Eculizumab as a Key Comparator for the Evaluation of Complement Targeted Novel Therapeutic Strategies with a QSP Model

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OBJECTIVE

- Paroxysmal nocturnal hemoglobinuria (PNH) is one of multiple diseases in which complement dysregulation, leading to overactivity (i.e., complement mediated inflammation and/or cell lysis), has been implicated as a causal mechanism of disease
- Eculizumab (ECU), a monoclonal antibody targeting complement protein C5, was FDA approved for the treatment of PNH in 2007, providing proof of concept that inhibiting complement activity could deliver therapeutic benefit
- To facilitate the development of novel complement targeted therapies, ECU was represented as a comparator drug in a quantitative systems pharmacology (QSP) model of complement

METHODS

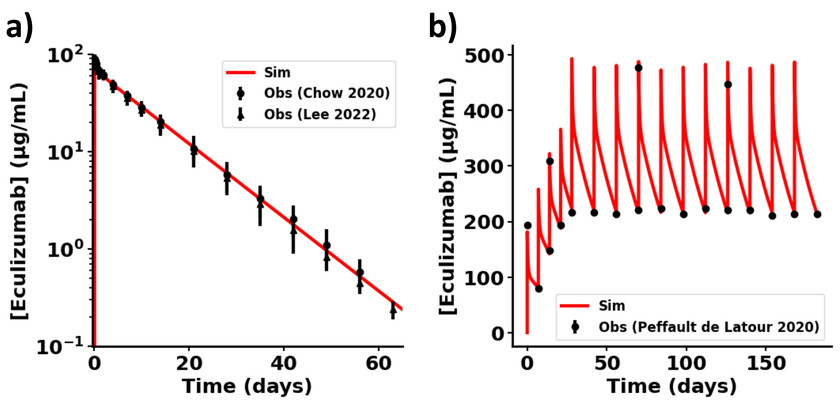
- COMPLEMENTsym™ is a QSP model[1] of fluid-phase complement (patho-)physiology based on publicly available literature
- The model includes simulated populations (SimPops®) representing normal healthy volunteers (NHV), as well as rheumatoid arthritis (RA) and PNH disease states
- ECU exposure was modeled using a two-compartment pharmacokinetic (PK) model (MonolixSuite™) to reproduce single dose data in NHVs[2,3], single dose data in RA patients[4], and repeat dose data in PNH patients[5]
- The PK model then predicted RA patient exposure from alternate protocols[4,6]
- ECU was modeled as reducing free C5. ECU activity was optimized to free C5 levels in PNH patients[7], with functional impact of reduced C5 on hemolysis in PNH patients[8] and in RA patients[4]
- The ECU representation was validated by combining the predicted exposures for three alternate repeat dosing protocols with the optimized parameter values for C5 reduction and hemolysis effect, and then comparing the resultant predictions with published data[6].

RESULTS

PK MODEL

Figure 1. Simulation results for optimization of two-compartment Monolix model of ECU. (a) Single dose 300 mg ECU IV infusion data in NHVs.[2,3] (b) Repeat dosing ECU IV infusion data in PNH patients[5]. Patients received 600mg QW for 4 weeks during the induction phase, followed by 900mg Q2W in the maintenance phase. Published data are indicated in black symbols. Simulation results are in red. (c) Comparison of pharmacokinetic characteristics for single dose ECU in RA patients: 8 mg/kg (optimization) and 4 mg/kg (validation).

NHV - optimization | PNH - optimization | RA – optimization and validation



c)

	Model Optimization		Model Validation	
	Obs[4]	Sim (70 kg)	Obs[4]	Sim (70 kg)
Dose	8 mg/kg	560 mg	4 mg/kg	280 mg
n	6	1	6	1
Cmax (µg/mL)	182 ± 19	178.4	111 ± 53	89.2
AUC_t (µg hr/mL)	35.6 ± 6.5	35.7	13.3 ± 13.5	17.9
AUC_∞ (µg h/mL)	37.8 ± 5.9	37.2	22.2 ± 13.7*	18.6
CL (mL/hr	20.3 ± 4.7	15.0	16.2 ± 7.2*	15.0
V_d (L)	5.0 ± 3.6	4.8	7.5 ± 4.7^	4.8
$t_{1/2}$ (h)	197 ± 198	224	281+298^	224

*n = 4, ^n = 5

Parameter	Unit	Description	NHV	PNH	RA
Cl	mL/h	Central compartment clearance rate	15.6	9	15
V1	mL	Volume of central compartment	3329	3298	3100
Q	mL/h	Intercompartmental clearance	34.8	39.6	37
V2	mL	Volume of peripheral compartment	875.6	1998	1500

Table 1. Parameters for two-compartment model optimized for NHV, PNH patients, and RA patients.

RA - predictions

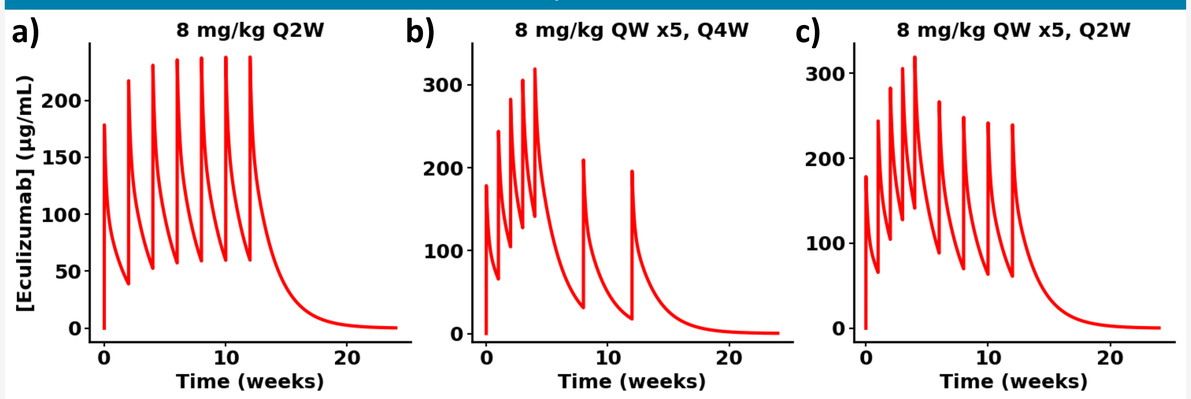


Figure 2. Predicted plasma exposure following repeat eculizumab dosing in RA patients as seen in (6). RA patients were treated for 12 weeks according to the following: (a) 8 mg/kg Q2W, (b) 8 mg/kg QW x5, Q4W, and (c) 8 mg/kg QW x5, Q2W. No PK data were identified for this study. Simulation assumes 70 kg individual.

QSP MODEL

Hemolysis is a key, measurable endpoint often used as a metric of efficacy for treatments targeting the complement pathway. Both alternative pathway (AP)-driven hemolysis and classical pathway (CP)-driven hemolysis are represented in COMPLEMENTsym. Both representations associate free C5 concentrations to hemolysis. Free C5 during ECU administration is optimized to data from treatment-naïve PNH patients[7] (Fig 5). The AP-driven hemolysis representation is optimized based on data of serum lysis during ECU administration in PNH patients[8] (Fig 6). The representation of CP-driven hemolysis was optimized on single dose ECU data in RA patients[4] and validated on multi-dose ECU data in RA patients[6] (Fig 7).

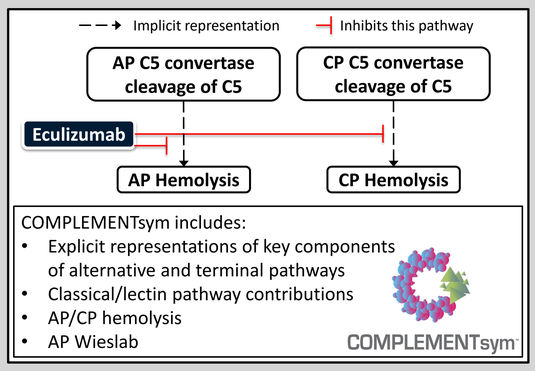


Figure 4. Schematic of hemolysis representations in COMPLEMENTsym.

Optimization of free C5 and AP-driven hemolysis in PNH patients

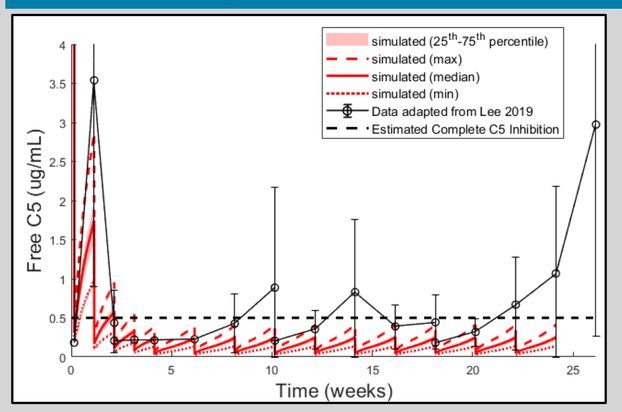


Figure 5. ECU representation optimized to free C5 during clinical dose administered to treatment-naïve PNH simulated population[7].

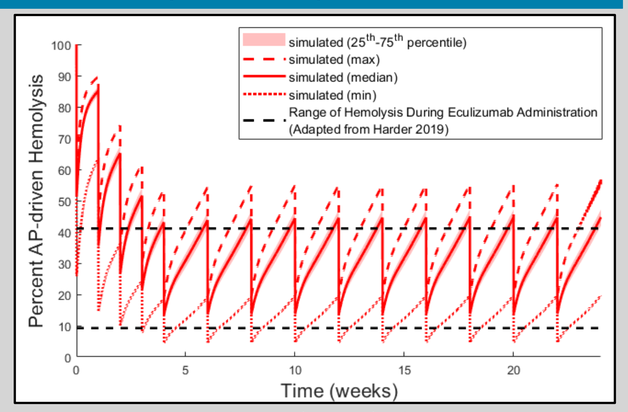
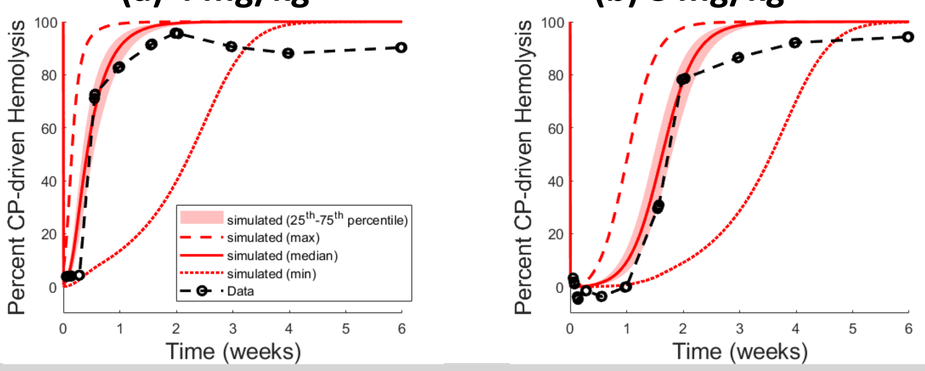


Figure 6. AP-driven hemolysis representation optimized to reproduce reduced serum lysis during ECU administration[8].

Optimization of CP-driven hemolysis in RA patients



Validation of CP-driven hemolysis in RA patients

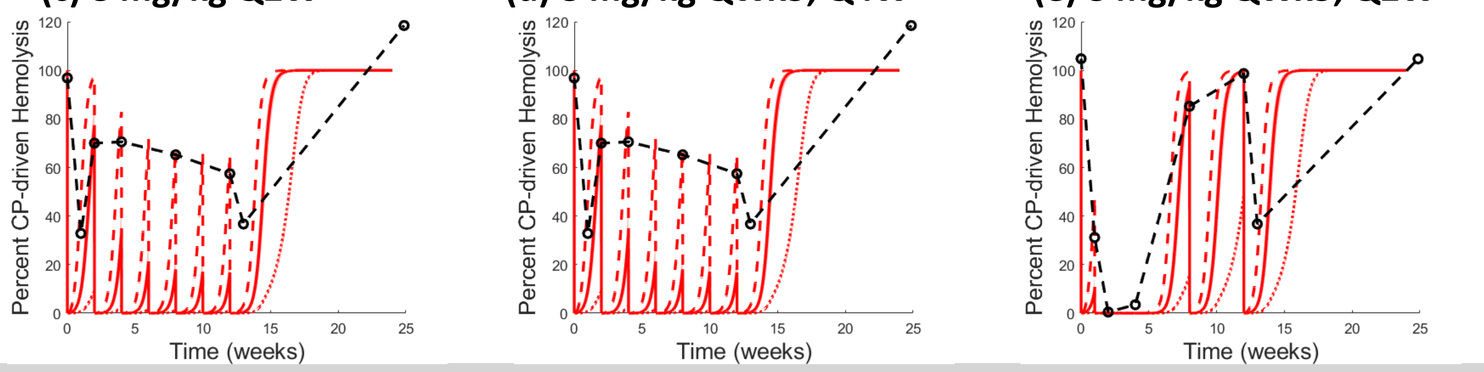


Figure 7. Observed *vs.* optimized (a,b) and validated (c,d,e) dosing protocol-dependent CP response to ECU in RA patients[4,6] and RA SimPops. Results following (a) 4 mg/kg[4] and (b) 8 mg/kg[4], (c) 8 mg/kg Q2W dosing[6], (d) 8 mg/kg QW dosing for five weeks, then Q4W dosing[6], and (e) 8 mg/kg QW dosing for five weeks, then Q2W dosing[6]. Reported data are in black symbols and lines; simulation results are in red.

CONCLUSION

- Simulated ECU exposure and activity were consistent with optimization and validation data
- The QSP model, COMPLEMENTsym, was qualified using available clinical data
- This work demonstrated successful association of a fluid phase analyte with a clinically relevant endpoint (i.e., hemolysis)
- Successful representation of eculizumab provides a comparator compound against which novel complement therapies could be evaluated in head-to-head comparisons or as combination therapies

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