Optimizing anti-TNF therapy in inflammatory bowel disease
Brandse, J.F.

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CHAPTER 5

The impact of pharmacokinetics and early appearance of antidrug antibodies on response to infliximab induction therapy in moderate-to-severe ulcerative colitis, a prospective study

J. F. Brandse, R. A. Mathôt, D. van der Kleij, T. Rispens,
Y. Ashruf, J. M. Jansen, S. Rietdijk, M. Löwenberg,
C. Y. Ponsioen, S. Singh, G. R. van den Brink, G. R. A. M. D’Haens

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ABSTRACT

Background and aim
The pharmacokinetics of infliximab (IFX) during induction treatment for Ulcerative Colitis (UC) have not been studied. We investigated serum IFX concentrations and early appearance of antibodies to infliximab (ATI) during induction treatment in moderate-to-severe UC.

Methods
Moderate-severe UC patients (endoscopic Mayo ≥ 2) receiving IFX induction treatment were enrolled prospectively. Serial serum and fecal samples were collected for 6 weeks and tested for IFX concentrations, ATI, C-reactive protein (CRP), albumin and fecal calprotectin.

Treatment success was defined as endoscopic response (≥ 1 point reduction in the endoscopic Mayo score) at week 8.

Results
Nineteen of the 20 included patients completed the conventional IFX induction regimen (5mg/kg at week 0, 2 and 6). Eleven patients (58%) showed endoscopic response. The median (IQR) serum IFX concentration at week 6 was 8.1 (3.0-13.7) ug/ml in responders versus 2.9 (0.01-5.8) ug/ml in non-responders (P=0.03). ATIs were detected in 7 patients as early as on day 18 (median 28, 18-42). Six of the 8 non-responders tested ATI+ compared to 1/11 responders (P<0.01, OR:30, 95%CI:2.2-406.2). ROC analysis revealed that baseline CRP > 50mg/l was associated with lower week 0-6 drug exposure by area under the curve (AUC) (587 vs. 1361 mg/L/day, P=0.001). The median AUC for serum IFX was 1230 mg/L/day in non-responders and 1352 mg/L/day in responders (p=0.65).

Conclusions
Week 6 IFX concentrations separated responders from non-responders significantly. Early development of ATI impaired IFX concentrations and predicted non-response. Patients with high baseline serum CRP levels had lower serum IFX concentrations and worse outcome.
Background

Infliximab (IFX) is effective to induce and maintain clinical remission and mucosal healing in patients with moderate-to-severe ulcerative colitis (UC).\(^1\,^2\) Combination therapy of IFX with azathioprine was shown to be superior to monotherapy with either agent alone for achieving corticosteroid-free remission at 16 weeks.\(^3\) However, approximately one third of UC patients have no or limited response to IFX induction therapy, a phenomenon which is called ‘primary non-response’. In addition, approximately one quarter of patients lose response to IFX during the first year of maintenance therapy.\(^1\,^4\) Loss of response has been associated with the appearance of neutralizing antidrug antibodies and with low serum drug concentrations, even in the absence of neutralizing antibodies, in patients with Crohn’s disease during IFX maintenance treatment.\(^5\,^6\) In UC, undetectable IFX trough levels (measured immediately prior to infusion during maintenance therapy) have been associated with a higher risk of colectomy.\(^7\) Most conventional antidrug antibody assays cannot measure antidrug antibodies in the presence of circulating drug. Therefore, the early development of antidrug antibodies during IFX induction therapy and its relation to IFX concentrations and response have not been studied in detail, so far.

Several factors are known to affect serum concentrations of therapeutic anti-TNF antibodies, such as the presence of neutralizing anti-drug antibodies and the use of concomitant immunomodulators. Furthermore, mode of administration (intravenous versus subcutaneous), body weight, high serum C-reactive protein (CRP) concentrations and low serum albumin concentrations (both reflecting a high inflammatory load) have also been suggested to affect anti-TNF serum concentrations.\(^6\,^8\,^9\)

The current IFX dosing regimen (5mg/kg at week 0, 2 and 6) is based on the original prospective registration trials, which excluded hospitalized patients with steroid refractory acute severe UC.\(^1\) This population was studied in a different placebo-controlled trial in Sweden, reporting a decreased colectomy rate in hospitalized UC patients that were treated with a single IFX infusion compared to placebo.\(^2\) Furthermore, a French head-to-head comparative study of IFX and ciclosporin in hospitalized patients with severe UC refractory to intravenous steroids, revealed that rescue therapy with ciclosporin was not superior to IFX, leading to ‘treatment failure rates’ in 60 and 54% of patients respectively. In this ‘CYSIF’ trial, ciclosporin was administered using predefined therapeutic drug monitoring ranges, whereas IFX was given at standard doses.\(^10\)

The optimal therapeutic range for serum concentrations of IFX during induction therapy in UC is unknown. The available pharmacokinetic data of IFX in UC are solely derived from patients receiving maintenance therapy and population computer modelling.\(^11\,^14\)

However, the situation during induction therapy in the acute phase of UC is considerably different from that in the maintenance phase. It has been hypothesized that
patients with a high inflammatory burden during the induction phase have an accelerated clearance of anti-TNF antibodies due to massive presence of (circulating and tissue) TNF and fecal loss of the therapeutic antibody.\textsuperscript{15, 16} This hypothesis has already led to dose intensification in clinical practice at certain medical centres. Recently an Irish group reported a reduction in the colectomy rate after the introduction of an ‘accelerated IFX dosing regimen’ when compared to a historical cohort.\textsuperscript{17}

To test the hypothesis that patients with high inflammatory burden have higher clearance, we conducted a prospective multicenter pharmacokinetic study of IFX induction therapy in patients with moderate-to-severely active UC. We aimed to investigate whether antidrug antibodies appear during IFX induction therapy in patients with moderate-to-severe UC and if in patients with high inflammatory burden enhanced clearance of IFX contributes to primary non-response.
PK and early antidrug antibodies of infliximab induction in UC

Methods

This prospective cohort study was performed at two centres in Amsterdam, the Netherlands (an academic referral center, the Academic Medical Center and a regional teaching hospital, OLVG), between July, 2012 and March, 2014. Consecutive anti-TNF naïve adults with moderate-to-severe UC (endoscopic Mayo score 2 or 3) were included after giving informed consent. Following negative screening for tuberculosis and gastrointestinal infections, infliximab was administered intravenously at a dose of 5 mg/kg, either during admission or at the outpatient infusion clinic. Further infusions (5mg/kg) were given at week 2 and 6, in accordance with the IFX label. Corticosteroids were allowed during the study and gradually tapered after the second IFX infusion. For patients that used thiopurines (azathioprine or 6-mercaptopurine) at baseline, doses were kept stable throughout the induction phase. In thiopurine naïve patients, 6-mercaptopurine was introduced 7 days after the first IFX infusion except in case of prior intolerance or other contraindications.

Patients were monitored intensively from the day before the first infusion up to week 6, with consecutive measurements of serum IFX, antibodies to IFX (ATI), C-reactive protein (CRP) and albumin and fecal calprotectin concentrations at day 0 (1hr after the end of the first infusion), day 1, 4, 7, 11, 14 (immediately before and 1hr after infusion), and day 18, 21, 28 and 42. (supplementary figure 1)

<table>
<thead>
<tr>
<th>IFX1</th>
<th>IFX2</th>
<th>IFX3</th>
<th>Endo</th>
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<tbody>
<tr>
<td>week 0</td>
<td>week 2</td>
<td>week 6</td>
<td>week 8</td>
</tr>
<tr>
<td>days</td>
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<td>0</td>
<td>1</td>
<td>4</td>
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<td>14</td>
<td>18</td>
<td>21</td>
<td>28</td>
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<tr>
<td>42</td>
<td>56</td>
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<td></td>
</tr>
</tbody>
</table>

serum and stool

Fecal calprotectin concentrations were measured using an ELISA (Bühlmann, Schönenbruch, Switzerland). Fecal supernatants were diluted if fecal calprotectin results were above the upper limit of detection of the test (1800 ug/g).

Clinical response was monitored weekly using the Simple Clinical Colitis Activity Index (SCCAI). All patients underwent a sigmoidoscopy at baseline before IFX was started and at week 8 after treatment initiation. Endoscopic disease severity was assessed by an independent reader (blinded to the study results) on video’s or endoscopic photographs using the Mayo endoscopic subscore. Endoscopic response was defined as improvement by at least 1 point and mucosal healing as a Mayo endoscopic score ≤1. Absence of response was defined as a lack of endoscopic improvement and/or clinical deterioration with a need for additional unscheduled IFX dosing or colectomy within 3 months. The decision for additional unscheduled IFX dosing or colectomy was made without knowledge of the serum IFX or anti-IFX antibody concentrations.
Serum infliximab and antibodies to IFX

All serum samples were analyzed for IFX concentrations by Sanquin Laboratories (Amsterdam, The Netherlands) using a previously validated radioimmunoassay. Antibodies to IFX (ATIs) were measured with a homogeneous mobility shift assay (Prometheus Laboratories, San Diego, CA). This assay is, contrary to conventional bridging ELISAs, able to detect anti-IFX antibodies in the presence of drug. The Homogeneous mobility shift assay uses fluorescently labeled IFX to isolate anti-IFX antibodies complexes based on their molecular weight. Anti-IFX complexes are quantified by size-exclusion high performance liquid chromatography (SE-HPLC) with fluorescent detection.

Statistical analysis and PK modelling

We used descriptive statistics and data are presented as non-normally distributed with medians and interquartile ranges (IQR). Differences in area under the serum concentration versus time curve (AUCs; see below) were analyzed using the Mann-Whitney U test, whereas a Fisher’s exact test was used for univariate analysis of predictors of response, which were further analyzed by ROC analysis. For correlation analysis a Spearman’s rank correlation coefficients were determined. A P value <0.05 was considered statistically significant. SPSS® software version 20.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis.

IFX concentrations at the different time points were analyzed simultaneously by non-linear mixed-effects modelling software (NONMEM (version 7.2.0), Globomax LLC, Ellicott City, Maryland, USA). The time profile of the IFX concentrations was described using a 2-compartment PK model. Estimated parameters were clearance (CL), volume of distribution of the central compartment (V1), intercompartment clearance (Q) and volume of distribution of the peripheral compartment (V2). Inter-patient variability and covariance were estimated for CL, V1 and V2.

Correlations between pharmacokinetic parameters and covariates were evaluated in an attempt to explain the inter-patient variability in the pharmacokinetic parameters CL, V1 and V2. The evaluated covariates included antibodies to IFX, serum CRP, albumin concentrations and body weight. The covariate model was built using stepwise forward inclusion (P<0.05) followed by backward elimination (P<0.01).

Individual pharmacokinetic parameter estimates were obtained by Bayesian analysis using the final population model. The individual parameters were used to calculate the area under the curve (AUC) for serum infliximab concentrations versus time. (For further details about the pharmacokinetic analysis, see the supplementary method section)
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This study was approved by the local medical ethical committee in accordance with Dutch national legislation. Written informed consent was obtained from all patients. All co-authors had access to the study data and reviewed and approved the final manuscript.
Results

Twenty consecutive UC patients were included between July, 2012 and March, 2014. All but one patient suffered from severe Mayo 3 colitis at baseline endoscopy and one third of patients were hospitalized at initiation of IFX therapy. Patient and baseline characteristic are shown in table 1.

<table>
<thead>
<tr>
<th>TABLE 1. Baseline Characteristics</th>
<th>N=20</th>
</tr>
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<tbody>
<tr>
<td>Gender, Male (n) %</td>
<td>13 (65%)</td>
</tr>
<tr>
<td>Age (years), median (IQR)</td>
<td>36 (27-44)</td>
</tr>
<tr>
<td>Weight (kg), median (IQR)</td>
<td>70 (61-75)</td>
</tr>
<tr>
<td>Disease duration (years), median (IQR)</td>
<td>6 (0-13)</td>
</tr>
<tr>
<td>Extent of UC, n (%):</td>
<td></td>
</tr>
<tr>
<td>Left-sided colitis</td>
<td>7 (35%)</td>
</tr>
<tr>
<td>Pancolitis</td>
<td>13 (65%)</td>
</tr>
<tr>
<td>Endoscopic Mayo score 3, n (%)</td>
<td>19 (95%)</td>
</tr>
<tr>
<td>Corticosteroid refractory, n (%)</td>
<td>19 (95%)</td>
</tr>
<tr>
<td>Hospitalized, n (%)</td>
<td>7 (35%)</td>
</tr>
<tr>
<td>Concomitant thiopurines, n (%)</td>
<td>11 (55%)</td>
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<tr>
<td>Serum Haemoglobin, (g/l), median (IQR)</td>
<td>115.9 (99.8-127.2)</td>
</tr>
<tr>
<td>Serum CRP (mg/l), median (IQR)</td>
<td>25.8 (4.2-84.8)</td>
</tr>
<tr>
<td>Serum Albumin (g/l), median (IQR)</td>
<td>37 (30-41)</td>
</tr>
<tr>
<td>Fecal Calprotectin (ug/g), median (IQR)</td>
<td>2030 (981-3183)</td>
</tr>
<tr>
<td>Clinical Colitis Activity Index, median (IQR)</td>
<td>10 (8-13)</td>
</tr>
</tbody>
</table>

Legends: UC; ulcerative colitis, CRP; C-reactive protein, IQR: inter quartile range

Clinical and endoscopic outcome

One patient received an additional and accelerated IFX infusion of 10 mg/kg on day 5 because of rapid disease exacerbation based on clinical and biochemical parameters. This patient was excluded from further analysis from that time point onwards. Subsequently, the patient improved rapidly and could be discharged from the hospital 6 days after the additional infusion. Two patients underwent a colectomy within 3 months of IFX initiation. These 3 patients were considered to have complete absence of response to conventional IFX induction therapy, whereas the remainder (n=17) at least showed some clinical benefit.

The standard IFX induction regimen resulted in an endoscopic response in 58% (11/19) and mucosal healing in 47% (9/19) of the patients. The baseline characteristics of the endoscopic responders compared to non-responders were not significantly different. (Supplementary table 1)
**Antibodies to IFX**

Antibodies to IFX were detected in 7/20 patients. These antibodies were measurable as early as day 18, 4 days after second infusion. Six of the seven patients with detectable ATIs were endoscopic non-responders at week 8 (P<0.01, OR:30). (table 2) The single patient with detectable ATIs that had an endoscopic response developed an acute infusion reaction at the fifth IFX infusion (ie at week 22). Concomitant use of immunomodulators did not significantly change the formation of anti-IFX antibodies.

**TABLE 2**

<table>
<thead>
<tr>
<th></th>
<th>ATI + (n=7)</th>
<th>ATI - (n=13)</th>
<th>P value, (OR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 6 IFX level(ug/ml), median [IQR]</td>
<td>0.0 (0.0-2.7)</td>
<td>8 (5.6-11.8)</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>Endoscopic non-responders</td>
<td>6/8</td>
<td>2/8</td>
<td>P&lt;0.01, OR:30</td>
</tr>
<tr>
<td>Endoscopic responders</td>
<td>1/11</td>
<td>10/11</td>
<td></td>
</tr>
<tr>
<td>Immunomodulator use</td>
<td>3/12</td>
<td>9/12</td>
<td>P=0.36</td>
</tr>
<tr>
<td>No immunomodulator</td>
<td>4/8</td>
<td>4/8</td>
<td></td>
</tr>
</tbody>
</table>

Legends: IFX; infliximab, ATI; anti-IFX antibodies, IQR; inter quartile range

**Pharmacokinetics**

Serum IFX concentrations showed considerable variation 1 hour after the first (range 70.2-148.1 ug/ml) and the second (46.8-200.5) infusion (figure 1).

**Figure 1. Infliximab concentrations**

**Figure 1. Serum infliximab (IFX) concentration versus time profile. Each dot represents a separate observation. The curve represents the median.**
The concentration-time profiles could be adequately described using a two-compartment model. After administration, IFX distributed mainly within the central compartment (plasma volume), with limited cellular penetration because of the high molecular weight and hydrophilicity of IFX; respective central and peripheral volumes of distribution were 3.3 L and 2.2 L. In the final pharmacokinetic multivariate model significant associations were found between IFX clearance and the presence of ATI and the serum albumin concentration. The pharmacokinetic parameters are presented in supplementary table 2. In the presence of ATI, typical clearance was more than doubled (increase from 0.43 L/day to 1.00 L/day, 2.3 fold, P<0.01), which is reflected in a much smaller AUC in these patients. (figure 2) As a result ATI decreased the distribution half-life from 2.0 to 1.5 days and the elimination half-life from 9.9 to 5.9 days. Serum albumin and clearance were negatively correlated (P<0.01). Clearance was 0.87, 0.54 and 0.40 L/day with serum albumin values of 25, 38 and 50 g/l, respectively.

Figure 2 2a: Area under the curve for serum infliximab concentration versus time, for antibody to infliximab positive patients versus antibody to infliximab negative patients. 2b and 2c: examples of infliximab concentration and ATI titer for 2 subjects from week 2-6.
Predictive baseline markers for serum infliximab concentrations (exposure)  

Individual PK profiles of serum IFX were obtained by Bayesian analysis using the developed multivariate model. (Supplementary methods) Based on Receiver Operating Curves (ROC) the AUC of serum IFX over time, a reliable reflection of drug exposure (the amount of circulating drug), was significantly smaller in patients with a baseline serum CRP >50 mg/l than in patients with CRP below 50 mg/l (587 vs. 1361 mg/L/day, P=0.001). Likewise, in patients with a baseline serum albumin level of <35 g/l, there was a trend towards a lower AUC compared to patients with higher serum albumin levels (636 mg/l/day versus 1354 mg/l/day, P= 0.07). Patients with high fecal calprotectin at baseline (>1800 μg/g) had a lower median AUC than patients with lower fecal calprotectin levels (1197 mg/l/day vs. 1422 mg/l/day), but this difference was not statistically significant (P=0.09). However, extent of disease, another marker of inflammatory load significantly influenced the AUC with lower drug exposure in patients with pancolitis compared to left-sided colitis (P=0.03). Finally the AUC was also reduced in hospitalized patients versus outpatients (P=0.02) and in those who concomitantly received prednisone (P=0.02). We did not find significant differences in drug exposure among patients with and without immunomodulators, although the study was not powered to show this. (figures 3a, 3b, 3c, 3d, 3e)  

**Figure 3** Figure 3a,b,c,d,e: Area under the curve (AUC) for serum infliximab (IFX) concentration versus time for serum C-reactive protein (CRP) ≤/≥50 mg/l (3a), serum albumin ≥/≤35 g/l (3b), Fecal calprotectin ≤/> 1800 ug/g(3c), co-immunomodulator use (3d) or hospitalization status (3e) at baseline.
Serum IFX concentration and endoscopic outcome

Endoscopic responders did not have a significantly different AUC compared to non-responders (1352 mg/L/day vs. 1230 mg/L/day, P=0.65), (figure 4a) However, the median serum IFX concentrations curves separated progressively after the second infusion, towards lower concentrations in endoscopic non-responders. As a consequence, the median week 6 IFX trough concentrations were significantly higher in endoscopic responders (8.1 [3.0-13.7] ug/ml) compared to endoscopic non-responders (2.9 [0.01-5.8] ug/ml) (P=0.03). At week 6 a serum IFX concentration of >6.6 ug/ml was identified as a cut-off for endoscopic response, with an odds ratio of 18.7 (1.6-223) (P=0.02). Receiver operator curve analysis revealed an AUC: 0.80, with a sensitivity of 88% and a specificity of 73%.

An explorative analysis of the subgroup of patients with complete absence of response (including the patient with an additional dose that was not included in the endoscopic response analysis and both patients that underwent colectomy), showed significantly lower AUC up to day 4 in these patients compared to the patients with clinical response (P<0.05) (figure 4b), suggesting that in this subgroup of patients with very severe colitis and lack of response clearance was dramatically increased resulting in a low AUC and therefore low drug exposure.

**Figure 4**: Area under the curve (AUC) for serum infliximab (IFX) concentration versus time for endoscopic response (4a) and absence of response (4b).
Discussion

In this intensive pharmacokinetic study we observed that anti-drug antibodies already appear during induction treatment, impair IFX drug concentrations and predict non-response in patients with moderate-severe UC. Furthermore, high baseline CRP levels had a strong negative impact on serum IFX concentrations in UC patients receiving conventional IFX induction therapy. In addition to baseline CRP, low serum albumin levels and extensive colitis correlated with lower serum IFX concentrations and a smaller AUC. Low serum IFX concentrations at week 6 were associated with a lack of endoscopic response. This observation is consistent with the hypothesis that patients with a high ‘inflammatory burden’ show increased clearance of IFX and may benefit from an intensified IFX induction schedule.

The appearance of antibodies to IFX had a clear impact on IFX PK in our study, leading to faster IFX clearance and lower serum drug concentrations. The formation of antidrug antibodies in association with response has previously been reported during IFX maintenance therapy, but in those studies patients often received ‘episodic’ treatment or had restarted IFX after a ‘drug holiday’. In contrast, our study only looked at anti-TNF naïve patients during the induction phase and the majority of patients were on concomitant immunosuppressive agents. Nevertheless, we observed detectable antibodies to IFX as early as before the third infusion in 7 out of 20 (35%) patients. Three patients (out of 12, ie 25%) who received concomitant treatment with immunosuppressive agents developed ATIs versus 4/8 (ie 50%) patients receiving IFX monotherapy (P=0.36). Although this difference was not statistically significant, this observation appears to confirm the potential protective role of concomitant immunomodulators to prevent formation of ATIs. Besides prevention of ATI formation, concomitant immunomodulatory therapy has also been associated with higher serum IFX concentrations in the absence of detectable ATIs. In our cohort, concomitant immunomodulators did not influence serum IFX concentrations, possibly because certain patients (2/11) started their immunomodulators 7 days after IFX initiation. The effect of thiopurines on IFX pharmacokinetics might require a more, however the correlation between duration of thiopurine treatment and serum IFX concentration has not yet been examined.

Looking at IFX exposure over time as ‘area under the curve’ the most striking difference was observed in the first 4 days following the first IFX infusion among patients with complete absence of response and responders. This supports the hypothesis that the amount of TNF to be neutralized is the highest at the start of induction treatment and that the standard dose of IFX does not suffice in the presence of overwhelming inflammation in some patients. Serum IFX concentrations at week 6 were indeed lower in endoscopic non-responders compared to endoscopic responders establishing an association between serum IFX concentration and endoscopic response.
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Post infusion ‘peak’ IFX concentrations were obtained 1 hour after the first and second infusion. This approach has previously been described in patients with rheumatoid arthritis receiving 3 or 10mg/kg infliximab.26 These concentrations approximate the maximum concentration (Cmax) for infliximab and are directly proportional to the intravenous dose over this range. Strikingly, in the current study we observed a wide variation in IFX ‘peak’ concentrations, which did however not correlate with endoscopic response. One hour post infusion is probably too short to measure the effects of TNF neutralization or drug loss in the feces. During maintenance therapy the measurement of functionally active IFX in the serum directly after an infusion has been suggested to be predictive for loss of response to IFX maintenance therapy in patients with Crohn’s disease, but data in ulcerative colitis are lacking.27

The clearance of IFX in the present study was much higher than previously reported in patients with rheumatoid arthritis and ankylosing spondylitis and in a heterogeneous cohort of IBD patients mostly receiving maintenance IFX.26,28-31 The higher clearance observed in the current study may be explained by the fact that we measured serum IFX levels at the start of treatment in the most severe phase of the disease, associated with the highest degree of inflammatory burden. This high inflammatory load may have led to rapid consumption of therapeutic antibodies in the vascular and intestinal compartments.

In line with earlier observations during IFX maintenance therapy, we found a striking correlation between high serum CRP or low serum albumin and lower IFX levels during induction therapy.32 The serum CRP could even serve as a marker for low IFX levels and associated loss of response in patients on maintenance therapy. An increase in CRP can reflect a decreasing serum IFX level preceding loss of response to IFX maintenance therapy in patients with Crohn’s disease.33 Similarly, pre-treatment baseline CRP levels correlated negatively with serum trough IFX levels at 14 weeks after the start of treatment in RA patients.34 Although CRP elevation is often absent in mild-to-moderately active UC, it was elevated at baseline in 15/20 (75%) patients in our cohort and it proved to be a useful marker of inflammatory load and a predictor of low serum IFX concentrations.35

Patients with lower serum albumin concentration also had a significantly higher IFX clearance and shorter half-life than patients with high serum albumin. Correlation between serum IFX correlation and serum albumin has previously been described during IFX maintenance therapy.31,36 It is hypothesized that the common rescue pathway for both albumin and IgG, involving the neonatal Fc receptor (FcRn), may be responsible for the correlation between serum albumin and serum IFX levels. Serum albumin reflects the efficacy of FcRn salvage recycling by non-competitive binding with IgG. The FcRn facilitates IgG and albumin homeostasis by recycling them across cell membranes back to the central circulatory system.36,37
Our study did not confirm body weight as an independent factor influencing serum drug concentrations. In an earlier study during maintenance therapy, body weight was reported to affect infliximab PK: with higher clearance and increase of total volume of distribution at higher body weights, while low body weight associated with decreased serum IFX concentrations.\textsuperscript{31, 38} Our study cohort may have been too small to confirm those findings and during induction therapy the impact of the disease severity to clearance is probably much more important than body weight, the only factor for which the dose was corrected in this study.

Besides classic proteolysis, IFX also disappears from the circulation through intestinal protein loss. Fecal excretion of IgG has been related to disease activity.\textsuperscript{36} We previously reported fecal loss of IFX in patients with severe ulcerative colitis.\textsuperscript{16} The relationship between fecal loss and serum IFX concentrations remains unclear, since serum concentrations are influenced by multiple other factors and the concentrations of fecal IFX may be affected by the presence of proteases. Furthermore, it is still poorly understood how different body compartments affect each other’s pharmacokinetics and pharmacodynamics. Intravenously administered TNF antibodies bind to soluble and membrane bound TNF, whereby TNF in various compartments may create TNF concentration gradients, hence leading to TNF redistribution.\textsuperscript{40} The kinetics of TNF and antibodies to TNF in the serum and the intestinal tissue most likely affect and alter each other. The mucosal concentrations of IFX are likely to be at least as important as serum concentrations with respect to the pharmacodynamics. Recently mucosal anti-TNF concentrations and the ratio of anti-TNF-to-TNF in tissue were reported to be lower in severely inflamed parts of the colon, which suggested that mucosal inflammation is the most likely cause of antibody loss.\textsuperscript{41}

In the single patient that was given an accelerated IFX infusion in an attempt to avoid colectomy, day 4 serum IFX concentrations were extremely low as a consequence of dramatically increased clearance. By administering a second dose at 10 mg/kg, we were able to achieve clinical, biochemical and endoscopic response and the patient avoided colectomy. This observation is in line with previous reports that an accelerated IFX induction regime may reduce the need for short-term colectomy.\textsuperscript{17}

A limitation of our study is the rather small sample size which rendered the regression analysis for predictors of response somewhat challenging. Despite this, however, our study provided relevant new insights in the early pharmacokinetics of IFX in severe UC. The numerous serial measurements allowed for an accurate AUC estimation and the PK modelling identified serum albumin and CRP at baseline and the formation of detectable ATIs at week 6 as factors influencing IFX serum concentrations and clearance.

In conclusion, anti-drug antibodies already appear during induction treatment, impair IFX serum concentrations and predict non-response in patients with UC. UC patients with
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high baseline serum CRP and low serum albumin levels exhibit increased clearance of the drug and lower serum IFX concentrations during IFX induction therapy, predicting poor endoscopic outcome. Our data therefore support the hypothesis that a antidrug antibodies and high ‘inflammatory burden’ result in increased clearance of IFX and may contribute to primary non-response. Larger prospective trials are warranted to investigate early antidrug antibody formation and if patients with high inflammatory burden consistently benefit from a more intensified IFX induction therapy and if primary non-response to IFX can thereby be prevented.

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REFERENCES


