Anti-TNF therapy in inflammatory bowel disease
Towards personalized medicine
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General introduction
INTRODUCTION

The main types of inflammatory bowel disease (IBD) are ulcerative colitis (UC) and Crohn’s disease (CD). UC and CD are chronic auto-immune diseases that mainly involve the gastrointestinal tract. In the Netherlands, IBD affects approximately 80,000 patients.\(^1\) The precise etiology of IBD is unknown, but is attributed to a combination of environmental factors, genetic susceptibility, and a dysregulated immune system.\(^2\)–\(^4\)

Although the earliest description of UC dates back to the ancient Greek, the term for UC as we know it today, was first used in 1859.\(^5\) UC is limited to the colon and is characterized by diffuse inflammation of the mucosa. Severe inflammation and the induction of pro-inflammatory mediators result in the development of extensive superficial mucosal ulceration.\(^6\) Based on the extension of the colitis, UC is classified into proctitis, left-sided colitis, pan-colitis or segmental colitis.\(^7\) Main complaints of UC consist of abdominal pain with diarrhea and rectal blood loss, besides fatigue. In 1932, the term CD was first described by Dr. Burrill Crohn and colleagues.\(^8\) CD mostly presents in the terminal ileum and colon, but can present throughout the whole gastrointestinal tract.\(^9\) CD is characterized by aggregation of macrophages and inflammation is typically transmural.\(^8\) Symptoms of CD depend on the location, extent and behavior of the disease. In patients with colonic disease, abdominal pain and diarrhea accompanied with rectal blood loss is mostly seen. Up to a third of the CD patients present with perianal disease and half of the patients develop extra intestinal manifestations over time, such as peripheral arthritis or erythema nodosum.\(^10\)

Treatment options for IBD have evolved over time and now include 5-aminosalicylates (for UC), corticosteroids, immunomodulators (thiopurine/methotrexate) and monoclonal antibodies (mAbs) targeting tumor necrosis factor (TNF; infliximab, adalimumab, golimumab), α4β7 (vedolizumab), and IL-12/IL-23p40 (ustekinumab).\(^11\)–\(^12\) The small molecule tofacitinib, a janus kinase (JAK) inhibitor, is the most recently approved agent for UC.\(^13\) Various agents are currently being evaluated in phase II and III clinical trials targeting inflammatory cytokines (such as anti-IL-23 and anti-IL36 receptor), leukocyte trafficking (anti-MadCam antibodies, anti-αEβ7 antibodies and sphingosine-1-phosphate receptor agonists) or the intestinal microbiome.\(^14\)–\(^18\) Phosphodiesterase-4 inhibitors (such as apremilast and roflumilast) and JAK inhibitors (including filgotinib and upadacitinib) are promising small molecules.\(^19\)–\(^21\)

Anti-TNF

In the early 90’s, TNF was found to be increased in serum, stool, and colonic tissue of IBD patients.\(^22\)–\(^25\) TNF is a pro-inflammatory cytokine produced as a transmembrane cytokine (mTNF) and released in its soluble form (sTNF) after conversion by TNF converting enzyme (TACE).\(^26\) In 1998, the first mAb targeting TNF was used in clinical practice. All anti-TNF agents are mAbs of the immunoglobulin G1 (IgG1) type. These IgG1 mAbs consist of a F(ab’) fragment and a Fc-portion, as shown in Figure 1. The F(ab’) fragment is able to form a complex with TNF and the Fc-portion activates Fc-receptor mediated complement-
dependent cytotoxicity (CDC) and antibody-dependent cell cytotoxicity (ADCC). Binding of anti-TNF to TNF prevents TNF from TNF-receptor mediated cellular functions, such as cell activation, immune regulation and cytokine and chemokine production. In addition, the mechanism of action of anti-TNF agents has also been attributed to the induction of wound-healing macrophages and inhibition of IL-12/IL-23. In Europe, there are three anti-TNF agents registered for the use in IBD patients. Infliximab (IFX) was the first anti-TNF mAb used in the treatment of IBD. IFX is an intravenously administered chimeric mAb, being of human and murine origin.31,32 Adalimumab (ADL) is a fully human, subcutaneously administered anti-TNF agent, registered for both CD and UC. Lastly, golimumab (GLM) is the third anti-TNF agent registered as a subcutaneously agent in the treatment of UC.

Pharmacokinetics and pharmacodynamics of anti-TNF
Pharmacokinetics describes the process of “what the body does to the drug” in terms of absorption, distribution, metabolism, and excretion. Pharmacodynamics describes “what the drug does to the body”. Anti-TNF mAbs are administered parenterally, by either intravenous or subcutaneous administration. Following intravenous administration (as is the case for IFX), the maximum concentration ($C_{\text{max}}$) in the blood is immediately reached. After subcutaneous administration, $C_{\text{max}}$ of anti-TNF agents (ADL, GLM) is reached after several days. Because of the high molecular weight and hydrophilicity, there is limited distribution of anti-TNF mAbs into peripheral tissue and volume of distribution is approximately equal to the extracellular fluid volume. Also, because of their size, anti-TNF mAbs are not eliminated via the kidney or the liver, but via alternative pathways. Although the precise clearance mechanism is not yet fully understood, anti-TNF mAbs are mainly eliminated via proteolytic degradation in the reticuloendothelial system. For patients with moderate to severe active UC, IFX was also found to be eliminated via the faeces.

Variability in PK parameters results in variability in measured drug concentrations. With population PK, variability in PK parameters is studied within a specific population after administration of the drug of interest. This variability is first quantified and then attributed to fixed and random effects. Fixed effects include patient variables, such as weight or disease severity, that are observable for each patient. Random effects cannot be predicted in advance and include random variability that exists between patients, i.e. interindividual variability. For the drug of interest, patient variables that are identified to be associated with PK parameters can then be used for dose optimization. For IFX, more severe disease (e.g. reflected by decreased serum albumin level) is associated with higher clearance and consequently lower drug concentrations. In clinical practice, IFX treatment intensification therefore needs to be considered in a patient with a decreased albumin level.

Anti-TNF treatment optimization
Despite proven efficacy, up to 30% of the patients with IBD do not respond to anti-TNF
therapy at all, i.e. primary non-responders. During maintenance treatment, another 30% of the patients who initially responded to anti-TNF therapy, will lose response over time (i.e. secondary non-responders). To overcome primary and secondary non-response, therapeutic drug monitoring (TDM) is of value to optimize anti-TNF treatment. TDM is defined as measuring a drug concentration and, depending on the result and based on PK principles, adjusting dose and/or dosing intervals in order to maintain the drug concentration within a certain therapeutic range to optimize treatment outcomes. For anti-TNF agents, higher trough levels in IBD patients during maintenance treatment have been associated with improved treatment outcomes. In general, IFX TLs above 3 µg/ml are associated with optimal clinical and endoscopic outcomes during maintenance treatment.

One of the main causes for secondary non-response in IBD patients treated with anti-TNF is the formation of anti-drug antibodies (ADA). When a patient develops ADA, anti-TNF trough concentrations are usually low or even undetectable and disease activity is increased. The formation of ADA depends on several factors, including the extent of humanization of the mAb. Chimeric compounds, such as IFX, are more likely to elicit an immune response that results in ADA formation compared to fully human compounds such as ADL and GLM. Second, subcutaneous administration, in which the skin barrier is crossed, is more likely to elicit an immune response compared to intravenous administration. The overall percentage of patients that develops anti-drug antibodies against anti-TNF is highly variable and depends on the type of assay used, but up to 65% has been reported. In a clinical setting, drug-sensitive ADA assays are mostly being used to assess ADA status. Drug-sensitive assays are not able to detect ADA when the drug is still present in the blood, whereas drug-tolerant assays are not limited by the presence of the drug. Drug-tolerant assays are mainly used in a research setting, but would allow closer follow-up of the effect of dose intensification on ADA concentrations in a clinical setting.

Aim and outline thesis
The overall aim of this thesis includes characterization of anti-TNF pharmacokinetics and pharmacodynamics and focuses on optimization of TDM for IBD patients on anti-TNF treatment.

Chapter 1 contains the general introduction, in which the objectives and study outline are described.

Chapter 2 presents an introduction to pharmacokinetic and pharmacodynamic principles in the treatment of UC.

Chapter 3 and 4 elaborate on population PK models of respectively ADL and GLM. For ADL, a population PK model was built with retrospective data of CD patients mainly on
ADL maintenance therapy. For the GLM population PK model a prospective study was conducted with UC patients during induction and maintenance treatment.

**Chapter 5** describes the PK/PD relationship of IFX in the treatment of CD patients.

**Chapter 6** proposes a mechanistic PK model to describe the interaction between anti-TNF (IFX) and its target TNF in a UC population.

**Chapter 7 and 8** present the results of prospective studies to evaluate the performance of dried blood samples to measure IFX and ADL serum concentrations in IBD patients.

In **Chapter 9** we evaluate the role of the area under the curve (AUC) compared to serum trough concentrations for TDM of IFX.

**Chapter 10** describes the result of a prospective TDM-trial in which patients on IFX maintenance treatment were dose optimized by a dashboard system, based on serum trough concentrations.

In **Chapter 11** the results presented in this thesis are discussed in a broader content.
REFERENCES


Introduction


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