Monoclonal Antibodies for the Treatment of the C3 Glomerulopathies

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Our understanding of glomerular disease has been steadily progressing from pattern-based histologic classification and empirical immunosuppressive treatments to better molecular characterization of disease and, albeit more slowly, to more targeted therapies. The group of diseases collectively known as membranoproliferative GN (MPGN) has recently been the beneficiary of such a step forward (for review, see refs. 1–3). This histopathological pattern of MPGN can variably result from infection, autoimmune and rheumatologic disease, or monoclonal gammopathy; in such cases, both immunoglobulins and complement factor 3 (C3) are observed on immunofluorescence (IF) of the biopsy specimen. Another major subgroup of MPGN, largely consisting of the two disorders dense deposit disease (DDD; previously known as MPGN type II) and C3 GN (C3GN), arise from dysregulation of the alternative complement pathway. In contrast to the former subgroup of immune complex– or monoclonal immunoglobulin-associated MPGN, these C3 glomerulopathies are distinguished by the presence of C3, but not immunoglobulin, by IF.

DDD and C3GN are rare entities but are important to recognize, because they can occur early in life, lead to ESRD, and recur in the renal allograft. DDD is characterized ultrastructurally by pathognomonic dense deposits, consisting of complement factors and regulators (4), within the lamina densa of the glomerular basement membrane. Although the major histopathologic pattern in the glomerulus is one of MPGN, other proliferative patterns can be seen (5). Approximately 50% of DDD patients will progress to ESRD within 10 years of diagnosis, and disease is likely to recur in the kidney allograft (6). C3GN has only recently been identified as a distinct entity that often exhibits an MPGN pattern of injury (7), featuring subendothelial and/or subepithelial deposits of similar molecular composition to those found in DDD (8).

Treatment of DDD and C3GN has been somewhat empirical and includes renin-angiotensin system inhibition to reduce proteinuria, plasmapheresis to remove pathogenic autoantibodies, and/or immunosuppressants such as prednisone, cyclosporine, or alkylating agents (5,6). As evidenced by the relatively poor prognosis, especially in DDD, the efficacy of these treatments has been limited, and disease-specific agents are sorely needed.

The majority of patients with DDD have circulating autoantibodies known as C3 nephritic factor (C3NeF) that stabilize the alternative pathway C3 convertase by conferring resistance to factor H–mediated decay, thereby leading to persistent complement activation. C3NeF may be less frequently present in C3GN (7,8). It may be possible to forestall disease progression with frequent plasmapheresis treatments, but this is an impractical long-term therapeutic solution. The humanized monoclonal anti-CD20 antibody rituximab has been used as adjunctive therapy in an attempt to deplete the B cells responsible for producing C3NeF, but the results have thus far been limited (9,10).

Genetic mutations and/or polymorphisms in complement regulatory factors have recently been implicated in the pathogenesis of DDD and C3GN, as well as atypical hemolytic-uremic syndrome (aHUS). A detailed review of the complement system and its various fluid-phase and tissue-bound regulators in these diseases is beyond the scope of this editorial, and the reader is instead directed to several excellent reviews of this topic (3,11–13). These inherited mutations, in addition to acquired antibodies that can disrupt function of the inhibitory complement factors, can alter the delicate balance of complement regulation. Mutations or disease-associated alleles in complement factors (C3) and regulatory factors (*e.g.*, factor H [CFH], membrane cofactor protein [MCP], and CFH-related proteins), as well as inhibitory autoantibodies to factors H, I, and B, have been described in patients with DDD and C3GN (2). Therefore, therapy targeted to pathways of complement activation and regulation may offer a directed and more efficacious treatment modality for these diseases.

Eculizumab is a humanized monoclonal antibody that binds to complement factor 5 (C5). C5 normally undergoes proteolytic cleavage by C5 convertases generated by the classic, alternative, or lectin pathways to generate C5b, which promotes the association of the remaining terminal complement components into a pore-like structure known as the membrane attack complex (MAC). The other cleavage product formed by C5 convertase is C5a, a powerful chemoattractant for inflammatory cells. MAC inserts locally into cell membranes causing cell lysis. Nucleated host cells have innate resistance to MAC because of surface-bound complement regulatory factors and the ability to shed portions of the damaged cell membrane. However,

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with unrestrained complement activation as occurs in DDD or C3GN, even host cells can be damaged or destroyed. The binding of eculizumab to C5 prevents its cleavage and thereby inhibits assembly of the terminal complement components to form the MAC, protecting local tissues from complement-mediated cytotoxicity.

Eculizumab was initially shown to be effective in humans in therapeutic trials in paroxysmal nocturnal hemoglobinuria, caused by a deficiency in cell membrane–anchored complement regulatory factors (14). The major adverse effect of treatment was increased susceptibility to meningococcal infection, and thus vaccination against meningococcus is now standard of care prior to treatment with eculizumab. More recently, eculizumab has been granted approval by the US Food and Drug Administration for the treatment of aHUS because of its efficacy in this distinct complement regulatory disorder (15,16).

It is within this context that Bomback *et al.* (17), in this issue of *CJASN*, have conducted a pilot, proof of concept study to assess the utility and safety of eculizumab for the treatment of six patients with either DDD or C3GN over a 1-year course. The scope of the study is admittedly limited, largely because of the rarity of these disorders, and the therapeutic effect at first glance is small and not universal. However, the findings need to be interpreted in light of a lack of other effective therapies and the often inexorable progression of these disorders to ESRD. By these measures, the study was a clear success. Moreover, their results have recently been corroborated by several other case reports (9,10,18,19).

The subjects in the current study included three cases each of DDD and C3GN, occurring in the native or transplant kidney, who were eligible for inclusion because of AKI ($n=2$) or significant proteinuria, with or without AKI ($n=4$). A screen for underlying disorders of the complement regulatory system identified pathologic variants of CFH and MCP in one patient each, C3NeF in three patients, but no mutations in CFI, CFB, CFHR5, and no autoantibodies against factors H or B. Of note, three had elevated levels of soluble MAC (sMAC) prior to treatment, indicating activation of terminal complement cascade. Treatment consisted of four weekly intravenous infusions of 900 mg eculizumab, followed by 1200 mg every 2 weeks for the remainder of the year-long treatment course. Proteinuria, serum albumin and creatinine, and complement levels were monitored throughout, and a repeat renal biopsy was performed in all but one patient at the conclusion of the study.

The results were remarkable for a rapid and sustained improvement in renal function in the two patients recruited for AKI. Another patient exhibited decreased proteinuria and improved histopathology as assessed by repeat renal biopsy, which was also seen in three other patients. In all, four of the six patients showed some degree of clinical or histologic improvement after 1 year of treatment with eculizumab. There were no adverse effects reported.

It is notable that several patients had a worsening of their disease after cessation of eculizumab and subsequent improvement after re-initiation of treatment, arguing strongly for a true biological effect. A similar finding was described in a recent case report of a patient with DDD who achieved a decline in proteinuria and improved histopathological parameters in response to eculizumab (19). When the treatment was interrupted, significant proteinuria returned, but was again ameliorated with the resumption of eculizumab. As stated by Bomback *et al.*, the optimal duration of treatment remains to be defined.

Another clinical manifestation of DDD is the presence of macular drusen caused by retinal damage from deposits that form in Bruch's membrane, between the choriocapillaris and retinal pigment epithelium. The risk of long-term visual sequelae in DDD is approximately 10% (11). Three of the patients in the current study exhibited drusen on fundoscopic examination at the start of the study (including one patient with C3GN), but did not show a clear improvement after treatment with eculizumab.

The authors provide a speculative but coherent explanation as to why the response to eculizumab might have been limited to those with elevated baseline serum levels of sMAC, as these patients already had evidence of activation of the terminal complement cascade that would be amenable to interruption by eculizumab. Another case report also supports this hypothesis (9). If such findings relating the presence of elevated sMAC to efficacy of eculizumab are confirmed, a reasonable proportion of patients might be eligible for treatment. Cross-sectional analysis of complement regulatory parameters in patients with DDD and C3GN indicate that sMAC is elevated in a significant proportion (8,20). It is possible that even more patients would be eligible if sMAC was measured at several time points prior to therapy, because intrinsic complement regulation might only intermittently be overwhelmed due to complement-activating microbial infections, for example.

In summary, this study by Bomback *et al.* provides important preliminary evidence of the potential impact of eculizumab for treatment of the C3 glomerulopathies DDD and C3GN. In light of the poor performance of more traditional, nonselective immunosuppressive therapies, the ability of eculizumab to reverse clinical and pathologic findings in these disorders is astounding. This small but important study paves the way for additional research on eculizumab and other future agents that can target the alternative complement pathway in the C3 glomerulopathies.

Disclosures

None.

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