ASSOCIATION BETWEEN FECAL CALPROTECTIN VALUES AND INFLIXIMAB TROUGH LEVELS IN INFLAMMATORY BOWEL DISEASE PATIENTS

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BACKGROUND

The Monitoring of monoclonal Antibodies Group in Europe (MAGE) recommends measuring biologics concentrations in inflammatory bowel diseases (IBD)[1] and available evidence indicates that this strategy results in clinical benefit and in cost savings[2]. Routine therapeutic drug monitoring (TDM) of IFX and Bayesian prediction as a rational decision tool in combination with follow-up of clinical response for individual dose adjustment has been implemented in our center.

OBJECTIVES

- First goal was to evaluate the relationship between fecal calprotectin (FCP), as a measure of disease activity, and IFX trough concentrations (C_{min}) in three groups of patients: (1) IFX C_{min}< 3 mg/L, (2) IFX C_{min}= 3-7 mg/L and (3) IFX C_{min}> 7 mg/L..
- A second goal was to determine the use of IFX C_{min} as a clinical predictor of FCP<250 mcg/g and to assess the discriminate ability of FCP to predict subtherapeutic IFX C_{min} (defined as C_{min}< 3mg/L).

METHODS

Study design and population: Prospective study of IBD patients treated with maintenance IFX between January 2014 and February 2017.
Evaluations: Blood samples, drawn immediately before IFX infusion to determine IFX C_{min} and fecal samples, within the same IFX cycle of administration to determine FCP, were obtained during the study.
•We measured IFX serum Cmin using a commercially available validated enzyme-linked immunosorbent assay (ELISA) kit (Promonitor®).
•FCP values, obtained within the same infusion cycle as C_{min}, were determined using ELISA.

Statistical and Pharmacokinetic analysis:
•C_{max} and AUC were estimated[3], using Nonmem®7.3.
• Receiver Operating Characteristic (ROC) curves were used to assess the discriminative ability of IFX C_{min} to predict FCP<250mcg/g and discriminative ability of FCP to predict IFX C_{min}<3 mg/L. Statistical analysis was performed using SPSSv19.
Ethical considerations: The study was approved by the Clinical Research Ethics Committee and all patients gave written informed consent.

RESULTS

Study population

A total of 89 patients were included, of whom 46.1% were women. Patients characteristics are shown in Table 1.

Covariate	n=89 patients
Gender	41 (46.1%) female, 48 (53.9%) male
Diagnosis	57 (64%) CD, 32 (36%) UC
Weight	70.5 Kg (60-83)
PCR	1.7 mg/L (0.9-4.7)
Albumin	4.4 g/dL (4.2-4.7)
Smoking habit	15 (17%)
Concomitant immunosupressive therapy	62 (70%)

Table 1. Patients characetristics. CD: Crohn's disease. UC: ulcerative colitis.

FCP and IFX exposure

188 samples were analyzed. Overall mean FCP and IFX C_{min} were 233 mcg/g and 4.1 mg/L, respectively. Nine samples were positive for ATI (5%) (see Table 2). Figure 1 shows de percentage of FCP <250mcg/g according to IFX C_{min}.

FCP (mcg/g)	**233** (77-1225)
FCP<250 mcg/g, n (%)	*97 (52%)*
FCP<150 mcg/g, n (%)	*81 (43%)*
FCP<50 mcg/g, n (%)	*33 (18%)*
C_{min} (mg/L)*	**4.1** (1.9-6.9)
C_{min}<3 mg/L, n (%)	*69 (37%)*
C_{min}=3-7 mg/L, n (%)	*74 (39%)*
C_{max} (mg/L)	**104.4** (99.9-143.8)
AUC (mg/h/L)	**30973.0** (23226.0-39208.8)

Table 2. FCP, C_{min}, C_{max} and AUC values.

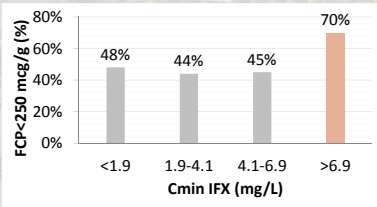

Figure 1. Percentage of samples with FCP <250 mcg/g according to quartiles of C_{min} IFX. The percentage of samples with FCP<250 mcg/g in the last quartile of C_{min} IFX is 1.6 times higher (70%) than in the first, second and third quartiles (45%).

There is higher percentage of samples with C_{min} IFX ≥ 3 mg/L when FCP<250 mcg/g vs FCP≥250 mcg/g (69% vs 57%). Also, the median C_{min} was lower when FCP was ≥250 mcg/g compared with <250 mcg/g (respectively 3.62 vs. 4.7 mg/L; p=0.043) (see Table 3).

FCP	< 250 mcg/g	≥ 250 mcg/g
n=188 samples	n=97 (52%)	n=91 (48%)
C_{min} IFX (mg/L)*	4,7	3,62
C_{min}<3 mg/L, n (%)	*n=30 (31%)*	*n=39 (43%)*
C_{min} =3-7 mg/L, n (%)	*n=35 (36%)*	*n=39 (43%)*
C_{min}>7 mg/L, n (%)	*n=32 (33%)*	*n=13 (14%)*
C_{max} IFX (mg/L)	102,8	107,03
AUC ((mg/L/h)	32386	29876
CRP (mg/L)	1	2.5

Table 3. C_{min}, C_{max} and AUC between FCP. Values are shown as a median. *p=0.043.

Association between FCP and IFX C_{min}

Based on ROC curve analysis, a IFX C_{min} cut-off of >7 mg/L (AUC=0.586; IC95%: 0.504-0.667) was associated with FCP <250 mcg/g (85.7% specificity, 32.9% sensitivity) (see figure 2 and table 4).

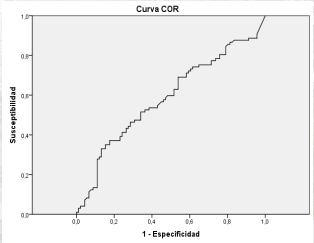

Figure 2. ROC for IFX C_{min} to predict FCP <250 mcg/g.

FCP<250 mcg/g		
IFX C_{min} (mg/L)	Sensitivity	Specificity
1.90	0.773	0.264
3.03	0.691	0.439
4.11	0.557	0.560
5.61	0.412	0.736
7.00	0.329	0.857
10.55	0.082	0.934

Table 4. Sensitivity and specificity values, according to IFX Cmin, to predict FCP <250 mcg/g.

A FCP< 26 mg/L (AUC= 0.596,IC95%: 0.509-0.683) was associated with IFX C_{min} ≥3 mg/L (100% specificity, 100% sensitivity)

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CONCLUSIONS

✓ Significantly higher IFX C_{min} were observed when FCP<250 mcg/g compared to FCP≥250 mcg/g. Also, percentage of samples with C_{min}≥ 3 mg/L is higher when FCP<250 mcg/g vs FCP≥250 mcg/g (36% vs 28%).
✓ IFX C_{min} was a modest predictor of FCP<250 mcg/g and FCP was a modest biomarker to predict C_{min} <3 mg/L.

References: (1) Dressen E. Clinical Pharmacology: Advances and Applications 2017;9:101-111.. (2) Martelli L, Olivera P, Roblin X, et al. J Gastroenterol 2017; 52:19-25(. 3) Fasanmade AA, Adedokun OJ, Blank M, et al. Clin Ther 2011;33:946-64.