Prediction of a Claudin 18.2 targeted Antibody Drug Conjugate Pharmacokinetics in Cancer Patients Using PBPK Modeling and Simulation

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Purpose

Antibody- drug conjugates (ADCs) are anticancer drugs where a monoclonal antibody, targeting specifically tumor cells, is linked to a toxophore which is released inside tumor cells, thus killing them without harming healthy cells.[1] Although Physiologically-Based Pharmacokinetics (PBPK) modeling has become an important tool in drug development to mechanistically characterize drug exposure in different tissues[2], very few PBPK models have been developed so far for ADCs, none with the PK-Sim®/MoBi® software.

Objective

The aim of the present analysis was to build and qualify a human PBPK model for ADCs within the PK-Sim®/MoBi®[3] Open System Pharmacology platform.

Material & Methods

- **Patients**: Gastric or pancreatic cancers (109 patients)
- **Drug:** Anti-CLDN18.2 ADC (SHR-A1904)
- **Administration:** Intravenously (IV) , every three weeks
- **Data:** 3 clinical studies
- **Observations:** 908 and 824 plasma observations for ADC and deconjugated toxophore, respectively
- **Model structure:** See Figure 1
- **Workflow:** See Figure 2
- **Model optimizations:** See Table 1
- **Model validation[4,5]**: See Figure 3 and Results

Model structure

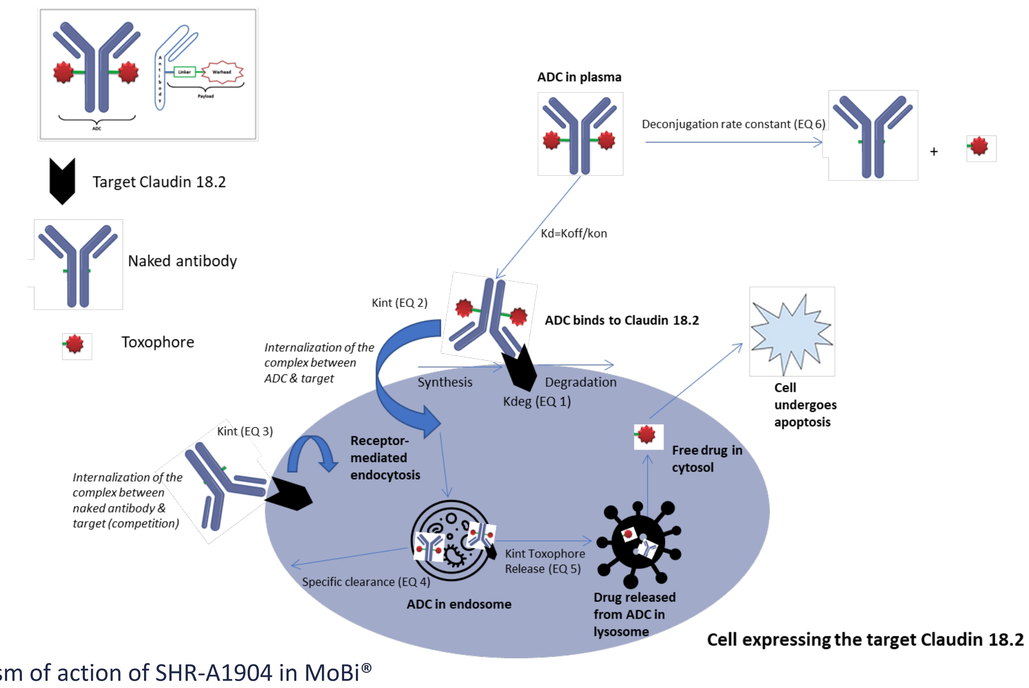

Figure 1: Specific mechanism of action of SHR-A1904 in MoBi®

Figure 2: PBPK modeling strategy : Workflow of the analysis

Base PBPK model in PK-Sim® for the ADC, the toxophore and the naked antibody separately
- Input PBPK parameters measured *in vitro* or predicted from the compound structure (toxophore)
- Typical patient with average age & weight from clinical studies

⇩ Export to MoBi®

Mechanistic model in MoBi® with integration of
- Target-mediated drug disposition
- Nonspecific catabolism
- Deconjugation of the toxophore
- Renal clearance for the toxophore

⇩ Model verification using observed data for ADC and toxophore (908 and 824 plasma observations respectively)

Parameter identifications
- Degradation rate constant of CLDN18.2 (Kdeg)
- Reference concentration of the target CLDN18.2
- Deconjugation rate constant of the toxophore
- Lipophilicity (log P) of the toxophore
- Nonspecific hepatic clearance of the toxophore
- Passive renal clearance modulated by the fraction of glomerular filtration (%)

⇩ Comparison between observed and simulated PK parameters (C_{max} and AUC) for both compounds

Model validation
- Predicted error ratio (two-fold criteria)[4,5]
- Parameter sensitivity analysis (PSA) on fitted parameters

Results

- While the PK-Sim® model captured the ADC concentration-time profile following IV administration of multiple escalating doses, additional clearance mechanisms such as TMDD and deconjugation elimination pathways were essential to improve the fit of the ADC elimination phase via a more physiological implementation.
- In MoBi®, three and four parameters were optimized for the ADC and the toxophore, respectively.
- The PK data was adequately captured for both ADC and toxophore, with a predicted error ratio included within the two-fold range: C_{max_ADC} (1.07-1.50), $C_{max\_toxophore}$ (0.69-1.44), $AUC_{0\text{-}504h\_ADC}$ following the first administration (0.59-0.98) and $AUC_{0\text{-}504h\_toxophore}$ (0.82-1.38).

Parameter	Start value	Final value
Degradation rate constant of CLDN 18.2 (Kdeg) (1/h)	1.00	0.03
Reference concentration of 18.2 (nmol/L)	10.00	5.86
Deconjugation rate constant (1/h)	0.10	7.72 E-03
Lipophilicity of the toxophore (Log P)	2.21	1.00
Nonspecific hepatic clearance of the toxophore (1/h)	3.01	300.00
Passive renal clearance of the toxophore modulated by the fraction of glomerular filtration (%)	1.00	30.00

Table 1: Optimizations of the final model

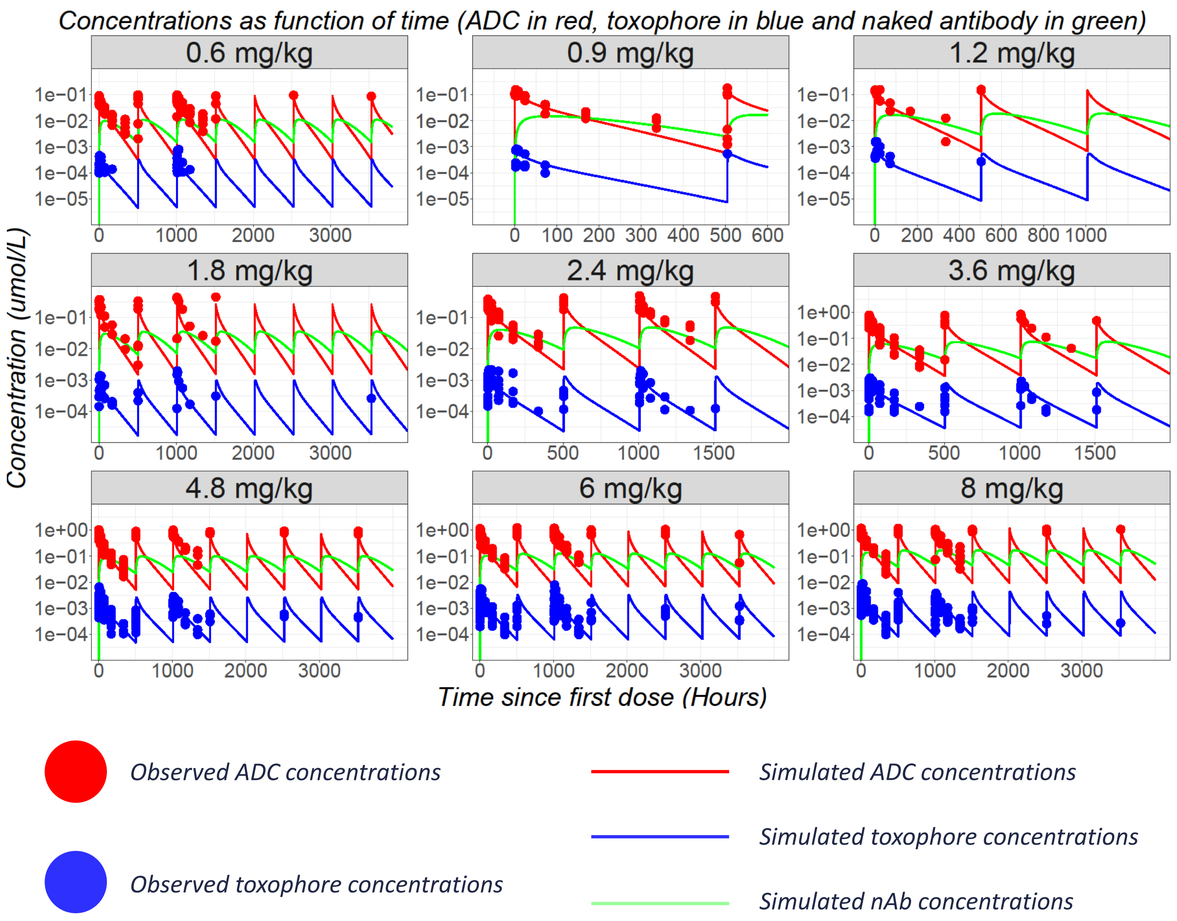

Figure 3: Observed (dots) and simulated (lines) SHR-A1904 (ADC in red) and SHR169106 (toxophore in blue) concentration time-course in cancer patients following IV administration (Final Mobi® model)

Conclusion

- The present analysis described the few steps toward the building of a PBPK model, capturing data of the anti-CLDN18.2 ADC and toxophore, including the parameter's optimization of the TMDD and deconjugation processes.
- This study paves the way for PBPK modeling of other ADCs currently in development using a similar approach within the PK-Sim / Mobi platform.

References:

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