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The ACCOLADE study on C3 glomerulopathy

The selective C5a receptor inhibitor avacopan could be used in future to treat immune-mediated inflammatory disorders in C3G renal disease.

ABSTRACT: C3 glomerulopathy is a rare disease in which the deposition of C3 protein causes severe inflammation of the glomeruli, which can progress to end stage kidney disease requiring dialysis or transplantation. A new study demonstrates that the inflammatory C5a receptor can be selectively blocked with avacopan [1]. This targeted intervention in the immune system is much less risky than general immunosuppression.

C3 glomerulopathy (C3G) is a very rare immunological (or more precisely: complement-mediated) inflammation of the glomeruli. Due to progressive renal dysfunction, many such patients have to go on dialysis or receive a kidney transplant after about ten years. C3G has to date been treated by lowering blood pressure and proteinuria and by non-specific immunosuppression. In order to compare different therapeutic approaches in the future, a 'European Register for C3 glomerulopathy and immune-complex-mediated MPGN', in which cases are systematically registered, was initiated in 2015.

Pathogenetic dysregulation in the 'alternative complement signaling pathway' of the immune system leads to glomerular deposits of complement factor C3 (a protein). Permanent overactivation of the signaling cascade also causes elevated levels of the C5 and C5a factors. C5a is a potent inflammatory mediator that acts via the associated C5a receptor. In preclinical studies, C3G progression was markedly slowed with the selective C5a receptor inhibitor avacopan.

The ACCOLADE study conducted a randomized, double-blind placebo-controlled investigation into the use of avacopan in C3G patients. For 26 weeks, they received either 30 mg of orally administered avacopan twice daily (n=28), or placebo (n=29). The C3G Histologic Index (C3HI 'Disease Activity Score') was used to measure changes in histology over time by means of repeat kidney biopsies (higher values indicating severe disease). Secondary endpoints were the histologic disease chronicity score (degree of fibrosis), the glomerular filtration rate (eGFR), and proteinuria (UPCR – urinary protein to creatinine ratio).

The patients had been diagnosed with C3G 46-48 months on average before enrollment; in the avacopan group, the mean eGFR was 76.27 ml/min/1.73 m^2; proteinuria (> 1 g/g) was present in 76.9% of patients. In the placebo group, eGFR was 73.42 ml/min/1.73 m^2, while 69.2% had proteinuria (> 1 g/g).

At 26 weeks, the C3HI activity score improved by 0.2% in the avacopan group, but worsened by 20.6% in the placebo group. The C3HI chronicity score increased by 31.7% in the avacopan group and by 57.5% in the placebo, which equates to an absolute change of 0.8 versus 1.6, respectively. The eGFR changes were also statistically significant; in the avacopan group, eGFR increased by 4.8% on average and decreased in the placebo group by 5.9% (p=0.02). Patients with a previous eGFR less than 60 ml/min/1.73 m^2 benefited particularly from the therapy, as their eGFR increased by 13% (compared to a 6.1% decrease for placebo). Proteinuria also improved in the avacopan group. The tolerability and safety profile of avacopan did not differ on the whole from placebo.

'In patients with C3 glomerulopathy, targeted therapy aimed at the complement system provides the best possible route to slow disease progression,' explains Dr Bomback. 'In addition, the more selectively we target the causal disease mechanisms in the immune system, as was done in this study at the C5a receptor with avacopan, the less the immune system as a whole is suppressed, which should also yield not only more effective but also less toxic therapies.'

'Targeted immunomodulation is already used to treat various diseases and will play an increasingly important role in the future if we want to treat C3G effectively yet safely.'

[1] 2478 Andrew Bomback, New York. Orally administered C5aR Inhibitor Avacopan in a randomized, double blind, Placebo-controlled Study (ACCOLADE) for Treatment of C3 Glomerulopathy

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