Title: Mechanistic Interpretation of Indirect-Response Models for Drugs with Target-Mediated Disposition

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Objectives: To derive indirect response models (IRM) from the target-mediated drug disposition (TMDD) equations [1-4], and on the example of simulated PK-PD data to demonstrate that IRM can be used to estimate TMDD parameters and unobservable unbound target concentrations.

Methods: TMDD equations and its quasi-steady-state (QSS) approximation were used to derive the IRM equations for total target concentrations. The ability of IRM to estimate the TMDD parameters and predict unobservable unbound target concentrations were investigated using population PK-PD simulations in NONMEM. The simulated dataset included rich data from two studies. Study 1 included 4 cohorts of six subjects administered single 100 nmol IV, 300 nmol SC, 1000 nmol IV, or 3000 nmol SC doses. Study 2 included two 100-subject arms administered multiple 1000 or 3000 nmol SC doses at 4 week intervals. PK parameters of the simulation model were typical of monoclonal antibodies. TMDD binding and target turnover parameters were similar to those estimated for omalizumab [5,6] with the elimination rate of the drug-target complex (k_{int}) 5 times lower than the elimination rate of the unbound target (k_{deg}). The unbound drug and total target concentrations were simulated from the TMDD model. The QSS approximation and IRM were used for estimation.

Results: Direct correspondence between the parameters of the TMDD (QSS) equation for the total target concentration

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

and IRM was established:

$$dR_{tot}/dt = k_{syn} - k_{\deg}R_{tot}[1 + E_{\max}C/(K_{SS} + C)]; \qquad E_{\max} = k_{\text{int}}/k_{\deg} - 1;$$

$$dR_{tot}/dt = k_{syn} - k_{\deg}R_{tot}[1 - E_{\max}C/(K_{SS} + C)]; \qquad E_{\max} = 1 - k_{\text{int}}/k_{\deg}.$$

This correspondence allows estimating TMDD parameters (production rate k_{syn} of the unbound target, degradation rate k_{deg} of the unbound target, quasi-steady state constant K_{SS}, and degradation rate of the drug-target complex k_{int}). Then, the drug-target complex concentration RC and the unobservable unbound target concentration R can be computed as

$$RC = R_{tot}C/(K_{SS} + C); \quad R = R_{tot}K_{SS}/(K_{SS} + C) \quad .$$

In the simulation study, IRM (that utilized individual predictions of free drug concentrations provided by the empirical PK model) precisely estimated the TMDD population parameters with less than 7% bias and less than 5% relative standard error, and provided unbiased and precise population and individual predictions of the total and unbound target concentrations.

Possible extension of the obtained results includes generalization to the TMDD systems with cooperative or allosteric binding. For these systems, the total target concentration can be described by the equation

$$dR_{tot}/dt = k_{syn} - k_{\deg}R_{tot} - (k_{\text{int}} - k_{\deg})R_{tot}C^{\gamma}/(K_{SS}{}^{\gamma} + C^{\gamma})$$

that is equivalent to the indirect response models

$$dR_{tot}/dt = k_{syn} - k_{\deg}R_{tot}[1 + E_{\max}C^{\gamma}/(K_{SS}{}^{\gamma} + C^{\gamma})]; \qquad E_{\max} = k_{\text{int}}/k_{\deg} - 1;$$

$$dR_{tot}/dt = k_{syn} - k_{\deg}R_{tot}[1 - E_{\max}C^{\gamma}/(K_{SS}{}^{\gamma} + C^{\gamma})]; \qquad E_{\max} = 1 - k_{\text{int}}/k_{\deg}.$$

Then, the drug-target complex concentration RC and the unobservable unbound target concentrations R can be computed as

$$RC = R_{tot}C^{\gamma}/(K_{SS}{}^{\gamma} + C^{\gamma}), \qquad R = R_{tot}K_{SS}{}^{\gamma}/(K_{SS}{}^{\gamma} + C^{\gamma}).$$

Conclusions: The equation for the total target concentration of the QSS approximation coincides with the indirect-response model with inhibition (when $k_{int} < k_{deg}$) or stimulation (when $k_{int} > k_{deg}$) of elimination. The simulated population PK-PD study demonstrated that for drugs with TMDD, IRM is in fact a mechanistic model that can be used to estimate the TMDD model parameters and the unobservable unbound target concentrations that are important for pharmacodynamic modeling.

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