Characterization of Anti-Drug Antibodies Using a Bivariate Mixed Hidden-Markov Model

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Introduction

Certolizumab Pegol (Cimzia®) is a PEGylated antibody fragment used in the treatment of rheumatoid arthritis (RA). After administration, the immune system may produce specific anti-drug antibodies (ADA), which may influence Cimzia®'s pharmacokinetics (PK). ADA against Cimzia® have been characterized with an ELISA technique and can result in transient or persistent PK effects[1]. Due to drug interference with its measurement assay, false negative data may arise. Thus, in some patients, ADA may not be measureable despite the disposition of the drug being altered. In this work, a novel model-based method for ADA characterization is presented using mixed hidden Markov models (MHMM), allowing for inferences about ADA formation given a set of ADA and drug PK observations[2,3].

Objectives

i) Develop and apply a bivariate two-state MHMM to PK and ADA data following Cimzia administration.

ii) Determine whether parameter estimates are reasonable and whether the model can predict individual state sequences to identify onset of ADA production.

Methods

Data, model and estimation

- Phase II data from a clinical trial aiming to assess the efficacy and safety of 6 doses (50-800 mg) of Cimzia® versus placebo administered Q4W in patients with RA was used in this work. The total number of evaluated patients was 239 with an average of 9 PK/ADA observations over a maximum of 13 weeks.
- ADA were measured using an ELISA and subjects were considered to be positive when ADA > 2.4 U/mL.
- A previously developed PK model not including ADA as a covariate was fit to data following the first dosing occasion. The resulting model was used to predict the PK observations following the subsequent dosing occasions. The obtained individual weighted PK residuals (PK_{RES}) were used in addition to ADA measurements (ADA_{MEAS}) as continuous dependent variables to inform the MHMM.
- The MHMM (Fig. 1) included 2 hidden states; no ADA production (S_{NOADA}) and ADA production (S_{ADA}), transition probabilities; from S_{NOADA} to S_{ADA} (π_{N-A}) and from S_{ADA} to S_{NOADA} (π_{A-N}), and the estimated modes for the PK_{RES} and ADA_{MEAS} in the respective states and associated variances ($\omega^2_{PK_{RES}}$ and $\omega^2_{ADA_{MEAS}}$, respectively). PK_{RES} and ADA_{MEAS} were assumed to be normally distributed through a bivariate Gaussian function.

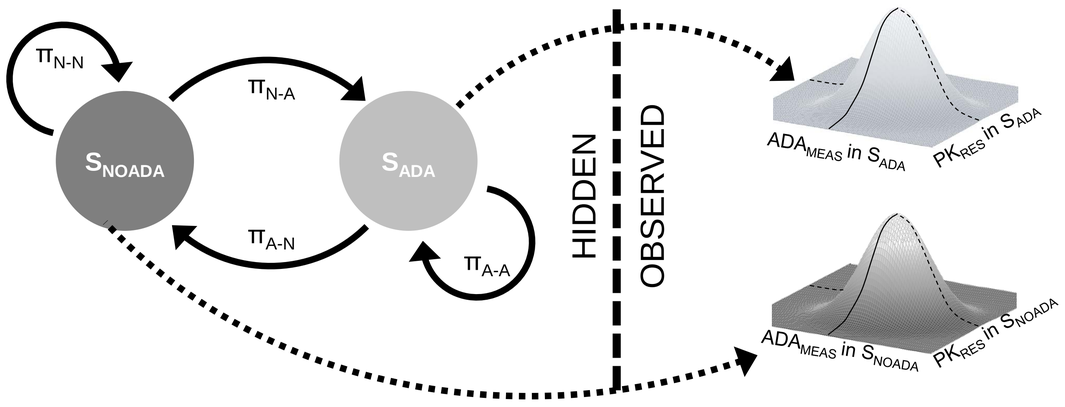

Figure 1: Bivariate MHMM structure.

- Parameter estimation was performed in NONMEM 7.3 using IMPMAP.
- Estimated parameters were compared with the expected parameter estimates given knowledge of the system.

Individual state predictions compared with clinical ADA positivity

- The model with the best individual state sequence predictions (subjectively chosen after looking at the individual plots) was chosen over models with the most accurate parameter estimates.
- Individual state predictions were obtained using the Viterbi algorithm implemented using a user-written NONMEM subroutine.
- Clinical ADA positivity (ADA_{MEAS} > 2.4 U/mL) was compared to the model predicted ADA states in the individuals with regards to the time-to-positive ADA as it may be of interest to identify ADA early.

Conclusions

- ✓ Parameter estimates resulting from the MHMM were reasonable and close to the expected parameter values.
- ✓ The model was able to characterize ADA against Cimzia® and suggested that ADA occur earlier than conventional ELISA ADA measurements.
- ✓ The results suggest that the bivariate MHMM may be able to identify ADA based on ADA assay and/or PK impact.

Results

Data, model and estimation

Parameter estimates resulting from the model were in-line with the expected parameter values (Table 1). Initially, the mode for ADA_{MEAS} in S_{ADA}, was estimated to 8.69 resulting in poor predictions of individual state sequences. ADA_{MEAS} in S_{ADA} was therefore fixed to 2.4 U/mL, the clinical cutoff point for ADA positivity. None of the individuals in the data had obvious transient ADA formation, the estimate for π_{A-N} therefore approached 0. Interindividual variability (IIV) was only included on the transition parameters in the model. The estimation of IIV proved to be difficult and these were associated with high %RSE (>100), in agreement with previous investigations[4]. However, individual state sequence predictions were markedly improved with the addition of IIV.

Table 1: Fixed effect parameter estimates in the MHMM.

Parameter	Estimation	Expectation	Rationale
π_{N-A}	0.08	<0.5	Majority of observations in the data should not be associated with ADA, individuals are therefore likely to stay in S_{NOADA}
π_{A-N}	10E-5	~0	There were very few (if any) individuals with transient ADA
PK_{RES} in S_{NOADA}	0.36	~0	PK residuals are anticipated to be close to zero when the model describes adequately the data - when there is no ADA
PK_{RES} in S_{ADA}	-1.4	<0	Negative residuals imply PK model overprediction - anticipated when ADA is being produced
ADA_{MEAS} in S_{NOADA}	0.6 FIX	0.6	When there is no ADA production, ADA levels should be LOQ (0.6 U/mL)
ADA_{MEAS} in S_{ADA}	2.4 FIX	>2.4	When there is ADA production, ADA levels should be greater than the clinical cutoff point for positivity (2.4 U/mL)
$\omega^2_{PK_{RES}}$	0.58	None	We do not have an expectation for $\omega^2_{PK_{RES}}$ as the scaling of the residuals did not result in unit variance
$\omega^2_{ADA_{MEAS}}$	3.5	None	The variance of the ADA measurements is relatively high (ADA measurement range = [0.6, 300])
Correlation in S_{NOADA}	-0.12	< 0 or ~ 0	The correlation between the ADA measurements and PK residuals should be negative in S_{ADA}
Correlation in S_{ADA}	-0.15	< 0	

Individual state predictions compared with clinical ADA positivity

Individual state sequence predictions are illustrated in Fig. 2. Both false positives and false negatives appear to be identified with the developed model (Patients 3 and 4 in Fig. 2, respectively). However, other sources than ADA resulting in possible model misspecification are not considered resulting in a possible overprediction of the number of ADA positive subjects.

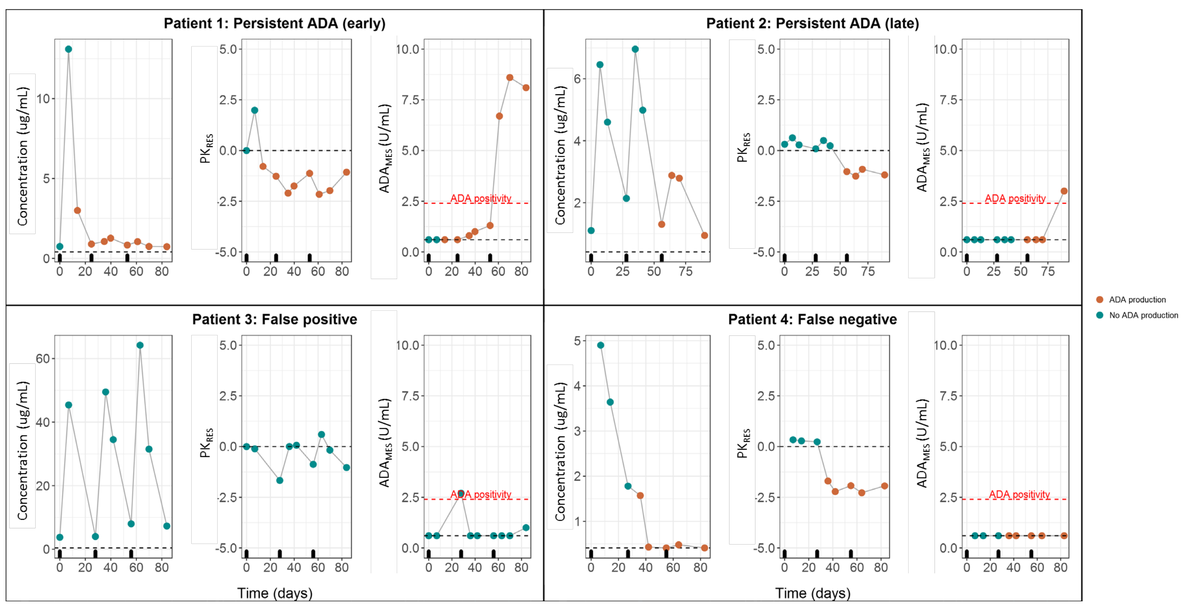

Figure 2: Concentrations (left panel), PK residuals (middle panel) and ADA measurements (right panel) for 4 selected individuals in the dataset. The color of the points indicates the model predictions of ADA states (orange for ADA production and cyan for no ADA production). The rug (black ticks on the x-axis) indicates dosing times for each individual. The black dashed line (left panel) indicates the LOQ of Cimzia, the red dashed line (right panel) indicates the cutoff-point for ADA positivity for the ADA measurements. The model predicted ADA state appears to relatively correlated with the ADA measurements where high ADA measurements are most often associated with a model predicted state signaling ADA production.

The average times to positivity were 47.7 and 60.9 days for the model predicted states and clinical positivity, respectively.

References

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