Infliximab trough levels may predict sustained response to infliximab in patients with Crohn's disease ☆

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Abstract

Background and aims: Over 10% of Crohn's disease (CD) patients annually lose response to infliximab. Infliximab trough levels (TL), concomitant immunosuppressants and endoscopic healing were proposed as predictors of favourable infliximab outcome. We assessed infliximab TL measured after induction therapy as predictors of sustained clinical response. Furthermore, we tried to identify other predictors of long-term benefit of infliximab therapy.
Methods: We included CD patients treated with infliximab between October 2007 and March 2010 who responded to 3-dose induction followed by maintenance therapy and in whom blood samples taken at treatment week 14 or 22 were available in blood bank. Sustained response to infliximab was defined as absence of treatment failure due to loss of response or drug intolerance.
Results: Eighty four patients were included. Sustained response to infliximab was observed in 47 (56%) patients during a median follow-up of 25 months (14–37). Infliximab TL>3 μg/ml were associated with a decreased risk of treatment failure (HR 0.34; 95% CI: 0.16–0.75), whereas the presence of antibodies against infliximab and need for corticosteroids increased this risk (HR 4.34; 95% CI: 1.51–12.5 and HR 2.49, 95% CI: 1.08–5.73, respectively). No impact of concomitant

thiopurines was observed, although patients receiving thiopurines had higher infliximab TL than those without immunomodulators (5.51 vs. 0.71 μg/ml; p=0.01).

Conclusion: During a median follow up of 2 years sustained response to infliximab was observed in slightly more than half of CD patients. Infliximab TL>3 μg/ml at the start of maintenance regime were predicative of sustained response to infliximab.

1. Introduction

Infliximab, a monoclonal IgG1 antibody against tumour necrosis factor alpha (TNF-α) has been shown to be effective in induction as well as in maintenance of remission in patients with both luminal and fistulizing Crohn's disease (CD).[1,2] In clinical practice initial response to infliximab is high with up to 90% of individuals with CD responding to induction treatment.[3] However, a substantial proportion of patients subsequently lose their response during the maintenance regime, with reported annual rates ranging from 10% to 50%.[4] Maintenance of sustained response has therefore become one of the most challenging clinical problems for CD patients treated with infliximab.

Several studies have identified different factors to be associated with sustained clinical response to infliximab.[5-8] Available data suggest a relationship between clinical efficacy and serum trough levels of infliximab, while detection of antibodies to infliximab (ATI) as such seems to be less relevant parameter.[6,9] Concomitant immunosuppressive therapy has been shown to improve long-term efficacy of infliximab in both controlled trial[5] and a retrospective study from tertiary centre,[8] although this finding was not confirmed in another large cohort study.[3] Another factor influencing the duration of clinical benefit of infliximab is mucosal healing. Disappearance of mucosal lesions has been demonstrated to decrease the number of surgical procedures and to have a clear steroid-sparing effect.[7,10,11] Moreover, a relationship between concomitant immunosuppressive therapy, infliximab trough levels, mucosal healing, and clinical efficacy has been found in SONIC trial.[5]

From the clinical point of view, reliable and easily evaluable predictors of long-term therapeutic outcome are of great importance. Therefore, the primary aim of our study was to assess the potential of infliximab trough levels measured after induction therapy as predictors of sustained clinical response in a group of CD patients followed in a large, tertiary IBD centre. Furthermore, we tried to identify other potential predictors of long-term benefit of infliximab therapy.

2. Patients and methods

The study population originated from a cohort of CD patients treated in our centre with infliximab between October 2007 and March 2010. Included patients had to be responders to 3 induction doses as assessed by treating physician and had to obtain at least one maintenance infliximab infusion. Furthermore, their blood samples taken at early phase of maintenance therapy at week 14 or 22 had to be available in the blood bank.

The general treatment policy with infliximab in our centre is based on 3 induction infusions (0, 2nd, 6th week) followed by maintenance therapy every 8 weeks in individuals with an initial good response as considered by treating physician. If an intensification regime is needed, either shortening of interval to 6 or 4 weeks, and/or increased dose to 10 mg/kg is applied based on the clinical situation.

Reviewing the medical records, patients were retrospectively assessed for sustained response to infliximab with a follow-up until the end of May 2011. Definition of sustained response was adopted from the definitions used previously.[12-14] In this study patients were considered to have the sustained response in case of absence of treatment failure due to loss of response or drug intolerance and if there was no need for surgery, new introduction of immunomodulators, corticosteroids or their dose increase during infliximab therapy. Need for intensification of infliximab treatment with a subsequent restoration of clinical response was not judged as treatment failure.

Data on patients' demographics, clinical characteristics, C-reactive protein (CRP) level, details on infliximab treatment and concomitant medication were prospectively registered and then retrieved from medical files.

2.1. Measurement of infliximab trough levels and ATI

Infliximab trough levels and ATI were measured from blood samples obtained immediately prior to application of maintenance infusion at week 14 or 22. Blood samples were taken from the cubital vein. Clotted blood samples were centrifuged for 10 min at ambient temperature and 1300 g and separated serum aliquots were frozen at −80 °C and placed to the IBD serum bank. The frozen serum samples were thawed once on ice before analysis.

Infliximab trough levels were detected using Q-INFLIXI ELISA Quantitative Analyses (Matriks Biotek, Ankara, Turkey). This solid phase enzyme-linked immunosorbent assay is based on the sandwich principle. Standards and serum samples were incubated in the microtitre plate coated with the reactant for infliximab. After incubation and washing, a horseradish peroxidase (HRP) conjugated probe was added and binded to infliximab captured by the reactant on the surface of the wells. Following incubation, wells were washed and the bound enzymatic activity was detected by addition of chromogen-substrate. The colour developed was measured at 450 nm using a MRXII photometer (Dynatech, UK) and analysed by Revelation software (Dynatech, UK). The lowest detectable level that can be distinguished from the zero standard is 0.03 μg/ml. Precision values of the kit are Intra-assay CV<8% and Inter-assay CV<8% for infliximab range 0.3–300 μg/ml. The cut-off level of 3 μg/ml was recommended

by the manufacturer based on their own study and other works.[15]

ATI were detected by sandwich enzyme-linked immunosorbent assay with the use of Q-ATI ELISA Quantitative Analyses (Matriks Biotek, Ankara, Turkey). Briefly, during the first incubation period, ATI in patient serum samples were captured by the drug infliximab coated on the wall of the microtiter wells. After washing away the unbound components from samples, a peroxidase-labelled specific conjugate was added to each well and then incubated. After a second washing step, the bound enzymatic activity was detected by the addition of tetramethylbenzidine (TMB) chromogen-substrate. Finally, the reaction was terminated with an acidic stop solution. The intensity of the reaction colour measured at 450 nm using a MRXII (Dynatech, UK) was directly proportional to the concentration of ATI in sample. The reference range 0–8 ng/ml was used on the basis of their own lab reference ranges using the data from their own equipment and healthy blood donor sera with antibodies against infliximab <8 ng/ml being considered negative and >8 ng/ml positive. In case of infliximab levels>3 μg/ml antibodies were considered inconclusive due to their interference with infliximab.

2.2. Statistical analyses

Standard descriptive statistical analyses were performed, including the frequency distributions for categorical data and calculation of median and range or interquartile range (IQR) for continuous variables.

Univariate and multivariate logistic regression analyses have been performed to calculate the marginal and adjusted odds ratios for the evaluation of the relationship between the sustained response to infliximab by 1 year and the following predictors: biological naivety, concomitant medication, prior bowel surgery, indication to biological therapy, age, disease duration, infliximab trough levels, ATI and CRP level. Due to collinearity between infliximab levels and ATI, these variables were analysed separately. Kaplan–Meier curves with accompanied logrank tests were used for time to the loss of sustained response. Univariate and multivariate Cox proportional hazard models with marginal and adjusted hazard ratios were used to analyse the effect of considered predictors on time to loss of sustained response and time to intestinal surgery. Mann–Whitney test and Fisher's Exact test were used for comparison of infliximab trough levels and rate of ATI in a subgroup of patients. Relation between mean CRP level during maintenance infliximab treatment, infliximab trough levels and ATI was analysed by Mann–Whitney test. A p value smaller than 0.05 was considered significant.

The area under the receiver operating characteristic (ROC) curve with 95% confidence interval and positive and negative predictive values to predict sustained response to infliximab for cut-off value of infliximab trough level 3 μg/ml was calculated.

The analyses were performed using the R software version 2.15.1 (R Development Core Team, 2012). ROC analysis was performed using the R package ROCR.[16]

3. Results

A total of 184 patients with CD were treated with infliximab in our centre between October 2007 and March 2010. Of them,

84 patients were eligible for the study being treated with maintenance therapy and having their blood samples available for measurement of infliximab trough levels. The patients' demographic and clinical characteristics at infliximab start are presented in Table 1.

3.1. Sustained response to infliximab

During a median follow-up of 25 months (range 14–37) sustained clinical response to infliximab was observed in 47 (56%) patients. The cumulative probability of sustaining in clinical response was 72.5% (±5%) at 12 months, 64% (±5%) at 18 moths and 53% (±6%) at 24 months (Fig. 1). Six (13%) patients of those with sustained response needed intensification of infliximab, with shortening of the infusion interval and dose increase to 10 mg/kg in 5 patients and 1 patient, respectively. The median time to intervention was 9 months (range 5–26).

Thirty-seven (44%) patients did not have sustained response to infliximab. Of them 24 (65%) discontinued the therapy due to the loss of response, 4 (11%) because of infusion reaction and 8 (22%) individuals stopped the therapy because of adverse events (skin complication in 5, drug-induced systemic lupus in 1, newly developed arthralgia in 1 and pulmonary mycobacteriosis in 1 individual). One patient continued infliximab until the end of follow-up; however needed systemic corticosteroids for relapse of CD while on biologic therapy.

Table 1 Patients clinical and demographic characteristics at infliximab start.

	n (%)
Females	46 (54)
Age (years); median (range)	31 (17–62)
Disease duration (months); median (range)	58 (1–390)
Biological naivety	69 (82)
Disease localization [a]	
-L1	29 (35)
-L2	15 (18)
-L3	40 (48)
-L4+/−L1/2/3	9 (11)
Disease behaviour [a]	
-B1	44 (52)
-B2	21 (25)
-B3	19 (23)
-p+/−B1/2/3	38 (45)
Previous intestinal surgery	20 (24)
Indication to infliximab	
-Luminal disease +/−EIM	67 (80)
-Perianal disease +/−luminal/EIM	17 (20)
Medical therapy	
-Thiopurines	38 (45)
-Systemic corticosteroids	22 (26)
-Topical corticosteroids (budesonide)	25 (30)
-Mesalazine	41 (49)

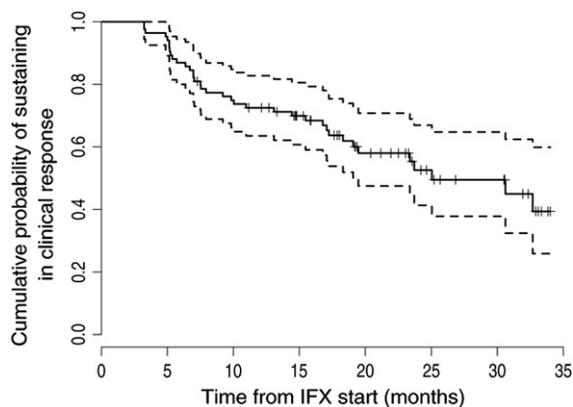[a] Montreal classification; EIM — extraintestinal manifestations.

Figure 1 Sustained clinical response to infliximab (IFX) in 84 patients treated with maintenance regime. Dashed lines show 95% confidence interval.

3.2. Infliximab trough levels and ATIs

The median infliximab trough level measured at week 14–22 of biological treatment was 4.04 μg/ml (IQR 0.52–9.33) with therapeutic levels (>3 μg/ml) being measured in 46 (55%) individuals. The median trough levels were significantly higher in patients with concomitant thiopurines compared to those without concomitant immunosuppression (median 5.51 vs. 0.71 μg/ml, p=0.01). No other factor such as biological naivety or corticosteroids at treatment start had impact on infliximab trough levels.

Fourteen (17%) patients were found to have positive ATI with a median titre of 124.89 ng/ml (IQR 22.01–182.75), 24 (28%) were ATI negative and in 46 patients (55%) the result was inconclusive. Similar to the infliximab trough levels, patients on concomitant immunosuppressive therapy had significantly lower frequency of antibodies compared to individuals without immunosuppressants (5% vs. 26%, p=0.017). No impact of corticosteroids and biological naivety was observed.

3.3. Infliximab trough levels, ATIs and CRP

Patients with infliximab trough levels>3 μg/ml had significantly lower level of mean CRP measured during the maintenance phase of biological treatment than individuals with lower drug levels (median CRP 4.2 mg/l vs. 9.6 mg/l, p=0.001). However, there was no difference in mean CRP levels comparing individuals with positive and negative ATIs (median CRP 11.2 mg/l vs. 10.3 mg/l, p=0.54).

3.4. Predictors of sustained response to infliximab

Looking at sustained response one year after infliximab start, univariate logistic regression analysis identified infliximab trough levels (OR 0.25; 95% CI: 0.09–0.69) and inconclusive antibodies (OR 0.30; 95% CI: 0.09–0.95) to be the factors associated with this treatment outcome. In multivariate analysis, however, only infliximab level remained the statistically significant predictor of sustained response (OR 0.31; 95% CI: 0.10–0.96). Patients with trough levels>3 μg/ml at weeks 14–22 were thus less likely to lose the sustained

response to infliximab than those with subtherapeutic levels (Table 2).

Using time analyses, 3 factors were found to have a significant impact on risk of loss of sustained response in univariate analysis (Table 3 and Fig. 2): infliximab trough levels>3 μg/ml (HR 0.31; 95% CI: 0.16–0.62) and inconclusive ATI (HR 0.38; 95% CI: 0.18–0.83) were identified to have protective effect, whereas the need for corticosteroids at infliximab start (HR 2.37; 95% CI: 1.15–4.91) increased the risk of loss of response to infliximab. Prior intestinal surgery decreased the likelihood of loss of sustained response with borderline significance (HR 0.39; 95% CI: 0.15–1.00). In multivariate model, infliximab trough levels>3 μg/ml were shown to be a positive predictor of sustained response to infliximab (HR 0.34; 95% CI: 0.16–0.75), while positive ATI (HR 4.34; 95% CI: 1.15–12.46) and concomitant corticotherapy at infliximab start (HR 2.49; 95% CI 1.08–5.73) increased the risk of treatment failure (Table 3).

The area under the ROC curve for prediction of loss of response to infliximab by 1 year using infliximab trough levels was 0.703 (95%CI: 0.571–0.834) (Fig. 3). Sensitivity, specificity, positive and negative predictive values for cut-off 3 μg/ml were 70%, 62%, 41% and 84%, respectively.

3.5. Surgery

Fifteen (18%) patients underwent intestinal resection (+/−strictureplasty) after a median time of 17 months (6–34) since the start of infliximab therapy. No clinical or laboratory predictor of intestinal surgery was identified (data not shown).

4. Discussion

Infliximab is now commonly used in patients with IBD to achieve and maintain clinical response and remission. Predicting long-term outcome of infliximab therapy could improve effectiveness and decrease the risk of adverse events during maintenance phase of treatment. However, despite the fact that several potential predictors were identified in patients with CD, there is still substantial need to confirm the results in the setting of the routine clinical practice.

The present study assessed the impact of infliximab trough levels and other factors on long-term clinical benefit of infliximab in a cohort of CD patients treated in our centre. Over a median follow-up of two years sustained clinical response to infliximab was observed in slightly more than half of the patients. Patients with infliximab levels above 3 μg/ml at the beginning of maintenance phase (week 14 or 22 of infliximab treatment) had about 66% lower likelihood to lose their clinical response until the end of follow-up as compared to individuals with subtherapeutic levels. In contrast, presence of ATIs and need for corticosteroids at infliximab start increased the risk of treatment failure. No other factors such as concomitant immunosuppression, age, disease duration, or naivety to previous biologic therapy were found to have an impact on long-term clinical outcome, although individuals with concomitant immunosuppressants at infliximab start had significantly higher infliximab trough levels at the beginning of maintenance phase than those without immunosuppression.

Table 2 Predictors of loss of sustained response to infliximab by 1 year after treatment start.

	OR (95%CI) univariate	P	OR (95%CI) multivariate including IFX TL	P	OR (95%CI) multivariate including ATI	P
IFX TLs (>3 μg/ml)	0.25 (0.09–0.69)*	0.008	0.31 (0.10–0.96)*	0.04	–	–
ATI (reference: negative)		0.02		–		0.08
Inconclusive	0.30 (0.09–0.95)*		–		0.40 (0.11–1.37)	
Positive	1.67 (0.44–6.33)		–		2.06 (0.42–10.08)	
Biological naivety	0.71 (0.21–2.34)	0.57	0.39 (0.07–2.07)	0.27	0.35 (0.06–1.93)	0.23
Concomitant thiopurines [a]	0.42 (0.15–1.17)	0.10	0.65 (0.21–2.06)	0.46	0.73 (0.22–2.38)	0.60
Concomitant steroids [a]	1.70 (0.63–4.59)	0.30	1.31 (0.43–3.98)	0.63	1.45 (0.47–4.54)	0.52
Prior bowel surgery	0.39 (0.10–1.48)	0.17	0.36 (0.06–2.02)	0.25	0.34 (0.06–1.95)	0.23
Indication to IFX therapy (perianal vs. luminal)	0.78 (0.22–2.69)	0.69	0.73 (0.19–2.79)	0.64	0.66 (0.17–2.60)	0.55
CRP at week 10 >5 mg/l	1.93 (0.55–6.81)	0.31	–	–	–	–
Age [b]	1.00 (0.96–1.05)	0.94	1.02 (0.97–1.08)	0.47	1.01 (0.96–1.07)	0.64
Disease duration (months)[b]	1.00 (0.99–1.00)	0.43	1.00 (0.99–1.01)	0.71	1.00 (0.99–1.01)	0.82

Univariate and multivariate logistic regression analysis;
OR, odds ratio, CI, confidence interval; IFX TLs, infliximab trough levels; ATI, anti-infliximab antibodies; CRP, C-reactive protein.
* statistically significant results; [a] at IFX start; [b] increase by 1.

Association between serum infliximab trough concentrations and clinical efficacy in CD patients has been studied by several investigators.[5,6,17,18] In a randomized, double-blind study comparing infliximab plus azathioprine versus infliximab or azathioprine monotherapy,[5] patients with the most effective regime (combo therapy) had significantly higher median trough levels of serum infliximab at week 30 as compared with infliximab monotherapy group. Similarly, in the COMMIT trial, patients with detectable trough levels of infliximab experienced better therapeutic results than subjects with levels below detectable cut-off.[17] In another study, Maser et al.[6] found that CD patients with detectable serum infliximab had significantly lower likelihood of treatment discontinuation before 1 year of therapy. Furthermore, in the same cohort, a strong relationship between detectable infliximab and clinical remission, CRP level, and endoscopic improvement has been demonstrated.[6] However, in that study serum drug concentrations were measured after a minimum of 6 scheduled maintenance infusions with median interval from baseline infusion of 88 weeks.[6] Finally Steenholdt et al.[18] have confirmed significantly lower infliximab levels in patients with loss of response as compared to those with maintained response.

Although patients with therapeutic infliximab levels seem to have better treatment outcome overall, the implication of drug level measurement in clinical practice for an individual patient is still not clear. A substantial proportion of patients maintain long-term remission despite undetectable or subtherapeutic infliximab levels, or lose their response having high serum levels of the drug.[6,18,19] An ongoing prospective trial adjusting infliximab dosing according to pharmacokinetic parameters should address this clinically important issue.[20]

Table 3 Predictors of loss of sustained response to infliximab.

	HR (95%CI) univariate	P	HR (95%CI) multivariate including IFX TL	P	HR (95%CI) multivariate including ATI	P
IFX TLs (>3 μg/ml)	0.31 (0.16–0.62)*	<0.001	0.34 (0.16–0.75)*	0.007	–	–
ATI (reference: negative)		0.001		–		<0.001
Inconclusive	0.38 (0.18–0.83)*		–		0.49 (0.21–1.14)	
Positive	1.74 (0.78–3.86)		–		4.34 (1.51–12.5)*	
Biological naivety	1.27 (0.52–3.07)	0.60	0.49 (0.13–1.76)	0.27	0.31 (0.09–1.13)	0.08
Concomitant thiopurines[a]	0.73 (0.38–1.41)	0.35	1.00 (0.49–2.07)	1.00	1.39 (0.63–3.08)	0.41
Concomitant steroids[a]	2.37 (1.15–4.91)*	0.02	1.72 (0.79–3.76)	0.17	2.49 (1.08–5.73)*	0.03
Prior bowel surgery	0.39 (0.15–1.00)	0.05	0.30 (0.08–1.08)	0.07	0.29 (0.08–1.05)	0.06
Indication to IFX therapy (perianal vs. luminal)	1.04 (0.48–2.28)	0.92	0.86 (0.38–1.97)	0.72	0.56 (0.23–1.36)	0.20
CRP at week 10 >5 mg/l	1.36 (0.59–3.17)	0.47	–	–	–	–
Age [b]	0.99 (0.96–1.02)	0.56	1.02 (0.98–1.05)	0.39	1.00 (0.97–1.04)	0.86
Disease duration (months)[b]	1.00 (0.99–1.00)	0.34	1.00 (0.99–1.01)	0.81	1.00 (0.99–1.01)	0.68

Univariate and multivariate Cox proportional hazard model;
HR, hazard ratio, CI, confidence interval; IFX TLs, infliximab trough levels; ATI, anti-infliximab antibodies; CRP, C-reactive protein.
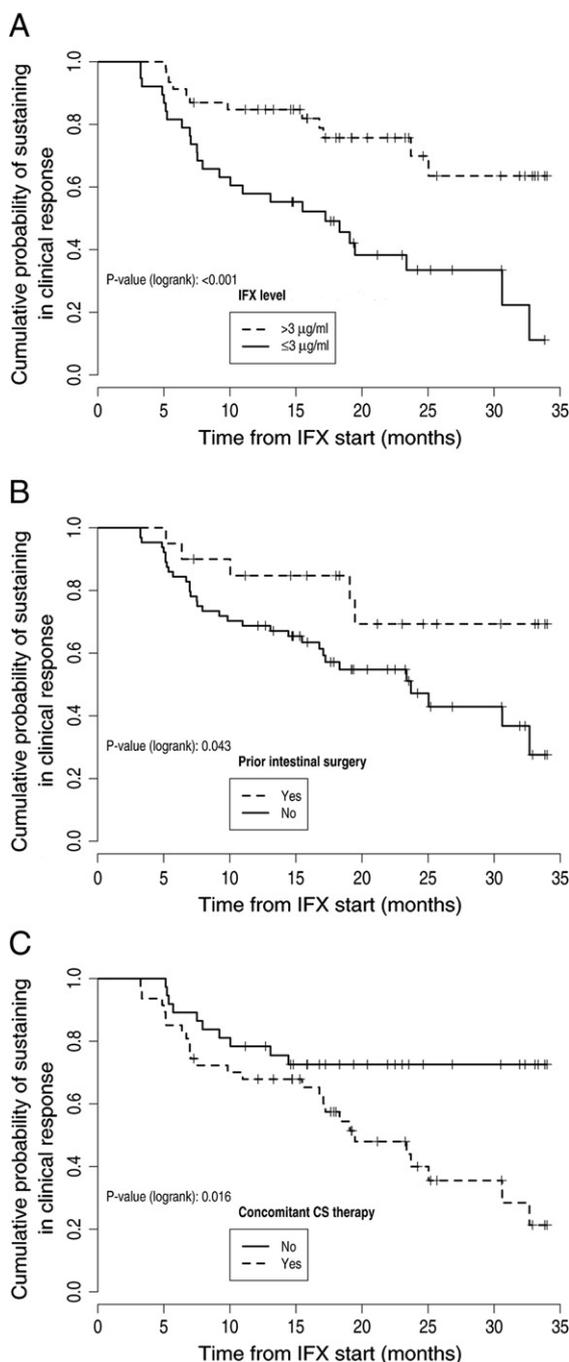* Statistically significant results; [a] at IFX start; [b] increase by 1.

Figure 2 Sustained clinical response to infliximab (IFX) stratified by IFX trough levels at the beginning of the maintenance therapy (A), previous intestinal surgery (B), and concomitant treatment with corticosteroids (CS) at IFX start (C).

Figure 3 Receiver operating characteristic (ROC) curve of infliximab (IFX) trough levels to predict the loss of response to IFX by 1 year.

Regarding the ATI, available data suggest that their presence might have negative impact on clinical outcome, although this effect is not absolute.[9] In a retrospective study from Mayo clinic, Affif et al.[21] found that the presence of ATI decreased the likelihood of restoring clinical effect by infliximab intensification in patients with secondary loss of response to infliximab. On the other hand, ATI positivity has not been found to affect the rate of clinical remission, endoscopic improvement, or CRP level in CD patients on
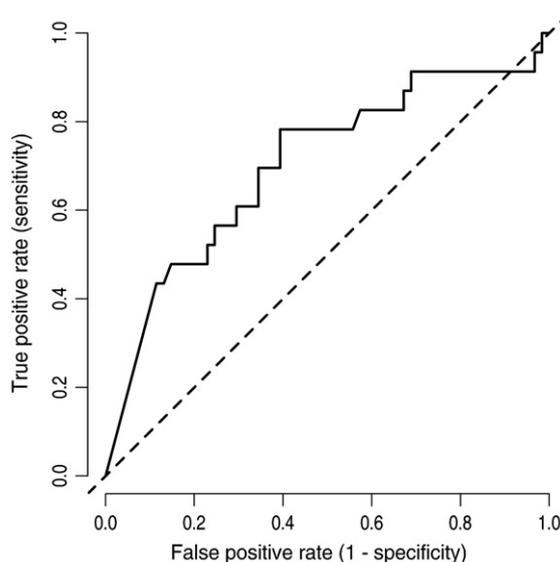
long-term infliximab therapy.[6] Although our data indicate the negative impact of ATI positivity on long-term clinical outcome, we believe that the interpretation of ATI status should be made with caution. In fact, there is also evidence that concentration of ATI may fluctuate and even disappearance of ATI has been observed after intensification of infliximab.[9]

So far, the measurement of infliximab trough levels together with ATI has been suggested useful in patients with secondary loss of response. Afif et al.[21] have shown that in patients with subtherapeutic concentrations and ATI negativity, infliximab dose escalation was superior to switch to another biologic compound. On the other hand, a recently performed retrospective study did not confirm usefulness of such assessment.[22] In a group of 76 IBD patients (72% of them with CD) losing response to infliximab, clinical improvement after intensification of infliximab was observed irrespective of infliximab serum concentrations.[22]

Using the ROC analysis, Steenholdt et al. identified an optimal cut-off value of infliximab at 0.5 μg/ml; subjects with infliximab levels below that point had an increased risk of loss of response with sensitivity of 86% and specificity of 85%.[18] In our study infliximab levels < 3 μg/ml discriminated the risk of loss of response with sensitivity of 70% and specificity of 62%.

In contrast to Maser's[6] and Steenholdt's studies,[18] trough levels in our cohort were measured at the very start of the maintenance phase and thus may be used as a predictor of future course of CD under long-term infliximab therapy. Similar to our study, the predictive value of post-induction infliximab trough levels has recently been assessed in a post-hoc analysis of ACCENT I trial.[20] The study demonstrated significant difference in week 14 infliximab trough levels between patients with and without sustained response (median level 4.0 μg/ml vs. 1.9 μg/ml, respectively, p=0.033) with trough levels of 3.5 μg/ml having the best sensitivity and specificity of 54% and 72%, respectively, to predict the long-term benefit to infliximab.[20] Lower sensitivity and specificity in our study as well as ACCENT I subanalysis as compared to Steenholdt's

study probably reflects the fact that the two former studies used trough levels obtained after the induction period, while in the later study infliximab trough levels obtained just prior to the last patient's infusion were analysed.[18,20]

There is an increasing evidence of beneficial effect of concomitant thiopurines on the efficacy of infliximab treatment. The most relevant evidence of this favourable synergistic effect has been provided by the prospective randomized SONIC trial.[5] Similarly, a retrospective study by Sokol et al.,[8] has demonstrated that immunosuppressive co-treatment to maintenance infliximab reduces IBD activity regardless of the immunosuppressive status at infliximab onset. Our study failed to show an impact of concomitant immunosuppressants on infliximab outcome as did several previous studies.[23,24] A potential explanation of our negative result might be the fact that, whereas individuals in SONIC trial[5] had relatively short disease duration (mean 2.3 years) and were naïve to immunosuppressive therapy, our patients were characterized by longer disease duration (median almost 6 years) and most of them have already failed thiopurines prior to start of infliximab. On the other hand, a positive pharmacokinetic effect was observed in our patients on combination therapy with significantly higher trough levels of infliximab in individuals on concomitant thiopurines.

In our study, sustained response was defined as an absence of treatment failure due to both loss of response to infliximab and drug intolerance. Including patients with side effects of therapy into the non-sustained response group might seem somewhat controversial, especially with regard to the pharmacokinetic variables assessed in our cohort. However, it is clinically meaningful that the need to discontinue therapy for adverse events is usually considered as treatment failure. Moreover, similar definition for treatment failure as in our study was also used in other studies,[12–14] including the study primarily focused on pharmacokinetics of anti TNF-α drugs.[14] Finally, infliximab trough levels were only one of the predictors evaluated in this study with the others being potentially associated with treatment failure as defined in our study.

Limitations of our study include retrospective nature of the study, although no prospective study so far has been designed to assess predictors of long-term effect of infliximab, and most data come either from retrospective studies, or post-hoc analyses of prospectively designed controlled trials. Moreover, some factors undoubtedly influencing disease course (i.e. smoking) have not been included in the analysis. Furthermore, patients treated with infliximab in our centre prior to era of pharmacokinetic assessment were also omitted. Finally, using the measurement of infliximab levels potentially elicits a technical problem, as assay methodology and sensitivity differ. Therefore, comparisons between results obtained by different assays have to be done with caution.

In conclusion, we have shown that CD patients with therapeutic trough levels of infliximab measured at the beginning of the maintenance phase have significantly higher chance to sustain their long-term clinical response to infliximab. On the other hand, the presence of ATIs and need for corticosteroids at infliximab initiation increased the risk of treatment failure. No other predictor of sustained response has been found in our study, although there was an indirect effect of concomitant thiopurines in terms of significantly higher trough levels of infliximab. The use of the post-induction trough level of infliximab might thus help to better decide on an optimal long-term therapy. Nevertheless, further prospective studies with interventions based on drug levels are needed to confirm usefulness of therapeutic drug monitoring in prediction of long-term efficacy of biologic therapy. A potential effect of dosing intervention based on the serum infliximab levels should also be evaluated.

Conflict of interest statement

Dr. Bortlik has received honoraria for lectures from MSD and Abbott Laboratories.

Dr. Lukas is a consultant for MSD and Abbott Laboratories.

Acknowledgement

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