NICE advice

Prevention of recurrence of C3 glomerulopathy post-transplant: eculizumab

Evidence summary
Published: 26 June 2015

www.nice.org.uk/guidance/esuom44

Key points from the evidence

The content of this evidence summary was up-to-date in June 2015. See summaries of product characteristics (SPCs), British national formulary (BNF) or the MHRA or NICE websites for up-to-date information.

Summary

No evidence was found to determine whether prophylactic use of eculizumab is effective and safe for preventing recurrence of C3 glomerulopathy after kidney transplantation. Unsurprisingly, given the challenges of performing studies in rare diseases, the evidence for using eculizumab to treat C3 glomerulopathy in people who had experienced recurrence of the condition post-transplant is confined to 10 case reports. Eculizumab improved or stabilised signs of C3 glomerulopathy in 7 cases. A partial response was seen in 1 case, and it was ineffective in 2 cases. More evidence is needed to better assess the

safety and efficacy of eculizumab in this heterogeneous condition and to determine which patients are most likely to respond treatment.

Regulatory status: Eculizumab (Soliris) is licensed in the UK for treating adults and children with atypical haemolytic uraemic syndrome (aHUS) or paroxysmal nocturnal haemoglobinuria (PNH). Use of eculizumab to treat people with C3 glomerulopathy, or to prevent recurrence of the condition, is off-label.

Effectiveness	**Safety**
No evidence was found on using eculizumab for preventing recurrence of C3 glomerulopathy post-transplant. For treating recurrence of C3 glomerulopathy post-transplant: • eculizumab was found to improve or stabilise measures of renal function and/or findings on renal biopsy in 3 people in a small open-label study by Bomback et al. (2012) and single cases reported by Le Quintrec et al. (2015), McCaughan et al. (2012), Sanchez-Moreno et al. (2014) and Ariceta et al. (2013). • disease progression was only partially prevented by eculizumab in a single case reported by Gurkan et al. (2013). • Dorje et al. (2014) and Jordan et al. (2013) each report single cases where eculizumab was ineffective.	• Eculizumab was generally well-tolerated by the 10 cases in the literature. The case described by Jordan et al. (2013) experienced herpes zoster infection. • According to the summary of product characteristics, the most common adverse effect of eculizumab is headache. The most serious adverse reaction is meningococcal sepsis. • Other common adverse effects include aspergillus infection, bacterial and viral infection, thrombocytopenia, leukopenia, haemolysis and anaphylaxis.

Patient factors	Resource implications
• Vaccination against meningococcal infection is essential before and during treatment with eculizumab. However, vaccination may not be sufficient to prevent infection. • Eculizumab is administered by intravenous infusion. The optimal dosage regimen for C3 glomerulopathy is unclear. • Assuming eculizumab is found to be effective, long-term treatment may be required, as recommended for aHUS and PNH.	• The cost of 1 vial of eculizumab 300 mg concentrate for solution for infusion is £3150.00 excluding VAT (MIMS, June 2015). • Based on the dosing regimen used in most of the cases with C3 glomerulopathy, the cost of 5-week initiation treatment is £50,400 excluding VAT. The annual cost of maintenance treatment with eculizumab 1200 mg is £327,600 excluding VAT.

Introduction

C3 glomerulopathy is a type of membranoproliferative glomerulonephritis in which dysregulation of the alternative complement system pathway (part of the body's immune system) causes deposits of complement protein C3 in the kidney. C3 glomerulopathy is subdivided into C3 glomerulonephritis (C3GN) and dense deposit disease (DDD) based on electron microscopy.

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 2 years. After kidney transplantation, 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 and agents have not been tested in robust clinical trials, probably because performing randomised controlled trials is difficult in rare diseases. In people who have not had a kidney transplant, nonspecific immunomodulatory agents such as cyclophosphamide and mycophenolate mofetil are sometimes used. However, the efficacy of such agents in recurrent C3 glomerulopathy is thought to be limited. Other treatments which have been used include plasma exchange, rituximab (with or without

plasma exchange) and eculizumab.

Full text of introduction.

Product overview

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 membrane attack complex, C5b-9, which causes cell lysis and death in pathogens.

Full text of product overview.

Evidence review

- This evidence summary considers the evidence for using eculizumab to prevent recurrence of C3 glomerulopathy in people who have had a kidney transplant. Use of eculizumab to treat C3 glomerulopathy in people who have not had a transplant is outside the scope of the evidence summary, as is use to prevent antibody-mediated rejection of a transplanted kidney.
- The searches performed for the evidence summary found no studies or case reports of eculizumab to prevent recurrence of C3 glomerulopathy after a kidney transplant. A small open-label study (n=6, 3 post-transplant) and 7 reports of single cases who had recurrence of C3 glomerulopathy post-transplant and were using eculizumab to prevent progression of the disease were found.
- Bomback et al. (2012) performed a prospective single-arm open-label pilot study of eculizumab for treating 6 people with C3 glomerulopathy, of whom 3 (1 with DDD and 2 with C3GN) had recurrent disease after kidney transplantation. Stable renal function and improvements on renal biopsy were seen in 1 person with recurrence of DDD and 1 person with recurrence of C3GN. Improvement in serum creatinine but no changes on biopsy were seen in the second person with recurrence of C3GN.
- An open-label study (Gurkan et al. 2013) reported treatment of 1 person who experienced C3GN post-transplant. Eculizumab only partially prevented progression of C3GN in this case. Renal function initially improved but proteinuria subsequently deteriorated, and worsening disease was seen on biopsy.

- Le Quintrec et al. (2015) discussed 3 cases who received eculizumab for C3 glomerulopathy, 1 of whom had received a kidney transplant. In this person, eculizumab treatment was associated with improvement in renal function and improvements on biopsy for up to 28 months.

- McCaughan et al. (2012) reported a case with recurrent DDD post-transplant who was treated with eculizumab. Renal function improved immediately following treatment and was sustained for 11 weeks. Follow up biopsy was not reported.

- Sanchez-Moreno et al. (2014) described treatment with eculizumab in a case with recurrent DDD post-transplant. Renal function improved and became normal following treatment, over 30 months. Biopsy showed no progression of DDD.

- Three case reports are available as abstracts only, providing limited information. Ariceta et al. (2013) reported that eculizumab improved renal function and caused remission of disease on biopsy in a case with recurrent DDD post-transplant. Dorje et al. (2014) found that eculizumab was ineffective in a case with recurrence of C3GN post-transplant. Jordan et al. (2013) reported that 1 case with recurrent C3GN did not improve with eculizumab treatment and lost his transplanted kidney.

- The number of case reports was too small to assess adverse effects; however, none were reported in the majority of cases. The case described by Jordan et al. (2013) experienced herpes zoster infection.

- According to the summary of product characteristics, the most common adverse reaction reported in 302 people with PNH and aHUS (the licensed indications) in clinical trials and in postmarketing reports was headache (occurring in more than 1 in 10 people, mostly in the initiation phase). The most serious adverse reaction was meningococcal sepsis (occurring in between 1 in 10 and 1 in 100 people). To reduce the risk of meningococcal infection, all patients must be vaccinated before receiving eculizumab and revaccinated according to current medical guidelines. However, vaccination may not be sufficient to prevent infection. Other common adverse effects seen in between 1 in 10 and 1 in 100 people include aspergillus infection, bacterial and viral infection, thrombocytopenia, leukopenia, haemolysis and anaphylaxis.

- This evidence review includes information on only 10 people. Case reports are subject to bias and confounding and provide only low quality evidence for interventions. Although eculizumab improved or stabilised signs of C3 glomerulopathy in most cases, improvements in both renal function and biopsy were not always found, only a partial response was seen in 1 case and eculizumab was ineffective in 2 further cases. In

addition, it is possible that cases in which eculizumab was unsuccessful are under reported in the literature.

- C3 glomerulopathy is a heterogeneous condition associated with many different abnormalities in the alternative complement system pathway, and the degree of C5 convertase dysregulation varies between individuals. Therefore, people may not universally respond to eculizumab therapy. It is currently unclear whether it is possible to identify who will respond to eculizumab treatment using genetic and antibody testing for complement abnormalities. It has been proposed that elevated C5b-9 levels, an increase in or appearance of C5b-9 deposits in the kidney, and the presence of marked inflammatory changes on biopsy might be predictors of response to treatment. Longer, larger, statistically powered and adequately controlled studies are needed to better evaluate eculizumab for treating C3 glomerulopathy post-transplant, in terms of outcomes such as patient survival, graft survival, adverse effects and quality of life. However, rare diseases present challenges in optimal study design.
- In people in whom eculizumab is effective, long-term treatment may be necessary (as recommended in aHUS and PNH) because eculizumab does not address the underlying complement abnormality, but merely prevents downstream formation of C5b-9. Bomback (2014a) notes that whether the drug is considered lifelong therapy is influenced by the high cost of eculizumab treatment and the potential for infection with prolonged use. Different doses of eculizumab were used in the cases and the optimal regimen for people with recurrence of C3 glomerulopathy is unclear.

Full text of evidence review.

Context and estimated impact for the NHS

The dose of eculizumab used in the majority of cases with C3 glomerulopathy was 900 mg weekly for 4 weeks, then 1200 mg for 1 week and subsequently every 2 weeks.

Based on this dosing regimen, the cost of the 5-week initiation phase is £50,400 and the cost of 4 weeks' maintenance treatment is £25,200 (excluding VAT), not including any other costs incurred when eculizumab is, for example, diluted and administered. The annual cost of treatment in the maintenance phase is £327,600 (excluding VAT).

Full text of context and estimated impact for the NHS.

About this evidence summary

'Evidence summaries: unlicensed or off-label medicines' summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. The summaries provide information for clinicians and patients to inform their decision-making and support the construction and updating of local formularies.

The summaries support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

The strengths and weaknesses of the relevant evidence are critically reviewed within this summary, **but this summary is not NICE guidance**.

Full evidence summary

Introduction

Membranoproliferative glomerulonephritis (MPGN) includes several heterogeneous types of glomerulonephritis characterised by deposits in the glomerular mesangium of the kidney and thickening of the basement membrane. MPGN was previously categorised as type I, II or III, depending on the location and type of electron dense deposits seen on histology. It is now broadly categorised into:

- immunoglobulin-mediated MPGN (typically caused by circulating immune complexes secondary to infections such as hepatitis B or C, or autoimmune conditions such as systemic lupus erythematosus)
- complement-mediated MPGN (in which deposits of complement protein C3 are caused by dysregulation of the alternative complement system pathway, part of the body's immune system) and
- MPGN that is not immunoglobulin- or complement-mediated.

Complement-mediated MPGN is known as C3 glomerulopathy and is subdivided into C3 glomerulonephritis (C3GN) and dense deposit disease (DDD; previously MPGN type II) based on electron microscopy. C3 glomerulopathy is associated with complement abnormalities in the alternative complement system pathway. These abnormalities vary

between people and can be caused by acquired antibodies (most commonly C3 nephritic factor) or genetic mutations in complement or complement regulatory proteins. Genetic and antibody testing to identify the underlying complement abnormality can help to establish a diagnosis and inform therapeutic decision making (Barbour et al. 2015). More detail is available in a consensus report on the definition of C3 glomerulopathy, appropriate complement investigations that should be considered, and how complement therapeutics should be explored in the condition (Pickering et al 2013).

C3 glomerulopathy is rare, comprising 1.34% of biopsies with an incidence of 1–2 per million population per year. It affects people of all ages, although DDD may present at a younger age than C3GN. The renal prognosis in C3 glomerulopathy is poor, with a 30% risk of end stage renal disease at 2 years. More than half of people with DDD progress to end stage renal disease within 10 years of diagnosis. After kidney transplantation, the risk of recurrence of DDD in the transplanted kidney is over 70% and can be delayed many years, with more than a 50% chance of graft loss. C3GN recurs in approximately two thirds of people with transplants, at a median of 28 months post-transplant. Graft loss is common (50%) and occurs a median of 18 months after identification of C3GN. Risk factors for recurrence of C3 glomerulopathy post-transplant are currently not known (Barbour et al. 2015).

Information on MPGN, DDD and C3GN for clinicians and patients is available on RareRenal.org. The information contained on the site is the opinion of the expert Rare Disease Groups that are authorised by the Renal Association. Information that is considered to be 'evidence-based' is referenced in the text of the website.

The optimal management of people with C3 glomerulopathy (affecting their own and/or a transplanted kidney) is uncertain. Treatment recommendations are based on the current understanding of underlying complement abnormalities but have not been rigorously tested in robust clinical trials, probably because performing randomised controlled trials is difficult in rare diseases. In people who have not had a kidney transplant, nonspecific immunomodulatory agents such as corticosteroids, cyclophosphamide and mycophenolate mofetil are sometimes used to decrease production of antibodies, with the aim of reducing inflammation resulting from uncontrolled complement activation and inhibiting the effects of anaphylotoxins. However, the efficacy of such agents in recurrent C3 glomerulopathy is thought to be limited. Plasma exchange may be beneficial to replace missing complement factors in people with certain genetic mutations. Other treatments which have been used include bortezomib, rituximab (with or without plasma exchange) and the anticomplement therapy, eculizumab (Barbour et al. 2015, Pickering et al 2013).

The searches performed for this evidence summary identified a 1-year open-label study (Bomback et al. 2012, n=6 [see evidence review]) and multiple case reports describing the use of eculizumab for treating people with C3 glomerulopathy who had not had a kidney transplant. Many of these suggest that eculizumab may be effective for improving renal function in some people with this condition. However, case reports provide only low quality evidence and these results require confirmation in controlled studies. Use of eculizumab to treat people with C3 glomerulopathy who have not had a transplant is outside the scope of this evidence summary, which considers the evidence for using eculizumab to prevent recurrence of C3 glomerulopathy in people who have had a kidney transplant.

Eculizumab has been used to treat and prevent antibody-mediated rejection in people with kidney and other transplants. This indication is also outside the scope of this evidence summary. A draft clinical commissioning policy discusses Eculizumab for the treatment of refractory antibody-mediated rejection post kidney transplant (January 2014) and concludes that NHS England will not routinely commission eculizumab for this use. The quality of evidence supporting the use of eculizumab for antibody-mediated rejection was found to be 'very low' and limited to uncontrolled studies, including case series and case reports.

A randomised open-label phase II clinical trial (n=102) has been undertaken to assess the safety and efficacy of eculizumab for preventing antibody-mediated rejection in people with kidney transplants from living donors (NCT01399593). A company press release states there was no statistically significant difference between the eculizumab group and the control group who received standard care in the rate of the primary composite end point (biopsy-proven antibody-mediated rejection, graft loss, death or loss to follow-up at week 9 post-transplant).

Product overview

Drug action

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). See the summary of product characteristics for more information.

Regulatory status

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). 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 prevent recurrence of the condition, is off-label.

In line with the guidance from the General Medical Council (GMC), it is the responsibility of the prescriber to determine the clinical need of the patient and the suitability of using eculizumab outside its authorised indications.

Cost

The cost of 1 vial of eculizumab 300 mg concentrate for solution for infusion is £3150.00 excluding VAT (MIMS, June 2015).

According to the summary of product characteristics, in people weighing 40 kg or more, the usual dose given by intravenous infusion is:

- initially 900 mg weekly for 4 weeks, then 1200 mg for 1 week and subsequently every 2 weeks in aHUS
- initially 600 mg weekly for 4 weeks, then 900 mg for 1 week and subsequently every 2 weeks in PNH.

In people weighing less than 40 kg, the dose is adjusted according to weight.

The cost of the 5-week initiation phase in people weighing 40 kg or more is £50,400 in aHUS and £34,650 in PNH. The cost of 4 weeks' treatment in the maintenance phase is £25,200 in aHUS and £18,900 in PNH. This is the cost of eculizumab only (excluding VAT) and does not include any other costs incurred, such as dilution and administration.

In aHUS and PNH, the summary of product characteristics advises that treatment is continued for the patient's lifetime, unless discontinuation of eculizumab is clinically indicated.

Evidence review

This evidence summary considers the evidence for using eculizumab to prevent recurrence of C3 glomerulopathy in people who have had a kidney transplant. Use of eculizumab to treat C3 glomerulopathy in people who have not had a transplant is outside the scope of the evidence summary, as is use to prevent antibody-mediated rejection of a transplanted kidney.

The extensive searches performed for the evidence summary found no studies or case reports of eculizumab being used prophylactically to prevent recurrence of C3 glomerulopathy after a kidney transplant. Limited evidence from a small open-label study (Bomback et al. 2012, n=6 [3 post-transplant]) and 7 reports of single cases was found for using eculizumab to treat C3 glomerulopathy in people who experienced recurrence of the condition post-transplant.

Bomback et al. 2012

- **Design:** this study was a prospective, single-arm, open-label pilot study undertaken in a single US centre. It assessed the efficacy and safety of eculizumab for treating adults with C3 glomerulopathy confirmed by biopsy.
- **Patients:** it included 3 adults with DDD and 3 adults with C3GN, of whom 3 (1 with DDD and 2 with C3GN) had undergone kidney transplantation from a living related donor. All participants had proteinuria of at least 1 g/day, a urine protein:creatinine ratio greater than 1 g/g, or acute kidney injury (defined as a more than 50% increase in serum creatinine from baseline). Exclusion criteria included age less than 18 years, use of rituximab or another monoclonal antibody within 6 months, inability to taper off other immunomodulatory therapies (including high-dose steroids more than 10 mg daily prednisolone or equivalent) unless indicated for prophylaxis against transplant rejection, other renal disease that would affect interpretation of study results, and estimated glomerular filtration rate below 30 ml/minute per 1.73 m^2. Five of the participants had been treated with immunomodulatory agents, including steroids, before initiation of eculizumab, including all those post-transplant. See table 1 for baseline characteristics of the participants who had undergone kidney transplantation.
- **Intervention and comparison:** Participants received eculizumab 900 mg intravenously once weekly for 4 weeks, then 1200 mg intravenously in week 5 and every 2 weeks thereafter for 53 weeks in total.

- **Outcomes:** In people with proteinuria, the primary end point was change in proteinuria over the treatment period. In people with acute kidney injury, the primary end point was change in serum creatinine over the treatment period. Secondary end points included changes in renal histopathology on repeat biopsy performed after 1 year of treatment. Various laboratory measurements were also performed every 4 weeks. No statistical analysis was performed because of the small number of participants.

Baseline characteristics of the 7 cases reported in the literature who were taking eculizumab for recurrence of C3 glomerulopathy post-transplant are included in table 1.

Table 1 Summary of baseline characteristics of individual patients receiving eculizumab for treatment of C3 glomerulopathy post-transplant

Study	Gender	Age (years)	Transplant	Biopsy	Genetic and complement testing	Previous treatment for C3 glomerulopathy
Bomback et al. 2012	M	42	Living donor, sibling	DDD	C3NeF negative. No mutations or autoantibodies. C5b-9 not available	Steroids pre-transplant. Tacrolimus and mycophenolic acid post-transplant
Bomback et al. 2012	M	22	Living donor, mother	C3GN	C3NeF positive. No mutations or autoantibodies. C5b-9 elevated	Steroids pre- and post-transplant. Tacrolimus and mycophenolate mofetil post-transplant
Bomback et al. 2012	M	20	Living donor, mother	C3GN	C3NeF positive. MCP mutation. C5b-9 borderline elevated	Rituximab pre-transplant. Steroids post-transplant. Tacrolimus and mycophenolate mofetil pre- and post-transplant

Gurkan et al. 2013	M	21	Living donor, related	C3GN	C3NeF positive. 3 DDD-associated variants in complement factor H. C5b-9 elevated	Pre-transplant not reported. Rituximab post-transplant
Le Quintrec et al. 2015	F	63	Not reported	C3GN	C3NeF negative. No mutations or autoimmune disease. C5b-9 elevated	Pre-transplant not reported. Steroids and plasma exchange post-transplant
McCaughan et al. 2012	F	29	Living donor, sibling	DDD	C3NeF positive. No mutations or autoantibodies. C5b-9 not reported	Pre-transplant not reported. Steroids, plasma exchange, rituximab, mycophenolate mofetil post-transplant
Sanchez-Moreno et al. 2014	F	14	Living donor, father	DDD	C3NeF positive. No mutations or autoantibodies. C5b-9 not reported	Steroids, plasma exchange, rituximab pre-transplant. Plasma exchange post-transplant
Ariceta et al. 2013[a]	F	13	Not reported	DDD	C3NeF positive. No mutations or autoantibodies. C5b-9 not reported	Steroids and cyclophosphamide pre-transplant. Plasma exchange and rituximab post-transplant

Dorje et al. 2014[a]	M	19	Living donor	C3GN	C3NeF not reported. No mutations or autoantibodies. C5b-9 elevated	Mycophenolate mofetil, ciclosporin, tacrolimus, rituximab and plasma exchange pre-transplant.
Jordan et al. 2013[a]	M	Not reported	Living donor	C3GN	Not reported	Pre-transplant not reported. Intravenous immunoglobulin plus rituximab and plasma exchange post-transplant
Abbreviations: C3GN, C3 glomerulonephritis; C3NeF, C3 nephritic factor; C5b-9, membrane attack complex, an indicator of activation of the terminal complement cascade; DDD, dense deposit disease; F, female; M, male; MCP, membrane cofactor protein. [a] Abstracts only.						

Clinical effectiveness

Bomback et al. 2012

Overall, proteinuria and renal function improved or stabilised in 4 out of 6 participants in this study who were treated with eculizumab for 53 weeks, and improvements were seen in the 3 participants with recurrent disease in their transplanted kidney. Stable renal function and improvements on renal biopsy were seen in 2 people (1 person with recurrence of DDD and 1 with recurrence of C3GN), and improvement in serum creatinine but no changes on biopsy were seen in the third (with recurrence of C3GN). See table 2 for more details.

Individual cases

An open-label study (Gurkan et al. 2013) reported treatment of 1 person who experienced C3GN post-transplant. The eculizumab dosing regimen and treatment duration (53 weeks) was the same as in Bomback et al. (2012). Eculizumab only partially prevented progression

of C3GN in this case. Renal function initially improved but proteinuria subsequently deteriorated, and worsening disease was seen on biopsy.

Le Quintrec et al. (2015) discussed 3 cases who received eculizumab for C3 glomerulopathy, 1 of whom had received a kidney transplant. In this person, eculizumab treatment (900 mg weekly for 4 weeks then 1200 mg fortnightly) was associated with improvement in renal function and improvements on biopsy for up to 28 months.

McCaughan et al. (2012) reported a case with recurrent DDD post-transplant who was treated with eculizumab 900 mg on 2 occasions a week apart, followed by 600 mg every 2 weeks. Renal function improved immediately following treatment and was sustained for 11 weeks. Follow-up biopsy was not reported.

Sanchez-Moreno et al. (2014) described treatment of a case with recurrent DDD post-transplant. Eculizumab 900 mg was given weekly for 4 weeks, followed by 1200 mg every 2 weeks for 1 year, then every 3 weeks for 1 year, and every 4 weeks at the time of reporting. Renal function improved and became normal following treatment, over 30 months. Biopsy showed no progression of DDD.

Three case reports are available as abstracts only, providing limited information:

- Ariceta et al. (2013) reported that eculizumab (900 mg weekly for 4 weeks, then 1200 mg for 1 week and every 2 weeks thereafter) improved renal function and caused remission of disease on biopsy after 6 months in a case with recurrent DDD post-transplant.
- Dorje et al. (2014) found that eculizumab (900 mg weekly for 4 weeks, then 1200 mg fortnightly) was ineffective over 3 months in a case with recurrence of C3GN post-transplant.
- Jordan et al. (2013) primarily considered eculizumab for antibody-mediated rejection in 6 people. One case with recurrent C3GN was also included. He did not improve with eculizumab treatment (initial dose 1200 mg followed by 900 mg weekly up to 4 doses) and lost his transplanted kidney.

More details on these cases are reported in table 2.

Table 2 Summary of results

Study (case details)	Renal function	Renal biopsy	C5b-9	Relapse on discontinuation
Bomback et al. 2012 (M, 42 years, DDD)	Urine protein:creatinine ratio improved and stabilised during treatment. Serum creatinine and serum albumin generally remained stable	Decreased mesangial proliferation and less extensive deposits	Normal throughout treatment	No: laboratory tests 4 and 8 weeks after completing treatment were unchanged
Bomback et al. 2012 (M, 22 years, C3GN)	Urine protein:creatinine ratio, serum creatinine and serum albumin were generally stable throughout treatment	Decreased mesangial and endocapillary proliferation, and reduced inflammatory cells within glomeruli	Decreased and remained normal throughout treatment	Yes: recurrent active C3GN 7 weeks after discontinuation Eculizumab was restarted along with plasma exchange and steroids, which improved renal function
Bomback et al. 2012 (M, 20 years, C3GN)	Serum creatinine improved during treatment. Urine protein:creatinine ratio and serum albumin remained stable	No change	Decreased to normal by week 4	No: laboratory tests 4 and 8 weeks after completing treatment were unchanged

Gurkan et al. 2013 (M, 21 years, C3GN)	Serum creatinine improved during treatment. Proteinuria initially improved but worsened again at 9 months	Increased fibrosis and continuously active C3GN with persistent membranoproliferative changes and large subendothelial deposits	Decreased to normal	Not applicable. Treatment continued with the addition of ACE inhibitor and ARB treatment to manage proteinuria
Le Quintrec et al. 2015 (F, 63 years, C3GN)	Serum creatinine and eGFR improved. Urine protein:creatinine ratio and serum albumin remained stable	Regression of glomerular inflammatory changes and disappearance of C3 and C5b-9 deposits	Decreased to normal	Not applicable. Treatment continued
McCaughan et al. 2012 (F, 29 years, DDD)	Creatinine and urine albumin:creatinine ratio improved during treatment	Not reported	Not reported	Not reported
Sanchez-Moreno et al. 2014 (F, 14 years, DDD)	Proteinuria resolved and serum creatinine improved during treatment	No progression of mesangial proliferation, capillary thickening or deposits	Completely inhibited	Not applicable. Treatment continued
Ariceta et al. 2013[a] (F, 13 years, DDD)	Proteinuria resolved. Renal function improved	Glomerular C3 deposits disappeared	Not reported	Not reported

Dorje et al. 2014[a] (M, 19 years, C3GN)	Serum creatinine worsened during treatment	No improvement	Improved	Not reported
Jordan et al. 2013[a] (M, age unknown, C3GN)	No response	Intense C3 deposits pre- and post-treatment	Not reported	Not applicable. Graft lost
Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; C3GN, C3 glomerulonephritis; C5b-9, membrane attack complex; DDD, dense deposit disease; eGFR, estimated glomerular filtration rate; F, female; M, male. [a] Abstracts only.				

Safety and tolerability

No adverse events, including infections, were reported in the pilot study by Bomback et al. (2012) or the cases reported by Gurkan et al. (2013), Le Quintrec et al. (2015), Sanchez-Moreno et al. (2014) or Ariceta et al. (2013). Eculizumab was well tolerated by the case discussed by McCaughan et al. (2012). In Jordan et al. (2013), the case experienced herpes zoster infection. Adverse effects were not reported by Dorje et al. (2014).

Summary of product characteristics

The most common adverse reaction reported in 302 people treated with eculizumab for PNH and aHUS in clinical trials and in postmarketing reports was headache (occurring in more than 1 in 10 people, mostly in the initiation phase). The most serious adverse reaction was meningococcal sepsis (occurring in between 1 in 10 and 1 in 100 people). To reduce the risk of meningococcal infection, all patients must be vaccinated at least 2 weeks before receiving treatment with eculizumab and revaccinated according to current medical guidelines. However, vaccination may not be sufficient to prevent infection and all patients should be monitored for early signs of meningococcal infection. UK guidelines for the prevention of meningococcal disease in people receiving eculizumab for the treatment of aHUS recommend the use of long-term prophylactic antibiotic treatment in addition to vaccination.

Other common adverse effects seen in between 1 in 10 and 1 in 100 people include aspergillus infection, bacterial and viral infections, thrombocytopenia, leukopenia, haemolysis, anaphylaxis, decreased appetite, dizziness, dysgeusia (taste distortion), hypotension, dyspnoea and other respiratory tract symptoms, gastrointestinal upset, rash and pruritus, alopecia, muscle and joint pain, oedema, pyrexia, chills and fatigue. See the summary of product characteristics for more details.

Evidence strengths and limitations

No evidence was found on whether prophylactic use of eculizumab is effective and safe for preventing recurrence of C3 glomerulopathy after kidney transplantation. The evidence included in this evidence summary considers the use of eculizumab for treating C3 glomerulopathy (C3GN and DDD) in people who had experienced recurrence of the condition post-transplant.

No published randomised controlled trials were identified. The evidence review is based on a small case series and 7 case reports and includes information on only 10 people (4 with recurrence of DDD and 6 with recurrence of C3GN). This number is too small to reliably assess efficacy or safety. Also, case reports are subject to bias and confounding and provide only low quality evidence for interventions. Although eculizumab improved or stabilised signs of C3 glomerulopathy in most cases, improvements in both renal function and biopsy were not always found, only a partial response was seen in 1 case (Gurkan et al. 2013) and eculizumab was ineffective in 2 cases (Dorje et al. 2014 and Jordan et al. 2013). In addition, it is possible that cases in which eculizumab was unsuccessful are under reported in the literature (publication bias). Proteinuria and appearance on biopsy are surrogate markers of response, which may not correlate well with clinical outcomes and need to be interpreted with caution. The maximum follow-up reported in the cases was 30 months and longer-term follow-up is needed to assess outcomes such as graft survival.

Bomback et al. (2012) proposed that normalisation of elevated C5b-9 (the membrane attack complex) might be a marker of eculizumab's ability to improve disease parameters. However, Gurkan et al. (2013) suggested that, although eculizumab inhibits production of C5b-9, dysregulation of the alternative complement pathway can remain. Dorje et al. (2014) found that eculizumab was ineffective although C5b-9 levels were reduced, but speculated that treatment was started too late (6 months after C3GN was diagnosed). Le Quintrec et al. (2015) proposed that, as well as elevated C5b-9 levels, an increase in or appearance of C5b-9 deposits in the kidney, and the presence of marked inflammatory

changes on biopsy might be predictors of response to eculizumab.

C3 glomerulopathy is a heterogeneous condition associated with many different abnormalities in the alternative complement system pathway, and the degree of C5 convertase dysregulation varies between individuals. Therefore, people may not universally respond to eculizumab, which binds to C5, preventing the generation of C5b-9. Bomback (2014a and 2014b) has discussed that C3 convertase dysregulation may be more dominant than C5 convertase dysregulation in some people, and that eculizumab might potentially aggravate C3 glomerulopathy in these cases because of a feedback effect on the C3 complement pathway when C5 is blocked. Bomback notes that one of the major challenges in treating people with C3 glomerulopathy with eculizumab is how to distinguish between people with primarily C3 convertase dysregulation and those with primarily C5 convertase dysregulation. In Bomback et al. (2012), the author aims to link clinical response to complement abnormalities caused by autoantibodies and genetic mutations. However, it is currently unclear whether it is possible to identify who will respond to eculizumab treatment using genetic and antibody testing for complement abnormalities.

Specialists involved in the production of this evidence summary have advised that recurrent C3 glomerulopathy is likely to be identified earlier in transplanted patients than in the general population, and so the prognosis may be better in the transplanted kidney than the native kidney. In people in whom eculizumab is effective, long-term treatment may be necessary because eculizumab does not address the underlying complement abnormality, but merely prevents downstream formation of C5b-9. One case in Bomback et al. (2012) experienced recurrence of C3 glomerulopathy within 8 weeks of stopping treatment, but 2 did not. Bomback (2014a) notes that whether the drug is considered to be lifelong therapy is influenced by the high cost of eculizumab treatment and the increased potential for infection with prolonged use. The risk of infection may be particularly important in people with a kidney transplant who are already receiving immunosuppression to prevent graft rejection. Different doses of eculizumab were used in the cases and the optimal regimen for people with recurrence of C3 glomerulopathy is unclear.

Longer, larger, statistically powered and adequately controlled studies are needed to better evaluate eculizumab for treating C3 glomerulopathy post-transplant, in terms of outcomes such as patient survival, graft survival, adverse effects and quality of life. However, rare diseases present challenges in optimal study design. In the UK, a registry (the RaDaR initiative) has been established to combine experience from people with

MPGN, DDD and C3GN with the aim of improving understanding of what causes the diseases and speeding up the development of treatments. The National study of MPGN/DDD/C3G aims to understand and identify causative factors.

Context and estimated impact for the NHS

Cost effectiveness

No cost-effectiveness studies of eculizumab for C3 glomerulopathy were identified.

The dose of eculizumab used in the majority of cases with C3 glomerulopathy was 900 mg weekly for 4 weeks, then 1200 mg for 1 week and subsequently every 2 weeks.

Based on this dosing regimen, the cost of the 5-week initiation phase is £50,400 and the cost of 4 weeks' maintenance treatment is £25,200 (excluding VAT), not including any other costs incurred when eculizumab is, for example, diluted and administered. The annual cost of treatment in the maintenance phase is £327,600 (excluding VAT).

Current drug usage

No information on the use of eculizumab for any indication in UK clinical practice was identified.

Relevance to NICE guidance programmes

The use of eculizumab for C3 glomerulopathy is not appropriate for referral for a NICE technology appraisal and is not currently planned into any other work programme.

NICE has issued the following guidance relating to this evidence summary:

- Eculizumab for treating atypical haemolytic uraemic syndrome (NICE highly specialised technologies guidance 1).
- Acute kidney injury: Prevention, detection and management of acute kidney injury up to the point of renal replacement therapy (NICE guideline CG169).
- Immunosuppressive therapy for renal transplantation in children and adolescents

(NICE technology appraisal guidance 99, currently being updated).

The following related NICE technology appraisals are also being developed:

- Everolimus for the prevention of organ rejection in kidney transplantation (anticipated publication date to be confirmed).
- Belatacept for the prevention of organ rejection in kidney transplantation (anticipated publication date to be confirmed).

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Development of this evidence summary

The integrated process statement sets out the process NICE uses to select topics for the evidence summaries for unlicensed/off-label medicines and how the summaries are developed, quality assured and approved for publication.

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Declarations of interest

Dr Stephen Kardasz and Elizabeth Lamerton declared no relevant interests.

Andrea Devaney has received a lecturing honorarium from Novartis for speaking at an

international meeting on her local centre experience of switching to generic immunosuppressants in solid organ transplant recipients.

About this evidence summary

'Evidence summaries: unlicensed or off-label medicines' summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. The summaries provide information for clinicians and patients to inform their decision-making and support the construction and updating of local formularies.

The summaries support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

The strengths and weaknesses of the relevant evidence are critically reviewed within this summary, **but this summary is not NICE guidance**.

ISBN: 978-1-4731-1279-7