Proactively Optimized Infliximab Monotherapy Is as Effective as Combination Therapy in IBD

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Background: Infliximab (IFX) discontinuation is not uncommon during the first year of treatment due to inadequate drug concentrations and anti-IFX antibodies (ATI). Both combination therapy and proactive therapeutic drug monitoring (pTDM) are used to decrease ATI and increase IFX durability. We proposed that monotherapy (Mono) is as effective as combination therapy (Combo) if the first maintenance infusion is dosed based on week 10 pTDM.

Methods: In a retrospective cohort of 83 patients with inflammatory bowel disease (IBD), we examined the frequency of IFX discontinuation, ATI, infusion reactions, and IFX concentrations during the first year of treatment in patients receiving week 10 pTDM-guided IFX monotherapy (Mono pTDM; n = 16) compared with patients on mono (n = 32) or combination therapy (n = 35) in whom TDM was introduced at or after week 14, per standard of care (SOC).

Results: The frequency of IFX discontinuation was lower with Mono pTDM compared with Mono SOC (P = 0.04) but did not differ with Combo SOC (P = 1). At first TDM, no patient in the pTDM strategy had ATI, vs 41% in Mono SOC (P = 0.002) and 6% in Combo SOC (P = 1). Of the 13 subjects with ATI in Mono SOC, 7 (47%) had ATI already at week 14. IFX trough concentrations with Mono pTDM were higher during maintenance compared with Mono SOC (9.5 vs 6.4 µg/mL, P = 0.04) but not Combo SOC.

Conclusions: Infliximab durability did not differ between patients on IFX monotherapy dosed based on p-TDM and patients receiving combination therapy. In the absence of concomitant immunosuppression, proactive TDM may improve IFX durability by maintaining higher IFX concentrations entering into maintenance. Further studies are needed to confirm our findings.

Key Words: proactive therapeutic drug monitoring, infliximab optimization, infliximab durability, infliximab monotherapy

INTRODUCTION

Infliximab, a chimeric antibody to tumor necrosis factor–α (TNF-α), is a highly effective treatment for induction and maintenance of remission in Crohn's disease (CD) and ulcerative colitis (UC).[1, 2] Despite its efficacy, up to 40% of patients do not respond to treatment or lose response over time[1–4] or experience infusion reactions leading to treatment discontinuation.[5] The current literature suggests that low-serum infliximab (IFX) concentrations and the development of antibodies to IFX (ATI) are 2 major factors impacting the sustainable efficacy of IFX.[6] These 2 factors are inter-related as inconsistent or insufficient exposure to IFX is associated with an increased risk of developing ATI.[7, 8] Different strategies have been evaluated in clinical studies and have entered into clinical practice to optimize IFX dosing and prevent ATI development. The most well known is the use of a concomitant immunomodulator, either a thiopurine or methotrexate, which has been shown to be associated with higher trough IFX concentrations and lower rates of ATI.[9–11] This strategy, however, is less widely adopted among pediatric providers given the malignancy risks of thiopurines both as monotherapy and in combination therapy with anti-TNF medications.[12] An alternative strategy consists of proactively adjusting IFX dosing with the goal of achieving and maintaining IFX concentrations within a therapeutic window while the patient is clinically stable.[13, 14] This is in direct contrast to the more standard approach, in which dose adjustments are made reactively based on drug concentrations taken at the time of loss of response. A proactive strategy not only favorably impacts IFX durability, but also the long-term outcomes.[13–15] Studies have shown that trough concentrations collected postinduction and before the first maintenance infusion at week 14 are associated with IFX

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durability.[16, 17] If patients have subtherapeutic concentrations at the start of the maintenance phase, it will be difficult for these patients to achieve therapeutic concentrations in the absence of dose escalation and they will be at increased risk of ATI development and loss of response. Thus proactive TDM (pTDM) may be better defined as drug concentrations that guide the timing and total dose of the first maintenance infusion. We hypothesized that dosing decisions based on an IFX concentration obtained at week 10 (4 weeks before the first maintenance dose) could be an effective strategy to reduce ATI formation, enhance IFX durability, and negate the need for combination therapy. We aimed to compare IFX durability and ATI rates with proactive TDM with dosing decisions based on IFX concentrations or clinical judgment at week 14 or thereafter.

METHODS

Study Design and Patient Population

This was a retrospective cohort study conducted at a single tertiary care inflammatory bowel disease (IBD) center (Susan and Leonard Feinstein Inflammatory Bowel Disease Clinical Center, Mount Sinai Hospital, New York, NY, USA). Eligible patients were diagnosed with IBD based on standard criteria and were younger than age 25 years at the start of IFX treatment between January 2014 and May 2016. Patients must have received a standard induction regimen with IFX infusion at 5 mg/kg on weeks 0, 2, and 6 and have remained on the same treatment regimen, either as combination therapy or monotherapy, until week 26 or until IFX discontinuation or the development of ATI. Exclusion criteria included previous exposure to IFX, pregnancy or planning pregnancy, first maintenance dose before week 14 based on clinical judgment alone and without knowledge of IFX concentration, enrollment in other clinical studies, no ATI and infliximab measurement during the first year of treatment, incomplete therapeutic information, and no follow-up. Patients were followed up until 1 year of treatment, or until infliximab discontinuation if before 1 year.

IFX TDM–Based Dosing Strategies

Mono pTDM: Patients received IFX as monotherapy and had their first IFX concentration and ATI measurement performed at week 10 to guide dosing and timing of the first maintenance infusion. Patients in the Mono pTDM group were both dose- and frequency-adjusted when the week 10 IFX level was <20 ug/mL. Frequency-only or no adjustments were made when IFX levels were between 20 and 25 ug/mL, and no adjustments were made when IFX levels were >25 ug/mL. All the patients managed with Mono pTDM belonged to a single provider (M.C.D.), who in late 2015 introduced this approach to manage patients who started IFX as monotherapy. Dosing decisions based on week 10 IFX concentrations were aimed to achieve a trough concentration between 5 and 10 ug/mL at the first maintenance infusion and were based on a presumed 14-day half-life.

Standard of care (SOC) patients on either IFX monotherapy (Mono SOC) or combination (Combo SOC) therapy were not optimized before entering into maintenance and did not have a level 4 weeks before planned week 14 infusion. These patients were managed by multiple providers at the IBD center.

Data Collection

Information collected from electronic medical records included data on the patient's disease history (age at diagnosis, time to IFX introduction since diagnosis, disease extension, and behavior according to the Montréal classification), treatment history (prior surgeries, prior biologics) and disease activity, evaluated with clinical indices (Pediatric Ulcerative Colitis Activity Index [PUCAI] or partial Mayo score for UC, weighted Pediatric Crohn's Disease Activity Index [wPCDAI] or Harvey-Bradshaw score for CD), and inflammatory biomarkers (erythrocyte sedimentation rate [ESR], C-reactive protein [CRP], albumin) at the time of IFX introduction. Data collected during follow up included IFX concentrations and ATI levels, timing and indication for first IFX and ATI measurement, IFX discontinuation, infusion reactions, IFX dosing changes, and changes in treatment strategy (immunomodulator discontinuation or introduction). All ATI and IFX concentrations were measured via homogeneous mobility shift assay (HMSA) (Prometheus Labs, San Diego, CA, USA).[18]

Outcomes Measures

The primary outcomes were the frequency and cumulative probability of IFX discontinuation during the first year of treatment. Secondary outcomes included ATI frequency and probability of ATI-free survival after 1 year of treatment, and frequency of infusion reactions and IFX discontinuation related to ATI and infliximab concentrations at follow-up.

Statistical Analysis

Categorical variables were summarized by frequencies and were compared across independent groups with the chi-square or Fisher exact test where appropriate; numerical variables with asymmetrical distribution were summarized by median and interquartile range (IQR) and compared by the Kruskal-Wallis test. The time to infliximab discontinuation was calculated by survival analysis according to the Kaplan-Meier method, and the log-rank test was used for comparison of different groups. A receiver operating characteristic (ROC) analysis for the sensitivity and specificity of ATI concentrations for predicting infliximab discontinuation was performed, and the Youden Index was calculated to find the cutoff of ATI concentrations with the highest combined sensitivity and specificity for infliximab discontinuation in our cohort. Sensitivity and specificity of the same cutoff value were then calculated for infusion

reactions. *P* values were calculated 2-tailed, and a *P* value <0.05 was considered for significance. Statistical analysis was made using SPSS, version 22.0 (IBM corp, Amnork, NY, USA).

RESULTS

Patient Population

A total of 136 patients receiving IFX infusions during the period from January 2014 to May 2016 met the inclusion criteria. After applying the exclusion criteria, 83 patients were eligible for analysis (Fig. 1). Fifty-two patients (47%) were males; the median age at IFX introduction (IQR) was 12 (10–15) years. Seventy-six patients (92%) had Crohn's disease (CD), and 7 patients (8%) had ulcerative colitis (UC); 38 patients (34%) were diagnosed within the 6 months before IFX introduction. Sixteen patients (20%) were dosed based on a Mono pTDM strategy, 32 patients (38%) based on a Mono SOC strategy, and 35 patients (42%) based on a Combo SOC strategy. Baseline disease characteristics were comparable among groups, except for prior surgeries and penetrating behavior, which were more frequent in patients in the Mono SOC group compared with patients in the Combo SOC group (Table 1).

TDM Measurements

A total of 243 measurements were available for the entire cohort. Sixty-five measurements (27%) were drawn in the Mono pTDM; 94 (39%) and 84 (35%) were drawn in the Mono SOC and Combo SOC groups, respectively. The median number of measurements per patient is reported in Table 2. The first IFX and ATI measurements were performed at week 14 in 18 (56%) and 17 (49%) patients in the Mono SOC and Combo SOC groups. All Mono pTDM patients had their first level before the planned week 14 infusion. Six patients (38%) in the Mono pTDM group had a second IFX measurement drawn at the first maintenance infusion. At the time of the first TDM measurement, symptoms that raised the concern for active disease or ATI were present in 1 patient (6%) in the Mono pTDM group, 11 patients (34%) in the Mono SOC group, and 8 patients (23%) in Combo SOC group ($P = 0.07$ for Mono pTDM vs Mono SOC, $P = 0.24$ for Mono pTDM vs Combo SOC). Complaints were gastrointestinal symptoms in 13 patients, fatigue or arthralgia in 4, infusion reactions in 2. All 16 patients in the Mono pTDM group had at least 1 subsequent TDM measurement after week 10, with all measurements either scheduled with the purpose of checking the appropriateness of IFX dosing or of following ATI. Only 1 of 16 patients (6%) reported gastrointestinal symptoms at the time. Of the patients in the Mono SOC and Combo SOC groups who did not discontinue IFX treatment after the first TDM measurement, 23 of 28 patients (82%) in the Mono SOC group and 28 of 34 patients (82%) in the Combo SOC group had at least 1 subsequent TDM. Subsequent TDM measurements were performed as a reactive measure, due to the presence of gastrointestinal symptoms or infusion reactions, in 10 patients (35%) in the Mono SOC group and 9 patients (26%) in the Combo SOC group.

Infliximab Concentrations and Dosing Strategies

The median postinduction IFX concentration in the Mono pTDM group (IQR) was 23.9 (17.5–27.1) µg/mL. IFX concentrations at time of the first maintenance infusion in the

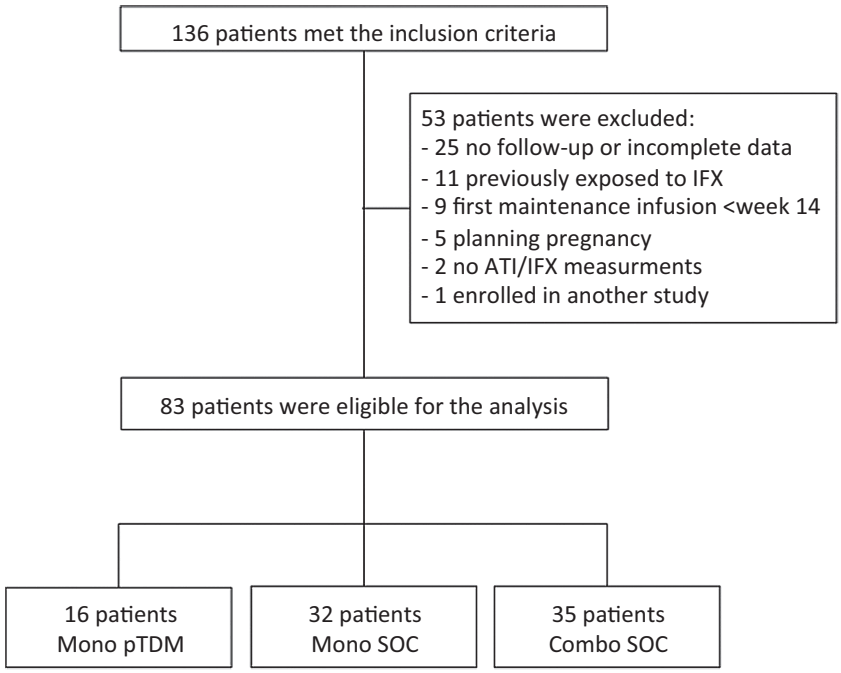

FIGURE 1. Flow chart of patients evaluated for the study and distribution within the study groups.

TABLE 1: Baseline Demographic and Disease Characteristics of Patients

Characteristics	Mono pTDM (n = 16)	Mono SOC (n = 32)	Combo SOC (n = 35)	*P*
Male sex, No. (%)	11 (68.8)	22 (68.8)	19 (54.3)	0.41
Age at diagnosis, median (IQR), y	14.0 (9.8–15)	12.0 (10–15)	12 (9–14)	0.47
Age at IFX initiation, median (IQR), y	14.5 (12–16.8)	14.0 (11.3–16.8)	14 (11–16)	0.59
IFX use within 6 m of diagnosis, No. (%)	9 (56.3)	12 (37.5)	17 (48.6)	0.43
CD, No. (%)	15 (93.8)	28 (87.5)	33 (94.3)	0.59
Complicated behavior, No. (%)				
Stricturing (B2)	0	2 (7.1)	0	0.17
Penetrating (B3)	0	4 (14.3)	0	0.04[a]
Disease location, No. (%)				
Ileal (L1)	2 (13.3)	5 (17.9)	6 (18.2)	10.0
Colonic (L2)	1 (6.7)	2 (7.1)	3 (9.1)	10.0
Ileocolonic (L3)	12 (80.0)	20 (71.4)	24 (72.7)	0.82
Upper tract (L4)	7 (46.7)	18 (64.3)	17 (51.5)	0.46
Perianal (p)	6 (40.0)	5 (17.9)	4 (12.1)	0.08
UC, No. (%)	1 (6.3)	4 (11.8)	2 (5.7)	0.59
Disease location, No. (%)				
Left-sided (E2)	1	2 (50.0)	0/1	10.0
Extensive (E3)	0	2 (50.0)	1/1	10.0
Prior IMM, No. (%)	4 (25)	11 (34.4)	15 (42.9)	0.45
Prior biologic, No. (%)	1 (6.3)	3 (9.4)	1 (2.9)	0.51
Prior surgeries,[b] No. (%)	0 (0)	4 (12.5)	0 (0)	0.04[b]
Moderate/severe disease,[c] No. (%)	3/16 (18.8)	3/18 (16.7)	7/24 (29.2)	0.67
Albumin, median (IQR), gr/dl	3.6 (3.4–3.9)	3.8 (3.3–4.2)	4.0 (3.5–4.3)	0.29
ESR, median (IQR), mm/h	28 (18.0–41.0)	24 (14.0–37.3)	32 (12–49.0)	0.74
CRP, median (IQR), mg/L	5.25 (1.4–23.9)	8.05 (1.4–34.1)	7.8 (2.1–33.5)	0.75
Methotrexate, No. (%)	—	—	23 (65.7)	—
6-mercaptopurine, No. (%)	—	—	12 (34.3)	—

Abbreviation: IMM, immunomodulator.
[a] Combo SOC vs Mono SOC = 0.04; Mono pTDM vs Mono SOC = 0.28.
[b] Combo SOC vs Mono SOC = 0.05; Mono pTDM vs Mono SOC = 0.29.
[c] wPCDAI > 40, PUCAI > 34, HB > 7.

Mono pTDM group did not differ significantly from the week 14 levels of the Combo SOC group, but both were higher than measured among the Mono SOC group (Table 2). For those patients who had trough measurements after week 14, patients in the Mono pTDM group had significantly higher median IFX trough concentrations compared with the Mono SOC group during follow-up ($P = 0.04$) (Table 2). Based on week 10 TDM, the first maintenance infusion was adjusted in 9 patients (56%) overall. In 6 patients (38%), IFX was administered at a dose higher than 5 mg/kg, 8 patients (50%) received the first maintenance infusion before week 14, and 5 patients (31%) received both dose and frequency changes. Nine patients (28.1%) from the Mono SOC group and 4 patients (11%) from the Combo SOC group had their dose adjusted based on week 14 concentrations. During maintenance, 11 of 16 patients (68%) in the Mono pTDM group and 13 of 35 patients (37%) in the Combo SOC group were dose-adjusted based on IFX trough concentrations. Of the 29 patients in the Mono SOC group who continued IFX treatment beyond week 14, 14 patients (48%) were dose-adjusted based on TDM. Before the end of follow-up, IFX was de-escalated, either reducing drug dosing or drug frequency, in 3 of 16 patients (18%) in the Mono pTDM group, 7 of 32 patients (21%) in the Mono SOC group, and 4 of 35 patients (11%) in the Combo SOC group.

Antibodies to Infliximab

A total of 25 patients (30%) were ATI positive at least at 1 time point during the entire period of follow-up. Fifteen of these 25 (60%) were ATI positive at the time of the first TDM measurement. There were no ATI detected at the time of first TDM,

TABLE 2: Infliximab Measurements and Infliximab Concentrations

	Mono pTDM	Mono SOC	*P* Mono pTDM vs Mono SOC	Combo SOC	*P* Mono pTDM vs Combo SOC	*P* MonoSOC Vs Combo SOC
IFX measurements						
Per patient, median (IQR)	4.0 (3.0–5.0)	3.0 (1.0–3.25)	0.004	2.0 (2.0–3.0)	0.00	0.56
IFX concentrations, µg/mL						
All trough concentrations, median (IQR)	9.1 (6.2–13.0)	5.4 (1.7–10.8)	0.002	7.7 (3.8–12.6)	0.24	0.035
At 1st maintenance infusion,[a] median (IQR)	7.8 (5.3–9.8)	2.9 (1.0–5.5)	0.02	7.6 (4.2–13.8)	0.97	0.004
After 1st maintenance infusion, median (IQR)	9.5 (6.3–13.9)	6.4 (2.6–12.5)	0.04	7.6 (3.1–11.9)	0.1	0.51

[a] Data available for 6 of 16 patients in the Mono pTDM group, 18 of 32 in the Mono SOC group, and 17 of 35 patients in Combo SOC group.

at week 10, in the Mono pTDM group, as compared with 13 of 32 patients (41%) in the Mono SOC group and 2 of 35 (6%) patients in the Combo SOC group ($P = 0.002$ for Mono pTDM vs Mono SOC, $P = 1$ for Mono pTDM vs Combo SOC). Of the 13 subjects in the Mono SOC group, 7 (47%) had their first ATI measured as early as week 14. After the week 10 measurement, 5 of 16 patients (31%) in the Mono pTDM group developed ATI at a median (IQR) of 22 (20–36) weeks of treatment. Another 4 patients in the Mono SOC group, for a total of 17 patients (53%; 31% v s53%, $P = 0.15$), and 1 in the Combo SOC group, for a total of 3 patients (9%; 31% vs 9%, $P = 0.09$), became ATI positive after the first measurement in those who had a repeat measurement. The Kaplan-Meier analysis for the probability of ATI-free survival during the year of follow-up is illustrated in Figure 2. The median ATI level at the time of initial detection (IQR) was 5.2 (4.7–8.1) U/mL in the Mono pTDM group, 8.8

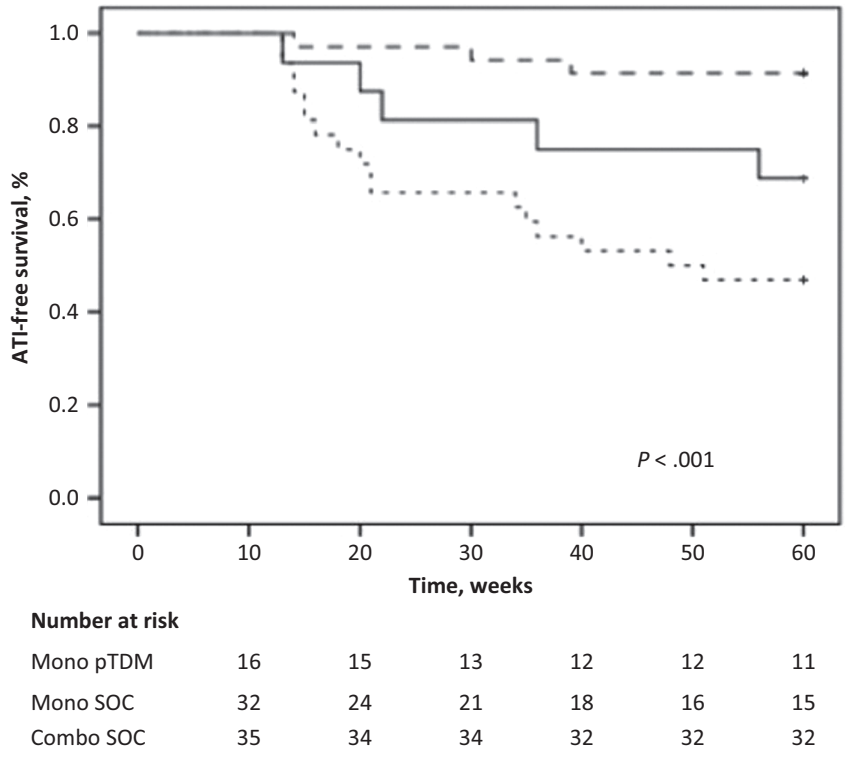

FIGURE 2. Kaplan-Meier estimates for ATI-free survival in patients in the Mono pTDM group (solid line) compared with patients in the Mono SOC group (dotted line) and patients in the Combo SOC group (dashed line).

(5.13–10.8) U/mL in the Mono SOC group, and 9.0 (6.6–9.1) U/mL in the Combo SOC group ($P = 0.27$ for Mono pTDM vs Mono SOC, $P = 0.6$ for Mono pTDM vs Combo SOC).

At last follow-up, 11 of 25 (44%) ATI-positive patients cleared their ATI: 2/5 (40%) Mono pTDM, 7/17 (41%) Mono SOC, 2/3 (67%) Combo SOC (NS across all groups). Thus, 3 of 16 patients (18.8%) in the Mono pTDM group, 10 of 32 patients (31%) in the Mono SOC group, and 1 of 35 patients (3%) in the Combo SOC group had ATI as of last follow-up ($P = 0.49$ for Mono pTDM vs Mono SOC, $P = 0.09$ for Mono pTDM vs Combo SOC, $P = 0.002$ for Mono SOC vs Combo SOC). The median IFX concentrations observed in samples with ATI were significantly higher in patients in the Mono pTDM group compared with patients in the Mono SOC (6.4 vs 1.0 µg/mL, $P = 0.02$) and Combo SOC (6.4 vs 0 µg/mL, $P = 0.01$) groups. At the time of initial ATI finding, IFX levels were very low or undetectable (≤1.0 µg /mL) in 11 of 17 of patients (64%) in the Mono SOC group, 3 of 3 patients (100%) in the Combo SOC group, and 1 of 5 patients (20%) in the Mono pTDM group ($P = 0.09$ for the 3 groups). Therapeutic interventions in patients with ATI consisted of IFX dose escalation in 5 patients (100%) in the Mono pTDM group, 11 (65%) patients in the Mono SOC group, and 2 patients (67%) in the Combo SOC group. An immunomodulator was added in 4 patients (80%) in the Mono pTDM group and 7 patients (41%) in the Mono SOC group and was later discontinued, before the end of follow-up, in 3 patients and 1 patient in the Mono pTDM and Mono SOC groups, respectively.

IFX Durability

Nine of the 83 patients (11%) discontinued IFX during the 1-year follow-up. No patients in the Mono pTDM group discontinued IFX, as compared with 8 of 32 patients (25%) in the Mono SOC group and 1 of 35 patients (3%) in the Combo SOC group ($P = 0.04$ for Mono pTDM vs Mono SOC, $P = 1$ for Mono pTDM vs Combo SOC, $P = 0.01$ for Mono SOC vs Combo SOC). The median time to discontinuation (IQR) was 38 (20.5–42) weeks in the Mono SOC group. The only patient in the Combo SOC group who discontinued IFX did so at week 30. The Kaplan-Meier analysis of the cumulative probability of IFX discontinuation for the 3 TDM strategies is illustrated in Figure 3. All 9 patients (100%) who discontinued IFX treatment had ATI, vs 16 of 74 patients (22%) who were still on IFX treatment at 1 year ($P < 0.001$). Rates of discontinuation were not associated with disease behavior at baseline or prior surgical history. IFX discontinuation was associated with infusion reactions in 6 patients (67%), of whom 5 were in the Mono SOC group and 1 was in the Combo SOC group. ROC analysis of highest ATI concentrations observed for each patient showed a cutoff of ATI ≥9.1 U/mL to be a good predictor for IFX discontinuation (area under the curve, 0.89; 89%

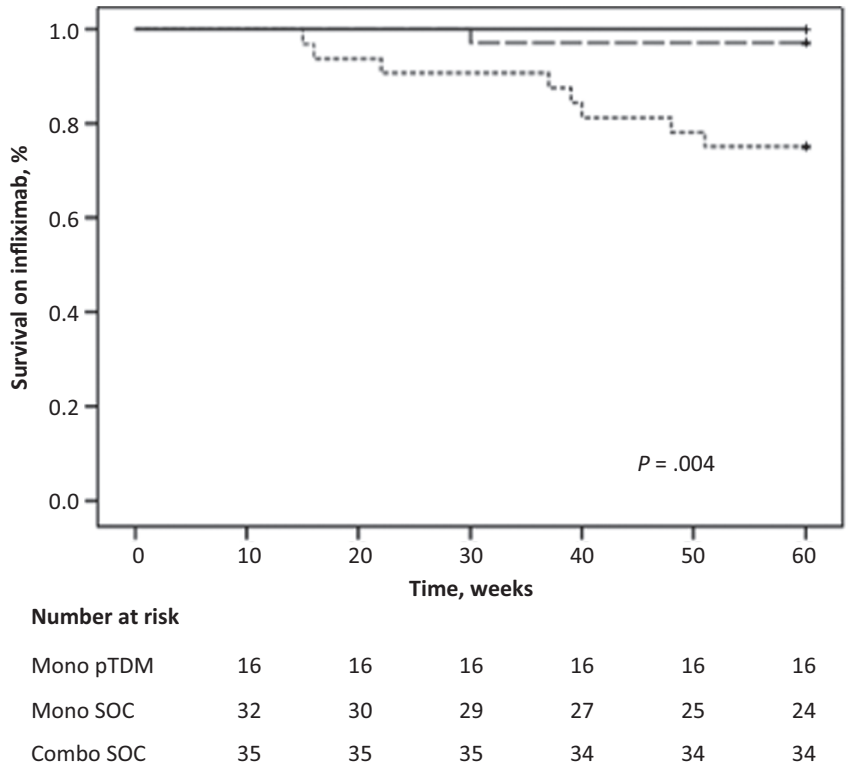

FIGURE 3. Kaplan-Meier curve representing the time to infliximab discontinuation in patients in the Mono pTDM group (solid line) compared with patients in the Mono SOC group (dotted line) and patients in the Combo SOC group (dashed line).

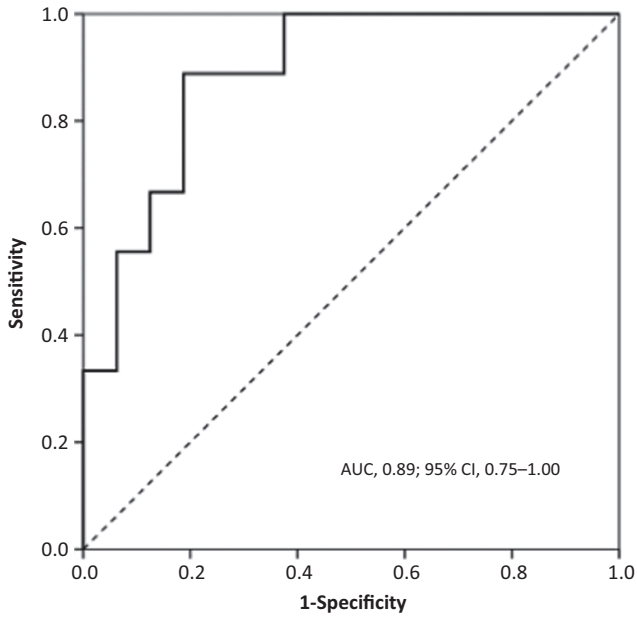

FIGURE 4. ROC curve for the sensitivity and specificity of ATI concentrations for predicting infliximab discontinuation. Abbreviation: AUC, area under the curve.

sensitivity, 81% specificity, and 73% positive predictive value, with 93% negative predictive value), as illustrated in Figure 4. The same cutoff value was also a good predictor for infusion reactions (86% sensitivity, 72% specificity, and 55% positive predictive value with 93% negative predictive value). Twenty percent (1/5) of patients in the Mono pTDM group, 53% (9/17) in the Mono SOC group, and 33% (1/3) in the Combo SOC group developed ATI ≥9.1 U/mL ($P = 0.32$ for Mono pTDM vs Mono SOC, $P = 1$ for Mono pTDM vs Combo SOC).

DISCUSSION

In this single-center retrospective study, infliximab durability did not differ between patients on infliximab monotherapy dosed based on proactive TDM and patients receiving combination therapy. Data on the benefits of proactive TDM on infliximab durability and immunogenicity in IBD are still limited. A positive effect has been reported by Vaughn et al. in a retrospective study where patients on maintenance infliximab managed with proactive TDM who achieved infliximab levels >5 µg/mL had a longer infliximab durability compared with patients who had reactive testing or empiric dose escalation.[13] This observation was confirmed in a multicenter retrospective study by Papamichael et al., where patients managed with proactive TDM had greater infliximab durability, fewer IBD-related surgeries or hospitalizations, and lower risk of ATI and of infusion reactions compared with patients in whom TDM was used at the time of loss of response or infusion reactions.[19,20] Both studies differ from ours in several aspects. Most importantly, they both defined proactive TDM as drug monitoring performed in asymptomatic patients and compared this strategy with reactive TDM. Moreover, patients were already on maintenance therapy, often beyond the first year of treatment, and no distinction was made with respect to the treatment strategy (monotherapy or combination therapy).

Overall, 30% percent of patients in our cohort had ATI, and this was the predominate influence on drug discontinuation. Almost half of the patients on infliximab monotherapy who had the first TDM measurement at week 14 were ATI positive. Even though the frequency of ATI during follow-up did not significantly differ between patients on proactive TDM and patients on monotherapy managed per standard of care, when developing ATI, patients on proactive TDM maintained significantly higher IFX concentrations and had lower median ATI levels. Also, when comparing infliximab concentrations on measurements performed at week 14 or thereafter, irrespective of the ATI status, patients on proactive TDM maintained significantly higher IFX concentrations compared with patients on monotherapy managed per standard of care. Altogether, these observations suggest that, in the absence of concomitant immunosuppression, proactive TDM may improve the durability of infliximab monotherapy by maintaining higher infliximab concentrations entering into maintenance, ultimately modulating the clinical impact of ATI. The correlation between week 14 infliximab concentrations and long-term outcomes has been well established. Singh et al. found infliximab level cut-points of 3, 4, and 7 µg/mL at week 14 to predict persistent remission at 1 year, with predictive values of 64%, 76%, and 100%, respectively.[17] In the post hoc analysis of the ACCENT trial, Cornillie at al. found that higher infliximab trough levels (≥3.5 µg/mL) at week 14 were associated with sustained clinical remission at week 54,[16] advancing the hypothesis that detectable infliximab levels at this time could prevent ATI formation. In the same study, ATI status was assessed at week 14 only in a minority of patients (22/147) using an enzyme-linked immunosorbent assay method; thus it is possible that the lower infliximab concentrations in patients without sustained response could reflect the presence of ATI already at this time point.

Week 14 infusion is the first 8-week interval postinduction, and, given the high variability in the individual pharmacokinetics profile of infliximab, standard dosing may not guarantee adequate exposure until week 14 in every patient. In the study by Cornille et al., almost 70% of patients at week 14 had a drug concentration below the identified threshold of 3.5 µg/mL for sustained remission.[16] These findings suggest that introducing TDM before week 14 would improve durability. A more recent pediatric study by Stein et al. explored the usefulness of week 10 infliximab concentrations to predict infliximab durability, observing that patients on treatment at 1 year had higher median infliximab concentrations at week 10 compared with patients discontinuing the medication (>20.4 vs 8.7 µg/mL).[21] In this same study, an association was found

between undetectable ATI at week 10 and ongoing infliximab at 1 year, which is in keeping with our observations.

Some limitations of the present study are acknowledged. The small number of patients, the retrospective nature of the study, and the fact that patients in the pTDM group were under a single physician may limit the generalizability of our findings. Additionally, the influence of pTDM beyond 1 year was not evaluated, and it is not possible to say weather patients in the pTDM group who developed ATI discontinued infliximab after one year. This, however, is the first study investigating the impact on infliximab durability of a proactive therapeutic drug monitoring strategy introduced at week 10 to infliximab monotherapy. Additionally, the standard of care arm was not protocolized, which meant the timing of TDM and dosing decisions were up to the treating physician. Although a limitation, the objective of the study was to demonstrate that standard of care was inferior to proactive TDM, especially in the face of monotherapy.

Our study demonstrates that patients on infliximab monotherapy who were managed with proactive therapeutic drug monitoring introduced at week 10 to optimize infliximab dosing improved infliximab durability during the first year of treatment. In the absence of concomitant immunomodulation, maintaining higher infliximab concentrations entering into maintenance may counteract the clinical impact of ATI and could represent an alternative strategy to combination therapy. A prospective study replicating our findings and evaluating the cost-effectiveness of optimized infliximab monotherapy vs combination therapy strategies is warranted.

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