Covariate analysis of infliximab in Crohn's disease using available pharmacokinetic models as prior

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Background and Objectives

A substantial proportion of patients with Crohn's disease lose response to the monoclonal antibody infliximab (IFX) [1]. In some patients, maintenance IFX therapy induces an immune reaction and development of anti-drug antibodies (ADAs). ADAs have been associated with increased drug clearance (CL), acute infusion reactions and loss of response. ADAs developed in different individuals differ in terms of affinity to IFX, abundance, biologic effect (neutralising/non-neutralising) and persistence of the immune reaction. To date, the ADA impact on IFX CL is often assessed as a binary covariate. This study aimed to elaborate the PK model of IFX in Crohn's disease exploiting the prior knowledge from two published population pharmacokinetic (PK) models [2,3] to further assess covariates affecting CL with a focus on the implementation of ADAs.

Results

The PK models showed good parameter agreement, both when compared internally (Table 1) as well as with general PK traits of the monoclonal antibody drug class [8].

The resulting prior-model was a 2-compartment model using the transformed estimates from the Fasanaad model for V1, V2 and Q.

All structural parameters were scaled allometrically with body weight (fixed exponents).

Typical CLs were assumed to represent the mean of the population and other covariate relations originally included in the models were removed.

Due to the sparse data situation, V1, V2 and Q as well as their IVVs were fixed during further model development. CL and IVV for CL were implemented using the PRIOR functionality using 2 priors (re-parametrised CL estimates, Table 1).

Results (cont.)

All implementations of the ADA covariate improved the fit of the base model (Table 2). The HUMSA ADA concentration caused the highest drop in OFV as well as the best improvement in predictive performance (GOF plots and VPCs). The implementation largely corrected for the slight over-prediction of concentrations in ADA+ samples and under-prediction of the ADA- samples as seen in the base model (Figure 1).

No other candidate covariate was found significant.†

Table 2. Parameter estimates from base model and different ADA covariate models. Values in grey columns are based on ADA information from the HUMSA and the white columns are based on RGA.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Base model</th>
<th>ADA+ patient</th>
<th>ADA+ sample</th>
<th>ADA- patient</th>
<th>ADA- sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>OFV</td>
<td>-414</td>
<td>-442</td>
<td>-444</td>
<td>-447</td>
<td>-422</td>
</tr>
<tr>
<td>ΔOFV (base)</td>
<td>-28.1</td>
<td>-29.9</td>
<td>-33.6</td>
<td>-7.69</td>
<td>-97.5</td>
</tr>
<tr>
<td>CL l/day</td>
<td>0.318 (4.7)</td>
<td>0.265 (6.0)</td>
<td>0.275 (6.4)</td>
<td>0.289 (5.0)</td>
<td>0.304 (4.8)</td>
</tr>
<tr>
<td>Q l/day</td>
<td>0.147</td>
<td>1.27</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADA impact</td>
<td>0.700 (25)</td>
<td>0.451 (24)</td>
<td>0.1038 (24)</td>
<td>0.538 (45)</td>
<td>0.301 (38)</td>
</tr>
<tr>
<td>IV CL/CV</td>
<td>32.9 (3.3)</td>
<td>32.2 (3.3)</td>
<td>32.6 (3.3)</td>
<td>32.4 (3.3)</td>
<td>32.7 (3.4)</td>
</tr>
<tr>
<td>IV V2/CV</td>
<td>12.6†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prop error</td>
<td>50.6 (7.8)</td>
<td>47.9 (10.4)</td>
<td>47.2 (8.6)</td>
<td>43.5 (10.9)</td>
<td>50.7 (11)</td>
</tr>
</tbody>
</table>

Fixed, Values are estimates (%RSE).

Figure 1. (right). Visual predictive checks for base and selected ADA model. Upper: IFX concentration versus days after dose. Lower: fraction below the quantification limit. Lines: 10%, 50% and 90% percentiles (blue: observed, black: simulated). Shaded areas: 95% confidence intervals.

Figure 2 (below). Observed IFX concentrations versus individual and population predictions (inlet) for the selected ADA model.

Conclusions and Perspectives

Based on data from an investigator-initiated clinical study and two published PK models we confirmed and elaborated the impact of ADAs on IFX CL. The total ADA concentration (HUMSA) improved the predictive performance the most.

No other covariate was found significant, potentially as a result of the low patient number in this dataset. Although not identified here, sAb, for example, may still be a covariate to consider as it recently was confirmed in a population model for inflammatory bowel diseases [9].

The developed PK model will be used to investigate the PK/PD relationship of IFX in CD, aiming to identify the effective therapeutic range.

References


CLINICAL PHARMACY