Anti-TNF therapy in inflammatory bowel disease

Towards personalized medicine

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General discussion, summary, and future perspectives
The introduction of anti-tumour necrosis factor (TNF) monoclonal antibodies (mAbs) more than two decades ago has led to a major improvement in the treatment of inflammatory bowel disease (IBD). To date, anti-TNF agents still represent one of the most powerful classes of drugs for IBD with extensively proven efficacy. Nonetheless, primary non-response occurs in up to 30% of patients, and up to 50% of patients lose response over time (secondary nonresponse). To understand the mechanisms behind the phenomenon of primary and secondary non-response, understanding of factors that influence the pharmacokinetics and pharmacodynamics of mAbs is most important. In this general discussion and summary, the results of our studies investigating how pharmacokinetic and pharmacodynamic principles may optimize anti-TNF treatment are summarized. Also, the main findings are discussed and placed in a broader perspective. Part I focuses on the pharmacokinetic and pharmacodynamic considerations in anti-TNF treatment and part II emphasizes on the use and optimization of therapeutic drug monitoring (TDM).

Part I Pharmacokinetics and pharmacodynamics

Following a general introduction to this thesis (Chapter 1), an overview of clinical pharmacokinetic and pharmacodynamic considerations of treatment options for patients with ulcerative colitis (UC) is given in Chapter 2. Treatment of UC according to the step-up approach consecutively consists of 5-aminosalicylates, corticosteroids, immunomodulators (thiopurines/methotrexate) and mAbs (infliximab (IFX), adalimumab (ADL), golimumab (GLM), vedolizumab). More recently, the small molecule tofacitinib and the monoclonal antibody ustekinumab were registered for treatment of UC. For anti-TNF agents, higher serum concentrations have been associated with improved treatment outcomes. Monitoring of trough levels and adjusting dose and/or dosing interval based on pharmacokinetic principles, i.e. performing TDM, is of great interest to optimize anti-TNF therapy. In general, a more severe disease status is associated with an increased clearance of anti-TNF agents, resulting in lower serum concentrations. Also, the association between immunogenicity (development of antibodies against anti-TNF) and increased clearance of anti-TNF has repeatedly been demonstrated. In clinical practice, TDM for anti-TNF agents is usually performed in a reactive manner. When a patient is suspected of (secondary) loss of response with confirmed active disease, a serum concentration and anti-drug antibody status are measured, usually at trough. For patients on IFX maintenance treatment with sub-therapeutic serum trough concentrations, the proven concentration-effect relationship for IFX justifies increasing the dose or decreasing the dosing interval in order to regain clinical response. In addition, detectable anti-drug antibodies can be overcome by the addition of an immunomodulator. When a patient is lacking or losing response and TDM shows sufficiently high concentrations of IFX, switching to another therapy is to be considered. Potential benefit of TDM in a proactive manner remains an interesting concept to prevent under and over dosing potentially resulting in a flare of the disease. Also, TDM might also have a beneficial effect during induction therapy.
IFX serum concentrations during induction therapy are associated with improved clinical and endoscopic outcomes and an accelerated IFX induction regimen could reduce early colectomy rates in patients with severe UC. 37-42

In Chapter 3 we aimed to find patient factors associated with the pharmacokinetics of ADL in patients with Crohn’s disease (CD). Five models from the literature describing population pharmacokinetics of ADL in inflammatory diseases were selected. These models were applied to our retrospective cohort of CD patients treated with ADL. Measured concentrations were either under or overestimated by the selected models and a novel population pharmacokinetic model was developed. In this model, clearance increased 4-fold in the presence of detectable anti-drug antibodies. Also, patients with ADL every week dosing showed a 40% higher ADL clearance. In clinical practice, ADL treatment is intensified when patients experience a higher disease burden. Increased disease activity may be the result of lower drug concentrations due to higher clearance of the drug. However, increased disease activity may also increase clearance due to increased target engagement (target-mediated drug disposition).43 This implies that patients with a higher disease burden, i.e. higher TNF load, have a faster clearance than patients in remission. Dosing of ADL every week would then reflect the higher inflammatory load of the patient. In particular, a positive association between disease activity (in terms of C-reactive protein (CRP)) and ADL clearance has been shown by others.26,44

Also for GLM, anti-drug antibodies increase clearance and result in low or even undetectable GLM concentrations as described in Chapter 4. Patients with moderate to severe UC were enrolled in a prospective trial and started on GLM induction therapy, followed by GLM maintenance therapy with a total follow-up time of one year. Although limited by a small sample size, an association was found between low serum albumin levels and increased GLM clearance. Albumin, like mAbs, interacts with the neonatal Fc-receptor (FcRn), thereby prolonging half-life. Lower albumin concentrations, reflecting a more severe disease status, could reflect a lower number of FcRns, thereby explaining an increased clearance. In clinical practice, patients with low albumin levels, should therefore be considered for dose escalation. For GLM, there are however limited possibilities to optimize the current therapy when a patient is suspected of loss of response. Following induction therapy of 200 mg and 100 mg at week 0, and 2, respectively, maintenance GLM therapy consists of 50 mg or 100 mg every 4 weeks for patients with a body weight <80 or ≥80 kg, respectively. Recently, the label of GLM changed which made it possible for patients with a body weight <80 kg to also receive 100 mg GLM as maintenance therapy. As recently shown, in patients with a lower body weight and non-response to GLM induction therapy, 100 mg SC at week 6 resulted in a meaningful proportion (28%) of patients achieving a clinical response at week 14.45 In our study population, 7 out of 20 patients were subject to secondary loss of response, of which 4 patients received 50 mg SC maintenance therapy. Also for these patients, dose optimization could have potentially resulted in regaining response.
On top of pharmacokinetic-based monitoring, pharmacodynamic-based monitoring might be used to optimize anti-TNF therapy (Chapter 5). With pharmacokinetic-based monitoring, dosing is guided by measuring serum drug concentrations. As for pharmacodynamic-based monitoring, dosing is guided by changes in biomarkers that represent disease activity, such as fecal calprotectin. Fecal calprotectin is shown to be a surrogate marker of mucosal disease severity and can therefore be used for pharmacodynamic monitoring. In a post-hoc analysis of a phase 4, randomized, double-blind, controlled, parallel-arm, multicenter study, a population pharmacokinetic and pharmacodynamic model was developed to describe the relation between IFX dose, IFX exposure, fecal calprotectin concentrations and attainment of endoscopic remission. The model was able to properly describe the data and supports the use of combined pharmacokinetic and pharmacodynamic monitoring in anti-TNF treated patients. Colombel and colleagues have previously evaluated the use of pharmacodynamic monitoring (‘tight control’) in the treatment of CD patients starting on ADL treatment. For the tight control group, treatment escalation was driven by the combination of clinical symptoms (Crohn’s disease activity index (CDAI) score) and biomarkers (fecal calprotectin and CRP) and treatment escalation in the clinical management group was driven by clinical symptoms (CDAI) alone. The use of biomarkers for treatment escalation resulted in superior clinical and endoscopic outcomes than symptoms-driven decisions alone and supports the use of a combined strategy to improve treatment outcomes.

In Chapter 6 we aimed to describe the relationship between IFX (anti-TNF) and TNF concentrations in UC patients. IFX binds with high affinity to its target TNF, resulting in the formation of stable IFX-TNF complexes. Target-mediated drug disposition (TMDD) is described for monoclonal antibodies that bind with high affinity to their target, to such an extent that it affects the pharmacokinetics of the drug. At low concentrations the monoclonal antibody is eliminated via lysosomal degradation through binding to its target, while at high concentrations, this elimination route becomes saturated and elimination occurs via a linear, non-saturable proteolytic pathway. As a result, clearance is higher at low monoclonal antibody concentrations. Evaluation of a full TMDD model to describe the IFX-TNF relationship in UC patients resulted in an unstable model, being highly dependent on initial estimates. Therefore, an approximation of the TMDD model was used. A quasi-steady state (QSS) approximation assumes an equilibrium between free drug-receptor concentrations and formation of the complex. This TMDD-QSS approximation accurately described the IFX-TNF data in our UC patients. This model might serve as a basis for a more mechanistic model in which the total fate of TNF can be investigated. In an ideal setting, IFX and TNF concentrations measured in serum, tissue and fecal samples would then need to be available. It was previously shown that higher TNF tissue concentrations might serve as a predictor for treatment outcomes. The proposed mechanistic model would provide more extensive knowledge about the total fate of TNF and could be used to investigate the relationship between suppression of TNF and the response to IFX therapy. As a result,
IFX response might be predicted based on TNF concentrations and this would potentially support individualized IFX treatment.

**Part II Therapeutic drug monitoring**

Although TDM is useful in personalization of anti-TNF therapy, TDM is also subject to several limitations. As a first and most important limitation, treatment goals have evolved over time and have not been finally established yet. The treatment goal for IBD patients has moved from clinical remission towards more advanced outcomes such as mucosal healing. Also, patient reported outcomes are becoming more important, and the patient's quality of life has been proposed as the ultimate goal in both CD and UC. Different treatment goals require different target concentrations. For IFX, higher IFX TLs are for example needed to obtain endoscopic remission (≥9.7 mg/L) compared to biochemical remission (≥2.2 mg/L). For histological healing, IFX TLs ≥9.8 mg/L are required in CD and ≥10.5 mg/L in UC patients. In addition, for CD patients with perianal fistulas, there is increasing evidence that higher IFX serum concentrations are needed for complete disease control compared to patients without fistulizing disease. As a second limitation, TDM in clinical practice is hampered by the time between blood sample withdrawal and availability of results. As a consequence (for IFX), dose adjustment usually can only be carried out at the following infusion 8 weeks later, a delay that may significantly reduce the utility of TDM. Dried blood samples (DBS) could be used to measure IFX and ADL concentrations in a more timely manner. In this case, results of the measurements of DBS will be present when the patient visits the clinic and the dose can be adjusted immediately. At the same time, venous blood collection becomes unnecessary. Chapter 7 presents the results of a prospective observational study in which dried bloods sample (DBS) IFX results were compared to serum IFX concentrations in IBD patients. Results for measured IFX serum concentrations using DBS were highly comparable to measured IFX serum concentrations after conventional venepuncture. In clinical practice, patients can perform DBS at home and send directly to the laboratory. The mid-infusion sample can be used as an alternative to a trough concentration, e.g. with the use of a dashboard system. Timely adjustments to IFX therapy can be facilitated this way. Also, for the conduction of pharmacokinetic research for which multiple serum samples are required, DBS could ease the study burden for the enrolled patient. Similar results were found for DBS used to measure ADL concentrations in IBD patients (Chapter 8). ADL results from DBS were compared to ADL serum concentrations. To evaluate home-sampling, patients performed DBS at home and results were compared to ADL serum concentrations estimated by Bayesian forecasting. For each patient, one ADL serum concentration from venepuncture was used as input to predict the ADL concentration at the time of DBS performed at home. Although no proportional or systematic bias was found between DBS results from home-sampling and estimated ADL serum concentrations, high variability was seen. Further simulations showed that this variability can be reduced when two concentration time points are used as input in the Bayesian forecasting, instead
of one concentration-time point. Time between blood sample withdrawal and availability of results can also be reduced by means of rapid serum anti-TNF testing. With such a point-of-care test, results are available within 20 minutes which also would facilitate clinical decision-making.

Although concentration-effect relationships for the purpose of TDM for anti-TNFs have been extensively documented, still half of the patients during maintenance are subject to secondary loss of response. Therefore, one could argue if trough concentrations are the best pharmacokinetic marker to use for prediction of optimal anti-TNF treatment outcomes. The use of the area under the curve (AUC) was evaluated for patients on IFX maintenance therapy to predict treatment outcomes (Chapter 9). First, AUC and trough concentrations showed moderate correlation. For patients on an 8-weekly dosing interval with a trough concentration between 3 and 7 mg/L, the generally proposed therapeutic window of IFX, AUC ranged from 680 – 1936 mg/L*day. In addition, median AUC was lower in patients not in biochemical remission, compared to patients in biochemical remission, while both groups had a IFX trough concentration <3 mg/L. IFX trough concentration may therefore be considered not to adequately reflect the exposure of an individual patient to IFX. Simultaneously, however, AUC did not show to be a better predictor of biochemical remission (CRP<5 mg/L) in these patients compared to IFX trough concentrations.

TDM-based personalized dosing seems to be an optimal strategy to prevent under and over dosing, despite limited evidence in favor of proactive dose adjustments with anti-TNF agents. To date, three prospective trials have been published that evaluated the use of proactive TDM during anti-TNF maintenance treatment. IBD patients in remission were included in the TAXIT trial and were dose optimized before start of the study to obtain an IFX trough concentration between 3 and 7 mg/L. Optimizing patients to a target trough concentration between 3 and 7 mg/L resulted in a longer relapse-free survival rate. However, clinical remission rates were similar in patients receiving TDM-based dosing compared to patients receiving clinically based (based on clinical symptoms and CRP) dosing of IFX. In the TAILORIX trial anti-TNF naïve CD patients were randomized between IFX dose adaptations based on TDM, clinical symptoms, and biomarkers or dose adaptations based on clinical symptoms alone during maintenance treatment. IFX dosing that was based on TDM, clinical symptoms and biomarkers proved not to be superior compared to treatment intensification based on clinical symptoms alone. More recently, Assa and colleagues compared proactive versus reactive TDM of ADL in paediatric CD. A proactive approach in this study population resulted in significant higher rates of clinical remission during maintenance treatment compared to a reactive approach. Chapter 10 describes our most recent prospective TDM trial in which IBD patients in clinical remission received IFX dosing guided by a dashboard system, compared to continued IFX dosing without any dose adaptations. A dashboard system is a valuable tool for non-pharmacologists to use population-based pharmacokinetic models. For patients in the precision dosing group, the dashboard system calculated the dose and timing of the next IFX infusion in order...
to maintain a trough concentration of ≥3 mg/L. Loss of clinical response was observed in 14/39 (36%) patients in the conventional dosing group compared to 4/32 (13%) patients in the precision dosing group (p=0.03) after 1 year of follow-up. Moreover, patients in the proactive dose adjustment group had significantly lower fecal calprotectin levels. These results support the use of such a dashboard system to facilitate TDM and optimize treatment outcomes.

The interest in personalized anti-TNF therapy in IBD patients is growing. Findings from this thesis support the use of personalized medicine for anti-TNF treated IBD patients. To make the best use of TDM, a most optimal treatment goal still has to be defined for IBD. Treatment goals have evolved over time, and now point into the direction of mucosal healing, e.g. histopathological remission, as a gold standard. Treatment goals also depend on the type and extent of the disease, e.g. perianal disease in CD patients requires higher anti-TNF serum concentrations. Not only pharmacokinetic-based dose adjustments, but also pharmacodynamic-based dose adjustments will guide future anti-TNF treatment. Such a combined monitoring strategy in a pro-active TDM setting is expected to be the most effective future strategy to prevent secondary loss of response. Additionally, by reducing the time between blood samples and availability of results, TDM can be further optimized and already be implemented during induction therapy. Also, dose reduction of anti-TNF agents in IBD patients who are in remission with supra-therapeutic anti-TNF serum levels might not only benefit patients, but will also result in significant cost savings. In conclusion anti-TNF agents are one of the most powerful therapeutic agents to treat IBD. Individualized dosing of these therapeutic antibodies will conceivably further improve outcomes.
REFERENCES


General discussion


