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Higher Trough Concentrations of Infliximab are Associated with Clinical Remission and Mucosal Healing in Patients with Inflammatory Bowel Disease

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Abstract

Objective: Few studies have correlated the infliximab (IFX) trough concentration, clinical remission (CM) and mucosal healing (MH). The purpose of the study was to determine if higher IFX trough levels are associated with MH and CR, in a group of Brazilian inflammatory bowel disease patients.

Methods: Cross-sectional study of 51 IBD patients in IFX maintenance therapy, at a medical center, in Brazil. IFX serum levels were obtained from blood samples collected immediately before drug infusion. The IFX trough levels were correlated with clinical and endoscopic scores and a univariate analysis was conducted to identify factors associated with CR and MH.

Results: IFX trough concentration ≥ 2 µg/mL was associated with higher CR (84.2% vs. 28.1%; P<0.001) and MH (83.3% vs. 25.0%; P=0.001). Trough levels of 2.0 µg/mL were 89% specific for CR (sensibility=66%; P<0.001) and 89% specific for MH (sensibility =64%; P<0.001). On univariate analysis, IFX trough concentration was the only variable associated with CR and MH.

Conclusion: The study found a significant association between IFX trough level ≥ 2 µg/mL, CR and MH. Therapeutic drug monitoring is an important tool in IBD patients and should routinely be performed to optimize treatment.

Keywords: Infliximab; Therapy; Monitoring; Biologic availability; Crohn disease; Ulcerative colitis; Remission induction

Introduction

There is increasing evidence that clinical remission (CR) and mucosal healing (MH) are associated with better response to treatment, less hospitalization, lower surgery rates, and improved quality of life in patients with inflammatory bowel disease (IBD) [1,2]. Infliximab (IFX), an anti-tumor necrosis factor alpha (TNF-α) antibody, has promoted MH and improved long-term outcomes in patients with moderately to severely active Crohn's disease (CD) and ulcerative colitis (UC) [3,4]. Despite its effectiveness in both induction and maintenance of remission, a substantial number of patients will eventually loose response [5,6]. Sustained response, long-term CR and complete MH have become major goals in IBD therapy. Recent studies have shown that IFX trough levels higher than 2-3 µg/mL are associated with greater probability of MH and sustained remission [7,8]. However, therapeutic drug monitoring is hardly ever performed in our country. Drug monitoring helps identifying non-responders, who require an alternative treatment, and may prevent over medicalization by allowing reduction of IFX dosage in patients with excessively high bioavailability of the drug. The purpose of the present study was to investigate the association between IFX trough levels and response to treatment, in a group of Brazilian IBD patients.

Methods

Study design setting and participants

A cross-sectional study was conducted at the Proctogastro Clinic, located in the city of Ribeirão Preto, São Paulo, Brazil. Patients with CD or UC receiving maintenance IFX therapy were recruited, from 1st to 31st December 2015. Primary non-responders were not included. The local Institutional Review Board approved the study and all patients provided written informed consent.

Definition of clinical remission and mucosa healing

In patients with CD, CR was defined as a Harvey-Bradshaw Index ≤ 4 and MH as a Simple Endoscopic Score ≤ 2. In patients with UC, CR was defined as a Partial Mayo Score ≤ 2 (with no individual subscore >1) and a Mayo Endoscopic Subscore ≤ 1. CR assessment was performed on the same day of IFX infusion, before blood collection. Elective ileocolonoscopies performed on the same month of blood collection were considered eligible for mucosal healing assessment.

Determination of infliximab serum levels

IFX trough levels were obtained from blood samples collected immediately before drug infusion. Quantitative determination in serum was performed with RIDASCREEN® IFX Monitoring (R-Biopharm AG, Darmstadt, HE), a highly specific monoclonal antibody (MA-IFX6B7) described elsewhere [9]. Levels were divided into three

categories: undetectable (<0.03 μg/mL), low (0.03-2 μg/mL) and adequate (≥ 2 μg/mL).

Statistical analysis

Categorical variables were expressed as frequencies/percentages and continuous variables as means ± standard deviation. One-Sample Kolmogorov-Smirnov test was used to assess the normality of continuous variables. ANOVA test was used to compare continuous variables. Fisher's exact test or $\chi 2$ were used to compare categorical variables. The correlation between IFX trough levels, CR and MH was performed through a receiver operating characteristic curve (ROC) analysis. All p-values were 2-sided, and a significance level of 5% was established. Statistical analysis was performed with IBM® SPSS® Statistics 20 (IBM SPSS, Costa Mesa, CA).

Results

A total of 51 IBD patients were included in the study (44 with CD and 7 with UC). Mean age was 34 ± 13 years. Main characteristics of patients are summarized in Table 1. Mean duration of IFX therapy was 32.1 ± 24 months. Infusion doses were 5 mg/kg in 46 (90.2%) and 10 mg/kg in 5 (9.8%) cases. Intervals between infusions were 8 weeks in 43 (84.4%) and less than 8 weeks in 8 (15.6%) cases. Combination therapy with azathioprine was observed in 16 (31.4%) patients. Concomitant steroid therapy was not reported. Thirty-two patients (62.7%) provided recent ileocolonoscopies and were considered eligible for MH.

	Frequency	
Characteristics	n	(%)
Gender Male Female	32 19	(62.7) (37.3)
Ethnicity White Non-White**	42 9	(82.4) (17.6)
Diagnosis Crohn Disease	44	(86.3)
Ulcerative Colitis	7	(13.7)
Crohn Disease location Ileocolonic Ileal Colonic Anal	18 15 7 4	(40.9) (34.1) (15.9) (9.1)
Ulcerative Colitis location Pancolitis Left sided Proctitis	5 1 1	(71.4) (14.3) (14.3)
Clinical Remission	25	(49.0)
Mucosal Healing*	15	(29.4)
Infliximab TC Undetectable (TC < 0.03 μg/mL) Low (0.03 ≤ TC < 2 μg/mL) Adequate (TC ≥ 2 μg/mL)	19 13 19	(37.3) (25.4) (37.3)
*Mucosal healing was not accessed in 19 (37.3%) patients ** Afro-American and Mixed Race Brazilians		

Table 1: Main characteristics of patients.

The median IFX trough concentration was 1.81 μg/mL (range, 0-10.6 μg/mL). The mean trough level was higher in patients with CR (2.85 μg/mL vs. 0.82 μg/mL; P=0.002) and MH (3.2 μg/mL vs. 1.1 μg/mL; P=0.03) (Figure 1). Similarly, increases in IFX trough concentrations were associated with higher rates of CR and MH (Table 2). No difference in median IFX trough levels was observed across the categories of patients with or without azathioprine combination therapy (1.20 × 0.23 μg/mL; P=0.497). On ROC analyses, serum levels of 2.0μg/ml were 89% specific for CR (sensibility=66%; P=0.001) and 89% specific for MH (sensibility=64%; P<0.001), as illustrated in Figure 2. FX trough concentration was the only variable associated with CR and MH. No association was identified with other variables (age, gender, ethnicity, diagnosis and azathioprine usage). The results of the univariate analysis are shown in Table 3.

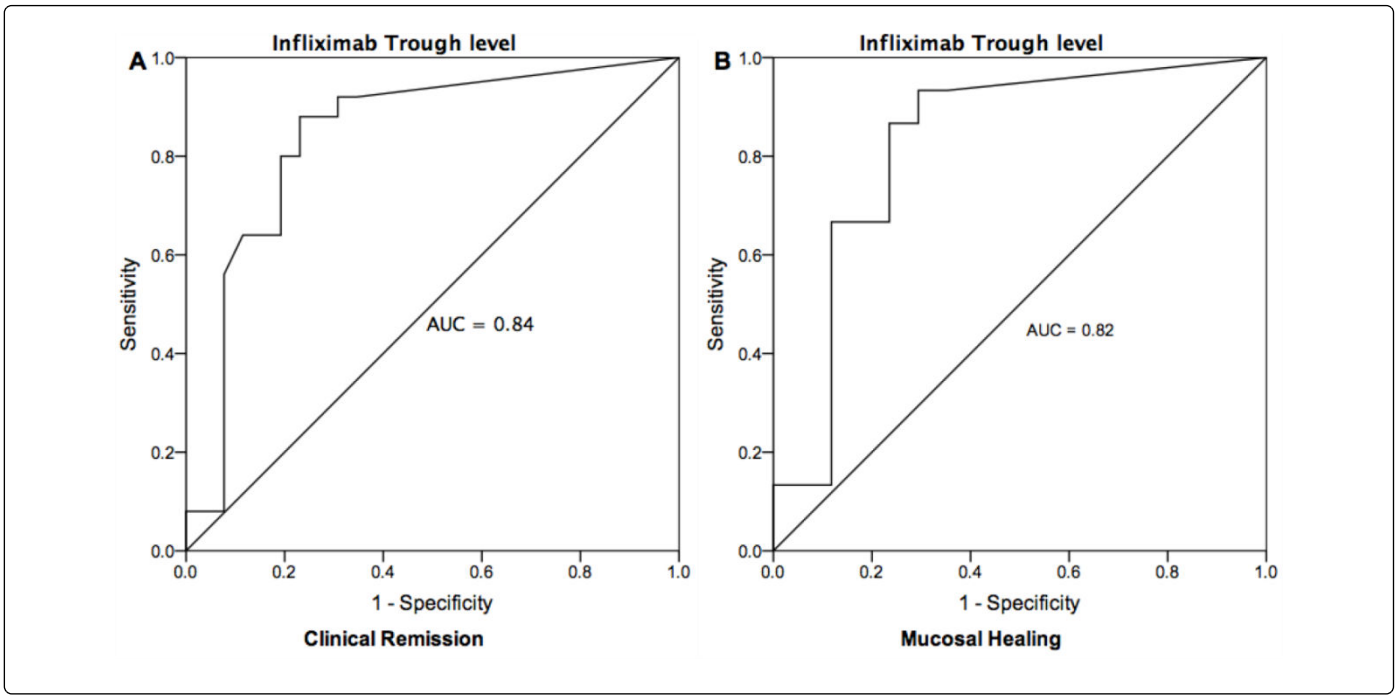

Figure 1: Median Infliximab trough concentrations in patients with and without clinical remission (A) and mucosal healing (B). CR, clinical remission. MH, mucosal healing. IFX-TC, infliximab trough concentration.

	Clinical Remission			Mucosal Healing		
IFX-TC interval	n	(%)	P	n	(%)	P
Undetectable (<0.03 µg/mL)	2	(10.5)	< 0.001	1	(8.3)	0.001
Low (0.03-2 µg/mL)	7	(53.8)		4	(50.0)	
Adequate (≥ 2 µg/mL)	16	(84.2)		10	(83.3)	
IFX-TC, infliximab trough concentration						

Table 2: Percentage of clinical remission and mucosal healing according to infliximab trough concentration intervals.

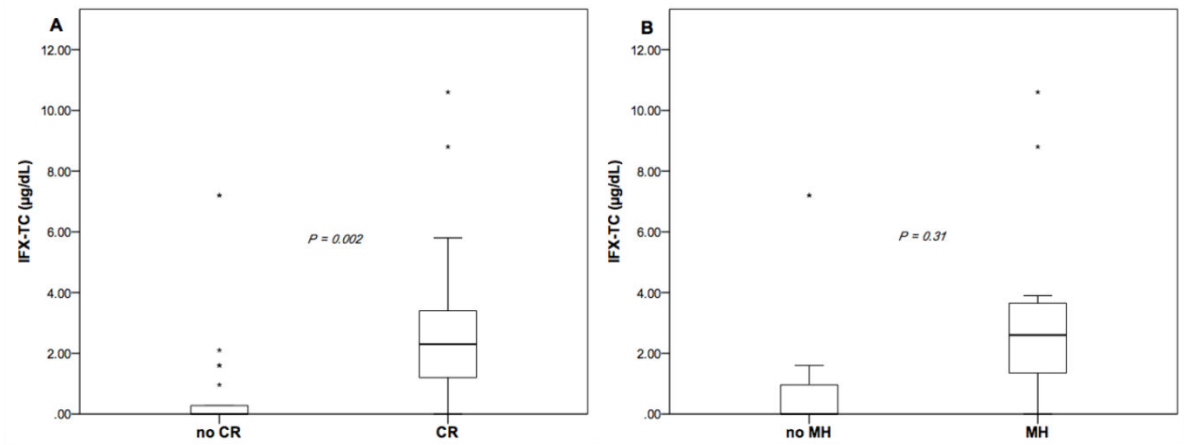

Figure 2: Correlation between IFX trough levels, clinical remission (A) and mucosal healing (B).

	Univariate Analysis					
	Clinical Remission			Mucosal Healing *		
Variables	n	(%)	P	n	(%)	P
Age (years) <40 ≥ 40	8 17	(57.0) (45.9)	.541	8 7	(38.1) (63.6)	.266
Gender Male Female	15 10	(46.9) (52.6)	.776	8 7	(40.0) (58.3)	.467
Ethnicity White Non-white	22 3	(52.4) (33.3)	.465	12 3	(48.0) (42.9)	1.000
Diagnosis Crohn Disease Ulcerative Colitis	24 1	(54.5) (14.3)	.099	14 1	(56.0) (14.3)	.088
Azathioprine Receiving Not receiving	8 17	(50.0) (48.6)	1.000	7 8	(53.8) (42.1)	.720
Trough IFX concentration <2 µg/mL ≥ 2 µg/mL	9 16	(28.1) (84.2)	<0.001	5 10	(25.0) (83.3)	0.003

Table 3: Univariate analysis of variables associated with mucosal healing and clinical remission.

Discussion

Compared to empirical decision, therapeutic IFX monitoring has become a more rational and cost-effective strategy for drug optimization, in IFX-treated IBD patients [8,10]. Higher IFX trough levels are associated with better disease control in terms of MH, sustained long-term remission rates, fewer surgeries, less hospitalization and enhanced quality of life [11-13]. The present study assessed the correlation between the IFX trough levels, CR and MH in a group of patients with IBD treated in our center. We observed that patients with trough levels ≥ 2 µg/mL had higher rates of CR and MH. No other factors such as concomitant use of azathioprine, age, diagnosis (UC or CD) and ethnicity were related with CR and MH. Association between IFX trough levels, CR and MH has been studied by several investigators [5,11,14]. A retrospective analysis of the ACCENT I trial found a significant association between IFX trough levels ≥ 3 µg/mL and sustained remission [15]. A prospective

randomized control trial, involving 263 IBD patients, targeted subjects' IFX trough concentrations to 3-7 μg/mL and observed a more effective and safer use of the drug, in the first year of maintenance therapy [8]. In the COMMIT trial, patients with detectable trough levels of IFX had better response compared with patients with levels below the optimal threshold [16]. Maser et al. found correlation between IFX serum levels and CR, CRP level and endoscopic improvement [17]. Steenholdt et al. found lower IFX concentration in individuals with loss of response compared to those with sustained response [18]. Bortlik et al. have shown that CD patients with therapeutic IFX trough levels measured at the beginning of the maintenance phase have significantly higher chance to sustain their long-term clinical response to IFX [5]. The TAXIT trial recommended dose-escalation in patients with trough concentration ≤ 3 μg/mL and who are loosing response. This resulted in C-reactive protein (CRP) normalization and increased rates of CR in patients with CD. After dose optimization, dose monitoring was associated with few flares during the treatment [8]. More recently, a systematic review of 12 studies reporting IFX levels observed that an IFX trough level >2 μg/mL was statistically associated with clinical and endoscopic remission [7]. In the present study, IFX trough level ≥ 2 μg/mL was the only factor associated with CR and MH. Monitoring patients' IFX trough levels results in a more efficient use of the drug. However, therapeutic drug monitoring is not available in our country. It is important to dose IFX levels because up to 60% of patients with initial response later have secondary loss of response requiring dose escalation or switch to another anti-TNF to recapture response [3,15,19,20]. Therapeutic drug monitoring may help the physicians optimizing anti-TNF therapy, improving clinical and safety outcomes and potentially decreasing the costs. To our knowledge, this is the first study correlating IFX pharmacokinetics and patients' outcome, in our country. Some important study limitations should be noted. First, MH was not accessed in all patients, as well as other biochemical parameters such as fecal calprotectin and CRP. Second, IFX levels should have been measured in more than one infusion. However, a prospective study is been conducted with continued IFX monitoring. Finally, the quantitative analysis with RIDASCREEN® IFX Monitoring has never been performed in our country, which raises concern about the methodology. In conclusion, IFX trough level ≥ 2 μg/mL was associated with significantly higher rates of CR and MH. Therapeutic drug monitoring is an important tool in patients losing response. Further prospective studies with higher number of patients and with increase follow-up is need to prove our results.

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