Impact of rise in anti-drug antibodies on the pharmacokinetics of the monoclonal antibody adalimumab

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INTRODUCTION

- Human monoclonal antibodies (mAbs) are a fast-growing class of biotherapeutics
- Pharmacokinetic (PK) characteristics of mAbs are complex and highly variable between individuals
  - Nonlinear elimination[1]
  - Influence of anti-drug antibodies[2]

AIM

- Quantitate pharmacokinetics (PK) of the monoclonal antibody adalimumab, with specific focus on the role of anti-drug antibodies (ADAs) on elimination process

METHODS

PK and immunogenic data from a biosimilarity trial[3] (n=198) of adalimumab in which healthy volunteers received single s.c. dose of 40 mg of ONS-3010 (test product, T), Humira® EU or Humira® US (reference product, R)

- Blood samples (n=5203) were obtained at 54 min pre-dose, 2, 12, 24 hours post-dose, then 2 times per day for 8 days followed by weekly sampling until week 10 and analyzed for adalimumab
- Four ADA observations were obtained per individual

- **Population PK model development**
  - Structural model development included comparison of
    - One, two or three compartments
    - Linear and/or non-linear absorption
    - Linear and/or non-linear elimination
  - Log normal interindividual variability was assumed
  - Residual variability
    - Additional, proportional or combined error models were tested
  - Covariates that were tested;
    - Weight, height, age, BMI, BSA, LBW, dosing formulation
    - ADAs as continuous covariate, based on linear interpolation between the observations
  - Model evaluation was performed using
    - Goodness-of-fit plots, numerical analysis, visual predictive check, bootstrap analysis

RESULTS

Exploration of the data showed that individuals with high ADAs exhibited reduced total exposure over time (Fig. 1)

- **One-compartment model** with linear absorption and Michaelis-Menten elimination best described the data
- **Anti-drug antibodies**
  - Implementation of ADAs as direct effect on Vmax greatly improved the individual fits
  - ADA ranged from [60 – 57953.5 ng/mL] for which a scaling factor (SF) was required
  - As a result, the overall Vmax ranged from [37.77 – 357.89 µg/h] in the final model
- **Interindividual variability** was identified on Ka, V and KM (Table 1)
- **Residual variability** was best described by proportional error model
- **Covariates**
  - Weight on V (0.47**) according to V = V * WT/WTmedian
  - Dosing formulation could **not** be identified as a covariate on any of the PK parameters
- **Model evaluation & predictive performance**
  - PK parameter show high accuracy and precision (Table 1)
  - GOF: observations follow central and individual trend of (Fig. 2)
  - VPC: captures central trend (Fig. 3 & 4)

$$DADT(1) = -KA*A(1)$$

$$DADT(2) = KA*A(1) - (Vmax*(1+ADA*SF))*C/(KM+C)$$

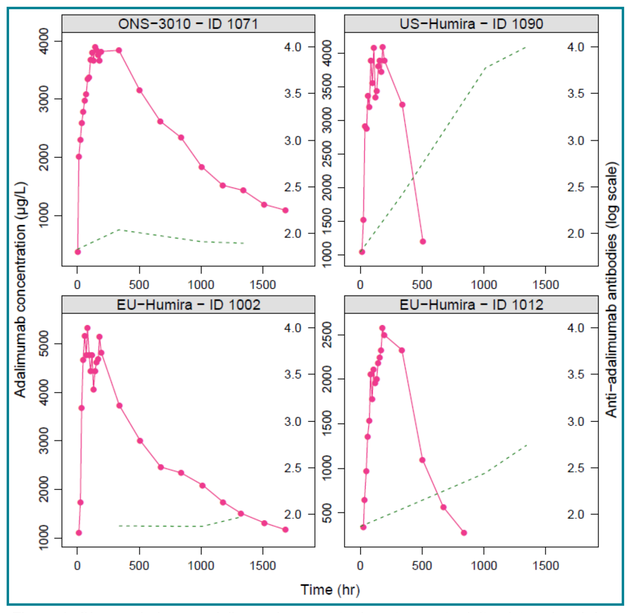


Figure 1: Observed plasma adalimumab concentrations (magenta, left axis) and anti-drug antibody concentrations (green, right axis, log transformed) presented over time. Two left graphs represent typical individuals with low anti-drug antibody concentrations, two right graphs represent typical individuals with high drug concentrations.

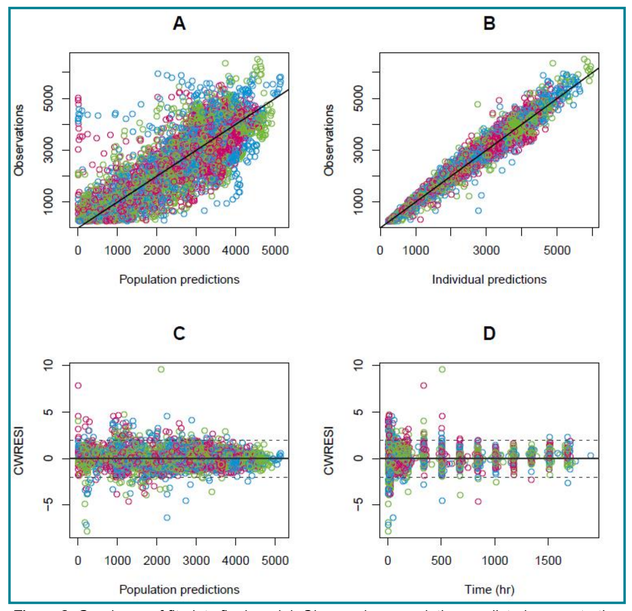
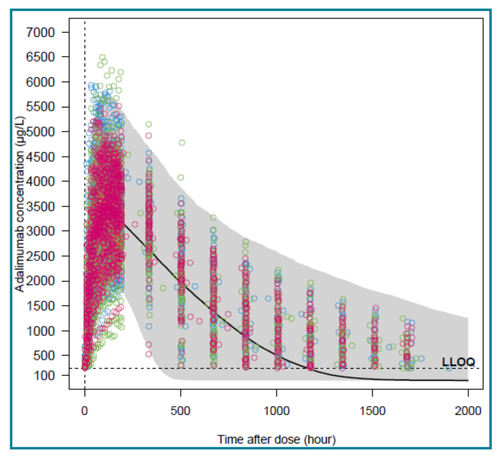


Figure 2: Goodness of fit plots final model. Observed vs population predicted concentration (A), observed vs individual predicted concentration (B), conditional weighted residuals with interaction (CWRESI) vs time (C), conditional weighted residuals vs population predictions (D). Each treatment is represented by different color (blue: EU-licensed Humira, green: US-licensed Humira, magenta: ONS-3010).

	Final model	Without covariate ADA	Bootstrap results
OFV	54214.583	54653.983	54343.4
Fixed effects[a]	**Estimate** (RSE%)		**Parameter mean** (95%-CI)
K_A (h^{-1})	0.027 (4.28)	0.025 (4.32)	0.026 (0.024 – 0.029)
V (L)	9.25 (1.59)	8.89 (1.55)	9.2 (8.83 – 9.54)
V_{max} (µg·h^{-1})	37.5 (6.91)	73.8 (2.43)	45.9 (31.4 – 59.9)
K_M (µg·L^{-1})	1510 (12.5)	2100 (7.61)	1637 (1235 – 2106)
Scaling factor	0.00309 (24.3)	-	0.00156 (0.00024 – 0.00525)
Random effects	**Estimate** (CV%)		**Parameter mean** (95%-CI)
$\omega^2 K_A$	0.361 (65.9)	0.354 (65.2)	0.359 (0.275 – 0.452)
ω^2 V	0.0396 (20.1)	0.0396 (20.1)	0.0391 (0.0296 – 0.0525)
$\omega^2 K_M$	0.796 (110)	0.841 (115)	0.6996 (0.374 – 1.375)
ω^2 Scaling factor	1.85 (232)	-	6.36 (0.001 – 0.0166)
Residual error			
σ^2 proportional	0.0122	0.0147	0.0127 (0.0104 – 0.0146)

Table 1: Population PK parameters estimates of final model with inclusion of ADA effect on Vmax and reduced model without inclusion of ADA effect on Vmax together with bootstrap results. RSE; residual standard error, CV; coefficient of variation, ω2; between-subject variance, σ2; residual variance, CI; confidence-interval.



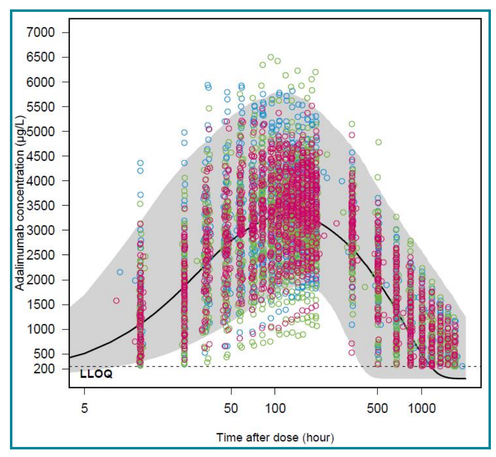


Figure 3 & 4: Visual predictive checks of final model.
Amount is specific per treatment. Per individual (n=198), 360 timepoints were simulated (0h – 300h; every 2.5h, 300h – 1000h; every 5h, 1000h – 2000h; every 10h. Each treatment is represented by different color (blue: EU-licensed Humira, green: US-licensed Humira, magenta: ONS-3010).

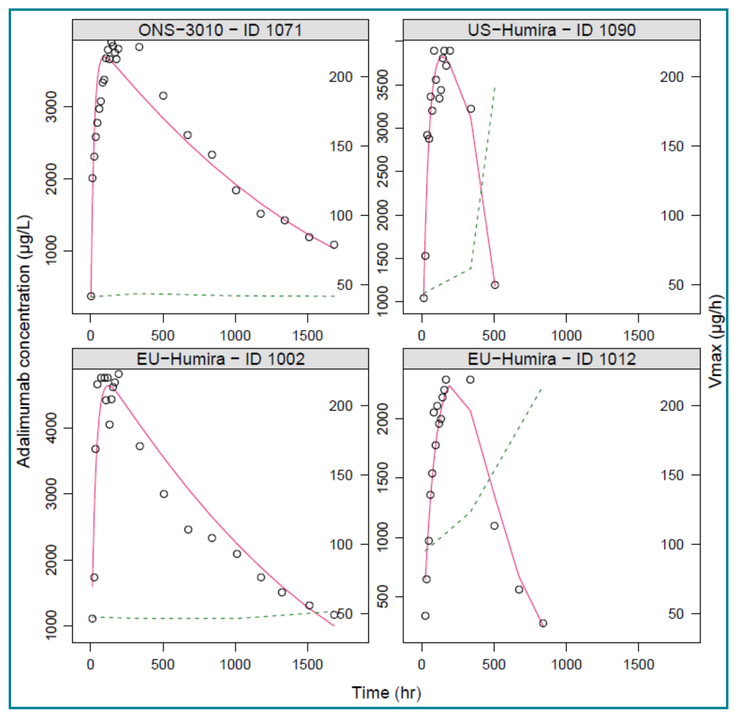


Figure 5: Observed plasma adalimumab concentrations (black circles, left axis) and individual predictions (magenta, left axis) and maximum elimination rate (green stripes, right axis) presented over time. Two left graphs represent typical individuals with lower Vmax, rates two right graphs represent typical individuals with high Vmax rates.

CONCLUSIONS

- **PK model suggests that a rise in anti-drug antibodies significantly increases the Michaelis-Menten clearance of adalimumab by increasing Vmax**

DISCUSSION

- ADAs may contribute to **reduced exposure** and hence **lower efficacy**
- In future studies with more data on ADAs appears superior to the currently applied linear interpolation

REFERENCES

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