Monoclonal Antibody-Drug Conjugates: Simplification of Equations and Model-Independent Assessment of Deconjugation Rate

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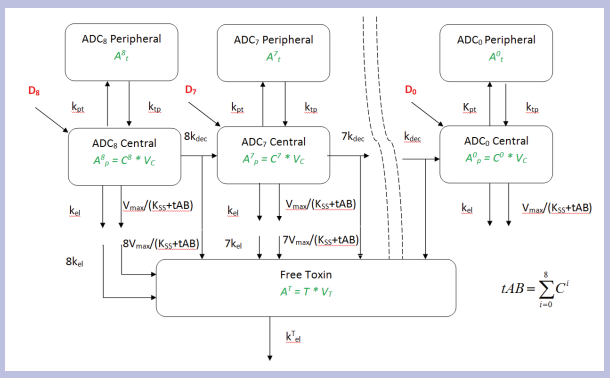
OBJECTIVES

- To simplify equations that describe distribution, deconjugation, elimination and interaction with the target of antibody-drug conjugates (ADC) under specific assumptions
- To propose a model-independent method of assessing deconjugation rate

METHODS

ADC-target system includes the naked antibody (ADC^0), ADCs with various loads (ADC^i, i=1,8), released toxin (T), free target (R), and various antibody ADC-target complexes (RC^i, i=0,8). It was assumed that ADC parameters are independent of drug-to-antibody ratio (DAR), deconjugation rate is proportional to DAR, and internalization rate is high. Under these assumptions, Michaelis-Menten-type equations that describe ADCs were derived in [1]:



$$\frac{dC^i}{dt} = \frac{k_{tp} A^i{}_t}{V_c} - (k_{el} + k_{pt}) C^i - \frac{V_{max} C^i}{K_{SS} + tAB} + (i+1) k_{dec} C^{i+1} - i \cdot k_{dec} C^i;$$

$$\frac{dA^i{}_t}{dt} = k_{pt} C^i \cdot V_c - k_{tp} A^i{}_t; \qquad (C^9 = 0) \qquad (1)$$

$$\frac{dT}{dt} = V_c \sum_{i=1}^{8} i \cdot \left(k_{dec} + k_{el} + \frac{V_{max}}{K_{SS} + tAB} \right) C^i - k^T{}_{el}\, T; \qquad T(0) = 0;$$

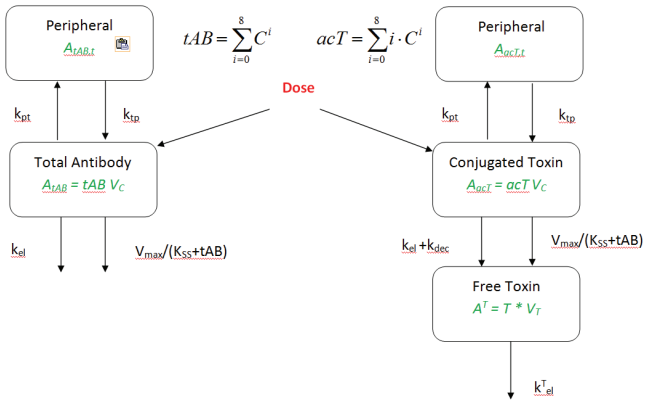
$$C^i(0) = \frac{D_i}{V_c}; \qquad tAB = \sum_{i=0}^{8} C^i; \qquad i = 0,\ldots,8.$$

These equations were further simplified to describe the observed quantities: total antibody concentration (tAB), concentration of the antibody-conjugated toxin (acT), and concentration of the free toxin (T). Unobserved concentrations of each of the ADC species over time could then be obtained using the parameters of this system.

RESULTS

The system of equations for all ADC species with different DARs was reduced to two coupled two-compartment models with the combined linear and Michaelis-Menten elimination terms for two observed quantities (tAB and acT).

System shares most of the parameters !



$$\frac{d\,tAB}{dt} = \frac{k_{tp} A_{tAB,t}}{V_c} - (k_{el} + k_{pt}) tAB - \frac{V_{max}\, tAB}{K_{SS} + tAB};$$

$$\frac{d\,A_{tAB,t}}{dt} = k_{pt}\, tAB \cdot V_c - k_{tp} A_{tAB,t};$$

$$\frac{d\,acT}{dt} = \frac{k_{tp} A_{acT,t}}{V_c} - (k_{el} + k_{pt} + k_{dec}) acT - \frac{V_{max}\, acT}{K_{SS} + tAB};$$

$$\frac{d\,A_{acT,t}}{dt} = k_{pt}\, acT \cdot V_c - k_{tp} A_{acT,t} \qquad (2)$$

$$\frac{dT}{dt} = V_c \left(k_{dec} + k_{el} + \frac{V_{max}}{K_{SS} + tAB} \right) acT - k^T{}_{el}\, T; \qquad T(0) = 0;$$

$$tAB(0) = \frac{D_{tAB}}{V_c}; \qquad acT(0) = \frac{D_{acT}}{V_c}; \quad tAB = \sum_{i=0}^{8} C^i; \quad acT = \sum_{i=0}^{8} i \cdot C^i$$

- Equations for acT differ from those for tAB by an additional term k_{dec}acT (elimination due to deconjugation) and by the denominator of the Michaelis-Menten term that is expressed as (K_{SS}+tAB) instead of the expected (K_{SS}+acT).
- Unobserved concentrations of each of the ADC species over time can now be computed from (1) using the obtained parameters and tAB over time.

For ADCs with linear kinetics (V_{max} = 0)

- Equations for tAB and acT become independent;
- The parameters differ by only one term: deconjugation constant k_{dec};
- Deconjugation constant k_{dec} can be easily estimated given the observed quantities:
- If deconjugation rate is small relative to total antibody clearance, then tAB = acT/mDAR, where mDAR is mean DAR of the dosing solution.

$$k_{dec} = \frac{1}{V_C} \left(\frac{D_{acT}}{AUC_{acT}} - \frac{D_{tAB}}{AUC_{tAB}} \right).$$

CONCLUSIONS

Under certain assumptions the pharmacokinetics of ADCs can be described by two coupled two-compartment systems with parallel linear and Michaelis-Menten elimination. In linear case, equations decouple allowing for independent fit, and ADC deconjugation rate constant can be computed using known doses and the observed AUC data. Simultaneous fit of tAB and acT data should lead to more precise identification of the model parameters.

REFERENCES: [1] Leonid Gibiansky, Ekaterina Gibiansky, Monoclonal Antibody-Drug Conjugates (ADC): TMDD Equations, Approximations, and Identifiability of Model Parameters, PAGE 21 (2012) Abstr 2606 [www.page-meeting.org/?abstract=2606]