symptoms of patients intolerant for 5-ASA after 5-ASA rechallenge and thereafter the effectiveness of a rapid desensitization protocol in UC patients with a demonstrated 5-ASA intolerance. In Chapter 3 we describe a patient with therapy refractory UC who developed a mesalazine luxated auto-immune hepatitis/PSC overlap syndrome.

In Chapter 4 we used a cohort who developed nephrotoxicity subsequent to 5-ASA administration to characterize the clinical features of this serious adverse event and then perform the first genome wide association study to identify genetic risk factors for the development of a drug-induced renal injury.
Part II: Anti-TNF alpha antibodies

In Chapter 5 we determined the correlation between academically developed assays (Leuven and Amsterdam) that were used in several studies to detect IFX drug levels and ATI and are routinely applied in patient diagnostics, and a commercially available assay (further referred to as BMD ELISA). In Chapter 6 we compared the TNF-alpha-neutralizing capacity of all commercially available anti-TNF-alpha drugs. Furthermore, we tested the neutralizing capacity of ATI, as well as their cross-reactivity with IFX, ATI, ADA and antibodies to Adalimumab. Finally, we tested if antibodies towards the original IFX cross-react with the biosimilar of IFX (CT-P13 [Inflectra]). Our aim in Chapter 7 was to replicate known HLA regions and identify novel (non-HLA) genetic regions associated with the development of antibodies to IFX and ADA. In Chapter 8 we described a retrospective study with pharmacokinetic model for IFX in IBD patients that can be used for dose-optimization of IFX and to predict serum trough levels in this population. In Chapter 9 we described that Colopulse tablets perform comparably in healthy volunteers and CD patients and show no influence of food and time of food intake on bioavailability. This chapter is a precursor study of the protocol described in Chapter 10. In Chapter 10 we prepare a protocol Towards Mucosal Application of IFX (TOMATE study). The objective of this protocol is to describe a study to treat patients with active ileo-colonic CD with orally administered ColoPulse IFX tablets instead of intravenously administrated IFX. Efficacy and safety will be investigated as well as oral IFX pharmacokinetics and the development of ATI due to oral IFX treatment.
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Part I: Mesalazine