بسم الله الرحمن الرحيم

Eculizumab in recurrence of C3 glomerulopathy post-kidney transplant

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MPGN Case

In 1393/ 9, a 28 year old male was referred to Hasheminejad Kidney Center with lower extremity edema and hypertension since 5 month ago. He had proteinuria within nephritic range (15368 mg/24hr), hematuria with dysmorphic RBCs and high serum Cr about 3.7 mg/dl. C3 and CH50 are low. Other serologic tests are negative.

MPGN Case. KIDNEY BIOPSY in 1393/9

- Diffuse Proliferative Glomerulonephrirtis that are in favor of C3 Glomerulopathy. Acute Tubulointerstitial Nephritis. IFTA: 25- 30%
- IF: IgM,C1q, Lambda and kappa shows 1+ segmental deposits. C3 shows 3+ mesangial and capillary deposits.

MPGN Case

- Despite the treatments (methyl prednisolone, cyclophosphamide 500 mg × 2 (sever infection), rituximab 500 mg), creatinine increased and the patient underwent routine dialysis in 1394/4 with the diagnosis of ESKD.
- In 1395, pre-transplant evaluation was done.
- C3 and CH50 were low.
- FH, FB, CD46, ADAMTS 13 Auto-Ab & ADAMTS 13 Activity : NL
- FI: 40 (38- 58)

MPGN Case

- The patient was transplanted from a brain-dead donor on 1395/8. He received ATG (375 mg). After transplantation, he developed DGF. Kidney biopsy report (1395/8):
- Acute vascular Rejection, CCTT type II compatible with type 2 of Banff scoring system - Acute Tubular Injury.
- The patient was discharged after 13 days with creatinine 3.2 mg/dl with prednisolone, Mycophenolate sodium and tacrolimus.

MPGN Case

- Four months after kidney transplantation, creatinine reached 1.3 mg/dl and one year later (1396/9) it was 1.6 mg/dl. In 1397/2, creatinine was 2.2 mg/dl and urine protein 24h: 6300 mg/24h. Transplanted kidney biopsy was done.

Transplanted kidney biopsy in 1397/2

- 31 glomeruli, one is globally sclerosed. The glomeruli are mostly enlarged showing increased cellularity and endocapillary proliferation making lobular accentuation associated with some PMN infiltration and thick glomerular basement membrane showing foci of double contour appearance. Two glomeruli shows cellular crescent formation. The interstitium show edema and lymphocytic infiltration in about 5-10% .IF: C3 shows 3+.
- 1)Diffuse Membranoroliferative Glomerulonephrirtis, Recurrent C3 Glomerulopathy,
- 2) Acute Cellular Rejection, CCTT type I compatible with borderline rejection of Banff scoring system .
- 3) Foci of peritubular capillaritis that although it is not conclusive but could be suspicious of Antibody Mediated Acute Rejection,

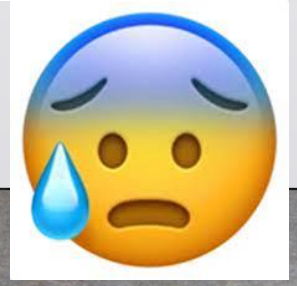
MPGN Case

- According to the biopsy report, **methylprednisolone and 5 cessation plasmaphereses** were performed and the creatinine, which raised to 3.3 mg/dl during hospitalization, was reduced to 2.2 mg/dl. Three months later (1397/5) creatinine was 2.9 mg/dl and proteinuria was 4300 mg/ 24h, and the patient received **300 mg of eculizumab**. After 15 days, creatinine was 1.7 mg/dl and proteinuria was 6100 mg/ 24h . Tow months later, creatinine was 2.4 mg/dl and **oral cyclophosphamide** was started. During the next 4 months, there were two episodes of severe diarrhea and acidosis and two episodes of upper respiratory tract infection. creatinine was 3.2 mg/dl on 1397/9 and 5.1 mg/dl on 1397/12. On 1398/3 (three years after transplantation), the patient became ESKD and underwent routine dialysis.

MPGN Case

- 7 months later, the patient came to clinic with gross hematuria despite administration of Myforetic (720 mg/day) and prednisolone (10 mg/day), and cystoscopy was performed. 5 days later, kidney transplant nephrectomy was performed and the pathology report was:
- - Acute cellular Rejection
- -Chronic active vascular rejection
- - Chronic active antibody mediated rejection
- - Remarkable fibrosis
- - Area of hemorrhage and necrosis
- - Proliferative glomerular changes

MPGN TREATMENT



medical sciences

MDPI

Article

Treatment of C3 Glomerulopathy in Adult Kidney Transplant Recipients: A Systematic Review

Maria L Gonzalez Suarez [1,2,*], Charat Thongprayoon [2,*], Panupong Hansrivijit [3], Karthik Kovvuru [4], Swetha R Kanduri [4], Narothama R Aeddula [5], Aleksandra I Pivovarova [1], Api Chewcharat [6], Tarun Bathini [7], Michael A Mao [8], Arpita Basu [9] and Wisit Cheungpasitporn [1,2,*]

12 cohort studies and 5 case series

- 122 KTx patients with C3G (73 C3GN) and 49 dense deposit disease (DDD)).
- The pooled estimated **rates of allograft loss** among KTx patients with **C3G** were:

  33% after eculizumab (21 patient overall)

  42% after therapeutic plasma exchange (TPE)

  81% after rituximab

- Subgroup analysis Pooled estimated rates of allograft loss:

  in **C3GN** KTx patients 22% after eculizumab, 56% after TPE, and 70% after rituximab.

  in **DDD** KTx patients 53% after eculizumab. Data on allograft loss in DDD after TPE (1 case series)

- pooled estimated rates of allograft loss in 66 patients without treatment (38 C3GN, 28 DDD): 32% for C3GN and 53% for DDD,

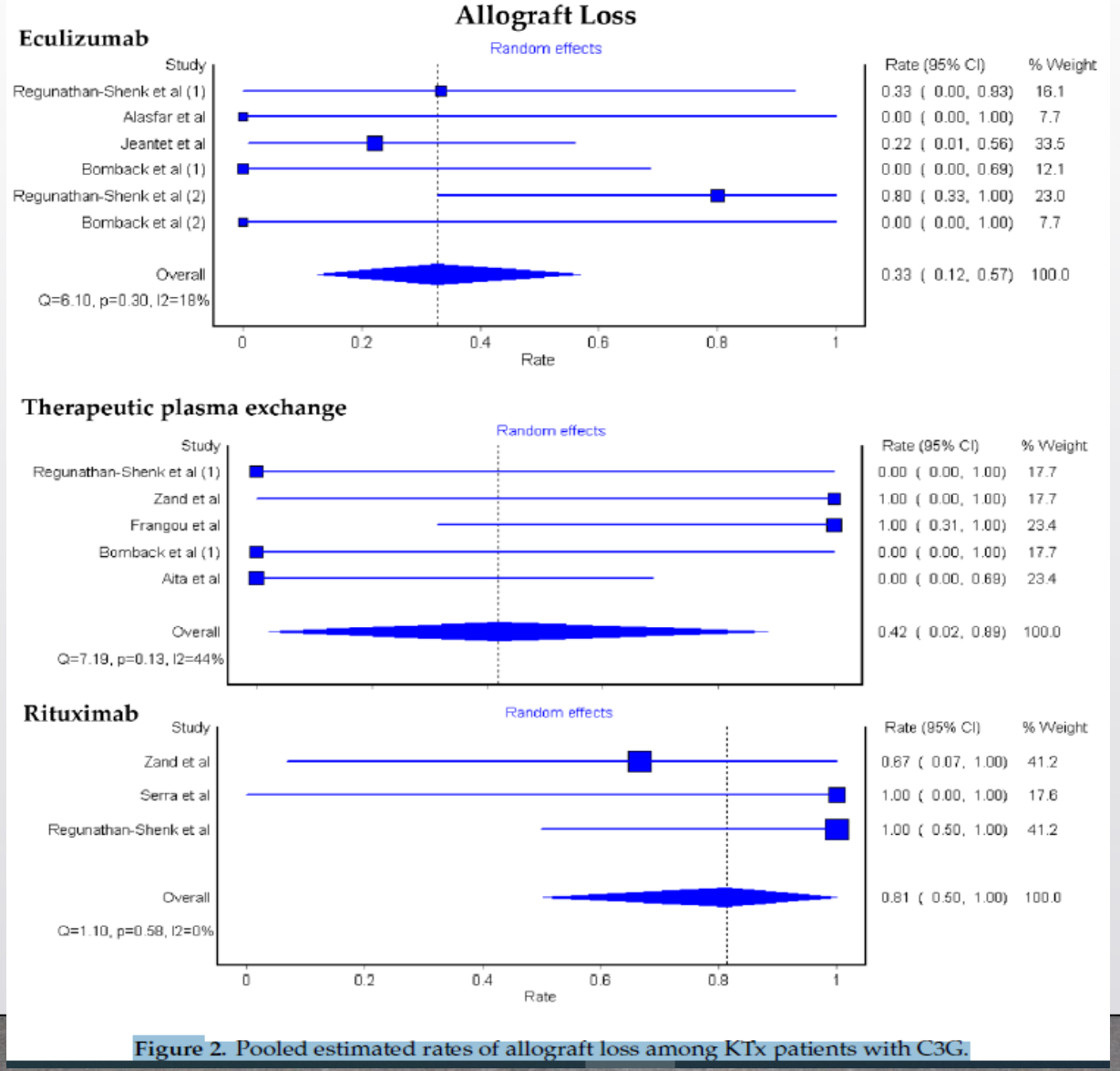


Figure 2. Pooled estimated rates of allograft loss among KTx patients with C3G.

Systematic Review

Table 1. Characteristics of the included studies in this systematic review of outcomes of KTx patients with C3GN.

C3GN among KTx Recipients															
Authors	Type of Study	Patients (n)	Age at Time of Diagnosis/ Transplant, Median (Years)	Females (n)	Time to Dialysis or KTX, Median (Months)	Type of KTX	Complement Abnormality	Median Follow-Up (Months)	Median Time from KTx to Recurrence (Months)	Recurrence	Rituximab, Graft Failure (n)	Eculizumab, Graft Failure (n)	PLEX + Steroids, Graft Failure (n)	No Therapy for Recurrence, Graft Failure (n)	Graft Failure, Total (n)
Regunathan-Shenk et al., 2019 [48]	Cohort	12	22	3	48	LRKTx, 7 LUKTx, 3 DDKTx, 2	CD46, 1 C3Nef, 2 C5Nef, 1 None, 1 Not done, 7	76	-	8, yes 2, probable2, no	0	3, 1 (1 treated with Eculizumab + PLEX)	1, 0	9, 2	3
Zand et al., 2014 [50]	Cohort	21	20.8	9	42.3	LKTx, 17 DDKTx, 4	-	73.9	28	14, yes 7, no	3, 2	0,0	1 + plus autologous peripheral stem cell transplant, 0 1 treated with steroids alone, 1	10, 0	7
Frangou et al., 2019 [71]	Cohort	17	46.7	4	-	LRKTx, 3 LUKTx, 3 DDKTx, 11	CFHR5, 17	157	37	3, yes 9, probable	0,0	0,0	2, 2	14, 3	5
Serra et al., 2018 [72]	Case series	3 (de novo)	66	1	-	DDKTx, 3	None, 2 Anti-CFH ab, 1	-	72	3 de novo	1, 1	0	0	2, 2	3
Wong et al., 2016 [73]	Case series	4 (familial)	26.5	2	-	DDKTx, 4	-	-	97	2, yes	0	0	0	2, 1	1
Alasfar et al., 2016 [74]	Cohort	5	37.4	3	-	DDKTx,1 LUKTx, 1	-	63.6	-	2, yes	0	1,0	0	1, 1	1
Jeantet et al., 2017 [75]	Cohort	9	-	-	-	-	-	-	1.5	9, yes	0	9, 2	0	0	2
Bomback et al., 2012 [32]	Case series	2	21	2	-	-	C3Nef, 2	-	2.5	2	-	2, 0 (1 treated with Eculizumab + PLEX, steroids)	1, 0	0	0

Abbreviations: KTX, kidney transplant; LKTx, living donor kidney transplant, LRKTx, living-related kidney transplant; LUKTx, living unrelated kidney transplant; DDKTx, deceased donor kidney transplant; PLEX, plasma exchange.

Systematic Review

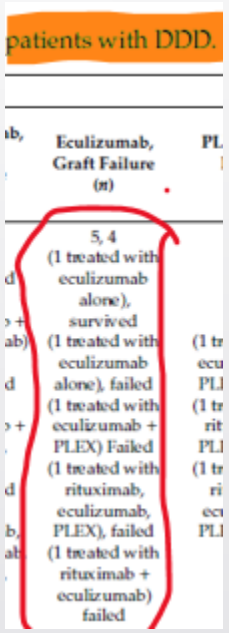
Table 2. Characteristics of the included studies in this systematic review of outcomes of KTx patients with DDD.

DDD among KTx Recipients															
Authors	**Type of Study**	**Patients, (*n*)**	**Age at Time of Diagnosis/ Transplant, Median (Years)**	**Females (*n*)**	**Time to Dialysis or KTx, Median (Months)**	**Type of KTx**	**Complement Abnormality**	**Median Follow-Up (Months)**	**Median Time from KTx to Recurrence**	**Recurrence (*n*)**	**Rituximab, Graft Failure (*n*)**	**Eculizumab, Graft Failure (*n*)**	**PLEX, Graft Failure (*n*)**	**No Therapy, Graft Failure (*n*)**	**Graft Failure, Total (*n*)**
Regunathan-Shenk, 2019 [48]	Cohort	7	30	2	-	LRKTx, 3 LUKTx, 2 DDKTx, 2	C3Nef, 3 CFI, 1 Anti-CFH ab, 1 Not done, 2	-	-	5, true 3, Probable 1, no	3, 3 (1 treated with rituximab + eculizumab) failed (1 treated with rituximab + PLEX), failed (1 treated with rituximab, eculizumab, PLEX), failed	5, 4 (1 treated with eculizumab alone), survived (1 treated with eculizumab alone), failed (1 treated with eculizumab + PLEX) Failed (1 treated with rituximab, eculizumab, PLEX), failed (1 treated with rituximab + eculizumab) failed	3,3 (1 treated with eculizumab + PLEX) Failed (1 treated with rituximab + PLEX), failed (1 treated with rituximab, eculizumab, PLEX), failed	3, 2	7
Aita et al., 2006 [76]	Case series	2	25	0	-	LRKTx, 2	-	6	-	-	0	0	2, 0	0	0
LeQuintrec et al., 2013 [77]	Case series	15	-	-	-	-	-	-	-	5	0	0	0	5, 3	3
Andresdottir et al., 1999 [78]	Cohort	13	23	7	84	DDKTx, 12 LRKTx, 1	-	29	2.9	11	0	0	0	11, 8	8
Droz et al., 1979 [79]	Cohort	11	-	-	-	DDKTx, 7 LRKTx, 4	-	30	4	9	0	0	0	9, 2	2
Bomback et al., 2012 [32]	Case series	1	42	1	-	LRKTx, 1	Negative	-	20	1	0	1, 0	0	0	0

Abbreviations: KTX, kidney transplant; LKTx, living donor kidney transplant, LRKTx, living-related kidney transplant; LUKTx, living unrelated kidney transplant; DDKTx, deceased donor kidney transplant; PLEX, plasma exchange.

Systematic Review

- 5, 4 (1 treated with Eculizumab alone), Survived (1 treated with Eculizumab alone), failed (1 treated with eculizumab + PLEX) Failed (1 treated with rituximab, eculizumab, PLEX), failed (1 treated with rituximab + eculizumab) failed.


patients with DDD.

Eculizumab, Graft Failure (n)
5, 4 (1 treated with eculizumab alone), survived (1 treated with eculizumab alone), failed (1 treated with eculizumab + PLEX) Failed (1 treated with rituximab, eculizumab, PLEX), failed (1 treated with rituximab + eculizumab) failed

- The Median follow-up period was 6 to 197 months.
- Time from transplantation to the recurrence : 1.5 months to 97 months post-KTx.
- Up to 80% of C3G treated patients with elevated sMAC responded to eculizumab.
- **sMAC levels** have been suggested as a serum marker for alternative complement pathway activation.

AJKD

Original Investigation

Kidney Transplantation in C3 Glomerulopathy: A Case Series

Renu Regunathan-Shenk, Rupali S. Avasare, Wooin Ahn, Pietro A. Canetta, David J. Cohen, Gerald B. Appel, and Andrew S. Bomback

median time to recurrence: 14 months in C3GN versus 15 months in DDD

3 patients who received rituximab….. all required initiation of dialysis

7 patients who received eculizumab …..Three of these patients maintain CKD stage 3 status at the time of follow-up

Table 3. Eculizumab Response in 7 C3G Patients With Posttransplantation Recurrence

ID	Dx of Recurrence	Allograft Biopsy Features	SMAC Level Before Eculizumab, mg/L	Recurrence to Initiation of Eculizumab, mo	Treatment Duration, mo	Response to Treatment	Outcome
C3GN1	True	MesGN	0.32	1	12	Yes	CKD 3
C3GN10	Probable	TMA	NT	5	>12	Yes	CKD 3
C3GN11	True	MesGN	0.27	0.75	3.5	No	Initiation of dialysis
DDD2	Probable	MesGN	NT	0.5	12	Yes	Initiation of dialysis and repeat Tx
DDD3	Probable	MesGN	NT	28	NA	No	eGFR < 15
DDD4[a]	Probable	TMA	NT	39	3	No	Initiation of dialysis
DDD7[b]	Probable	MPGN	1.27	7	>12	No	Initiation of dialysis and repeat Tx
DDD7[c]	True	MesGN	0.68	0.9	4	Yes	CKD 3

O4

ECULIZUMAB IN C3 GLOMERULOPATHY RECURRENCE AFTER KIDNEY TRANSPLANT

G. Jeantet, D. Bertrand, D. Anglicheau, N. Jourde-Chiche, P. Gatault, E. Cassuto, F. Fakhouri, V. Fremeaux-Bacchi, A.L. Sellier-Leclerc, A. Lionet, M. Rabant, M. Le Quintrec

4, Transplantation rénale-Néphrologie, Montpellier, France

Clinical GC3 recurrence occured in more than 50% after renal transplantation and is the first cause of allograft loss at 5 years post-transplantation. Eculizumab (EC) has been used in severe GC3 on native kidney and in few cases in graft recurrence with mitigate results. The aim of this study was to evaluate EC efficacy in graft GC3 recurrence in french cohort. We retrospectively analyzed patients who received EC for a clinical GC3 graft recurrence. Clinical recurrence was defined by a proteinuria >0.7 g/g and/or increasing serum creatinine > 30% from the baseline. Recurrence had to be proven by graft biopsy and was considered by C3 deposits without associated rejection. Data were collected the day of recurrence, the first day of EC starting and at the last follow up. Partial remission (PR) was defined by stabilization (±25%)or improvement of serum creatinine and proteinuria reduction upper than 50%. Complete remission (CR) is defined by a normalized serum creatinine (basal value) and proteinuria lower than 0.5 g/g. 9 patients received EC for GNC3 recurrence. The mean time of recurrence diagnosis was 44 days. (7 in the first 3 months including 3 in the first month). At diagnosis serum creatinine was 220 µmol/L (range : 114–304 µmol/L) and proteinuria was 0.60 g/g (range : 0–6.2 g/g). In all graft biopsies, C3 deposit was positive. At EC initiation mean proteinuria was 1.9 g/g (range 0.60–3.97 g/g) and mean serum creatinine was 200 µmol/L (range 122–304 µmol/L). After a median follow-up of 14 months, two patients had CR, 3 had PR. 4 patients had no remission and 2 non-responders lost their graft. Median of serum creatinine was 160 µmol/L (range 76–690) and median proteinuria 0.9 g/g. Conclusion : 5/9 patients had a good had a response to EC with improved renal function an proteinuria reduction. EC could be an option for recurrence treatment in selective patients. Complement analysis performed but not yet analyzed may help to select the good responders.

Clin J Am Soc Nephrol. 2012 May; 7(5): 748–756.
doi: 10.2215/CJN.12901211

PMCID: PMC3338285
PMID: 22403278

Eculizumab for Dense Deposit Disease and C3 Glomerulonephritis

Andrew S. Bomback,[✉*] Richard J. Smith,[†] Gaetano R. Barile,[‡] Yuzhou Zhang,[†] Eliot C. Heher,[§] Leal Herlitz,[‖]

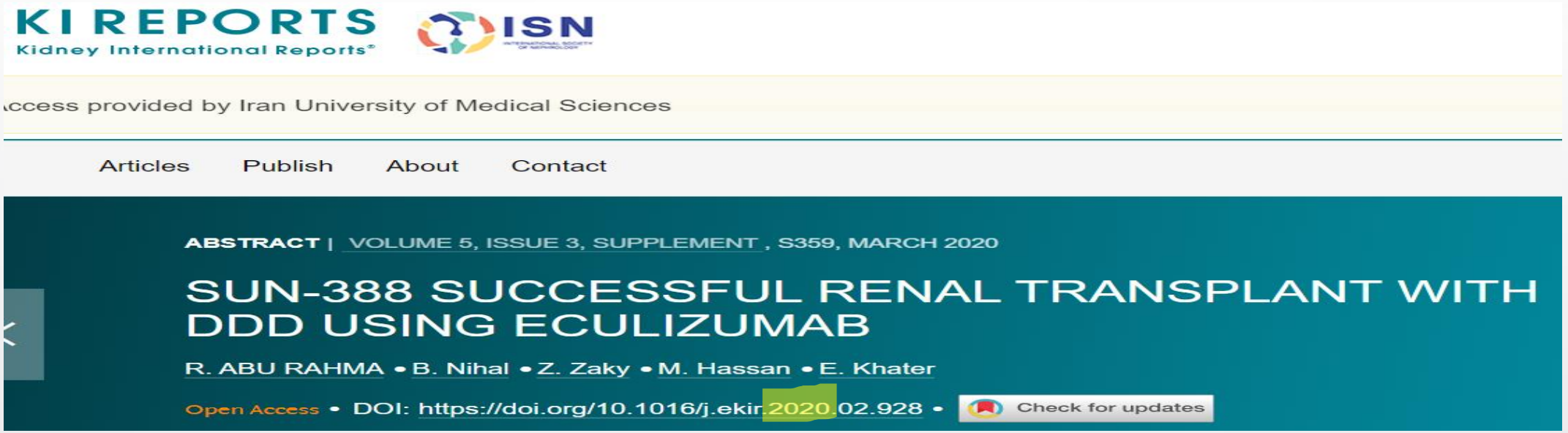
six subjects with DDDor C3 GN were treated with eculizumab every other week for 1 year. All had proteinuria >1 g/d and/or AKI (3 TX).

After 12 months, two subjects reduced serum creatinine (2.4—1.4, 2.1—1.7),

one subject reduction in proteinuria,

one subject had stable laboratory parameters but histopathologic improvements.

Elevated serum MAC levels normalized on therapy and paralleled improvements in creatinine and proteinuria.



A 17 Y/O female presented with nephrotic range proteinuria (8 g) & serum creatinine of 39 mmol/L. She was treated as minimal change disease (no biopsy) with steroids,. At Age of 21, a renal biopsy was done which was consistent with Dense Deposit Disease (DDD). She was maintained on Cyclo/MMF/prednisone. A year later the patient developed progressive worsening renal functions (S Cr 345mmol/L & PCR 11). She was initiated on dialysis in March 2019 and underwent a living donor kidney transplant from her father in August 2019. She received Basiliximab (IL2 receptor antibody blocker) for induction and was maintained on tacrolimus/MMF/prednisone. She received Eculizumab (1200 mg) 1 week prior to the transplant and was maintained on 900 mg Eculizumab every 2 weeks for a total of 3 months posttransplant. At the last follow up, she had stable renal allograft function with serum creatinine around 80 mmol/L and no proteinuria.

Published in final edited form as:

Pediatr Nephrol. 2013 October ; 28(10): 1975–1981. doi:10.1007/s00467-013-2503-y.

Eculizumab and Recurrent C3 Glomerulonephritis

Sevgi Gurkan, MD[1], Billie Fyfe, MD[2], Lynne Weiss, MD[1], Xue Xiao[3], Yuzhou Zhang, PhD[3],

The index patient is a 21-year-old white male with allograft recurrence of C3GN.A year after his transplant a biopsy revealed recurrent disease. Functional complement studies identified a decrease in the level of alternative pathway serum proteins and an elevation in soluble membrane attack complex (s**MAC**).

Two years after his initial transplant, the patient received a preemptive second kidney transplant from a living related donor for worsening proteinuria and disease progression. Two months after his transplant, serum C3 levels were undetectable and C3Nefs remained positive although the patient was clinically stable with a serum creatinine at 1.5 mg/dl and no proteinuria. However within 4 months, the patient started having proteinuria and was placed on rituximab therapy at a fixed dose of 100 mg IV weekly for 4 weeks. Only a minimal clinical and laboratory response was observed. Because sMAC and C3Nefs remained elevated, eculizumab therapy was started. The patient initially received eculizumab at 900 mg intravenously weekly for 4 weeks. On week 5, the dose was increased to 1200 mg intravenously and was continued at this level every other week for a total treatment period of 53 weeks.

- Eculizumab treatment resulted in: *normalization of sMAC

  * decline in serum creatinine from 1.5 to 1.3 mg/dl (persisted throughout the duration of therapy)

  * *proteinuria initially improved (after 6 months). At 9 month, proteinuria increased (urine protein/creatinine ratio >1 mg/mg)

  * repeat allograft biopsies showed progression of disease.

- Clinical and histopathologic data suggest a partial response to eculizumab in this patient. While eculizumab blocked activation of the terminal complement cascade, persistent dysregulation of alternative pathway remained, showing that eculizumab alone cannot control disease in this patient.

Clinical Commissioning Policy: Eculizumab in the treatment of recurrence of C3 glomerulopathy post-kidney transplant (all ages)

First published: February 2017

Prepared by NHS England Specialised Services Clinical Reference Group for Renal Services

NHS England

Starting criteria (NHS/ England)

- only if all the following clinical criteria are met:

1.A primary renal diagnosis of C3 glomerulopathy confirmed by renal biopsy.

2. Recurrent disease characterised on biopsy by an active glomerulonephritis with cellular crescents.

3. Evidence of glomerular C9 deposition on transplant biopsy.

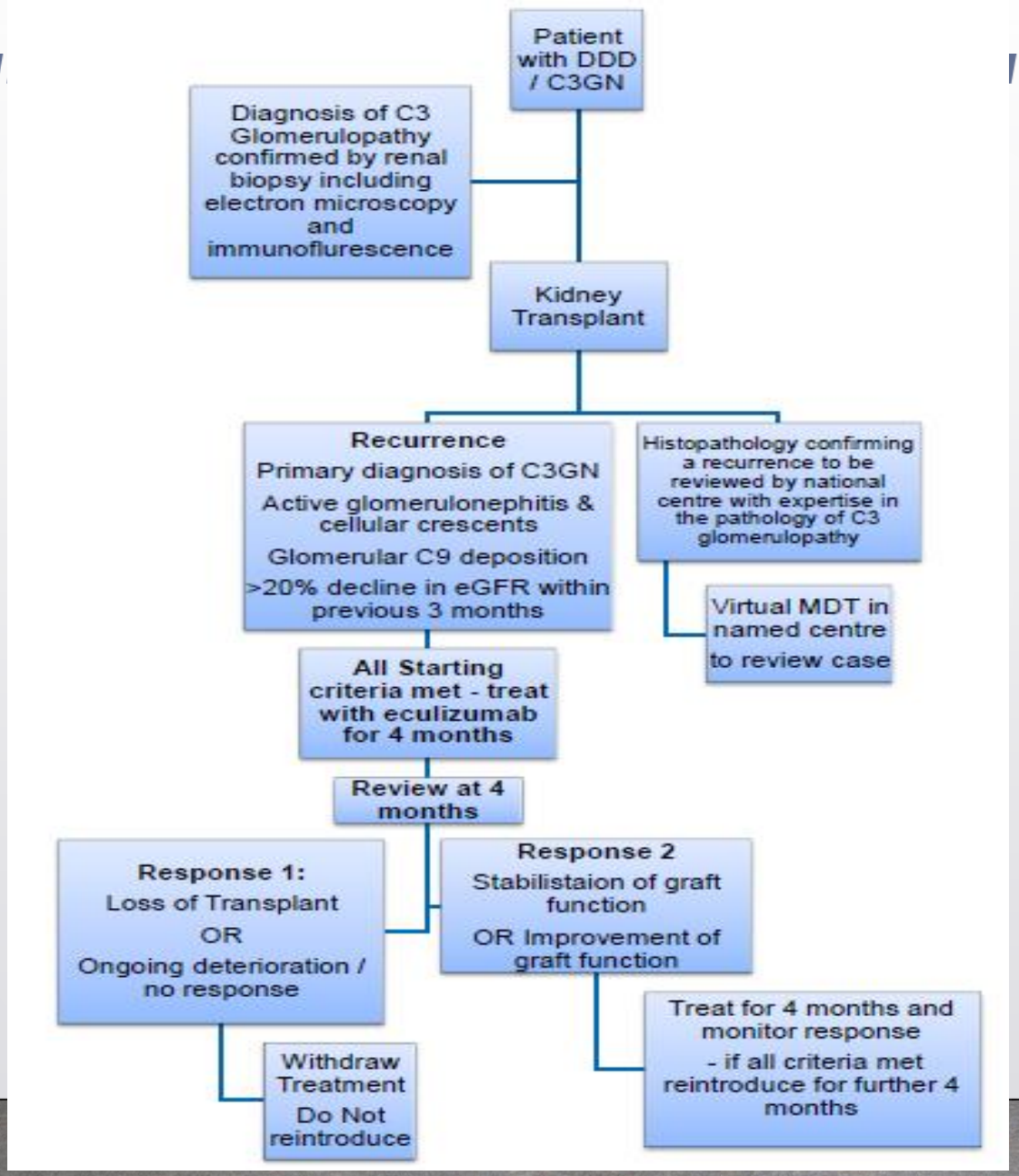
4. Recurrent disease occurring at any time post-transplant.

5. Evidence at the time of recurrence of a significant decline of transplant function (>20% decline in eGFR) within the previous three months. (not necessary if the recurrence occurs immediately after transplantation when transplant function has not yet been established).

6. No other cause for the decline in transplant function can be identified

Stopping criteria (NHS/ England)

- Treatment should be continued for four months. The possible outcomes at or before this time are:
- 1. Loss of the transplant despite treatment.
- 2. Ongoing deterioration in graft function (eGFR) with no evidence of a response to treatment.
- 3. Stabilisation of graft function (eGFR).
- 4. An improvement in graft function (eGFR).
- For 1 and 2, eculizumab should be withdrawn and not reintroduced. For 3 and 4, eculizumab should also be withdrawn after four months of treatment but could be reintroduced for a further four month period followed by further review if there is a subsequent deterioration in graft function (of a similar magnitude to that defined in criterion e) of the starting criteria), which on biopsy is shown to be due to active recurrent disease.


Patient with DDD / C3GN
Diagnosis of C3 Glomerulopathy confirmed by renal biopsy including electron microscopy and immunoflurescence
Kidney Transplant
Recurrence
Primary diagnosis of C3GN
Active glomerulonephitis & cellular crescents
Glomerular C9 deposition
>20% decline in eGFR within previous 3 months
Histopathology confirming a recurrence to be reviewed by national centre with expertise in the pathology of C3 glomerulopathy
Virtual MDT in named centre to review case
All Starting criteria met - treat with eculizumab for 4 months
Review at 4 months
Response 1:
Loss of Transplant
OR
Ongoing deterioration / no response
Response 2
Stabilistaion of graft function
OR Improvement of graft function
Withdraw Treatment
Do Not reintroduce
Treat for 4 months and monitor response
- if all criteria met reintroduce for further 4 months

ECULIZOMAB in MPGN

- **WHEN….**
- **HOW MUCH….**
- **SUCCESS RATE….**