Title: Monoclonal Antibody-Drug Conjugates (ADC): 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 model-independent method to assess deconjugation.

Methods: This work continues investigation of ADC equations started in [1]. 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, the system of equations for ADC species with different DARs was simplified to describe two observed quantities: total antibody concentration (tAB) and concentration of the antibody-conjugated toxin (acT). Unobserved concentration-time courses of each of the ADC species could then be predicted using the parameters of this system.

Results: Under the described assumptions, 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). Equations for acT differed 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 was expressed as (K_{SS}+tAB) instead of the expected (K_{SS}+acT). Here k_{dec} and K_{SS} are deconjugation rate constant and quasi-steady-state constant, respectively. If the non-linear part of elimination is negligible, equations de-couple allowing for a separate fit. In this case k_{dec} can be computed as $k_{dec}V = D_{acT}/AUC_{acT} - D_{tAB}/AUC_{tAB}$, where V is volume of the central compartment, D_{tAB} is dose of total antibody, $D_{acT} = D_{tAB}$* mDAR (mDAR is mean DAR of the dosing solution), and AUC_{acT} and AUC_{tAB} are the observed areas under acT and tAB concentration-time curves. If deconjugation rate is small relative to total antibody clearance, then tAB = acT/mDAR.

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 observed AUC data. Simultaneous fit of tAB and acT data should allow for more precise identification of 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]