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Eculizumab treatment for rescue of renal function in IgA nephropathy

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Abstract

Background

IgA nephropathy is a chronic glomerulonephritis with excessive glomerular deposition of IgA1, C3 and C5b-9, which may lead to renal failure.

Case diagnosis/treatment

We describe the clinical course of an adolescent with rapidly progressive disease leading to renal failure in spite of immunosuppressive treatment. Due to refractory disease he was treated with eculizumab (anti-C5), for three months, in an attempt to rescue renal function. Treatment led to clinical improvement with stabilization of the glomerular filtration rate and reduced proteinuria. Discontinuation of treatment led to rapid deterioration of renal function. This was followed by a single dose of eculizumab, which again reduced creatinine levels temporarily.

Conclusions

Early initiation of eculizumab in patients with progressive IgA nephropathy may have a beneficial effect by blocking complement-mediated renal inflammation.

Keywords: IgA nephropathy, complement, eculizumab

Introduction

IgA nephropathy is the most common form of chronic glomerulonephritis worldwide. Patients typically present in the second or third decade of life with continuous asymptomatic microscopic hematuria interspersed by recurrent episodes of macroscopic hematuria and proteinuria in association with upper respiratory tract or gastrointestinal infections. Certain patients present with acute nephritic and/or nephrotic syndrome. The disease may have a slow progressive course leading to renal failure in up to 40% of cases. Renal biopsies typically exhibit mesangioproliferative lesions in glomeruli with mesangial deposits of IgA, C3, and, to a lesser extent IgG and IgM. More severe lesions develop in progressive cases, including crescent formation, endocapillary proliferation, glomerulosclerosis, as well as interstitial, tubular and vascular affection [1].

The pathogenesis of IgA nephropathy has yet to be fully elucidated. The IgA1 found in the circulation and deposited in glomerular lesions was shown to be galactose-deficient, forming immune complexes with IgG or IgA1 [2, 3]. Genome-wide association studies identified loci in the *MHC*, *CFH/CFHR, HORMAD2* as well as other genes associated with IgA nephropathy [4]. The association with the *CFH/CFHR* locus may eventually give insight into the role of complement and the major soluble inhibitor of the alternative pathway, factor H (encoded by *CFH*), in the pathogenesis of IgA nephropathy. Homozygous deletions of factor H-related protein 3/1 (*CFHR3/1*) were considered protective [4] while few patients were found to have a factor H dysfunction or mutation [5-7].

Clinical, serological and histopathological studies have demonstrated that complement is activated during IgA nephropathy. In addition to C3 deposits in the mesangium, biopsies labelled positively for properdin and the membrane attack complex (MAC, C5b-9) [8, 9] as well as some labelling for C4d, mannose-binding lectin, ficolin [10] and C4-binding protein [11]. Properdin and soluble MAC were also elevated in patient urine [12]. C3 levels in serum are usually normal but degradation products, such as iC3b-C3d, may be elevated, suggesting activation of the alternative pathway [13]. Furthermore, decreased circulatory C3 levels and increased C3 deposition were suggested to be predictors of worse outcome [14]. Complement activation may thus contribute to renal inflammation during progressive IgA nephropathy [15]. Based on these findings suggesting complement activation in IgA nephropathy we treated a young patient with severe IgA nephropathy with the anti-C5 antibody eculizumab in an attempt to salvage renal function.

Case report

A previously healthy 16 year-old white male presented in 2012 with one week's history of edema, weight gain and fatigue. At admission he had a pulse rate of 83/min, normal peripheral perfusion and respiration, and a blood pressure of 142/93 mmHg. The plasma creatinine level was mildly elevated to 114 μmol/L (reference value 60-105 μmol/L) and plasma albumin was 19 g/L (reference value: 36-48 g/L). Urinalysis exhibited microscopic hematuria and proteinuria with a urinary albumin/creatinine ratio of 864 g/mol (normal range <3.8 g/mol). He was initially treated with prednisolone 80 mg/day and referred to Skåne University Hospital in Lund for investigation. Renal biopsy exhibited a mesangioproliferative pattern with fibrocellular crescents in 2 of 15 glomeruli. Immunofluorescence showed intense mesangial staining for IgA and C3 and weak IgG and IgM staining. C5b-9 staining was noted in capillary walls. He was diagnosed with IgA nephropathy. The pathological score according to the Oxford classification [1] was M1 S1 E1 T1. Creatinine levels increased to 165 μmol/L and the patient was treated with intravenous methyl-prednisolone pulses and high-dose oral prednisolone followed by mycophenolate mofetil and various anti-hypertensive medications (furosemide, felodipine, labetolol) (Figure 1). An initial improvement in plasma creatinine and albumin was noted during the first four months of treatment (Figure 1) accompanied by a decrease in edema. However, approximately 5-6 months after the initiation of treatment a slow rise in creatinine was noted as well as increased proteinuria in spite of continuous treatment with prednisolone (25 mg q.o.d.) and mycophenolate mofetil (750 mg b.i.d.). Losartan (12.5 mg q.d. initially, later increased to 25 mg b.i.d) and enalapril (2.5 mg b.i.d.) treatment were initiated but were not beneficial in controlling urinary protein losses. The patient experienced subjective clinical worsening with

fatigue and massive edema. The glomerular filtration rate (GFR) measured by iohexol clearance was 40 ml/min/1.73m^2 10 months after presentation.

A second renal biopsy was performed one year after debut and exhibited fibrocellular and fibrous crescents in 80% of glomeruli as well as deposits of IgA, C3 (Supplementary figure 1A-C) and IgG. The pathological score was M1 S1 E1 T2. Staining for deposition of C5b-9 exhibited prominent glomerular staining (Supplementary figure 1D). The GFR showed a marked decrease to 20 ml/min/1.73m^2. Due to rapid progression of renal failure and pronounced clinical worsening a decision was made to attempt to block renal inflammation with eculizumab. The patient was treated for a total of three months during which enalapril and mycophenolate mofetil were discontinued as no beneficial effect of these treatments was noted. Eculizumab was initially given once weekly (900 mg) for four weeks followed by treatment every other week (1200 mg) following the dose routine for the treatment of atypical hemolytic uremic syndrome (aHUS). Immediately after the initiation of treatment a drop in serum creatinine (from 369 to 300 μmol/L within 6 days, and to 239 μmol/L one month later) and in proteinuria was noted (Figure 1). However, when alternate week treatment was commenced creatinine levels rose again (to 309 μmol/L). Assuming that the patient's massive proteinuria contributed to urinary loss of eculizumab the treatment schedule was switched to once weekly at half the recommended dose recommended for adults (i.e. 600 mg/week). The creatinine levels were stable and this regimen was used until treatment was discontinued after three months. A quantitative complement function assay (Wielisa, Eurodiagnostica, Malmö Sweden) was monitored indicating total blockade. Levels of C3 were normal both before and during treatment with no elevation of C3dg. After the initial

improvement in creatinine a slow rise back to the initial level was noted. However, the urinary protein losses diminished and remained lower while the clinical situation improved and edema resolved. The GFR at the end of treatment was 19 ml/min/1.73m^2. Weekly controls after discontinuation of eculizumab showed that serum creatinine and albumin levels were stable as long as complement function was blocked. The patient was transferred to the adult nephrology unit at this stage. Six weeks after discontinuation of eculizumab complement function recovered and one week later a pronounced rise in serum creatinine was noticed while proteinuria increased (Figure 1). A marked daily increase in creatinine was noted and after 3 days a single dose of eculizumab (900 mg) was administered, again leading to an improvement of renal function, albeit at a higher creatinine level. A third renal biopsy performed at the same time showed that 75% of glomeruli were sclerotic and 2 of 20 exhibited fibrotic crescents. The pathological score was M1 S1 E1 T1. Deposits of IgA, C3 and IgG were noted (staining for C5b-9 was not performed). At this point a decision was made by the attending physicians to discontinue eculizumab treatment due to advanced renal failure. Four weeks after the single dose of eculizumab a rapid and sharp rise in creatinine was noted and the patient commenced peritoneal dialysis.

Discussion

Complement activation is not considered to be the primary event triggering renal dysfunction in IgA nephropathy. Nonetheless, prominent complement deposition in glomeruli occurs and most probably contributes to extensive renal inflammation with subsequent cell injury. Glomerular complement deposition and urinary MAC have been associated with more severe renal injury [10, 12, 14]. Kiryluk et al suggested that patients with IgA nephropathy might benefit from treatment with recombinant factor H or anti-C5 antibodies [15]. This report describes the first patient with IgA nephropathy treated with anti-C5 antibody. The beneficial effect on renal function and clinical improvement lasted as long as the patient was treated with eculizumab. Discontinuation of treatment led to worsening of renal function that was once again hampered by a single dose of eculizumab. Initiation of treatment earlier on in the course of disease may have had a more favorable outcome. Nevertheless, treatment prevented clinical deterioration even late in the course of disease.

Eculizumab has a half-life of up to 15 days (median 11 days). Thus a total normalization of complement function can be expected approximately one month after discontinuation. In our patient a very rapid deterioration occurred approximately 6-7 weeks after termination of treatment when complement function had normalized. When eculizumab was readministered the decrease in renal function was again hampered suggesting that the rapid progression of renal failure in this patient was mostly due to complement activation. Unlike patients with aHUS, patients with IgA nephropathy may not require total blockade of the terminal complement pathway to prevent progression and could thus possibly be treated with eculizumab at longer intervals than every other week, depending on the degree of proteinuria. Furthermore,

we speculate that complement-related biomarkers such as circulating C3 degradation products and soluble MAC, in plasma or urine, as well as staining for C5b-9 in renal biopsies, may be useful in determining which patients will benefit from eculizumab treatment. This remains to be evaluated in other patients.

Eculizumab was used here as a rescue therapy due to a progressive worsening in renal function. It is a very expensive drug and not approved for use in IgA nephropathy. During the short treatment period of three months the patient improved clinically and subjectively. Patients with IgA nephropathy may benefit from complement inhibition when renal function worsens. This question should be addressed in future clinical studies as this will determine if complement activation contributes to the pathology in IgA nephropathy and if eculizumab has a role in the treatment of this disease.

Disclosures

Diana Karpman was the national coordinator in Sweden of the international trial of Eculizumab (Alexion) during 2009-2010.

Lisa Sartz is the national coordinator of the Alexion aHUS registry in Sweden.

References

1. Cattran DC, Coppo R, Cook HT, Feehally J, Roberts IS, Troyanov S, Alpers CE, Amore A, Barratt J, Berthoux F, Bonsib S, Bruijn JA, D'Agati V, D'Amico G, Emancipator S, Emma F, Ferrario F, Fervenza FC, Florquin S, Fogo A, Geddes CC, Groene HJ, Haas M, Herzenberg AM, Hill PA, Hogg RJ, Hsu SI, Jennette JC, Joh K, Julian BA, Kawamura T, Lai FM, Leung CB, Li LS, Li PK, Liu ZH, Mackinnon B, Mezzano S, Schena FP, Tomino Y, Walker PD, Wang H, Weening JJ, Yoshikawa N, Zhang H (2009) The Oxford classification of IgA nephropathy: rationale, clinicopathological correlations, and classification. Kidney Int 76:534-545

2. Tomana M, Matousovic K, Julian BA, Radl J, Konecny K, Mestecky J (1997) Galactose-deficient IgA1 in sera of IgA nephropathy patients is present in complexes with IgG. Kidney Int 52:509-516

3. Hiki Y, Odani H, Takahashi M, Yasuda Y, Nishimoto A, Iwase H, Shinzato T, Kobayashi Y, Maeda K (2001) Mass spectrometry proves under-O-glycosylation of glomerular IgA1 in IgA nephropathy. Kidney Int 59:1077-1085

4. Gharavi AG, Kiryluk K, Choi M, Li Y, Hou P, Xie J, Sanna-Cherchi S, Men CJ, Julian BA, Wyatt RJ, Novak J, He JC, Wang H, Lv J, Zhu L, Wang W, Wang Z, Yasuno K, Gunel M, Mane S, Umlauf S, Tikhonova I, Beerman I, Savoldi S, Magistroni R, Ghiggeri GM, Bodria M, Lugani F, Ravani P, Ponticelli C, Allegri L, Boscutti G, Frasca G, Amore A, Peruzzi L, Coppo R, Izzi C, Viola BF, Prati E, Salvadori M, Mignani R, Gesualdo L, Bertinetto F, Mesiano P, Amoroso A, Scolari F, Chen N, Zhang H, Lifton RP (2011) Genome-wide association study identifies susceptibility loci for IgA nephropathy. Nat Genet 43:321-327

5. Watanabe S, Yamaguchi Y, Suzuki T, Ikezoe M, Matsumoto N, Chikamoto H, Nagafuchi H, Horita S, Hattori M, Shiraga H, Tokumoto T, Tanabe K, Toma H, Ito K (2001) Inherited factor H dysfunction and complement-associated glomerulonephritis in renal grafts of first and second transplantations. Clin Transplant 15 Suppl 5:45-50

6. Schmitt R, Krmar RT, Kristoffersson A, Soderberg M, Karpman D (2011) IgA nephropathy associated with a novel N-terminal mutation in factor H. Eur J Pediatr 170:107-110

7. Edey M, Strain L, Ward R, Ahmed S, Thomas T, Goodship TH (2009) Is complement factor H a susceptibility factor for IgA nephropathy? Mol Immunol 46:1405-1408

8. Stangou M, Alexopoulos E, Pantzaki A, Leonstini M, Memmos D (2008) C5b-9 glomerular deposition and tubular alpha3beta1-integrin expression are implicated in the development of chronic lesions and predict renal function outcome in immunoglobulin A nephropathy. Scand J Urol Nephrol 42:373-380

9. Rauterberg EW, Lieberknecht HM, Wingen AM, Ritz E (1987) Complement membrane attack (MAC) in idiopathic IgA-glomerulonephritis. Kidney Int 31:820-829

10. Roos A, Rastaldi MP, Calvaresi N, Oortwijn BD, Schlagwein N, van Gijlswijk-Janssen DJ, Stahl GL, Matsushita M, Fujita T, van Kooten C, Daha MR (2006) Glomerular activation of the lectin pathway of complement in IgA nephropathy is associated with more severe renal disease. J Am Soc Nephrol 17:1724-1734

11. Miyazaki R, Kuroda M, Akiyama T, Otani I, Tofuku Y, Takeda R (1984) Glomerular deposition and serum levels of complement control proteins in patients with IgA nephropathy. Clin Nephrol 21:335-340

12. Onda K, Ohsawa I, Ohi H, Tamano M, Mano S, Wakabayashi M, Toki A, Horikoshi S, Fujita T, Tomino Y (2011) Excretion of complement proteins and its activation marker C5b-9 in IgA nephropathy in relation to renal function. BMC Nephrol 12:64

13. Wyatt RJ, Kanayama Y, Julian BA, Negoro N, Sugimoto S, Hudson EC, Curd JG (1987) Complement activation in IgA nephropathy. Kidney Int 31:1019-1023

14. Kim SJ, Koo HM, Lim BJ, Oh HJ, Yoo DE, Shin DH, Lee MJ, Doh FM, Park JT, Yoo TH, Kang SW, Choi KH, Jeong HJ, Han SH (2012) Decreased circulating C3 levels and mesangial C3 deposition predict renal outcome in patients with IgA nephropathy. PLoS One 7:e40495

15. Kiryluk K, Novak J, Gharavi AG (2013) Pathogenesis of immunoglobulin A nephropathy: recent insight from genetic studies. Annu Rev Med 64:339-356

Figure legend

Figure 1: P-creatinine and u-albumin/creatinine ratio in relation to treatments

A flow-chart showing levels of plasma creatinine (depicted in blue) and urinary albumin/creatinine ratio (red) over time and in relation to various treatments. The time intervals are shown on the X axis. Treatments are depicted on the top of the panel and the glomerular filtration rate (GFR) on the bottom.

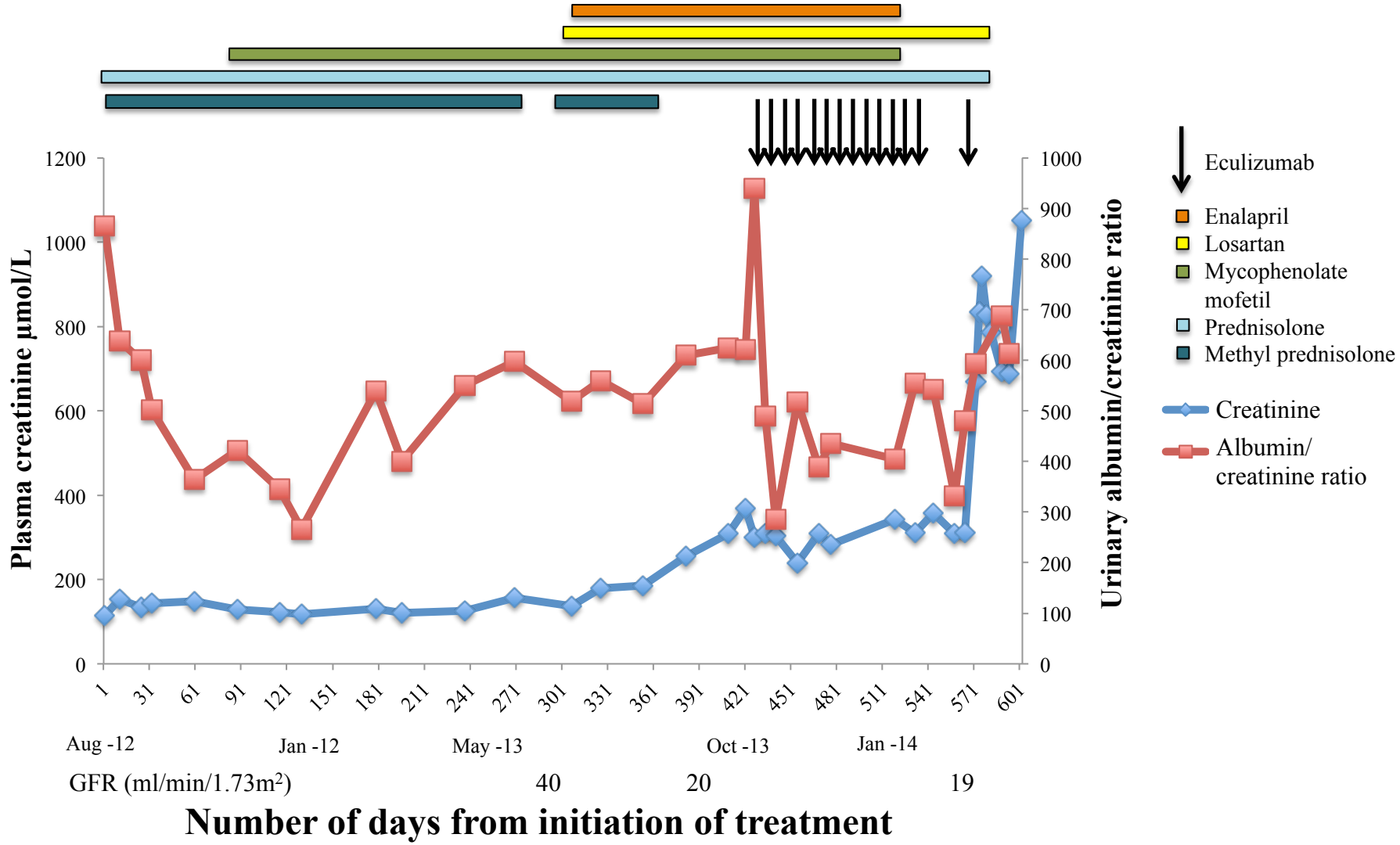
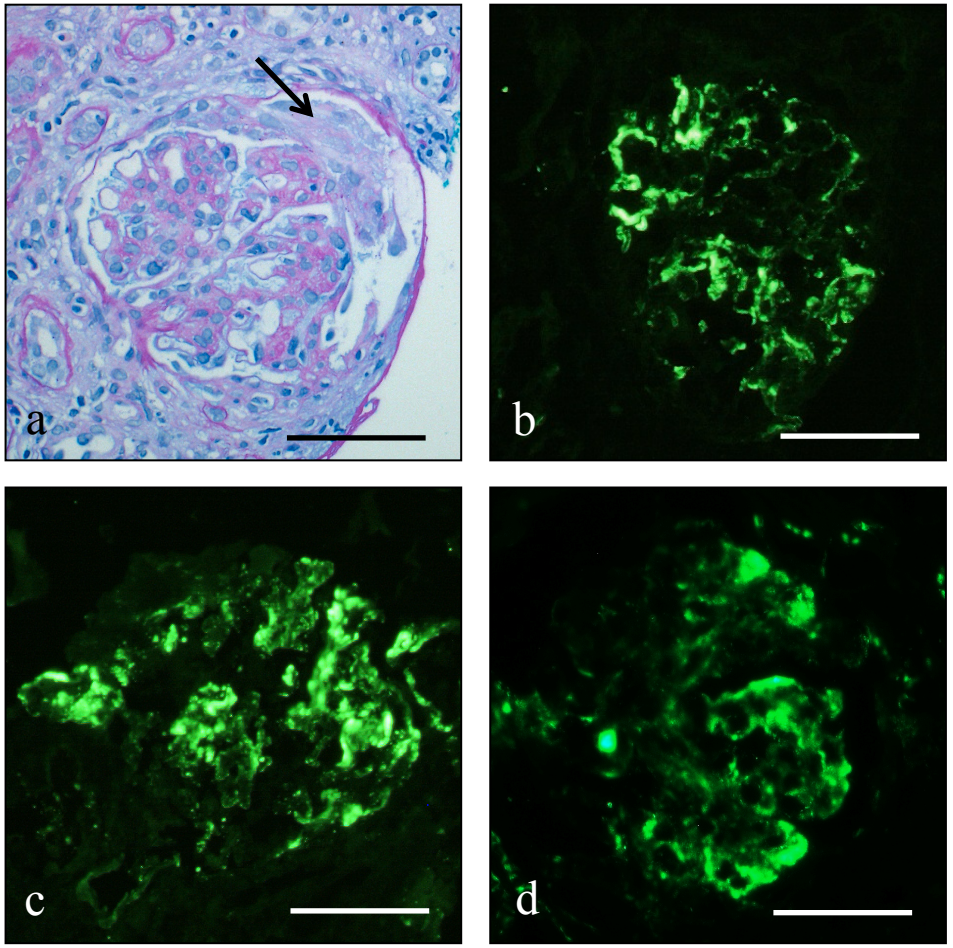

Plasma creatinine µmol/L
Urinary albumin/creatinine ratio
Eculizumab
Enalapril
Losartan
Mycophenolate mofetil
Prednisolone
Methyl prednisolone
Creatinine
Albumin/ creatinine ratio
Aug -12
Jan -12
May -13
Oct -13
Jan -14
GFR (ml/min/1.73m²)
40
20
19
Number of days from initiation of treatment

Figure 1



Supplementary figure 1: Renal biopsy from the patient with IgA nephropathy
Pathology specimens obtained at the second renal biopsy. A) Glomerulus stained with hematoxylin/eosin demonstrating a fibrocellular crescent (arrow) and a mesangioproliferative pattern. The tubulointerstitium shows fibrotic changes and inflammatory infiltrates. Glomeruli exhibited positive mesangial immunofluorescent and subendothelial staining for IgA (B) and C3 (C) performed by hospital routines. D) Similar staining for C5b-9 was performed using primary mouse anti-human C5b-9 antibody (Dako, Glostrup, Denmark), or mouse IgG2a (Dako) as the isotype control (not shown), followed by secondary anti-mouse Alexa-Fluor 488-conjugated antibody (Molecular Probes, Eugene, OR). C5b-9 staining was more prominent in the capillary walls as well as in the mesangium. Scale bars 100 μm.