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Application of C5 inhibitors on glomerular diseases

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The complement cascade is a complex system leading to the generation of inflammatory molecules like C3a and C5a, and to the formation of the membrane attack complex, C5b-9, which has potent lytic properties on cells and bacteria, especially the encapsulated ones, like nesseria meningitides.
Since complement is involved in the pathophysiology of many inflammatory diseases, a large number of drugs (> than 30) is being developed: monoclonal antibodies, small peptides or proteins, synthetic molecules, siRNA, each of which targeting a specific step of the activation cascade.

In renal diseases, complement inhibition has been used successfully in atypical hemolytic uremic syndrome (aHUS), and to a lesser extent in C3 glomerulopathy, lupus nephritis and membranous nephropathy. Several trials are underway at the present time.

In aHUS, the rationale to use C5 inhibition is straightforward since it is well known that in this disease the overactivation of the alternate pathway leads to an uncontrolled and deleterious C5b-9 formation, which induces severe endothelial lesions, platelet aggregation and thrombi formation in the microcirculation. The kidney is the main, but not the only, injuried organ during this process. The major breakthrough came about 10 years ago when eculizumab, a monoclonal humanized anti-C5 antibody became available. The rapid correction of hematological parameters (hemolysis and thrombocytopenia) and the slow improvement of the renal function were observed in more than 70% of the patients. Ten years after, it is clear that this treatment has dramatically changed the life of these patients who less frequently progress to terminal renal failure. The risk of meningococcal infection is well known, and is signicantly decreased by vaccination against the various serotypes (A,C, W, Y and B) of nesseria meningitides and in some countries by oral penicillin prophylaxis. More recently, a new anti-C5 mAb, ravulizumab, was engineered from eculizumab, so that this antibody can be recycled at the cell surface through the FcRn receptor. It has a prolonged half life and duration of action, and it can be administrated only every 8 weeks, as compared to every 2 weeks for eculizumab. Excellent efficacy and tolerance were observed in a cohort of aHUS adult patients, naïve from any anti-C5 treatment before.

Similarly, it was very effective in a cohort of young aHUS patients, some naïve from prior treatment, and other having been switched from eculizumab to ravulizumab. Other anti-C5 drugs, anti-CFD or CFB drugs are being evaluated in aHUS.

In C3 glomerulopathy, the role of complement is very likely since the disease develops in patients with an overactivation of the alternate pathway of complement, related to a complete CFH deficiency, or to C3nef activity. Therefore eculizumab was administred in patients with C3G. Several case reports were encouraging, but more recently, case series indicated that many patients with C3G do not respond to eculizumab. Several trials are in progress to determine if C5 blockade may be of interest in some patients and which predictive factors of a good response can be identified.
In ANCA associated vasculitis (AAV), the pathogenic role for anti-MPO antibodies could be demonstrated in vivo in an experimental model in mice. Thereafter, a new, orally active synthetic molecule, avacopan, was demonstrated to be a potent and selective C5aR1 antagonist. It has been used in patients with AAV in a randomized trial with conventional immunosuppression with cyclophosphamide or rituximab, and it was shown that avacopan was equivalent to prednisone at 21 weeks, but it provided a better result at 1 year in terms of clinical remissions and relapses. This result opens a new era in the treatment of AAV, where side effects of steroids which compromise the prognosis of many patients will be eliminated.

In IgA nephropathy also, there are some indirect evidence that the complement system may play a pathogenic role. *CFHR1-CFHR3* deletions seem to be protective in this disease, while some *CFHR5* variants are associated with poor prognosis. Mesangial deposition of hypo galactosylated IgA is usually associated with C3, C4d, MBL or MASP deposits. Several trials are under progress but there is no evidence that blockade of C5 or of C5aR1 will provide any benefit. Similarly, other trials will evaluate the C5 blockers in lupus nephritis, membranous nephropathy or IC-MPGN.
In conclusion, the best evidence was obtained in aHUS with the C5 inhibitors, eculizumab and more recently ravulizumab. In AAV, avacopan, a C5aR1 antagonist, seems effective and would allow to not use steroids in many patients. Several other C5 blockers are under investigation and, hopefully, some of them will be available in a near future for a better treatment of glomerular diseases.