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Complement Inhibition in IgA Nephropathy

Hajeong Lee
Seoul National University Hospital, Republic of Korea

IgA Nephropathy (IgAN) is the most common primary glomerulonephritis worldwide, characterized by mesangial IgA1 deposits and progressive renal function decline in a significant proportion of patients. Despite advances in supportive care and immunosuppressive therapies, up to 30% of patients progress to end-stage kidney disease within 20-25 years of diagnosis. The pathogenesis of IgAN is complex, involving a multi-hit process including galactose-deficient IgA1 production, autoantibody formation, immune complex deposition, and subsequent complement activation leading to glomerular injury. Emerging evidence strongly implicates complement pathway activation as a critical mediator of glomerular inflammation and fibrosis in IgAN. Histopathological studies consistently demonstrate C3 co-deposition with IgA1 in glomeruli, and genetic studies have identified complement-related risk variants. Both the alternative and lectin pathways appear particularly relevant in IgAN pathogenesis. The alternative pathway amplification loop enhances C3 activation following IgA deposition, while the lectin pathway is activated by mannose-binding lectin recognition of galactose-deficient IgA1. Given the central role of complement activation in IgAN, targeted inhibition of complement components represents a promising therapeutic strategy. The mechanistic rationale for targeting complement in IgAN stems from the goal of interrupting upstream drivers of glomerular injury, thereby reducing proteinuria and preserving renal function. Several complement-targeting approaches are under investigation. We will highlight emerging complement-targeted therapies. Notably, the oral factor B inhibitor iptacopan has demonstrated significant proteinuria reduction in IgAN. In a phase 3 trial, iptacopan achieved a ~38% greater reduction in proteinuria versus placebo at 9 months on top of standard care, leading to its accelerated approval as the first complement inhibitor for IgAN. An antisense oligonucleotide targeting factor B (IONIS-FB-LRx) similarly reduced proteinuria by ~44% in a phase 2 study, and a phase 3 trial is ongoing. In contrast, the lectin pathway inhibitor narsoplimab (anti-MASP-2) did not meet its primary endpoint in a phase 3 trial, despite promising

early-phase results. We will also discuss other investigational approaches, including proximal complement blockade at C3 (pegcetacoplan) and terminal pathway inhibition (e.g., C5 monoclonal antibodies and C5a receptor antagonists). While terminal complement inhibitors like eculizumab have shown anecdotal benefits in severe IgAN, robust trial data in primary IgAN are awaited. Complement inhibition has emerged as a promising therapeutic strategy for IgAN, particularly for patients with persistent proteinuria despite optimized supportive care. While targeting the alternative pathway has shown the most consistent benefit to date, additional studies are needed to define the long-term impact on renal survival, identify biomarkers predictive of complement pathway activation, and determine optimal timing and combination strategies for intervention. Ongoing clinical trials and mechanistic studies are expected to further refine the role of complement-targeted therapy in the management of IgAN.

Keywords: IgA nephropathy, Pathogenesis, Alternative complement pathway, Complement inhibition, Treatment