NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Eculizumab for the treatment of atypical haemolytic uraemic syndrome (aHUS)

Thank you for agreeing to give us your views on the condition, the technology and the way it should be used in the NHS.

Patients, carers and patient organisations can provide a unique perspective on the condition and the technology, which is not typically available from the published literature.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Where appropriate, please provide case studies of individual patients, their families or carers. Please do not exceed 30 pages.

About you

Your name: [redacted]

Name of your organisation: Kidney Research UK

Brief description of the organisation:
Kidney Research UK is the leading national charity funding research to save lives from kidney disease and kidney related illnesses. This cutting-edge research has always focused on the causes, prevention and treatment of kidney disease. The charity also dedicates its work to providing health information and raising awareness of kidney disease.

Our mission is to fund life-saving research into kidney disease, to improve the quality of life of those with kidney disorders and to increase public awareness of kidney health.

Our three main aims are:
Funding and supporting research - improving the understanding of kidney disease, its causes, prevention and treatment.
Providing kidney-related health information
Raising awareness of kidney disease - informing and updating people interested in learning more about kidney disease and the needs of those affected.

Our vision is a world free from kidney disease.

Are you (tick all that apply):

- a patient with the condition for which NICE is considering this technology?
- a carer of a patient with the condition for which NICE is considering this technology?
- an employee of a patient organisation that represents patients with the condition for which NICE is considering the technology? If so, give your position in the organisation where appropriate (e.g. policy officer, trustee, member, etc)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Eculizumab for the treatment of atypical haemolytic uraemic syndrome (aHUS)

- *I am a Kidney Research UK-funded research professional who investigates atypical haemolytic uraemic syndrome, nominated to comment on this issue on behalf of the charity.*

- other? (please specify)

How does the condition impact on patients, their families or carers?

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Eculizumab for the treatment of atypical haemolytic uraemic syndrome (aHUS)

1(i). Please describe whether patients experience difficulties or delays in receiving:
- a diagnosis
- appropriate treatment
- helpful information about the condition

and the impact these difficulties have on patients and their families or carers.

Delays / Difficulties in diagnosis

Atypical HUS is a rare disease (incidence $2/10^6$) and as with any rare disease diagnosis would generally be made by a specialist physician. Simple blood tests (full blood count and urea and electrolytes), however, would reveal abnormalities that should prompt rapid referral from the GP to a specialist service.

Further investigation would thereafter rule out the other differential diagnosis. The main differential diagnosis is Shiga Toxin associated HUS. Stool culture Serology and PCR would eliminate this as a cause. Another key differential is TTP which must be eliminated by ADAMTS13 activity assays. Other differentials include SLE, Scleroderma, Cobalamin C and HIV which can be eliminated by simple blood tests.

Thereafter genetic analysis for complement genes should be performed to aid prognosis and management and provide counselling to family members.

In cases where the individual presented late in the course of disease when the disease is “burnt out” and the kidneys are small and scarred, a diagnosis may not be possible at first presentation. It may only become apparent in this situation when the individual is transplanted and has recurrent aHUS.

Appropriate treatment

It is universally recognised that Eculizumab is the gold standard for treatment for aHUS. Currently there is only a temporary arrangement for treatment of aHUS with Eculizumab in England. If Eculizumab is not funded in the long term then patients in the UK will be receiving an inferior treatment to patients in the rest of the developed World.

Prior to its introduction, treatment consisted of plasma exchange with the difficulties of vascular access in young children and the risk of line related infections. Long term plasma exchange exposed the patient to these ongoing risks. Over time it frequently became impossible to treat patients with plasma exchange due to allergic responses to plasma. In the long term many patients developed ESRD. Eculizumab overcomes these difficulties

In patients who presented too late for plasma exchange or in those in whom plasma exchange failed, renal transplantation was usually unsuccessful due to recurrent disease . This resulted in a lifetime on dialysis for these patients. Eculizumab has the potential to allow successful renal transplantation in these patients.

Impact on patients and their families or carers

Plasma exchange was the only available treatment for patients with aHUS. This necessitated hospital visits 3 times / week for 4 hours. As plasma exchange is a specialist service this usually necessitated travel to a regional centre. This causes

great difficulty for the patient and careers.

Plasma exchange requires long term vascular access with the associated infection risk which is an additional burden to patients

Patients are aware that the plasma exchange will eventually fail leading to long term dialysis. A renal transplantation in aHUS usually failed due to recurrent disease with associated morbidity and mortality. The patients were therefore aware that they faced a lifetime on dialysis with no hope of a transplant. They are aware that their life expectancy is shorter if they stay on dialysis rather than receiving a renal transplant.

Eculizumab treatment requires an injection every 2 weeks which can be performed in the patient's house. This is minimally intrusive allowing the patient to lead a normal life. It an also be given to individuals with aHUS already on dialysis who require a transplant. As such these patients now have the hope of receiving a transplant and having a normal life.

(ii) Please describe how patients and their families or carers have to adapt their lives as a result of the condition, and the impact the condition has on the following aspects:

- physical health
- emotional wellbeing
- everyday life (including if applicable: ability to work, schooling, relationships, social functioning)
- other impacts not listed above

Prior to the availability of Eculizumab, patients with aHUS faced the prospect of a life time on either plasma exchange (until the kidney eventually failed) or dialysis. They could not receive a kidney transplant as the disease would come back with potentially life threatening consequences.

Emotionally it is very difficult for a patient and their families to know that the rest of their life will amount to three times a week trips to hospital for plasma exchange or dialysis with no hope or a renal transplant.

Such highly intense hospital treatment makes normal schooling or work impossible for the patient and careers.

Physical Health will be much improved over a lifetime on dialysis if patients can have normal renal function (either by saving the native kidneys or allowing a renal transplant) with Eculizumab treatment

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Highly Specialised Technology Evaluation

Eculizumab for the treatment of atypical haemolytic uraemic syndrome (aHUS)

What do patients, their families or carers consider to be the advantages and disadvantages of the technology for the condition?

2. Advantages

(i) Please list the specific aspect(s) of the condition that you expect the technology to help with. For each aspect you list please describe, if possible, what difference you expect the technology to make for patients, their families or carers.

Eculizumab is more efficacious in treating aHUS and keeping patients off dialysis.

It allows patients on dialysis to receive a kidney transplant.

Treatment will allow a normal life with a return to normal schooling or work

It will mean that 3 times a week trips to hospital for 4 hours (not including transport time) will come to an end. Eculizumab is a short injection every 2 weeks which can be done at home

Patients will be healthier and, by extrapolating outcome data on dialysis patients, have a longer life expectancy.

(ii) Please list any short-term and long-term benefits that patients, their families or carers expect to gain from using the technology. These might include the effect of the technology on:

- the course and outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (lifestyle, work, social functioning etc.)
- other quality of life issues not listed above
- other people (for example friends and employers)
- other issues not listed above

Treatment of patients with Eculizumab is undoubtedly a step change in the management of aHUS.

Prior to its introduction, treatment consisted of plasma exchange with the difficulties of vascular access in young children and the risk of line related infections. Long term plasma exchange exposed the patient to these ongoing risks. Over time it frequently became impossible to treat patients with plasma exchange due to allergic responses to plasma. In the long term many patients developed ESRD. Eculizumab overcomes these difficulties

In patients who presented too late for plasma exchange or in those in whom plasma exchange failed, renal transplantation was usually unsuccessful due to recurrent disease . This resulted in a lifetime on dialysis for these patients.

Eculizumab has the potential to allow successful renal transplantation in these patients.

It is clearly demonstrated in the seminal Lemaire et al paper that not only is Eculizumab effective, it also significantly improves patients' quality of life. It will allow them to lead a normal life.

3. Disadvantages

Please list any problems with or concerns you have about the technology.

Disadvantages might include:

- aspects of the condition that the technology cannot help with or might make worse
- difficulties in taking or using the technology
- side effects (please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- impact on others (for example family, friends, employers)
- financial impact on the patient or their family (for example cost of travel needed to access the technology, or the cost of paying a carer)

A terminal pathway complement inhibitor will predispose to infections with encapsulated organisms. Vaccination and prophylactic antibiotics reduce the risk of this.

4. Are there differences in opinion between patients about the usefulness or otherwise of this technology? If so, please describe them.

None in my experience

5. Are there any groups of patients who might benefit **more** from the technology than others? Are there any groups of patients who might benefit **less** from the technology than others?

In a study in PNH a single nucleotide polymorphism in the gene encoding C5 has been reported in 2% of the Japanese population which results in treatment failure with eculizumab. Likewise in an aHUS patient with a mutation in the non-complement protein, DGKε, Eculizumab did not stop disease . Genetic screening therefore must be undertaken in all patients. If either of these variants were to be detected then there would be no rationale for Eculizumab therapy and it could be discontinued.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Eculizumab for the treatment of atypical haemolytic uraemic syndrome (aHUS)

6. Comparing the technology with alternative available treatments or technologies

NICE is interested in your views on how the technology compares with existing treatments for this condition in the UK.

(i) Please list current standard practice (alternatives if any) used in the UK.

Prior to Eculizumab standard treatment for aHUS would have been

a) Plasma infusion / Plasma Exchange

b) Long term renal replacement therapy

c) Isolate renal transplantation

d) Combined kidney-liver transplantation (high mortality)

(ii) If you think that the new technology has any **advantages** for patients over other current standard practice, please describe them. Advantages might include:
- improvement of the condition overall
- improvement in certain aspects of the condition
- ease of use (for example tablets rather than injection)
- where the technology has to be used (for example at home rather than in hospital)
- side effects (please describe nature and number of problems, frequency, duration, severity etc)

Eculizumab is a revolution in the management of aHUS

1) It is more effective than plasma exchange, often rescuing patients who were not responding to plasma exchange.
2) Eculizumab requires only 2 weekly injections which can be given at home whereas dialysis or plasma exchange require 3 times / week hospital visits of >4hrs
3) It does not require long term vascular access
4) Isolated renal transplantation in aHUS is usually associated with early recurrent aHUS in the renal transplant. This carries substantial morbidity and mortality for the patient. Rescue plasma exchange is rarely successful . Eculizumab will allow for patients to be transplanted.
5) Combined liver kidney transplantation carries a high mortality (~30%) and few experts would recommend this in the Eculizumab era.

(iii) If you think that the new technology has any **disadvantages** for patients compared with current standard practice, please describe them. Disadvantages might include:
- worsening of the condition overall
- worsening of specific aspects of the condition
- difficulty in use (for example injection rather than tablets)
- where the technology has to be used (for example in hospital rather than at home)
- side effects (for example nature or number of problems, how often, for how long, how severe).

A terminal pathway complement inhibitor will predispose to infections with encapsulated organisms. Vaccination and prophylactic antibiotics reduce the risk of this.

7. Research evidence on patient, family or carer views of the technology

(i) If you are familiar with the evidence base for the technology, please comment on whether patients' experience of using the technology as part of their care reflects that observed under clinical trial conditions.

Patients' views of Eculizumab treatment are overwhelmingly positive and reflect the increased quality of life seen in the clinical trial

(ii) Are there any adverse effects that were not apparent in the clinical trials but have come to light since the treatment has become available?

No

(iii) Are you aware of any research carried out on patient, family or carer views of the condition or existing treatments that is relevant to an evaluation of this technology? If yes, please provide references to the relevant studies.

Quality of life is assessed by Lemaire et al

Lemaire M, Fremeaux-Bacchi V, Schaefer F, Choi M, Tang WH, Le Quintrec M, et al. Recessive mutations in DGKE cause atypical hemolytic-uremic syndrome. Nat Genet 2013;45(5):531-6.

8. Availability of this technology to patients

(i) What key differences, if any, would it make to patients, their families or carers if this technology was made available?

Eculizumab will

1) Prevent patients developing end stage renal failure and requiring renal replacement therapy
2) It will prevent patients going to hospital for >4hrs three times a week for dialysis
3) It will allow patients with aHUS who were previously “untransplantable” to successfully undergo renal transplantation
4) It will allow patients to lead a normal life with only an injection every 2 weeks

(ii) What implications would it have for patients, their families or carers if the technology was **not** made available?

If Eculizumab is not made available

1) Patients will develop end stage renal failure
2) They will spend a lifetime on dialysis (3x week)
3) Their schooling / work will suffer
4) There will be no prospect of isolated kidney transplant
5) They will be forced to contemplate the highly risky liver kidney transplant (~30% mortality in aHUS)
6) They will see patients from all other countries in the developed World receive a highly efficacious medication which they cannot get

(iii) Are there groups of patients that have difficulties using the technology?

No

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for the treatment is licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

N/A

Please tell us what evidence should be obtained to enable the Evaluation Committee to identify and consider such impacts.

Other Issues

Please consider here any other issues you would like the Evaluation Committee to consider when evaluating this technology.

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