



Clinical Commissioning Policy: Eculizumab for the treatment of refractory antibody mediated rejection post kidney transplant

Reference: NHS England A07/P/b

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Additional Circulation List	Regional Medical Directors; Regional Directors of Specialised Commissioning; Regional Clinical Directors of Specialised Commissioning; Regional Directors of Nursing
Description	NHS England has adopted a policy to not routinely commission this specialised treatment as described in this document.
Cross Reference	
Superseded Docs (if applicable)	
Action Required	
Timing / Deadlines (if applicable)	
Contact Details for further information	jeremyglyde@nhs.net for policy issues

Document Status

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1 Executive Summary

Policy Statement

NHS England does not routinely commission Eculizumab for the treatment of refractory antibody mediated rejection post kidney transplant.

In creating this policy NHS England has reviewed this clinical condition and the options for its treatment. It has considered the place of this treatment in current clinical practice, whether scientific research has shown the treatment to be of benefit to patients, (including how any benefit is balanced against possible risks) and whether its use represents the best use of NHS resources.

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

Eculizumab is a drug, which is licensed for some indications, that kidney transplant doctors have thought might work to help treat some types of rejection that might occur after a patient receives a kidney transplant. A review of the published evidence from research has failed to find good evidence that the possible benefits

from using Eculizumab outweigh any problems such as side effects for the patient from the drug. Also, the research papers differ in the suggested dose for Eculizumab. This policy states that NHS England will not currently fund this drug for these reasons. If better evidence becomes available then this policy can be reviewed.

2 Introduction

Antibody mediated rejection (AMR) is a challenge for the long term survival of grafts in kidney transplantation. It is an important cause of poorly functioning kidney grafts and of graft loss. AMR typically occurs early after transplantation in approximately 5% to 7% of patients receiving grafts. Reports suggest that from 12% to 37% of kidney transplant recipients with acute AMR do not respond to treatment and eventually lose their grafts.

The recipient's antibodies may react against a kidney graft and there are a number of existing treatments to try and counter this with varying degrees of evidence to support the presumed benefits over any risks. Early AMR, primarily occurring within the first month after transplantation, has emerged as the next major complication using the current protocols and treatment regimens. The use of the term refractory means that rejection has continued despite the use of the currently recognised treatments.

Some clinicians have started to use Eculizumab for the treatment of difficult episodes of kidney rejection and have requested that this drug is considered for routine commissioning and funding. However, Eculizumab does not have a license or marketing authorization for this clinical indication.

A review of the current literature in relation to the use of Eculizumab (a monoclonal antibody against C5) in the treatment of refractory AMR has been carried out. This review, and this policy, do not cover the use of eculizumab in the prevention of antibody mediated rejection in patients receiving transplants to which they have high levels of pre-formed HLA-specific antibodies.

3 Definitions

Renal transplant: the replacement of a patient's kidneys with a kidney from a donor when the patient's own kidneys have stopped working.

Antibody mediated rejection (AMR): After a kidney has been transplanted some patients experience episodes where the body tries to reject the new kidney as it recognizes that it is different. In some cases this happens through the creation of antibodies that act against the kidney. There are recognized treatments to try and suppress this reaction but they do not work in all cases, in which case the AMR is termed refractory.

Licensed indication for a pharmaceutical drug: When a drug has sufficiently good research then the company manufacturing it and holding the patent can apply to the appropriate national authority to be given permission to market the drug in line with certain detailed specifications, such as the dose, length of treatment and the types of patients eligible to receive the drug. If a drug is not authorized or licensed then it is considered that there are sufficient uncertainties such that the company cannot actively market it for use with patients.

Good clinical evidence: It is generally regarded that randomized controlled trials (RCTs) provide the best evidence for a treatment for patients and as to whether any benefits clearly outweigh any risks or problems. In the early stages of drug research clinicians may report their experience of using a drug with certain patients (often termed case series). These studies are regarded as preliminary studies for further more detailed research but on their own are subject to bias.

Systemic review: A review of all the clinical research evidence that can be found for a treatment. Systemic means that the review is carried out against certain specified criteria and research questions so that the quality of the available evidence is better understood.

4 Aims and Objectives

This policy aims to:

- Specify the clinical circumstances whereby NHS England will commission or not commission Eculizumab for the treatment of refractory AMR

The objectives are to:

- Clarify how the evidence and its quality determines the clinical commissioning position of NHS England for Eculizumab for the treatment of refractory AMR.

The specific questions that were addressed in the review of the research literature were on the clinical effectiveness, safety and cost effectiveness of Eculizumab and the review forms the basis for this policy statement.

5 Epidemiology and Needs Assessment

In the financial year 2013/14, 3,054 kidney only transplants were performed in the UK. The risk adjusted 5 year graft and patient survival following a deceased donor transplant are 85% and 89% respectively, and 91% and 95% for living donor transplants (NHS Blood and Transplant (NHSBT) Activity Report 2013/14).

Antibody-mediated rejection (AMR) typically occurs early after transplantation in approximately 5% to 7% of recipients. Literature reports suggest that 12% to 37% of kidney transplant recipients with acute AMR do not respond to treatment and eventually lose their grafts. Some of these patients are those who have been considered potential candidates for Eculizumab.

6 Evidence Base

NHS England concluded that there was not sufficient evidence to support the routine commissioning of this treatment for the indication. In the interests of transparency the evidence base that was described by the CRG is summarised below.

The evidence review found only one study meeting the inclusion criteria which was a well conducted systematic review (Roberts et al 2012, SIGN Level of Evidence 1++), which reported the evidence supporting the use of Eculizumab to be 'very low' i.e. limited to uncontrolled studies, including case series and

case reports. There is a paucity of randomized controlled trials. The small number of uncontrolled studies, case series and case reports published suggest that Eculizumab can be safely and effectively used as rescue therapy in AMR. However these results are based on short follow up duration and it is unclear how long treatment should continue, a particularly important issue given the expense of the drug. Some studies have used historical controls to compare the effectiveness of therapies. There is also bound to be some publication bias related to selective publication of positive studies. No cost-effectiveness studies were found.

In the setting of kidney transplantation, there is still very limited evidence suggesting Eculizumab is efficient in treating refractory antibody-mediated rejection. The results of existing clinical usage and of ongoing studies needs to be thoroughly evaluated and further high quality studies may need to be performed in order to determine the clinical efficacy, safety and cost-effectiveness of this very active but also very expensive drug before it can be recommended in current clinical practice.

7 Rationale behind the Policy Statement

The main conclusion of the evidence review was that the quality of evidence supporting the use of Eculizumab was reported to be 'very low', i.e. limited to uncontrolled studies, including case series and case reports. The dose and the length of treatment if it were to be used as a rescue treatment are not yet clarified by the evidence. The high cost of the drug was mentioned in reports. The uncertainty around the overall benefit means that it is difficult to evaluate the cost effectiveness and at this stage without evidence of benefit then its overall value would be broadly judged as poor.

8 Criteria for Commissioning

Eculizumab will not be funded for the treatment of refractory AMR through routine commissioning and therefore there are no criteria that can be defined which would merit the use of Eculizumab in this setting.

9 Patient Pathway

The existing patient pathway for a patient receiving a renal transplant is described in Section 2.2 of the NHS England Service Specification for Renal Transplant, no: Ao7/S/a, available on the NHS England website.

10 Governance Arrangements

Not applicable.

11 Mechanism for Funding

This commissioning policy specifies that funding is not available for the use of Eculizumab.

12 Audit Requirements

Audit is not needed as this commissioning policy currently specifies that funding is not available for the use of Eculizumab.

13 Documents which have informed this Policy

Evidence review undertaken by NHS England.

14 Links to other Policies

This policy follows the principles set out in the ethical framework that govern the commissioning of NHS healthcare and those policies dealing with the approach to experimental treatments and processes for the management of individual funding requests (IFR).

15 Date of Review

This policy will be reviewed in April 2017 unless information is received which indicates that the proposed review date should be brought forward or delayed.

References

1. NHS England. October 2013. Evidence Review: Eculizumab and Bortezomib for the treatment of refractory antibody mediated rejection post kidney transplant. Reference: NHS England/ A07/P/a.
2. Roberts DM, Jiang SH, Chadban SJ. The treatment of acute antibody-mediated rejection in kidney transplant recipients-a systematic review. *Transplantation*. 2012 Oct 27;94(8):775-83.