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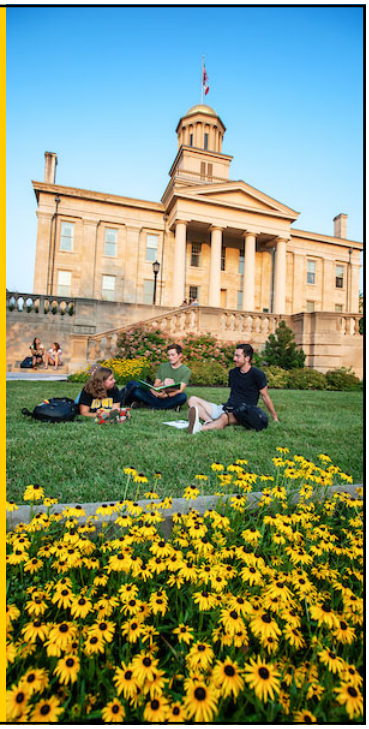
C3G Natural History Study

C3G- Its Natural History



Monica Hall
October 14, 2023

1

2023 Natural History Database Updates:

Population:

261 Patients:

- 78 with DDD
- 143 with C3GN

Age of Onset:

- Age range 2-71 yrs. Old
- Average age: 16 years

Biopsy Validation:

- Partnership with Dr. Pat Walker at Arkana Laboratories.
- 71% of baseline biopsies completed

Genetic & Biomarker Tests

- 94% have genetics completed
- 1411 biomarker panels complete
- Biomarkers ranged from 1-24 per person

2

Longitudinal Complement Biomarker Trend in C3G

(EMCHD – Spain – Monica)

Goals:

- To estimate the extent to which C3 levels and renal filtering function change in response to disease progression.
- To describe the relationship between these two disease related biomarkers.

Findings

50 patients from our NHxS Database:

- 16% had a normal C3 at time of diagnosis & continued a normal C3 throughout follow-up (median 7.2 yrs)
- 34% maintained a low C3 across all timepoints.
- 44% had a low C3 at dx, however recovered to the normal range over time (70% within 1st 2 yrs)
- In this cohort, a lower C3 predicted a greater risk for declining eGFR.

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3

Trending C3 Before and After Transplant in C3G Patients

(ASN – Washington, DC - Monica)

What did we look at:

- DDD and C3GN patients (13)
- 62% had a positive nephritic factor at the time of native kidney diagnosis.
- 46% had a gene variant
- 38% had clinical & histological recurrence in their allograft
- 86% of patients with a known C3 at time of transplant had a low C3

Findings:

- Low C3 at time of TP was associated with greater risk of recurrence of disease in the transplanted kidney.
- Recurrence can occur in the setting of a normal C3.
- C3 measurement alone is not a clear predictor of risk for recurrence.
- Histologic recurrence without clinical (rise in UPC, serum creatinine and the presence of urine blood) recurrence can occur.

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4

Pregnancy Outcomes in C3G

(ASN – Virtual/San Diego – Lauren)

Our cohort:

- 61 pregnancies
  - 46 deliveries
  - 25 mothers with C3G

Findings:

- 55.7% uneventful live births
- 19.7% of these live births via C-section
- 19.7% of pregnancies spontaneously aborted
- 3.3% of pregnancies were electively aborted
- 1.6% of pregnancies had an ectopic pregnancy

ALL SIMILAR Rates TO OVERALL POPULATION of Pregnant Moms.

Risk Factors:

- Creatinine 1.5 or > prior to pregnancy
- UPC 1.5 or greater
- Uncontrolled hypertension
- "Active" biomarker panel

TAKE AWAY's:

Most C3G Pregnancies go smoothly, with small increases in BP, sCr and proteinuria.

*Please have a baseline High-Risk OB appointment when 1st pregnant and collaborate with nephrologist.

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5

Predicting Post-Transplant Disease Recurrence in C3G

(EMCHD – Switzerland – Lauren)

Our Cohort:

- 40 C3G patients who had transplants
- All had genetics and biomarkers done

Results:

- 11/40 had documented recurrence
- Recurrence patients had elevated C3Nef, C5Nef, C3c, c3c/C3 ratio and sC5b-9 **and** a C3 < 90.
- Genetics did enhance the sensitivity of transplant risk recurrence.

Our Findings:

Knowing a patient's particular biomarkers and genetics pre-transplant, we can offer a PTxRR:

Post-Transplant Recurrence Risk Score

With offering a PTxRR score to patients care team pre-transplant, **we can be proactive and have a plan in place to hopefully prevent detriment to the transplanted kidney by initiating necessary treatment strategies when signs of recurrence arise.**

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6

Clinical and Histological Correlations in C3G

(2023 – ICW – Newcastle, UK - Jill)

The Basics:

- 96 patients with C3G
- Examined the relationship between onset biopsy characteristics and clinical lab values (eGFR, UPC and C3) both at onset and over time.
- Reviewed the effects of immunosuppression and ACEi/ARB's.
- Reviewed kidney biopsy markers
  - Chronicity: Sclerosis and IFTA
  - Acuity: mesangial hypercellularity, endocapillary proliferation, and leukocyte infiltration.

Findings:

- Greater severity of chronic changes noted on a biopsy was correlated with a > risk of GFR loss.
- A person with a lower C3 when diagnosed, indicating complement activation, also had > degree of acuity noted on bx (hypercellularity proliferation and leukocyte infiltration).
- There was no significant correlation between improvement in GFR or C3 and the use of "standard" immune suppression or ACEi/ARB medications.

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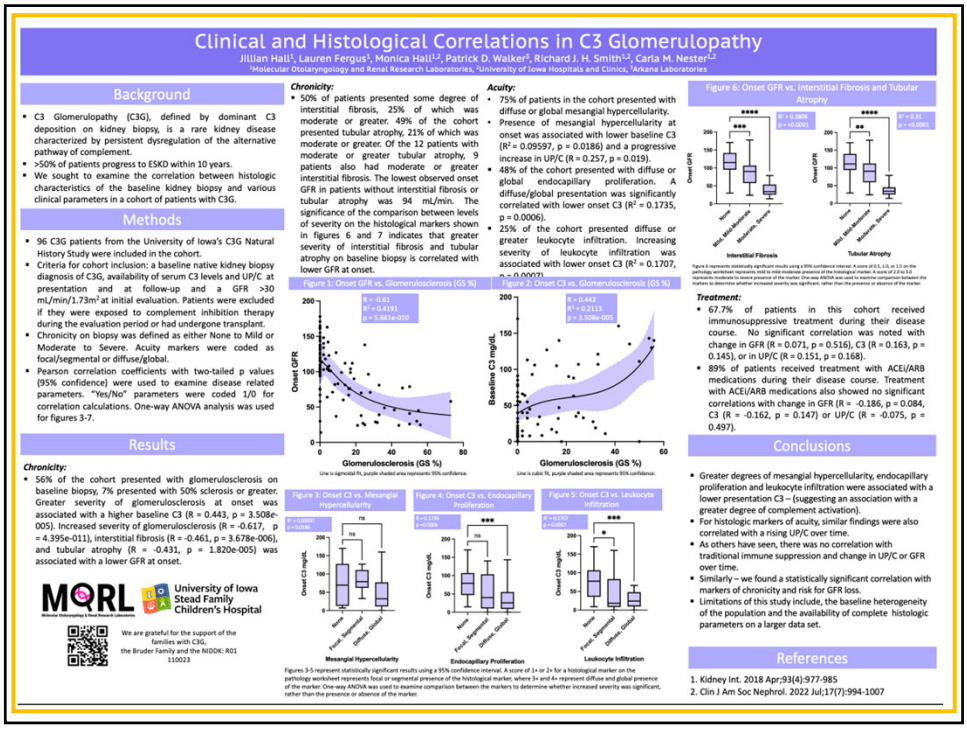
7



Clinical and Histological Correlations in C3 Glomerulopathy

Jillian Hall[1], Lauren Fergus[1], Monica Hall[1,2], Patrick D. Walker[3], Richard J. H. Smith[1,2], Carla M. Nester[1,2]

[1]Molecular Otolaryngology and Renal Research Laboratories, [2]University of Iowa Hospitals and Clinics, [3]Arkana Laboratories

Background

- C3 Glomerulopathy (C3G), defined by dominant C3 deposition on kidney biopsy, is a rare kidney disease characterized by persistent dysregulation of the alternative pathway of complement.
- >50% of patients progress to ESKD within 10 years.
- We sought to examine the correlation between histologic characteristics of the baseline kidney biopsy and various clinical parameters in a cohort of patients with C3G.

Methods

- 96 C3G patients from the University of Iowa's C3G Natural History Study were included in the cohort.
- Criteria for cohort inclusion: a baseline native kidney biopsy diagnosis of C3G, availability of serum C3 levels and UP/C at presentation and at follow-up and a GFR >30 mL/min/1.73m^2 at initial evaluation. Patients were excluded if they were exposed to complement inhibition therapy during the evaluation period or had undergone transplant.
- Chronicity on biopsy was defined as either None to Mild or Moderate to Severe. Acuity markers were coded as focal/segmental or diffuse/global.
- Pearson correlation coefficients with two-tailed p values (95% confidence) were used to examine disease related parameters. "Yes/No" parameters were coded 1/0 for correlation calculations. One-way ANOVA analysis was used for figures 3-7.

Results

Chronicity:

- 56% of the cohort presented with glomerulosclerosis on baseline biopsy, 7% presented with 50% sclerosis or greater. Greater severity of glomerulosclerosis at onset was associated with a higher baseline C3 (R = 0.443, p = 3.508e-005). Increased severity of glomerulosclerosis (R = -0.617, p = 4.395e-011), interstitial fibrosis (R = -0.461, p = 3.678e-006), and tubular atrophy (R = -0.431, p = 1.820e-005) was associated with a lower GFR at onset.

Chronicity:

- 50% of patients presented some degree of interstitial fibrosis, 25% of which was moderate or greater. 49% of the cohort presented tubular atrophy, 21% of which was moderate or greater. Of the 12 patients with moderate or greater tubular atrophy, 9 patients also had moderate or greater interstitial fibrosis. The lowest observed onset GFR in patients without interstitial fibrosis or tubular atrophy was 94 mL/min. The significance of the comparison between levels of severity on the histological markers shown in figures 6 and 7 indicates that greater severity of interstitial fibrosis and tubular atrophy on baseline biopsy is correlated with lower GFR at onset.

Acuity:

- 75% of patients in the cohort presented with diffuse or global mesangial hypercellularity.
- Presence of mesangial hypercellularity at onset was associated with lower baseline C3 (R^2 = 0.09597, p = 0.0186) and a progressive increase in UP/C (R = 0.257, p = 0.019).
- 48% of the cohort presented with diffuse or global endocapillary proliferation. A diffuse/global presentation was significantly correlated with lower onset C3 (R^2 = 0.1735, p = 0.0006).
- 25% of the cohort presented diffuse or greater leukocyte infiltration. Increasing severity of leukocyte infiltration was associated with lower onset C3 (R^2 = 0.1707, p = 0.0007).

Figure 1: Onset GFR vs. Glomerulosclerosis (GS %)

Figure 2: Onset C3 vs. Glomerulosclerosis (GS %)

Figure 3: Onset C3 vs. Mesangial Hypercellularity

Figure 4: Onset C3 vs. Endocapillary Proliferation

Figure 5: Onset C3 vs. Leukocyte Infiltration

Figures 3-5 represent statistically significant results using a 95% confidence interval. A score of 1+ or 2+ for a histological marker on the pathology worksheet represents focal or segmental presence of the histological marker, where 3+ and 4+ represent diffuse and global presence of the marker. One-way ANOVA was used to examine comparison between the markers to determine whether increased severity was significant, rather than the presence or absence of the marker.

Figure 6: Onset GFR vs. Interstitial Fibrosis and Tubular Atrophy

Figure 6 represents statistically significant results using a 95% confidence interval. A score of 0.5, 1.0, or 1.5 on the pathology worksheet represents mild to mild-moderate presence of the histological marker. A score of 2.0 to 3.0 represents moderate to severe presence of the marker. One-way ANOVA was used to examine comparison between the markers to determine whether increased severity was significant, rather than the presence or absence of the marker.

Treatment:

- 67.7% of patients in this cohort received immunosuppressive treatment during their disease course. No significant correlation was noted with change in GFR (R = 0.071, p = 0.516), C3 (R = 0.163, p = 0.145), or in UP/C (R = 0.151, p = 0.168).
- 89% of patients received treatment with ACEi/ARB medications during their disease course. Treatment with ACEi/ARB medications also showed no significant correlations with change in GFR (R = -0.186, p = 0.084, C3 (R = -0.162, p = 0.147) or UP/C (R = -0.075, p = 0.497).

Conclusions

- Greater degrees of mesangial hypercellularity, endocapillary proliferation and leukocyte infiltration were associated with a lower presentation C3 – (suggesting an association with a greater degree of complement activation).
- For histologic markers of acuity, similar findings were also correlated with a rising UP/C over time.
- As others have seen, there was no correlation with traditional immune suppression and change in UP/C or GFR over time.
- Similarly – we found a statistically significant correlation with markers of chronicity and risk for GFR loss.
- Limitations of this study include, the baseline heterogeneity of the population and the availability of complete histologic parameters on a larger data set.

References

1. Kidney Int. 2018 Apr;93(4):977-985
2. Clin J Am Soc Nephrol. 2022 Jul;17(7):994-1007

We are grateful for the support of the families with C3G, the Bruder Family and the NIDDK: R01 110023

8

Change in GFR and UPC Before and After Eculizumab

(ASN – Philadelphia, PA – 2023 – Tina)

Initial Thoughts:

- Eculizumab is a monoclonal antibody that binds the complement protein C5, blocking the cleavage into C5a and C5b, therefore preventing the formation of the C5b-9 (membrane attack complex MAC)….is this enough to change C3G disease trajectory?

Cohort:

14 patients with C3G on Eculizumab for a time of 2-5 years

- Our goal was to examine the difference in eGFR and UPC trends before and after Eculizumab initiation.

Findings:

- **Most patients showed no significant change in disease trajectory with Eculizumab therapy.**
- General trend towards worsening kidney function following eculizumab, though **with a slight decrease in UPC.**
  - The GFR had a median difference from pre- to post-eculizumab of -6.47 per year.
  - UPC had a median difference from pre- to post-eculizumab of -0.26 per year.

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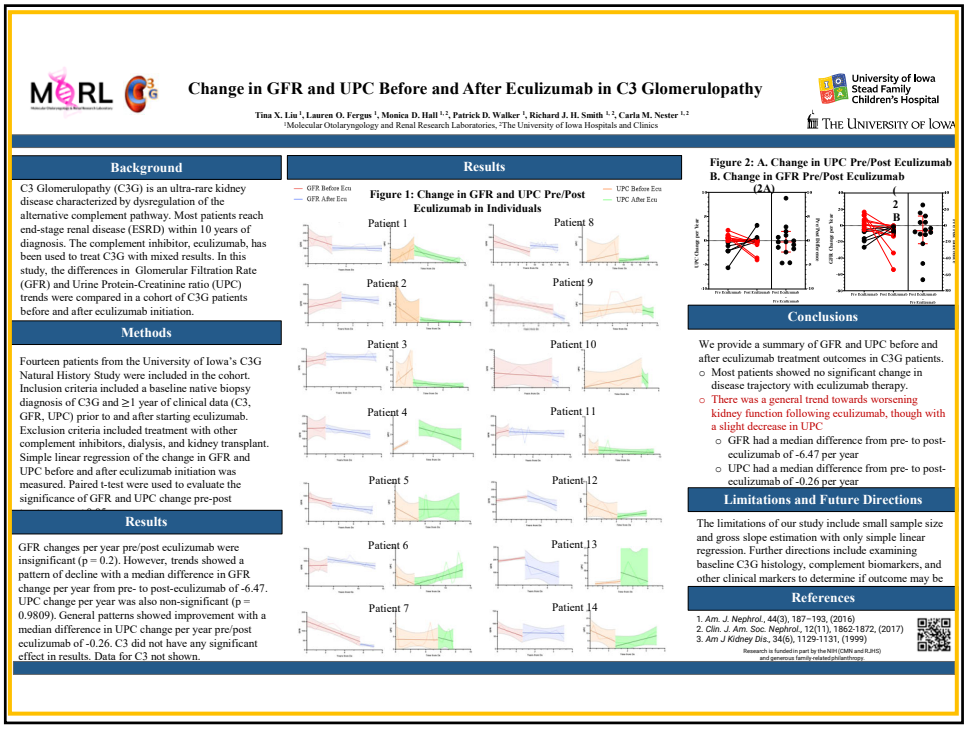
9



Change in GFR and UPC Before and After Eculizumab in C3 Glomerulopathy

Tina X. Liu [1], Lauren O. Fergus [1], Monica D. Hall [1,2], Patrick D. Walker [1], Richard J. H. Smith [1,2], Carla M. Nester [1,2]
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Background

C3 Glomerulopathy (C3G) is an ultra-rare kidney disease characterized by dysregulation of the alternative complement pathway. 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. In this study, the differences in Glomerular Filtration Rate (GFR) and Urine Protein-Creatinine ratio (UPC) trends were compared in a cohort of C3G patients before and after eculizumab initiation.

Methods

Fourteen patients from the University of Iowa's C3G Natural History Study were included in the cohort. Inclusion criteria included a baseline native biopsy diagnosis of C3G and ≥1 year of clinical data (C3, GFR, UPC) prior to and after starting eculizumab. Exclusion criteria included treatment with other complement inhibitors, dialysis, and kidney transplant. Simple linear regression of the change in GFR and UPC before and after eculizumab initiation was measured. Paired t-test were used to evaluate the significance of GFR and UPC change pre-post

Results

GFR changes per year pre/post eculizumab were insignificant (p = 0.2). However, trends showed a pattern of decline with a median difference in GFR change per year from pre- to post-eculizumab of -6.47. UPC change per year was also non-significant (p = 0.9809). General patterns showed improvement with a median difference in UPC change per year pre/post eculizumab of -0.26. C3 did not have any significant effect in results. Data for C3 not shown.

Results

Figure 1: Change in GFR and UPC Pre/Post Eculizumab in Individuals

GFR Before Ecu · GFR After Ecu · UPC Before Ecu · UPC After Ecu

Patient 1 · Patient 8 · Patient 2 · Patient 9 · Patient 3 · Patient 10 · Patient 4 · Patient 11 · Patient 5 · Patient 12 · Patient 6 · Patient 13 · Patient 7 · Patient 14

Figure 2: A. Change in UPC Pre/Post Eculizumab
B. Change in GFR Pre/Post Eculizumab

(2A) (2B)

Conclusions

We provide a summary of GFR and UPC before and after eculizumab treatment outcomes in C3G patients.

- Most patients showed no significant change in disease trajectory with eculizumab therapy.
- There was a general trend towards worsening kidney function following eculizumab, though with a slight decrease in UPC
  - GFR had a median difference from pre- to post-eculizumab of -6.47 per year
  - UPC had a median difference from pre- to post-eculizumab of -0.26 per year

Limitations and Future Directions

The limitations of our study include small sample size and gross slope estimation with only simple linear regression. Further directions include examining baseline C3G histology, complement biomarkers, and other clinical markers to determine if outcome may be

References

1. *Am. J. Nephrol.*, 44(3), 187–193, (2016)
2. *Clin. J. Am. Soc. Nephrol.*, 12(11), 1862-1872, (2017)
3. *Am J Kidney Dis.*, 34(6), 1129-1131, (1999)

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10

Thank You!

- Any Questions?

If you have C3G and are not in our C3G Natural History, but interested in participating, please contact:

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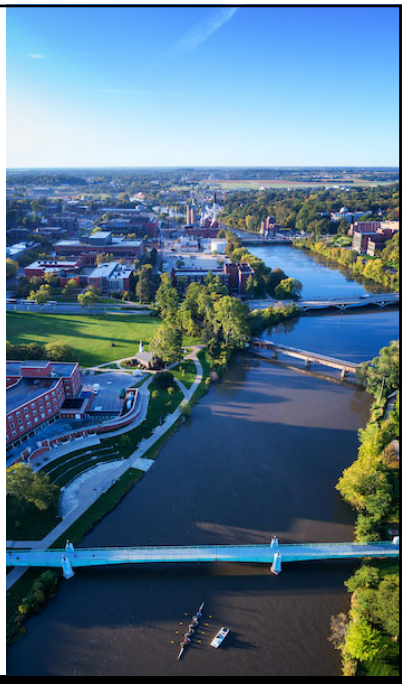

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11