Modeling Platform to Describe Pharmacokinetic Properties of vc-MMAE Antibody-Drug Conjugates

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Purpose

Antibody-drug conjugates (ADCs) developed using valine-citrulline-MMAE (vc-MMAE) platform consist of a monoclonal antibody covalently bound with potent anti-mitotic toxin (MMAE) through a protease-labile linker (MC-VC-PAB). The similarity of vc-MMAE ADC structures resulted in similar PK characteristics at clinical relevant doses. The goal of this analysis was to develop a mega model that simultaneously described antibody-conjugated MMAE (acMMAE) data from multiple vc-MMAE ADCs, and assess differences and similarities of model parameters and model predictions among different compounds.

Methods

Clinical PK data of eight vc-MMAE ADCs were obtained from eight studies with ADC doses ranging from 0.1 to 3.2 mg/kg every 3 weeks (Q3W). A population PK mega-model for the eight ADCs was developed using acMMAE data from all studies. Initially, all data were treated as coming from the same ADC. Two-compartment models with time-dependent clearance and parallel linear and Michaelis-Menten elimination were explored. After the base model was selected, a covariate model was developed. Effects of major covariates (body weight, sex, and dose) were evaluated by inclusion in the model. Other covariates (race, age, albumin concentration, creatinine clearance) were evaluated using the diagnostic plots. Diagnostic plots were used to confirm that parameter dependencies of covariate effects for each ADC were in agreement with the unified covariate 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 evaluated. Alternatively, the inter-compound variability was described explicitly using the third random effect level (inter-compound variability), 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 unified model (two-compartment model with time dependent clearance, clearance and volume increasing with weight, volume higher for males, and clearance mildly decreasing with the nominal dose) described acMMAE PK of eight ADCs. Michaelis-Menten elimination had only minor effect on PK and was not included in the model. Time-dependence of clearance 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, clearance and central volume were similar among ADCs, with the inter-compound variability of 17% and 7% respectively. Similar results (15% and 5% respectively) were obtained when the inter-compound variability was described explicitly using LEVEL option. Differences between 8 investigated ADCs were minor relative to the inter-subject variability as illustrated in Figure 1.

Conclusion

The developed population mega-model successfully described acMMAE PK of eight ADC compounds. PK of acMMAE are largely comparable across different vc-MMAE ADCs. The model can be applied to predict properties of vc-MMAE ADCs under development, estimate individual exposure for the subsequent PK-PD analysis, and project optimal dosing regimens.

Figure 1: Time courses of acMMAE following administration of 1.8 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.