EVALUATION OF A POPULATION PHARMACOKINETIC MODEL OF INFLIXIMAB IN RHEUMATOID ARTHRITIS FOR PREDICTION OF INDIVIDUAL DOSAGE REQUIREMENTS

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BACKGROUND

Infliximab (IFX) is a quimeric anti-tumour necrosis factor-α (anti-TNFα) monoclonal antibody used in rheumathoid arthritis (RA). Its variable clinical response is in part due to the large inter-patient variability observed in serum IFX concentrations.

PURPOSE

The aim of this preliminary study was to evaluate a previously developed population pharmacokinetic model (PPK) for IFX in RA patients as a support tool to guide dosing during therapy and improve response using a external dataset .

MATERIAL AND METHODS

• 16 RA patients (6 with concomitant psoriasis) receiving IFX between July 2014 and July 2015 were included. All patients were treated according to Spanish Society of Rheumatology (SER) recommendations. The standard regimen for IFX was 3 mg/kg at week 0,2 and 6 and then every 8 weeks. Dose adjustments could have been done according to clinical response.

•Serum trough IFX concentrations (C_{min}) and ATI were determined using a validated enzyme-linked immunosorbent assay (ELISA) (Pomonitor®).

•Clinical response was assessed by a rheumatologist by the measurement of the disease activity score (DAS28), number of tender joints and number of swollen joints.

Pharmacokinetic analysis:

•PPK model reported by Ternant D et al (1) was implemented in NONMEM® 7.2. software to be used as a Bayesian predictor:

- •A two open compartment model was parameterized in terms of central (VC) and peripheral (VP) distribution volumes and distributional (CLD) and plasma (CL) clearances.
- •Body weight on Vc and methotrexate (MTX) coadministration and C-reactive protein on CL were the most influential covariates.

•The posterior Bayesian estimates of IFX were predicted by the model and bias (median prediction error, ME%) and precision (root of median squared prediction error, RMSE%) were computed (2).

RESULTS

• A total of 36 serum samples were available for analysis. Baseline characteristics of our study population are shown in Table 1. Median (range) pre-infusion dose and dosing interval were 3 mg/kg (3-5) and 8 weeks (6-10), respectively.

Characteristics	Patients (n=16)
Gender (men/women)	2/14
Age (years)	60.3 (99-78)
Weight (kg)	66 (44-102)
Body surface area (m^2)	1.66 (1.36-1.99)
Serum albumin (g/L)	43 (38-48)
Leucocytes (x 10^9/L)	7.20 (4.10-12.30)
DMARD (yes/no)	15/1
Disease status	
ESR (mm)	10 (2-76)
CRP (mg/L)	3.60 (0.50-60.70)
DAS28	2.26 (0.63-4.71)
Number of tender joints	0 (0-8)
Number of swollen joints	0 (0-8)

Table 1. Patient characteristics. Results are shown as median (range). ESR: Erythrocyte sedimentation rate. CRP: C.reactive protein. DMARD; disease-modifying antirheumatic drug (methotrexate or leflunomide). DAS28: disease activity score for tender and swollen joints.

• 81% of patients received IFX at 3mg/kg/8 weeks, 6% at 5mg/kg/6 weeks and 13% at 3mg/kg/10 weeks. C_{min} distribution according to dosing regimen is shown in Figure 1. Median (range) C_{min} was 0.29 mg/L (0.01-3.87) and 32.4 % of patients had C_{min} > 1.5 mg/L. ATI were detected in the pre-infusion of 2 patients; these patients were also treated with MTX.

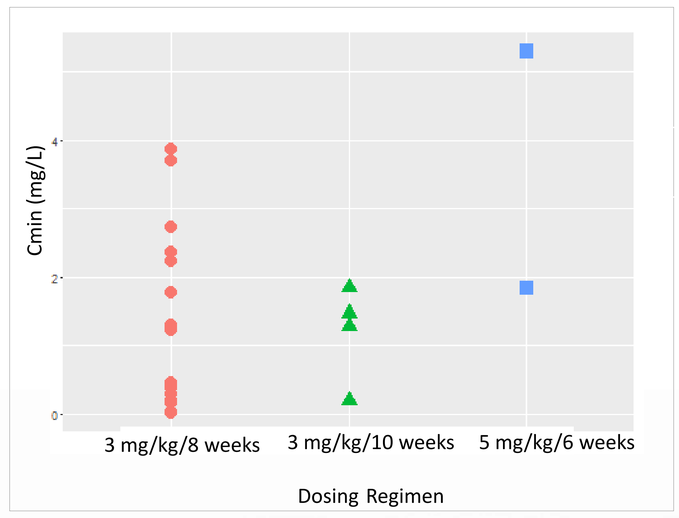

Figure 1. C_{min} distribution according to dosing regimen.

• Bias and precision estimated values were -0.060 mg/L (95% CI: -0.538-0.373) and 0.107 mg/L (95% CI: 0.018-0.670), respectively (Figure 2).

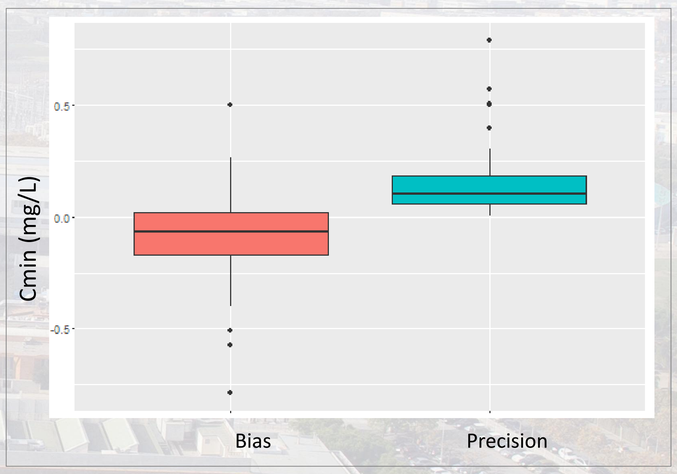

Figure 2. Bias and precision values.

CONCLUSIONS

- Acceptable bias and precision values were found.
- The model reported by Ternant D et al (1) could guide to select the most relevant individual factors explaining variability in future studies.
- Preliminary results of the current study suggested that the PPK model developed by Ternant D et al (1) could guide initial dose calculations and dose adjustment of IFX in rheumatoid arthritis patients. However further validation studies with larger datasets would be required, in the future, before implementing this model as a support tool during the therapeutic drug monitoriing of IFX.

References:

(1)Ternant D., Ducourau E., Perdriger A. et al. Relationship between inflammation and infliximab pharmacokinetics in rheumatoid arthritis. Br J Clin Pharmacol 2013;78(1):118-128.

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