I-21

vc-MMAE antibody-drug conjugates: a unified model describes pharmacokinetics of eight different compounds

Leonid Gibiansky[2], Matts Kågedal[1], Jian Xu[1], Nina Wang[1], Charles Chen[1], Sandhya Girish[1], Jin Jin[1], Chunze Li[1]
(1) Genentech, Inc., South San Francisco, CA; (2) QuantPharm LLC, North Potomac, MD

ABSTRACT

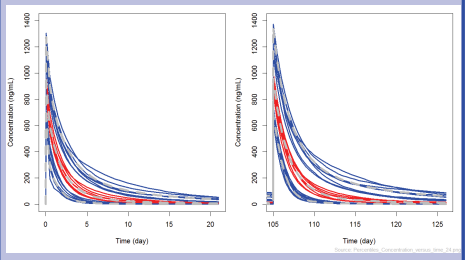
Purpose: ADCs developed using Vc-MMAE platform share the same antibody technology, linker, and toxin (MMAE). The similarity of ADC structures resulted in similar PK properties. The goal of the analysis was to develop a mega model that simultaneously described antibody-conjugated MMAE (acMMAE) data from multiple ADCs, and assess differences and similarities of model parameters and predictions among different compounds.

Methods: Clinical data of 8 ADCs were obtained from 8 studies with ADC doses ranging from 0.1 to 3.2 mg/kg every 3 weeks (Q3W). Initially, data were treated as coming from the same ADC. Models with time-dependent clearance (CL) and parallel linear and Michaelis-Menten (MM) elimination were explored. Effects of weight, sex, and dose were evaluated by inclusion in the model. After the unified covariate model was developed, differences in model parameters between ADCs were investigated. A series of mega-models, from the model with all common parameters to the model with all compound-specific parameters were developed. Alternatively, the inter-compound variability was described explicitly using the third random effect level implemented using LEVEL option of Nonmem 7.3. Visual predictive checks (VPC) were used to assess ability of the models to predict PK for each compound.

Results: A two-compartment model with time dependent CL; CL and central volume (VC) increasing with weight; VC higher for males; and CL mildly decreasing with the dose described acMMAE PK of 8 ADCs. MM elimination had only minor effect on PK and was not included in the final model. Time-dependence of CL had no effect beyond the first dosing cycle. The model with all parameters shared by all compounds provided reasonable acMMAE predictions and VPC plots for all compounds. For the model with all compound-specific parameters, CL and VC were similar among ADCs, with the inter-compound variability of 17% and 7%. Similar results (15% and 5%) were obtained when the inter-compound variability was described using LEVEL option. Differences among ADCs were minor relative to the inter-subject variability as illustrated in Figure 1.

Conclusions: The population mega-model successfully described acMMAE PK of 8 ADCs. PK of acMMAE are largely comparable across different vc-MMAE ADCs. The model can be applied to predict properties of ADCs under development, estimate individual exposure for the subsequent PK-PD analysis, and propose optimal dosing regimens. PK of acMMAE is similar among ADCs of the same platform.

Figure 1: Time courses of acMMAE following administration of 2.4 mg/kg doses were simulated. **Red and blue lines**: medians and 95% prediction intervals of simulated individual concentration-time courses of eight ADCs for model with compound-specific parameters. **Gray lines**: medians and 95% prediction intervals for the model with compound-independent properties. **Left**: Concentrations following the first dose; **Right**: Steady-state concentrations.



Data

Table 1 Observed acMMAE data from 8 different compounds

Compound (Target)	Number of Subjects	Number of Samples	Doses
CD22	89	1775	0.1 - 3.2 mg/kg Q3W
CD79B	95	1812	0.1 - 2.4 mg/kg Q3W
ETBR	51	793	0.3 - 2.8 mg/kg Q3W
MUC16	74	258	0.3 - 3.2 mg/kg Q3W
NAPI2B	68	753	0.2 - 2.8 mg/kg Q3W
Steap1	57	1596	0.3 - 2.8 mg/kg Q3W
Drug X	<30	~1300	0.3 - 2.4 mg/kg Q3W
MsLN	49	1011	0.2 - 2.8 mg/kg Q3W
Total	~500	~9500	0.1 - 3.2 mg/kg Q3W

Model Structure

According to [1], acMMAE PK can be described by a linear two-compartment model. Two-compartment linear model with time-dependent clearance was used:

$$CL=CL_T \cdot \exp(-K_{DES} \cdot T)+CL_{INF}$$

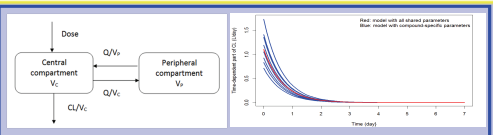
Proportional error model was used:
Random effects on CL, V_C, V_P, Q, CL_T, and ε
Final Covariate Model:

$$CL_{INF} \sim (WT/75)^{CLWT} \cdot (Dose/2.4)^{CLdose}$$

$$V_C \sim (WT/75)^{VWT} \cdot (V_{SEX})^{SEX}$$

$$V_P \sim (WT/75)^{VWT} \cdot (V_{SEX})^{SEX}$$

$$Q \sim (WT/75)^{QWT}$$



Model with all compound-specific parameters (Nonmem 7.3.0 coding)

Method 1 (Inter-compound variability with $LEVEL option)

```
$PK
…
 CLINF = EXP(MU_1+ETA(1)+ETA(7))
 VC    = EXP(MU_2+ETA(2)+ETA(8)) …
…
$LEVEL
NDRUG=(8[1],9[2],10[3],11[4],12[5],13[6])
$OMEGA BLOCK(2)
 0.16          ; 1 IIV_CL
 0.04 0.027    ; 2 IIV_V1
…
$OMEGA
 0.1           ; 8 IDV for CL
 0.1           ; 9 IDV for V1
 …
$EST METHOD=IMPMAP INTERACTION   ; recommended with
;                                ; $LEVEL
```

Method 2 (Compound-specific THETA parameters)

```
$INPUT … DRUG …
$ABBR REPLACE THETA(DRUG_CL) = THETA(1,12 to 18 by 1)
$ABBR REPLACE THETA(DRUG_V1) = THETA(2,19 to 25 by 1)
…..
$PK
….
 MU_1 = THETA(DRUG_CL)+…; MU-ref . NOT required
 MU_2 = THETA(DRUG_V1)+ …
CLINF = EXP(MU_1+ETA(1)
VC    = EXP(MU_2+ETA(2)
…
$THETA
 (0,0.29,1)     ; 1 CLINF
 (0,1.21,2)     ; 2 VC
…
 (0,0.29,1)x7   ;12-18 CLINF
 (0,1.21,2)x7   ;19-25 VC
 …
```

Summary for models with compound-specific parameters

1. Model parameters for Method 1 model are provided in Table 1; Method 1 and Method 2 results were similar;
2. Inter-compound variability (ICV) was much smaller than inter-individual variability (IIV);
3. Method 1: All model parameters, except ICV, were estimated precisely; ICV was estimated with large RSEs;
4. Method 1 ICV results were consistent with the summary statistics for Method 2 variability of population parameters among 8 compounds (Table 2);
5. Both methods provided good fit of individual data, good fit of each compound data, and good agreement of observed data and simulations (Visual Predictive Check diagnostics);
6. Time-dependent part of clearance declined rapidly, reaching negligible levels by Day 3 differences between the first-dose PK and steady state PK were relatively minor (Figure 1);
7. As would be expected, acMMAE steady-state CL_{inf}, V_C, V_P, and Q increased with weight;
8. acMMAE central and peripheral volume were slightly larger in males;
9. Unexpectedly, acMMAE steady-state CL_{inf} mildly decreased with dose increase. While we were not able to find any plausible biological or clinical explanation, the effect was consistent among most compounds. It remained in the model even when additional nonlinear elimination pathways were added.

Table 1 Model with $LEVEL Option

Parameter	Units	Typical Value		IIV		ICV	
		Value	RSE%	CV%	RSE%	CV%	RSE%
CL_{INF}	L/day	1.37	3.1	39.2	5.3	14.5	83.6
V_C	L	3.40	1.1	15.4	8.0	5.4	363
V_P	L	2.74	3.3	50.4	8.4	23.8	292
Q	L/day	0.362	3.4	47.5	8.5	16.0	99.4
Kdes	1/day	4.47	4.6				
CL_T	L/day	2.60	7.6	94.5	10.0	18.7	94.3
CL_{WT}		0.507	19.2				
V_{WT}		0.496	7.1				
V_{SEX}	Fold	1.14	1.3				
Q_{WT}		0.347	34.2				
CL_{dose}		-0.211	9.6				
σ^2_{prop}		CV=14.9%	5.5	46.1	6.0		

Model Simplification

The following models were compared:

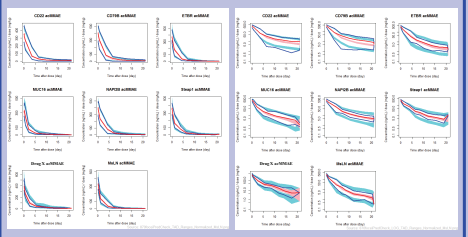
1. Models with all common parameters (FOCEI and IMPMAP fit);
2. Models with all compound-specific parameters (Method 1 and Method 2)
3. Models with compound specific CL and VC and common values of all other parameters (Method 1 and Method 2)

Results are presented in Table 2. Typical parameters were similar across all models confirming the similarity of PK properties of eight ADCs.

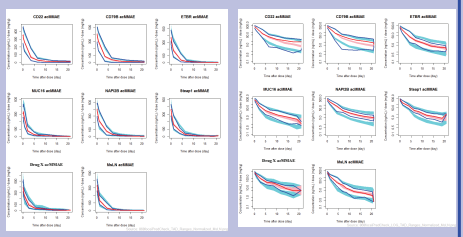
Table 2 Major model parameters: comparison between models

Parameter	All shared parameters		All compound-specific parameters		Compound-specific CL and VC; all other parameters are shared	
	FOCEI	IMPMAP	Method 2 (FOCEI) Geometric mean (CV)	Method 1 Value (ICV)	Method 2 (FOCEI) Geometric mean (CV)	Method 1 Value (ICV)
CL (L/day)	1.38	1.37	1.39 (0.149)	1.37 (0.145)	1.37 (0.170)	1.37 (0.144)
V_1 (L)	3.33	3.34	3.44 (0.070)	3.40 (0.0539)	3.43 (0.065)	3.40 (0.053)
V_2 (L)	2.63	2.65	2.54 (0.340)	2.74 (0.238)	2.70	2.7
Q (L/day)	0.367	0.364	0.398 (0.401)	0.362 (0.160)	0.361	0.363
K_{DES} (1/day)	4.97	4.59	4.77	4.47	4.47	4.51
CL_T (L/day)	3.41	2.64	3.20 (0.349)	2.60 (0.187)	3.11	2.58

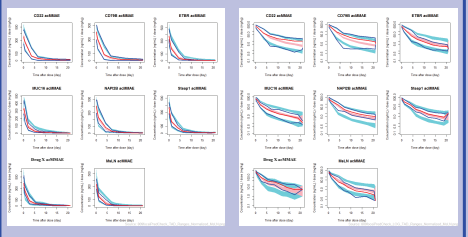
Comparison of VPC Diagnostic Plots
Method 2, all compound-specific parameters
Best possible



Method 2, compound-specific CL and VC parameters
Nearly as good as the best



Model with all common parameters
Minor discrepancies at low concentrations



SUMMARY AND CONCLUSIONS

- A two-compartment linear population mega-model with time-dependent clearance successfully described acMMAE PK of eight different ADC compounds based on the same platform;
- Pharmacokinetics of acMMAE are largely comparable across different vc-MMAE ADCs, with CV of inter-compound variability 2-3 times smaller than CV of inter-individual variability;
- The model can be applied to predict properties of vc-MMAE ADCs under development, estimate individual exposure for the subsequent PK-PD analysis, and investigate optimal dosing regimens.

REFERENCES

[1] Leonid Gibiansky, Ekaterina Gibiansky, Target-Mediated Drug Disposition Model and its Approximations for Antibody-Drug Conjugates, JPKPD, 2014; 41(1):35-47. doi: 10.1007/s10928-013-9344-y