NHS England

Clinical Commissioning Policy Proposition: A06X03 Eculizumab in the treatment of recurrence of C3 glomerulopathy post-kidney transplant – All Ages

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Contents

1 Executive Summary

Policy Statement

NHS England will commission eculizumab for the treatment of recurrence of C3 glomerulopathy post-kidney transplant in accordance with the criteria outlined in this document.

In creating this policy NHS England has reviewed the literature and options for treatment. It has considered the place of eculizumab in current clinical practice and whether its use represents the best use of NHS resources.

This policy document outlines the arrangements for the commissioning and funding of eculizumab for the population in England.

Equality Statement

NHS England has a duty to have regard to the need to reduce health inequalities in access to health services and health outcomes achieved as enshrined in the Health and Social Care Act 2012. NHS England is committed to fulfilling this duty as to equality of access and to avoiding unlawful discrimination on the grounds of age, gender, disability (including learning disability), gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, gender or sexual orientation. In carrying out its functions, NHS England will have due regard to the different needs of protected equality groups, in line with the Equality Act 2010. This document is compliant with the NHS Constitution and the Human Rights Act 1998. This applies to all activities for which NHS England is responsible, including policy development, review and implementation.

Plain Language Summary

C3 glomerulopathy is a type of glomerulonephritis in which dysregulation of the alternative pathway of the complement system (a component of the immune system) results in abnormal accumulation of the complement protein C3 within the kidney. C3 glomerulopathy includes C3 glomerulonephritis (C3GN) and dense deposit disease (DDD). The incidence of C3 glomerulopathy is 1–2 per million population per year. Renal prognosis is poor, with a 30% risk of end stage renal disease at two years. With some exceptions, the risk of recurrence in the transplanted kidney is over 70%, with more than a 50% chance of graft loss.

The optimal management of people with C3 glomerulopathy (affecting their own and/or a transplanted kidney) is uncertain because existing therapies have not been tested in robust clinical trials. This is most likely due to the inherent difficulties in performing randomised controlled trials in rare disease. In people who have not had a kidney transplant, immunomodulatory agents such as glucocorticoids, mycophenolate mofetil, cyclosporine,

tacrolimus and cyclophosphamide have been used. However, evidence for the efficacy of such agents is limited and none are considered to represent definitive therapy. Other proposed treatments include plasma exchange, rituximab (with or without plasma exchange) and eculizumab.

2 Introduction

This document describes the evidence that has been considered by NHS England in formulating a proposal to routinely commission Eculizumab for the treatment of recurrence of C3 glomerulopathy. This document also describes the proposed criteria for commissioning, proposed governance arrangements and proposed funding mechanisms.

For the purpose of consultation NHS England invites views on the evidence and other information that has been taken into account as described in this policy proposition.

A final decision as to whether Eculizumab for the treatment of recurrence of C3 glomerulopathy will be routinely commissioned is planned to be made by NHS England by June 2016 following a recommendation from the Clinical Priorities Advisory Group.

3 Proposed Intervention and Clinical Indication

Eculizumab (Soliris, Alexion Pharma UK) is a recombinant humanised monoclonal antibody that binds to complement protein C5, inhibiting its cleavage to C5a (a proinflammatory anaphylatoxin) and C5b and preventing the generation of the terminal complement complex C5b-9 (membrane attack complex), which causes cell lysis and death in pathogens.

Eculizumab has a marketing authorisation in the UK for treating adults and children with atypical haemolytic uraemic syndrome (aHUS) or paroxysmal nocturnal haemoglobinuria (PNH) (summary of product characteristics for Soliris[1]).

Like C3 glomerulopathy, aHUS and PNH are complement-mediated diseases, which stimulated interest in using eculizumab to treat this condition.

Use of eculizumab to treat people with C3 glomerulopathy, or to treat recurrence of the condition in a transplanted kidney, is outside the approved indications.

4 Definitions

C3 glomerulopathy (C3G) is a renal disease due to abnormal control of complement activation, deposition, or degradation and characterized histologically by predominant glomerular complement C3 deposition and electron-dense deposits [Pickering et al, 2013]. It is identified on renal biopsy by the finding of complement C3 that is at least two orders of magnitude more intense than any other immune reactant [Hou et al, 2014]. C3G includes the sub-types dense deposit disease (DDD) and C3 gomerulonephritis (C3GN).

5 Aims and Objectives

This policy proposition considered treatment with eculizumab for those patients (both adults and children) with C3 glomerulopathy who experience recurrent disease post renal transplant.

The objectives were to consider where there is the risk of the rapid (within months) loss of a transplanted kidney to highly aggressive recurrent disease.

6 Epidemiology and Needs Assessment

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 glomerular filtration rate (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 end-stage renal disease (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 were 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). End-stage renal failure (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). Ten 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.

7 Evidence Base

NHS England has concluded that there is sufficient evidence to support a proposal for the routine commissioning of this treatment for the indication

Refractory C3G refers to declining renal function that is unresponsive to typical immunosuppressive modalities utilised to treat glomerulonephritis. 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.

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].

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). Table 1 summarises the reported literature. 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. With the exception of one open label uncontrolled trial, these consist of case reports. There is no controlled clinical trial data on the use of eculizumab in C3G and it is not licensed for the treatment of C3G.

The recommendations are derived from evidence defined as SIGN level Grade D.

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.

Table 1

Evidence Type/SIGN grade/Reference	Diagnosis (age/sex)	Indication	Treatment duration (months)	Clinical Response	Comments
Case report SIGN grade 3 Daina et al 2012	DDD (22F)	Creatinine rise and proteinuria	11	Yes	Proteinuria fell to non-nephrotic range
Case report SIGN grade 3 Vivarelli et al 2012	DDD (17/M)	Proteinuria	18 + 9	Yes	Glomerular sclerosis and tubular atrophy developed despite reduction in glomerular C5b-9 Reduction in proteinuria Rise in proteinuria on treatment cessation which improved on treatment re-commencement
Case report SIGN grade 3 McCaughan et al 2012	DDD in renal allograft (29F)	Creatinine rise and proteinuria	2.5	Yes	Crescentic DDD
Open labelled non-controlled case series SIGN grade 3 Bomback et al 2012	DDD (22M)	Creatinine rise	12	Yes	rise in serum creatinine rise on treatment cessation
	DDD (42M)	Creatinine rise and proteinuria	9	No	No
	DDD in renal allograft (32M)	Creatinine rise and proteinuria	12	Yes	fall in proteinuria
	C3GN (25M)	Creatinine rise and proteinuria	12	No	No
	C3GN in renal allograft (22M)	Creatinine rise and proteinuria	12	No	Patient developed a post-trial period rise in creatinine associated with crescentic C3GN improved on combination of plasma exchange, pulse steroids and re-commencement of eculizumab
	C3GN in renal allograft (20M)	Creatinine rise	12	Yes	Yes
Case report SIGN grade 3 Gurkan et al	C3GN in renal allograft	Creatinine rise and proteinuria	12	Partial response	Primary renal diagnosis of DDD Allograft biopsy 6 and

2013	(21M)				12 month post-treatment initiation showed disease progression
Case report SIGN grade 3 Besbas et al 2013	C3GN (16F)	Proteinuria	10	No	C3GN with membranoproliferative changes
Case report SIGN grade 3 Kerns et al 2013	C3GN (16M)	Proteinuria	3.5	Yes	Reduction in proteinuria
Case report SIGN grade 3 Rousset-Rouviere et al 2014	DDD (8F)	Creatinine rise and proteinuria	6	Yes	Crescentic DDD with positive glomerular C5b-9 Normalisation of both creatinine and proteinuria
Case report SIGN grade 3 Ozkaya et al 2014	DDD (14F)	Proteinuria	8	Yes	Crescentic DDD Normalisation of proteinuria
Case report SIGN grade 3 Berthe-Aucejo et al 2014	DDD (17M)	Proteinuria	4	No	
Case report SIGN grade 3 Sanchez-Moreno et al 2014	DDD in renal allograft (14f)	Proteinuria	30	Yes	Normalisation of proteinuria No histological progression on renal biopsy 6 months after treatment onset
Case series SIGN grade 3 Le Quintec et al 2015	C3G (27F)	Creatinine rise and proteinuria	ongoing	Yes	Proliferative C3G with positive glomerular C5b-9 Reduction in glomerular inflammation and C5b-9 on treatment Normalisation of proteinuria
	C3G in renal allograft (63F)	Creatinine rise	ongoing	Yes	Proliferative C3G with positive glomerular C5b-9 Reduction in glomerular inflammation and C5b-9 on treatment
	C3G (45M)	Creatinine rise and proteinuria	ongoing	Yes	Proliferative C3G with positive glomerular C5b-9 Reduction in glomerular

					inflammation and C5b-9 on treatment Partial reduction in proteinuria
Case report SIGN grade 3 Payette et al 2015	C3GN (5M)	Proteinuria	19	Yes	Endocapillary proliferation Reduction in proteinuria Rise in proteinuria on treatment cessation which improved on treatment re-commencement
Case report SIGN grade 3 Haffner et al 2015	C3GN (15F)	Proteinuria	10	Yes	Partial reduction in proteinuria
Case report SIGN grade 3 Inman et al 2015	C3GN (38F)	Dialysis-dependent	ongoing	Yes	Crescentic C3GN Dialysis-independent on treatment
Case series SIGN grade 3 Oosteveld et al 2015	DDD 5 cases (1.9M, 6.4F, 6.9F, 5.8M, 12.9F)	Creatinine rise and proteinuria	ongoing in n=4 cases	Yes	Response seen in all cases which included 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 (soluble C5b-9 levels)

8 Proposed Criteria for Commissioning

NHS England will commission eculizumab for the treatment of recurrence of C3 glomerulopathy post-kidney transplant in accordance with the criteria outlined in this document. The aim of this commissioning policy is to prevent the rapid (within months) loss of a transplanted kidney to highly aggressive recurrent disease.

NHS England will not routinely commission eculizumab for the treatment of low grade recurrent disease.

In creating this policy NHS England has reviewed the literature and options for treatment including the NICE Evidence Review "ESUOM44, *Prevention of recurrence of C3 glomerulopathy post-transplant: eculizumab,* June 2015". It has considered the place of eculizumab in current clinical practice.

This policy document outlines the proposed arrangements for the commissioning and funding of eculizumab for the population in England.

Starting criteria

NHS England will commission eculizumab for the treatment of recurrent disease post-transplant in patients with C3 glomerulopathy **only if all** the following clinical criteria are met:

a. A primary renal diagnosis of C3 glomerulopathy confirmed by renal biopsy including light microscopy, immunofluorescence and electron microscopy.
b. Recurrent disease characterised on biopsy by an active glomerulonephritis with cellular crescents. Histopathology will be reviewed by a single centre with expertise in the pathology of C3 glomerulopathy.
c. Evidence of glomerular C9 deposition on transplant biopsy.
d. Recurrent disease occurring at any time post-transplant.
e. Evidence at the time of recurrence of a significant decline of transplant function (>20% decline in eGFR) within the previous three months. This criterion will not be necessary if the recurrence occurs immediately after transplantation when transplant function has not yet been established.
f. No other cause for the decline in transplant function can be identified.

Figures provided by NHSBT show that in the past ten years 39 patients with DDD have been transplanted. In the same period, three patients with DDD have lost their transplant to recurrent disease. There are a total of 59 patients in the UK with a functioning kidney transplant whose primary renal disease is said to be DDD and there are currently six patients on the active transplant waiting list. From the available published information, we estimate that 70% of patients will develop recurrent disease at some stage and that a maximum of 50% of patients with recurrent disease will meet the above criteria. Whilst the information available from NHSBT may be subject to underreporting it is estimated that **fewer than five patients per year will meet all the above criteria**.

If all the criteria are met, eculizumab should be started using the same dose as recommended for the treatment of atypical haemolytic uraemic syndrome (at www.rarerenal.org).

Stopping criteria

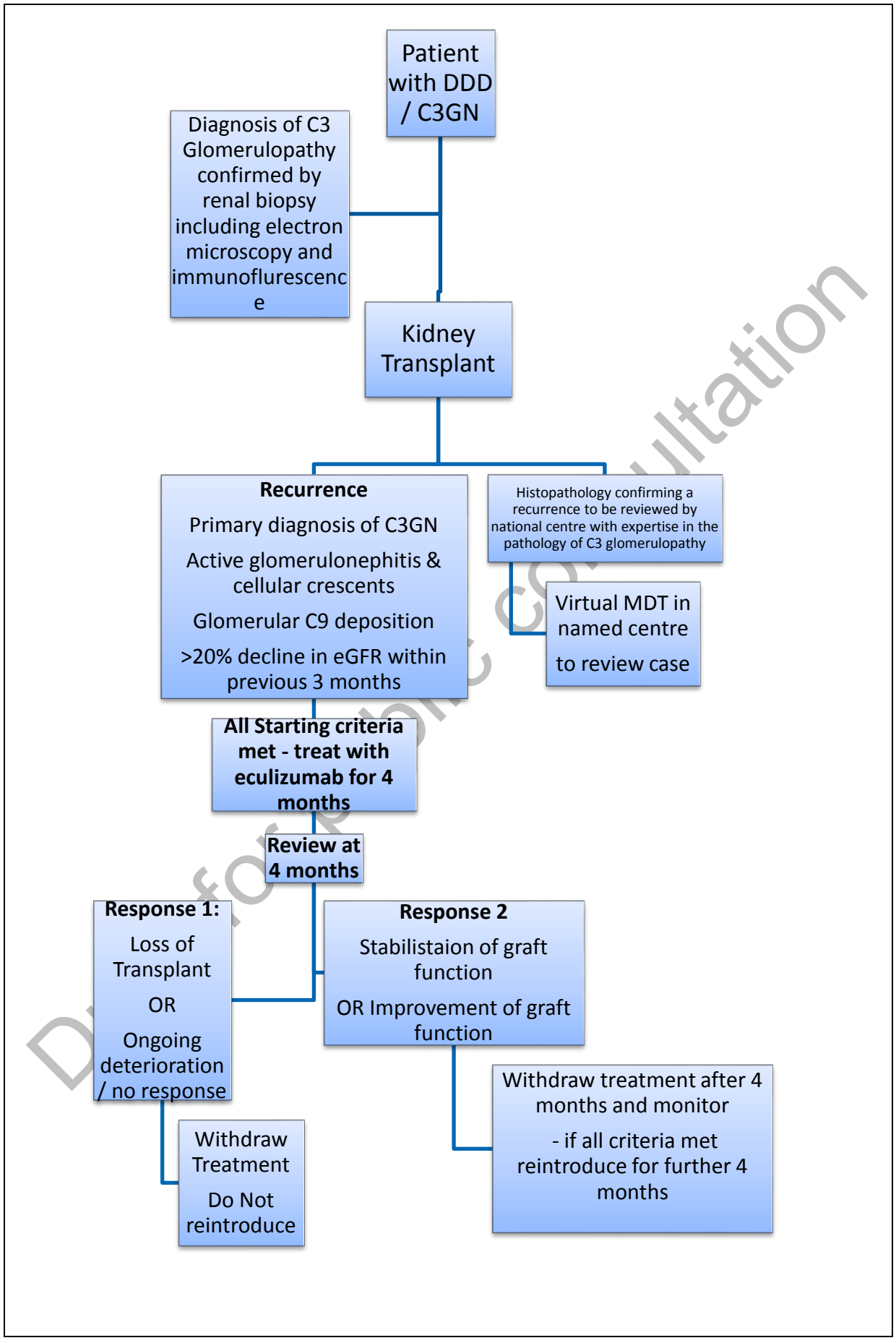
Treatment should be continued for four months. The possible outcomes at or before this time are:

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. Again, there should be no other identifiable cause for the decline in transplant function.

9 Proposed Patient Pathway

It is proposed that decisions about the commencement, monitoring and stopping of treatment will be made in conjunction with the national named expert reference centre MDT. Ongoing care should continue to be provided locally but with co-ordination through the virtual MDT to reach a decision with the national named expert centre.



10 Proposed Governance Arrangements

Access to treatment will be decided at a national MDT supported by a national named expert centre but will be delivered locally to patients.

Potential cases require a multidisciplinary assessment via a 'virtual MDT' with the named expert reference centre. Histopathology confirming a diagnosis of recurrence is required and would be reviewed by a single centre with expertise in the pathology of C3 glomerulopathy. Clinicians will be required to provide all relevant information.

The Highly Specialised Services Team and Renal CRG Chair should be informed of each case.

Due to the uncertainty about the evidence base the policy will be in force for 3 years from publication to support data collection and review of efficacy, unless superseded by other NHS England policy.

11 Proposed Mechanism for Funding

NHS England will be responsible for commissioning eculizumab in line with this policy on behalf of the population of England. The drug will be funded through local specialised commissioning teams. A proposed commercial in confidence agreement is under discussion.

12 Proposed Audit Requirements

A register of all cases to include clinical details and outcomes will be developed and held by the expert centre. Clinicians will be required to record both short and long term outcomes of individuals with recurrent C3 glomerulopathy post-kidney transplant treated with eculizumab.

The dataset will be agreed by NHS England and will be mandatory for providers to complete.

13 Documents That Have Informed This Policy Proposition

ESUOM44, *Prevention of recurrence of C3 glomerulopathy post-transplant: eculizumab,* June 2015 NICE

14 Date of Review

This document will lapse upon publication by NHS England of a clinical commissioning policy for the proposed intervention that confirms whether it is routinely or non-routinely commissioned. If approved the Policy will be in force for 3 years post publication unless superseded by other NHS England policy.

Glossary

aHUS - atypical haemolytic uraemic syndrome

C3 - complement component 3

C3G - C3 glomerulopathy

C3GN - C3 gomerulonephritis

C5 - complement component 5

C9 - complement component 9

CFHR5 - complement factor H-related 5

DDD - dense deposit disease

eGFR - estimated glomerular filtration rate

ESRD - end-stage renal disease

ESRF - end-stage renal failure

GFR - glomerular filtration rate

IFR – individual funding request

MDT - multi-disciplinary team

NHSBT - NHS blood and transplant

PNH - paroxysmal nocturnal haemoglobinuria

SIGN - Scottish Intercollegiate Guideline Network

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Version Control Sheet

Version	Section/Para/Appendix	Version/Description of Amendments	Date	Author/Amended by
1	Whole document	Various	21/09/15	Working Group
2	Whole document	Starting and stopping criteria	06/10/15	Working Group
3	Whole document	Re-formatting	31/10/15	AJR
4	Pathway	Clarified stopping criteria	20/01/16	UP
5	Review	Clarified review date	20/01/16	UP
6	Whole document	Post Engagement	17/02/16	JG
7	Whole document	Post CPAG	05/03/16	UP
8	S.7 and S.11	Post CET comment	15/03/16	UP

END