A Biomarker-Focused QSP Model of Complement Alternative and Terminal Pathways to Evaluate Potential Targets for Therapeutic Impact in Complement-Associated Diseases: Paroxysmal Nocturnal Hemoglobinuria (PNH) as a Case Study

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OBJECTIVE & PURPOSE

- Complement overactivity has been implicated in multiple diseases, including PNH
  - PNH is associated with overactivity of the complement alternative pathway, driven by deficiencies in regulatory proteins
- Therapeutic targeting of complement is complicated by feedback loops, redundant functions, and availability of druggable targets
- Here, a QSP model, COMPLEMENTsym™, focused on alternative and terminal pathway complement analytes in circulation is described, including simulated populations (SimPops®) of normal healthy volunteers (NHVs) and PNH patients
- This work aimed to evaluate the impact of exemplar treatments to validate the model for predictive use

METHODS

- QSP model, COMPLEMENTsym, leveraged published models[1–4] and publicly available data informing complement pathways and kinetics
- NHV SimPops (N>5000) developed based on publicly available data supporting known variability in key parameters, qualified against clinical data ranges for 13 analytes
- Simulated PNH disease state developed including increased convertase dissociation rate as a proxy for reduced CD55
- PNH SimPops (N>2000) incorporates NHV variability in addition to disease specific modifications, qualified against data for 4 analytes
- Exemplars optimized (and validated when possible) against published analyte or hemolysis data

QSP MODEL

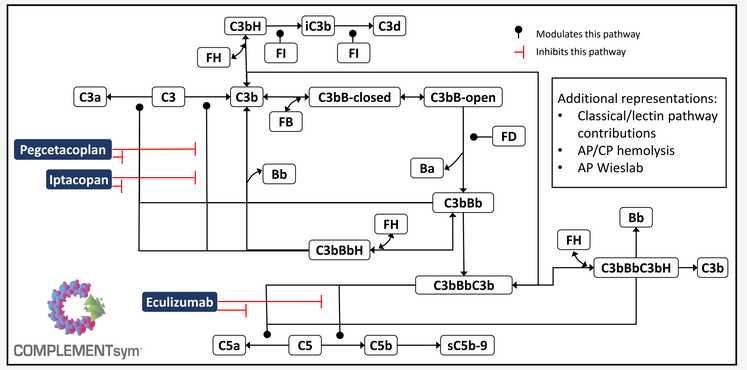

Fig 1. Schematic of complement pathways included in QSP model and where exemplars impact the system.

The PNH SimPops has baseline elevated complement activity compared to the NHV SimPops (3.5x increase in sC5b-9).

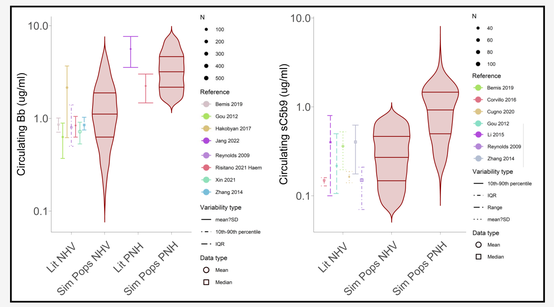

Fig 2. NHV and PNH SimPops baseline Bb (left) and sC5b-9 (left) concentrations compared to literature data.

RESULTS

Eculizumab

Eculizumab is a monoclonal antibody binding C5, reducing complement activity by suppressing the terminal pathway. Eculizumab was simulated with average exposure profile for 600 mg weekly for four weeks followed by 900 mg every other week.

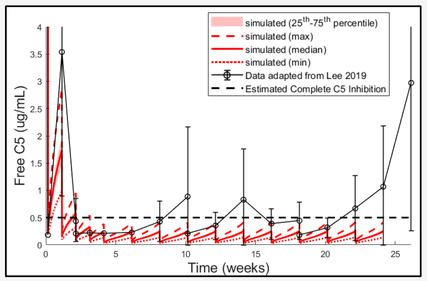

Fig 3. Eculizumab representation optimized to free C5 during clinical dose administered to treatment-naïve PNH simulated population[5].

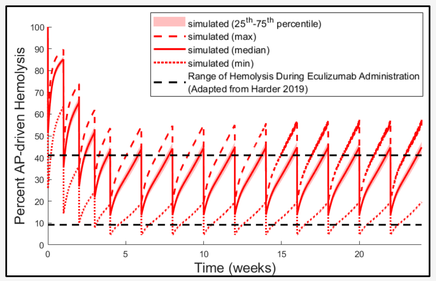

Fig 4. AP-driven hemolysis representation optimized to reproduce reduced serum lysis during eculizumab administration[6].

Pegcetacoplan

Pegcetacoplan targets the C3/C3b binding site, suppressing AP activity. In COMPLEMENTsym, the pegcetacoplan representation is based on clinical data[7]. Simulated pegcetacoplan treatment (270 mg/day) in treatment-naïve PNH SimPops and eculizumab-treated PNH SimCohorts recapitulated published C3 elevations without optimization[8,9].

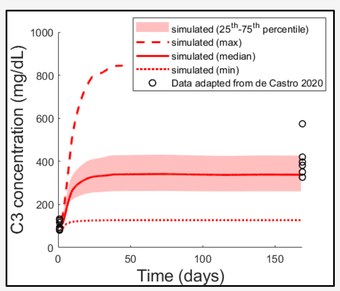

Fig 5. Simulated C3 concentrations during pegcetacoplan treatment in patients with eculizumab background compared to Day 1 and Day 169 clinical data[8].

Iptacopan

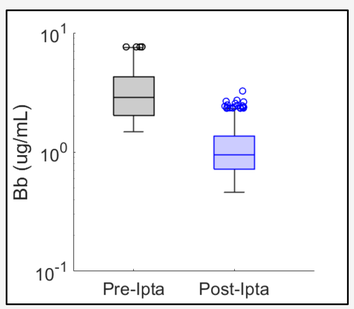

Fig 6. Simulated Bb concentrations in eculizumab-treated PNH SimCohorts before and after treatment with iptacopan.

Iptacopan targets the active site of Factor B, suppressing AP activity. Simulated iptacopan in treatment-naïve PNH SimPops was optimized to reproduce published reductions in Bb[10]. A PNH cohort was developed to match sC5b-9 concentrations of PNH patients on eculizumab prior to treatment with iptacopan[11]. Simulating iptacopan (200 mg twice a day) in this cohort reduces average Bb from 3.29 ug/mL to 1.08 ug/mL over 13 weeks, consistent with published reductions in Bb from 4.871 ug/mL to 1.198 ug/mL[11].

Predicted sC5b-9 Outcomes

Treatment-naïve PNH SimPops simulated with exemplars, assuming average exposure, demonstrates different responsiveness as quantified by sC5b-9 concentrations.

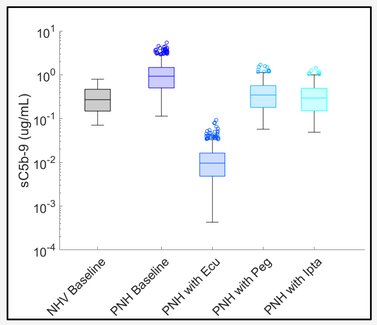

Fig 7. Simulated sC5b-9 concentrations for NHV and PNH SimPops baselines compared to post-treatment values for 24 week simulations of treatment-naïve PNH patients on eculizumab, pegcetacoplan, and iptacopan monotherapies.

CONCLUSION

- SimPops demonstrate consistency with complement analytes in health and disease
- Disease representation is strengthened by reproducing clinical data from PNH patients treated with eculizumab, pegcetacoplan, and iptacopan
- This work establishes a model and framework to evaluate novel targets and compounds for complement-associated diseases

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