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GLOMERULAR DISEASE

Eculizumab for the treatment of MPGN

Three letters published side-by-side in the *New England Journal of Medicine* describe the use of eculizumab to successfully treat membranoproliferative glomerulonephritis (MPGN). The authors of these studies say that their findings support a role for complement dysregulation in the pathogenesis of MPGN and that targeting complement might be effective for some patients.

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MPGN most commonly affects children and frequently progresses to end-stage renal disease. In the first letter, Erica Daina and colleagues describe the case of a teenage patient with nephrotic-range proteinuria and a low level of C3 who was diagnosed with dense-deposit disease (also known as MPGN type II). Administration of rituximab reduced levels of C3 nephritic factor to near-normal, but did not resolve the patient's proteinuria. The researchers performed screening of complement regulatory genes and found that the patient expressed a variant of factor H that is associated with dense-deposit disease. They also found low levels of plasma C5 and a high level of the terminal complement complex sC5b–9. Daina and colleagues hypothesized that administration of the anti-C5 antibody eculizumab to inhibit C5b–9 formation might protect the patient's kidneys from complement-mediated damage. Over 48 weeks of follow-up after eculizumab administration, the patient's serum levels of total protein and albumin normalized, creatinine level decreased, and proteinuria declined, concomitantly with normalization of plasma C5b–9 levels. "We speculate that following sequential blood sC5b–9 levels might help in predicting the response to eculizumab in dense-deposit disease", they conclude.

Marina Vivarelli *et al.* describe the case of another patient with dense-deposit disease associated with polymorphisms in the gene that encodes complement factor B. The patient had relapsing proteinuria, microhematuria and low levels of C3. The researchers administered eculizumab in addition to prior therapy with ramipril and losartan, which led to a decline in the patient's proteinuria and hematuria and an increase in plasma protein levels. Repeat biopsies performed 6 months and 18 months after eculizumab initiation revealed a reduction in mesangial proliferation and glomerular capillary loop thickness. Electron microscopy at 18 months indicated a reduction in dense deposits. Proteinuria increased following an interruption of treatment after 18 months but decreased again once eculizumab therapy was resumed. Vivarelli *et al.* believe that their findings support a role for C5 activation in the pathophysiology of some cases of dense-deposit disease and suggest that anti-C5 antibodies represent a valuable therapeutic option for these patients.

Seetha Radhakrishnan and co-workers describe the treatment of a patient with MPGN type I, the most common form of MPGN. The patient presented with nephrotic-range proteinuria, peripheral edema and anemia. The patient's clinical status deteriorated despite treatment with glucocorticoid pulses, mycophenolate mofetil, and immune globulin infusions. The researchers found that the patient had undetectable levels of C3 and very high levels of C5b–9, indicating strong alternative pathway activation. They were unable to detect plasma complement factor H-related protein 1. The patient's clinical status continued to deteriorate, even after several plasma infusions and plasma exchanges had been performed. Administration of eculizumab, however, normalized kidney function, recovered thrombocytopenia and anemia and eventually resolved proteinuria and hypoalbuminemia. "Recovery of this severely ill patient ... suggests that complement control ... may be an effective strategy in patients with refractory MPGN", say the researchers.

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Original articles Daina, E. *et al*. Eculizumab in a patient with dense-deposit disease. *N. Engl. J. Med*. **366**, 1161–1163 (2012) | Vivarelli, M. *et al*. Eculizumab for the treatment of dense-deposit disease. *N. Engl. J. Med*. **366**, 1163–1165 (2012) | Radhakrishnan, S. *et al*. Eculizumab and refractory membranoproliferative glomerulonephritis. *N. Engl. J. Med*. **366**, 1165–1166 (2012)