Pharmacokinetics of Antibody-Drug Conjugates: TMDD Equations, Approximations, and Identifiability of Model Parameters

Leonid Gibiansky, Ekaterina Gibiansky QuantPharm LLC, North Potomac MD, USA (www.quantpharm.com)

Purpose:

- To derive equations that describe antibody-drug conjugates (ADC); their distribution, deconjugation, elimination and interaction with the target;
- To derive Michaelis-Menten approximation of these equations;
- To investigate identifiability of model parameters given typically available measurements and clinically feasible sampling schemes.

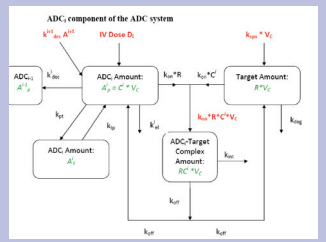
Methods:

ADC - target system includes the naked antibody (ADC^0), ADCs with various loads (ADC^i, i=1,8), released drug (L), free target (R), and various antibody ADC-target complexes (RC^i, i=0,8). TMDD equations to describe concentration-time course of the ADC - target system were derived.

General TMDD Equations for ADC

Red: input; *Green:* amounts; **Black**: rate constants. **Flux = rate x amount**

ADC_i with *i* drug molecules is shown. Released drug compartment (L) is not shown.



$$\frac{dC^i}{dt} = \frac{k_{tp}A^i_t}{V_c} - (k^i_{et} + k_{pt})C^i - k_{on}C^i \cdot R + k_{off}RC^i;$$
$$+ k^{i+1}_{dec}C^{i+1} - k^i_{dec}C^i; \quad (k^0_{dec} = 0;\ k^9_{dec} = 0);$$

$$\frac{dA^i_t}{dt} = k_{pt}C^iV_c - k_{tp}A^i_T; \quad C^i(0) = D^i/V_c; \quad A^i_t(0) = 0;$$

$$\frac{dR}{dt} = k_{syn} - k_{deg}R - k_{on}C \cdot R + k_{off}RC; \quad R(0) = k_{syn}/k_{deg};$$

$$\frac{dRC^i}{dt} = k_{on}C^i \cdot R - (k_{int} + k_{off})RC^i; \quad RC^i(0) = 0;$$

$$\frac{dL}{dt} = V_c\sum_{i=1}^{8}(k^i_{dec}C^i + i \cdot k^i_{et}C^i + i \cdot k_{int}RC^i) - k^L_{et}L; \quad L(0) = 0;$$

$$C = \sum_{i=0}^{8}C^i; \quad RC = \sum_{i=0}^{8}RC^i; \quad i = 0,\ldots,8.$$

Assumptions (in addition to the commonly used TMDD assumptions):

- ADC species with different DAR values (drug antibody ratio) have the same volume of distribution and inter-compartment rate constants, but may differ by non-specific clearance;
- ADC species with different DARs have the same target properties k_{on}, k_{off} and k_{int};
- Released drug can be described by a one-compartment model;
- Deconjugation can occur only in the central compartment;
- Eliminated ADC releases the drug load to the central compartment.

Quasi-Steady-State and Rapid Binding Approximations

From $$k_{on}C^i \cdot R - (k_{off} + k_{int})RC^i = 0; \quad i = 0,\ldots,8$$

we derive $$\frac{C \cdot R}{RC} = K_D + \frac{k_{int}}{k_{on}} = K_{SS}; \quad RC = \frac{R_{tot}C}{K_{SS} + C}; \quad R = \frac{R_{tot}K_{SS}}{K_{SS} + C}$$

Therefore $$\frac{C^i \cdot R}{RC^i} = K_{SS}; \quad RC^i = \frac{R_{tot}C^i}{K_{SS} + C}, \quad i = 0,\ldots,8$$

Then unbounded ADC concentrations C^i can be found as a solution of the system of equations: $$C^i_{tot} = C^i + \frac{R_{tot}C^i}{K_{SS} + C}; \quad i = 0,\ldots,8 \quad C = \sum_{i=0}^{8}C^i$$

Then QSS Approximation is given by:

$$\frac{dC^i_{tot}}{dt} = \frac{k_{tp}A^i_t}{V_c} - (k^i_{et} + k_{pt})C^i - \frac{R_{tot}k_{int}C^i}{K_{SS} + C} + k^{i+1}_{dec}C^{i+1} - k^i_{dec}C^i;$$

$$\frac{dA^i_t}{dt} = k_{pt}C^iV_c - k_{tp}A^i_t; \quad A^i_t(0) = 0; \quad (k^0_{dec} = 0; \quad k^9_{dec} = 0);$$

$$\frac{dR_{tot}}{dt} = k_{syn} - k_{deg}R_{tot} - (k_{int} - k_{deg})\frac{R_{tot}C}{K_{SS} + C}; \quad R_{tot}(0) = R_0 = \frac{k_{syn}}{k_{deg}};$$

$$\frac{dL}{dt} = V_c\sum_{i=1}^{8}(k^i_{dec}C^i + i \cdot k^i_{et}C^i + i \cdot k_{int}RC^i) - k^L_{et}L; \quad L(0) = 0.$$

Assumptions: Same as QSS (RB) assumptions of conventional TMDD.

Limitations: Cannot be resolved analytically; needs further simplification.

Possible generalizations: deconjugation in the peripheral compartments; delayed and/or incomplete release of the drug load by the eliminated ADC species; two-compartment PK of the released drug.

Possible simplifications: decrease the number of ADC species; use linear model (V_{max}=0).

Michaelis-Menten Approximations

Assumptions (same as MM assumptions of conventional TMDD): Total target concentration is small, for example, when internalization rate is high

$$\frac{dC^i}{dt} = \frac{k_{tp}A^i_t}{V_c} - (k^i_{et} + k_{pt})C^i - \frac{R_{tot}k_{int}C^i}{K_{SS} + C} + k^{i+1}_{dec}C^{i+1} - k^i_{dec}C^i;$$

$$\frac{dA^i_t}{dt} = k_{pt}C^iV_c - k_{tp}A^i_t; \quad (k^0_{dec} = 0; \quad k^9_{dec} = 0);$$

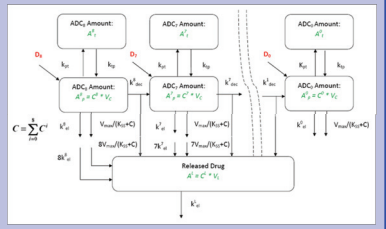
$$\frac{dR_{tot}}{dt} = k_{syn} - k_{deg}R_{tot} - (k_{int} - k_{deg})\frac{R_{tot}C}{K_{SS} + C}; \quad R_{tot}(0) = k_{syn}/k_{deg};$$

$$\frac{dL}{dt} = V_c\sum_{i=1}^{8}(k^i_{dec}C^i + i \cdot k^i_{et}C^i + i \cdot k_{int}RC^i) - k^L_{et}L; \quad L(0) = 0;$$

$$C^i(0) = D_i/V_c; \quad C = \sum_{i=0}^{8}C^i; \quad i = 0,\ldots,8.$$

When k_{int}=k_{deg}, R_{tot} is constant, TMDD elimination is described by the Michaelis-Menten term with V_{max}=$R_{tot}k_{int}$, K_M=K_{SS}.

ADC parameters assumed to be independent of DAR: V_c, k_{pt}, k_{tp}.



ADC parameters that may depend on DAR: CL_i, i = 0,…,8; k^i_{dec}; i = 1,…,8.

Identifiability of model parameters was investigated using PFIM 3.2 (Bazzoli, Retout, Mentré, 2010; http://www.pfim.biostat.fr**)**

Measurable quantities:

$$C = \sum_{i=0}^{8}C^i; \quad L_C = \sum_{i=1}^{8}i \cdot C^i; \quad C^L = L/V_L.$$

RESULTS

- The ADC system can be described using the general TMDD framework with an additional element that accounts for the deconjugation process.
- Given the typically available measurements, parameters of the individual ADC species (ADCs with specific DARs) are not identifiable.
- Assumptions that relate ADC and ADC-target parameters with different DARs are required.
- In particular, the system where ADC model parameters do not depend on DAR is identifiable.
- The system where parameters linearly depend on DAR is identifiable.
- Deconjugation rate of individual ADC species can be identifiable only under specific assumptions on how deconjugation rate depends on DAR; the individual ADC deconjugation rates cannot be estimated from the typically available data.

CONCLUSIONS

- Michaelis-Menten approximation of the TMDD model can be used to describe the interaction of ADC with the target when internalization rate is fast.
- Assumptions that describe dependence of the ADC parameters on drug load are necessary to make the system identifiable.
- In particular, the system with ADC parameters linearly dependent on DAR is identifiable.