

Target-mediated clearance of ofatumumab: a tale of different disease states

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Introduction

- Ofatumumab is an IgG1 human monoclonal antibody that specifically recognizes a unique epitope on the human CD20 molecule.
- CD20 is expressed on normal B lymphocytes from the pre-B-lymphocyte stage to the mature B-lymphocyte stage and across B-cell malignancies.
- Ofatumumab is indicated for the treatment of patients with refractory chronic lymphocytic leukemia (CLL).
- Ofatumumab is under investigation in other hematological malignancies (follicular lymphoma, diffuse large B-cell lymphoma, frontline and relapsed CLL) and autoimmune conditions (rheumatoid arthritis, multiple sclerosis).

Objectives

- Revise a previous population pharmacokinetic (popPK) model for ofatumumab [1] based on additional data in refractory CLL (Study Hx-CD20-406)
- Analyze the differential impact of the disease state on target-mediated clearance (TMC).

Methods

Data

- PK data from four phase I/II or II clinical studies with a total of 477 patients and 6845 observations:
- Rheumatoid arthritis (RA): 2 doses two weeks apart, 300-1000 mg, N=187 (ClinicalTrials.gov registry number: NCT00291928)
- Follicular lymphoma (FL): 4 weekly doses, 300-1000 mg, N=38 (NCT00092274)
- Relapsed CLL (relCLL): 4 weekly doses, 100-2000 mg, N=33 (NCT00093314)
- Refractory CLL (refCLL): 12 doses, 300 mg + 11x 2000 mg, N=219 (NCT000349349)

PK Modeling

- Non-linear mixed effects modeling approach using NONMEM® (ADVAN6): Models were prioritized using objective function values, mechanistic plausibility of parameters, and performance in visual predictive checks.
- Model was developed without post-baseline (BL) B-cell counts; however, post-BL CD19 B-cell counts were available for validation.

Results

Model Development

- Starting PK model for model revision: linear two-compartment PK model representing nonspecific clearance (NSC) combined with a TMC component implemented as turnover of normalized target level and irreversible drug/target binding (Fig. 1, [1]). Different parameterizations quantifying relative degree of the TMC effect were explored.
- Target input rate BIN (proportional to target steady-state level for given BOUT) set to ratio of geometric mean of CD19 count for each study to the geometric study mean for refCLL.
- Adjustment factors accounting for differences in CD20 expression per B cell and nodal vs. peripheral disease were used for relCLL and FL.
- The target elimination rate BOUT set according to the disappearance rates of circulating B cells reported in [2] for CLL vs. healthy subjects.
- The terminal half-life of 21.8 days for the linear model component is consistent with other IgG antibodies.

Model Diagram & Equations

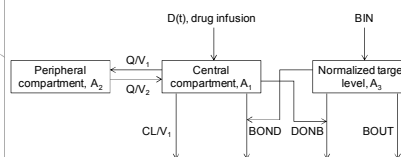


Fig. 1: Model diagram (see parameter table for parameter definitions)

$$\begin{aligned}\frac{dA_1}{dt} &= -\frac{CL}{V_1} A_1 - \frac{Q}{V_1} A_1 + \frac{Q}{V_2} A_2 - BOND \cdot A_3 \cdot A_1 / V_1 + D(t) \\ \frac{dA_2}{dt} &= \frac{Q}{V_1} A_1 - \frac{Q}{V_2} A_2 \\ \frac{dA_3}{dt} &= BIN - BOUT \cdot A_3 - DONB \cdot A_3 \cdot A_1 / V_1\end{aligned}$$

Eq. 1: Model equations (see parameter table for parameter definitions)

B-cell Count by Disease

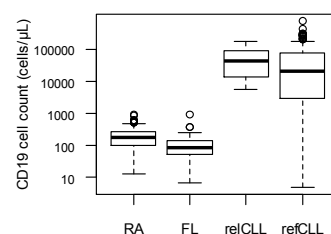


Fig. 2: CD19 B-cell count by disease state (bold bar, median; box, inter-quartile range)

Model Parameters

Parameter [Unit]	Estimate	RSE
Fixed Effects		
CL – Systemic clearance [L/hr]	0.00745	3.6%
V ₁ – Central volume [L]	3.26	2.0%
Q – Intercompartmental clearance [L/hr]	0.0222	11.5%
V ₂ – Peripheral volume [L]	2.07	3.3%
DONB – Drug on B-cell interaction rate constant [1/(μg/mL·hr)]	0.186	10.3%
BOND – B cell on drug interaction rate constant [1/(μg/mL·hr)]	0.335	7.1%
BOND_FL – BOND adjustment factor for FL	10.1	17.1%
BOND_relCLL – BOND adjustment factor for relCLL	0.0901	16.9%
BIN_FL – Target input rate [1/hr]	0.00705	N/A
BIN_RA – Target input rate [1/hr]	0.0141	N/A
BIN_relCLL – Target input rate [1/hr]	3.21	N/A
BOUT_RA – target output rate [1/hr]	0.00241	N/A
BOUT_(FL, relCLL, refCLL) – target output rate [1/hr]	0.000963	N/A
BSA on CL – Exponent	1	N/A
BSA on V ₁ – Exponent	0.814	16.0%
BSA on V ₂ – Exponent	0.813	29.6%
GEN on V ₁ – fractional change female vs male	-0.115	24.3%
IGG on CL – fractional change wrt centered baseline IgG	0.0258	20.2
Random Effects		
ω ² _{CL} – Inter-individual variability for CL	0.276	10.2%
ω ² _{V1} – Inter-individual variability for V ₁	0.076	16.1%
ω ² _{V2} – Inter-individual variability for V ₂	0.229	17.5%
ω ² _{BIN} – Inter-individual variability for BIN	0.608	12.7%
σ ² _{additive} – additive residual error	14.8	41%
σ ² _{proportional} – proportional residual error	0.0199	6.9%

CD19 Cell Count and Target-Mediated Clearance

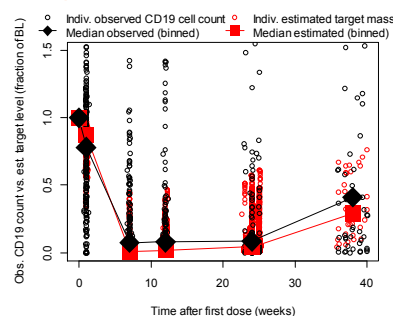


Fig. 3: Observed CD19 B-cell count vs. predicted target mass (normalized to baseline) for refCLL study

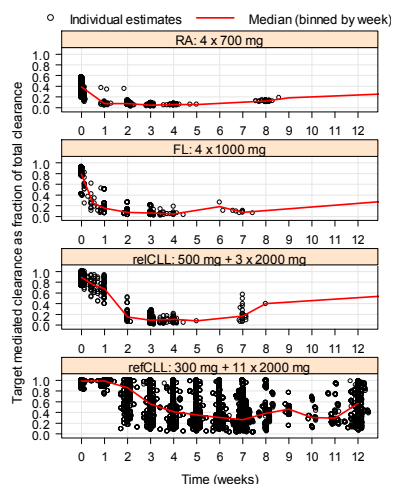


Fig. 4: Estimated TMC as fraction of total clearance (NSC + TMC) for selected regimens

Conclusions

- Medians of estimated target mass and observed B-cell numbers tracked each other well for refCLL (Fig. 3).
- Baseline B-cell counts (Fig. 2) and estimated effect of target-mediated clearance (Fig. 4) varied widely between disease states:
- RA: smallest TMC effect
- FL: TMC larger than NSC only in the days after the first dose, then relatively small
- relCLL: TMC larger than NSC only following first two doses, then relatively small
- refCLL: For many patients, TMC dominates NSC throughout trial; on average, relative TMC effect is reduced during 8 weekly doses with an increase after switch to monthly dosing
- Model allows the simulation of ofatumumab PK in untested disease populations if baseline B-cell counts are available and data/hypotheses for B-cell distribution (nodal vs. peripheral) and CD20 expression are available.

References

- [1] Sale M, Jewell RC, Patel BR. Ofatumumab population pharmacokinetic analysis in patients with chronic lymphocytic leukemia (CLL), follicular lymphoma (FL), and rheumatoid arthritis (RA). ACoP 2011.
- [2] DeRoche J et al. Reduction of B cell turnover in chronic lymphocytic leukaemia. Br J Haematol. 2008; 143:240-247.

Acknowledgments

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