Further Insights into iptacopan Mode of Action in IgA Nephropathy Through Protein Profiling

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Introduction

Primary IgA nephropathy (IgAN) is the most prevalent form of glomerulonephritis affecting approximately 2.5 per 100,000 persons worldwide[1]. The pathophysiology follows a 'multiple hit' hypothesis[2]:

1) Elevated production of galactose-deficient IgA1 (Gd-IgA1)
2) Subsequent increase in production of autoantibodies targeting Gd-IgA1
3) Formation of IgA1-containing immune complexes (ICs)
4) Deposition of these ICs in the kidneys, causing glomerular and renal tubular injury.

Dysregulation of the alternative complement pathway (AP) plays a crucial role on the fourth "hit". Iptacopan (LNP023) is a potent oral complement inhibitor targeting factor B, crucial in the AP dysregulation seen in IgAN. The findings from iptacopan 200mg b.i.d IgAN Phase 2 (NCT03373461) showed dose-dependent reduction in proteinuria and AP inhibition following treatment[3].

This study aims to further explore the mechanism of action of iptacopan on IgAN pathophysiology via protein profiling.

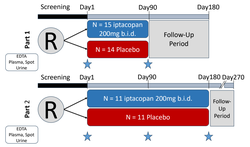
Methods

SomaScan® platform uses 7,596 (7K) SOMAmer® reagents, single-stranded DNA aptamers, to simultaneously measure 6,596 unique human proteins. The 7K includes 62 complement-related proteins (e.g., intact proteins and some activation products (C3a, C3a desArg, C3b, iC3b, C3d, C5a, C4a, C4b)).

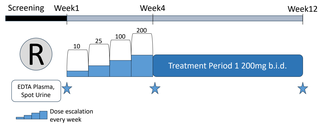
SomaScan® was performed using plasma and urine samples from iptacopan IgAN Ph2 (NCT03373461). Day 1 and Day 90 plasma samples from Parts 1 and 2 were pooled to increase statistical power. A longitudinal model, corrected for sex, age, and batch as covariates, was used to estimate changes in protein expression from baseline between the 200mg b.i.d. treatment and placebo groups. Multiple-test correction was performed using the Benjamin-Hochberg procedure (FDR), selecting proteins with FDR ≤ 0.05 and absolute fold change >0.1. For urine analysis, due to limited sample size and variability of sample matrix, box plots and Mann-Whitney U test were used. Pearson correlation assessed changes from baseline at Day 180 in plasma proteins affected by iptacopan 200 mg b.i.d against changes in the 24-hour protein creatinine ratio.

To explore whether the plasma proteome changes are specific to IgAN, SomaScan analysis was performed in C3 Glomerulopathy (C3G), a disease driven by dysregulation of the AP (iptacopan Ph2 cohort A (NCT03832114)).

IgAN (NCT03373461) Study Design

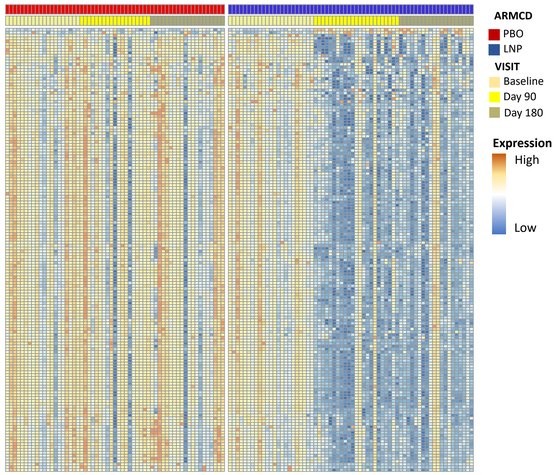


C3G Cohort A (NCT03832114) Study Design

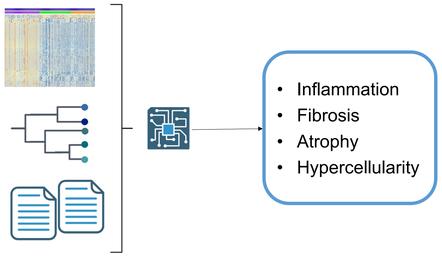


Results

Fig.1) Heatmap of plasma SOMAmer® changes in IgAN patients: 154 plasma proteins are modulated by iptacopan 200mg b.i.d. at Day 90 and Day 180.

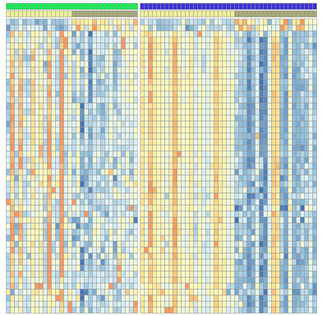


Placebo on the left (first line - red) and iptacopan 200mg b.i.d on the right side (first line - dark blue) across timepoints: baseline (second line – light yellow), Day 90 (second line - yellow), Day 180 (second line – brown). Color intensity of individual cells indicates magnitude of change, with darker colors representing greatest change.

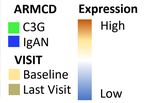


Panel A) We analyzed the 154 proteins modulated by iptacopan 200 mg twice daily in IgAN. Based on a comprehensive review of scientific literature and pathway analysis, several of these proteins are involved in inflammation, fibrosis, atrophy, and hypercellularity. Thus, we hypothesize that the iptacopan mechanism of action may involve these pathways.

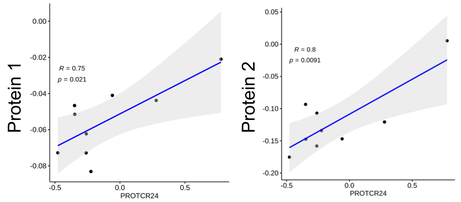
Panel B) Similarities in iptacopan-induced plasma proteome changes in two complement-mediated renal diseases: Heatmap of plasma SOMAmer® changes common in IgAN and C3G.



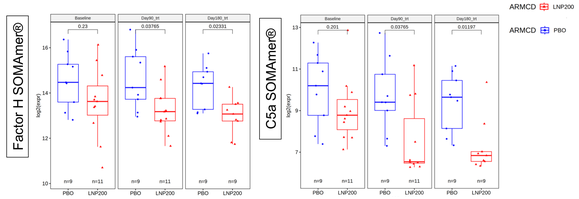
209 plasma proteins are modulated by iptacopan 200mg b.i.d. in C3G cohort A (data not shown). 49/209 plasma proteins are common in C3G (left - green) and IgAN (right - purple); baseline (first line - yellow), end of treatment (first line - brown)



Panel C) Of the 154 plasma proteins modulated by iptacopan, 8 exhibited a significant correlation between their change from baseline (y-axis) and change in the 24-hour urine protein creatinine ratio (x-axis) at Day 180. Two representative plots are showed below.



Panel D) iptacopan 200mg b.i.d. downregulates key components of AP in urine from IgAN patients: Urine SOMAmers differentially expressed in IgAN compared to healthy controls are identified and their change with iptacopan 200mg b.i.d (red) compared to placebo (blue) evaluated.



- In IgAN patients, 154 distinct plasma proteins are significantly modulated by iptacopan 200mg b.i.d compared to placebo (except for 2, proteins are downregulated with treatment) (**Fig.1**)
- Most of these proteins have not been reported in IgAN patients, suggesting novel biological processes
- The findings implicate changes in key biological pathways like inflammation, fibrosis and atrophy and hypercellularity (**Panel A**)
- Plasma proteome analysis in C3G reveals similarity with findings in IgAN (**Panel B**)
- Correlation with change in proteinuria at Day 180 is observed for 8/154 plasma proteins (**Panel C**)
- Small sample size and complexity of urine matrix limited the power of proteome analysis. Analysis of selected urine SOMAmer® suggest treatment-induced modulation of urine complement proteins such as but not limited to Factor H and C5a (**Panel D**)

Conclusions

The plasma proteome data in IgAN suggest that reduction in proteinuria and AP inhibition by iptacopan involve biological pathways such as inflammation, hypercellularity, fibrosis and atrophy.

Common changes in plasma proteome in the two complement-mediated diseases IgAN and C3G suggest some similarities in iptacopan biological effects.

Future work will focus on replicating these findings using larger datasets from both blood and disease-relevant tissues. Additionally, we will validate selected proteins through targeted assays.

References

[1]*McGrogan A., et al. Nephrol Dial Transplant. 2011;26:414-30*
[2]*Suzuki H., et al. J Am Soc Nephrol. 2011;22:1795-803*
[3]*Zhang H., et al. Kidney Int 2023 (in press)*

Disclosures
AG,ML,AK,AS,CH,MM,MAV,DK are employees of Novartis and own stocks of Novartis.
AZ,OI, OK, YS has served as an advisor/consultant for Novartis.

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