Title: Further insights into iptacopan mode of action in IgA nephropathy through protein profiling

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Character count (with space): 2373/2500

Abstract:

Background: IgA nephropathy (IgAN) can lead to progressive loss of kidney function, with ~30% of patients with proteinuria 1-2 g/day progressing to kidney failure within 10 years. Effective treatments are needed to improve patient outcomes. Iptacopan is a proximal complement inhibitor that specifically binds factor B and inhibits the alternative complement pathway (AP). In a Phase 2 study (NCT03373461), iptacopan treatment led to a dose-dependent reduction in proteinuria and inhibition of the AP in patients with IgAN (1, 2).

Methods: SomaScan – a large proteomics platform (~7500 proteins), and statistical analysis were used to examine iptacopan's impact on plasma proteins. Statistical threshold for biomarker definition was set to adjusted p-value < 0.05 and absolute log Fold Change > 0.1.

Results: iptacopan treatment resulted in a significant modulation of 81 distinct plasma proteins in IgAN patients after 90-days treatment, persisting at the 180-day timepoint. Except for four, proteins were downregulated. Approximately two-thirds of the proteins are likely originated from the kidney (Fig.1, proteins in blue), amongst which 4 proteins were reported to have increased expression in kidney from IgAN patients (BCL2L1, HES1, LTβR, C8). These proteins are thought to be released by cellular mechanisms like necrosis, apoptotic vesicles, proteolysis, and cell activation (Fig.1). From scientific literature, the findings are implicating changes in key biological pathways like inflammation, hypercellularity, fibrosis and atrophy. Taking inflammation as an example, the downregulation of OSM, IL-1F6 and IL-34 with iptacopan may indicate a reduction in macrophages activation and cytokines release, and inflammation. This underscores the potential of iptacopan to modulate protein expression across these pivotal biological processes in the context of IgAN patients.

Conclusion:

This data suggests that iptacopan may contribute to reduction of renal inflammation, hypercellularity, fibrosis and atrophy in patients with IgAN. The relevance of these encouraging early findings will necessitate confirmation in a larger data set and at tissue level.

Figure 1: Mapping plasma proteins likely originated from kidney to biological functions.