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

Introduction

Primary IgA nephropathy (IgAN) is the most prevalent form of glomerulonephritis affecting approximately 2.5 per 100,000 persons worldwide. The pathology follows multiple pathways:

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

Disregulation of the alternative complement pathway (AP) plays a crucial role on the fourth "hit". Iptacopan (LNP0203) 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 (NCT03333461) showed dose-dependent reduction in proteinuria and AP inhibition following treatment.

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) SomaMers™ 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, C3d, C3, C5b, C5a, 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 ≥ 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 assessment, 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 protein changes are specific to IgAN, SomaScan analysis was performed in C3 Glomerulonephritis (C3GN), a disease driven by dysregulation of the AP (iptacopan Ph2 cohort A (NCT03823114)).

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.

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 protein changes in two complement-mediated renal diseases: changes common in IgAN and C3GN.

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 shown below.

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

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 proteins in the two complement-mediated diseases IgAN and C3GN suggest some similarities in iptacopan biological effects.

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

References


Disclosures

All authors participated in the development of the poster for presentation.

Funding

This study was sponsored by Novartis Pharma AG, Basel, Switzerland.

Acknowledgments

Acknowledgements

ASN23
FR-P0706

Andrea Grioni, Mykola Lysteskyi, Anna Kostikova, Anastasia Zuh, Okysana Ikert, Oksandr Karmash, Yayana Shahal, Anna Schubert, Claire Harris, Matthias Meier, Marie-Anne Valentin, Dmitri Kollins
Biomedical Research, Basel, Switzerland; Biomedical Research, Cambridge, United States; Biomedical Research, London, United Kingdom; Novartis Pharma AG, Basel, Switzerland; Yvan Franco National University of Lyon

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