# Proactive Infliximab Drug Monitoring Is Superior to Conventional Management in Inflammatory Bowel Disease

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**Background:** Increasing evidence supports the use of reactive therapeutic drug monitoring (TDM) in Crohn's disease (CD) and ulcerative colitis (UC) following secondary loss of response. It is still unknown if proactive TDM can improve clinical outcomes.

**Methods:** Consecutive patients completing infliximab (IFX) induction therapy were prospectively allocated into a proactive TDM protocol (pTDM). Before the fourth infusion and every 2 infusions, IFX trough levels and antidrug antibodies were measured using a drug-sensitive assay (Theradiag, Lisa Tracker). Treatment was proactively escalated aiming at an IFX trough level between 3 and 7 ug/mL (CD) and 5 and 10 ug/mL (UC). A retrospective cohort treated with IFX but without TDM served as the reference group. End points included the need for surgery, hospitalization, treatment discontinuation, and mucosal healing at 2 years of follow-up.

**Results:** Two hundred five patients were included, 56 in the proactive regimen. Treatment escalation was more common in pTDM patients (76.8% vs 25.5%; $P < 0.001$), who also required less surgery (8.9% vs 20.8%; $P = 0.032$) and presented higher rates of mucosal healing (73.2% vs 38.9%; $P < 0.0001$). Proactive TDM significantly decreased the odds of reaching any unfavorable outcome (odds ratio, 0.358; 95% confidence interval, 0.188–0.683; $P = 0.002$).

**Conclusions:** Proactive TDM is associated with fewer surgeries and higher rates of mucosal healing than conventional non-TDM-based management.

**Key Words:** inflammatory bowel disease, proactive therapeutic drug monitoring, infliximab

## INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) are 2 chronic immune-mediated diseases with variable courses and potential adverse outcomes, often requiring long-term immunosuppression. With the current nonbiological medical treatments, <50% of patients are expected to achieve sustained remission. In the last 2 decades, several biologic therapies have been made available, targeting specific immune pathways. Anti–tumor necrosis factor (TNF) alpha inhibitors have been shown to be effective in inducing clinical remission and mucosal healing and reducing the rates of hospital admission and surgery in patients with CD and UC.[1, 2] Unfortunately, >30% of patients are primary nonresponders and 20%–40% lose response or develop intolerance over time.[3] Recently, there has been increasing interest in using therapeutic drug monitoring (TDM) to increase the effectiveness of anti-TNF therapies. Data consistently associate higher infliximab (IFX) trough levels with increased rates of clinical remission, steroid-free clinical remission, mucosal healing, and perianal fistula response.[4–6] In a recent metanalysis, TDM was associated with higher cost-savings and anti-TNF persistence, with no apparent differences in other important outcomes compared with empirical dosing.[7] On the other hand, low IFX trough levels and positive antidrug antibodies correlate with loss of response and unfavorable outcomes.[8] Therefore, it seems plausible that proactive TDM, aiming at stable high levels of active drug while avoiding development of antidrug antibodies, could potentially improve clinical outcomes in CD and UC.

However, the studies available to date have shown conflicting results over the benefit of using proactive drug monitoring.[9–12]

In this study, we aimed to determine the 2-year outcomes of a proactive IFX TDM protocol in patients with UC and CD.

## METHODS

### Study Design and Patients

The study was conducted at the Department of Gastroenterology and Hepatology of Santa Maria University Hospital in Lisbon, Portugal. This was a comparative study including a prospective arm (pTDM) and a retrospective control

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group (no-TDM). Subjects had a confirmed diagnosis of CD or UC, in accordance with the criteria of the European Crohn and Colitis Association.[13] Consecutive patients who successfully completed IFX induction therapy (0, 2, 6 weeks) and met the inclusion/exclusion prerequisites for the study were included. General exclusion criteria included primary nonresponse to IFX (defined as an absence of response to the first 3 infusions), episodic treatment, previous major IBD surgery (total colectomy with ileal pouch–anal anastomosis or permanent ostomy), drug holiday during maintenance therapy (eg, pregnancy), and a follow-up <24 months. As mucosal healing was a target end point, patients without an endoscopy, before starting IFX and the end of the study, were excluded.

Demographic and clinical characteristics of the patients were collected from the patients' medical records. Consent for clinical use was requested from the patients before inclusion in the database. Patients in the proactive group gave formal consent before entering the study.

The study was approved by the hospital's institutional review board.

## Proactive Therapeutic Drug Monitoring

Before the administration of the fourth IFX infusion (14th week of treatment) and before every 2 infusions, blood was taken from subjects for assessment of IFX trough levels and antidrug antibodies. Treatment was proactively escalated aiming at a trough level between 3 and 7 µg/mL (CD) or 5 and 10 µg/mL (UC). These intervals were chosen in accordance with the clinical evidence available at the time.[3–5]

Trough levels and antidrug antibodies were measured using a drug sensitive assay (Theradiag, Lisa Tracker). All tests were performed at our institution. In patients with trough levels below the designated threshold, the decision to escalate by increasing the drug dosage (7.5 mg/kg or 10 mg/kg) or decreasing the interval of administration (every 6 or 4 weeks) was left to the clinicians' discretion. In patients with trough levels above the specified range, the decision to dose or interval de-escalation was also left to the attending clinician.

As we used an enzyme-linked immunosorbent assay (ELISA) methodology, test results were available 1 to 2 weeks after the infusion, meaning that changes in drug dose/interval were only performed on the subsequent infusion.

In patients with positive antidrug antibodies, drug escalation and the addition of an immunomodulator (in patients not already on combination therapy), a thiopurine or methotrexate was performed to reduce antibody burden. In the presence of persistent positive antibodies, IFX was discontinued and patients were switched to a different anti-TNF or another drug class.

## Retrospective Cohort

To evaluate the clinical benefits associated with the proactive treatment strategy, we compiled a control group including consecutive patients starting IFX between 2000 (5 years after IFX was first used in our institution) and 2014 (2 years before the start of the proactive TDM protocol).

In the control group, treatment escalation/de-escalation and drug discontinuation were left to the clinician's discretion and reflected the best clinical evidence available at the time.

## Study End Points

The primary outcomes of the study were the need for surgery, hospital admission, treatment discontinuation, and the rates of mucosal healing at the end of 2 years of IFX treatment. We also evaluated a compound unfavorable outcome including surgery, hospitalization, treatment failure, and no mucosal healing.

Surgery was defined as any perianal or bowel resection related to inflammatory bowel disease (excluding reconstruction of a previous stoma). Hospitalization was defined as any admission related to disease activity.

Treatment discontinuation was decided by the attending physician and presumably resulted from loss of response or relevant drug intolerance.

Endoscopic procedures were performed by experienced gastroenterologists or by supervised residents who were unaware of the patient's clinical information, current treatment regimen, IFX treatment strategy, and trough levels/antibodies.

Mucosal healing was defined as an absence of mucosal ulceration, excluding small aphthous lesions (CD nonoperated), a Rutgeerts score <i2 (CD operated), or a Mayo endoscopic subscore ≤1 (UC). Assessment was based on available reports, and therefore central reading was not available.

## Statistical Analysis

Continuous variables were expressed as median (range) and compared using the Mann-Whitney *U* test. Categorical variables were described using frequencies and percentages and compared using the chi-square test. Kaplan-Meier survival curves were used to assess outcome-free survival for each group and were compared using the log-rank test. Logistic regression was used for univariate and multivariate analyses with stepwise selection to investigate factors associated with any positive outcome. Variables with a $P$ value <0.1 in univariate logistic regression analysis were used in the multivariate logistic analysis. Results were expressed as odds ratio (OR) with 95% confidence interval (CI). The significance level was chosen at a $P$ value <0.05. Statistical analysis was performed using IBM Statistical Package for the Social Sciences (SPSS), version 21.0.

# RESULTS

## General Characteristics and Demographics

We included 205 patients in the study, 107 (52.2%) male, with median age at the end of IFX induction (range) of 37.0 (14.0–72.0) years. One hundred eighty-four patients (88.8%)

had no prior experience with anti-TNF drugs, and 138 (67.3%) were on concomitant immunomodulation. One hundred fifty-three patients (74.6%) had CD, and 52 (25.4%) had UC. Thirty-seven percent of patients with CD had a history of prior bowel surgery, and 32.7% had a past or current history of perianal disease. The median C-reactive protein at baseline (range) was 6.3 (0.1–175.0) mg/L (normal laboratory value, <5 mg/L). Endoscopic assessment showed signs of endoscopically active disease in all patients with UC and CD (nonoperated) at baseline. These results are available in Supplementary Table 1.

A review of the patient's demographics and disease characteristics is displayed in Table 1.

## Anti-TNF Treatment Strategies

The pTDM group included 56 patients (26.8%), and the control group included 149 patients.

Aside from a higher prevalence of UC in the pTDM group (41.1% vs 19.5%; $P = 0.002$), likely reflecting the increasing use of biologics in UC over time, baseline characteristics were similar between groups (Table 1).

Of note, 78 patients (38.0%) were on systemic steroids at baseline, 53 (35.6%) in the no-TDM group and 23 (41.1%) in the pTDM group ($P = 0.40$).

Baseline fecal calprotectin was available in 38 of 56 patients in the pTDM group: median (range) 929.5 (121–1371) ug/g.

## Therapeutic Drug Monitoring

The median (range) IFX trough levels and antidrug antibodies were 6.2 (0–16.0) µg/mL and 0 (0–200.0) U/mL, respectively. Although nonsignificant, the median trough levels were numerically higher in patients with CD compared with those with UC (6.32 [0–16.0] µg/mL vs 5.16 [0–16.0] µg/mL; $P = 0.07$).

According to the predesignated trough level intervals (3–7 µg/mL in CD and 5–10 µg/mL in UC), drug levels were infratherapeutic in 19.4% of all measurements in patients with CD and in >49.0% of all measurements in patients with UC ($P < 0.001$ between diseases). These results are plotted in Figure 1.

**TABLE 1.** Patients' Baseline Characteristics

| | Total Cohort | Group 1, No TDM | Group 2, pTDM | |
|---|---|---|---|---|
| | n = 205 | n = 149 | n = 56 | *P* |
| Median age at start of anti-TNF, y | 37 (14–72) | 37 (14–72) | 37 (18–70) | 0.79 |
| Median CRP at start of anti-TNF, mg/L | 6.3 (0.1–175) | 6.7 (0.1–175) | 4.2 (0.3–90.8) | 0.79 |
| Male sex | 107 (52.2) | 78 (52.3) | 29 (51.8) | 0.54 |
| IBD type | | | | |
| CD | 153 (74.6) | 120 (80.5) | 33 (58.9) | **0.002** |
| UC | 52 (24.9) | 29 (19.0) | 23 (41.1) | |
| Previous surgery CD | 57 (37.3) | 45 (37.5) | 12 (36.4) | 0.54 |
| UC extension | | | | |
| E2 (left-sided colitis) | 15 (28.8) | 7 (24.1) | 8 (34.8) | 0.31 |
| E3 (pancolitis) | 37 (71.2) | 22 (75.9) | 15 (65.2) | |
| CD location | | | | |
| L1 (ileal) | 39 (25.5) | 26 (25.5) | 13 (39.4) | 0.12 |
| L2 (colonic) | 18 (11.8) | 15 (12.5) | 3 (9.1) | |
| L3 (ileocolonic) | 96 (62.7) | 79 (65.8) | 17 (51.5) | |
| L4 (upper gastrointestinal disease) | 24 (15.7) | 20 (16.7) | 4 (12.2) | 0.16 |
| CD behavior | | | | |
| B1 (nonstricturing, nonpenetrating) | 54 (35.3) | 44 (36.7) | 10 (30.3) | 0.57 |
| B2 (stricturing) | 53 (34.6) | 39 (32.5) | 14 (42.4) | |
| B3 (penetrating) | 46 (30.1) | 37 (30.8) | 9 (27.3) | |
| Perianal disease | 50 (32.7) | 43 (35.8) | 7 (21.2) | 0.10 |
| Perianal disease active at baseline | 20 (40.0) | 17 (39.5) | 3 (42.9) | 0.61 |
| Anti-TNF naïve | 182 (88.8) | 134 (89.9) | 48 (85.7) | 0.27 |
| Immunomodulator | 138 (67.3) | 98 (65.8) | 40 (71.4) | 0.28 |
| Systemic steroids | 78 (38.0) | 53 (35.6) | 23 (41.1) | 0.40 |

Significant values are shown in bold. Data are presented as No. (%) or median (IQR).

Although detection of antidrug antibodies occurred more frequently in patients with UC (26.9% vs 10.0%; $P < 0.001$), a significant burden (>20 U/mL) was found in similar proportions between diseases (8.7% vs 4.4%; $P = 0.124$). A dot plot of antidrug antibodies according to IBD type is available as Supplementary Figure 1.

Median (range) IFX trough levels were similar in patients with and without immunomodulation (6.31 [0–16] µg/mL vs 5.6 [0–16] µg/mL; $P = 0.265$). The proportion of patients with significant antidrug antibodies (>20 U/mL) was also similar in patients with and without immunomodulation (6.3% vs 5.5%; $P = 0.533$).

## Infliximab Dose and Interval Escalation

As expected, cumulative treatment escalation rates were more common in the pTDM group than in the no-TDM group: 60.7% vs 16.8% ($P < 0.001$) at 1 year and 76.8% vs 25.5% ($P < 0.001$) at 2 years. A graphic representation of dose and interval escalation in the proactive group and a comparison of time until escalation in both groups are shown in Supplementary Figures 2 and 3.

## Long-term Outcomes According to the Treatment Strategy

The differences between the pTDM group and the no-TDM group with respect to the need for surgery, hospital admission, treatment discontinuation, and mucosal healing are shown in Figure 2. The survival curves for each group according to the former outcomes are shown in Figure 3.

### *Surgery*

By the end of the 2-year follow-up period, surgery was required in 36 patients (17.6%), 5 (8.9%) in the pTDM group and 31 (20.8%) in the no-TDM group ($P = 0.032$). Subgroup analysis showed a significant difference in UC (4.3% vs 27.6%; $P = 0.030$) but not in CD (12.1% vs 19.2%; $P = 0.254$). In patients with CD, rates of perianal surgery were nonsignificant between treatment strategies (3.0% vs 7.4%; $P = 0.363$). Patients in the pTDM group presented a longer time until surgery than the no-TDM group (log-rank $P = 0.048$).

### *Hospitalization*

Sixty-two patients (30.2%) required at least 1 hospital admission related to disease activity. There was a nonsignificant trend for lower hospitalizations in the pTDM group (21.4% vs 33.6%; $P = 0.06$). In subgroup analysis, the need for hospitalization reached statistical significance in UC (17.4% vs 44.8%; $P = 0.035$) but not CD (24.2% vs 30.8%; $P = 0.306$).

Time to hospitalization was similar between pTDM and no-TDM patients (log-rank $P = 0.125$), reaching statistical significance in UC (log-rank $P = 0.037$).

### *Treatment discontinuation*

Fifty-one patients (24.9%) discontinued IFX over the 2 years of follow-up, with similar rates between the proactive and control groups (21.4% vs 26.2%; $P = 0.306$). Subgroup analysis did not show a difference between groups in UC (39.1% vs 48.3%; $P = 0.35$) or CD (9.1% vs 20.8%; $P = 0.09$). The time to treatment discontinuation was also similar between the pTDM and no-TDM patients (log-rank $P = 0.435$). Eight patients (3.8%) discontinued treatment due to moderate to severe infusion reactions, with no difference between pTDM and no-TDM patients (3.6% vs 3.9%; $P = 0.634$). One patient (0.5%) in the no-TDM group discontinued treatment after a diagnosis of breast cancer.

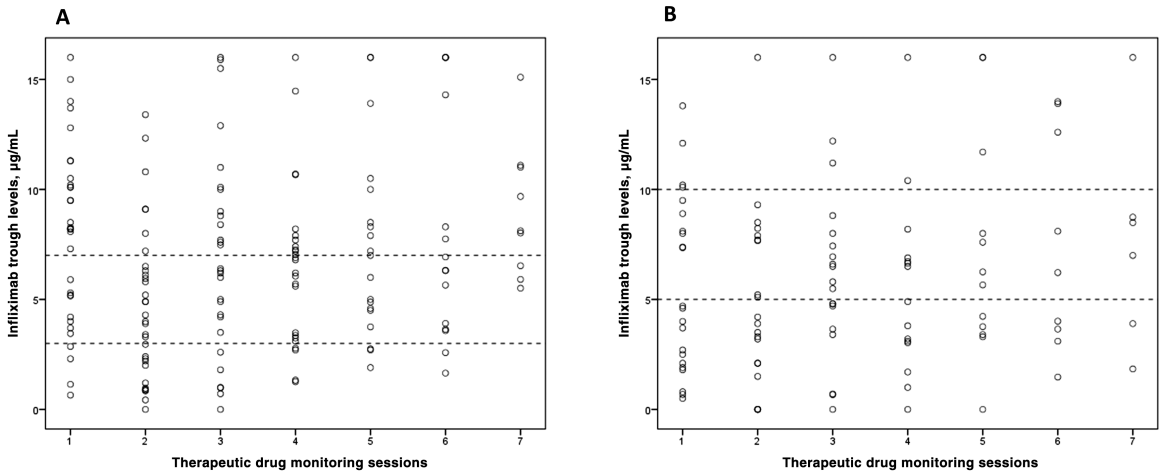


FIGURE 1. Infliximab trough levels in Crohn's disease (A) and ulcerative colitis (B) across measurements. The interval between the dotted lines represents the desirable trough levels. Values are expressed in ug/mL.

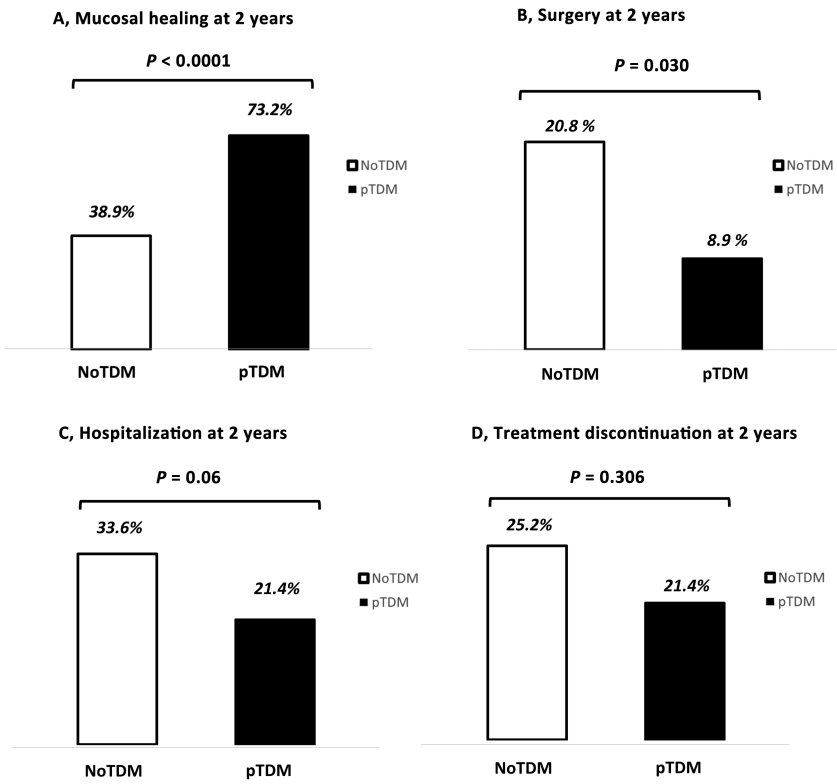


FIGURE 2. Proportion of patients with mucosal healing (A), surgery (B), hospitalization (C), and treatment discontinuation (D) at 2 years of infliximab treatment.

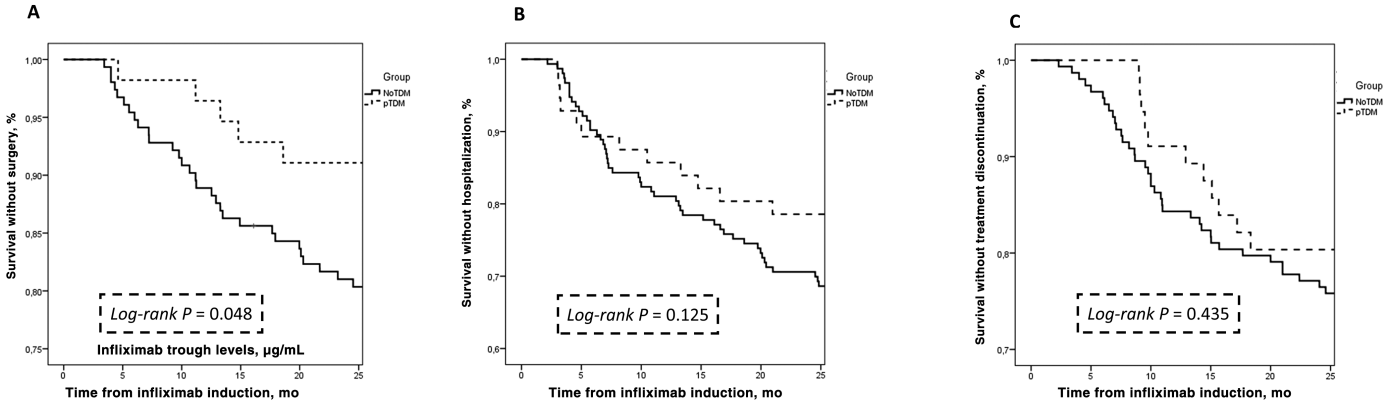


FIGURE 3. Sustained long-term clinical benefit of infliximab with respect to surgery (A), hospital admission (B), and treatment discontinuation (C).

Curiously, of the 154 patients who remained on IFX treatment during the study period, only 88 (57.1%) achieved mucosal healing (81.8% vs 47.3% in the pTDM and no-TDM groups, respectively; $P < 0.0001$), perhaps suggesting that in a significant percentage of patients, treatment was continued despite an insufficient response.

## *Mucosal healing*

After 2 years of biologic treatment, mucosal healing was achieved in 99 patients (48.3%). The proportion of patients achieving mucosal healing was highest in the pTDM group (73.2% vs 38.9%; $P < 0.0001$), with significance in both UC (69.6% vs 27.6%; $P = 0.003$) and CD (75.8% vs 41.7%; $P < 0.001$). The former was true for operated (75.0% vs 40.0%; $P = 0.033$) and nonoperated CD patients (76.2% vs 42.7%; $P = 0.006$).

## *Any unfavorable outcome*

A compound unfavorable outcome (surgery, hospitalization, treatment failure, and no mucosal healing) was reached

in 135 patients (65.9%), less often in the pTDM group (48.2% vs 72.4%; $P = 0.001$), with significance in CD (48.5% vs 70.0%; $P = 0.019$) and UC (47.8% vs 82.8%; $P = 0.009$).

### *Oral steroid use*

Although this was not a formal end point of the study, at the end of the follow-up, corticosteroid use was more common in the no-TDM group (24.8% vs 7.1%; $P = 0.044$).

## Prediction of Clinical Outcomes

A logistic regression analysis was computed including age, sex, inflammatory bowel disease type, prior anti-TNF exposure, immunomodulator use, and TDM strategy.

Immunomodulator use (OR, 0.442; 95% CI, 0.223–0.876; $P = 0.019$) and proactive TDM monitoring (OR, 0.358; 95% CI, 0.188–0.683; $P = 0.002$) were the sole independent factors associated with a lower likelihood of reaching any unfavorable outcome (Table 2).

Likewise, immunomodulator use (OR, 2.367; 95% CI, 1.251–4.477; $P = 0.008$) and proactive TDM monitoring (OR, 4.315; 95% CI, 2.164–8.605; $P < 0.001$) were the only factors independently associated with mucosal healing.

Finally, only the proactive TDM strategy was independently associated with a lower likelihood of requiring surgery (OR, 0.373; 95% CI, 0.137–0.989; $P = 0.05$).

## Role of Immunomodulation

In patients without proactive TDM, immunomodulation (vs no immunomodulation) was associated with higher rates of mucosal healing (49.0% vs 19.6%; $P < 0.001$), treatment discontinuation (18.4% vs 41.2%; $P = 0.003$), and lower rates of unfavorable outcomes (64.3% vs 88.2%; $P = 0.001$), but not surgery (20.4% vs 21.6%; $P = 0.513$) or hospitalization (29.6% vs 41.2%; $P = 0.108$).

In pTDM patients, immunomodulation had no influence on rates of mucosal healing (70.0% vs 81.3%; $P = 0.307$), treatment discontinuation (20.0% vs 25.0%; $P = 0.467$), hospitalization (20.0% vs 25.0%; $P = 0.467$), surgery (12.5% vs 0%; $P = 0.172$), or any unfavorable outcome (50.0% vs 43.8%; $P = 0.450$).

Patients without proactive TDM on immunomodulation were more likely to achieve mucosal healing (OR, 3.936; 95% CI, 1.774–8.731; $P = 0.001$) and less likely to reach any unfavorable outcome (OR, 0.240; 95% CI, 0.093–0.619; $P = 0.003$).

## Impact of Postinduction Infratherapeutic Trough Levels

The median IFX trough levels after induction (week 14) (range) were 8.2 (0.65–16.0) µg/mL in CD and 4.6 (0.50–13.8) µg/mL in UC ($P = 0.022$).

Taking this in consideration, week 14 drug levels were infratherapeutic in 76.5% of patients with UC and 25.6% of patients with CD ($P = 0.001$). However, this had no impact on the 2-year outcomes for mucosal healing ($P = 0.309$ and 0.313), surgery ($P = 0.420$ and 0.565), hospitalization ($P = 0.691$ and 0.596), treatment failure ($P = 0.330$ and 0.363) or any unfavorable outcome ($P = 0.676$ and 0.407) for CD and UC, respectively.

# DISCUSSION

We studied the short-term outcomes of a proactive drug monitoring strategy in patients with CD and UC. The results are novel in that we have shown that proactive TDM is associated with increased rates of mucosal healing and lower rates of unfavorable outcomes, namely surgery and endoscopic inflammation, when compared with a cohort managed without TDM.

Our results are distinct from the 2 available prospective trials, which failed to show a benefit of proactive treatment escalation.[9, 10]

In the Trough Concentration Adapted Infliximab Treatment (TAXIT) trial, patients with CD and UC on maintenance treatment with IFX were first optimized to a trough level between 3 and 7 µg/mL.[9] Clinical remission rates increased significantly in patients with CD but not UC. Participants were then randomized to receive conventional management (escalation based on symptoms and C-reactive protein) or concentration-based dosing (escalation aiming at a trough level

**TABLE 2.** Univariate and Multivariate Logistic Regression Analysis for Reaching any Unfavorable Outcome

| | Univariate Analysis | | Multivariate Analysis | |
|---|---|---|---|---|
| Predictive Factor | Odds Ratio (95% CI) | *P* | Odds Ratio (95% CI) | *P* |
| Male sex | 0.891 (0.479–1.659) | 0.717 | | |
| Age at IFX induction | 1.003 (0.978–1.028) | 0.814 | | |
| IBD type | 1.224 (0.580–2.582) | 0.597 | | |
| Immunomodulator use | **0.467 (0.230–0.949)** | **0.035** | **0.442 (0.223–0.876)** | **0.019** |
| Prior anti-TNF | 0.952 (0.359–2.525) | 0.921 | | |
| TDM strategy | **0.341 (0.174–0.668)** | **0.002** | **0.358 (0.188–0.683)** | **0.002** |

Unfavorable outcomes included surgery, hospitalization, and no mucosal healing. Variables were included in the multivariate analysis if in the univariate analysis the *P* value was <0.10. Values are expressed as odds ratio (95% confidence interval). Significant results are shown in bold.

between 3 and 7 µg/mL). After 1 year of follow-up, although no further improvement was seen in clinical remission rates, more relapses and antidrug antibodies were detected in the clinically based group. In the Trough Concentration Adapted Infliximab Treatment for Active Crohn's Disease (TAILORIX) trial, patients with CD on combined immunosuppression were randomized after induction to escalate based on symptoms, biomarkers, and trough levels (group A and B) or symptoms alone (group C). After 1 year, there was no difference in the proportion of patients in steroid-free remission and those who had achieved endoscopic healing.[10] However, the negative results might have resulted from the high rates of treatment escalation in the control group compared with the proactive group (40.0% vs 44.4% and 62.2%; $P = 0.47$). This most likely resulted from the low threshold for escalation (CDAI >220 at the current visit or a CDAI between 150 and 220 in the 2 weeks before the current visit). Furthermore, the short follow-up (1 year) might have been insufficient to show a difference between treatment strategies.

The potential benefits of proactive TDM have been demonstrated by 2 retrospective multicenter studies.[11, 12] In the first study, including patients on IFX maintenance, proactive TDM was associated with lower rates of treatment failure, serious infusion reactions, surgeries, hospitalizations, and antidrug antibodies.[11] However, it should be noted that reactive TDM included patients with symptoms suggestive of loss of response or drug intolerance, whereas proactive TDM included only asymptomatic patients. This may have led to an overestimation of the benefits of proactive TDM, as reactive patients were expected to present a worse prognosis from the start. In the second study, proactive and reactive TDM, after an initial reactive testing, were compared.[12] Proactive TDM was associated with greater drug persistence and fewer IBD-related hospitalizations.

Once again, the positive results should be interpreted with caution, as the definition of proactive TDM used in both studies (TDM in patients in clinical remission) differs from that used by the TAXIT, TAILORIX, and by our study (escalation to a target trough level irrespective of clinical, biomarker, or endoscopic activity).

One of the unexpected findings in this study was the similar rates of anti-TNF persistence in the proactive and empirical groups. We believe that this might have resulted from a temporal bias. Patients in the empirical cohort might have persisted longer on anti-TNF therapy due to a lack of available alternative therapies. Likewise, in the proactive group, a lower threshold to discontinue therapy (eg, mild to moderate infusion reactions, patient preference, low antibody titer) might have resulted from the availability of alternative therapies. This is supported by the high rates of anti-TNF persistence in control patients despite only half actually reaching mucosal healing.

Another interesting observation can be found in the analysis of the postinduction IFX levels in patients with UC and CD. More than 75% of patients with UC and 25% with CD had drug levels below the "therapeutic threshold" after induction.

Several studies have shown an association between low postinduction (week 14) IFX trough levels and worse disease control, with higher levels of C-reactive protein levels and loss of response.[14, 15] Curiously, there was no apparent impact of low postinduction IFX trough levels on the prognosis of our patients. Hypothetically, this may have resulted from our proactive treatment protocol, aiming at stable therapeutic drug levels over the 2-year study period.

Finally, regression analysis showed a benefit of immunomodulation in terms of mucosal healing and unfavorable outcomes. This is in accordance with previous findings in landmark studies such as the SONIC and UC-SUCCESS trials, which showed that combination therapy is superior to either therapy alone.[16, 17] However, the benefit was restricted to patients without proactive therapeutic drug monitoring. In fact, trough levels and treatment outcomes were similar in pTDM patients irrespective of immunomodulation. We believe that the benefit from immunomodulation in the conventional group probably resulted from an increase in IFX trough levels and a decrease in immunogenicity. This has previously been suggested in a post hoc analysis of the SONIC trial, where median trough levels were superior in patients undergoing combination therapy.[18] In addition, another post hoc analysis of the same study demonstrated that combination therapy was not more effective than monotherapy in patients with similar serum concentrations of infliximab.[19] The fact that proactive therapeutic drug monitoring might render the need for immunomodulation unnecessary has also been illustrated in a recent retrospective study.[20] This finding is of the utmost importance, especially considering the increasing concerns over the potential side effects associated with long-term thiopurine therapy.[21]

Our study presents some limitations. First, the empirical control group was retrospective, and therefore subject to potential bias. Second, the number of patients included in the proactive treatment strategy was rather small, making it impossible to reach significance in some outcomes and subgroup analyses. Although we might have increased our numbers by including patients already on IFX maintenance treatment at baseline, this would mean mixing patients on different treatment strategies (no-TDM and pTDM). We believe that restricting inclusion to patients finishing induction provides a better understanding of the potential benefits of proactive TDM.

Another limitation of our study comes from the test used to evaluate IFX trough levels and antibodies. As we used an ELISA test, results were typically available 1 to 2 weeks after the infusion. This means that optimization was only possible in the following infusion, with unknown consequences in the treatment group. Nevertheless, some preemptive actions were still possible such as addition of an immunomodulator, drug switch/swap, and/or preferential interval reduction (in patients with low trough levels). Point-of-care testing may be

an attractive alternative, as recent studies have shown an excellent correlation with conventional ELISA-based tests.[22, 23] Finally, our monitoring strategy assumed a higher target for trough levels in UC compared with CD. This differs from international recommendations such as those of the American Gastroenterology Association, which recommend a trough level >5 ug/mL in all patients. However, several studies have shown that UC requires more and earlier dose optimization compared with CD.[24, 25] It has also been shown that patients with UC present with absent IFX trough levels more often than patients with CD.[26] Several mechanisms might explain these results, including higher inflammatory burden, accelerated clearance, and loss of active drug through the diseased colon.[27] Taking this into account, we decided to choose a higher cutoff for optimization in these patients.

In conclusion, our study suggests that proactive TDM is associated with significant therapeutic benefits, including higher rates of mucosal healing and less surgery. Our data further add to the importance of therapeutic drug monitoring of IFX in inflammatory bowel disease.

## SUPPLEMENTARY DATA

Supplementary data are available at *Inflammatory Bowel Diseases* online.

## REFERENCES


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