MP 703

ECULIZUMAB FOR C3-GLOMERULONEPHRITIS RECURRENCE IN A RENAL TRANSPLANT

Authors: C. Dörje[1], G. Kovacevic[3], C. Hammarström[2], E.H. Strøm[2], H. Holdaas[1], K. Midtvedt[1], A.V. Reisæter[1]

Hospital: [1] Department of Transplant Medicine, [2] Department of Pathology, Oslo University Hospital – Rikshospitalet, Norway
[3] Medical Department Haugesund Hospital, Norway

OBJECTIVES

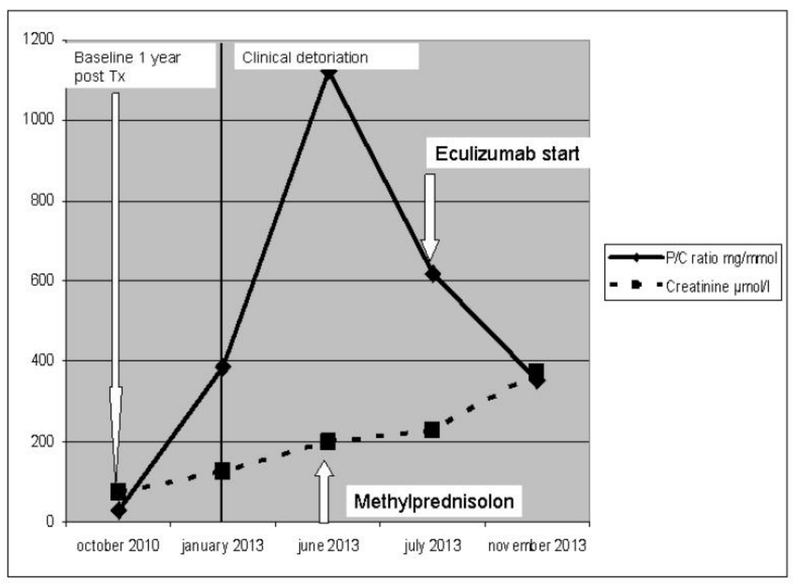
Introduction:

C3-glomerulonephritis (C3 GN) is associated with acquired or genetic dysregulation of the alternative complement pathway.
Eculizumab, a C5-complement antibody, blocks the final common complement pathway.

Objective:

In the absence of a disease specific therapy for C3 GN, Eculizumab emerged as a treatment option.[1,2]

Clinical course



CLINICAL CASE PRESENTATION

Primary kidney disease:
19 year old man, diagnosed with nephrotic syndrome 2004. Biopsy confirmed membranoproliferative glomerulonephritis (MPGN). Nephritic factor positive, characterized as dense deposit disease (DDD), although electron microscopy (EM) was uncharacteristic. Mycophenolate (MMF), Cyclosporine, Tacrolimus (Tac), Rituximab, plasma exchange were tried unsuccessfully. Hemodialysis 2008.

Transplant (Tx) history:
1. *Kidney Tx August 2009,* living donor mother, HLA mm 1-0-0, Basiliximab, Tac, MMF and steroids. Graft function with stable creatinine (s-crea) 90 µmol/l, urine protein/ creatinine (P/C) ratio < 30 mg/mmol, *low C3 0,47 g/l (0,7-1,2) from Tx*, C4 0,24 g/l (0,1-0,5), nephritic factor negative, no rejection.

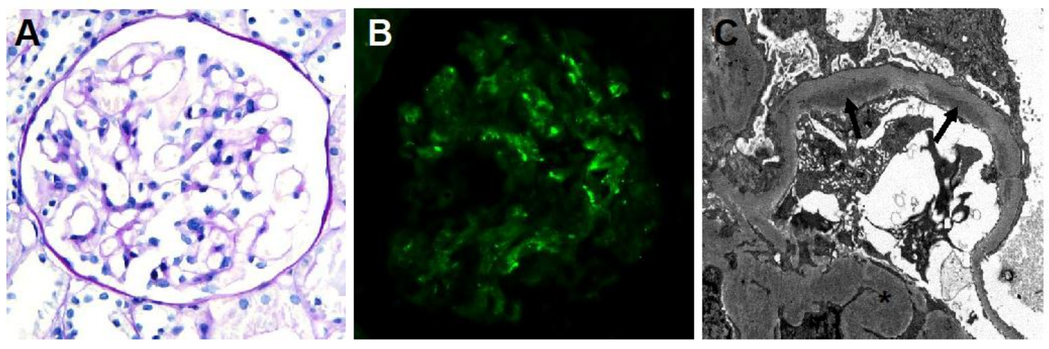
Protocol Tx biopsy at 6 weeks (Fig 1) and 1 year:
Subclinical recurrence of MPGN/ C3 GN in both biopsies, i0t0v0, C4d 0, IFTA grade 0

January 2013 (3,5 years post Tx) nephrotic proteinuria, P/C ratio 386 mg/ mmol and a rise in s-crea from 80 to 125 µmol/l.
Tx biopsy January 2013 positive staining for C3, negative immunoglobulines, i0t0v0, C4d 0, IFTA1.
EM: mesangial, subepithelial and intramembranous deposits, **C3-glomerulonephritis**.
Low C3 0,55 g/l, increased C5b-9/ membrane attack complex (MAC) 543(300).
Complement factor (CF) H and I normal, no Factor H antibodies or mutations in CFH, CFI, CFB, MCP, C3 or CFHR5. Persisting nephrotic syndrome. Eculizumab therapy discussed and rejected due to absence of inflammatory changes in the biopsy.
Tx biopsy June 2013 (Fig 2)
i3t2v0, C4d 0, IFTA grade 2, Recurrence C3 GN, crescents in 9 of 27 glomeruli.
Methylprednisolone 1250 mg i.v., s-crea rose to 290 µmol/l.
Tx biopsy July 2013
i2t1v0, C4d 0, IFTA grade 2, persisting recurrence, crescents 2 of 21 glomeruli.
Eculizumab rescue therapy was initiated July 2013 900 mg weekly for 4 weeks, 1200 mg every fortnight, total treatment duration 3 months.

RESULTS

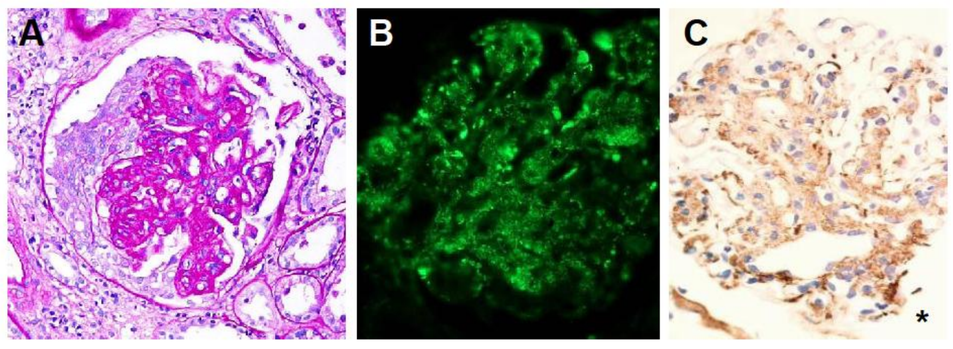
November 2013 s-crea 370 µmol/l, P/C ratio 352 mg/mmol, C5b-9 135, C3 0,78, C4 0,39, Alternative pathway (AP) effectively blocked
AP activity 4 (>10)
Tx biopsy November 2013
i1t1v0, C4d 0, IFTA grade 2, 5 of 19 glomeruli with crescents, C3 GN recurrence.
No improvement despite Eculizumab therapy, which was discontinued. Hemodialysis 3 weeks later.

Fig 1. 6 weeks post-tx



A: Normal glomeruli by light microscopy.
B: Deposition of C3 (green) by immunofluorescence.
C: Mesangial (*) and subendothelial/intramembranous (→) electron dense deposits by electron microscopy.

Fig 2. 4 years post-tx



A: Crescent and membranoproliferative pattern by light microscopy.
B: Deposition of C3 (green) by immunofluorescence.
C: Positivity for C5b-9/TCC (brown) by immunohistochemistry.
* staining performed by Dr. J. Mölne at Sahlgrenska University Hospital, Gothenburg, Sweden

CONCLUSIONS

Eculizumab was ineffective in our patient with recurrence of C3-glomerulonephritis. We speculate that the patient might have benefited from Eculizumab treatment, if started earlier. In perspective of costly therapy, better criteria are needed to define who could profit from Eculizumab therapy.

REFERENCES:

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