Global sensitivity analysis of a mechanistic PK/PD model for T cell engager-mediated peripheral B cell depletion

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Introduction

Auto-antibodies produced by B cells drive autoimmune diseases such as rheumatoid arthritis (1). B cell depletion aiming to restore normal B cell functioning has demonstrated clinical efficacy. T cell engagers create an immune synapse, linking CD20 receptors on B cells and CD3 receptors on T cells thereby forming a trimeric complex between the target B cell (T), the biologic drug (B), and the effector T cell (E), or 'TBE' complex that induces potent B cell killing (2), and potentially enables durable, drug-free remission.

Objective

To quantify the influence of model parameters on B cell outcomes under the mechanism evaluated.

Methods

We developed a mechanistic PK/PD model exploring the relationship between in vitro measured TBE kinetics at the receptor level and B cell depletion observed in patients (Figure 1). T cells were activated by the TBE complex concentration and regenerated using first-order kinetics. CD20 and CD3 synthesis and degradation were modeled explicitly, with drug-bound targets assumed to internalize (Figure 2). A scaling factor was incorporated, linking the receptor-level and cell-level models by representing the hypothetical microenvironment volume per B and T cell where TBE complex formation occurs (ξ_B and ξ_T, respectively).

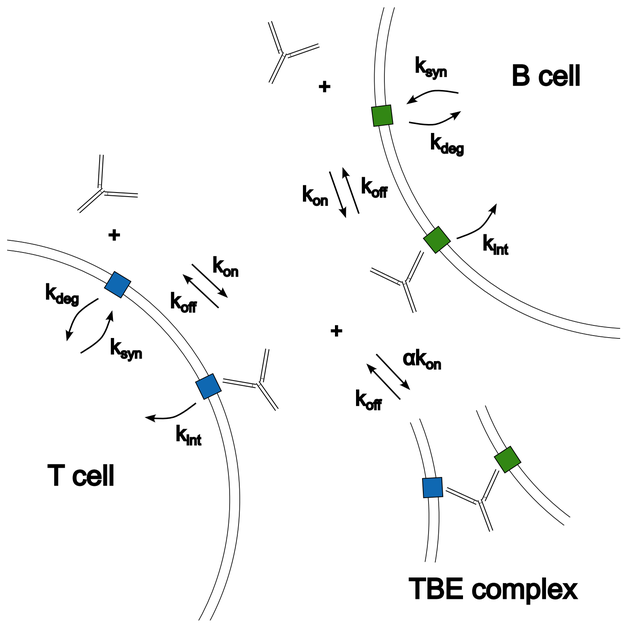

Figure 2. A hypothetical microenvironment was defined in which TBE complex formation takes place.

Digitized PK and B cell data derived from the mosunetuzumab Phase 1 first-in-human trial, presented at the 2025 EULAR conference was used to fit the model (3). T cell data was not available. A population PK and K-PD models were fitted using NONMEM to extract the necessary parameters. The lower limit of quantification for B cells in blood was 0.4 cells/µL. A Sobol global sensitivity analysis was conducted using the sensobol package in R to quantify the influence of model parameters on the outcomes under the mechanism evaluated (4). Evaluated outcomes included the peripheral B cell depletion AUC over 365 days, time to nadir, nadir depth, duration of depletion below 0.4 cells/µL, and time to 50% recovery. Only PD parameters not representing drug properties, that are relevant to decision making, and the potential to justify additional in vitro work were considered. All parameters were assumed to be log normally distributed with 30% CV. Parameter matrices were generated using quasi random sampling for 100,000 simulations and total order Sobol' indices were computed. The sensitivity analysis was conducted using two dosing scenarios: (1) a single 5 mg SC dose, representing the highest single dose, and (2) a combination regimen consisting of a 5 mg SC dose followed one week later by a 60 mg SC dose, representing the highest administered dosing scenario.

Results

A two-compartmental model with linear elimination described the PK data best. Goodness-of-fit plots and individual predictions are shown in Figure 3. In the PK/PD model, implementation of the scaling parameters ξ_B and ξ_T proved to be effective to capture B cell depletion. An overview of the parameters in the cell-level model can be found in Table 1. Across outcomes, the top three most influential parameters in terms of total-order Sobol' index are depicted in Figure 4.

Conclusion

ξ_T and CD3 expression consistently drive B cell depletion, supporting the need for a mechanistic model that explicitly includes T-cell dynamics, even though no T cell data was available. Future work includes conducting a structural sensitivity analysis by altering the T cell component of the model and re-evaluating the sensitivity outcomes under each structural scenario.

References

1. Albayrak et al. (2025). Br J Cancer.
2. Ceck et al. (2024). Cancers (Basel).
3. Chindalore et al. (2025). EULAR 2025.
4. Puy et al. (2022). Journal of Statistical Software.

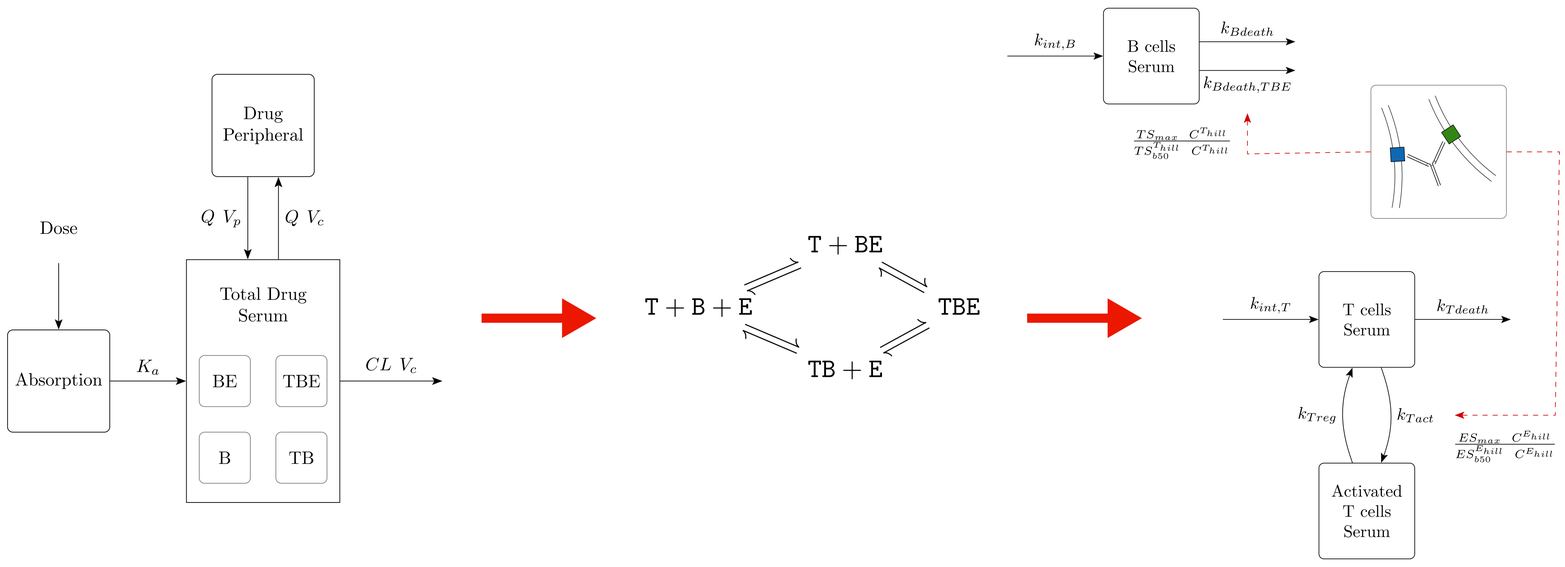

Figure 1. TBE complex concentration drives B cell killing and T cell activation.

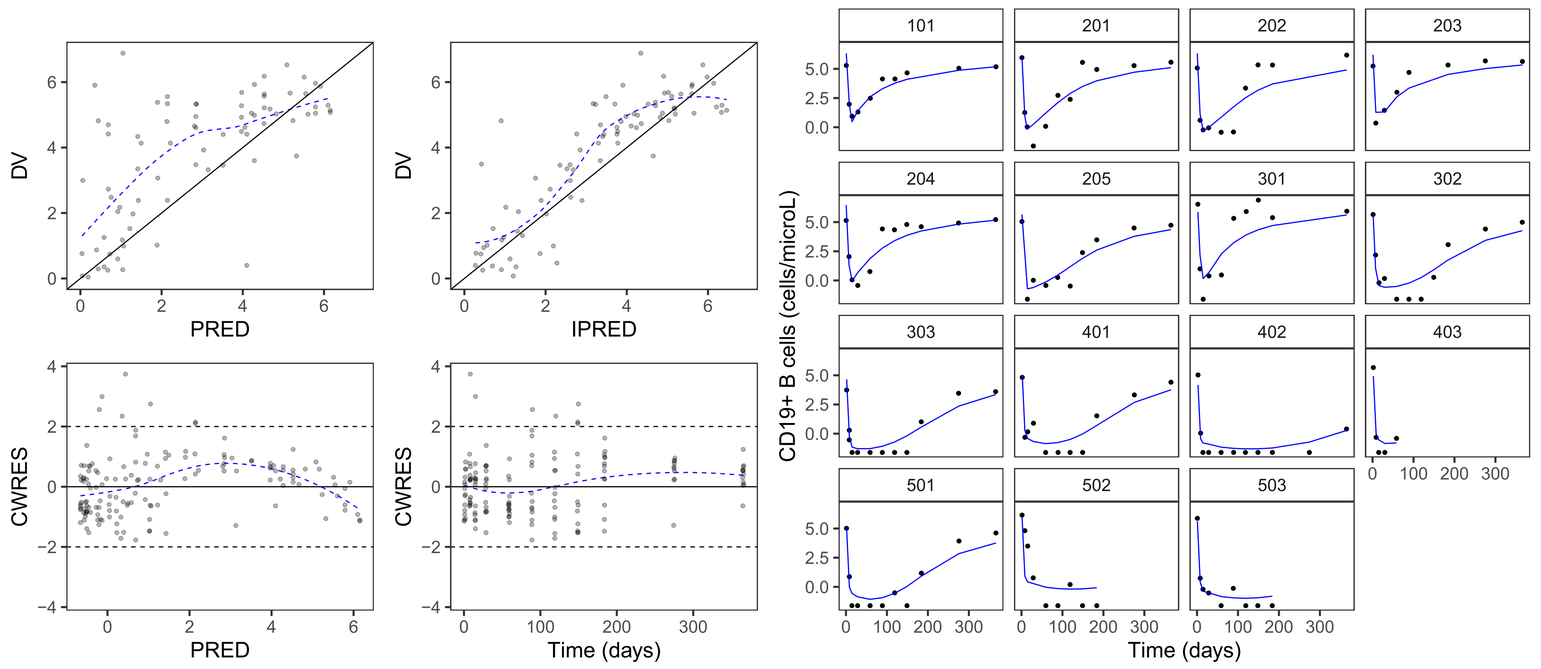

Figure 3. Goodness-of-fit plots and individual predictions of B cell data indicated that B cell depletion was well captured.

Table 1. Overview of the parameters in the cell-level model.

Parameter	Estimate	RSE (%)
CL (L/day)	1.11	-
IIV CL (%)	104	17.3
K_{Bdeath} (1/day)	0.00085	3.5
B cell serum at baseline (cells/microL)	596	8.1
$K_{Bdeath,TBE}$ (microL/cell/day)	3972	53.6
TS_{b50} (nM)	0.13	47.6
T_{HILL}	1	-
ξ_B (nL/cell)	995405	25.2
K_{Tdeath} (1/day)	0.00441	-
T cell serum at baseline (cells/microL)	415	-
K_{Tact} (1/day)	9.83	-
K_{Treg} (1/day)	0.10	-
ES_{b50}	0.00590	-
E_{max}	1	-
E_{HILL}	1	-
ξ_T (nL/cell)	0.00452	0.5
IIV B cell serum BL (%)	53	15.8
Additive Error (cells/microL)	1.09	11.2

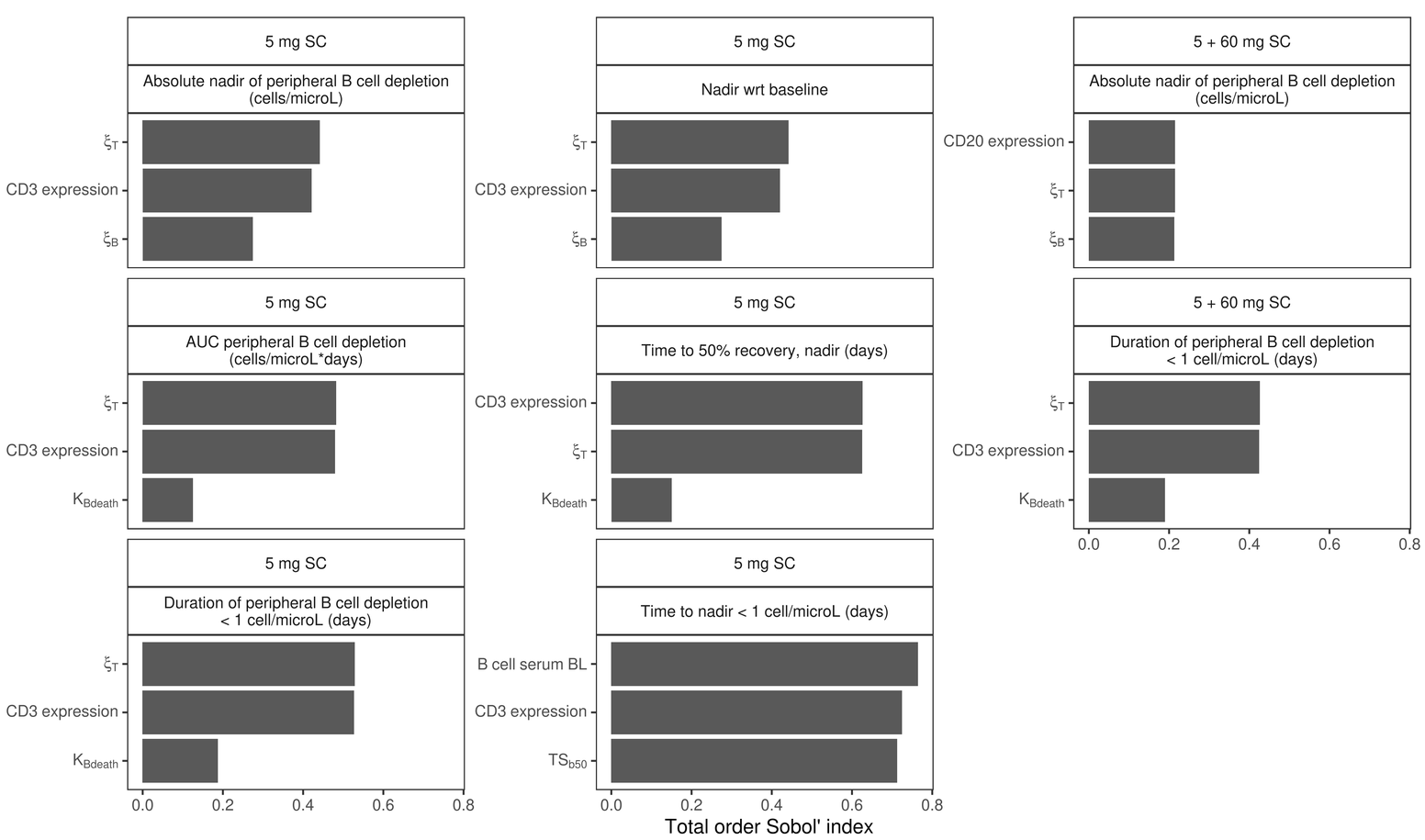

Figure 4. The top 3 most influential parameters in terms of total order Sobol' index.