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| 1 Indentionals, "Department of Castroonterology, Academic Medical Centre, Amsterdam, The Netherlands; ¹¹⁷ Department of Gastroenterology, Academic Medical Centre, Amsterdam, The Netherlands; ¹¹⁷ Department of Gastroenterology, University Hospitals Leuven, Leuven, Belgium 82 2 BACKGROUND & AIMS: In the TAILORIX trial, no benefit could be shown by inflixinab dose escalation based on pharmacokinetic (Inflixinabs serum concentrations) and pharmacokynamic (Diomarkers and symptoms) monitoring compared with dose escalation based on symptoms alone in patients with Croin's disease (CD). We investigated whether integration of pharmacokinetic (Inflixinab serum concentrations) and pharmacokynamic (Diomarkers and serum concentrations of Infliximab induction and pharmacokynamic monitoring can be used to evaluate responses to infliximab induction and pharmacokynamic monitoring can be used to evaluate responses to infliximab induction and pharmacokynamic monitoring can be used to evaluate responses to infliximab induction and pharmacokynamic monitoring can be used to evaluate responses to infliximab induction and pharmacokynamic monitoring can be used to evaluate responses to infliximab induction and pharmacokynamic monitoring can be used to evaluate responses to infliximab induction and pharmacokynamic monitoring compared with dose escalation, based on biomarkers and serum concentrations of infliximab induction and symptoms (the TAILORIX trial; n = 122). We analyzed data from this study to determine whether concentrations of infliximab were easociate responses of infliximab treatment. 90 3 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 tree easociate response relation the easocici response and reminstand | 20 | Huriez Hospital, Lille 2 (Maastricht The Nether | University, Lille, France; ""Department of Gastroenterology and Hepatology, University Medical Centre, lands: ##Department of Gastroenterology and Hepatology, Frasmus Medical Centre, Botterdam, The | /8 70 |
| Gastroenterology and Hepatology, University Prospitals Leuven, Leuven, Beigium 80 BACKGROUND & AIMS: In the TAILORIX trial, no benefit could be shown by infliximab dose escalation based on pharmacokinetic (infliximab serum concentrations) and pharmacokinetic 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 pharmacokynamic monitoring compared with dose escalation based on symptoms alone in patients with Crohn's disease (CD). We investigated whether integration of pharmacokinetic 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 remsission (CD endoscopic index of severity, <3), and absence of ulcers at weeks 12 and 54 of infliximab treatment. | 21 | Netherlands: ***Departr | nent of Gastroenterology. Academic Medical Centre, Amsterdam, The Netherlands: ^{###} Department of | 79 80 |
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| 37 Treatment. 95 38 treatment. 97 40 mg/L at week 6 were associated with endoscopic remission at week 2 and greater than 10.0 98 41 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 99 42 maintenance therapy, we found evidence for an exposure-response relationship only after 90 43 dose escalation; trough concentrations greater than 10.6 mg/L were associated with the 100 44 absence of ulcers at week 54 (positive predictive value, 49%; negative predictive value, 102 102 45 92%). Low fecal concentrations of calprotectin during therapy were associated with the 103 46 endoscopic response and remission (P < .05). Dose escalations increased trough concentration of calprotectin, despite | 36 | | (CD) endoscopic index of severity <3) and absence of ulcers at weeks 12 and 54 of infliximal | 94 |
| 38 96 39 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 yalues, 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 concent trations of infliximab; persistent increase in fecal concentration of calprotectin, despite | 37 | | treatment. | 95 |
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| 40 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 (<i>P</i> < .05). Dose escalations increased trough concentrations of calprotectin, despite adse escalation, was associated with a lack of endoscopic response and remission. A significantly higher proportion of patients with antibodies to infliximab, identified by a 107 | 39 40 | RESULTS: | Infliximab trough concentrations greater than 23.1 mg/L at week 2 and greater than 10.0 | 9/ |
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| 55 ease; CDAI, Crohn's disease activity index; CRP, C-reactive protein; fCaI, 113 56 fecal calprotectin; IQR, interquartile range; MH, mucosal healing; NPV, 114 57 pPV, positive predictive value; TAILORIX, ; TC, trough 58 concentration; TDM, therapeutic drug monitoring 115 | 54 | Abbreviations used in this area under the receiver one | paper: ATI, antibodies to infliximab; AUROC, erating characteristic curve: CD. Crohn's dis- | 112 |
| 56 tecal calprotectin; IQR, interquartile range; MH, mucosal healing; NPV, negative predictive value; PD, pharmacodynamic; PK, pharmacokinetic; PV, positive predictive value; TAILORIX,; TC, trough 114 57 PPV, positive predictive value; TAILORIX,; TC, trough 1542-3565/\$36.00 115 58 concentration; TDM therapeutic drug monitoring https://doi.org/0.05.020 116 | 55 | ease; CDAI, Crohn's disease | e activity index; CRP, C-reactive protein; fCal, | 113 |
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119 120 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.

 ${f M}$ ucosal 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 136 **Q14** 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 139 association between infliximab serum concentrations 140 and clinical and endoscopic outcomes.^{5,6} Based on these 141 observations, the concept of therapeutic drug monitoring 142 (TDM) was introduced. TDM traditionally refers to dose 143 adjustment based on drug serum concentrations and 144 antidrug antibodies (pharmacokinetic [PK] monitoring). 145 Although recent recommendations have suggested an 146 infliximab serum concentration at a trough of 5.0 mg/L 147 148 **Q15** to be "therapeutic" during maintenance therapy, evidence to support this recommendation was based mainly 149 on observational data.⁸ As such, TDM is not yet widely 150 used across the globe. To date, no solid therapeutic 151 thresholds have been established for MH.⁹ 152

On top of PK monitoring, there is growing interest 153 in pharmacodynamic (PD) monitoring. PD monitoring 154 implies dose optimization guided by the effects of the 155 drug on disease manifestations such as changes in 156 biomarkers. One prospective trial evaluated adalimu-157 mab dose optimization based on PD monitoring.¹⁰ In 158 this trial, it was shown that MH rates were higher 159 when dosing was based on symptoms and biomarker 160 monitoring (C-reactive protein [CRP] and fecal cal-161 protectin [fCal]) instead of monitoring symptoms 162 alone. 163

164 ^{Q16} In the TAILORIX trial, infliximab dose escalation was based on a combination of PK (infliximab serum con-165 centrations) and PD (symptoms and biomarkers) moni-166 toring and compared with dose escalation based on 167 symptoms alone.¹¹ No benefit could be shown for dose 168 escalation based on biomarkers and infliximab serum 169 concentrations as compared with symptoms. In the cur-170 rent post hoc PK-PD analysis of TAILORIX, we examined 171 the roles of PK and PD monitoring during infliximab in-172 duction and maintenance therapy for targeting endo-173 scopic outcomes. 174

Methods

The TAILORIX Trial

191 TAILORIX was a multicenter, randomized, double-192 blind, controlled trial that was designed to determine 193 the value of PK and PD monitoring during combined 194 infliximab-immunomodulator maintenance therapy, 195 with the goal to improve clinical and endoscopic remission rates in patients with CD.¹¹ Briefly, 122 biologically 196 197 naive patients with active luminal CD (active ulceration 198 at endoscopy, CD activity index [CDAI] >220, fCal >250 199 mg/kg, and/or CRP >5 mg/L) started standard inflix-200 imab induction therapy (5 mg/kg at weeks 0, 2, and 6) in 201 combination with an immunomodulator. From week 14 202 onward, patients were treated following 1 of 3 moni-203 toring algorithms to which the patients were assigned 204 randomly. Two algorithms combined PK and PD moni-205 toring (active arms; based on infliximab serum concen-206 trations at trough in combination with CDAI, fCal, and/or 207 CRP), although 1 algorithm used PD monitoring only 208 (control arm: based on CDAI). Based on these algorithms. 209 the infliximab dose was increased by 2.5 mg/kg (active 210 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

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233 and maintenance therapy. First, we evaluated the pre-234 dictive value of infliximab and biomarker concentrations 235 for endoscopic outcomes at weeks 12 and 54. Then, we 236 investigated whether biomarkers and other factors 237 influenced the infliximab PK. Finally, we examined the 238 effects of dose escalations. 239

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 243 Q18 address missing data.

Statistical Analyses

247 Descriptive statistics were stated as percentages for 248 discrete variables and as means \pm SD or median (inter-249 quartile range [IQR]) for continuous variables. Concen-250 trations that were lower than the limit of quantification 251 were replaced by the limit of quantification for statistical 252 analyses. The Fisher exact test or the Pearson chi-square 253 test was used for the analysis of discrete variables. A 254 paired 2-tailed Student t test or the Wilcoxon signed-255 rank test was used for analysis of paired measure-256 ments. Unpaired data were analyzed with the unpaired 257 Student *t* test or the Wilcoxon rank-sum test. Diagnostic 258 performance was assessed with receiver operating 259 characteristic analysis. Therapeutic threshold values 260 were selected using the Youden I statistic. Binary logistic 261 regression was conducted to identify independent pre-262 dictors of the endoscopic outcomes of infliximab therapy. 263 Collinearity between signifcant predictors was defned as 264 a variance inflation factor greater than 5. A 2-sided P 265 value of .050 or less denoted statistical signifcance. Sta-266 tistical analyses were performed using R (version 3.4.3; 267 R Core Team, Vienna, Austria). 268

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

283 Pharmacokinetic monitoring. Endoscopic response, 284 endoscopic remission, and absence of ulceration were 285 achieved at week 12 in 82 of 106 (77%), 54 of 106 286 (51%), and 38 of 102 (37%) patients with available 287 endoscopic data. Infliximab trough concentrations (TC) 288 at weeks 2, 6, and 12 were significantly higher in patients 289 achieving these endoscopic outcomes at week 12, 290 although there was considerable variability (Figure 1). A

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.

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 2A, 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 2B, 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 endo- Q19 scopic 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 \pm 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). 348

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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, <i>kg</i> (IQR) | 65 (57–75) |
| | Disease duration, median, <i>mo</i> (IQR) | 7 (1–78) |
| | Serology concentrations at baseline | |
| | C-reactive protein, median, <i>mg/L</i> (IQR) | 20.0 (9.0–36.5) |
| | Fecal calprotectin, median, mg/kg (IQR) | 1462.5 (725.8–1800.0) |
| | Albumin, median, <i>g/L</i> (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, | 9.4 (8.8–10.0) |
| | fL (IQR) | |
| 2 | Platelet count, median/mm ^o (IQR) | 368,000 (287,500–455,500 |
| | Lymphocyte count, median/mm [*] (QH) | 1700 (1200–2200) |
| | White blood cell count, median/mm ² (IQR) | 8480 (7100–10,645) |
| | Endoscopy at baseline | 7 (10, 15) |
| | Cronn's disease endoscopic index of seventy, median (IQR) | / (10-15) 26:10:71 (22:16:61) |
| | Disease location, mean coloning, in (%) | 20.19.71 (22.10.01) |
| | Disease Denavior, nonsultating nonperetaing subtaining peretaining, in (70) | 85.17.14 (75.15.12) |
| | Patients with ATIs n (%) | 21 (18) |
| | Samples available n | 1329 |
| | Samples with undetectable infliximability (%) | 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 382 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 385 46 and greater than 7.3 mg/L at week 54 were associ-386 ated with an absence of ulceration at week 54 (Supplementary Table 3). At all other time points, infliximab concentrations during maintenance therapy 390 were not significantly different between patients achieving the endoscopic outcomes or not (P > .05, data not shown). However, when pooling all infliximab TCs 392 from week 14 through week 54, these were significantly higher in patients achieving absence of ulceration (P <394 .0001), with a threshold of 8.9 mg/L established. 395

The higher infliximab TCs in patients with absence of 396 ulceration were driven by the subgroup of patients who 397 earlier were dose-escalated to 10 mg/kg (P < .0001) 398 (Supplementary Table 3). An infliximab TC greater than 399 400 10.6 mg/L on dose escalation was associated with 401 absence of ulceration at week 54 (PPV, 49%; NPV, 92%; AUROC, 0.71; 95% CI, 0.62-0.79) (Figure 2C). Although 402 the median TC at weeks 46 and 54 were similar for pa-403 tients on 5 and 10 mg/kg infliximab maintenance doses 404 405 (P > .05), the variability in the observed TC was higher in the latter subgroup (at week 46: IQR, 4.4-8.9 and 3.5-9.8 406

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, Q20 7-105 d) (\sim 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 63 457 patients. Infliximab TCs increased on dose escalation 458 (from 3.2 mg/L [IQR, 1.2-4.9 mg/L] to 6.0 mg/L [IQR, 459 3.6–8.9 mg/L] 8 weeks later; P < .0001 (Supplementary 460 Figure 4A). Eight weeks after dose escalation, infliximab 461 TCs were similar in patients who achieved the endo-462 scopic outcomes and those who did not (also when only 463 considering the subgroup of patients with infliximab TCs 464

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PK–PD of Infliximab in CD 5



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.

<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 3A).

517 After dose escalation, we observed a significant 518 decrease in fCal, but not in CRP level (P = .049 and P =519 .193, respectively) (Supplementary Figure 4B and C). fCal 520 concentrations measured 8 weeks after dose escalation 521 were significantly lower in patients who achieved 522 endoscopic response, endoscopic remission, and absence



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.



.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 750 _{Q21}



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/L¹⁶) and week 6 (3.5 mg/L¹⁴) 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

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week 46. We derived an infliximab TC threshold on dose 848 escalation of 10.6 mg/L for predicting absence of ulcer-849 ation, which is higher than the 3.0 mg/L,¹⁷ 4.0 mg/L,¹⁸ 850 and 6.0 mg/L^{19} thresholds previously suggested for 851 achieving MH in patients with CD. As compared with the 852 5.0 mg/L threshold suggested by Vande Casteele et al⁸ 853 for symptom control, we conclude that higher inflix-854 imab TCs may need to be targeted for achieving MH on 855 1-year maintenance therapy. 856

Before dose escalation, the median infliximab TC was 857 3.2 mg/L. Eight weeks later, the median infliximab TC 858 was 6.0 mg/L. At weeks 46 and 54, the median infliximab 859 TC was 6.1 mg/L, with no significant difference between 860 patients who remained on 5-mg/kg infliximab vs those 861 who previously were dose-escalated to 10 mg/kg, 862 showing that overall, the TAILORIX dose escalation al-863 gorithm was successful for restoring the infliximab TC. 864 However, the variability in infliximab TC was larger in 865 patients who were dose-escalated, showing a clear sep-866 aration between endoscopic responders and non-867 responders, which eventually allowed the identification 868 of an exposure-response relationship toward the end of 869 the maintenance therapy. This observation reinforces 870

that perhaps the lower disease activity in patients with MH is responsible for the lower infliximab clearance and thus higher trough concentrations.

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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 halflife (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 921 validated the use of fCal as a reliable biomarker pre-922 dicting endoscopic improvement.²⁰ Already from week 923 2 onward, fCal concentrations were predictive for MH 924 and this association persisted throughout the entire 925 infliximab treatment. Therefore, we recommend moni-926 toring of fCal during infliximab therapy. Although 927 infliximab TC right at dose escalation had no predictive 928

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929 value for MH, fCal allowed a rapid distinction between 930 patients who were likely to achieve absence of ulcer-931 ation and those who were not. Therefore, we recom-932 mend monitoring of fCal at dose escalation. 933 Nevertheless, when fCal does not normalize, the 934 infliximab TC provides information on the mechanism 935 of failure (PK- vs PD-driven failure) and thus can guide 936 clinical decision making. Therefore, we recommend a 937 tiered approach for monitoring infliximab TC (PK 938 monitoring) and fCal (PD monitoring) during dose 939 escalation (Figure 5).

940 Our results support a role for monitoring fCal and TC 941 during infliximab maintenance therapy. Nevertheless, 942 TAILORIX did not show improved outcomes when 943 infliximab doses were escalated based on infliximab TCs 944 and biomarkers in addition to symptoms. Although 945 TAILORIX was a pilot study, the primary outcome was 946 achieved in numerically even more patients in the con-947 trol group. However, many patients in the control group 948 were dose-escalated based on symptoms (irrespective of 949 fCal and CRP), and response rates were relatively high, thereby reducing the window of opportunity for addi-950 951 tional TDM. This might be owing to a performance bias 952 because patients and/or physicians could prompt dose 953 escalations by over-reporting symptoms, although CDAI 954 also is known to incur considerable variability in its 955 scoring.²¹ Furthermore, as we showed in this post hoc 956 study, the target of 3.0 mg/L used in TAILORIX was 957 probably too low for achieving the primary end point 958 that included absence of ulceration. Besides a well-959 chosen control group, a more appropriate target con-960 centration, and possibly the opportunity to allow dose 961 de-escalations, future TDM studies might benefit from 2 962 recent evolutions in the field of TDM. These evolutions 963 focus mainly on the application of TDM at the point of care, using rapid assays and model-based computer-964 assisted dosing.^{22,23} In TAILORIX, dose escalations based 965 966 on biomarkers and CDAI were performed at the point of 967 care (same day as measured), whereas dose escalations 968 based on infliximab concentrations were not (8 weeks 969 later), thereby giving unequal chances to PK and PD 970 monitoring.

971 This TAILORIX post hoc analysis had some limita-972 tions. The analyses were not powered to identify the 973 predictive value of PK and PD monitoring for targeting 974 endoscopic outcomes. Although the primary end point of 975 TAILORIX was corticosteroid-free remission (CDAI, 976 <150) at all visits between weeks 22 and 54 with the 977 absence of ulcers at week 54 and no surgery for bowel 978 resection or abscess, we assessed endoscopic outcomes, 979 knowing that endoscopic outcomes are associated with 980 improved clinical outcomes and a reduction of hospital-981 izations and surgery.¹ In addition, the assessment of 982 composite end points may impact the ability to identify 983 relationships when there is heterogeneity between the 984 different outcome components. Therefore, further anal-985 ysis is needed to investigate associations with clinical outcomes and composite outcomes. In addition, the 986

available case analysis may have caused a selection bias987and our findings may not be applicable for other patient988populations (eg, more longstanding CD), patients on989infliximab monotherapy, or patients with prior biological990treatment.991

To conclude, the results of this TAILORIX post hoc 992 analysis support a role for infliximab TC monitoring 993 during induction therapy. During maintenance therapy, 994 995 the identification of an exposure-response relationship was observed only upon dose escalation. If a patient is 996 997 dose-escalated based on increased fCal, the infliximab TC increases, but it is only a normalization of fCal that 998 predicts absence of ulceration. Only after a while does 999 infliximab TC in patients with a persistently increased 1000 fCal (and thus a poor prognosis) tend to be lower than 1001 1002 infliximab TCs in patients with a normalized fCal (and thus a good prognosis). Nevertheless, to rule out 1003 increased infliximab clearance (eg, resulting from ATIs) 1004 and thus lower exposure, we recommend combining PD 1005 monitoring (based on fCal) with PK monitoring (based 1006 on infliximab TC, and, if necessary, ATI) for reactively 1007 1008 optimizing infliximab maintenance therapy in patients with CD (Figure 5). Future prospective trials are needed 1009 to evaluate this proposed TDM algorithm in maintenance 1010 therapy. 1011

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 1167023 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 remission, 7 achieved endoscopic endoscopic response, and 6 had no ulcers at week 54 (Supplementary Table 5).



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| Time point | Endoscopic outcome | Trough concentration, <i>mg/L</i> , means [95% CI] | P value | Empiric AUROC, means (95% CI) | Threshold Youden (se, or |
|------------|----------------------------------|--|---------|----------------------------------|--|
| 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) |

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

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. ^aStatistical significance was not achieved.

^bPatients who did not achieve the endoscopic outcomes.

^cPatients 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 | |
|----------------------|----------|-----------------------|------|-----------|-----------------------|------|----------|-----------------------|------|-----------|-----------------------|------------|
| | Ectimata | SE | | Ectimata | SE | | Ectimata | SE | | Ectimato | SE | D |
| | LStimate | Endoscopic response | Г | Estimate | Endoscopic response | F | Estimate | Endoscopic response | | Estimate | Endoscopic response | • <i>F</i> |
| 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 | 0.000079 | .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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| 80 | 80 | 80 | 80 | 80 | 80 | 80 | 80 | 80 | 20 | 70 | 70 | 70 | 70 | 70 | 20 | 20 | 20 | 07 | : 6 | ς β |) (06 | , 0 | 6 | 8 | 8 | 8 | 8 | 8 | 05 | 205 | s S | 50 | 50 | 20 | 05 | 50 | 20 | 30 | $\frac{2}{4}$ | 2 | 24 | 23 | $\frac{1}{4}$ | 64 | 23 | 2 G | 23 | 22 | 25 | 33 | 3 8 | 2 5 | 3 8 | 3 8 | 3 3 | 3 3 |
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| 6 | Ú1 | 4 | , ù | N |) ⊢ | - (| \circ | 9 | ∞ | · ~ | JC | 2 | S | 4 | | ວ I | \sim | 1 | 0 | 9 | \sim | - ` | 10 | J C | <u>ካ</u> - | Р (| ມ∣ | N | <u> </u> | 0 | 9 | ∞ |) – J | ι O | νu | n f | \geq (| ່ມເ | \mathbf{N} | - | 0 | 9 | ∞ | \neg | 9 | Un | 4 | ίΩ. | \sim - | - < | ъч | | $\sim \infty$ | 10 | r u | λ 4 | $\sim \alpha$ | 2 N |) <u> </u> | 0 | 9 |
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| Time point | Endoscopic outcome | Trough concentration, mg/L, means [95% CI] | P value | Empiric AUROC, means (95% Cl) | 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] $(n = 56)^{a}$ 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 | $5.6 [4.8-6.3] (n = 142)^a$ | <.0001 | 0.58 (0.53-0.63) | 8.9 (0.87, 0.28, 0.33, 0.84, 1.21, 0.46) |

7.0 [5.7–8.3] (n = 347)^b 5.5 [4.6-6.5] (n = 51)^a

10.4 [8.9–11.9] (n = 85)^b

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

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; $\alpha = 0.05/6$.

<.0001

0.71 (0.62-0.79)

Jd ratio; L. 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. ^aPatients who did not achieve the endoscopic outcomes.

^bPatients who did achieve the endoscopic outcomes.

10 mg/kg subgroup

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10.6 (0.94, 0.42, 0.49, 0.92, 1.62, 0.14)

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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 | |
| | | 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 | - | | 7 - 1 | 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 | _ | _ | - 4 | - | - | _ | -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 | - | - | - | - | | 7 | | - | - | 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.

 $\begin{array}{r} & 22263\\ & 22264\\ & 22266\\ & 22272\\ & 222$

-, 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. | | | |
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