



EXCEPTIONAL CASE

Use of eculizumab in crescentic IgA nephropathy: proof of principle and conundrum?

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Abstract

IgA nephropathy (IgAN) is characterized by a variable clinical course and multifaceted pathophysiology. There is substantial evidence to suggest that complement activation plays a pivotal role in the pathogenesis of the disease. Therefore, complement inhibition using the humanized anti-C5 monoclonal antibody eculizumab could be a rational treatment. We report here a 16-year-old male with the vasculitic form of IgAN who failed to respond to aggressive conventional therapy including high-dose steroids, cyclophosphamide and plasma exchange and who was treated with four weekly doses of 900 mg eculizumab followed by a single dose of 1200 mg. He responded rapidly to this treatment and has had a stable creatinine around 150 µmol/L (1.67 mg/dL) for >6 months. However, proteinuria was unabated on maximal conventional anti-proteinuric treatment, and a repeat renal biopsy 11 months after presentation revealed severe chronic changes. We believe this case provides proof of principle that complement inhibition may be beneficial in IgAN but also that development of chronicity may be independent of complement.

Key words: complement, eculizumab, fibrosis, IgA nephritis

Introduction

The pathogenesis of IgA nephropathy (IgAN) involves multiple 'hits' [1, 2]. It is thought that increased levels of circulating galactose-deficient IgA1 in association with the production of unique anti-glycan antibodies leads to the formation of pathogenic IgA1 containing circulating immune complexes that are deposited within the mesangium leading to activation of mesangial cells and thus glomerular damage. That complement components including C3, C4d, C5b-9, properdin, factor H, C4BP and MBL are deposited within the glomerulus in IgAN has been known for some time [3–5]. In addition it has been shown that

there are genetic susceptibility factors for IgAN that involve complement. A common deletion in the regulators of complement activation cluster at 1q32, which incorporates the genes (*CFHR3* and *CFHR1*) encoding factor H-related protein 3 and 1, has been shown to protect against IgAN [6], possibly by reducing the ability of complement factor H-related proteins to inhibit the regulatory function of CFH [7]. It thus seems possible that complement inhibition might be beneficial in the treatment of IgAN and in particular the crescentic form with rapidly progressive glomerulonephritis (RPGN), which has a poor prognosis [8]. We report here the use of eculizumab in a young man with Henoch–Schönlein purpura and crescentic IgAN.

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Case history

A 16-year-old man was admitted in September 2013 with a 2-week history of mild abdominal pain, arthralgia and purpura on the lower extremities. He had previously been treated with penicillin for an unconfirmed diagnosis of erysipelas. Blood pressure was 116/69 mmHg, serum creatinine was 59 $\mu\text{mol/L}$ (1.08 g/dL) and creatinine clearance 159 mL/min. Urinalysis showed haematuria and proteinuria. Serum albumin was 30 g/L but there was no evidence of oedema. Since 2010 he had been treated with atomoxetine for attention deficit-hyperactive disorder. Otherwise there was no significant past medical history. He reported occasional use of marihuana, amphetamines and cocaine. He smoked 15–30 cigarettes daily. Serological tests to exclude ANCA-associated vasculitis and SLE were negative. C3 and C4 levels were normal. A diagnosis of Henoch-Schönlein purpura was made and he was started on an angiotensin-converting enzyme inhibitor. Two months later he was readmitted with increasing creatinine of 98 $\mu\text{mol/L}$ (1.11 g/dL) and declining serum albumin of 19 g/L.

A biopsy (Figure 1A) revealed epithelial crescents in 6 of 14 glomeruli, mesangial hyperplasia, endocapillary hypercellularity and deposition of both IgA (++++/4+) and C3 (+++/4+) on immunofluorescence (M1 S0 E1 T0 according to Oxford classification).

Because of the rapid loss of renal function and the acute changes on biopsy with no evidence of chronic damage it was elected to treat him with prednisolone 40 mg daily and cyclophosphamide 100 mg (1.5 mg/kg) [9]. He was also anticoagulated with warfarin and low molecular weight heparin. Despite this, renal function deteriorated further. He was, therefore, given three daily pulses of methylprednisolone 500 mg followed by

five plasma exchanges (40 mL/kg). This did not result in any improvement. As a last resort—and without any direct proof of complement involvement—we decided to treat with eculizumab. Four weekly doses of 900 mg were administered intravenously followed by a single dose of 1200 mg accompanied throughout by penicillin. Immediately after the first dose of eculizumab a remarkable improvement in renal function was evident. After 3 months cyclophosphamide was replaced with azathioprine and the dose of prednisolone was tapered. The course is shown in Figure 2.

A further renal biopsy (Figure 1B) taken 11 months after presentation revealed chronicity with 2 of 19 glomeruli completely and 7 partially sclerosed, tubular and interstitial changes with 50% atrophy and fibrosis. There was evidence of residual activity with a single glomerulus showing a cellular crescent. According to Oxford classification the changes were considered as M1 S1 E1 T1. Accordingly, renal function slowly declined to end-stage in spring 2015 with unabated nephrotic range proteinuria but consistently well-controlled blood pressure.

Further complement analysis has been undertaken. C3 was 1.77 g/L, C4 0.30 g/L, factor H 0.79 g/L and factor I 81 mg/L. CD46 expression on peripheral blood mononuclear cells was normal and factor H autoantibody screening was negative. Mutation screening of CFH, CFI, CD46, C3 and CFB showed no abnormalities. Multiplex ligation-dependent analysis (MLPA) showed no evidence of genomic disorders affecting CFH or CFHR1-5.

Discussion

KDIGO guidelines recommend that steroids and cyclophosphamide be used to treat crescentic (>50% crescents) IgAN [10–12] with RPGN. We report here a case of crescentic IgAN unresponsive to this regimen. Furthermore, the introduction of plasma exchange did not appear to be beneficial. Therefore, because of the possible involvement of complement in the pathogenesis of IgAN we elected to treat the patient with eculizumab as a last resort. With this there was a significant immediate improvement in renal function. Proteinuria, however, persisted and a repeat renal biopsy has shown evidence of chronicity. As with all anecdotal

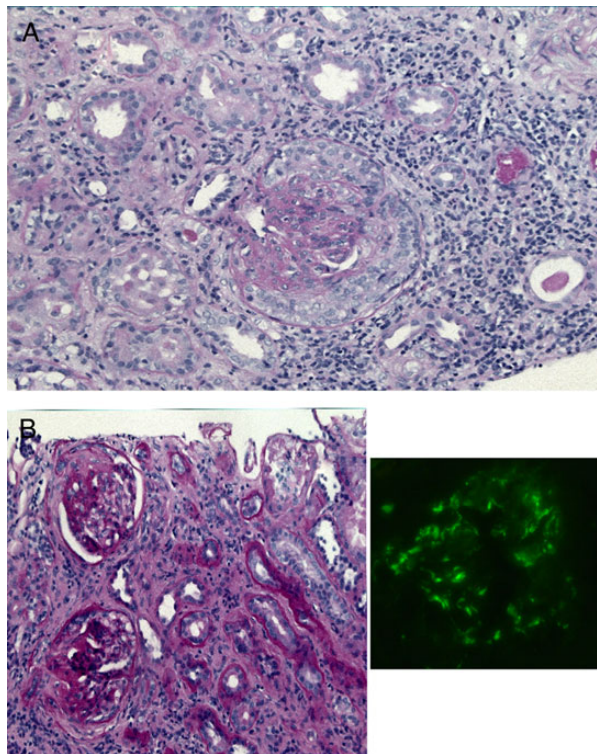


Fig. 1. (A) Glomerulus with a cellular crescent in a first renal biopsy; $\times 20$, PAS. (B) Segmental glomerulosclerosis and atrophy of tubuli and fibrosis of interstitium in a second renal biopsy 11 months later, $\times 20$, PAS (left) and IgA immunofluorescence (right).

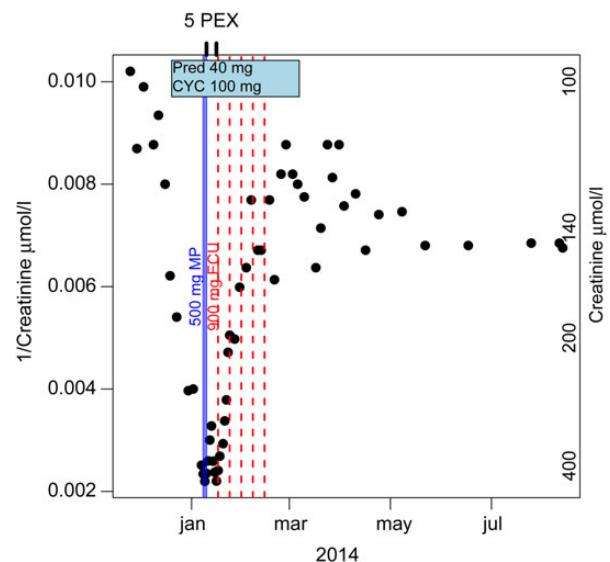


Fig. 2. Course of the disease.

reports it is difficult to know whether the improvement in renal function can be ascribed to the intervention. It is indeed possible that the effect of the massive therapy provided incidentally materialized at exactly the moment eculizumab was started. There is, however, evidence emerging from other forms of glomerulonephritis that complement blockade may play a role in inducing remission in aggressive forms including crescentic dense deposit disease [13–15] and lupus nephritis [16]. This is perhaps not surprising given that complement activation results in the generation of powerful inflammatory anaphylatoxins such as C5a. This is supported by the temporal relationship seen in the time course. Macrohaematuria may cause acute kidney injury and persistent injury [11] but one would then expect tubular injury rather than crescentic disease on biopsy. Notwithstanding free haemoglobin could exacerbate the disease process by activating complement [17].

Use of eculizumab in another patient with IgAN has been reported [18]. In that case eculizumab was started when deterioration in renal function occurred despite treatment with mycophenolate mofetil and steroids. The introduction of eculizumab was associated with temporary stabilization in renal function but the therapy was eventually withdrawn when a further renal biopsy showed severe chronicity. These two cases suggest that the mechanisms underlying chronic progression may not be amenable to complement inhibition as we provided it. Recently it was shown that inhibiting C5aR resulted in more rapid amelioration of proteinuria than steroid in patients with ANCA-positive vasculitis [19].

Conclusion

Following the comprehensive treatment in our patient, crescents improved, but nonetheless severe and progressive chronicity developed. If this deterioration is the result of the initial severe crescentic disease, perhaps earlier treatment with eculizumab could improve the final outcome. However, it is also possible that even if complement is involved in the causation of nephritis, either components proximal to the effect of eculizumab could be paramount or there is no direct relationship between initial inflammation and development of chronic scarring. Many more complement studies would be needed to assess these possibilities. We were not able to accomplish that during the acute treatment of our desperately ill patient.

Patient consent

The patients concerned in this case report consented to its publication after seeing the final version.

Conflict of interest statement

T.R. has received lecture fees from Alexion Pharmaceuticals. T.H.J.G. has received honoraria for consultancy work from Alexion Pharmaceuticals.

(See related articles by Rojas-Rivera *et al.* Rapidly progressive IgA nephropathy: a form of vasculitis or a complement-mediated disease? *Clin Kidney J* (2015) 8: 477–481 and by Yang *et al.* Clinical features of IgA nephropathy with serum ANCA positivity: a retrospective case–control study. *Clin Kidney J* (2015) 8: 482–488.)

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