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Pharmacodynamic (PD) Model of Neutrophil Margination to Describe Transient Effect of Sarilumab on Absolute Neutrophil Count (ANC) in Patients With Rheumatoid Arthritis (RA) After Single-Dose Administration

Pavel Kovalenko,[1] Anne Paccaly,[1] Anita Boyapati,[1] Christine Xu,[2] John D. Davis,[1] A. Thomas DiCioccio[1]

[1]Regeneron Pharmaceuticals, Inc, Tarrytown, NY, USA; [2]Sanofi Genzyme, Bridgewater, NJ, USA

INTRODUCTION

- Sarilumab is an investigational human mAb that blocks interleukin 6 (IL-6) from binding to both membrane-bound and soluble IL-6Rα. IL-6 is a cytokine key to the pathogenesis of rheumatoid arthritis (RA) known to be linked to joint inflammation and destruction. By binding to IL-6Rα with high affinity, sarilumab blocks the binding of IL-6 and interrupts the inflammatory signaling cascade mediated through this pathway
- Absolute neutrophil count (ANC) measured in the blood also appears to be a function of concentration of IL-6Rα blockers.[1] The absence of both impairment in neutrophil activity[1] and association of decrease in ANC with infectious adverse events[2,3] implies that neutrophil margination and not neutrophil destruction may explain the observed decrease in ANC

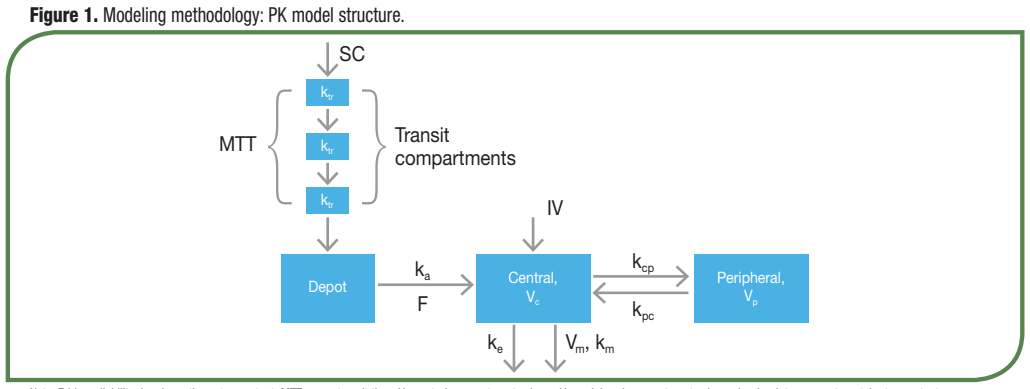
OBJECTIVES

- To present a pharmacodynamic (PD) model that explains the time course of the decrease and recovery of ANC, that describes potential margination of neutrophils from the circulation, and that accounts for the rapid development of ANC-specific tolerance, after a single dose of sarilumab

METHODS

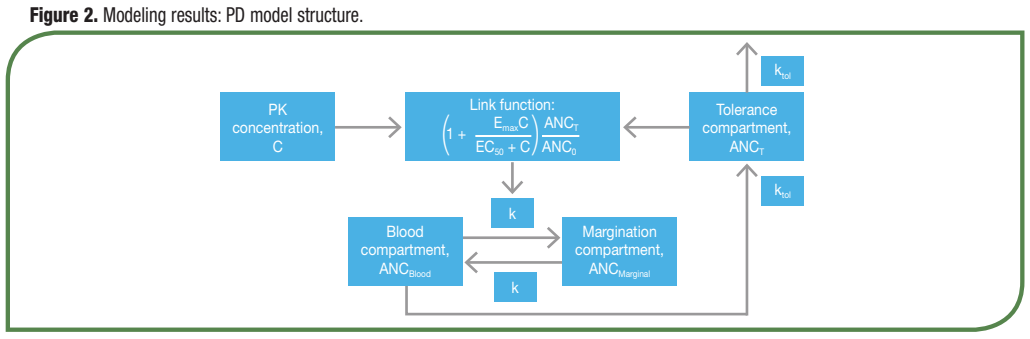
- The 6R88-RA-1309 study (NCT02097524) was a phase 1b, randomized, open-label, pharmacokinetic (PK), PD, and safety study assessing a single dose of subcutaneous (SC) sarilumab and intravenous (IV) tocilizumab in patients with RA who were on stable doses of methotrexate. This study was not designed to show statistical differences between treatments but rather to provide additional PK/PD data to better understand the clinical context of the existing PD data. Only sarilumab results are presented in this poster
- Baseline demographic characteristics were similar among treatment groups. Most patients were Caucasian (83.2%) and non-Hispanic (52.5%), with a mean (standard deviation [SD]) age of 55 (11.7) years and a mean (SD) body mass index of 31.3 (6.54) kg/m^2. The majority of patients were female (86.1%), which is consistent with the disease profile for RA. Most patients had ANC <5.99 10^3/μL (83.2%) at baseline
- Measures of ANC (n=950) were collected from 56 patients who received a single SC dose of sarilumab 150 or 200 mg. The 1:1 randomization was stratified by screening ANC (<5.99, ≥5.99 10^3/μL)
- Monolix 2016R1 and NONMEM 7.3 software packages were used
- The data were analyzed using stochastic approximation expectation-maximization (SAEM) and importance sampling methods (IMP). Sequential PK/PD modeling was conducted to avoid an impact of PD models on PK parameters
- A 2-compartment PK model with parallel linear and Michaelis-Menten elimination, as well as with 3 transit compartments accounting for lag time after SC injection, was implemented to model sarilumab concentrations (Figure 1)
- Different PD models were tested to characterize the effect of sarilumab on ANC while accounting for margination and tolerance. They included a margination model (MM) and indirect response model (IRM). Tolerance was tested in MM and IRM to account for an observed attenuation of drug effect on ANC over time
- As an effort to validate the model, bootstrapping, empirical assessment of stability (randomly changing initial PD parameters), and multiple sensitivity analysis were conducted

Figure 1. Modeling methodology: PK model structure.



Note: F, bioavailability; k_a, absorption rate constant; MTT, mean transit time; V_c, central compartment volume; V_p, peripheral compartment volume; k_{cp}, k_{pc}, intercompartmental rate constants; k_e, elimination rate constant; V_m, maximum target-mediated rate of elimination; k_m, Michaelis-Menten constant.

Figure 2. Modeling results: PD model structure.



Note: C, concentration of sarilumab; E_{max}, maximal effect of sarilumab on intercompartmental rate; EC_{50}, concentration of sarilumab causing half-maximal effect; ANC_T, ANC in tolerance compartment; ANC_0, estimated baseline ANC; ANC_{Blood}, ANC in blood; $ANC_{Marginal}$, marginated ANC; k, intercompartmental rate; k_{tol}, tolerance rate.

RESULTS

- The structure of the MM model is depicted in Figure 2. The MM was represented by central and margination compartments with neutrophils circulating between these compartments
- An assumption in the MM model was that, after dosing, both production and elimination of neutrophils do not change and, therefore, the total ANC stays constant; thus, the production and elimination of neutrophils were not modeled to avoid overparameterization
- The link function was imposed on the rate from central to margination compartment, increasing margination when sarilumab is introduced
- The tolerance was apparent based on visual examination of the ANC data. Observed tolerance was manifested by a nadir in ANC that precedes the maximal drug concentrations and counterclockwise hysteresis in presence of inhibition[4] or by absence of plateau in nadir when ANC response was saturated
- The implementation of tolerance provided significant improvement of the MM model, with a change in objective function value (OFV) of 143.60
- The tolerance was specific to ANC. For example, there were absolutely no signs of tolerance to sarilumab in C-reactive protein or any other efficacy biomarkers collected during this study. No tolerance to sarilumab was observed during clinical development based on improvement in RA symptoms and suppression of bone destruction
- While implementing between-subject variability in the intercompartmental rate (parameter k in Figure 2) led to statistically significant improvement in OFV, it also reduced stability of the model and increased variability in estimated parameters; even though results were interpretable and useful when the interindividual variability in k was implemented, a more stable model was chosen as the final one
- As an empirical assessment of stability, the MM was executed 6 times, implementing random variability in initial PD parameters from -40% to +60%. The analyses indicated that (a) PD parameters were consistent across runs; (b) SAEM converged well; and (c) a small variability in OFV across model runs did not interfere with decision-making
- The following analyses are examples of those that were conducted but did not lead to meaningful improvement of the MM: (a) Hill coefficient was added to the link function; (b) additive model of residual variability was tested; (c) tolerance feedback affecting EC_{50} was tested; (d) different intercompartmental rates were allowed in the model; (e) different in and out rates for the tolerance compartment were allowed in the model; and (f) different functions for the feedback of the tolerance compartment were evaluated
- In addition to the MM (Figure 2), an indirect-response model[5] was tested with sarilumab concentration linked to k_{in} or k_{out}. Tolerance was implemented similarly to the MM. Based on OFV and assessment of stability, the IRM with link function imposed on k_{out} performed better than that imposed on k_{in}, and MM performed better than both versions of IRM
- The MM is the biologically most plausible model, considering the margination of neutrophils to be the underlying mechanism for the decrease in ANC observed with IL-6 inhibitors. The margination and tolerance are consistent with the absence of both impairment in neutrophil activity[1] and lack of association of decrease in ANC with increased risk of infection[2,3]
- PD parameters and bootstrap confidence intervals for the MM are presented in the Table. In this table, β stands for a parameter explaining an impact of a covariate. Parameters are defined in Figure 2

Table. Population PD Parameters for Margination Model

Parameter name	Parameter value	%RSE	Wald test, *P* value	Difference in OFV	Bootstrap median (95% CI)
Parameters					
ANC_0 (10^3/μL)	4.02	2			4.00 (3.83, 4.25)
k (1/day)	6.45	4			6.39 (4.73, 8.40)
E_{max} (unitless)	4.00	14			3.70 (2.44, 5.90)
EC_{50} (mg/L)	6.59	15			6.06 (2.96, 11.1)
k_{tol} (1/day)	0.169	10			0.172 (0.126, 0.218)
Covariates					
β(ANC_B on ANC_0)	0.823	6	$<10^{-10}$	139.79	0.835 (0.710, 0.938)
β(ANC_B on EC_{50})	-1.39	14	$<10^{-10}$	12.71	-1.39 (-2.50, -0.0205)
Omegas					
ω (ANC_0)	0.154	9			0.154 (0.0966, 0.213)
ω (E_{max})	0.869	9			0.885 (0.701, 1.11)
Standard deviations of residual errors					
$\sigma_{exponential}$	0.251	2			0.249 (0.229, 0.265)
$\sigma_{additive}$	0.001	Fixed			0.001 (fixed)

- While the parameters appeared biologically plausible and consistent with the data, E_{max} and EC_{50} should not be directly compared with their published IRM counterparts due to different physiologic meaning. The tolerance rate k_{tol} was very similar across tested MM and IRM as well as across different versions of these models
- The half-life of 4.10 days derived as $\ln(2)/k_{tol}$ shows the speed of the tolerance onset, suggesting it mostly occurs within one treatment interval of 2 weeks
- Based on the values of k and E_{max} (Table), the baseline and maximal central-to-margination half-lives are ~2.6 and ~0.52 hours, respectively. If a sudden change in sarilumab concentration in serum from 0 to a saturating level occurs, instantaneous half-life of margination immediately after the increase accounting for bidirectional flow of neutrophils is 0.64 hours. This theoretical example implies that an effect of margination may be fully observed within several hours and, in the presence of concentrations of sarilumab sufficient to saturate target, may be notably reduced by tolerance within several days. This is inconsistent with an impairment in granulopoiesis and a hematopoietic defect, which may take days to manifest as decreased ANC[6-8] and consistent with known neutrophil dynamics and potential relocalization
- Diagnostic plots for the MM are presented in Figures 3 through 8, illustrating a good model fit

Examples of diagnostic plots for margination model

Figure 3. VPC by treatment group.

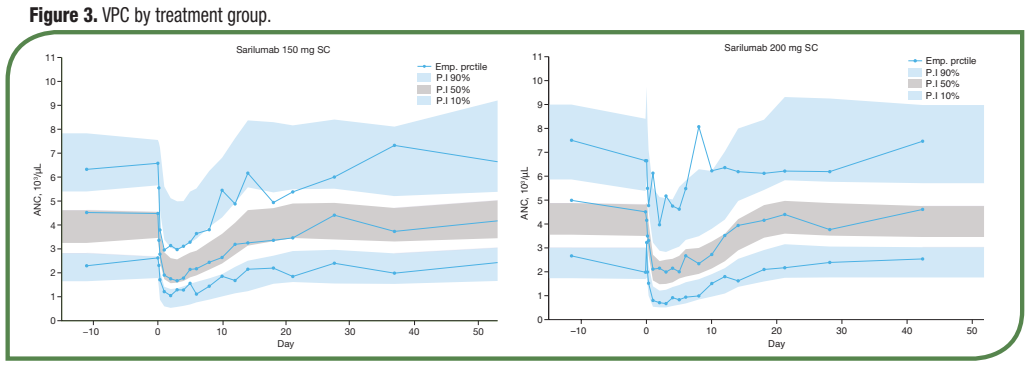


Figure 4. Distribution of individual parameters.

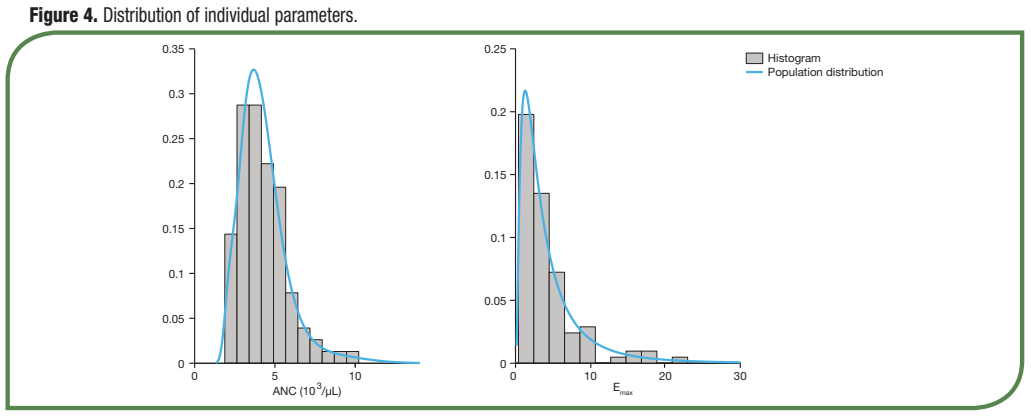


Figure 5. Observed vs PRED ANC.

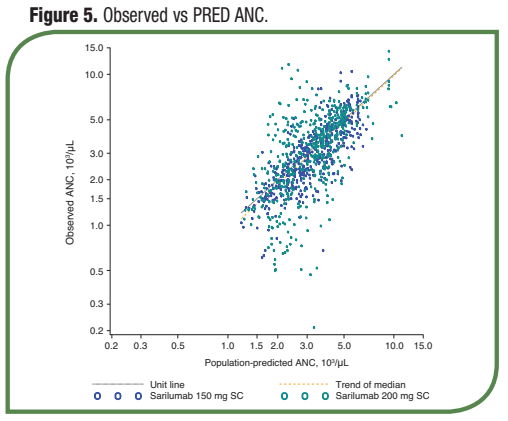


Figure 6. Observed vs IPRED ANC.

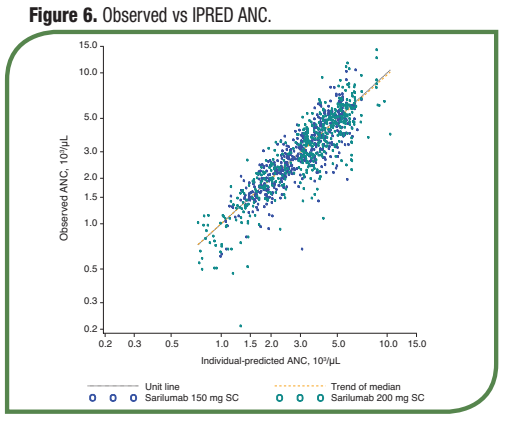


Figure 7. IWRES vs time.

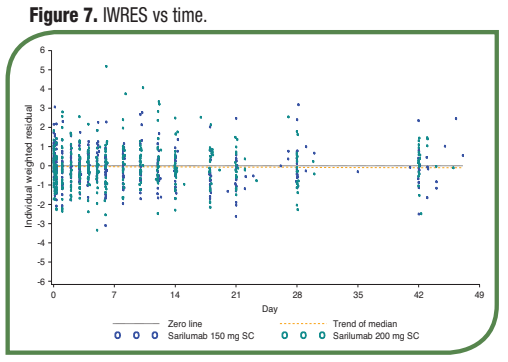
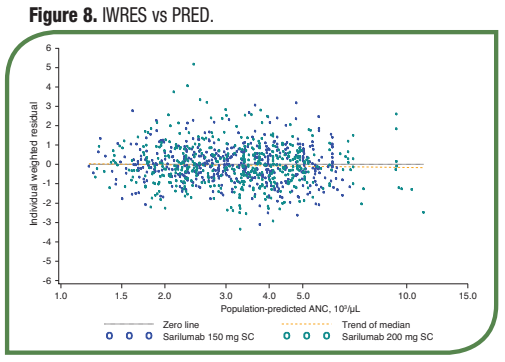


Figure 8. IWRES vs PRED.



CONCLUSIONS

- A PD model that implements neutrophil margination with ANC-specific tolerance and describes the mechanism of transient decreases in ANC observed with IL-6 inhibitors was constructed
- The margination model describes the data well and is consistent with known neutrophil dynamics and potential relocalization as opposed to a hematopoietic defect, which may take days to manifest as decreased ANC
- The margination and tolerance are consistent with the absence of both impairment in neutrophil activity and lack of association of decrease in ANC with increased risk of infection

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Author Disclosures: Pavel Kovalenko, Anne Paccaly, Anita Boyapati, John D. Davis, and A. Thomas DiCioccio are employees of Regeneron Pharmaceuticals, Inc, and may hold stock and/or stock options in the company. Christine Xu is an employee of Sanofi Genzyme and may hold stock and/or stock options in the company.

References: 1. Wright et al. *Rheumatology (Oxford).* 2014;53:1321-1331. **2.** Genovese et al. *Arthritis Rheumatol.* 2015;67:1424-1437. **3.** Maini et al. *Arthritis Rheum.* 2006;54:2817-2829. **4.** Gabrielsson et al. *Pharmacokinetic and Pharmacodynamic Data Analysis: Concepts and Applications, Fourth Edition.* 2007. **5.** Gibiansky et al. Poster presented at: ACoP; October 12-15, 2014; Las Vegas, NV. **6.** Kolaczkowska et al. *Nat Rev Immunol.* 2013;13:159-175. **7.** Li et al. *Cancer Chemother Pharmacol.* 2016;77:703-712. **8.** Ozawa et al. *Cancer Sci.* 2007;98:1985-1992.