Characterization of binding between OSM and mAb in RA patient study: an extension to TMDD models

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Introduction

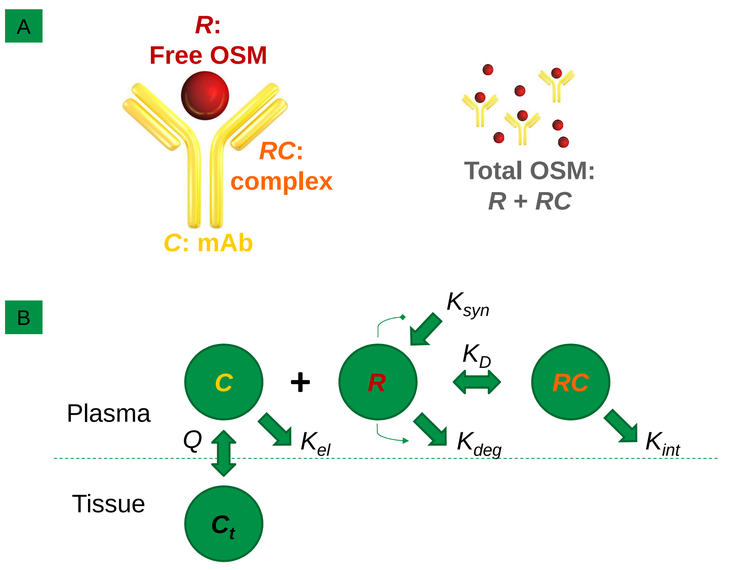
A humanised IgG1 monoclonal antibody (mAb) against human Oncostatin M (OSM) is being developed for the treatment of rheumatoid arthritis (RA) [1,2]. Oncostatin M is a member of the interleukin (IL)-6 family of secreted cytokines and is present in the inflamed synovium and blood of patients with RA.

Objectives

This work aims to describe and explain the relationship between mAb and OSM plasma levels and to characterize the in vivo equilibrium dissociation constant.

Materials & Methods

- Plasma levels of total drug (free mAb + mAb-OSM complex) and free and total OSM (free OSM + complex) were measured after intravenous and subcutaneous administration of various drug amounts to 131 patients with RA.
- Using Monolix 4.2.2 software, a mixed-effect model for mAb pharmacokinetics (PK) was developed and estimated on the available measures to discard possible non linearity in the kinetics due to the binding of the drug with the target.
- The individual estimates of the PK parameters were included in a binding model implemented to fit the observed kinetics of free and total OSM.
- 28% of free OSM measures were below limit of quantification (10 pg/ml, except for repeated dose (RD) and subcutaneous (SC) treatments): their cumulative probability distribution was adequately considered during likelihood computation.
- The target-meditated drug disposition (TMDD) model [3] was not able to contemporary fit the two sets of measures, and the equilibrium dissociation constant (K_D) value estimated from the total OSM measures (less noisy than the free OSM measures: standard deviation = 5.8 vs 13.4 pg/ml for placebo data) was far from the in vitro value (~ 1 nM).
- More elaborated models able to describe all the data together were developed with Monolix 4.2.2.



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$$K_{int} = K_{el}$$
$$K_{syn,0} = R_0 \times K_{deg,0}$$
$$K_{syn} = K_{syn,0} + \left[\max\left(0, \frac{R_0}{R} - th\right)\right]^{\alpha}$$
$$K_{deg} = K_{deg} \times \left(\frac{R}{R_0}\right)^{\beta}$$

TMDD equations with quasi−equiulibrium approximation [3]

FIGURE 1 Schematic representation of the modelled entities (A); compartmental description of the TMDD model (B); equations implemented in the TMDD model.

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Results

- Drug kinetics was found to be linear.
- The best model (**FIG. 1** to **5, TABLE 1**) able to reproduce the relationship between drug level, free and total plasma OSM includes the activation of a gradient-related OSM release in plasma: when OSM concentration in plasma falls below a given threshold *th*, K_{syn} increases according to a power law.
- Such hypothesis is supported by consequent K_D estimates similar to the in vitro measure (17 nM), and by the existence of intracellular preformed stocks of OSM in human neutrophils from which the cytokine is released besides being synthesized de novo [4].
- Moreover, K_{deg} was found to depend on the ratio between plasma OSM concentration and baseline according to a power law.

TABLE 1 Estimated parameter values of the developed model.

	mAb kinetics					TMDD						
Param.	Cl_{el}	Q	Vol	Vol_t	Ka	K_D	K_{int}	$K_{deg,0}$	R_0	α	β	th
typical value	0.0046	0.012	0.038	0.035	0.14	17	0.11	0.04	15	7.7	0.60	2.6
5th perc. IIV	0.0025	0.005	0.019	0.021	0.14	10	0.06	0.02	7	6.8	0.55	2.2
95th perc. IIV	0.0084	0.023	0.069	0.053	0.14	26	0.24	0.13	42	8.6	0.67	4.7
units	L/Kg/ day	L/kg/ day	L/kg	L/kg	1/day	nM	1/day	1/day	pg/mL	-	-	-

IIV = Inter-Individual Variability

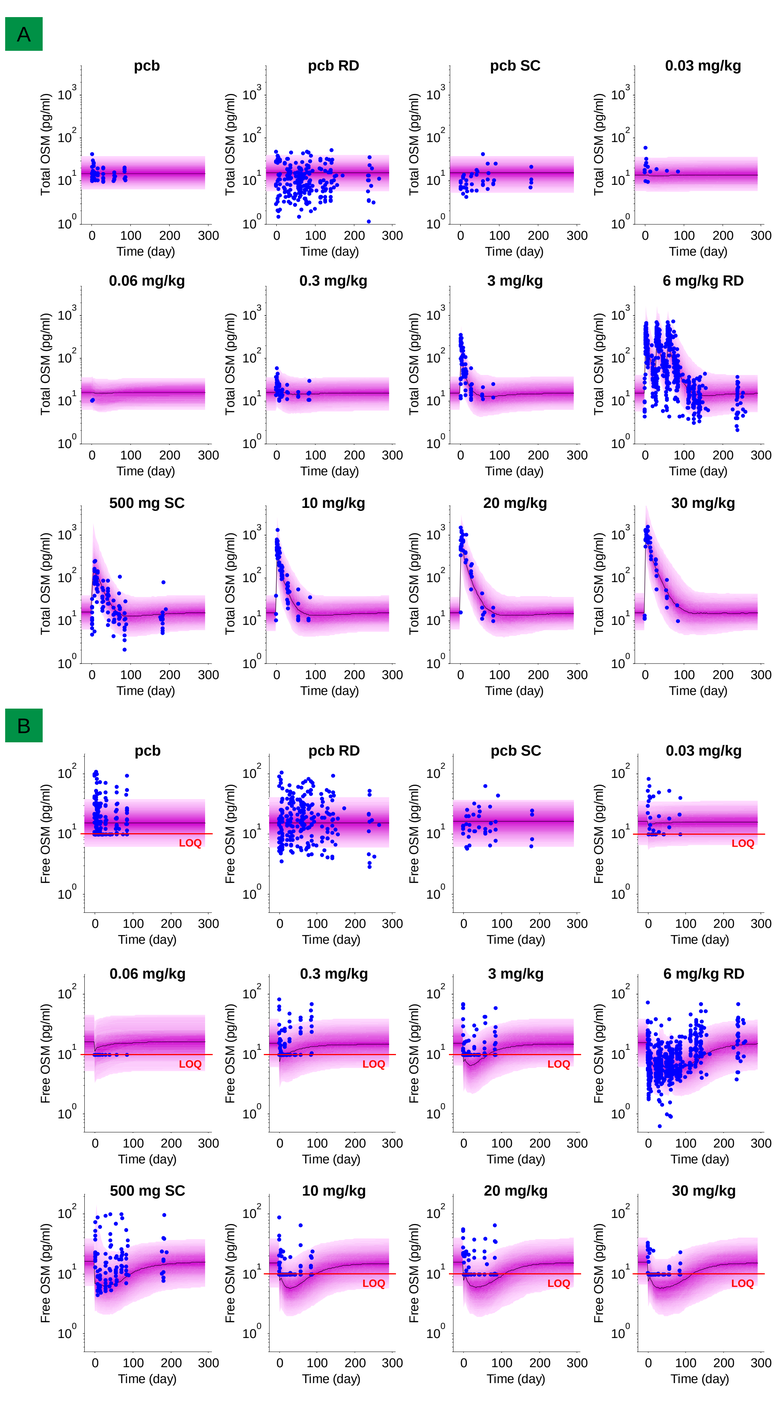

FIGURE 2 Prediction plots (A: total OSM, B: free OSM): observations and 90% prediction interval according to parameters IIV (LOQ = Limit Of Quantification).

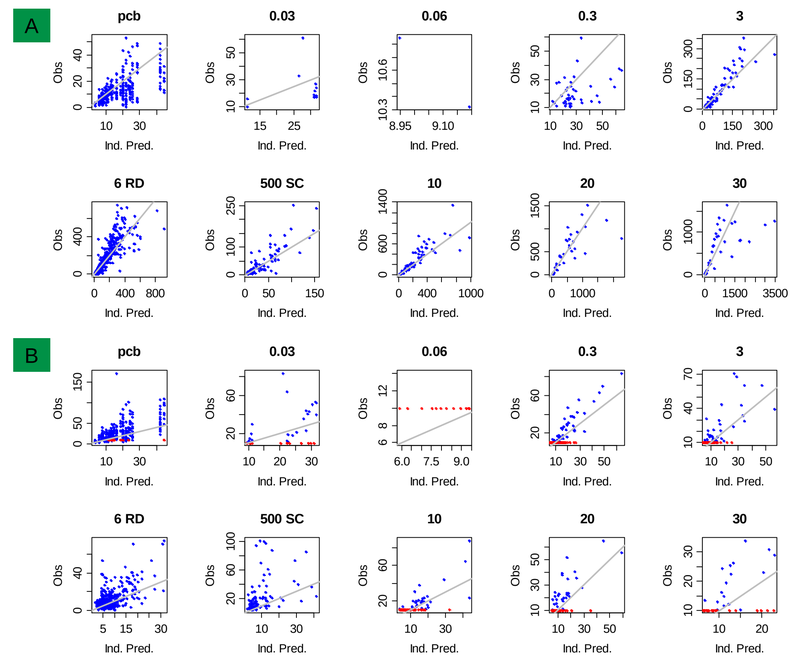

FIGURE 3 Goodness of fit plots (A: total OSM, B: free OSM; BQL data in red).

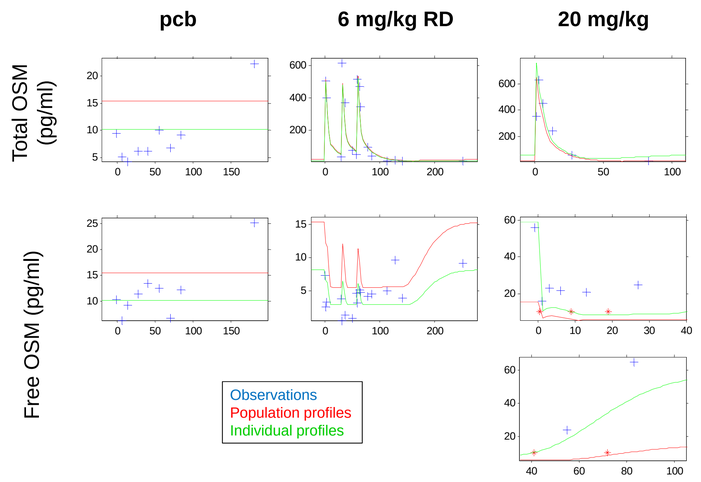

FIGURE 4 Individual fits for three representative subjects (for the third one time range for free OSM is split in two parts).

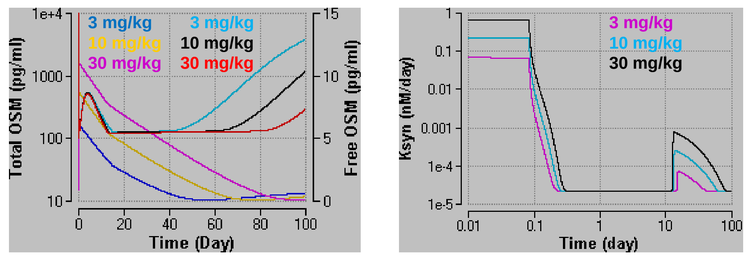

FIGURE 5 Time-course of total and free plasma OSM (left) and K_{syn} (right) for three different doses according to the typical values of the parameters of the developed model.

Conclusions

- Understanding antibody interaction with its target at physiological level is essential in better predicting clinical outcomes and TMDD models are generally adopted for this purpose. This analysis provides a real case in which TMDD models have been modified to successfully describe the kinetics of drug and target and to provide in vivo estimates of their binding rates.
- A model for modulation of synthesis of OSM has been proposed which takes into account the available knowledge about cellular mechanisms underlying OSM kinetics. Such model might prove useful to increase the understanding of outcomes of future studies involving OSM.

References

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