Classical Complement Activation in Lupus Nephritis Correlates with Disease Biomarkers: Results from Two Observational Studies

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INTRODUCTION

Systemic Lupus Erythematosus (SLE) is driven by autoantibodies to surface antigens including DNA and even C1q itself.

- Surface attack by phagocytic cells through the major immune cell recruitment and activation by soluble factor.
- Direct membrane damage/cell lysis by the C5b-9 membrane attack complex pore.
- Pathways to activate complement are as follows: Sanguine Study: UCSF Study: before C4 cleavage has the maximum impact by inhibiting "downstream" process, take hold results in deposition of a covalent opsonin, beyond which... point of classical complement activation.

MEMBERS

- Memorial significance (CSS).
- HC: Healthy controls; LN: lupus nephritis; PACA: pathogenic anti-C1q autoantibodies.
- Pathogenesis: Cellular membranes that were stained for complement substances include, clearance products, and the inevitable actin bundles.

OBJECTIVES

- Primary composite score that captures biopsied findings of patients with lupus nephritis (LN) were used to determine the relative impact of plasma-based autoantibodies (PACAs) and in vitro protein levels (Crup+C) on LN

METHODS

- UCB Study: Analysis of 63 patients, 38 with active lupus ("LO", "LN") and 25 without active lupus ("LON", "LNO") were enrolled, along with 28 healthy controls from the California hood nephritis Study ("HNK") and another population-based registry. Diagnoses of lupus nephritis and disease activity were made by physician on study.
- Biomarkers: A novel correlation with biomarkers was observed for disease activity and complement components C1, C3, and C4.
- Internal Stress: Complement protein levels were assessed using plasma

CONCLUSIONS

- The classical complement pathway is a key driver of lupus pathology, potentiated by PACAs
- PACAs are associated with diminished renal function and disease activity
- PACAs are strongly linked to disease activity and are more efficient at activating the classical complement pathway
- PACAs potentiate complement driven local inflammation and increase likelihood of renal flares

REFERENCES

- Annexon Biosciences, Inc.; prior employment with Genentech; prior equity ownership in Sorrento Therapeutics, Inc.; 1, 2016-2020.
- Clq: Clearance of Clq antibodies from the circulation by hepatocytes, and its role in disease pathology.
- SLEDAI: Health status tools in patients with high complement activation and cell lysis.

RESULTS

- Figure 1. Classical Complement Activation Focused View

- Figure 2. SLEDAI, UPCR, dDNA Autoantibodies and PACAs Are Elevated in Active LN

- Figure 3. Classical Complement Activation and Consumption Are Driven by PACAs and Correlate with Disease in LN

- Figure 4. Classical Complement Consumption Correlates with C4d/C4 Activation Ratio

- Figure 5. Classical Complement Activity Highest in Patients with Active LN

- Figure 6. PACA1 Levels Correlate with Classical Complement Activity

- Figure 7. UPR Patients from an Independent Sanguine Cohort Are Also Enriched for High C4d/C4

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