IMPACT OF THE rs1143634 POLYMORPHISM OF IL1β ON INFLIXIMAB EXPOSURE IN CROHN'S DISEASE AND ULCERATIVE COLITIS PATIENTS

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BACKGROUND

Infliximab (IFX) predose concentrations (C_{min}) varies greatly between inflammatory bowel disease (IBD) patients. This variability is relevant because there is a relationship between C_{min} and clinical response.

Inter-patient pharmacokinetic (PK) and pharmacodynamic (PD) variability of IFX, clinical outcomes in IBD patients exhibit substantial inter-subject variability. An association between the rs1143634 C allele in IL1β and higher serum IL1β concentrations and a lower response to IFX in Crohn's disease (CD) patients has been reported[1]. Unraveling the impact of genetic polymorphisms on IFX exposure may help to refine therapy and improve clinical outcomes.

PURPOSE

To confirm the effect of the rs1143634 single-nucleotide polymorphism (SNP) of IL1β on IFX exposure and PK in CD and ulcerative colitis (UC) patients.

MATERIAL AND METHODS

- Patients receiving IFX between July 2013 and December 2014 were genotyped for IL1 β polymorphism.
- Associations between this SNP and C_{min} (mg/L), dose-adjusted C_{min} (C_{min}/D, mg.L-1/mg.month-1), area under the concentration-time curve (AUC, mg/h/L) and half-life ($t_{1/2}$, days) at steady-state were evaluated.
- C_{min} were measured using a validated enzyme-linked immunosorbent assay (ELISA) and polymorphism was determined by PCR.
- This study was approved by Hospital research ethics committee and written informed consent was obtained from each patient.
- Fasanmade AA et al[2] population PK model for CD was used in both CD and UC patients.
- PK and statistical analysis was performed using Nonmem®7.2 and SPSS v19, respectively.

RESULTS

- A total of 67 patients were included. Patient characteristics are shown in Table 1.

Gender (Women/Men), n (%)	34(51)/33(49)
C_{min} (mg/L), median (Q1-Q3)	3.27 (0.75-2.41)
ATI positive patients, n (%)	8 (12%)
SAC (g/L), median (Q1-Q3) CC/CT/TT	43 (41-45) 43/42.5/45
Cigarrette smoking, n(%)	14 (21)
Concomitant immunosupressive therapy, n(%)	48 (72)
CD, n(%) UC, n(%)	44 (66) 23 (34)
IFX Regimen	
5 mg/kg/8week, n(%)	50 (75)
Intensified regimen, n(%)	17(25)

Table 1. Characteristics of the study population. Cmin: pre-dose concentrations. ATI: antibodies toward infliximab. CD: Crohn's disease. UC: ulcerative colitis. IFX: infliximab.

- Distribution of allele frecuencies and C_{min} values according to the polymorphism are shown in Figure 1 and Figure 2, respectively.

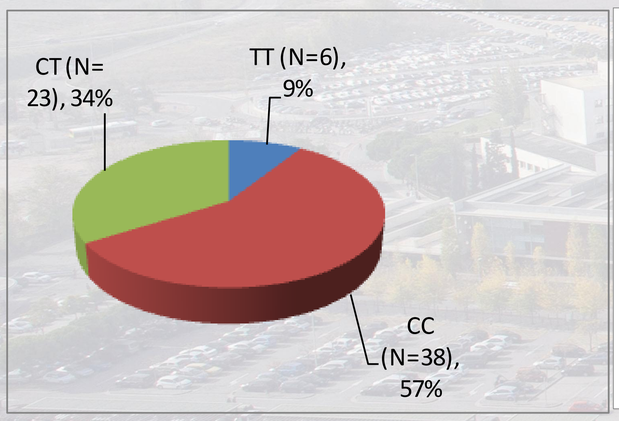

Figure 1. Distribution of allele frecuencies

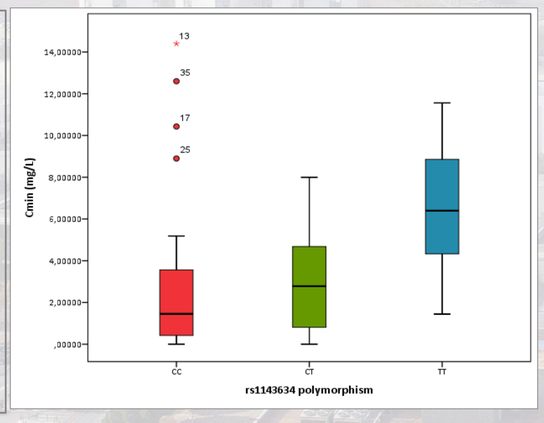

Figure 2. Cmin distribution according to the rs1143634 polymorphism.

All patients (n=67):

- Univariate analysis demonstrated that median C_{min}, C_{min}/D and AUC were statistically lower in carriers C patients than in TT patients. $t_{1/2}$ was significantly lower in CC patients than in CT or TT.
- All patients who developed antibodies toward IFX (ATI) were carriers C (15% of carriers C). 60% of carriers C patients had C_{min}<3 mg/L vs 17% of TT patients.

	CC	CT	TT	p
Cmin (mg/L)	**1.38**	**2.78**	**6.4**	**0.013**
Cmin/D	**0.04**	**0.069**	**0.153**	**0.019**
AUC (mg/h/L)	**21771**	**27825**	**35875**	**0.023**
Cmax (mg/L)	100.85	104.03	101.28	0.199
$t_{1/2}$ (days)	9.46	13.07	13.43	0.038

Table 2. Median estimated individual PK parmeters according to allele distribution.

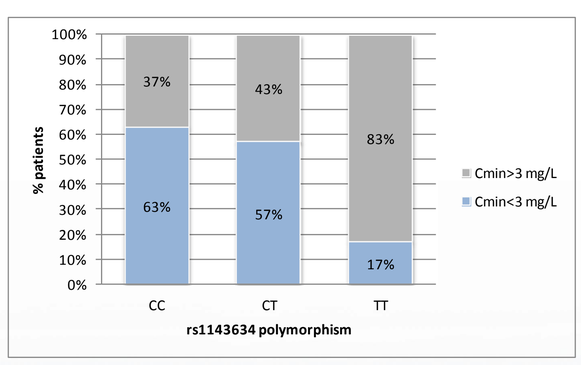

Figure 3. Percentage of patients with Cmin > 3mg/L according to the rs1143634 polymorphism.

ATI negative patients (N=59):

- 59 patients were ATI negative. The analisys of these patients showed that median Cmin and Cmin/D, were significantly lower in C carriers than in TT patients.

	CC	CT	TT	p
Cmin (mg/L)	**2.05**	**3.16**	**6.4**	**0.044**
Cmin/D	**0.05**	**0.079**	**0.135**	**0.038**
AUC (mg/h/L)	25132	28661	34881.5	0.076
Cmax (mg/L)	101.21	103.46	101.28	0.0596
$t_{1/2}$ (days)	10.49	13.11	13.44	0.098

Table 3. Median estimated individual PK parmeters according to allele distribution, in ATI negative patients.

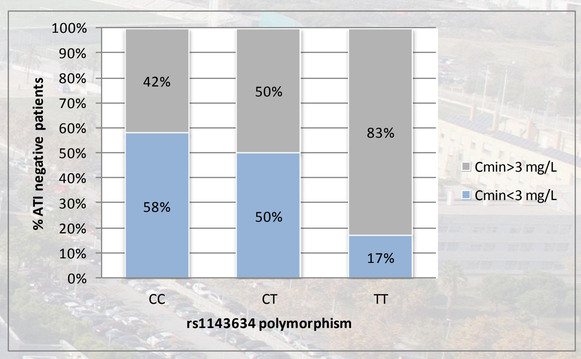

Figure 4. Percentage of patients with Cmin > 3mg/L according to the rs1143634 polymorphism in ATI negative patients.

CONCLUSIONS

- IL1β polymorphisms have a major influence on IFX exposure in IBD patients. C allele was correlated with lower C_{min} and C_{min}/D.
- These results support the importance of IL1 β polymorphisms in IFX induction dose optimization but further studies are needed.

References:

[1] Lacruz-Guzmán D, Torres-Moreno D, Pedrero F, Romero-Cara P, Garcia-Tercero I, Trujillo-Santos J,Conesa-Zamora P. Influence of polymorphisms and TNF and IL1β serum concentration on the infliximab response in Crohn's disease and ulcerative colitis. Eur J Clin Pharmacol. 2013 Mar;69(3):431-8. doi: 10.1007/s00228-012-1389-0. Epub 2012 Sep 8.

[2] Fasanmade AA, Adedokun OJ, Blank M et al. Pharmacokinetic properties of infliximab in children and adults with Crohn's disease: a retrospective analysis of data from 2 phase III clinical trials. Clin Ther 2011;33:946-64.

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