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A targeted treatment for IgA nephropathy at last?

Iptacopan, an oral, alternative complement pathway inhibitor of Factor B, could provide the first therapy targeted at one of the key drivers of IgAN

ABSTRACT: Due to the immunological pathogenesis of IgA nephropathy (IgAN), patients used to be given immunosuppressive therapy; however, this was shown to have no long-term benefit over optimal supportive therapy. Promising data from the interim analysis of a Phase II study with iptacopan [1] now show that the targeted inhibition of a specific factor of the immune system (complement factor B) allows a specific approach to therapy for IgAN without burdening patients with the severe side effects of immunosuppression.

IgA nephropathy (IgAN) is a chronic kidney disease occurring in young adults and is one of the most common reasons for kidney transplantation in this age group. IgAN is the most common form of glomerulonephritis (GN), i.e., immunologically induced inflammation of the renal glomeruli. It is characterized by glomerular deposition of immune complexes containing immunoglobulin A (IgA), and by a complex inflammatory response and progressive loss of kidney function. For many decades, IgAN has therefore been treated with anti-inflammatory or strong immunosuppressive agents. However, the STOP-IgAN study and its ten-year follow-up [2, 3] showed that the addition of immunosuppressive therapy to optimal supportive therapy (strict blood pressure control, proteinuria treatment with RAS blockers, dietary and lifestyle measures), has no additional benefit: During the follow-up period, approximately half of all patients reached the primary combined endpoint (progressive loss of renal function > 40%, dialysis requirement or mortality). However, immunosuppression increased the incidence of adverse effects, especially infections. The use of immunosuppressants in IgAN has since been increasingly questioned by experts and should only be applied to rapid-progressive courses. Long-term outcomes are generally unfavorable, so targeted therapy is still urgently needed in addition to optimization of supportive therapy.

It is now known that overactivity of the alternative complement signaling pathway of the immune system plays a role in the pathogenesis of IgAN, thereby increasing the chronic inflammation. Targeted inhibition of this signaling pathway is thus a logical therapeutic approach.

Iptacopan is an oral, highly selective inhibitor of complement factor B and the alternative complement signaling pathway, and has now been investigated in a randomized, double-blind placebo-controlled Phase II clinical trial. In Part 1, 46 IgAN patients received three different doses of iptacopan or placebo for 90 days. A further 66 patients were then treated in Part 2 with four doses of iptacopan or placebo for 180 days. The primary endpoint was the dose-response relationship in the improvement of proteinuria (as a 24-hr urine protein/creatinine ratio). All 112 patients have now been evaluated together (day 90). Secondary endpoints were safety and tolerability, as well as eGFR and biomarkers of the alternative complement signaling pathway. Five groups were compared: iptacopan 10mg (n=20); 50mg (n=19); 100mg (n=22); 200mg (n=26) and placebo (n=25). Four patients (3.6%) had discontinued treatment due to side effects (two in the placebo group and one in the Verum group) or to protocol errors (in one case).

The analysis showed a statistically significant dose-response effect of iptacopan versus placebo (p=0.038), with a 23% decrease in proteinuria under 200 mg iptacopan versus placebo at 90 days. Renal function (eGFR) showed a trend to stabilization, and biomarkers also improved (functional serum complement activity, concentration of complement factor Bb, and urinary excretion of soluble C5b-9 were measured). Side effects were mild (92%) to moderate (8%); there were no serious adverse effects. The most common side effects were headache (11.6%), back pain (6.3%), diarrhea (6.3%), vomiting (6.3%), but not related to the dose taken.

'This is the first study to report the safety and efficacy of targeted alternative complement pathway inhibition in IgAN patients, with the results showing a significant dose-dependent reduction in proteinuria and a trend to eGFR stabilization,' comments Dr Barratt. 'Iptacopan was also well tolerated and resulted in inhibition of various biomarkers of alternative pathway activity, supporting its further evaluation in the ongoing Phase III (APPLAUSE-IgAN) trial.'

[1] 2457 Jonathan Barratt, Leicester, UK. Interim Analysis of a Phase 2 Dose ranging Study to investigate the Efficacy and Safety of Iptacopan in Primary IgA Nephropathy.
[2] Rauen T, Wied S, Fitzner C et al. After ten years of follow-up, no difference between supportive care plus immunosuppression and supportive care alone in IgA nephropathy. Kidney Int 2020 Oct; 98 (4): 1044-1052
[3] Rauen T, Eitner F, Fitzner C et al. Intensive Supportive Care plus Immunosuppression in IgA Nephropathy. N Engl J Med 2015; 373: 2225-36

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