Título: Evaluación comparativa de la capacidad predictiva de distintos modelos PopPK para la individualización farmacoterapéutica de adalimumab en pacientes con Enfermedad Inflamatoria Intestinal

Autores: Márquez-Megías, S[1], Ramón-López, A[1,2], Más-Serrano, P[1,2,3], Díaz-González, M[3], Nalda-Molina, R[1,2].

[1] Universidad Miguel Hernández, Departamento de Ingeniería, Área de Farmacia y Tecnología Farmacéutica, Facultad de Farmacia, San Juan de Alicante, Alicante, España.

[2] Instituto de Investigación Sanitaria y Biomédica de Alicante (ISABIAL- Fundación FISABIO), Alicante, España.

[3]Hospital General Universitario de Alicante, Departamento de Farmacia, Unidad de Farmacocinética Clínica, Alicante, España.

ABSTRACT

Introduction: Adalimumab is an anti-TNF-α recombinant human monoclonal antibody, that has been approved as a therapeutic agent for the inflammatory bowel disease. The treatment with biological drugs can be benefited by the therapeutic drug monitoring (TDM), by calculating the Empirical Bayesian Estimates (EBEs) of the PK parameters. However, there are several Population Pharmacokinetic models (PopPKmod) in literature. A proper evaluation of these models in the target population should be performed before implanted in a clinical routine.

Objective: To evaluate the adequacy and the predictive performance of four PopPKmod of adalimumab in adult patients diagnosed with inflammatory bowel disease.

Methods:

Patients and PopPK models

A retrospective observational study was performed in the General Universitary Hospital of Alicante, with the following inclusion criteria: Adult patients with ulcerative colitis or Crohn's disease treated with adalimumab, with at least two trough plasma concentration (PC_T) between 2014 and 2018.

Four different PopPKmod were evaluated: FDA, 2008 (Mod-A), Ternant et al, 2015 (Mod-B), Sharma et al, 2015 (Mod-C) and Berends et al, 2018 (Mod-D). The models were implemented in NONMEM® v7.3.

Scenarios

The individual and population predictions of adalimumab concentrations were estimated from the four PopPKmod, by calculating the EBEs of the individual pharmacokinetic parameters. Two different scenarios were considered from the dataset to evaluate the model adequacy and predictive performance;

- **Scenario 1**: To evaluate the model adequacy, all PC_T were included, and their population predictions were compared with the observed PC_T
- **Scenario 2**: To assess the predictive performance, only the first PC_T of each patient were used to estimate the EBEs. The PC_T that were left out were evaluated with the individual prediction calculated by the EBEs.

Statistics

To validate the four PopPKmod, the bias and precision of the PC_T predictions were estimated by calculating the mean predictive error (MPE) and the mean square predictive error (MSPE), respectively. In both cases, the closest to zero, the most accurate and precise, respectively. Bland-Altman analysis were also performed to calculate the 95% agreement limits between individual predictions and observations.

Results: The dataset comprised 55 patients and 129 PC_T.

The model that performed better in term of bias and precision, in both scenarios, were MOD-B.

In the same way, the model that obtained a narrower agreement limits in the Blandman-Altman analysis was MOD-B.

Conclusions: The model adequacy analysis and the evaluation of the predictive performance of the four pharmacokinetic models found in literature showed that the model of Ternant D, et al performed better than the other 3.
Therefore, this model would be the preferred to be used in the clinical routine for the dose individualization of Adalimumab for patients with inflammatory disease, in the General Universitary Hospital of Alicante.