NHS England

Evidence Review:

Eculizumab in the treatment of recurrence of C3 glomerulopathy post-transplant

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Contents

1. Introduction

C3 glomerulopathy (C3G) is a rare disease with an estimated prevalence of 1-2 cases per million in the UK [Medjeral-Thomas et al, 2014]. The clinical course of C3G is derived from cohort studies, which include individuals with C3GN, DDD or both. Due to its rarity, cohort studies are necessarily of low patient number and controlled trials are lacking. The sub-types of C3G together with its variable clinical course result in considerable disease heterogeneity. The condition has a poor prognosis with 10 year renal survival of approximately 50% in most cases. The following summarises key points from some of the major cohort publications.

In a series of patients from France with C3G (including n=29 with DDD and n=56 with C3GN), the 10-year renal survival was 63.5% [Servais et al, 2012]. Cumulative renal survival was worse in adult patients with DDD; worse if GFR at diagnosis was <60mls/min per 1.73m2 but was not related to circulating complement C3 levels. Renal survival was greater with the use of either angiotensin-converting enzyme inhibition or receptor blockade but not with the use of immunosuppression. Recurrence rate in renal transplantation was 54.5% (n=6) for the DDD sub-group and 60% (n=6) for the C3GN sub-group.

In a series of patients from the UK and Ireland with C3G (including n=21 with DDD and n=59 with C3GN), age > 16 years, DDD subtype, and crescentic GN, but not low circulating C3 levels, were independent predictors of ESRD [Medjeral-Thomas et al, 2014]. Of the n=20 reaching ESRD, n=6 with DDD and n=7 with C3GN underwent renal transplantation. DDD recurred in all patients and contributed to graft loss in n=3. Recurrence occurred in n=4 of the C3GN patients who were transplanted and contributed to graft loss in n=3.

In a series of patients with DDD (n=32) from North America [Nasr et al, 2009] clinical follow up data was available for both children (n=13, mean follow up duration 79.4 months, range 2-288) and adults (n=14, mean follow up duration 48.5 months, range 4-156). ESRF was more common in adults (n=6, 42.9%) compared to children (n=1, 7.7%). By univariate analysis correlates of ESRF included older age and higher creatinine at biopsy but not circulating C3 levels. Combined treatment with immunosuppression and renin angiotensin system blockade was associated with better renal survival than either treatment modality alone. Notable patients who received immunosuppression therapy had higher percentage of crescents on renal biopsy. In an earlier study of DDD (n=27 patients), the presence of either crescents or glomerular neutrophils in the initial biopsy correlated with progressive disease [Bennett et al, Am J Kid Dis 1989].

In a series of paediatric patients from North America (n=75) assessing recurrence of DDD in renal transplant, the 5 year renal survival was approximately 50% [Braun et al, 2005]. The presence of crescents in renal transplant biopsies was associated with worse graft survival. There was no correlation between circulating C3 levels and disease recurrence (with or without graft failure) a finding that had been previously reported [Leibowitch et al, 1979].

In a series of adult patients from the Netherlands (n=11) with DDD and first renal transplant, all transplant biopsies performed due to raised serum creatinine showed recurrent DDD [Andresdottir et al, 1999]. In n=3 graft loss occurred as sole

consequence of disease recurrence and in these cases renal biopsy showed both crescents and neutrophils.

In CFHR5 nephropathy, a genetically characterized familial C3GN, renal failure is more common in male patients [Athanasiou et al, 2011]. In an assessment of n=82 cases, 18 individuals (20%) reached ESRD with a striking male preponderance (n=14 males and n=4 females). 10 of the 18 individuals with ESRD received 11 renal transplants: n=2 were deceased whilst n=8 had functioning grafts at the time of reporting (graft times 1-23 years). The development of proteinuria appears to be a poor prognostic sign, particularly in male patients, and decline in renal function is associated with fever-associated macroscopic haematuria.

2. Research Questions

The research question is: **What is the evidence that eculizumab is effective in refractory C3G?**

Refractory C3G refers to declining renal function that is unresponsive to typical immunosuppressive modalities utilised to treat glomerulonephritis. These include glucocorticoid therapy (oral or pulse treatment), mycophenolate mofetil, tacrolimus, cyclophosphamide and rituximab. In patients with rapidly deteriorating renal function plasma exchange has been utilised. None of these approaches alone, or in combination, have proven to be widely effective in the treatment of C3G. Consequently many patients with C3G develop refractory disease in either the native or transplant kidney.

3. Methodology

These reports were identified by literature searches.

Searches were performed using PubMed (www.ncbi.nlm.nih.gov) and conducted independently by Profs Matthew Pickering and Tim Goodship in August 2015.

Search terms used were: eculizumab, C3 glomerulopathy, Dense Deposit Disease.

The search was limited to reports published in the English language.

Table1: Scottish Intercollegiate Guideline Network (SIGN) levels of evidence

Level of evidence	Type of evidence
1++	High quality meta-analyses, systematic reviews of RCTs (including cluster RCTs), or RCTs with a very low risk of bias
1+	Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1–*	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High quality systematic reviews of, or individual high quality non-randomised intervention studies (controlled non-randomised trial, controlled before-and-after, interrupted time series), comparative cohort and correlation studies with a very low risk of confounding, bias or chance
2+	Well conducted, non-randomised intervention studies (controlled non-randomised trial, controlled before-and-after, interrupted time series), comparative cohort and correlation studies with a low risk of confounding, bias or chance
2–*	Non-randomised intervention studies (controlled non-randomised trial, controlled before-and-after, interrupted time series), comparative cohort and correlation studies with a high risk of confounding, bias or chance
3	Non-analytical studies (eg case reports, case series)
4	Expert opinion, formal consensus
*Studies with a level of evidence (–) should not be used as basis for making recommendations. *Source*: adapted from SIGN (2001).	

Table 2: Scottish Intercollegiate Guideline Network (SIGN) Grades of Evidence

Grades of recommendations
Grade 'A' At least one meta-analysis, systematic review, or RCT rated as 1++ and directly applicable to the target population ***or*** A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+ directly applicable to the target population and demonstrating overall consistency of results.
Grade 'B' A body of evidence including studies rated as 2++ directly applicable to the target population and demonstrating overall consistency of results ***or*** Extrapolated evidence from studies rated as 1++ or 1+
Grade 'C' A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results ***or*** Extrapolated evidence from studies rated as 2++
Grade 'D' Evidence level 3 or 4 ***or*** Extrapolated evidence from studies rated as 2+

Source: Adapted from the Scottish Intercollegiate Guidelines Network (SIGN), 2001

4. Results

Since there is no definitive therapy for C3G and it is a complement-associated disease, there are reports of the use of eculizumab in refractory disease. The prevention of C5 activation would be expected to stop the C5-mediated but not C3-mediated damage in C3G. Activation of C5 results in production of the pro-inflammatory molecule C5a and initiates complement terminal pathway activation. The therapeutic benefit of C5 inhibition is most likely to seen in situations where there is glomerular inflammation (e.g. crescents, endocapillary hypercellularity, neutrophil accumulation) together with evidence of glomerular C5 activation (readily detected by the presence of the terminal complement component C9). There is pre-clinical data to support this assertion using an experimental model of C3G [Pickering et al PNAS, 2006].

Table 1 summarises the reported literature. These reports include 27 patients: 12 aged 16 years or less. There were 15 patients with a diagnosis of DDD and 12 with a diagnosis of C3GN. There were 4 patients with treated for recurrent DDD in renal allograft [McCaughan et al, 2012; Bomback et al, 2012; Gurkan et al, 2013; Sanchez-Moreno et al, 2014]. There were 4 patients treated for recurrent C3GN in a renal allograft [Bomback et al, 2012; Le Quintrec et al, 2015].

From the published data, it is apparent that eculizumab is therapeutically beneficial in many patients with either C3GN or DDD (Table 3).

The magnitude of reported response in some cases is clearly clinically impactful. These include:

- Enabling one adult (Inman et al, 2015) and two paediatric (Oosteveld et al, 2015) patients to stop dialysis;
- Achieving resolution of nephrotic range proteinuria (Table 3);
- Enabling cessation of immunosuppressive medication and/or plasma exchange (Table 3);
- Preventing loss of renal allograft due to recurrent disease (McCaughan et al, 2012; Bomback et al, 2012 – case DDD3, case C3GN2, case C3GN3; Sanchez-Moreno et al, 2014; Le Quintrec et al, 2014)

In some cases of disease in the native kidney there is no response to eculizumab (Besbas et al, 2013; Bomback et al, 2012 – case DDD2, case – C3GN1; Berthe-Aucejo et al, 2014). Similarly, no response to recurrent disease in a renal allograft (Gurkan et al, 2013) has been reported.

Plasma C5b-9 elevation has been considered a potential marker of those most likely to respond to eculizumab. This is not supported by the published data where response to eculizumab has been reported in the setting of normal plasma C5b-9 levels (patient 3 and episode 1 in patient 4 reported in Oosterveld et al, 2015).

Glomerular C5b-9 represents evidence of either ongoing or recent C5 activation within the kidney. Where repeat biopsy data is available, glomerular C5b-9 has been

shown to reduce, sometimes markedly, during treatment (Vivarelli et al, 2012; Le Quintrec et al, 2015; Payette et al, 2015)

Clinical response appears to be most effective when there is evidence of glomerular inflammation, particularly crescentic disease with renal impairment: all three patients who became dialysis-independent during eculizumab treatment (Inman et al, 2015; Oosteveld et al, 2015) had crescentic glomerulonephritis.

Table 3

Clinical Effectiveness and / or safety					
Level of Evidence	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
3	Design: Case report Intervention: eculizumab Dose: 900 mg weekly for five infusions and then 1200 mg every 2 weeks Indication: creatinine rise and nephrotic-range proteinuria; unresponsive to glucocorticoids and rituximab Treatment duration: 48 week follow up C3G sub-type: DDD	Creatinine Proteinuria	The urinary protein level before treatment was 5.42 g per deciliter, and the serum creatinine level was 2.2 mg per deciliter (194.5 µmol per liter). Over a 48-week follow-up, the levels of serum total protein and albumin normalized, the level of creatinine decreased, and proteinuria declined below the nephrotic range Plasma C5b-9 normalized during treatment	Daina et al 2012	Plasma C3: LOW Plasma C5: LOW Plasma C5b-9: HIGH C3 nephritic factor: POSITIVE C5b-9 glomerular deposits: POSITIVE
3	Design: Case report Intervention: eculizumab Indication: recurrent disease in renal allograft unresponsive to corticosteroid, rituximab and plasmapheresis Treatment duration: 18 months (1st course) C3G sub-type: DDD	Creatinine Proteinuria	Proteinuria fell during 18 months of treatment Proteinuria increased on eculizumab cessation Proteinuria reduced during second course of eculizumab Renal biopsies at +6 months and + 18 months of treatment showed: • Apparent reduction in electron dense deposits • Progressive reduction of C3 and C5b-9 deposits • Progression of glomerular sclerosis and tubular atrophy observed	Vivarelli et al 2012	Plasma C3: LOW C3 nephritic factor: POSITIVE Renal biopsy pre-treatment: • Focal sclerosis in 40% of glomeruli pre-eculizumab treatment

Clinical Effectiveness and / or safety					
Level of Evidence	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
3	Design: Case report Intervention: eculizumab Dose: 900 mg on two occasions 1 week apart and then 600 mg once a fortnight. Indication: creatinine rise and proteinuria 4 weeks after renal transplantation Treatment duration: 2.5 months C3G sub-type: DDD	Creatinine Proteinuria	Immediate and sustained improvement in both clinical and biochemical parameters: Creatinine fell by 1.9 mg/dl during the first 2 weeks of therapy Concurrent reduction in the urinary albumin:creatinine ratio from 755 mg/mmol to 229 mg/mmol Two antihypertensive agents were successfully withdrawn without deterioration in blood pressure control	McCaughan et al 2012	Plasma C3: LOW C3 nephritic factor: POSITIVE Transplant biopsy, 5 weeks post-transplantation, was consistent with recurrent DDD: • cellular crescents and neutrophil polymorphs in the glomeruli with endocapillary proliferation • Strong linear C3 deposition along the GBM and ring-like C3 deposits within the mesangium. • Linear band-like electron dense deposits along the GBM and in the mesangium

Clinical Effectiveness and / or safety					
Level of Evidence	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
3	Design: Open labeled non-controlled case series Intervention: eculizumab Dose: 900 mg once weekly for 4 weeks and then 1200mg on week 5 and every other week afterward for a total period of 53 weeks Indication: creatinine rise and/or proteinuria Treatment duration: 12 months (n=5); 9 months (n=1) C3G sub-type: DDD (n=3); C3GN (n=3)	Creatinine Proteinuria Renal biopsy Parameters	Case - DDD1: • Decline in serum creatinine from 1.8 to 1.5 mg/dl within 4 weeks; improvement in renal function persisted throughout therapy • Normalization of elevated sMAC • Proteinuria levels remained consistently low throughout therapy • Repeat biopsy after 1 year of treatment showed decreased activity with no evidence of endocapillary proliferation • 4 and 8 weeks after cessation of eculizumab, creatinine rose to 1.5 and 1.7 mg/dl respectively Case - DDD2: • No clinical response: both creatinine and proteinuria rising over 40 weeks of therapy • Levels of sMAC were consistently normal pre-treatment • Subject withdrew from the study and declined repeat biopsy Case – DDD3: • Recurrent disease live-related renal transplant 20 months post-transplantation • Creatinine during the first 4 weeks of therapy (1.2 mg/dl) was lower than baseline (1.5-1.7) • After 1 year: proteinuria was 0.2-1.9 g/g • Repeat biopsy: less extensive deposits, decreased mesangial proliferation	Bomback et al 2012	Improvement in outcome measure(s) in cases: DD1, DD3, C3GN3 No improvement in outcome measure(s) in cases: DD2 C3GN1 Stable renal function in C3GN2 with some improvement on renal biopsy; recurrent disease on stopping eculizumab No adverse events, including no infections, were reported during the course of therapy for any subject

Clinical Effectiveness and / or safety					
Level of Evidence	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
3	Design: Open labeled non-controlled case series Intervention: eculizumab Dose: 900 mg once weekly for 4 weeks and then 1200mg on week 5 and every other week afterward for a total period of 53 weeks Indication: creatinine rise and/or proteinuria Treatment duration: 12 months (n=5); 9 months (n=1) C3G sub-type: DDD (n=3); C3GN (n=3)	Creatinine Proteinuria Renal biopsy Parameters	Case - C3GN1: • Eculizumab commenced whilst on prednisone and mycophenolate mofetil • Pre-treatment: creatinine had risen from 1.5 to 2.1 mg/dl, proteinuria from 2.1 to 4.6 g/g, • Pre-treatment renal biopsy: diffuse MPGN • Pre-treatment sMAC was normal • Initial improvement in proteinuria and creatinine but then rise in both • Renal biopsy at week 48 of therapy: increased chronicity with increased global sclerosis, persistent MPGN, active GN in the few open glomeruli, large sub-endothelial deposits Case – C3GN2: • Recurrent disease live-related renal transplant 4 months post-transplantation • After 1 year: creatinine, proteinuria, and serum albumin remained stable • Pre-treatment sMAC was elevated • Repeat biopsy: less mesangial and endocapillary proliferation • Active recurrent GN with renal impairment 7 weeks after stopping eculizumab; renal function improved on re-starting eculizumab	Bomback et al 2012	Improvement in outcome measure(s) in cases: DD1, DD3, C3GN3 No improvement in outcome measure(s) in cases: DD2 C3GN1 Stable renal function in C3GN2 with some improvement on renal biopsy; recurrent disease on stopping eculizumab No adverse events, including no infections, were reported during the course of therapy for any subject

Clinical Effectiveness and / or safety					
Level of Evidence	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
3	Design: Open labeled non-controlled case series Intervention: eculizumab Dose: 900 mg once weekly for 4 weeks and then 1200mg on week 5 and every other week afterward for a total period of 53 weeks Indication: creatinine rise and/or proteinuria Treatment duration: 12 months (n=5); 9 months (n=1) C3G sub-type: DDD (n=3); C3GN (n=3)	Creatinine Proteinuria Renal biopsy Parameters	Case – C3GN3: • Recurrent disease live-related renal transplant 1 month post-transplantation • creatinine fell from a peak of 2.0 mg/dl to 1.4 mg/dl by completion of therapy • Pre-treatment sMAC was modestly elevated • No significant decrease between pre- and post-treatment biopsies: mild mesangial proliferation with no endocapillary proliferation or exudative features in both	Bomback et al 2012	Improvement in outcome measure(s) in cases: DD1, DD3, C3GN3 No improvement in outcome measure(s) in cases: DD2 C3GN1 Stable renal function in C3GN2 with some improvement on renal biopsy; recurrent disease on stopping eculizumab No adverse events, including no infections, were reported during the course of therapy for any subject
3	Design: Case report Intervention: eculizumab Dose: 900 mg once weekly for 4 weeks and then 1200mg on week 5 and every other week afterward for a total period of 53 weeks Indication: recurrent disease in second live-related renal transplant 2 month post-transplantation Treatment duration: > 12 months C3G sub-type: DDD	change in proteinuria over the treatment period	Proteinuria increased Creatinine remained stable Repeat renal biopsies at +6 months and +12 months showed active disease with increased fibrosis (3% and 20%, pre- vs. pot treatment respectively)	Gurkan et al 2013	Plasma C3: LOW Plasma C5b-9: HIGH C3 nephritic factor: POSITIVE

Clinical Effectiveness and / or safety					
Level of Evidence	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
3	Design: Case report Intervention: eculizumab Dose: 900 mg weekly for four weeks then 1200 mg every 2 weeks Indication: refractory C3GN with nephrotic syndrome Treatment duration: 10 months C3G sub-type: C3GN	Proteinuria	Proteinuria did not improve Creatinine remained normal	Besbas et al 2013	Plasma C3: LOW
3	Design: Case report Intervention: eculizumab Dose: 900 mg weekly for four weeks then 1200 mg every 2 weeks Indication: refractory disease 44 months after clinical presentation Treatment duration: 3.5 months C3G sub-type: C3GN	Proteinuria	Reduction in proteinuria	Kerns et al 2013	Plasma C3: LOW Plasma C5b-9: HIGH

Clinical Effectiveness and / or safety					
Level of Evidence	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
3	Design: Case report Intervention: eculizumab Dose: 600 mg weekly for two weeks then 600mg twice monthly Indication: refractory disease with crescentic GN Treatment duration: 6 months C3G sub-type: DDD	Creatinine Proteinuria	Normalization of both proteinuria and creatinine	Rousset-Rouviere et al 2014	Plasma C3: LOW C3 nephritic factor: POSITIVE C5b-9 glomerular deposits: POSITIVE
3	Design: Case report Intervention: eculizumab Dose: 900 mg once weekly for 4 weeks and then 1200mg on week 5 and every other week thereafter Indication: refractory disease with crescentic GN, nephrotic range proteinuria, normal creatinine Treatment duration: 8 months C3G sub-type: DDD	Proteinuria	Normalization of proteinuria	Ozkaya et al 2014	Plasma C3: LOW C3 nephritic factor: POSITIVE Cyclophosphamide, plasma exchange and steroid therapy ineffective

Clinical Effectiveness and / or safety					
Level of Evidence	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
3	Design: Case report Intervention: eculizumab Dose: 900 mg once weekly for 4 weeks and then 1200mg on week 5 and every other week thereafter Indication: refractory disease with nephrotic range proteinuria, normal creatinine Treatment duration: 4 months C3G sub-type: DDD	Proteinuria	Proteinuria did not improve	Berthe-Aucejo et al 2014	Plasma C3: LOW Plasma C5b-9: HIGH C3 nephritic factor: POSITIVE
3	Design: Case report Intervention: eculizumab Dose: 900 mg once weekly for 4 weeks, then 1200mg every two weeks for one year, every three weeks for one year and then every four weeks Indication: recurrent disease in live-related renal transplant 3 month post-transplantation Treatment duration: 30 months C3G sub-type: DDD	Proteinuria	Resolution of proteinuria Renal allograft biopsy +6 months into treatment showed no progression	Sanchez-Moreno et al 2014	Plasma C3: LOW C3 nephritic factor: POSITIVE Proteinuria was previously only responsive to intensive plasma exchange

Clinical Effectiveness and / or safety					
Level of Evidence	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
3	Design: Case report Intervention: eculizumab Dose: 900 mg once weekly for 4 weeks, then 1200mg every two weeks Indication: see case descriptions Treatment duration: ongoing C3G sub-type: C3G	Creatinine Proteinuria Renal Biopsy Parameters	Case - C3G (27F): Pre-treatment: • Proliferative C3G with positive glomerular C5b-9 • Creatinine rise and proteinuria Post-treatment (>19 months): • Reduction in glomerular inflammation and C5b-9 deposition • Resolution of proteinuria Case - C3G in renal allograft (63F): Pre-treatment: • Proliferative C3G with positive glomerular C5b-9 • Creatinine rise Post-treatment (>32 months): • Reduction in glomerular inflammation and C5b-9 deposition • Fall in creatinine Case - C3G in renal allograft (45M): Pre-treatment: • Proliferative C3G with positive glomerular C5b-9 • Creatinine rise and proteinuria Post-treatment (>32 months): • Reduction in glomerular inflammation and C5b-9 deposition • Fall in creatinine and proteinuria	Le Quintrec et al 2014	

Clinical Effectiveness and / or safety					
Level of Evidence	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
3	Design: Case report Intervention: eculizumab Dose: 900 mg once weekly for 4 weeks, then 900mg every two weeks increasing to 1200mg every two weeks Indication: refractory C3GN Treatment duration: 3 years C3G sub-type: C3G	Proteinuria Renal Biopsy Parameters	Reduction in proteinuria from 5.3 to 1.3 g/day Rise in proteinuria on treatment cessation to 9 g/day, dropping to 0.8 g/day on re-introduction of eculizumab Immunosuppressive therapy successfully withdrawn Post-treatment (nearly 3 years after eculizumab started) renal biopsy: • Reduction in mesangial proliferation and glomerular neutrophils • Marked reduction in glomerular C5b-9 • No change in glomerular C3 staining	Payette et al 2015	Plasma C3: LOW Plasma C5b-9: HIGH C3 nephritic factor: POSITIVE C5b-9 glomerular deposits: POSITIVE
3	Design: Case report Intervention: eculizumab Dose: 900 mg once weekly for 4 weeks, then 900mg every two weeks increasing to every three weeks Indication: refractory C3GN with poor response to plasma exchange Treatment duration: 10 months C3G sub-type: C3G	Proteinuria eGFR	Reduction in proteinuria Increase in eGFR	Haffner et al 2015	Plasma C3: LOW Plasma C5b-9: HIGH C3 nephritic factor: POSITIVE

Clinical Effectiveness and / or safety					
Level of Evidence	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
3	Design: Case report Intervention: eculizumab Dose: not stated Indication: dialysis-dependent acute crescentic C3GN Treatment duration: ongoing C3G sub-type: C3G	Need for dialysis	Acute presentation with renal failure due to C3GN; dialysis instigated 4 days after clinical presentation Dialysis-independent 5 months after starting eculizumab	Inman et al 2015	Plasma C3: normal Plasma C5b-9: HIGH

3	Design: Open labeled non-controlled case series
	
	Intervention: eculizumab
	
	Indication: refractory DDD
	
	Treatment duration: ongoing in 4 cases
		Proteinuria
		eGFR
			Patient 1 (13yr F):
			• Plasma C5b-9 mildly elevated
			• Renal failure, nephrotic syndrome
			• Renal biopsy: diffuse global MPGN; interstitial inflammation
			• Outcome:
			  ○ Improvement in renal function and proteinuria
			
			Patient 2 (5.9yr M):
			• C3 nephritic factor: POSITIVE
			• Plasma C5b-9 elevated during second episode
			• Dialysis-dependent (episode 1); nephrotic syndrome (episode 2)
			• Renal biopsy: Crescentic GN; extensive interstitial inflammation (episode 1); MPGN (episode 2)
			• Outcome:
			  ○ Dialysis-independent (episode 1); resolution of nephrotic syndrome (episode 2)
				Oosteveld et al 2015	Response seen in all cases (n=7 treatment episodes)
					
					Response seen within 12 weeks of treatment initiation: two individuals became dialysis-independent
					
					Response did NOT correlate with level of a serum marker of C5 activation (plasma C5b-9 levels)

3	Design: Open labeled non-controlled case series
	
	Intervention: eculizumab
	
	Indication: refractory DDD
	
	Treatment duration: ongoing in 4 cases; at least 3 month treatment in all
		Proteinuria
		eGFR
			Patient 3 (8.4yr F):
			• Plasma C5b-9 normal
			• Renal failure, nephrotic syndrome
			• Renal biopsy: MPGN
			• Outcome:
			  ○ Resolution of nephrotic syndrome
			
			Patient 4 (6.4yr F):
			• C3 nephritic factor: POSITIVE
			• Plasma C5b-9 normal during first episode
			• Dialysis-dependent (episode 1); nephrotic syndrome (episode 2)
			• Renal biopsy: Crescentic GN; interstitial inflammation (episode 1)
			• Outcome:
			  ○ Dialysis-independent (episode 1); non-nephrotic proteinuria (episode 2)
			
			Patient 5 (11.8yr M):
			• Plasma C5b-9 elevated
			• Nephrotic syndrome
			• Renal biopsy: MPGN
			• Outcome:
			  ○ Resolution of nephrotic syndrome
				Oosteveld et al 2015	Response seen in all cases: 7 treatment episodes in 5 patients
					
					Response seen within 12 weeks of treatment initiation: two individuals became dialysis-independent
					
					Response did NOT correlate with level of a serum marker of C5 activation (plasma C5b-9 levels)
					
					Renal biopsy demonstrated glomerular C5b-9 in all cases which co-localised with C3

Table 4

Cost-effectiveness					
Level of Evidence	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
	No studies identified				

5. Summary of Evidence

- There is no controlled clinical trial data on the use of eculizumab in C3G.
- Eculizumab is not licensed for the treatment of C3G.
- With the exception of one open label uncontrolled trial, the literature consisted of case reports.
- Case reports and series of the use of eculizumab in C3G include its use in *de novo* disease and in recurrent disease in the renal transplant.
- These are all Scottish Intercollegiate Guideline Network (SIGN) levels of evidence grade 3 (non-analytical studies).
- From the published data, a therapeutic response to eculizumab in both native and allograft refractory disease is most often reported when there is evidence of glomerular inflammation, particularly crescentic disease with renal impairment.

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