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Higher Colonic Tissue Drug Concentrations of Subcutaneous Compared to Intravenous Administration of Infliximab Therapy in Patients With Inflammatory Bowel Disease

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ABSTRACT

Background: Intestinal tissue levels of infliximab (IFX) in patients with inflammatory bowel disease (IBD) treated with subcutaneous (SC) therapy have not been previously assessed.

Objective: To compare serum and colonic tissue IFX concentrations in IBD patients receiving SC versus intravenous (IV) IFX.

Methods: This observational cross-sectional study included IBD patients on stable SC or IV IFX maintenance therapy undergoing routine follow-up colonoscopy. Clinical activity required elevated CDAI or Mayo score plus ≥ 1 biomarker (fecal calprotectin > 250 μg/g or CRP > 5 mg/L). Blood samples and two colonic biopsies were collected for serum and tissue IFX measurements.

Results: Thirty-five patients were included. Serum and tissue IFX concentrations were significantly higher in the SC versus IV group (22 μg/mL vs. 9 μg/mL, $p < 0.001$; 25 μg/g vs. 10 μg/g, $p = 0.002$). Serum and colonic tissue IFX levels were positively correlated in both cohorts (IV: $r = 0.42$; $p = 0.014$; SC: $r = 0.43$; $p = 0.001$). Colonic tissue IFX concentrations were higher in patients with mild–moderate endoscopic activity than in those without active disease ($p < 0.001$). Serum and colonic tissue IFX levels both predicted sustained clinical remission, with optimal thresholds of 14.5 μg/mL ($p = 0.015$) and 17 μg/g ($p < 0.005$), respectively. Colonic tissue IFX showed higher predictive accuracy (AUROC 0.82, $p = 0.01$) than serum (AUROC 0.76, $p = 0.045$).

Conclusions: SC IFX achieved significantly higher serum and colonic tissue concentrations than IV IFX. Colonic tissue IFX levels demonstrated superior clinical relevance and may support future tissue-based therapeutic drug monitoring strategies in IBD.

The first two authors contributed equally to this article.

Key Summary

- Summarise the established knowledge on this subject
  - Serum and colonic tissue infliximab drug levels are correlated in IBD patients receiving intravenous therapy, with colonic tissue concentrations highest in areas of mild to moderate endoscopic inflammation and markedly reduced or absent in segments without visible inflammatory activity.
- What are the significant and/or new findings of this study?
  - Subcutaneous infliximab therapy achieved significantly higher serum and colonic tissue drug concentrations than intravenous infliximab in IBD patients.
  - IBD patients with higher colonic tissue infliximab concentrations had markedly better clinical outcomes.

1 | Background and Aims

Biologic therapies have revolutionized the management of inflammatory bowel disease (IBD), with infliximab (IFX) remaining a cornerstone in both Crohn's disease (CD) and ulcerative colitis (UC). Previous studies have widely described high concentrations of TNF in the intestinal mucosa of patients with IBD when compared with non-IBD controls [1–3]. Recently, subcutaneous (SC) administration of IFX has emerged as a promising alternative to intravenous (IV) administration, demonstrating non-inferior clinical and endoscopic outcomes [3]. In pharmacokinetic (PK) studies, SC administration of IFX resulted in significantly higher drug serum trough concentrations and comparable area under the curve (AUC) when compared to those with IV IFX [4].

Despite these advances, the ultimate therapeutic target of anti-TNF agents in IBD is the intestinal tissue [5]. A positive and gradual relationship between intestinal tissue concentrations of TNF and disease activity has been reported [6]. In a prospective study in patients with UC treated with IV IFX, higher drug tissue concentrations were associated with better disease outcomes, including long term clinical remission [7]. Thus, achieving adequate tissue concentrations of IFX may be critical for achieving a clinical response. However, data about the relationships between circulating and colonic tissue drug concentrations, especially in IBD patients treated with SC IFX, as well as the association between SC IFX serum and colonic tissue drug concentrations and disease outcomes are lacking.

Previous exploratory investigations, including the ATLAS study [8], have shown a positive correlation between serum and tissue infliximab (IFX) concentrations in patients receiving intravenous (IV) maintenance therapy. ATLAS also demonstrated that mucosal IFX concentrations generally mirror the degree of mucosal inflammation, although tissue drug levels tend to decline in the setting of severe disease. However, no study to date has specifically evaluated colonic tissue IFX concentrations in patients with IBD treated with the subcutaneous (SC) formulation.

The primary objective of this exploratory study was to compare serum and colonic tissue IFX concentrations in patients with IBD receiving a stable dose of either SC or IV IFX. A secondary objective was to assess the relationships between serum and colonic tissue drug concentrations and clinical activity, endoscopic disease severity, and IBD-related outcomes.

2 | Patients and Methods

2.1 | Study Cohort

This was a bicentric, cross-sectional exploratory study with a 12-month prospective follow-up conducted at Saint-Etienne and Lyon-Sud University Hospitals. Adult patients (≥ 18 years) with a confirmed diagnosis of inflammatory bowel disease (IBD) receiving maintenance therapy with either intravenous (IV) or subcutaneous (SC) infliximab (IFX) at a stable dose for more than 3 months were eligible. Patients were included at the time of a colonoscopy performed for either dysplasia surveillance or assessment of disease activity. In addition to patients receiving standard maintenance dosing, those undergoing IV IFX dose optimization (10 mg/kg every 8 or 4 weeks) or SC IFX dose escalation (120 mg weekly) were also eligible. Concomitant therapy with immunomodulators was permitted, whereas concomitant corticosteroid use was not allowed. Exclusion criteria comprised isolated perianal disease, isolated proctitis, pregnancy, and age under 18 years. All included patients were followed for a minimum of 12 months.

2.2 | Ethics Statement

This study was conducted in accordance with local legislation and institutional requirements. All patients provided written informed consent to the study, which was approved by the Center National Informatique et Liberté (CNIL number: 1849323).

2.3 | Measurement of Serum and Tissue IFX Concentrations

Serum infliximab (IFX) concentrations were measured at the time of routine colonoscopy in both the SC and IV cohorts. Blood samples for IFX measurement were collected at least 4 weeks after the last IFX infusion during the maintenance regimen. For colonic tissue IFX quantification, two biopsies were obtained from the most inflamed colonic segment; in the absence of visible endoscopic inflammation, samples were collected from normal-appearing mucosa. Biopsies were immediately frozen at −80°C and subsequently processed using the Bio-Plex Cell Lysis Kit. After colonic tissue cutting, homogenates were sonicated at 4°C (Omni Ruptor 205). Tissue and serum IFX concentrations were quantified using the commercial chemiluminescence-based iTrack10 assay (Theradiag, France) in a centralized laboratory, with all analyses performed in a blinded manner. All samples were processed following standardized protocols and the manufacturer's instructions. To verify the assay robustness, replicate extractions from the same biopsy were performed, showing very good repeatability (SD < 15%). Samples were diluted (1:20, 1:10, or 1:4 as

appropriate) with the assay buffer, and IFX concentrations were calculated from the standard curve and corrected for the dilution factor. The lower and upper limits of quantification for the assay were 0.3 μg/mL and 24 μg/mL, respectively. As the assay is drug-sensitive, anti-drug antibodies were assessed only in serum samples with IFX concentrations < 0.5 μg/mL.

2.4 | Definition of Disease Activity Using Clinical Scores and Inflammatory Biomarkers

Clinical disease activity was defined as a CDAI > 220 for CD or a Mayo score > 4 for UC in the presence of elevated inflammatory biomarkers (C-reactive protein > 5 mg/L or fecal calprotectin > 250 μg/g). Endoscopic activity was assessed by experienced endoscopists (X.R., S.N., L.B., A.S.P., and M.B.). For CD, the endoscopist first reported whether the mucosa was inflamed and then graded the severity of inflammation as 0 (no inflammation), 1 (mild), 2 (moderate), or 3 (severe). Mild inflammation corresponded to erythema and loss of vascular pattern with or without scattered aphthae; moderate inflammation to diffuse aphthous ulcerations or larger shallow ulcerations; and severe inflammation to deep ulcerations. For UC, endoscopic severity was scored using the Mayo Endoscopic Score (MES). All endoscopists were blinded to laboratory results and IFX concentrations. During follow-up of at least 12 months, sustained clinical remission was defined as the absence of clinical symptoms and no modification of IFX dosing, no switch to another therapy, and no IBD-related surgery. We also evaluated potential mismatches between serum and tissue IFX concentrations defined as high serum drug levels with low or undetectable tissue concentrations.

2.5 | Statistical Analysis

Categorical variables are presented as number and percentage, and quantitative data as mean ± standard deviation (SD) or median with IQR. Data were compared using Mann-Whitney *U* test for quantitative variables, and chi-square or Fisher's exact tests for categorical variables, as appropriate. Correlations were analysed using the Spearman test. Variables associated with investigated outcomes and also with colonic tissue IFX concentrations were identified by univariate analysis, and those with a p value < 0.10 were introduced in multivariate analysis using binary regression analysis. Given the limited sample size of our cohort ($n = 35$), we adopted a two-step statistical approach to identify independent factors associated with investigated disease outcomes and high colonic tissue IFX concentrations. For this purpose, we performed univariate analyses for each of the 11 parameters of interest (age, sex, IBD type, CD phenotype, disease duration, duration of IFX therapy, concomitant immunosuppressive treatment, SC vs. IV administration, serum IFX concentration after SC administration, clinical IBD activity, endoscopic IBD activity, and prior IFX dose intensification). Each parameter was evaluated individually using Kaplan-Meier survival curves to assess its association with disease outcomes or high colonic IFX tissue concentrations.

The best thresholds of serum and tissue IFX concentrations to predict the investigated outcomes as sustained clinical remission during follow-up were identified using receiver operating characteristic (ROC) curves with Youden index. Sensitivity (SN), specificity (SP), positive (PPV) and negative (NPV) predictive values as well as overall accuracies were determined according to the optimal thresholds using the Youden index. Kaplan–Meier analysis assessed the durability of IFX therapy. The overall accuracy was calculated by adding the true-positive and true-negative results divided by all results (true positive + true negative + false positive + false negative). Statistical analysis was conducted using IBM SPSS Statistics version 19.26 (Bois-Colombes, France).

3 | Results

3.1 | Population Characteristics

A total of 35 patients were included in the study (65% with CD; mean age 39.4 years; sex ratio 1.4) and were followed one year. Twenty-three patients received SC IFX and twelve received IV IFX. At inclusion, 40% of patients had clinically active disease and 57% had endoscopic activity. Demographic and clinical characteristics were generally comparable between the two cohorts, with two exceptions: IFX dose intensification was significantly more frequent in the IV cohort (91% vs. 9%; $p < 0.001$), and patients in the SC cohort were younger than those in the IV cohort ($p = 0.013$). Baseline patient's characteristics are summarized in Table 1.

3.2 | Relationships Between Serum and Tissue IFX Concentrations

The median serum IFX concentration was higher in the SC compared to the IV cohort (22 μg/mL [IQR: 11–22] vs. 9 μg/mL [IQR: 5.9–13.4], respectively; $p < 0.001$) (Figure 1A). The median colonic tissue IFX concentration was also significantly higher in the SC cohort compared with that in the IV cohort (25 μg/g tissue [IQR: 0–45] vs. 10 μg/g tissue [IQR: 0–15], respectively; $p = 0.002$) (Figure 1B). There was a statistically significant correlation between serum and colonic tissue drug concentrations for both the SC cohort ($r = 0.43$; $p = 0.001$) and for the IV cohort ($r = 0.42$; $p = 0.014$) (Figure 1C). In order to verify the robustness of the data obtained, several extractions of the same colonic biopsy were carried out for 10 patients (5 IV IFX and 5 SC IFX), demonstrating the very good repeatability of the tissue assays (SD < 15%) for all measurements. No difference in colonic tissue drug concentrations was observed between patients with UC and those with CD.

3.3 | Colonic Tissue Drug Concentrations According to Endoscopic and Clinical Activity

Colonic tissue IFX concentrations were significantly higher in patients with mild to moderate endoscopic activity compared with those in endoscopic remission and those with severe activity in both the IV and SC cohorts ($p < 0.01$) (Figure 2A). In the SC IFX

TABLE 1 | Baseline characteristics of patients treated with subcutaneous (SC) or intravenous (IV) IFX.

Characteristics	Total (n = 35)	SC IFX (n = 23)	IV IFX (n = 12)	p-value
Mean age, years (SD)	39.4 (15.5)	34.8 (14.5)	48.0 (14.0)	0.013
IFX duration, months (SD)	47 (39)	37 (31)	66 (46)	0.066
SC duration, months (SD)	—	26 (12)	—	—
Median tissue IFX concentration (μg/g, IQR)	14 (0–37)	25 (0–45)	10 (0–15)	0.002
Median serum IFX concentration (μg/mL, IQR)	16 (0–26)	22 (11–22)	9 (5.9–13.4)	< 0.001
Sex ratio (M:F)	1.5	1.4	1.6	—
Crohn's disease/Ulcerative colitis (%)	65/35	53/47	83/17	0.14
UC phenotype (% E3)	—	90%	—	0.85
CD phenotype (montreal classification)	—	3 L1, 6 L2, 3 L3	2 L1, 5 L2, 3 L3	0.15
Clinical activity: *N* (%)	14 (40)	9 (39)	5 (42)	0.86
Endoscopic activity: *N* (%)				
- None	16 (45.7)	9 (39.1)	7 (58.3)	0.54
- Mild	10 (28.5)	9 (39.1)	1 (8.3)	
- Moderate	8 (22.8)	5 (21.7)	3 (25)	
- Severe	1 (2.8)	0	1 (8.3)	
Immunomodulator co-treatment *N* (%)	7 (20)	5 (22)	2 (17)	0.54
IFX optimization *N* (%)	13 (37.1)	2 (9)	11 (91.6)	0.001

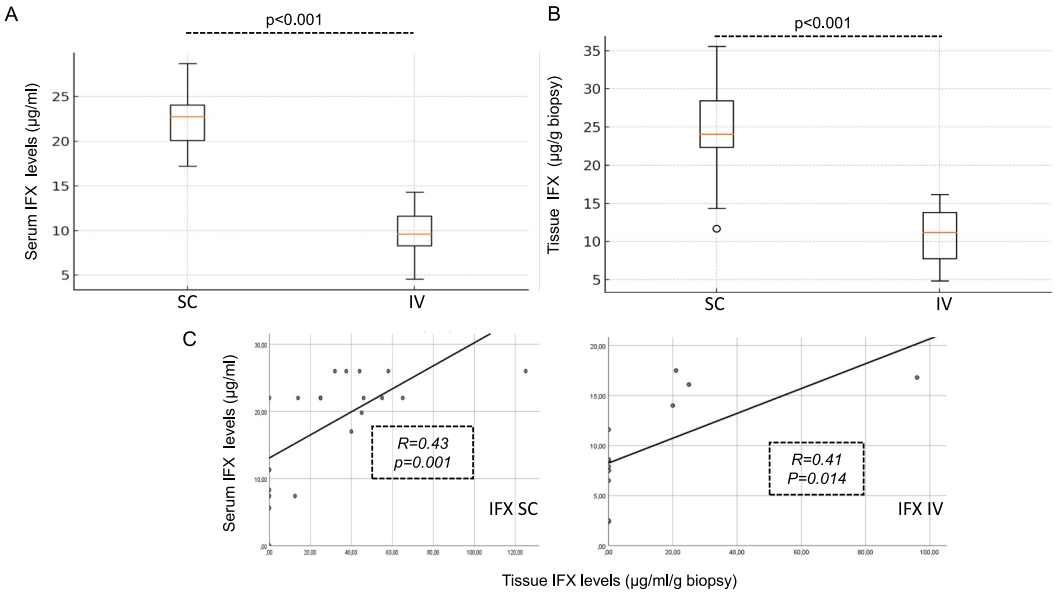

FIGURE 1 | IFX levels according to the mode of administration (SC vs. IV). (A) Serum IFX levels. (B) Colonic tissue IFX levels. (C) Correlations between serum IFX levels and tissue IFX levels.

group, median colonic tissue concentrations were 1 μg/g in endoscopic remission, 38 μg/g in mild activity, and 42 μg/g in moderate activity (p = 0.001); no patient had severe endoscopic disease. Similarly, in the IV IFX cohort, median colonic tissue concentrations were lower in endoscopic remission than in mild or moderate activity (2.2, 12.1, and 14.1 μg/g, respectively; p = 0.04). Only one patient had severe endoscopic activity, with a tissue drug concentration of 2.2 μg/g. Colonic tissue IFX concentrations were also significantly higher in patients with mild to moderate activity receiving SC IFX compared with those treated with IV IFX (38 and 42 μg/g vs. 14.2 and 12.1 μg/g, respectively; p < 0.001) (Figure 2A).

Regarding clinical activity, serum IFX concentrations tended to be lower, without reaching the significative threshold, in clinically active versus inactive patients (p = 0.06), while the SC/IV serum drug concentration ratio remained unchanged (Figure 2B).

3.4 | Serum/Tissue Ratios of IFX Concentrations According to Endoscopic Activity

In the SC IFX cohort, the serum-to-colonic tissue drug concentration ratio was significantly lower in patients with mild

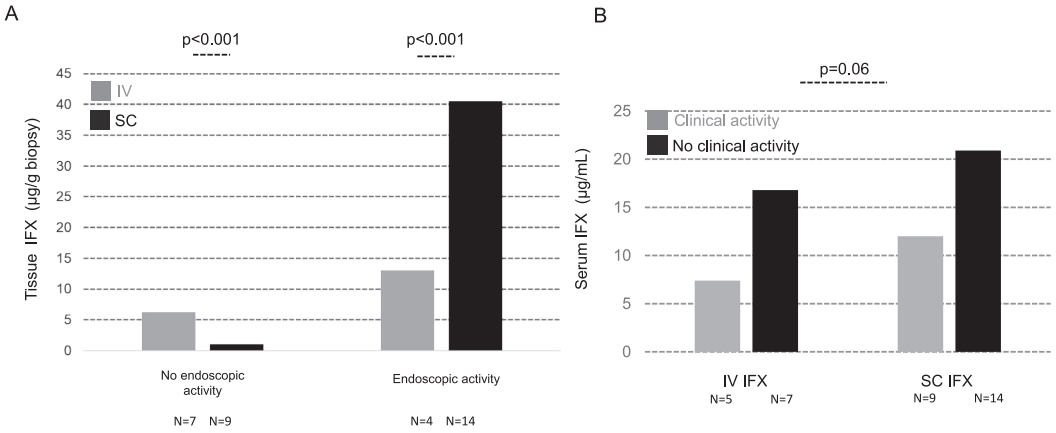

FIGURE 2 | Colonic tissue IFX levels according to endoscopic activity during SC and IV drug administration (A). Serum IFX concentrations according to clinical activity in SC and IV administration (B).

and moderate endoscopic activity (0.7 and 0.5, respectively) compared with those in endoscopic remission (3.2) ($p = 0.01$). No patients receiving SC IFX exhibited severe endoscopic activity. In the IV IFX cohort, the serum-to-colonic tissue ratio was likewise lower in patients with mild and moderate endoscopic activity (1.9 and 2.1, respectively) than in those in endoscopic remission (3.2) or with severe endoscopic activity (5.1), although this difference did not reach statistical significance ($p = 0.06$).

3.5 | Discrepancies Between Serum and Colonic Tissue IFX Drug Levels in Clinically Active Disease

Among the 14 patients with clinically active disease, there was a trend toward lower serum-to-colonic tissue IFX concentration ratios compared with patients in clinical remission ($p = 0.06$ for both), a finding likely driven by lower serum IFX concentrations in clinically active patients ($p = 0.06$). No mismatch—defined as high serum drug concentrations with low or undetectable colonic tissue IFX levels—was observed in this subgroup, except for a single patient in the IV IFX cohort who presented with severe endoscopic activity.

3.6 | Relationships Between Serum and Colonic Tissue IFX Concentrations at the Time of Colonoscopy and One-Year Clinical Disease Outcomes

Sustained clinical remission was assessed in all patients. Receiver operating characteristic (ROC) curve analyses were used to determine the optimal baseline serum and tissue IFX concentration thresholds at the time of colonoscopy for predicting 1-year sustained clinical remission, and Kaplan–Meier analyses evaluated treatment durability. After 1 year, 17 of 35 patients (49%) remained in clinical remission. The remission rate was significantly higher in patients treated with SC IFX (80%) than in those receiving IV IFX (20%). Baseline IFX concentrations were significantly higher in patients who achieved sustained remission. Median serum IFX levels were 12.6 µg/mL (IQR, 7.7–19) in patients who remained in remission versus 6.6 µg/mL (IQR, 3.6–8.4) in those who did not ($p = 0.01$). Similarly, median colonic tissue IFX concentrations were 19.5 µg/g (IQR, 9.5–20) in patients in sustained remission versus 8.4 µg/g (IQR, 4.7–11.3) in those who relapsed ($p < 0.005$). The thresholds with the best discriminative performance were ≥ 14.5 µg/mL for serum IFX concentrations (sensitivity 0.76; specificity 0.78; PPV 0.80; NPV 0.73; accuracy 0.77) and ≥ 17 µg/g for colonic tissue IFX concentrations (sensitivity 0.77; specificity 0.88; PPV 0.87; NPV 0.75; accuracy 0.81). Combining serum and colonic tissue IFX levels did not improve predictive accuracy compared with either marker alone. Kaplan–Meier survival analysis demonstrated significantly better treatment durability in patients with serum IFX ≥ 14.5 µg/mL ($p = 0.015$) and colonic tissue IFX ≥ 17 µg/g ($p < 0.005$) (Figure 3A–B). When comparing AUROC values, colonic tissue IFX concentrations alone (AUROC 0.82) and the combination of colonic tissue and serum concentrations (AUROC 0.83) performed similarly, both outperforming serum concentrations alone (AUROC 0.76) for predicting 1-year sustained remission (Figure 4).

3.7 | Predictive Factors for Elevated Colonic Tissue Drug Concentration (> 17 µg/g)

Univariate and multivariate analyses were performed to identify independent predictors of high colonic tissue IFX concentrations (> 17 µg/g), corresponding to the threshold most strongly associated with one-year sustained clinical remission (Table 2). Three variables were independently associated with high colonic tissue drug levels: SC administration (OR 2.25; 95% CI, 1.19–2.23; $p = 0.001$), serum IFX concentration (OR 1.63; 95% CI, 1.19–2.24; $p = 0.002$), and endoscopic activity (OR 2.04; 95% CI, 1.23–2.85; $p = 0.01$). Neither clinical disease activity, nor concomitant immunomodulator therapy significantly influenced colonic tissue IFX concentrations. ROC curve analysis identified a serum IFX threshold > 14.5 µg/mL as the optimal predictor of high colonic tissue drug concentrations (> 17 µg/g), with an AUROC of 0.94 and excellent diagnostic performance (sensitivity 0.94; specificity 0.94; PPV 0.94; NPV 0.94) (Figure 5).

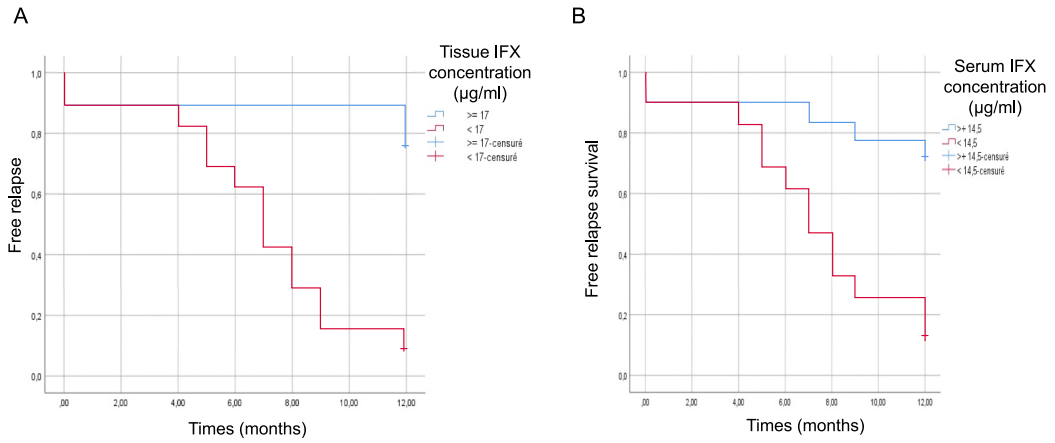

FIGURE 3 | Kaplan-Meier Curves depicting clinical remission during follow-up according to colonic tissue IFX concentration (A) to serum IFX concentration (B).

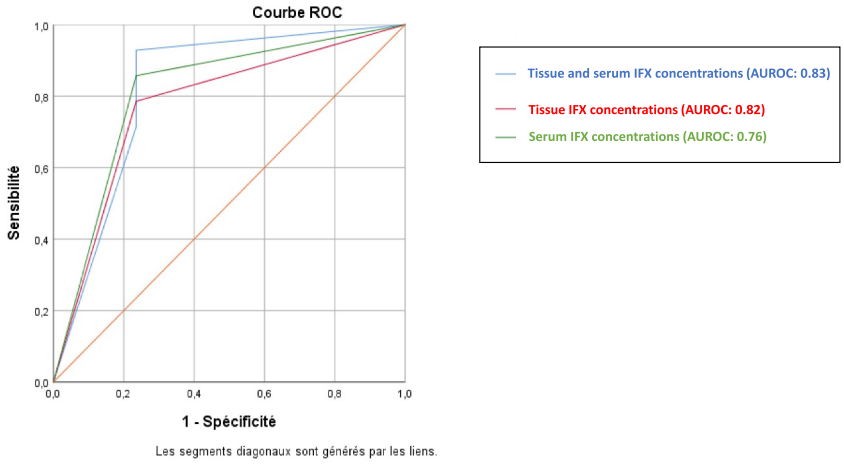

FIGURE 4 | ROC curves analysis to identify serum, colonic tissue and combined serum plus tissue drug concentrations to predict sustained clinical remission during the 1-year follow-up.

TABLE 2 | Independent factors associated with high tissue IFX > 17.0 µg/g of tissue using univariate and multivariate analysis.

Factors	Univariate analysis (*p* value)	Multivariate analysis OR, 95% CI
Age	0.52	
Male versus female	0.87	
CD versus UC	0.32	
Phenotype in CD patients	0.48	
Duration of disease	0.23	
Duration of IFX therapy	0.18	
IMMs	0.34	
SC versus IV	0.002	OR: 2.25 95% CI = [1.193–2.237] $p = 0.001$
Serum IFX concentration (µg/mL)	0.004	OR: 1.634 95% CI = [1.193–2.237] $p = 0.002$
Clinical activity (yes vs. no)	0.09	OR: 0.46 95% CI = [0.39–1.28] $p = 0.07$
Endoscopic activity (mild to moderate vs. absence)	0.001	OR: 2.04 95% CI = [1.23–2.85] $p = 0.01$
Optimization dose before inclusion	0.62	

4 | Discussion

The present prospective, cross-sectional exploratory study is the first to evaluate the relationship between serum and colonic tissue IFX concentrations in patients with IBD treated with either SC or IV IFX. We demonstrated that SC IFX administration resulted in significantly higher drug levels in both serum and colonic tissue compared with IV administration. Importantly, patients achieving higher colonic tissue IFX concentrations experienced significantly better clinical outcomes. These findings are clinically meaningful, as therapeutic efficacy ultimately depends not only on adequate systemic exposure but also on achieving sufficient drug concentrations at the site of inflammation. We also observed a significant positive correlation between serum and colonic tissue IFX concentrations in both treatment cohorts. These results confirm and extend prior observations from Yarur et al. (ATLAS study) [8], which reported similar relationships in patients receiving IV IFX. Tissue IFX concentrations were highest in colonic segments displaying mild to moderate endoscopic inflammation and were markedly reduced—or undetectable—in areas without endoscopic activity. These findings may be explained by increased local TNF production in the inflamed intestinal compartment, leading to greater local binding and retention of anti-TNF antibodies within the tissue. This concept is supported by previous data from the ATLAS study [8], which demonstrated a progressive increase in mean normalised tissue TNF levels with increasing inflammatory severity: 0.36 in non-inflamed tissue, 1.18 in mild inflammation, 6.88 in moderate inflammation, and 5.3 in severe inflammation ($p = 0.0042$). In addition, a significant positive correlation was observed between the grade of mucosal inflammation and normalised tissue TNF levels ($r = 0.4$, $p = 0.003$). Nevertheless, this remains a hypothesis and should be considered as a potential mechanistic explanation rather than a demonstrated causal mechanism.

Preliminary experiments assessing regional variability within the colon suggested that colonic tissue IFX levels were consistent across sampling sites. Attempts to quantify mucosal TNFα were unsuccessful, likely due to complex formation with IFX or concentrations below assay sensitivity. Patients with moderate endoscopic inflammation treated with SC IFX achieved markedly higher colonic tissue drug concentrations (median 42 μg/g) compared with those receiving IV IFX (median 12.1 μg/g), supporting the hypothesis that SC administration may provide superior tissue bioavailability. Finally, both serum and colonic tissue IFX concentrations were significantly associated with sustained clinical remission. Thresholds of 14.5 μg/mL (serum) and 17 μg/g (tissue) predicted 1-year remission with accuracies exceeding 80%. Although the colonic tissue IFX concentration displayed slightly better predictive performance, the sample size limits definitive conclusions. Notably, combining serum and colonic tissue measurements did not improve predictive accuracy beyond the performance of individual markers.

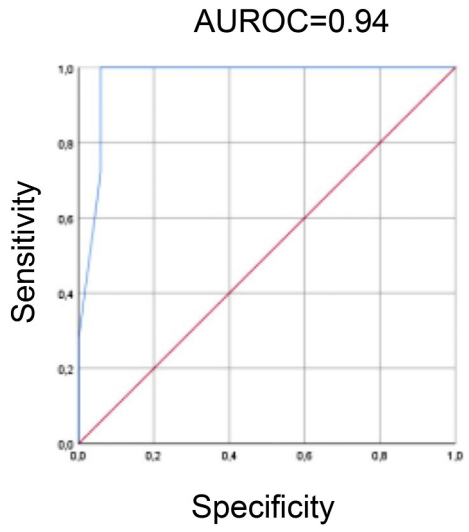

FIGURE 5 | ROC curve analysis to identify serum IFX trough levels predictive of colonic tissue IFX levels > 17.0 μg/g of tissue.

In a prospective study of 25 patients with CD treated with anti-TNF therapy, Yoshihara et al. [9] reported findings that contrast with ours: patients with higher drug levels in noninflamed tissue had significantly higher rates of sustained response compared with those with low tissue levels. Similarly, in a prospective cohort of UC patients receiving IV IFX, Choi et al. [10] demonstrated that lower mean tissue IFX concentrations were associated with a shorter time to relapse, whereas higher concentrations correlated with prolonged remission (Spearman $R = 0.77$, $p = 0.032$). Together, these studies highlight the potential relevance of tissue anti-TNF drug concentrations as a biomarker of disease control. In our cohort, we identified an optimal tissue IFX threshold of 17 μg/g for predicting sustained clinical remission at 1 year (AUROC 0.82). The optimal serum IFX threshold was 14.5 μg/mL (AUROC 0.76). The predictive performance of combining serum and colonic tissue concentrations (AUROC 0.83) was similar to that of tissue concentration alone. Although preliminary, these results suggest that therapeutic drug monitoring (TDM) based on colonic tissue IFX concentrations may play a future role in precision dosing strategies. Furthermore, a serum IFX level ≥ 14.5 μg/mL accurately predicted high tissue drug concentrations (> 17 μg/g; AUROC 0.94), a finding that could inform optimized TDM approaches aimed at achieving adequate mucosal exposure. Conversely, clinical disease activity, concomitant immunomodulator therapy, and disease duration were not associated with tissue drug concentrations, underscoring the limitations of systemic markers in capturing local drug exposure. The association between SC IFX administration and higher colonic tissue concentrations may also help explain the favourable real-world outcomes reported with SC IFX. For example, in the PEREM study [10], fewer than 5% of SC IFX–treated patients experienced loss of response at 1 year. In another recent study of patients with loss of response to IV IFX, switching to SC IFX resulted in high rates of clinical and endoscopic remission [11]. Notably, we observed no mismatch between serum and colonic tissue concentrations in clinically active patients treated with SC IFX, unlike in the ATLAS study using IV IFX [8]. This observation must be interpreted cautiously because of the absence of patients with severe endoscopic activity in the SC cohort.

We acknowledge several limitations in the present exploratory study. First, biopsy samples were obtained from a single colonic site per patient, limiting the assessment of intra-patient spatial variability. Second, TNF levels were not measured in tissue, preventing evaluation of the anti-TNF/TNF ratio, which may

provide greater mechanistic insight than absolute drug levels. Third, the timing of serum sampling in relation to the last IFX dose is a critical factor for interpretation, particularly in the IV cohort given the known pharmacokinetic variability between peak and trough concentrations. Blood samples for IFX measurements were collected at least 4 weeks after the last IFX infusion during the maintenance regimen; however, IFX tissue concentrations were not analysed according to precise sampling time points, although SC IFX is known to maintain stable serum concentrations across dosing intervals [11]. Fourth, sustained clinical remission was defined based on clinical assessment and treatment stability, without incorporating objective biomarkers (CRP, fecal calprotectin) or endoscopic reassessment; however, this definition aligns with clinically relevant treatment endpoints. In addition, endoscopic activity was assessed locally by experienced endoscopists blinded to IFX levels, using qualitative grading. We acknowledge that the absence of validated endoscopic scoring systems and the lack of central reading represent limitations of this study. Finally, this study was designed as an exploratory proof-of-concept investigation, with no a priori sample size calculation and the modest sample size as well as the cross-sectional design limit causal inference regarding long-term outcomes. Despite these limitations, our study benefits from a prospective multicenter design, standardized colonic tissue sampling, centralized blinded assays, and a direct comparison of two clinically relevant routes of IFX administration in well-matched cohorts. Moreover, colonic tissue IFX measurement demonstrated good reproducibility, with low inter- and intra-assay variability (< 20%).

In conclusion, SC IFX achieved significantly higher colonic tissue and serum concentrations than IV IFX in patients with IBD. Colonic tissue IFX concentrations correlated with serum drug levels and was a strong predictor of sustained clinical remission with an optimal threshold value of 17 μg/g. Serum IFX concentration above 14.5 μg/mL reliably predicted high colonic tissue drug exposure. These results strengthen the rationale for SC IFX as a preferred administration route and support future dedicated longitudinal studies integrating tissue-based TDM to optimize treatment personalization.

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Disclosure

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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