Simulation Investigation of the Integrated Pharmacokinetic (PK) Model for Antibody-Drug-Conjugates

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Background: Antibody-drug conjugates consist of mixtures of antibodies with different number of attached toxins (DAR, drug to antibody ratio). Measurements of components with different DARs are rarely available. Instead, total antibody (tAB) and unconjugated toxin (T) are measured. In addition, number of all toxins attached to antibodies (antibody-conjugated toxin, acT) or number of antibodies with at least one toxin attached (ADC) are measured. Theoretical investigation [1] indicated that tAB and acT can be described by two two-compartment models when ADC properties are independent of DAR. These models were successfully applied to clinical data [2]. While linear two or three compartment models described ADC in [3], no theoretical justification exists for these equations.

Objectives: To investigate, using simulations, relationships between acT, ADC, tAB, and T concentrations and to evaluate approaches for population PK modeling of ADC.

Methods: Concentrations of acT, ADC, tAB, and T were simulated using a linear 9-compartment model (**Figure 1**) with deconjugation in central and/or peripheral compartments for 100 subjects with rich sampling, moderate inter-subject and low intra-subject variability. The model approximated antibody-drug conjugates with linkers attached to disulfide bonds; these conjugates can retain mostly even number of toxins, with negligible fraction of ADC_8. Model parameters consistent with brentuximab vedotin [3] were used. Parameters were independent of DAR except deconjugation rate (k_{dec}) and clearance (CL) that were either DAR-independent or increased with DAR. Simulated concentrations were used as observations (in different combinations) to find the simplest models that provide adequate fit.

Results: tAB-acT-T or tAB-ADC-T triplets allowed identifying all parameters of the true model, including k_{dec} in each compartment and changes of k_{dec} and CL with DAR. acT-T, ADC-T, tAB-acT, or tAB-ADC pairs were sufficient to identify the true model assuming k_{dec} and CL are independent of DAR. tAB, acT, and ADC alone were described by two-compartment models. acT-T pairs were well described by two-compartment acT models with acT elimination directed to T compartment. ADC-T pairs were well described by two-compartment ADC models with ADC elimination directed to T compartment was multiplied by mono-exponential decay function that accounted for change of DAR with time after dose. However, the estimated parameters differed from true values. Without this function, the model was not as good, and appeared to suggest time-dependent clearance of T.

Conclusions: Simulations indicated that the true model is identifiable if tAB-acT-T or tAB-ADC-T concentrations are available. ADC and T can be described by empirical models with an estimated decay of DAR with time after dose. Applicability of the results to clinical data needs further investigation.

Reference:

[1] Gibiansky L, Gibiansky E, J Pharmacokinet Pharmacodyn. 2014 Feb;41(1):35-47.

[1] Lu D et al, CPT Pharmacometrics Syst Pharmacol. 2016, 5(12):665-673.

[3] Li H et al, J Clin Pharmacol. 2017, 57(9):1148-1158.

Figure 1: Equations for Antibody-Drug Conjugate System

$dA_1/dt = - (k_{10,6} + k_{12}) A_1 + k_{21} A_2 - R_1 k_{dec6} A_1$; ADC_6 central

$dA_2/dt = k_{12} A_1 - k_{21} A_2 - (1- R_1) k_{dec6} A_2$; ADC_6 peripheral

$dA_3/dt = R_1 k_{dec6} A_1 - (k_{10,4} + k_{12}) A_3 + k_{21} A_4 - R_1 k_{dec4} A_3$; ADC_4 central

$dA_4/dt = (1- R_1) k_{dec6} A_2 + k_{12} A_3 - k_{21} A_4 - (1 - R_1) k_{dec4} A_4$; ADC_4 peripheral

$dA_5/dt = R_1 k_{dec4} A_3 - (k_{10,2} + k_{12}) A_5 + k_{21} A_6 - R_1 k_{dec2} A_5$; ADC_2 central

$dA_6/dt = (1- R_1) k_{dec4} A_4 + k_{12} A_5 - k_{21} A_6 - (1 - R_1)* k_{dec2} A_6$; ADC_2 peripheral

$dA_7/dt = R_1 k_{dec2} A_5 - (k_{10,0} + k_{12}) A_7 + k_{21} A_8$; ADC_0 central

$dA_8/dt = (1- R_1) k_{dec2} A_6 + k_{12} A_7 - k_{21} A_8$; ADC_0 peripheral

$IN_1 = 6 k_{10,6} A_1 + 4 k_{10,4} A_3 + 2 k_{10,2} A_5$; $IN_2 = R_1 (k_{dec6} A_1 + k_{dec4} A_3 + k_{dec2} A_5)$

$IN_3 = (1-R_1) (k_{dec6} A_2 + k_{dec4} A_4 + k_{dec2} A_6)$;

$dA_9/dt = IN_1 + IN_2 + IN_3 - k_{TOX} A_9$; T central

$ADC_6 = A_1/V$; $ADC_4 = A_3/V$; $ADC_2 = A_5/V$; $ADC_0 = A_7/V$; $T = A_9/V_T$

$ADC = ADC_6 + ADC_4 + ADC_2$; $tAB = ADC + ADC_0$; $acT = 6 ADC_6 + 4 ADC_4 + 2 ADC_2$

Case 1: Load independent k_{dec} and CL_{DAR}: $k_{decDAR} = DAR\ k_{dec}$, $k_{10,DAR} = k_{10}$, DAR = 0, 2, 4, 6.

Case 2: k_{dec} increasing with DAR: $k_{dec,2} = 2 k_{dec}$, $k_{dec,4} = 6 k_{dec}$, $k_{dec,6} = 10 k_{dec}$, $k_{10,DAR} = k_{10}$, DAR = 0, 2, 4, 6.

Case 3: k_{dec} increasing with DAR: $k_{dec,2} = 2 k_{dec}$, $k_{dec,4} = 8 k_{dec}$, $k_{dec,6} = 32 k_{dec}$, $k_{10,DAR} = k_{10}$, DAR = 0, 2, 4, 6.

Case 4: CL_{DAR} increasing with DAR: $k_{dec,DAR} = DAR\ k_{dec}$, $k_{10,DAR} = k_{10} (1+0.25\ DAR)$, DAR = 0, 2, 4, 6.

Here k_{10}: ADC_{DAR} elimination rate, k_{12} and k_{21}: inter-compartment rate constants, k_{dec}: deconjugation rate, V: ADC_{DAR} central volume, V_T: volume of T compartment; k_{TOX}: toxin elimination rate; R_1 changes the fraction of overall deconjugation between compartments (R_1=1: deconjugation only in central compartment; R_1=0: deconjugation only in peripheral compartment; R_1=0.5: equal deconjugation rates in central and peripheral compartments).