



Dynamic interaction modeling of adalimumab and anti-drug antibodies in ankylosing spondylitis

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Background

Adalimumab (ADAL), a human immunoglobulin G1 monoclonal antibody, has been approved for the treatment of ankylosing spondylitis, a disease characterized by inflammation. Immune response following the administration of ADAL can lead to the generation of anti-drug antibodies (ADA) which may influence the pharmacokinetics of ADAL.

Objective

To develop an integrated model to describe the in-vivo kinetics of both ADAL and ADA in patients with ankylosing spondylitis.

Methods

Patients

A total of 132 patients treated with ADAL for ankylosing spondylitis were enrolled in the present study, yielding 539 trough concentrations of ADAL and 399 concentrations of ADA.

Sample measurement

The concentration of ADAL was measured using a validated sandwich enzyme-linked immunosorbent assay (ELISA). The concentration of ADA was measured by combining an electrochemiluminescence immunoassay with an immunomagnetic separation strategy.

Data analysis

Data analysis was performed using NONMEM. All parameters were estimated using NONMEM's first-order conditional estimation method (FOCE) with interaction (INTER). The model schematics is shown in Figure 1.

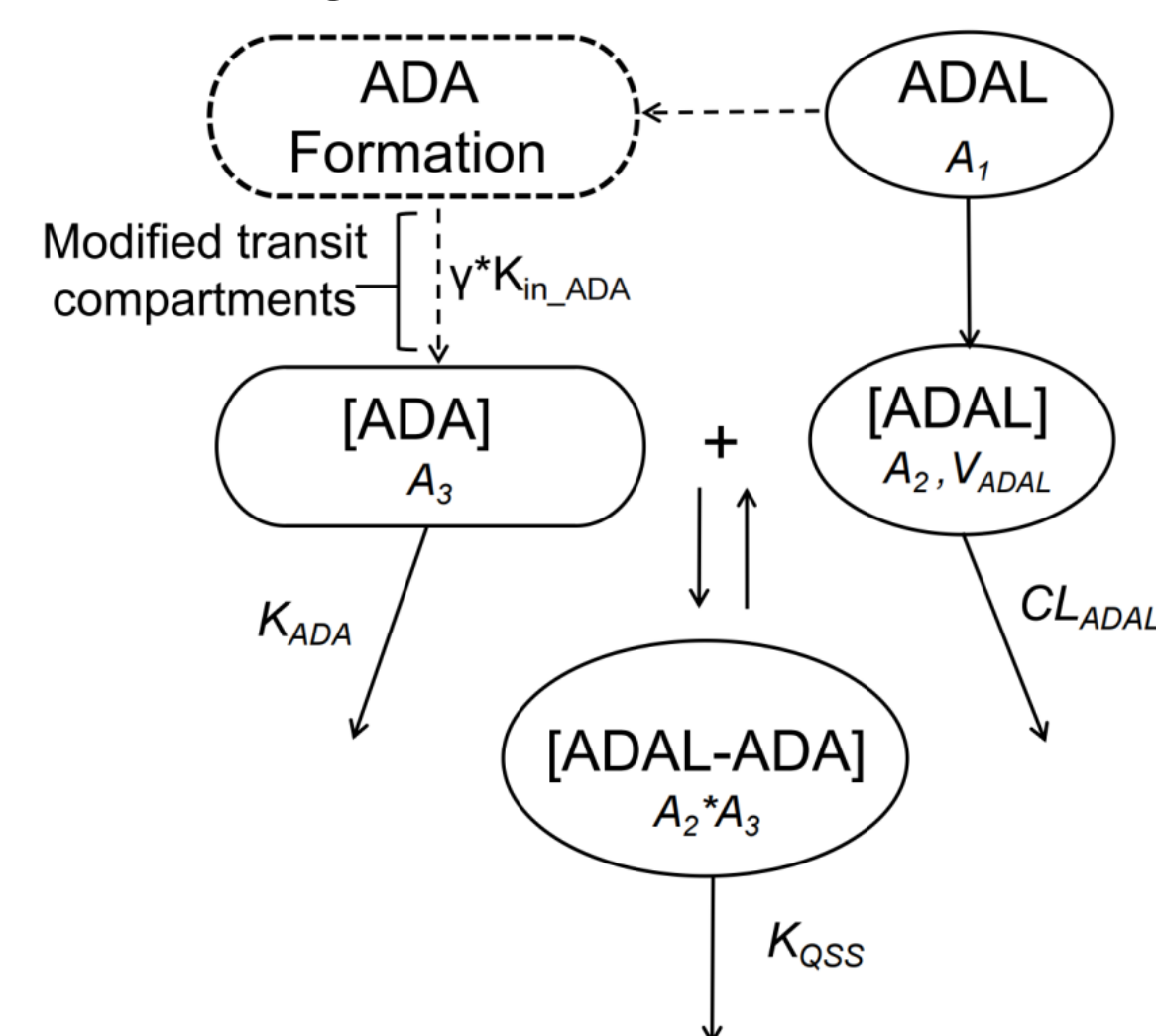


Figure 1. The schematic diagram of integrated adalimumab PK and ADA model structure. This diagram describes the adalimumab PK, the ADA formation and elimination, and the complex mediated pathways of ADAL and ADA.

The differential equations of the structural model schematics are shown as follow.

$$\frac{dA_{ADAL}}{dt} = K_a \times A_1 - \frac{CL_{ADAL}}{V_{ADAL}} \times A_2 - K_{QSS} \times \frac{A_2 \times A_3}{V_{ADAL}} \quad \text{Equation 1}$$

$$\frac{dA_{ADA}}{dt} = \gamma \times K_{in_ADA} - K_{ADA} \times A_3 - K_{QSS} \times \frac{A_2 \times A_3}{V_{ADAL}} \quad \text{Equation 2}$$

$$\gamma = 1 - \left[\sum_{i=1}^n \frac{(K_{tr} \times t)^{n-i}}{(n-i)!} \right] \times e^{-K_{tr} \times t} \quad \text{Equation 3}$$

Covariate model

A stepwise process was used to screen the potential covariates. All the covariates were individually introduced into the model to screen the significant covariates (significance level set at 0.01, df=1, and change in OFV=6.63). A nonparametric bootstrap analysis including all the screened significant covariates was subsequently performed for the full model. The 95% bootstrap confidence interval (CI) was used to determine whether the covariate explained part of the variability in the parameter, and the covariate was eliminated if this CI included a value indicating no effect of the covariate as a predictor of individual differences (intermediate model). Finally, each covariate was eliminated from the intermediate model to establish the final model (significance level set at 0.001, df=1, and change in OFV=10.83).

Model evaluation

The bootstrap resampling and prediction-corrected visual predictive check (pc_VPC) were used to evaluate the accuracy and robustness of the final model. The mean values and 2.5–97.5 percentiles of the parameter estimates obtained from the bootstrap replications were compared with the parameter estimates from the final model obtained from the original dataset.

Results

- An integrated model encompasses the dynamic interaction between ADAL bindings to ADA, and the increased clearance via complex mediated pathways, which are integral to the distribution and elimination processes of ADAL.
- A one-compartment model with first-order absorption and elimination was employed to characterize the pharmacokinetics of ADAL.
- A one-compartment model featuring modified transit compartments and first-order elimination was utilized to describe the in-vivo kinetic process of ADA.
- This modified approach effectively captures the dynamic nature of ADA, which demonstrates a delayed onset followed by intensified responses during subsequent repeated doses, while allowing for a reduction in ADA input following the variable duration of response intensification. The number of transit compartments was fixed at three.
- Body weight was introduced into the CL/F and V/F of ADAL with the allometric scaling model. Notably, the CL/F parameter of for ADAL increased with rising levels of C-reactive protein.

Table 2 Final model and Bootstrap parameters

Parameter	Original	average	2.5%ile	97.5%ile	RSE
POP_CL (L/d)	0.583	0.577	0.510	0.696	7.6%
POP_V (L)	14.1	13.9	12.0	15.2	5.4%
RUV_PROP_ADAL	0.139	0.137	0.0755	0.152	15.0%
RUV_ADD_ADAL (mg/L)	0.417	0.418	0.310	0.582	14.8%
POP_KIN_ADA (mg/d)	0.528	0.510	0.399	0.589	9.4%
POP_KTR (d-1)	0.0512	0.050	0.041	0.061	9.1%
POP_KADA (d-1)	0.182	0.182	0.154	0.287	70.8%
POP_KQSS (L/(d*mg*mg))	9.32	9.32	7.81	12.6	12.0%
RUV_PROP_ADA	0.5	0.499	0.433	0.543	5.0%
RUV_ADD_ADA (mg/L)	5.15E-05	5.15E-05	2.71E-05	1.08E-04	39.5%
FCRP_CL	0.234	0.172	0.077	0.269	27.9%
BSV_CL	0.509	0.509	0.447	0.605	7.3%
BSV_V	0.234	0.233	0.063	0.260	21.9%
BSV_Kin_ADA	0.696	0.695	0.477	0.943	17.3%
BSV_KTR	0.588	0.588	0.353	0.926	21.2%
BSV_KADA	0.089	0.089	0.065	0.174	287.4%
BSV_KQSS	1.396	1.393	0.955	1.645	12.0%
BOV_CL	0.319	0.318	0.217	0.370	11.2%
BOV_V	0.075	0.075	0.068	0.178	42.5%

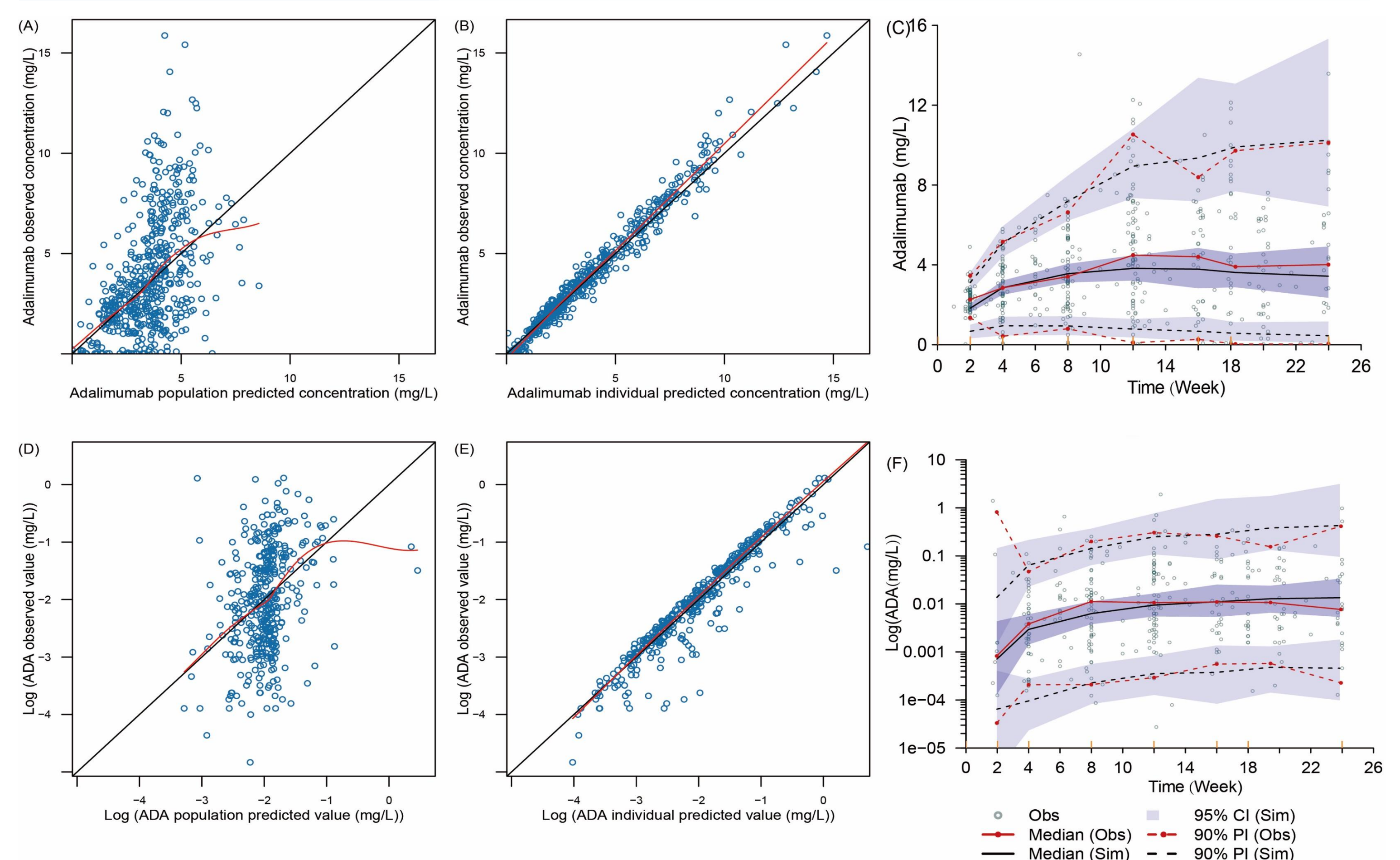


Figure 2. The goodness of fit (GOF) and prediction-corrected visual predictive checks (pcVPC) of the final model. A: ADAL observed concentrations v.s. population predicted value; B: ADAL observed concentrations v.s. individual predicted value; C: ADAL pcVPC; D: Log(ADA observed concentrations) v.s. Log(population predicted value); E: Log(ADA observed concentrations) v.s. Log(individual predicted value); F: ADA pcVPC.

Conclusion

- A dynamic interaction model of ADAL and ADA was established in patients with ankylosing spondylitis.
- The in-vivo kinetic parameters of ADA were estimated in these patients, which could be used to predict the dynamic profile, and subsequently inform the individual dosage of ADAL.

References

- Ponce-Bobadilla AV, Stodtmann S, Chen MJ, et al. Assessing the Impact of Immunogenicity and Improving Prediction of Trough Concentrations: Population Pharmacokinetic Modeling of Adalimumab in Patients with Crohn's Disease and Ulcerative Colitis. Clin Pharmacokinet. 2023;62(4):623-634.
- Williams JH, Liao KH, Yin D, et al. Implications of Immunogenicity Testing for Therapeutic Monoclonal Antibodies: A Quantitative Pharmacology Framework. AAPS J. 2024;26(2):31.
- Ding X, Xue L, Wang M, et al. Dynamics and implications of anti-drug antibodies against adalimumab using ultra-sensitive and highly drug-tolerant assays. Front Immunol. 2024; 15:1429544.

Table 1. Demographic characteristics of the patients

Patient characteristic	Value
Gender (male/female)	100 (75.8%) / 32 (24.2%)
Age (years, range)	36.1±9.4 (18-78)
Height (cm, range)	168.3±7.2 (150-186)
Weight (kg, range)	68.3±11 (44.5-100)
C-reactive protein (mg/L, range)	5.69±12.1 (0.06-171)
Albumin(g/L, range)	47.1±2.0 (31.5-53.3)