Examining the Clinical and Complement Biomarker Profiles in C3 Glomerulopathy Patients Treated with Targeted Complement Inhibitors

Lauren Fergus [1], Jillian Hall [1], Nicole Gerot [2], Matthew Allen [2], Monica D. Hall [1 2], Yuzhou Zhang [1], Richard J. H. Smith [1 2], Carla M. Nester [1 2]
[1] Molecular Otolaryngology and Renal Research Laboratories, [2] University of Iowa Health Care

Background

- C3 Glomerulopathy (C3G), defined by dominant C3 deposition on kidney biopsy, is a rare disease characterized by persistent dysregulation of the alternative complement pathway.
- Complement targeted therapeutics are currently not available for use; >50% of patients progress to ESRD within 10 years. As complement inhibitors progress through clinical trials, there are questions regarding their impact on the various aspects of disease as compared to current drugs.
- In this single-center study, we sought to describe and compare changes in clinical and complement biomarker labs before and after initiation of complement inhibitors or standard treatment.

Methods

- 19 pediatric and 24 adult C3G patients (n=43) from the University of Iowa's C3G Natural History Study were included in the cohort. 26 were enrolled in complement inhibitor (CI) trials. Specific trial n's are listed in Table 1.
- CI trials included Novartis APPEAR (NA-FBi), Novartis Extension (NE-FBi), MAP-LNP023 (NC-FBi), Apellis VALIANT (AV-C3i), MAP-APL2 (AC-C3i), Avacopan ACCOLADE (C5aRi), and Achillion (FDi). Guideline-recommended treatment groups included Eculizumab (C5i) and Mycophenolate Mofetil ± Prednisone (MMF±P). Controls were placebos in the Novartis APPEAR trial.
- Lab results were collected 0-6 months prior and 6-12 months after drug initiation. Complement biomarker testing included Complement C3 and Soluble C5b-9. Clinical biomarkers included eGFR and Urine Protein/Creatinine Ratio (UPC). Mean percent change from baseline was calculated from these timepoints and compared across treatment groups.

Results

- **Complement C3**: C3 showed little mean change in standard treatment and control groups (MMF±P, +7%, Control +9%), while CI groups ranged from decline (C5aRi -54%) and little change (C5i, +7%), to large increases, as was the case for most CI trials (+116-4523%).
- **eGFR:** NA-FBi, AV-C3i, and C5aRi groups showed small mean increases in eGFR (+1-23%), albeit with significant variability, while FDi had the greatest mean drop (-17%). Standard treatment and control groups demonstrated small changes in eGFR (MMF±P -6%, Control +4%), with similar variability to CI groups.
- **UPC:** All CI groups had a mean reduction in UPC after initiation, ranging from -1% (C5aRi) to -65% (NC-FBi). The control group showed little mean change (-2%), and MMF±P had a modest reduction in proteinuria (-20%).
- **Soluble C5b-9:** All CI groups showed a drop in Soluble C5b-9 besides C5aRi (+56%), with the largest declines observed in C3i (-80%- -75%) and FBi (-79%- -46%) trials. Standard treatment and control groups had modest (MMF±P, 13%) to no effect (Control, +1%).

Conclusions

- In our cohort, clinical and complement biomarker impact are mixed.
- Ultimately, two treatment groups, NA-FBi and AV-C3i, saw improvements in all four clinical markers– a circumstance which we may have predicted by underlying disease pathology of the alternative pathway.
- There were several treatment groups that saw improvements in three of four markers, providing additional options for potential clinical use. Complement inhibitors, as a whole, had improved outcomes when compared to standard MMF±P and controls.
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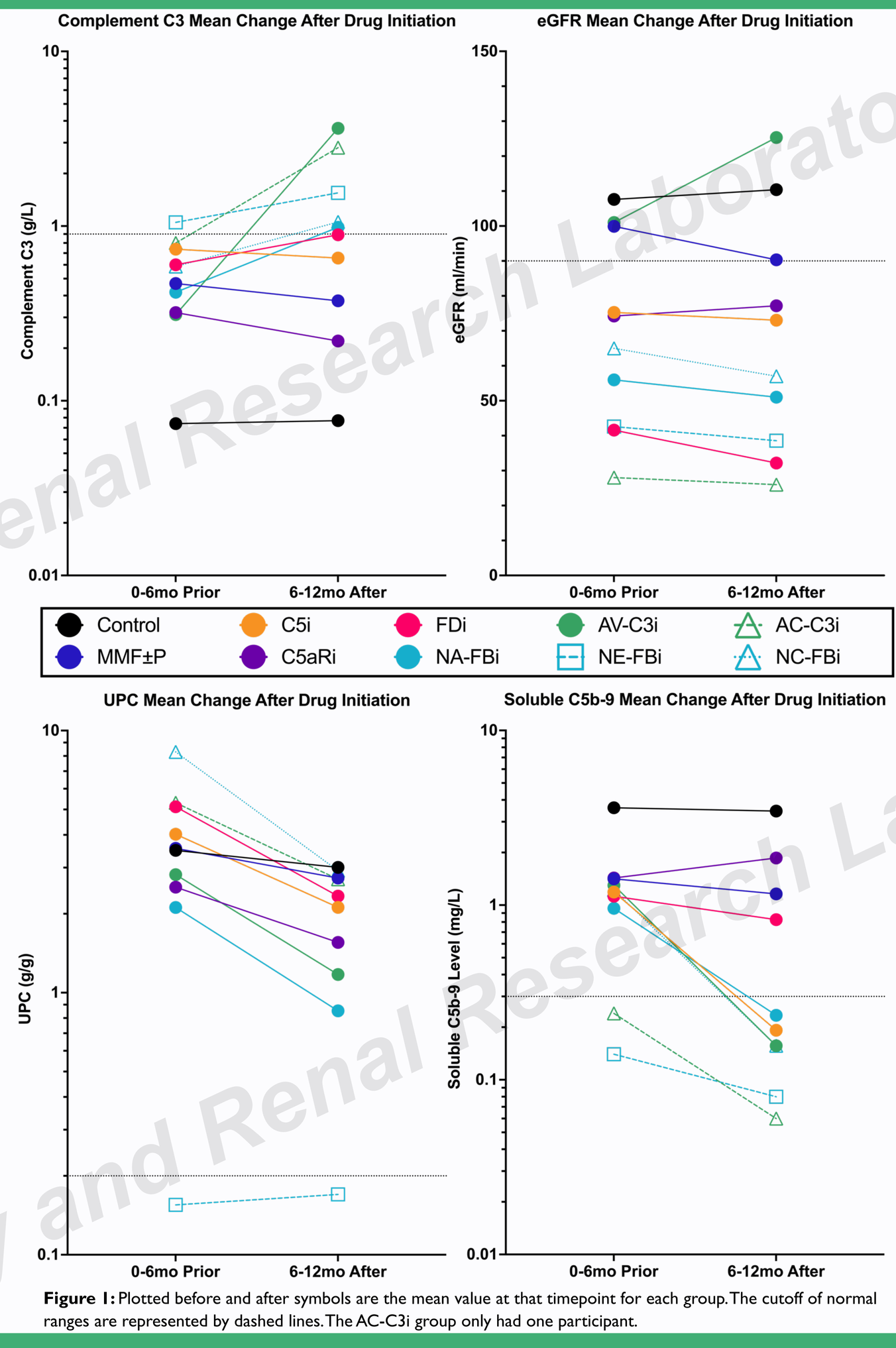

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FDi (n=5)	**+116%** (±217%)	-17% (±28%)	**-44%** (±36%)	**-15%** (±65%)	No
C5aRi (n=5)	-54% (±37%)	**+3%** (±14%)	-1% (±99%)	+56% (±56%)	No
C5i (n=10)	+7% (±10%)	-1% (±32%)	**-60%** (±44%)	**-66%** (±30%)	No
MMF ± P (n=9)	-4% (±75%)	-6% (±37%)	**-20% (±37%)**	**-13%** (±45%)	No
Controls (n=5)	+9% (30%)	**+4% (±13%)**	-2% (±48%)	+1% (±47%)	No

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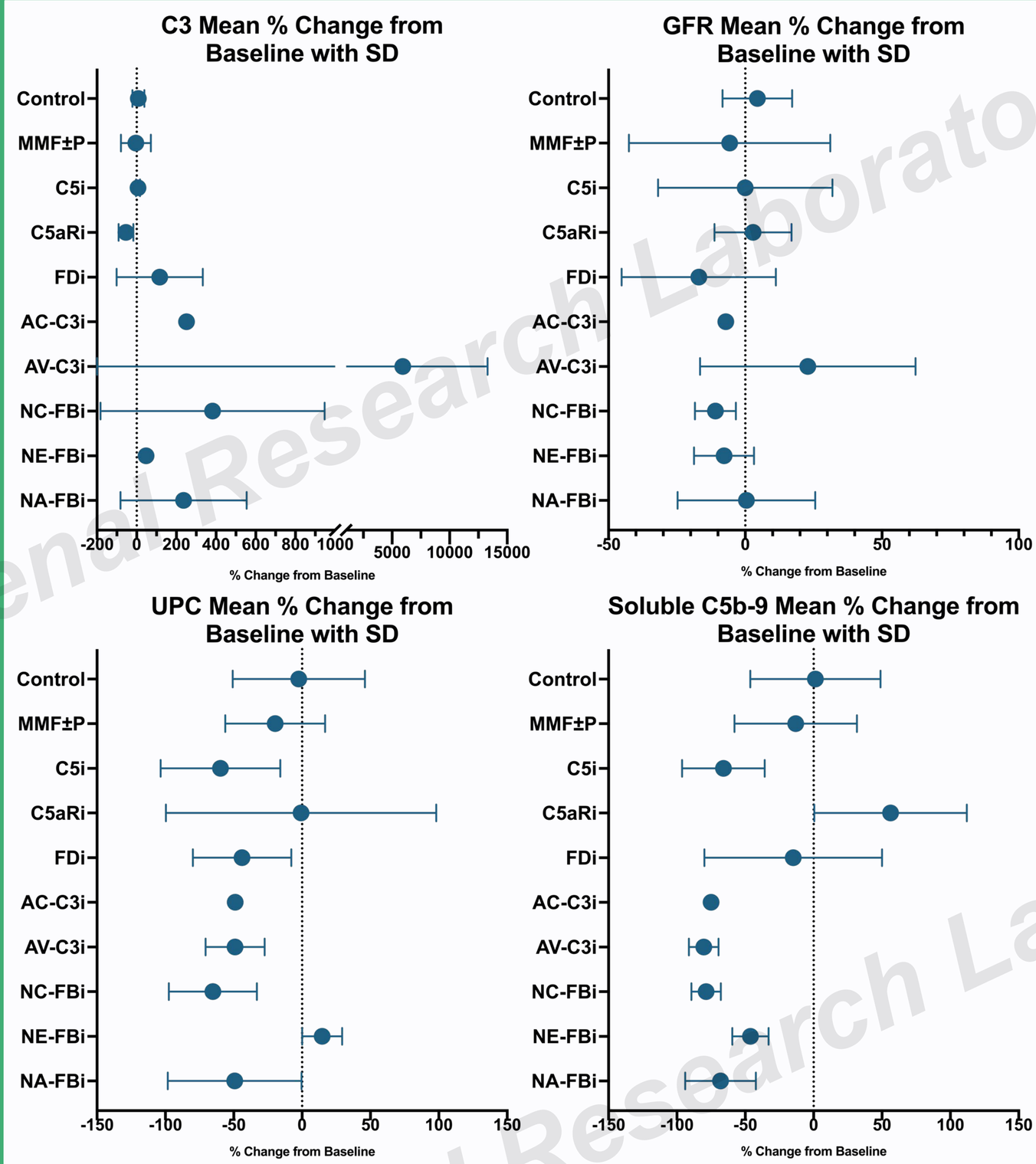

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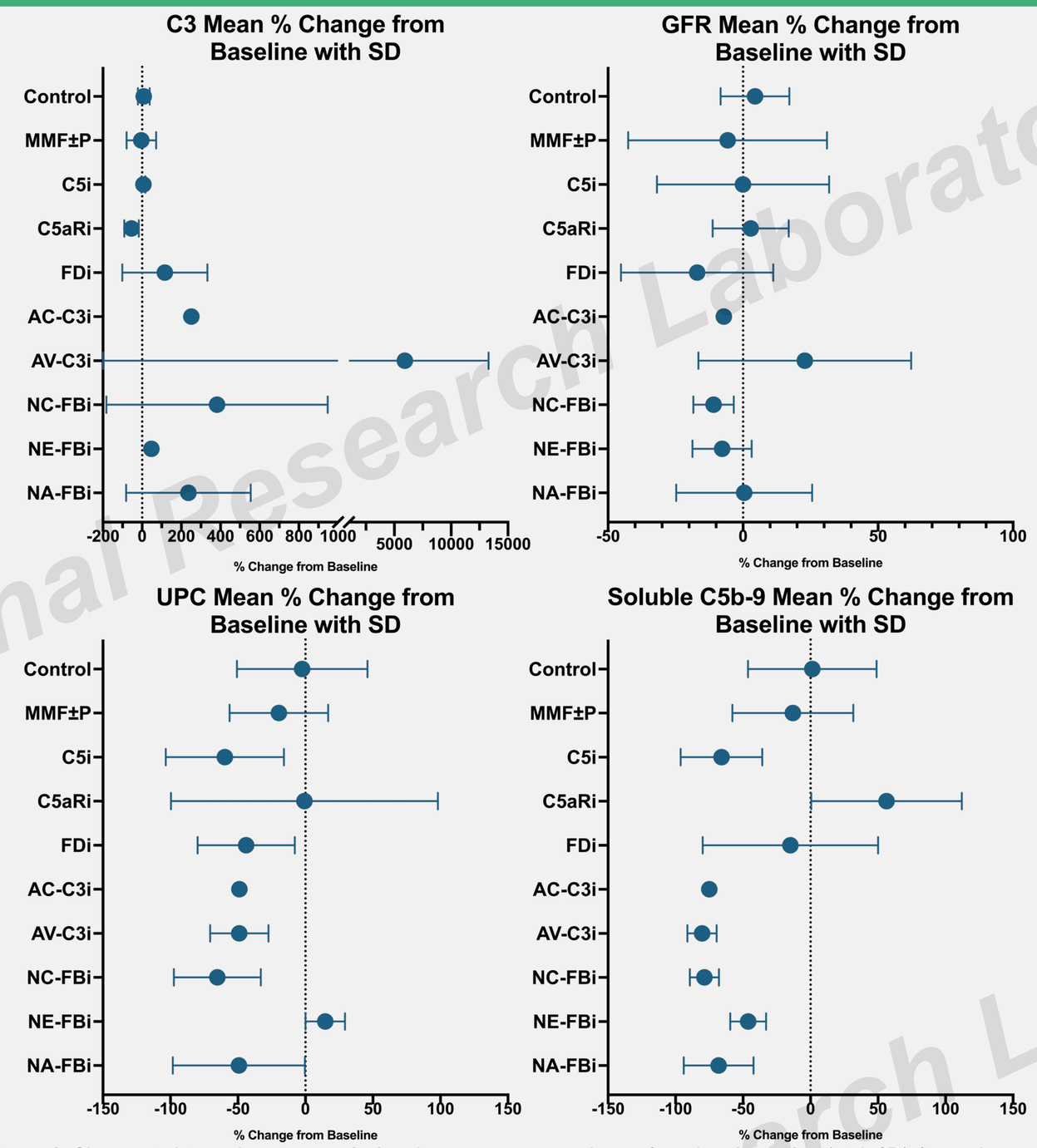

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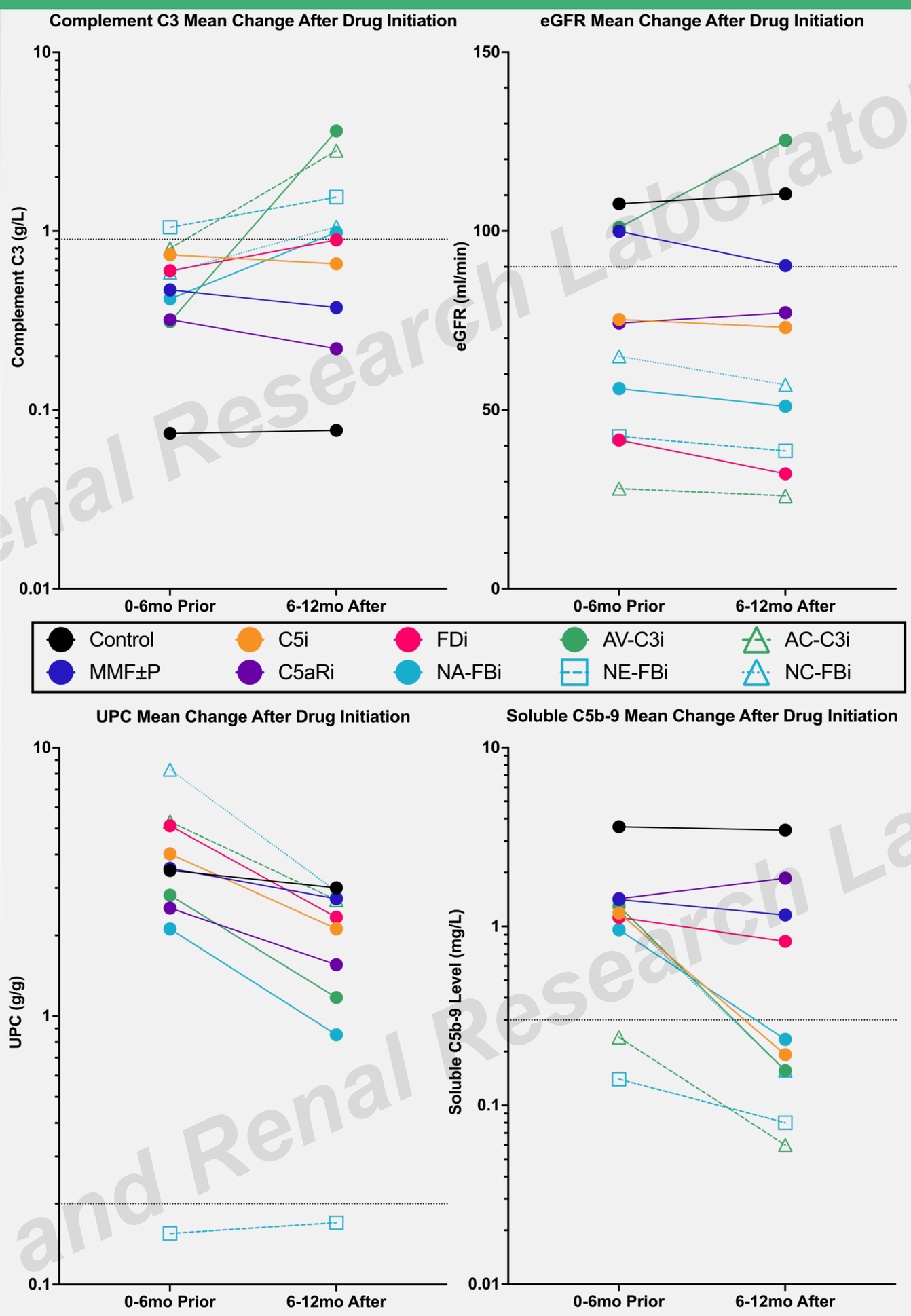

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