Monitoring a Combination of Calprotectin and Infliximab Identifies Patients With Mucosal Healing of Crohn's Disease

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Q10 Q11 **BACKGROUND & AIMS:** **In the TAILORIX trial, no benefit could be shown by infliximab dose escalation based on pharmacokinetic (infliximab serum concentrations) and pharmacodynamic (biomarkers and symptoms) monitoring compared with dose escalation based on symptoms alone in patients with Crohn's disease (CD). We investigated whether integration of pharmacokinetic and pharmacodynamic monitoring can be used to evaluate responses to infliximab induction and maintenance therapy, based on findings from endoscopy.**

METHODS: **We performed a post hoc analysis of patients with CD included in a trial to test the effects of infliximab dose escalation, based on biomarkers and serum concentrations of infliximab, on symptoms (the TAILORIX trial; n = 122). We analyzed data from this study to determine whether concentrations of biomarkers and serum concentrations of infliximab were associated with endoscopic outcomes (n = 116). The primary end points were endoscopic response (CD endoscopic index of severity decrease ≥50% from baseline), endoscopic remission (CD endoscopic index of severity, <3), and absence of ulcers at weeks 12 and 54 of infliximab treatment.**

RESULTS: **Infliximab trough concentrations greater than 23.1 mg/L at week 2 and greater than 10.0 mg/L at week 6 were associated with endoscopic remission at week 12 (positive predictive values, 72% and 76%; negative predictive values, 65% and 59%, respectively). During maintenance therapy, we found evidence for an exposure–response relationship only after dose escalation; trough concentrations greater than 10.6 mg/L were associated with the absence of ulcers at week 54 (positive predictive value, 49%; negative predictive value, 92%). Low fecal concentrations of calprotectin during therapy were associated with endoscopic response and remission ($P < .05$). Dose escalations increased trough concentrations of infliximab; persistent increase in fecal concentration of calprotectin, despite dose escalation, was associated with a lack of endoscopic response and remission. A significantly higher proportion of patients with antibodies to infliximab, identified by a**

Abbreviations used in this paper: ATI, antibodies to infliximab; AUROC, area under the receiver operating characteristic curve; CD, Crohn's disease; CDAI, Crohn's disease activity index; CRP, C-reactive protein; fCal, fecal calprotectin; IQR, interquartile range; MH, mucosal healing; NPV, negative predictive value; PD, pharmacodynamic; PK, pharmacokinetic; PPV, positive predictive value; TAILORIX, _____; TC, trough concentration; TDM, therapeutic drug monitoring.

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drug-tolerant assay, dropped out of the study compared with patients without antibodies ($P < .0001$).

CONCLUSIONS: **In a post hoc analysis of data from a trial to test the effects of infliximab dose escalation on symptoms, we found that during maintenance therapy, the combination of fecal concentration of calprotectin and trough concentration of infliximab can guide dose adjustment and increase the chances for endoscopic response and remission. ClinicalTrialsRegister.eu EudraCT no: 2011-003038-14.**

Keywords: Endoscopic Healing; Therapeutic Drug Monitoring; Pharmacokinetics; Immunogenicity.

Mucosal healing (MH) is an important end point for clinical trials in Crohn's disease (CD). Recently, international guidelines also adopted this concept into clinical practice, based on published evidence that MH is associated with a reduction in hospitalizations and surgery.[1] Treatment with infliximab is effective for inducing and maintaining MH in patients with luminal CD.[2,3] In the pivotal SONIC trial, 38% of patients showed disappearance of ulcerations by week 26 on infliximab therapy.[4]

Several retrospective cohort studies have shown an association between infliximab serum concentrations and clinical and endoscopic outcomes.[5,6] Based on these observations, the concept of therapeutic drug monitoring (TDM) was introduced. TDM traditionally refers to dose adjustment based on drug serum concentrations and antidrug antibodies (pharmacokinetic [PK] monitoring).[7] Although recent recommendations have suggested an infliximab serum concentration at a trough of 5.0 mg/L to be "therapeutic" during maintenance therapy, evidence to support this recommendation was based mainly on observational data.[8] As such, TDM is not yet widely used across the globe. To date, no solid therapeutic thresholds have been established for MH.[9]

On top of PK monitoring, there is growing interest in pharmacodynamic (PD) monitoring. PD monitoring implies dose optimization guided by the effects of the drug on disease manifestations such as changes in biomarkers. One prospective trial evaluated adalimumab dose optimization based on PD monitoring.[10] In this trial, it was shown that MH rates were higher when dosing was based on symptoms and biomarker monitoring (C-reactive protein [CRP] and fecal calprotectin [fCal]) instead of monitoring symptoms alone.

In the TAILORIX trial, infliximab dose escalation was based on a combination of PK (infliximab serum concentrations) and PD (symptoms and biomarkers) monitoring and compared with dose escalation based on symptoms alone.[11] No benefit could be shown for dose escalation based on biomarkers and infliximab serum concentrations as compared with symptoms. In the current post hoc PK–PD analysis of TAILORIX, we examined the roles of PK and PD monitoring during infliximab induction and maintenance therapy for targeting endoscopic outcomes.

Methods

The TAILORIX Trial

TAILORIX was a multicenter, randomized, double-blind, controlled trial that was designed to determine the value of PK and PD monitoring during combined infliximab–immunomodulator maintenance therapy, with the goal to improve clinical and endoscopic remission rates in patients with CD.[11] Briefly, 122 biologically naive patients with active luminal CD (active ulceration at endoscopy, CD activity index [CDAI] >220, fCal >250 mg/kg, and/or CRP >5 mg/L) started standard infliximab induction therapy (5 mg/kg at weeks 0, 2, and 6) in combination with an immunomodulator. From week 14 onward, patients were treated following 1 of 3 monitoring algorithms to which the patients were assigned randomly. Two algorithms combined PK and PD monitoring (active arms; based on infliximab serum concentrations at trough in combination with CDAI, fCal, and/or CRP), although 1 algorithm used PD monitoring only (control arm; based on CDAI). Based on these algorithms, the infliximab dose was increased by 2.5 mg/kg (active arm 1) or 5 mg/kg (active arm 2 and control arm).

CRP, fCal, infliximab, and antibodies to infliximab (ATI) were quantified at all patient visits (weeks 0, 2, 6, 12, 14, and every 4 weeks thereafter until week 54).[12] Albumin, hemoglobin, hematocrit, lymphocyte count, platelet count, mean platelet volume, and white blood cell count were assessed at the standard infliximab infusion time points only. Ileocolonoscopies were performed at weeks 0, 12, and 54, videorecorded, and scored by endoscopists who were blinded to patient identification and clinical data. The CD endoscopic index of severity and the absence and/or presence of ulceration were assessed. Endoscopic outcomes were endoscopic response (CD endoscopic index of severity decrease of at least 50% from baseline), endoscopic remission (CD endoscopic index of severity <3), and absence of ulceration at weeks 12 and 54.

Post Hoc Pharmacokinetic–Pharmacodynamic Analysis of TAILORIX

We evaluated the role of PK and PD monitoring for targeting endoscopic outcomes after infliximab induction

and maintenance therapy. First, we evaluated the predictive value of infliximab and biomarker concentrations for endoscopic outcomes at weeks 12 and 54. Then, we investigated whether biomarkers and other factors influenced the infliximab PK. Finally, we examined the effects of dose escalations.

These post hoc analyses were not prespecified per TAILORIX protocol. Only patients with informative PK data (at least 1 sample with detectable infliximab) were included. Available case analysis was implemented to address missing data.

Statistical Analyses

Descriptive statistics were stated as percentages for discrete variables and as means ± SD or median (interquartile range [IQR]) for continuous variables. Concentrations that were lower than the limit of quantification were replaced by the limit of quantification for statistical analyses. The Fisher exact test or the Pearson chi-square test was used for the analysis of discrete variables. A paired 2-tailed Student *t* test or the Wilcoxon signed-rank test was used for analysis of paired measurements. Unpaired data were analyzed with the unpaired Student *t* test or the Wilcoxon rank-sum test. Diagnostic performance was assessed with receiver operating characteristic analysis. Therapeutic threshold values were selected using the Youden J statistic. Binary logistic regression was conducted to identify independent predictors of the endoscopic outcomes of infliximab therapy. Collinearity between signifcant predictors was defned as a variance inflation factor greater than 5. A 2-sided *P* value of .050 or less denoted statistical signifcance. Statistical analyses were performed using R (version 3.4.3; R Core Team, Vienna, Austria).

All authors had access to the study data and reviewed and approved the final manuscript.

Results

Study Population

Among the 122 patients enrolled in the TAILORIX trial, 6 did not have informative PK data. Therefore, the current post hoc analysis included 116 of 122 (95%) patients (Table 1).

Induction Therapy

Pharmacokinetic monitoring. Endoscopic response, endoscopic remission, and absence of ulceration were achieved at week 12 in 82 of 106 (77%), 54 of 106 (51%), and 38 of 102 (37%) patients with available endoscopic data. Infliximab trough concentrations (TC) at weeks 2, 6, and 12 were significantly higher in patients achieving these endoscopic outcomes at week 12, although there was considerable variability (Figure 1). A TC greater than 23.1 mg/L at week 2 predicted endoscopic remission at week 12 (positive predictive value [PPV], 72%; negative predictive value [NPV], 65%; median area under the receiver operating characteristic curve [AUROC], 0.67; 95% CI, 0.57–0.78) (Figure 2*A*, Supplementary Table 1). A TC greater than 10.0 mg/L at week 6 predicted endoscopic remission at week 12 (PPV, 76%; NPV, 59%; AUROC, 0.64; 95% CI, 0.54–0.75) (Figure 2*B*, Supplementary Table 1). Furthermore, the proportion of patients achieving the endoscopic outcomes increased with higher infliximab TC quartiles (Supplementary Figure 1).

Pharmacodynamic monitoring. At baseline, CRP was the only biomarker correlating with endoscopic remission at week 12, with a median baseline CRP of 17.0 mg/L (IQR, 7.0–32.0 mg/L) in patients who achieved endoscopic remission, and 26.0 mg/L (IQR, 11.0–44.0 mg/L) in those without endoscopic remission ($P = .025$). Levels of albumin, fCal, hemoglobin, hematocrit, white blood cell count, lymphocyte count, platelet count, and mean platelet volume did not correlate with endoscopic outcomes. From the multivariable binary logistic regression model, a lower CRP was the only baseline predictor for endoscopic remission (log odds, -0.028 ± 0.013; $P = .029$) (Supplementary Table 2).

After the first infliximab dose, CRP decreased rapidly and only fCal, platelet count, and lymphocyte count were able to univariately predict which patients achieved the endoscopic end points (Supplementary Figure 2). From the multivariable models, higher fCal and lower platelet count were retained as predictors of failure to achieve the endoscopic outcomes (Supplementary Table 2).

What You Need to Know

Background

We investigated whether integration of pharmacokinetic and pharmacodynamic monitoring can be used to evaluate responses to infliximab induction and maintenance therapy, based on findings from endoscopy.

Findings

In a post hoc analysis of data from a trial to test the effects of infliximab dose escalation on symptoms, we found that during maintenance therapy, the combination of fecal concentration of calprotectin and trough concentration of infliximab can guide dose adjustment and increase the chances for endoscopic response and remission.

Implications for patient care

Fecal concentrations of calprotectin and trough concentrations of infliximab should be monitored during maintenance therapy of patients with Crohn's disease to determine chances of endoscopic response.

Table 1. Patient Characteristics

Parameter	Value
Patients, n	116
Baseline demographics	
Sex, female, n (%)	68 (59)
Age, median, *y* (IQR)	30 (22–45)
Body weight, median, *kg* (IQR)	65 (57–75)
Disease duration, median, *mo* (IQR)	7 (1–78)
Serology concentrations at baseline	
C-reactive protein, median, *mg/L* (IQR)	20.0 (9.0–36.5)
Fecal calprotectin, median, *mg/kg* (IQR)	1462.5 (725.8–1800.0)
Albumin, median, *g/L* (IQR)	39.0 (34.0–42.0)
Hemoglobin, median, *g/dL* (IQR)	12.7 (11.8–13.8)
Hematocrit, median, % (IQR)	39 (36–41)
Mean platelet volume, median, *fL* (IQR)	9.4 (8.8–10.0)
Platelet count, *median/mm*^{3} (IQR)	368,000 (287,500–455,500)
Lymphocyte count, *median/mm*^{3} (IQR)	1700 (1200–2200)
White blood cell count, *median/mm*^{3} (IQR)	8480 (7100–10,645)
Endoscopy at baseline	
Crohn's disease endoscopic index of severity, median (IQR)	7 (10–15)
Disease location, ileal:colonic:ileocolonic, n (%)	26:19:71 (22:16:61)
Disease behavior, nonstricturing nonpenetrating:stricturing:penetrating, n (%)	85:17:14 (73:15:12)
Infliximab dosages and ATIs during the study	
Patients with ATIs, n (%)	21 (18)
Samples available, n	1329
Samples with undetectable infliximab, n (%)	32 (2.4)
Samples with ATIs, n (%)	84 (6.3)
Samples with undetectable infliximab and ATIs, n (%)	26 (2.0)

ATI, antibody to infliximab; IQR, interquartile range; n, number of patients.

Maintenance Therapy

Pharmacokinetic monitoring. Endoscopic response, endoscopic remission, and absence of ulceration were observed in 74 of 83 (89%), 63 of 83 (76%), and 59 of 83 (71%) patients with endoscopic data available at week 54. An infliximab TC greater than 8.5 mg/L at week 46 and greater than 7.3 mg/L at week 54 were associated with an absence of ulceration at week 54 (Supplementary Table 3). At all other time points, infliximab concentrations during maintenance therapy were not significantly different between patients achieving the endoscopic outcomes or not ($P > .05$, data not shown). However, when pooling all infliximab TCs from week 14 through week 54, these were significantly higher in patients achieving absence of ulceration ($P < .0001$), with a threshold of 8.9 mg/L established.

The higher infliximab TCs in patients with absence of ulceration were driven by the subgroup of patients who earlier were dose-escalated to 10 mg/kg ($P < .0001$) (Supplementary Table 3). An infliximab TC greater than 10.6 mg/L on dose escalation was associated with absence of ulceration at week 54 (PPV, 49%; NPV, 92%; AUROC, 0.71; 95% CI, 0.62–0.79) (Figure 2*C*). Although the median TC at weeks 46 and 54 were similar for patients on 5 and 10 mg/kg infliximab maintenance doses ($P > .05$), the variability in the observed TC was higher in the latter subgroup (at week 46: IQR, 4.4–8.9 and 3.5–9.8 on 5 and 10 mg/kg doses, respectively) (Supplementary Figure 3). Furthermore, the proportion of patients achieving absence of ulceration were similar on 5-mg/kg infliximab doses (30 of 37; 81%) and 10-mg/kg infliximab doses (23 of 36; 64%) ($P = .121$).

Pharmacodynamic monitoring. From week 12 to week 54, fCal was significantly lower in patients achieving the endoscopic outcomes compared with patients who did not (Supplementary Figure 2, Supplementary Table 4). At multiple time points, albumin and CRP also predicted the endoscopic outcomes both in the univariable and multivariable analyses. The lag time between the latest calprotectin increase (>250 mg/kg) and the week 54 endoscopic assessment of ulceration was 50 days (IQR, 7–105 d) (~week 46 infusion) in patients with ulcers and 111 days (IQR, 53–195 d) (~week 38 infusion) in patients without ulcers ($P = .009$).

Effect of Dose Escalations

A total of 87 dose escalations were performed in 63 patients. Infliximab TCs increased on dose escalation (from 3.2 mg/L [IQR, 1.2–4.9 mg/L] to 6.0 mg/L [IQR, 3.6–8.9 mg/L] 8 weeks later; $P < .0001$) (Supplementary Figure 4*A*). Eight weeks after dose escalation, infliximab TCs were similar in patients who achieved the endoscopic outcomes and those who did not (also when only considering the subgroup of patients with infliximab TCs

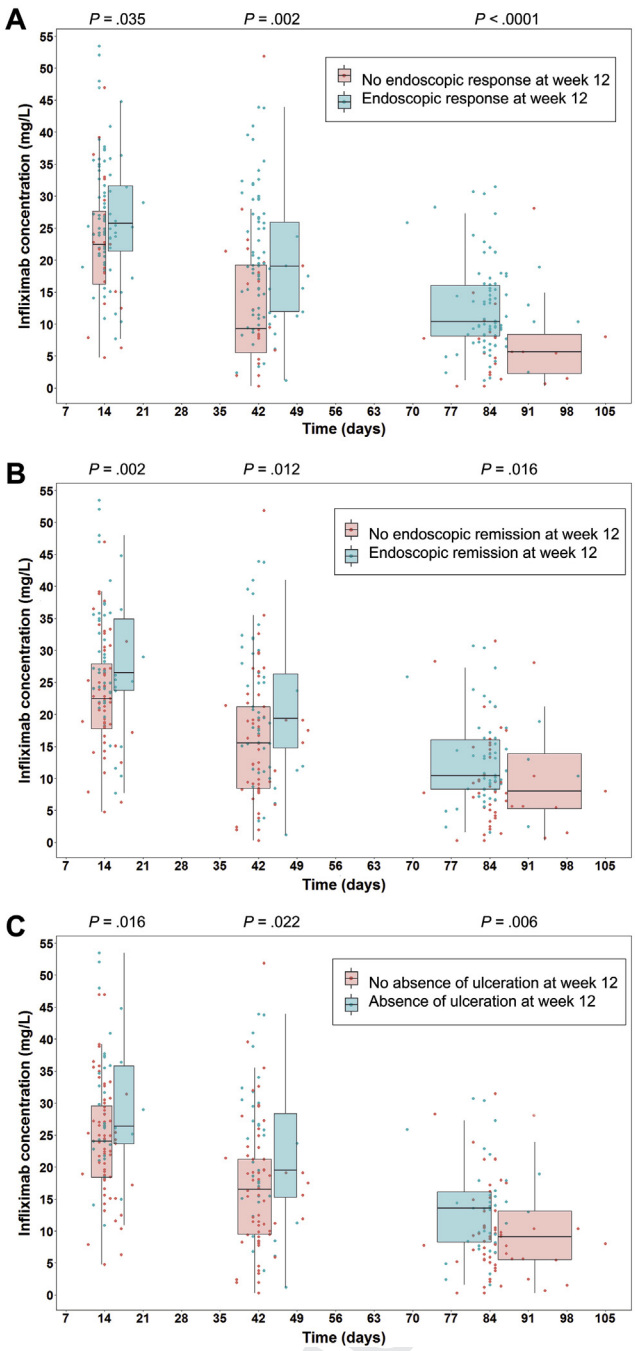

Figure 1. The relationship between infliximab trough concentrations during induction therapy and (*A*) endoscopic response, (*B*) endoscopic remission, and (*C*) absence of ulceration at week 12.

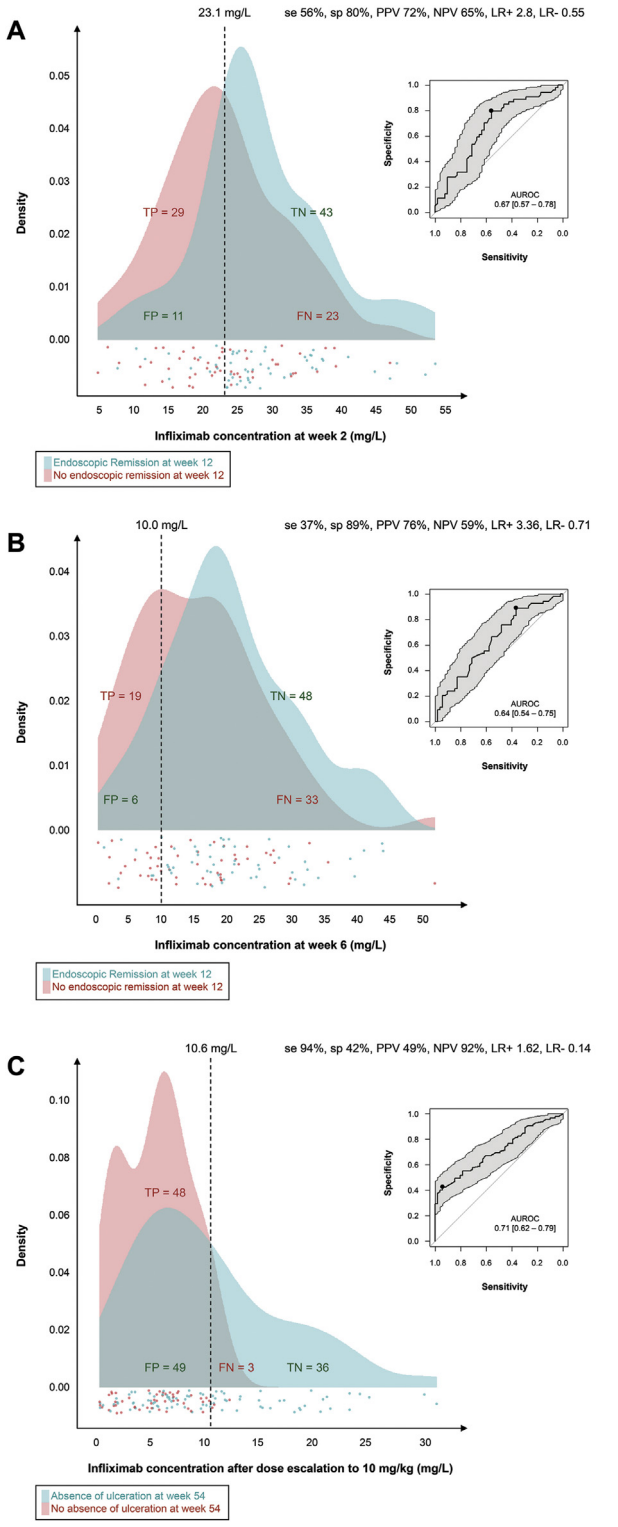

Figure 2. The distributions of infliximab serum trough concentrations at (*A*) week 2, (*B*) week 6, and (*C*) after dose escalation to 10 mg/kg in patients achieving mucosal healing (green) and not (red). (*Insert*) Receiver operator characteristic curve. The *grey shaded area* represents the 95% CI of the specificity (2000 bootstrap replicates). AUROC, area under the receiver operating characteristic curve, FN, false-negative patients; FP, false-positive patients; LR-, negative likelihood ratio; LR+, positive likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; se, sensitivity; sp, specificity; TN, true-negative patients; TP, true-positive patients.

<3.0 mg/L before dose escalation). Nevertheless, as time evolved, a separation in infliximab TC became clear between patients with and without ulceration at week 54 (Figure 3*A*).

After dose escalation, we observed a significant decrease in fCal, but not in CRP level ($P = .049$ and $P = .193$, respectively) (Supplementary Figure 4*B* and *C*). fCal concentrations measured 8 weeks after dose escalation were significantly lower in patients who achieved endoscopic response, endoscopic remission, and absence

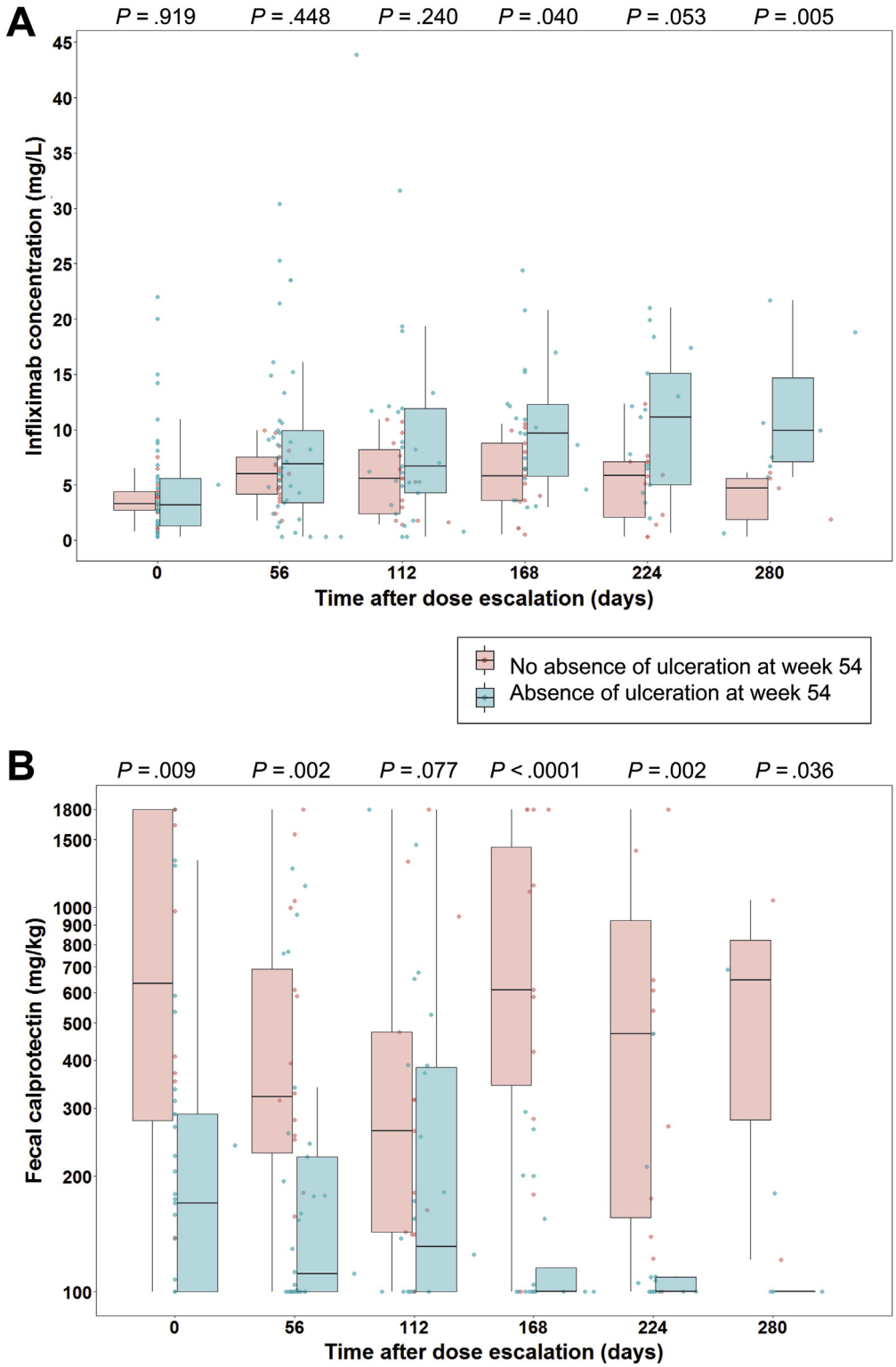

Figure 3. The relationship between (*A*) infliximab trough concentrations and (*B*) fecal calprotectin at dose escalation and absence of ulceration at week 54.

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of ulceration at week 54 ($P = .010$, $P = .005$, and $P = .003$, respectively) (Figure 3*B* and Supplementary Figure 5). Serum CRP concentrations 8 weeks after dose escalation were significantly lower in patients achieving absence of ulceration (5.5 mg/L [IQR, 2.0–8.8 mg/L] vs 1.0 mg/L [IQR, 1.0–3.8 mg/L] for patients achieving absence of ulceration or not, respectively; $P = .035$), but did not differ for the other endoscopic outcomes. The observed differences in fCal and CRP concentrations on dose escalation in terms of outcome attainment also were observed before dose escalation (data not shown).

In the subgroup of patients with increased fCal concentrations before dose escalation (>250 mg/kg), a

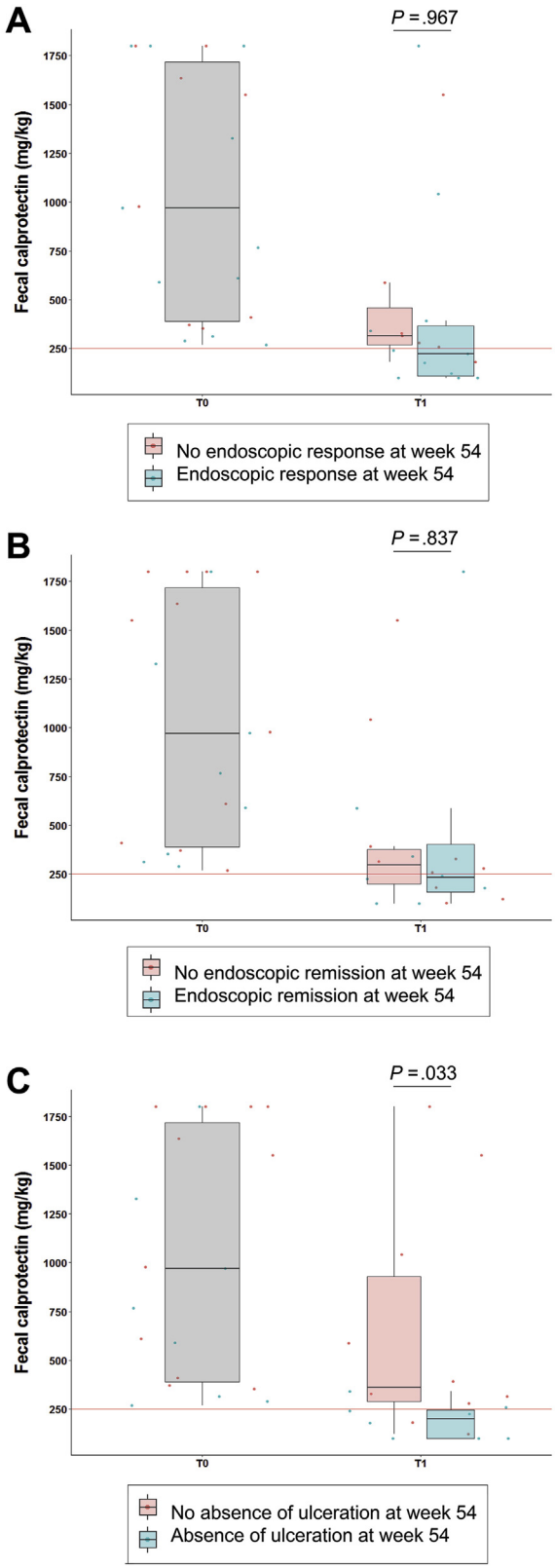

Figure 4. Fecal calprotectin concentrations at dose escalation between patients achieving (*A*) endoscopic response, (*B*) endoscopic remission, and (*C*) absence of ulceration at week 54 yes and no. The *red line* at 250 mg/kg represents the normal limit applied in the TAILORIX algorithm.

significant decrease was observed right at dose escalation, resulting in fCal concentrations after dose escalation that were significantly lower in patients without ulcers compared with patients with ulcers ($P = .033$) (Figure 4). In the subgroup of patients with increased CRP concentrations before dose escalation (>5.0 mg/L), a significant decrease was observed only in the patients who attained the endoscopic outcomes, but the obtained CRP concentration after dose escalation was not significantly different between patients attaining the outcomes or not ($P > .05$).

Immunogenicity

By using a drug-tolerant assay, ATIs were detected in 21 of 116 (18%) patients (Table 1, Supplementary Results).

Discussion

In this post hoc analysis of TAILORIX, we identified a clear relationship between infliximab TCs during induction therapy and endoscopic outcomes at week 12. We propose an infliximab TC threshold of 23.1 mg/L at week 2 and of 10.0 mg/L at week 6 based on the PPV of approximately 70%, indicating that subtherapeutic concentrations strongly compromise MH, thereby supporting a potential role for early dose optimization toward these thresholds. The NPV indicates the approximately 60% chance of achieving MH for the patients above the thresholds as compared with the 51% endoscopic remission rate in the overall population. Our findings are consistent with the study by Papamichael et al,[13] who proposed infliximab TC thresholds of 28.3 mg/L and 15.0 mg/L at weeks 2 and 6, respectively, for patients with ulcerative colitis to attain MH with infliximab induction therapy. Other studies have identified infliximab TC thresholds at week 2 (6.8 mg/L,[14] 16.9 mg/L,[15] 20.4 mg/L,[15] and 21.3 mg/L[16]) and week 6 (3.5 mg/L[14]) that relate to clinical efficacy assessed at week 14. Based on this comparison with literature data, we conclude that higher infliximab TCs may need to be targeted for achieving MH as compared with clinical outcomes. Nevertheless, prospective studies are warranted to confirm the causality in the exposure–response relationship. Although infliximab exposure can alter the disease activity, variations in disease activity can be responsible for fluctuations in infliximab exposure as well.

The clear exposure–response relationship observed during induction therapy was less convincing during maintenance therapy. However, in the subgroup of patients who underwent dose escalation to 10 mg/kg, the exposure–response relationship reappeared toward

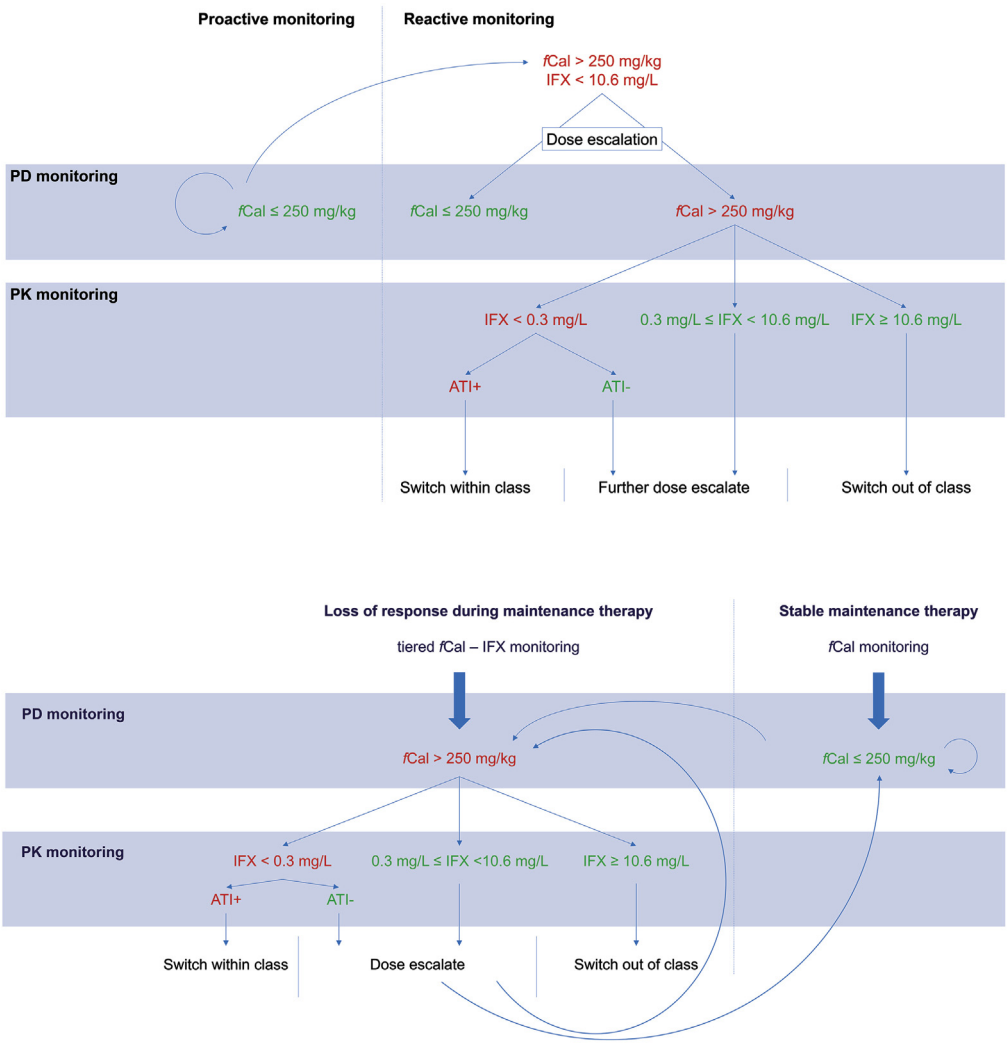

Figure 5. Algorithm implementing a tiered approach for pharmacodynamic (PD) and pharmacokinetic (PK) monitoring during infliximab (IFX) maintenance therapy. ATI, antibodies to infliximab; fCal, fecal calprotectin.

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week 46. We derived an infliximab TC threshold on dose escalation of 10.6 mg/L for predicting absence of ulceration, which is higher than the 3.0 mg/L,[17] 4.0 mg/L,[18] and 6.0 mg/L[19] thresholds previously suggested for achieving MH in patients with CD. As compared with the 5.0 mg/L threshold suggested by Vande Casteele et al[8] for symptom control, we conclude that higher infliximab TCs may need to be targeted for achieving MH on 1-year maintenance therapy.

Before dose escalation, the median infliximab TC was 3.2 mg/L. Eight weeks later, the median infliximab TC was 6.0 mg/L. At weeks 46 and 54, the median infliximab TC was 6.1 mg/L, with no significant difference between patients who remained on 5-mg/kg infliximab vs those who previously were dose-escalated to 10 mg/kg, showing that overall, the TAILORIX dose escalation algorithm was successful for restoring the infliximab TC. However, the variability in infliximab TC was larger in patients who were dose-escalated, showing a clear separation between endoscopic responders and nonresponders, which eventually allowed the identification of an exposure–response relationship toward the end of the maintenance therapy. This observation reinforces that perhaps the lower disease activity in patients with MH is responsible for the lower infliximab clearance and thus higher trough concentrations.

Within the subgroup of patients undergoing dose escalation, the exposure–response relationship was not observed immediately after dose escalation, but only after 3 infusions at the increased dose. This may be explained by the longer time required to reach steady state in patients with a longer infliximab elimination half-life (lower clearance). Because the exposure–response relationship appears only as time evolves, this might explain why it was observed only toward the end of the study. Therefore, we conclude that infliximab TCs right upon dose escalation are not informative for predicting MH.

By using the prospective TAILORIX cohort, we validated the use of fCal as a reliable biomarker predicting endoscopic improvement.[20] Already from week 2 onward, fCal concentrations were predictive for MH and this association persisted throughout the entire infliximab treatment. Therefore, we recommend monitoring of fCal during infliximab therapy. Although infliximab TC right at dose escalation had no predictive

value for MH, fCal allowed a rapid distinction between patients who were likely to achieve absence of ulceration and those who were not. Therefore, we recommend monitoring of fCal at dose escalation. Nevertheless, when fCal does not normalize, the infliximab TC provides information on the mechanism of failure (PK- vs PD-driven failure) and thus can guide clinical decision making. Therefore, we recommend a tiered approach for monitoring infliximab TC (PK monitoring) and fCal (PD monitoring) during dose escalation (Figure 5).

Our results support a role for monitoring fCal and TC during infliximab maintenance therapy. Nevertheless, TAILORIX did not show improved outcomes when infliximab doses were escalated based on infliximab TCs and biomarkers in addition to symptoms. Although TAILORIX was a pilot study, the primary outcome was achieved in numerically even more patients in the control group. However, many patients in the control group were dose-escalated based on symptoms (irrespective of fCal and CRP), and response rates were relatively high, thereby reducing the window of opportunity for additional TDM. This might be owing to a performance bias because patients and/or physicians could prompt dose escalations by over-reporting symptoms, although CDAI also is known to incur considerable variability in its scoring.[21] Furthermore, as we showed in this post hoc study, the target of 3.0 mg/L used in TAILORIX was probably too low for achieving the primary end point that included absence of ulceration. Besides a well-chosen control group, a more appropriate target concentration, and possibly the opportunity to allow dose de-escalations, future TDM studies might benefit from 2 recent evolutions in the field of TDM. These evolutions focus mainly on the application of TDM at the point of care, using rapid assays and model-based computer-assisted dosing.[22,23] In TAILORIX, dose escalations based on biomarkers and CDAI were performed at the point of care (same day as measured), whereas dose escalations based on infliximab concentrations were not (8 weeks later), thereby giving unequal chances to PK and PD monitoring.

This TAILORIX post hoc analysis had some limitations. The analyses were not powered to identify the predictive value of PK and PD monitoring for targeting endoscopic outcomes. Although the primary end point of TAILORIX was corticosteroid-free remission (CDAI, <150) at all visits between weeks 22 and 54 with the absence of ulcers at week 54 and no surgery for bowel resection or abscess, we assessed endoscopic outcomes, knowing that endoscopic outcomes are associated with improved clinical outcomes and a reduction of hospitalizations and surgery.[1] In addition, the assessment of composite end points may impact the ability to identify relationships when there is heterogeneity between the different outcome components. Therefore, further analysis is needed to investigate associations with clinical outcomes and composite outcomes. In addition, the available case analysis may have caused a selection bias and our findings may not be applicable for other patient populations (eg, more longstanding CD), patients on infliximab monotherapy, or patients with prior biological treatment.

To conclude, the results of this TAILORIX post hoc analysis support a role for infliximab TC monitoring during induction therapy. During maintenance therapy, the identification of an exposure–response relationship was observed only upon dose escalation. If a patient is dose-escalated based on increased fCal, the infliximab TC increases, but it is only a normalization of fCal that predicts absence of ulceration. Only after a while does infliximab TC in patients with a persistently increased fCal (and thus a poor prognosis) tend to be lower than infliximab TCs in patients with a normalized fCal (and thus a good prognosis). Nevertheless, to rule out increased infliximab clearance (eg, resulting from ATIs) and thus lower exposure, we recommend combining PD monitoring (based on fCal) with PK monitoring (based on infliximab TC, and, if necessary, ATI) for reactively optimizing infliximab maintenance therapy in patients with CD (Figure 5). Future prospective trials are needed to evaluate this proposed TDM algorithm in maintenance therapy.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2019.05.029.

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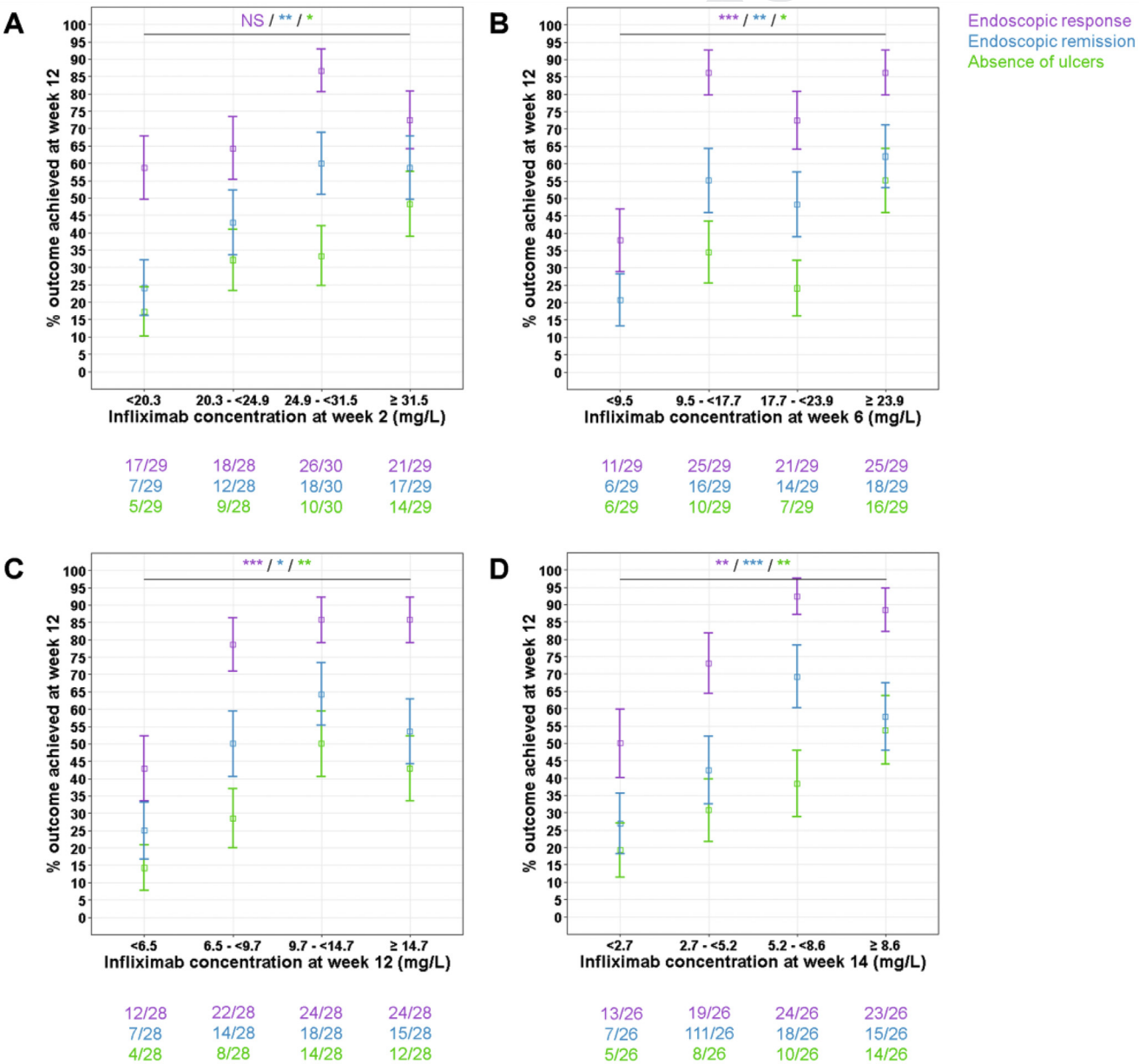
Supplementary Results

Immunogenicity

Three patterns of ATI detection were observed: persistent, transient, and on-off switch (Supplementary Figure 6). ATIs were detected persistently in 9 of 21 patients, despite dose escalation. In 6 of 21 patients, ATIs were detected following an on-off pattern, masked at midinfusion samples and after dose escalation. In the remaining 6 of 21 patients, ATIs were transient, as a result of or despite dose escalation.

Fifteen of 21 (71%) patients with ATIs dropped out before week 54, mainly because of lack of improvement (n = 7) and adverse events (n = 3). Hence, the drop-out rate in ATI+ patients (15 of 21) was significantly higher compared with patients with no confirmed ATI positivity (20 of 101 in the full TAILORIX data set) ($P < .0001$). Week 54 endoscopies were performed in 8 of 21 patients with ATIs (of which 3 were dropouts). All 8 patients achieved endoscopic remission, 7 achieved endoscopic response, and 6 had no ulcers at week 54 (Supplementary Table 5).



Supplementary Figure 1. Proportions of patients with moderate-to-severe Crohn's disease achieving endoscopic outcomes at week 12 by infliximab concentration quartiles at weeks (*A*) 2, (*B*) 6, (*C*) 12, and (*D*) 14. The mean proportion of target attainment ± SD, Cochran–Armitage test was used for trend. *$P < .05$, **$P < .01$, ***$P < .001$.

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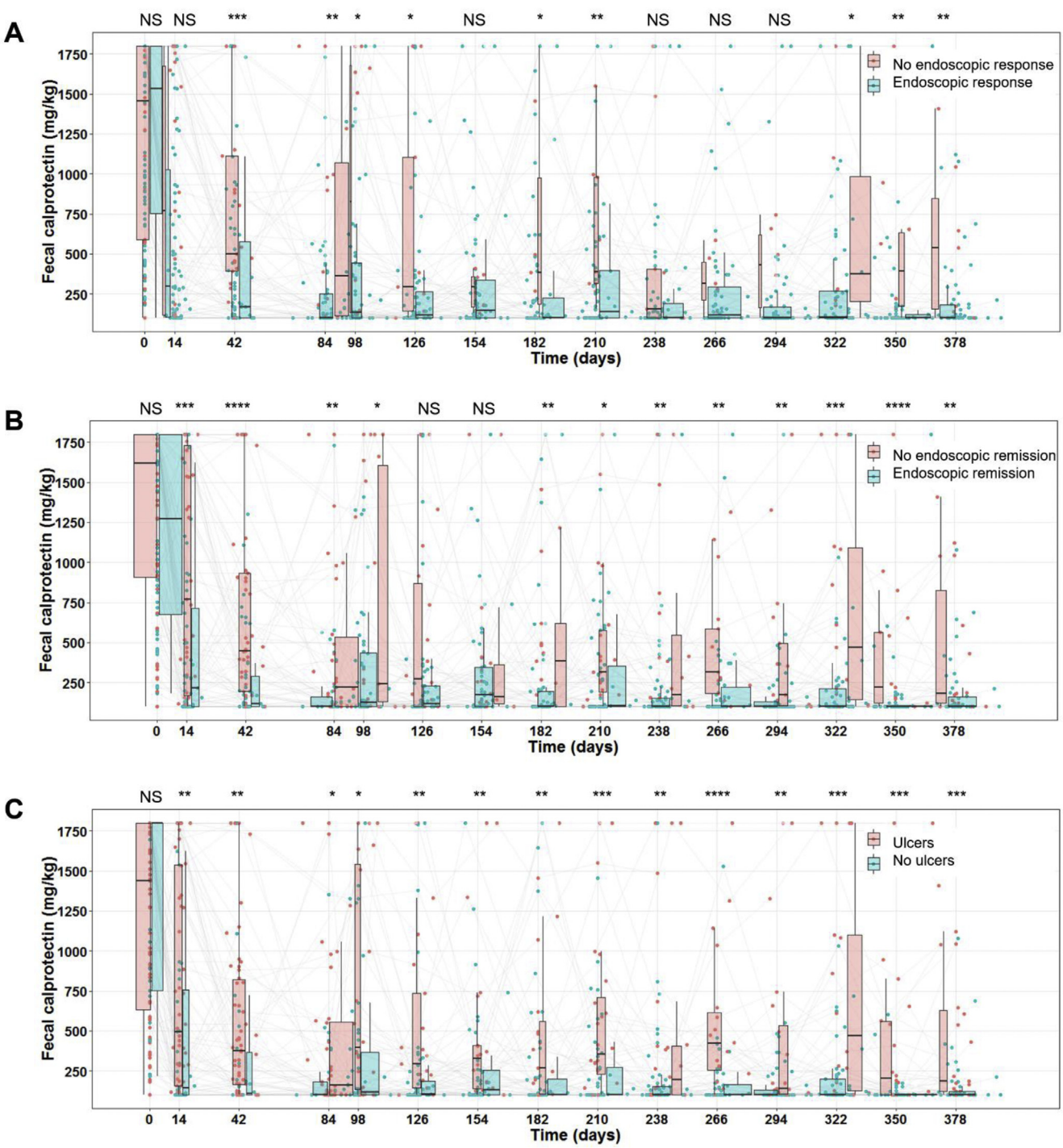
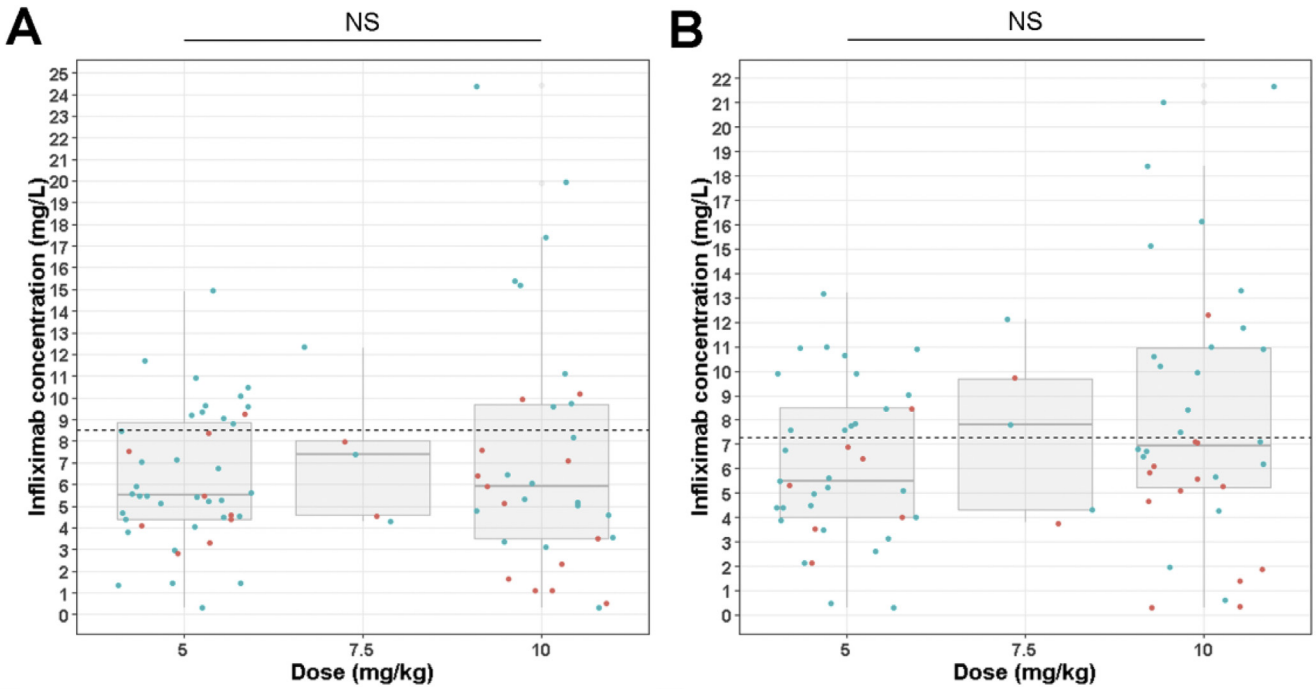
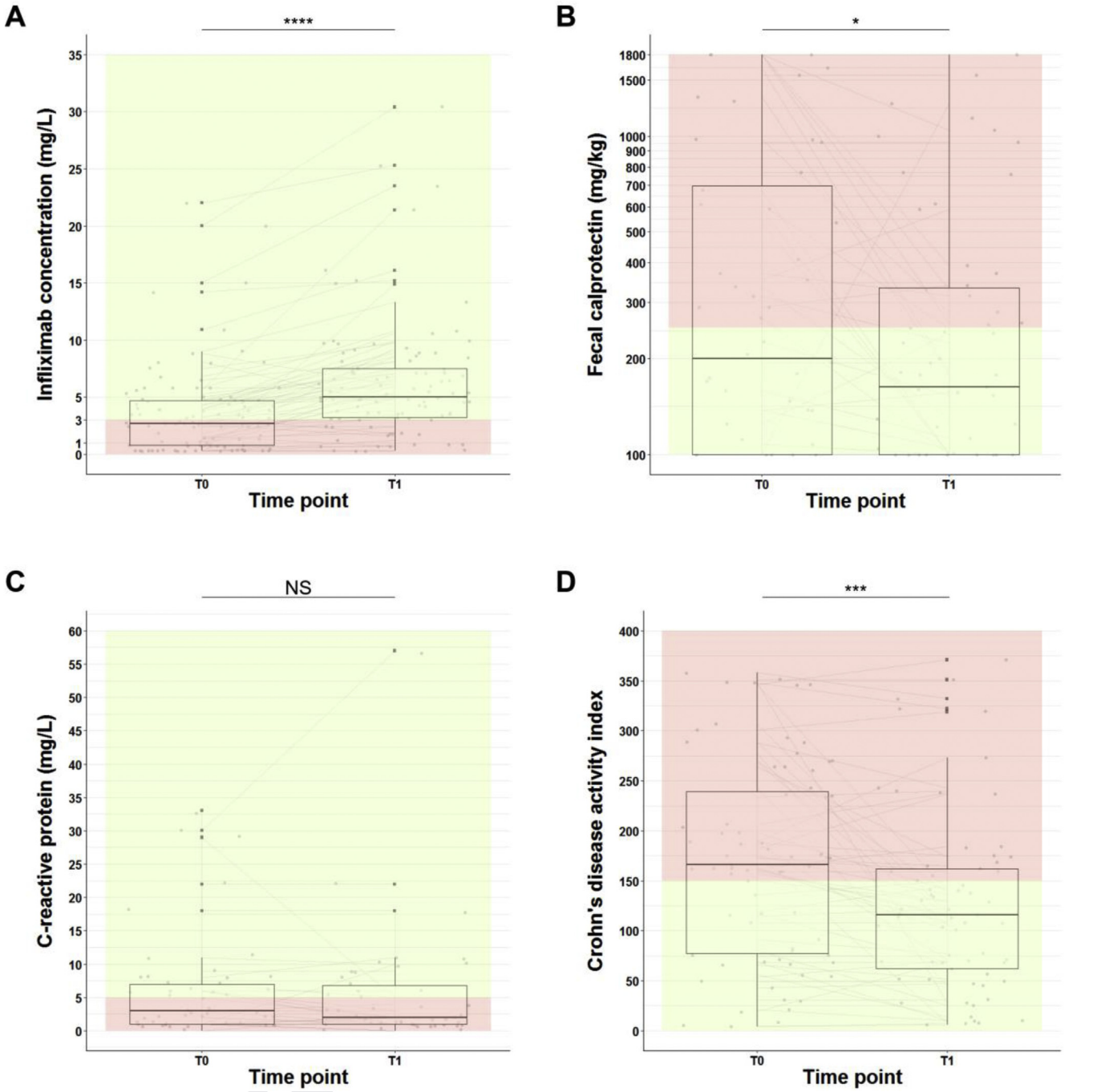


Supplementary Figure 2. The relationship between fecal calprotectin and (*A*) endoscopic response, (*B*) endoscopic remission, and (*C*) absence of ulceration at weeks 12 and 54 during infliximab induction and maintenance therapy, respectively, in patients with Crohn's disease. Tukey box plots, Wilcoxon rank-sum test. *$P < .05$, **$P < .01$, ***$P < .001$, ****$P < .0001$. Q25

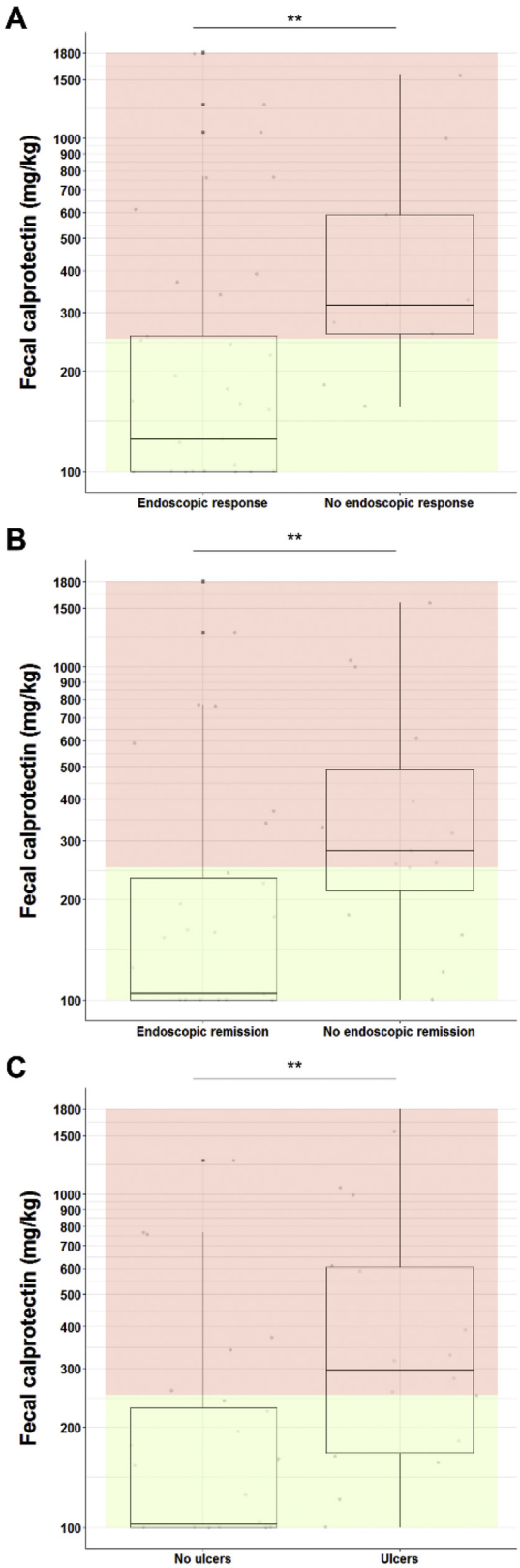


Supplementary Figure 3. Infliximab trough concentrations at (*A*) week 46 and (*B*) week 54 for patients that were on 5, 7.5, and 10 mg/kg infliximab 8 weeks earlier, achieving absence of ulceration at week 54 (in green) or not (in red). *Dashed lines* indicate the thresholds established using receiver operating characteristic analysis. Tukey box plots, Wilcoxon rank-sum test.

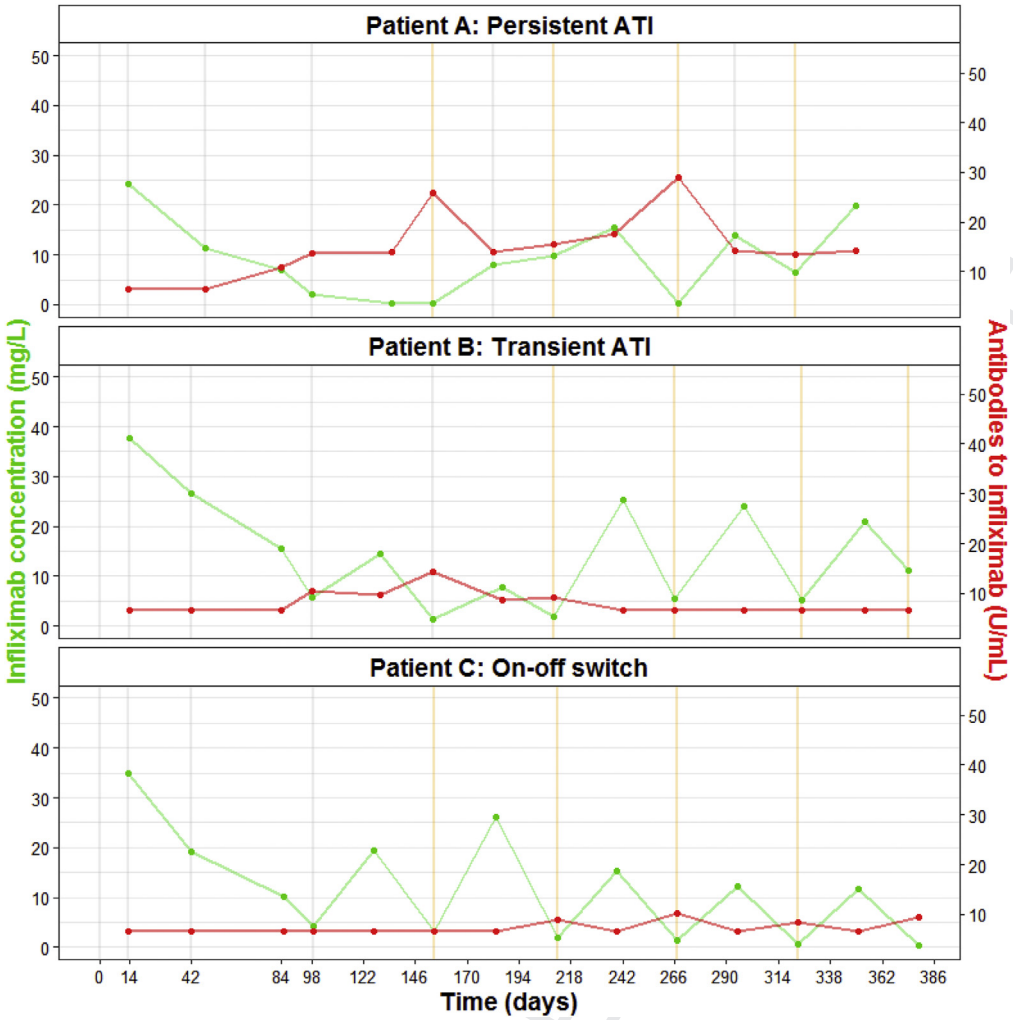


Supplementary Figure 4. Tukey box plots representing the change of (*A*) infliximab trough concentrations, (*B*) fecal calprotectin concentrations, (*C*) C-reactive protein in serum, and (*D*) the Crohn's disease activity index from before dose escalation (T0) to 8 weeks later after dose escalation (T1). *Green shaded areas* and *red shaded areas* indicate normal and abnormal values, respectively. A matched-pairs Wilcoxon rank-sum test was used. *$P < .05$, ***$P < .001$, ****$P < .0001$. Q26

web 4C/FPO



Supplementary Figure 5. Tukey box plots representing the difference of fecal calprotectin concentrations 8 weeks after dose escalation between patients achieving (*A*) endoscopic response, (*B*) endoscopic remission, and (*C*) absence of ulceration at week 54 yes and no. *Green shaded areas* and *red shaded areas* indicate normal and abnormal values, respectively. The Wilcoxon rank-sum test was used. $^{**}P < .01$.



Supplementary Figure 6. Representative patients with detection patterns of antibodies to infliximab (ATI): (*A*) persistent, (*B*) transient, and (*C*) on-off switch. Concentrations of infliximab are shown in green and concentrations of ATI are shown in red. *Transparent vertical lines* represent infliximab infusions of 5 mg/kg (grey) and 10 mg/kg (yellow).

Supplementary Table 1. The Exposure–Response Relationship During Infliximab Induction Therapy

Time point	Endoscopic outcome	Trough concentration, *mg/L*, means [95% CI]	*P* value	Empiric AUROC, means (95% CI)	Threshold Youden (se, sp, PPV, NPV, LR+, LR-)
Week 2	Endoscopic response[a]	22.4 [18.7–26.0] (n = 24)[b] 26.8 [24.9–28.7] (n = 82)[c]	.068	0.64 (0.50–0.78)	24.2 (0.71, 0.62, 0.35, 0.88, 1.87, 0.47)
	Endoscopic remission	23.0 [20.7–25.3] (n = 52)[b] 28.5 [26.1–30.9] (n = 54)[c]	.003	0.67 (0.57–0.78)	23.1 (0.56, 0.80, 0.72, 0.65, 2.80, 0.55)
	Absence of ulceration	24.1 [22.0–26.1] (n = 64)[b] 29.3 [26.5–32.0] (n = 38)[c]	.010	0.64 (0.53–0.75)	25.8 (0.62, 0.61, 0.73, 0.49, 1.59, 0.62)
Week 6	Endoscopic response	13.4 [9.4–17.3] (n = 24)[b] 19.8 [17.8–21.8] (n = 82)[c]	.017	0.70 (0.57–0.83)	9.7 (0.54, 0.87, 0.54, 0.87, 4.15, 0.53)
	Endoscopic remission	15.8 [13.3–18.4] (n = 52)[b] 20.7 [18.2–23.2] (n = 54)[c]	.015	0.64 (0.54–0.75)	10.0 (0.37, 0.89, 0.76, 0.59, 3.36, 0.71)
	Absence of ulceration	16.6 [14.3–18.8] (n = 64)[b] 21.6 [18.6–24.6] (n = 39)[c]	.020	0.63 (0.52–0.75)	23.5 (0.83, 0.44, 0.71, 0.61, 1.48, 0.39)
Week 12	Endoscopic response	7.0 [4.8–9.2] (n = 23)[b] 12.5 [11.1–14.0] (n = 82)[c]	.001	0.77 (0.65–0.88)	8.1 (0.74, 0.76, 0.46, 0.91, 3.08, 0.34)
	Endoscopic remission	9.9 [8.0–11.7] (n = 51)[b] 12.7 [11.0–14.4] (n = 54)[c]	.045	0.64 (0.53–0.74)	8.1 (0.51, 0.80, 0.70, 0.63, 2.55, 0.61)
	Absence of ulceration	10.0 [8.4–11.6] (n = 63)[b] 13.6 [11.6–15.6] (n = 38)[c]	.017	0.66 (0.55–0.77)	11.0 (0.73, 0.61, 0.75, 0.57, 1.87, 0.44)
Week 14	Endoscopic response	3.5 [2.1–4.9] (n = 23)[b] 6.9 [5.9–7.9] (n = 79)[c]	.002	0.76 (0.64–0.87)	5.2 (0.87, 0.59, 0.38, 0.94, 2.12, 0.22)
	Endoscopic remission	5.0 [3.8–6.3] (n = 51)[b] 7.3 [6.1–8.4] (n = 51)[c]	.019	0.67 (0.57–0.78)	5.2 (0.67, 0.65, 0.65, 0.66, 1.91, 0.51)
	Absence of ulceration	5.3 [4.2–6.3] (n = 61)[b] 7.7 [6.3–9.1] (n = 37)[c]	.021	0.67 (0.56–0.78)	4.8 (0.59, 0.70, 0.77, 0.51, 1.97, 0.59)

NOTE. No correction for multiple testing was performed. The Student *t* test was used for comparing concentrations of patients who did not achieve endoscopic outcomes and for patients who did.
AUROC, area under the receiver operating characteristic curve; LR-, negative likelihood ratio; LR+, positive likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; se, sensitivity; sp, specificity.
[a]Statistical significance was not achieved.
[b]Patients who did not achieve the endoscopic outcomes.
[c]Patients who did achieve the endoscopic outcomes.

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Supplementary Table 2. Overview of the Best Models With Predictors for the Endoscopic Outcomes After Infliximab Induction Therapy (at Week 12) in Patients With Crohn's Disease

	Week 0			Week 2			Week 6			Week 12		
	Estimate	SE	*P*	Estimate	SE	*P*	Estimate	SE	*P*	Estimate	SE	*P*
	Endoscopic response			Endoscopic response			Endoscopic response			Endoscopic response		
Albumin	–	–	–	0.065	0.055	.244	–	–	–	–	–	–
CRP	–	–	–	0.011	0.085	.896	-0.073	0.056	.188	–	–	–
fCal	–	–	–	**-0.0010**	0.00053	.050	-0.001	0.00071	.075	**-0.003**	0.001	.002
Mean platelet volume	–	–	–	0.517	0.396	.192	0.668	0.407	.100	0.744	0.414	.072
Platelet count	–	–	–	**0.000011**	0.0000047	.016	**0.000022**	0.0000072	.002	**0.000023**	0.0000079	.003
	Endoscopic remission			Endoscopic remission			Endoscopic remission			Endoscopic remission		
Albumin	-0.014	0.053	.789	–	–	–	–	–	–	–	–	–
CRP	**-0.028**	0.013	.029	0.0081	0.040	.840	0.034	0.064	.600	0.028	0.046	.547
fCal	–	–	–	**-0.0016**	0.00051	.001	**-0.0038**	0.001	.001	**-0.002**	0.001	.014
Lymphocyte count	–	–	–	-0.00063	0.00043	.142	–	–	–	–	–	–
Mean platelet volume	-0.096	0.234	.682	-0.452	0.295	.125	0.557	0.388	.151	–	–	–
Platelet count	–	–	–	–	–	–	**0.000013**	0.0000045	.005	**0.0000076**	0.0000037	.038
White blood cells	–	–	–	–	–	–	–	–	–	-0.00021	0.00014	.131
	Absence of ulceration			Absence of ulceration			Absence of ulceration			Absence of ulceration		
Albumin	–	–	–	-0.122	0.084	.149	–	–	–	–	–	–
CRP	–	–	–	0.076	0.059	.196	–	–	–	–	–	–
fCal	–	–	–	**-0.0012**	0.00057	.033	–	–	–	–	–	–
Hematocrit	–	–	–	-0.171	0.110	.119	–	–	–	–	–	–
Mean platelet volume	–	–	–	-0.164	0.323	.611	–	–	–	–	–	–
Platelet count	–	–	–	**-0.000011**	0.0000046	.021	–	–	–	–	–	–
White blood cells	–	–	–	**0.00041**	0.00016	.011	–	–	–	–	–	–

NOTE. Parameter effects can be interpreted only when the *z* statistic is significant (shown in bold). When a model only contains nonsignificant parameters, no values were provided in the table.
CRP, C-reactive protein; fCal, fecal calprotectin.
–, Parameters that were not retained in the models based on the small-sample corrected Akaike Information Criterion.

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Supplementary Table 3. The Exposure–Response Relationship During Infliximab Maintenance Therapy

Time point	Endoscopic outcome	Trough concentration, mg/L, means [95% CI]	*P* value	Empiric AUROC, means (95% CI)	Threshold Youden (se, sp, PPV, NPV, LR+, LR-)
Week 46	Absence of ulceration	5.2 [4.6–5.8] (n = 24)[a] 7.4 [6.1–8.7] (n = 58)[b]	.013	0.63 (0.50–0.76)	8.5 (0.88, 0.36, 0.43, 0.88, 1.38, 0.33) Q29
Week 54	Absence of ulceration	5.1 [4.5–5.8] (n = 22)[a] 8.0 [6.7–9.3] (n = 56)[b]	.002	0.69 (0.56–0.81)	7.3 (0.86, 0.52, 0.41, 0.91, 1.79, 0.27)
Pooled trough concentrations	Absence of ulceration	5.6 [4.8–6.3] (n = 142)[a] 7.0 [5.7–8.3] (n = 347)[b]	<.0001	0.58 (0.53–0.63)	8.9 (0.87, 0.28, 0.33, 0.84, 1.21, 0.46)
10 mg/kg subgroup		5.5 [4.6–6.5] (n = 51)[a] 10.4 [8.9–11.9] (n = 85)[b]	<.0001	0.71 (0.62–0.79)	10.6 (0.94, 0.42, 0.49, 0.92, 1.62, 0.14)

NOTE. No correction for multiple testing was performed. The Student *t* test was used for comparing concentrations of patients who did not achieve the endoscopic outcomes and patients who did. Bonferroni correction was used for multiple testing in the pooled data analysis; $\alpha = 0.05/6$.

AUROC, area under the receiver operating characteristic curve; LR-, negative likelihood ratio; LR+, positive likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; se, sensitivity; sp, specificity.

[a]Patients who did not achieve the endoscopic outcomes.

[b]Patients who did achieve the endoscopic outcomes.

Supplementary Table 4. Overview of the Best Models With Predictors for the Endoscopic Outcomes After Infliximab Maintenance Therapy (at Week 54) in Patients With Crohn's Disease

	Week 14			Week 22			Week 30			Week 38			Week 46			Week 46		
	Estimate	SE	*P*	Estimate	SE	*P*	Estimate	SE	*P*	Estimate	SE	*P*	Estimate	SE	*P*	Estimate	SE	*P*
	Endoscopic response			Endoscopic response			Endoscopic response			Endoscopic response			Endoscopic response			Endoscopic response		
Albumin	–	–	–	**0.348**	0.138	.012	0.285	0.173	.100	**0.361**	0.172	.036	**0.265**	0.128	.039	–	–	–
CRP	–	–	–	0.126	0.108	.244	0.106	0.137	.437	0.282	0.252	.263	0.083	0.124	.503	**-0.440**	0.218	.043
fCal	–	–	–	–	–	–	**-0.0073**	0.0032	.023	–	–	–	–	–	–	**-0.0055**	0.0028	.046
Hematocrit	–	–	–	–	–	–	0.357	0.197	.071	–	–	–	–	–	–	0.650	0.398	.103
Hemoglobin	–	–	–	0.874	0.569	.124	–	–	–	–	–	–	–	–	–	–	–	–
Lymphocyte count	–	–	–	0.0014	0.0010	.191	**0.0046**	0.00222	.039	–	–	–	0.00122	0.00085	.150	–	–	–
Platelet count	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	**0.000064**	0.000032	.045
Mean platelet volume	–	–	–	–	–	–	0.152	0.656	.817	–	–	–	–	–	–	2.166	1.522	.155
	Endoscopic remission			Endoscopic remission			Endoscopic remission			Endoscopic remission			Endoscopic remission			Endoscopic remission		
Albumin	0.137	0.0999	.169	–	–	–	–	–	–	0.101	0.116	.382	-0.016	0.096	.868	–	–	–
CRP	**0.190**	0.0969	.050	–	–	–	-0.055	0.045	.218	0.070	0.151	.646	0.021	0.082	.795	-0.050	0.098	.610
fCal	**-0.0020**	0.00095	.037	–	–	–	**-0.0025**	0.0012	.031	**-0.0027**	0.0014	.045	**-0.0021**	0.0010	.027	**-0.0033**	0.0012	.006
Lymphocyte count	0.00065	0.00052	.206	–	–	–	–	–	–	–	–	–	0.00056	0.00048	.245	-0.00074	0.00043	.085
Mean platelet volume	0.337	0.407	.409	–	–	–	-0.492	0.352	.162	-0.082	0.390	.835	-0.203	0.401	.612	–	–	–
White blood cell count	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	0.00038	0.00020	.063
	Absence of ulceration			Absence of ulceration			Absence of ulceration			Absence of ulceration			Absence of ulceration			Absence of ulceration		
Albumin	–	–	–	–	–	–	–	–	–	0.145	0.135	.281	-0.049	0.111	.657	–	–	–
CRP	–	–	–	–	–	–	-0.115	0.092	.211	-0.200	0.154	.192	-0.130	0.084	.122	**-0.584**	0.194	.003
fCal	–	–	–	–	–	–	**-0.0045**	0.0017	.008	**-0.0030**	0.0015	.045	**-0.0028**	0.0012	.023	**-0.0050**	0.0019	.008
Hemoglobin	–	–	–	–	–	–	–	–	–	0.467	0.300	.119	–	–	–	–	–	–
Lymphocyte count	–	–	–	–	–	–	–	–	–	–	–	–	**0.0024**	0.0009	.007	–	–	–
Platelet count	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	0.000010	0.0000063	.104
Mean platelet volume	–	–	–	–	–	–	-0.462	0.371	.214	-0.041	0.454	.929	0.061	0.440	.889	0.521	0.599	.385
White blood cell count	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	**0.00101**	0.00043	.018

NOTE. Parameter effects can be interpreted only when the *z* statistic is significant (shown bold). When a model contains only nonsignificant parameters, no values were provided in the table.
CRP, C-reactive protein; fCal, fecal calprotectin.
–, Parameters that were not retained in the models based on the small-sample corrected Akaike Information Criterion.

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Supplementary Table 5. Endoscopic Outcomes and ATI Patterns of the Eight Patients With ATI With an Available Week 54 Endoscopy

Patient	Endoscopic response	Endoscopic remission	Absence of ulceration	ATI pattern
1	Yes	Yes	Yes	On-off switch
2	Yes	Yes	Yes	Persistent
3	Yes	Yes	Yes	Transient
4	No	Yes	No	On-off switch
5	Yes	Yes	Yes	On-off switch
6	Yes	Yes	Yes	On-off switch
7	Yes	Yes	Yes	On-off switch
8	Yes	Yes	No	Transient

ATI, antibodies to infliximab.