Trends in Complement Pathway Biomarkers Before and After Eculizumab Initiation in C3 Glomerulopathy

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Background

- C3 Glomerulopathy (C3G) is an ultra-rare kidney disease characterized by alternative complement pathway dysregulation.
- Most patients reach end-stage renal disease (ESRD) within 10 years of diagnosis.
- The complement inhibitor, eculizumab, has been used to treat C3G with mixed results.
- We compared complement biomarker trends in a cohort of C3G patients before and after eculizumab treatment in responders and non-responders.

Methods

- 14 individuals from the University of Iowa's C3G Natural History Study examined.
- Responders were characterized with improved GFR change/year after initiation
- Non-responders were characterized with unchanged or worsening GFR change/year after initiation.
- Inclusion criteria consisted of baseline native biopsy diagnosis of C3G and ≥ 1 year of clinical data (C3, GFR, UPC) prior to and after starting eculizumab.
- Exclusion criteria included other complement inhibitors, dialysis, and kidney transplant.
- Simple linear regression of C3, C3CSA, C3CSAP, C4Nef, and Soluble C5b-9 Level before and after eculizumab initiation among responders and non-responders was measured.
- Paired t-test with p values were used to evaluate the significance; $p < 0.05$.

Results

- C3 did not change significantly over time before and after eculizumab ($p = 0.81$).
- Nephritic factors (C3CSA, C3CSAP, C4Nef) generally had a positive slope pattern prior to initiation and a negative slope after.
- C3CSA, C3CSAP, and C4Nef did not change significantly over time before and after eculizumab ($p = 0.43$; 0.16; 0.59; respectively)
- Responders with a positive C3 Nephritic Factor started out with a higher factor prior to initiation than non-responders ($p < 0.05$)
- sC5b-9 levels had a decreasing trend over time ($p < 0.05$).
- Responders of eculizumab had higher sC5b-9 levels prior to initiation than non-responders.

Conclusions

- Based on the data, treatment with eculizumab does not significantly change the C3, C3CSA, C3CSAP, and C4Nef over time prior to and after initiation.
- Among those with a positive C3 Nephritic Factor, individuals with a higher factor may have a better response to eculizumab than those without.
- Eculizumab significantly lowers sC5b-9 levels over time.
- Those who start out with higher sC5b-9 levels prior to initiation may have a better response to eculizumab treatment.

Limitations and Future Directions

- Limitations include sample size and limited availability of biomarkers over time.
- Future directions include examining baseline C3G histology, genetics, and other clinical markers to determine if outcome may be predicted.

Figure 1. C3 Trends Pre- and Post-Initiation Over Time

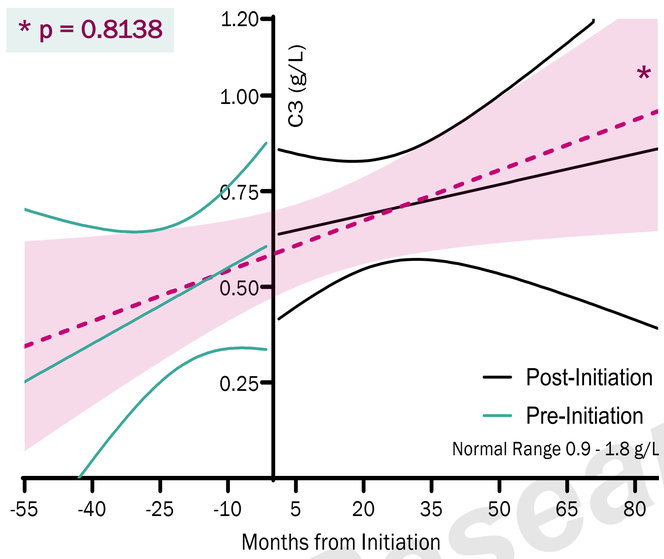


Figure 2. C3 Nephritic Factor (C3CSA) Pre- and Post-Initiation Over Time

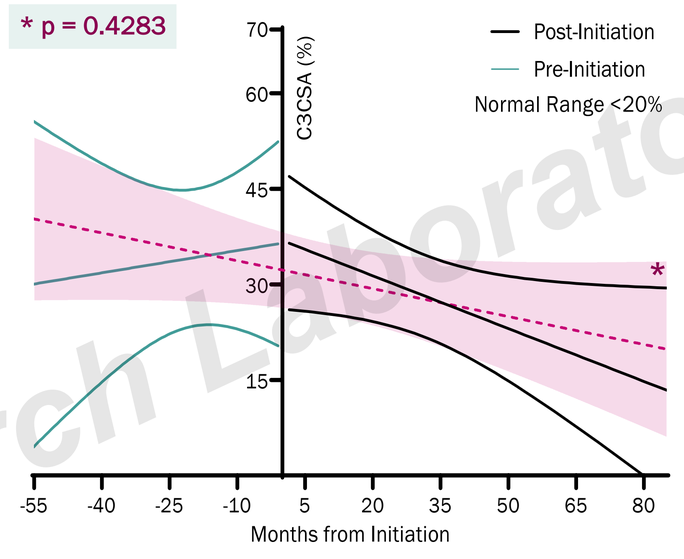


Figure 3. Comparison of Non-responders vs. Responders with Positive (+) C3 Nephritic Factor Prior to Initiation (C3CSA)

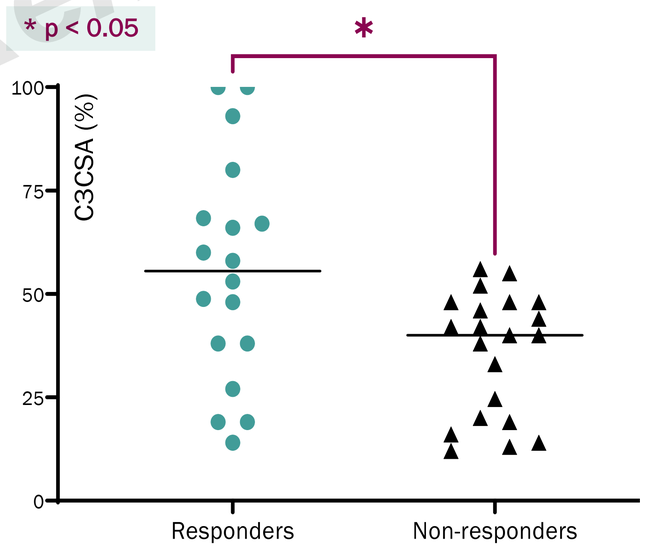


Figure 4. Patients Pre-/Post-Initiation with Positive (+) C5 Nephritic Factor (C3CSAP) vs. Patients Without (-) Over Time

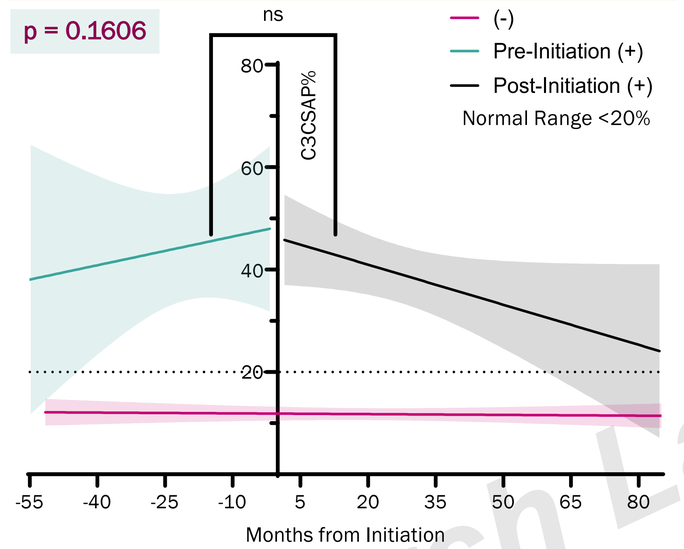


Figure 5. C4 Nephritic Factor (C4Nef) in Non-responders vs. Responders Over Time

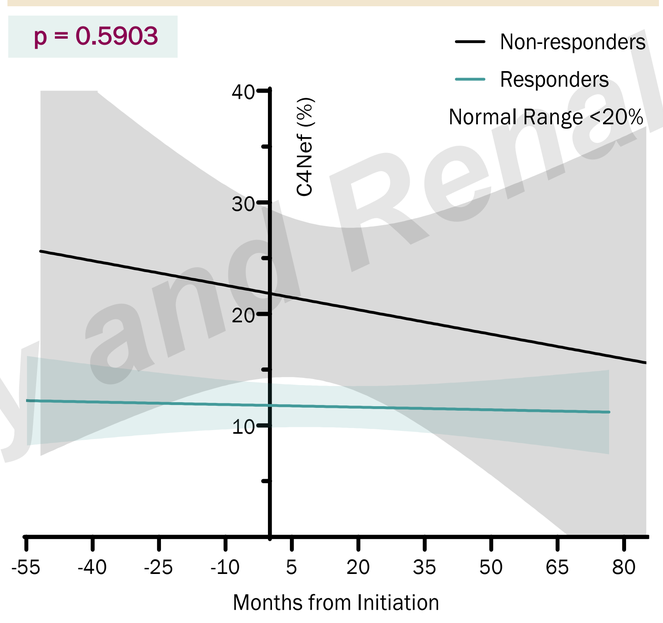


Figure 5. C4 Nephritic Factor (C4Nef) Pre-/Post-Initiation Over Time

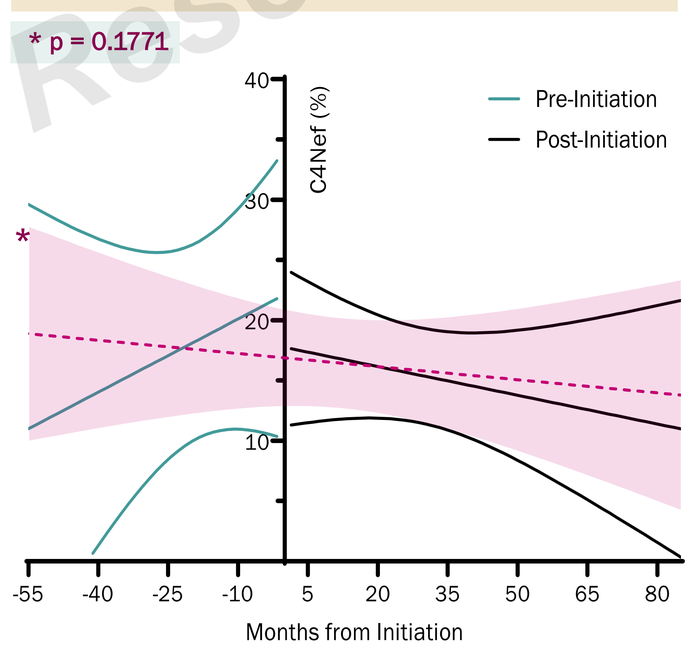


Figure 6. sC5b-9 Levels Pre- and Post-Initiation Over Time

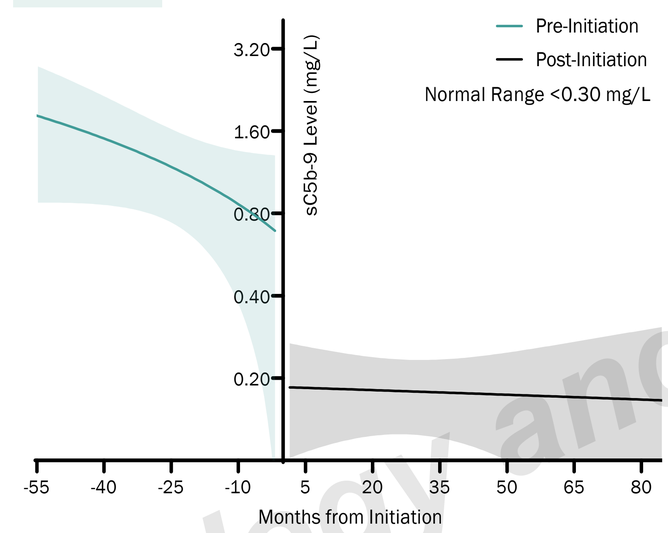
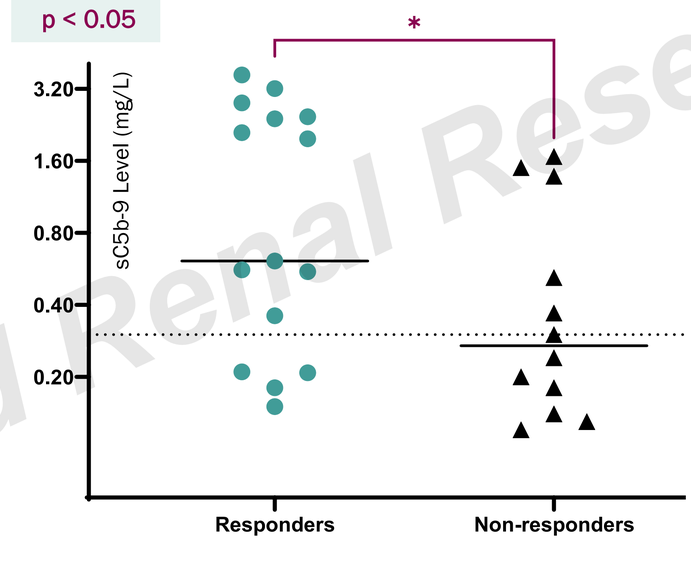


Figure 7. sC5b-9 Level Trends in Non-responders vs. Responders Over Time



References

1. *Am. J. Nephrol.*, 44(3), 187–193, (2016)
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3. *Am J Kidney Dis.,* 34(6), 1129-1131, (1999)

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