Clinical Commissioning Policy: Bortezomib for the Treatment of Refractory Antibody Mediated Rejection Post Kidney Transplant

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

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Policy Statement

NHS England will not routinely commission Bortezomib for the treatment of refractory antibody mediated rejection post kidney transplant in accordance with the criteria outlined in this document.

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.

This policy document outlines the arrangements for funding of this treatment for the population in England.

Equality Statement

Throughout the production of this document, due regard has been given to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited in under the Equality Act 2010) and those who do not share it.

Plain Language Summary

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

Bortezomib is a drug, which is licensed for some indications, that kidney transplant doctors have thought might work to help prevent 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 Bortezomib outweigh any problems such as side effects. If we are unsure about how well it works then its value is also uncertain. 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.

1. 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 grafts and of graft loss. AMR typically occurs early after transplantation in approximately 5%–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 Bortezomib for the treatment of difficult episodes of kidney rejection and have requested that this drug is considered for routine commissioning and funding. However, Bortezomib does not have a license or marketing authorization for this clinical indication.

A review of the current literature in relation to the use of Bortezomib (a therapeutic proteasome inhibitor) in the treatment of refractory AMR has been carried out.

2. 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 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 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 with 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.

3. Aim and objectives

This policy aims to:

- Specify the clinical circumstances whereby NHS England will commission or not commission Bortezomib for AMR.

The objectives are to:

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

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

4. Epidemiology and needs assessment

In the financial year 2012/13, 2998 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 88% respectively, and 91% and 96% for living donor transplants (NHS Blood and Transplant (NHSBT) Activity Report 2012/13).

Antibody-mediated rejection (AMR) typically occurs early after transplantation in approximately 5%–7% of recipients. Literature reports suggest that 12%–37% of kidney transplant recipients with acute AMR do not respond to treatment and eventually lose their grafts. These are the patients who potentially are the most likely candidates for Bortezomib.

5. Evidence base

Three studies were found meeting the inclusion criteria of the evidence review. One systematic review (Roberts et al 2012), one controlled trial (Waiser et al. 2012) and one case series (Nigos et al. 2012). No cost-effectiveness studies were found.

- The systematic review by Roberts et al. (with SIGN Level of Evidence 1++) concluded that the evidence supporting the use of Bortezomib is 'very low'. The review included 2 small, non-randomized controlled studies which suggested benefit from Bortezomib (Macaluso et al. 2011, Waiser et al. 2010. However, these were considered to be of low quality. Furthermore, the effects of dose and regimen on the clinical response were not apparent from the available data.

- The small case series by Nigos et al (2012) (with SIGN Level of Evidence 3) which included 6 patients had a short follow up (mean of 14 months) of which 2 did not respond to treatment. The 4 other patients has stable kidney function.

- A small non randomised trial by Waiser et al (2012) (with SIGN Level of Evidence 2-), assessed clinical effectiveness of Bortezomib (n=10) Vs historical controls (n=9) treated with rituximab. The Bortezomib regimen used was not sufficient to treat all episodes of AMR effectively (only 60% graft survival) however significantly better than the rituximab group (11% graft survival). A potential bias of the study is that it included a less aggressive immunosuppressive treatment regimen than most other studies, which included higher doses of rituximab, higher doses of IVIG, more PPH sessions, the addition of T cell-depleting antibodies and even splenectomy, which could be a reason why graft survival was small in control group.

Overall, the currently available evidence supporting the use of Bortezomib in patients with refractory AMR is limited following kidney transplantation. Further good quality studies are needed to establish its clinical efficacy, safety profile and cost-effectiveness.

6. Rationale behind the policy statement

The main conclusion of the evidence review was that the quality of evidence supporting the use of Bortezomib was reported to be 'very low', i.e. limited to uncontrolled studies, including case series and case 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.

7. Criteria for commissioning

Bortezomib will not be funded for AMR through routine commissioning and therefore there are no criteria that can be defined which would merit the use of Bortezomib.

8. 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 from the Specialised Services Resource section of the NHS England website and on the webpage relating to the Renal Transplant Clinic Reference Group (CRG).

9. Governance arrangements

The existing NHS England Service Specification for Renal Transplant, no. Ao7/S/a is available from the Specialised Services Resource section of the NHS England website and on the webpage relating to the Renal Transplant Clinic Reference Group. Specific governance arrangements are not appropriate for Bortezomib as this commissioning policy currently specifies that funding is not available for the use of Bortezomib.

10. Mechanism for funding

This commissioning policy currently specifies that funding is not available for the use of Bortezomib. If patients are considered to be exceptional then they can apply via the individual funding request process of NHS England.

11. Audit requirements

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

12. Documents which have informed this policy

Evidence review undertaken by NHS England.

13. 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).

14. Date of review

This policy will be reviewed in April 2016 unless information is received which indicates that the proposed review date should be brought forward or delayed.

References

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