NICE advice

C3 glomerulopathy in the native kidney: eculizumab

Evidence summary
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Key points from the evidence

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

Summary

It is difficult to perform studies in rare diseases; therefore, the evidence for using eculizumab to treat C3 glomerulopathy in people with their own, native kidneys is limited. This evidence summary outlines 20 cases that were reported in the literature. Eculizumab improved or stabilised signs of C3 glomerulopathy in 15 cases. An initial response followed by subsequent deterioration was seen in 3 cases, and treatment was ineffective in 2 cases.

Case reports provide only low quality evidence for interventions. Also, it is possible that cases in which eculizumab was unsuccessful are under reported in the literature

(publication bias). 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 is off-label.

Effectiveness	**Safety**
In people with C3 glomerulopathy in their native kidneys: • Eculizumab was found to improve or stabilise measures of renal function and/or findings on renal biopsy in 1 person in a small open-label study (n=6, 3 with native kidneys) and 14 cases. Kidney function did not always return to normal but 4 people stopped dialysis. • Renal function improved over 24 weeks but then deteriorated, and biopsy results worsened in 1 person taking eculizumab in the small open-label study. Similarly, in 1 case an initial response to treatment was seen but not sustained after 2 months and, in another case, mycophenolate had to be reintroduced after 16 weeks. • Two cases were reported where eculizumab was ineffective, including 1 in the small open-label study.	• Eculizumab was generally well-tolerated from the reports of the 20 cases in the literature. • 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, November 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 kidney condition characterised by abnormal deposits of complement protein C3 within glomeruli. It is caused by dysregulation of the alternative complement system pathway, which is part of the body's immune system. C3 glomerulopathy is subdivided into 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 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 is uncertain and agents have not been tested in robust clinical trials, probably because performing randomised controlled trials (RCTs) is difficult in rare diseases. Non-specific immunomodulatory agents such as cyclophosphamide and mycophenolate mofetil are sometimes used. 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 best available evidence for using eculizumab to treat people with C3 glomerulopathy in their own, native kidneys. Use of eculizumab to treat C3 glomerulopathy in people who have had a transplant is considered in the associated evidence summary on prevention of recurrence of C3 glomerulopathy post-transplant: eculizumab.

- The searches performed for this evidence summary found no RCTs assessing eculizumab for treating people with C3 glomerulopathy in their native kidneys. Limited evidence was found from a small open-label study (Bomback et al. 2012, n=6 [3 with native kidneys]) and 12 full case reports of 17 single cases. A further 10 reports (15 cases) were identified but are available only as conference abstracts and have been excluded from the evidence summary due to significant limitations in the reporting of findings.

- 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 (2 with DDD and 1 with C3GN) had their native kidneys. No statistical analysis was performed because of the small number of participants. Results were mixed. In the first person with DDD, proteinuria improved and remained consistently low throughout treatment, and improvements were seen on renal biopsy. Renal function did not improve in the second person with DDD, who subsequently withdrew from treatment at 40 weeks. In the third person, who had C3GN, renal function improved with eculizumab over the first 24 weeks; however, it worsened again over the second 24 weeks. Deterioration was also seen on biopsy in this person.

- An initial response to treatment was also seen in a case with DDD reported by Berthe-Aucejo et al. (2014), with improvement in serum albumin and normal sC5b-9 (soluble membrane attack complex, an indicator of activation of the terminal complement cascade). However, these subsequently deteriorated after 2 months' treatment and proteinuria was unchanged after 3 months' treatment. Similarly, Haffner et al. (2015), reported improvements in serum albumin and proteinuria and normalisation of eGFR in a person with C3GN, but mycophenolate subsequently needed to be reintroduced after 16 weeks following a further increase in proteinuria. Follow-up biopsy was not reported in these cases.

- A patient with C3GN described by Besbas et al. (2014) saw no improvements on treatment and still had proteinuria after receiving eculizumab for 10 months. Follow-up biopsy was not reported.

- Proteinuria improved and other measures of renal function such as serum creatinine, serum albumin or estimated glomerular filtration rate improved or were stable in 5 cases with C3GN reported by Inman et al. (2015), Kerns et al. (2013), Le Quintrec et al. (2015) (2 cases) and Payette et al. (2015). The case described by Inman et al. (2015) discontinued dialysis. Improvements or stability were seen on renal biopsy in 3 of the cases (Le Quintrec et al. 2015 [2 cases] and Payette et al. 2015). Follow-up biopsy was not reported in the other 2 cases (Inman et al. 2015 and Kerns et al. 2013).

- Similarly, proteinuria improved and other measures of renal function improved or stabilised in 9 cases with DDD reported by Daina et al. (2012), Oosterveld et al. (2015) (5 cases), Ozkaya et al. (2014), Rousset-Rouviere et al. (2014) and Vivarelli et al. (2012). Kidney function did not always return to normal, with various degrees of chronic kidney disease remaining. However, 3 cases no longer needed dialysis (Rousset-Rouviere et al. 2014 and Oosterveld et al. 2015 [2 cases]). Improvements were seen on biopsy in the case reported by Vivarelli et al. (2012). No improvements were seen in 1 case in Oosterveld et al. (2015). Follow-up biopsy was not reported for the other 7 cases.

- Renal function deteriorated in 6 cases (5 with DDD and 1 with C3GN) when eculizumab was stopped and subsequently improved again when treatment was restarted (Bomback et al. 2012, Oosterveld et al. 2015 [3 cases] Payette et al. 2015 and Vivarelli et al. 2012).

- The number of case reports was too small to assess adverse effects; however, none were reported in any of the cases.

- 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 20 people. Case reports are subject to bias and confounding and provide only low quality evidence for interventions. In addition, it is possible that cases in which eculizumab was unsuccessful are under reported in the literature (publication bias).

- 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 soluble 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, in terms of patient-oriented outcomes such as the need for dialysis or kidney transplantation, 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, MIMS, November 2015), 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. After kidney transplantation, the risk of recurrence in the transplanted kidney is over 70%, with more than a 50% chance of graft loss (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 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. Non-specific 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. 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).

This evidence summary considers the use of eculizumab for treating people with C3 glomerulopathy in their own, native kidneys. Use of eculizumab to treat people with C3 glomerulopathy who have had a kidney transplant is discussed in another evidence summary, prevention of recurrence of C3 glomerulopathy post-transplant: eculizumab.

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 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, November 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 best available evidence for using eculizumab to treat people with C3 glomerulopathy in their own, native kidneys. Use of eculizumab to treat C3 glomerulopathy in people who have had a transplant is considered in the associated evidence summary on prevention of recurrence of C3 glomerulopathy post-transplant: eculizumab.

The searches performed for this evidence summary found no randomised controlled trials (RCTs) assessing eculizumab for treating people with C3 glomerulopathy in their native kidneys. Limited evidence was found from a small single-arm, open-label study (Bomback et al. 2012, n=6 [3 with native kidneys]) and 12 full case reports of 17 single cases. A further 10 reports (15 cases) were identified but are available only as conference abstracts and have been excluded from the evidence summary due to significant limitations in the reporting of findings.

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: I**t included 3 adults with DDD and 3 adults with C3GN, of whom 3 (2 with DDD and 1 with C3GN) had their native kidneys. 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 corticosteroids 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. See table 1 for baseline characteristics of the participants with native kidneys.
- **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 20 cases reported retrospectively in the literature (from full case reports) who were taking eculizumab for C3 glomerulopathy in their native kidneys are included in table 1.

Table 1 Summary of baseline characteristics of individual patients receiving eculizumab for C3 glomerulopathy

Study	Gender and age (years)	Renal biopsy	Genetic and complement testing	Previous treatment for C3 glomerulopathy	Eculizumab dose (reported follow-up)
Bomback et al. 2012	M 22	DDD	C3NeF negative. CFH mutation. No autoantibodies. sC5b-9 elevated.	None.	As licensed for aHUS[a] (53 weeks).
Bomback et al. 2012	M 32	DDD	C3NeF positive. No mutations or autoantibodies. sC5b 9 normal.	Corticosteroids.	As licensed for aHUS[a] (40 weeks).
Bomback et al. 2012	M 25	C3GN	C3NeF negative. No mutations or autoantibodies. sC5b-9 normal.	Corticosteroids and mycophenolate.	As licensed for aHUS[a] (53 weeks).
Berthe-Aucejo et al. 2014	M 17	DDD	C3NeF negative. CFH mutation. Autoantibodies not reported. sC5b-9 originally elevated but normal when eculizumab treatment started.	Corticosteroids, plasma exchange and rituximab.	As licensed for aHUS[a] in weeks 1–7. Dose increased to1500 mg weekly at week 8, then to 1800 mg weekly at week 12 (111 days).
Besbas et al. 2014	F 16	C3GN	C3NeF negative. CFHR5 mutation. Weakly positive for IgM autoantibody only. sC5b-9 not reported.	Corticosteroids.	As licensed for aHUS[a] (10 months).

Daina et al. 2012	F 22	DDD	C3NeF positive. CFH mutations. Autoantibodies not reported. sC5b-9 elevated	Corticosteroids and rituximab.	As licensed for aHUS[a] (48 weeks).
Haffner et al. 2015	F 16	C3GN	C3NeF positive. No mutations or autoantibodies. sC5b-9 elevated.	Corticosteroids, plasma exchange and mycophenolate.	As licensed for aHUS[a] for 19 weeks then every 3 weeks (10.5 months).
Inman et al. 2015	F 38	C3GN	C3NeF negative. CFHR1 and CFHR3 mutations. No autoantibodies. sC5b-9 elevated.	Corticosteroids and plasma exchange.	As licensed for aHUS[a] (more than 12 months).
Kerns et al. 2013	M 16	C3GN	C3NeF negative. Mutations and autoantibodies not reported. sC5b-9 elevated.	Corticosteroids, plasma exchange, mycophenolate and tacrolimus.	Weekly for 4 weeks then every 2 weeks. Dose and duration not reported.
Le Quintrec et al. 2015	F 27	C3GN	C3NeF positive. No mutations or autoimmune disease. sC5b-9 normal.	None.	As licensed for aHUS[a] (19 months).
Le Quintrec et al. 2015	M 45	C3GN	C3NeF negative. No mutations or autoimmune disease. sC5b-9 elevated.	Corticosteroids and mycophenolate.	As licensed for aHUS[a] (6 months).

Oosterveld et al. 2015	F 13	DDD	C3NeF negative. CFHR1 and CFHR3 mutations (homozygous). No autoantibodies. sC5b-9 elevated.	Corticosteroids and plasma exchange.	As licensed for aHUS[a] (28 months).
Oosterveld et al. 2015	M 6	DDD	C3NeF positive. CFHR1 and CFHR3 mutations (heterozygous). No autoantibodies. sC5b-9 not available for 1st episode but raised at 2nd.	Corticosteroids, plasma exchange and IV immunoglobulin.	As licensed for aHUS[a] (29 months).
Oosterveld et al. 2015	F 8	DDD	C3NeF negative. No mutations. Anti-CFH antibodies. sC5b-9 normal.	None in the preceding month.	As licensed for aHUS[a] (16 months).
Oosterveld et al. 2015	F 6	DDD	C3NeF positive. CFHR1 and CFHR3 mutations (heterozygous). No autoantibodies. sC5b-9 normal.	Corticosteroids and plasma exchange. Mycophenolate temporarily added to eculizumab.	As licensed for aHUS[a] (18 months).
Oosterveld et al. 2015	M 12	DDD	C3NeF positive. No mutations or autoantibodies. sC5b-9 elevated.	Ciclosporin.	As licensed for aHUS[a] (12 months).

Ozkaya et al. 2014	F 16	DDD	C3NeF positive. CFH mutations. Autoantibodies and sC5b-9 not reported.	Corticosteroids, cyclophosphamide and plasma exchange.	As licensed for aHUS[a] (31 weeks).
Payette et al. 2015	M 8	C3GN	C3NeF positive. CFI mutation and CFH autoantibodies. sC5b-9 elevated.	Corticosteroids, rituximab and mycophenolate.	Induction dose 900 mg weekly then 900 mg every 2 weeks (19 months initially). After a 2-month break, the dose was increased to 1200 mg every 2 weeks (ongoing at 3 years).
Rousset-Rouviere et al. 2014	M 8	DDD	C3NeF positive. No mutations. Autoantibodies and sC5b-9 not reported.	Corticosteroids, mycophenolate and rituximab.	Induction dose 600 mg weekly then 600 mg every 2 weeks (196 days).
Vivarelli et al. 2012	M 17	DDD	C3NeF positive. CFB mutations. Autoantibodies and sC5b-9 not reported.	Plasma exchange.	As licensed for aHUS[a] (18 months). After a 6-month break, treatment was resumed (ongoing after a further 9 months).

Abbreviations: aHUS, atypical haemolytic uraemic syndrome; C3G, C3 glomerulopathy (C3GN or DDD); C3GN, C3 glomerulonephritis; C3NeF, C3 nephritic factor; CFB/I/H, complement factor B/I/H; CFHR1/3/5, CFH-related protein 1/3/5; DDD, dense deposit disease; F, female; IgM, immunoglobulin M; IV, intravenous; M, male; sC5b-9, soluble membrane attack complex (also known as sMAC), an indicator of activation of the terminal complement cascade.

[a]Initially 900 mg weekly for 4 weeks, then 1200 mg for 1 week and subsequently every 2 weeks.

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. However, results were mixed in the 3 participants with native kidneys. In the first person with DDD, proteinuria improved and remained consistently low throughout treatment, and improvements were seen on renal biopsy. When this person stopped taking eculizumab, renal function deteriorated so treatment was restarted. Renal function did not improve in the second person with DDD, who subsequently withdrew from treatment at 40 weeks. In the third person, who had C3GN, renal function improved with eculizumab over the first 24 weeks, allowing mycophenolate and prednisolone to be discontinued. However, it worsened again over the second 24 weeks and these treatments were reintroduced. Deterioration was also seen on biopsy in this person. See table 2 for more details.

Levels of soluble C5b-9 (sC5b-9 or soluble membrane attack complex, an indicator of activation of the terminal complement cascade) were raised in the first person with DDD and subsequently became normal with eculizumab treatment. In contrast, levels were normal before and during treatment in the other 2 participants. Therefore, Bomback et al. (2012) suggested that raised sC5b-9 might predict patients' response to eculizumab treatment.

Individual case reports

Daina et al. (2012) found that, over 48 weeks, a reduction in sC5b-9 to normal levels was associated with improvements in proteinuria and other measures of renal function in a patient with DDD who was taking eculizumab, supporting the hypothesis made by

Bomback et al. (2012). Follow-up biopsy was not reported.

Le Quintrec et al. (2015) discussed 3 cases who received eculizumab for C3 glomerulopathy, 2 of whom had C3GN in their native kidneys. Proteinuria, serum albumin, serum creatinine and estimated glomerular filtration rate (eGFR) improved in both patients over 19 months and 6 months respectively, and improvements were seen on renal biopsies. In 1 patient, sC5b-9 was elevated and became normal with treatment. However, it was normal before (and throughout) treatment in the other patient. Le Quintrec et al. (2015) suggest that it may not just be raised sC5b-9 that predicts response to treatment, as considered by Bomback et al. (2012), but C5b-9 deposition in the kidney may also predict response.

Payette et al. (2015) found that eculizumab improved proteinuria in a patient with C3GN over 19 months. Proteinuria subsequently worsened when treatment was stopped and, on restarting eculizumab (at a higher dose) 2 months later, proteinuria improved again and serum creatinine remained normal. Improvements were seen on follow-up biopsy. Levels of sC5b-9 were reported to be elevated initially; deposits of C5b-9 in the kidney were significantly decreased following treatment. The authors considered that, as well as elevated sC5b-9, the relatively short disease duration may have been a predictor of response in this patient.

Similar results were seen in the case with DDD reported by Vivarelli et al. (2012). Haematuria resolved and proteinuria, serum creatinine, serum albumin and serum proteins improved with eculizumab. Apart from creatinine, these parameters worsened when eculizumab was stopped after 18 months, and subsequently improved again when treatment restarted after 6 months. Improvements were also seen on biopsy, including a reduction in deposits of C5b-9. The authors suggest that eculizumab may be more effective if it is started early, before significant sclerosis has developed.

In contrast to the cases above, Berthe-Aucejo et al. (2014) found that eculizumab did not improve proteinuria in a patient with DDD and raised sC5b-9 over a 3 month period. Although sC5b-9 levels were initially normal, when the dose of eculizumab was increased after 2 months to completely block the complement cascade, a paradoxical increase was subsequently seen. Serum albumin improved initially before deteriorating again. Follow-up biopsy was not reported. The authors concluded that short-term blockade of complement is not successful in all patients with DDD.

Mixed results were seen with eculizumab in 3 cases with DDD and elevated sC5b-9 levels

reported by Oosterveld et al. (2015), although all responded to treatment. In the first case, some improvements in renal function and proteinuria were seen but stage 2 chronic kidney disease (CKD) remained. There were no improvements on repeat biopsy and eculizumab was stopped after 26 weeks. Similar results were seen in a second case whose renal function improved but did not become normal, with stage 1 CKD remaining after 12 months' treatment. In contrast, renal function improved substantially in the third case and dialysis was stopped. Eculizumab was discontinued after 6 months in this patient, but renal function subsequently deteriorated after 18 months. It became normal again when eculizumab treatment was resumed. Follow-up biopsies were not reported for the latter 2 cases and levels of sC5b-9 following eculizumab treatment were not reported for any of the 3 cases.

Levels of sC5b-9 following eculizumab treatment were also not reported for the remaining 8 cases included in this evidence summary. Two cases with DDD (and normal sC5b-9 levels) reported by Oosterveld et al. (2015) improved with eculizumab treatment. In 1 of these patients, dialysis was discontinued but renal function deteriorated when eculizumab was stopped after 3 months. Eculizumab was restarted after 5 months without treatment and renal function gradually improved again, although stage 3 CKD remained. In the other patient, renal function improved and became normal, with eculizumab treatment ongoing at 16 months. Follow-up biopsies were not reported.

Haffner et al. (2015) recorded partial remission in a patient with C3GN, with improvements in serum albumin and proteinuria and normalisation of eGFR following initiation of eculizumab treatment. However, mycophenolate subsequently needed to be reintroduced after 16 weeks following a further increase in proteinuria. Kerns et al. (2013) saw improvement in proteinuria and serum albumin in another patient with C3GN treated with eculizumab. Serum creatinine was stable. The case with DDD reported by Ozkaya et al. (2014) also saw improvements in renal function. Proteinuria improved dramatically after the first dose of eculizumab, and serum albumin improved gradually over the 31-week follow-up. Serum creatinine remained stable. Follow-up biopsies were not reported for these cases.

Rousset-Rouviere et al. (2014) found that a patient with DDD no longer needed dialysis after 1 dose of eculizumab. In addition, haematuria resolved and proteinuria and serum creatinine improved over 6.5 months. The patient with C3GN reported by Inman et al. (2015) also stopped dialysis following treatment with eculizumab for 5 months. In addition, renal function, proteinuria and serum creatinine improved over 12 months. Follow-up biopsies were not reported for these patients. Inman et al. (2015) concluded that

eculizumab may be appropriate for people with C3GN with limited duration and minimal fibrosis on biopsy, and that a minimum of 6 months' treatment may be necessary before treatment could be considered to have failed.

The patient described by Besbas et al. (2014) had C3GN with a novel mutation in complement factor H-related protein 5. After receiving eculizumab for 10 months, she still had proteinuria. Follow-up biopsy was not reported. The authors concluded that eculizumab seems to be ineffective in patients with this novel mutation.

More details on these cases are reported in table 2.

Table 2 Summary of results

Study (case details)	Renal function	Renal biopsy	sC5b-9	Relapse on discontinuation
Bomback et al. 2012 (M 22 years, DDD)	Serum creatinine improved. Proteinuria remained low throughout treatment.	Decreased activity with no evidence of endocapillary proliferation.	Improved and became normal.	Yes: after an 8-week break, serum creatinine and sC5b-9 increased and treatment was resumed.
Bomback et al. 2012 (M 32 years, DDD)	Serum creatinine and proteinuria worsened.	Repeat biopsy declined.	Normal before and throughout treatment.	Not applicable. The patient withdrew from the study at 40 weeks due to a lack of clinical response.

Bomback et al. 2012 (M 25 years, C3GN)	Proteinuria and serum albumin initially improved and corticosteroids and mycophenolate were discontinued. These measures of renal function subsequently deteriorated, as did serum creatinine.	Increased chronicity and continuously active glomerulonephritis.	Normal before and throughout treatment.	Not applicable. Corticosteroids and mycophenolate were restarted.
Berthe-Aucejo et al. 2014 (M 17 years, DDD)	Proteinuria was unchanged after 3 months' treatment. Serum albumin initially improved to day 25 but then returned to the initial level.	Not reported.	Initially normal. A paradoxical deterioration was then seen when the dose of eculizumab was increased.	The patient was lost to follow-up.
Besbas et al. 2014 (F 16 years, C3GN)	Proteinuria persisted, although serum albumin returned to normal. Serum creatinine was normal throughout.	Not reported.	Not reported.	Not applicable.

Daina et al. 2012 (F 22 years, DDD)	Proteinuria and serum creatinine improved, and serum total protein and albumin became normal.	Not reported.	Improved and became normal.	Not reported.
Haffner et al. 2015 (F 16 years, C3GN)	Proteinuria and serum albumin improved but did not become completely normal. eGFR became normal.	Not reported.	Not reported.	Not reported. Mycophenolate was started because proteinuria deteriorated again.
Inman et al. 2015 (F 38 years, C3GN)	Renal function, proteinuria and serum creatinine improved and dialysis was stopped.	Not reported.	Not reported.	Not reported.
Kerns et al. 2013 (M 16 years, C3GN)	Proteinuria improved. Serum creatinine remained stable and serum albumin improved.	Not reported.	Not reported.	Not reported.
Le Quintrec et al. 2015 (F 27 years, C3GN)	Proteinuria, serum albumin, serum creatinine and eGFR improved	Regression of glomerular inflammatory changes and a marked decrease in C5b-9 deposits.	Normal before and throughout treatment.	Not reported.

Le Quintrec et al. 2015 (M 45 years, C3GN)	Proteinuria, serum albumin, serum creatinine and eGFR improved.	Regression of glomerular inflammatory changes and a significant decrease in C5b-9 deposits.	Improved and became normal.	Not reported.
Oosterveld et al. 2015 (F 13 years, DDD)	Renal function and proteinuria improved but did not return to normal, with stage 2 CKD remaining.	Histologic features were unchanged.	Not reported.	Yes: eculizumab was stopped after 26 weeks. DDD recurred but was treated with plasma exchange and corticosteroids. The patient was stable with persistent stage 2 CKD at 28 months.
Oosterveld et al. 2015 (M 6 years, DDD)	Proteinuria, urine protein:creatinine ratio and serum creatinine improved. Nephrotic syndrome resolved and dialysis was no longer needed.	Not reported.	Not reported.	Yes: eculizumab was stopped after 6 months but resumed after 18 months without treatment. Renal function was normal at 29 months.

Oosterveld et al. 2015 (F 8 years, DDD)	Proteinuria, urine protein:creatinine ratio and serum creatinine improved. Nephrotic syndrome resolved.	Not reported.	Not reported.	Not applicable. Treatment continued. Renal function was normal at 16 months.
Oosterveld et al. 2015 (F 6 years, DDD)	Proteinuria, urine protein:creatinine ratio and serum creatinine improved. Nephrotic syndrome resolved and dialysis was no longer needed.	Not reported.	Not reported.	Yes: eculizumab was stopped after 3 months but resumed after 5 months without treatment. Renal function improved but stage 3 CKD remained at 18 months.
Oosterveld et al. 2015 (M 12 years, DDD)	Proteinuria, urine protein:creatinine ratio and serum creatinine improved.	Not reported.	Not reported.	Not applicable. Treatment continued. stage 1 CKD remained at 12 months.
Ozkaya et al. 2014 (F 16 years, DDD)	Proteinuria and serum albumin improved. Serum creatinine remained stable.	Not reported.	Not reported.	Not reported.

Payette et al. 2015 (M 8 years, C3GN)	Proteinuria improved.	Decreased mesangial proliferation and expansion, neutrophil infiltration and double contours. Significant decrease in C5b-9 deposits.	Not reported.	Yes: proteinuria worsened when treatment was stopped. On restarting eculizumab (at a higher dose), proteinuria improved again and serum creatinine remained normal.
Rousset-Rouviere et al. 2014 (M 8 years, DDD)	Haematuria resolved, and proteinuria and serum creatinine improved. Dialysis was no longer needed.	Not reported.	Not reported.	Not applicable. Treatment continued.
Vivarelli et al. 2012 (M 17 years, DDD)	Haematuria resolved and proteinuria, serum creatinine, serum albumin and serum proteins improved.	Decreased mesangial proliferation and thickness of glomerular capillary loops. Reduction in C5b-9 deposits.	Not reported.	Yes: haematuria, proteinuria, serum albumin and serum proteins worsened when eculizumab was stopped, and subsequently improved again when treatment restarted.
Abbreviations: C3GN, C3 glomerulonephritis; C5b-9, membrane attack complex; CKD, chronic kidney disease; DDD, dense deposit disease; eGFR, estimated glomerular filtration rate; F, female; M, male; sC5b-9, soluble membrane attack complex, an indicator of activation of the terminal complement cascade.				

Safety and tolerability

The authors of the pilot study, Bomback et al. (2012), and the cases reported by Berthe-Aucejo et al. (2014), Le Quintrec et al. 2015, Oosterveld et al. (2015), Ozkaya et al. (2014), Payette et al. (2015), Rousset-Rouviere et al. (2014), Vivarelli et al. (2012) stated that no adverse events, including infections, were reported.

There was no mention of adverse events in the cases reported by Besbas et al. (2014), Daina et al. (2012), Haffner et al. (2015), Inman et al. (2015), and Kerns et al. (2013).

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

Limited evidence was found to support the use of eculizumab to treat people with C3 glomerulopathy in their native kidneys. No published RCTs were identified and this evidence review is based on a small prospective case series (3 people) and 17 retrospective case reports (12 people with DDD and 8 people with C3GN in total). 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. It is possible that cases in which eculizumab was unsuccessful are under reported in the literature (publication bias). The searches performed for this evidence summary identified a further 10 conference abstracts reporting 15 cases of C3 glomerulopathy treated with eculizumab, all of whom improved with treatment. However, cases that do not respond to treatment are probably less likely to be reported at conferences.

A further limitation of the evidence is that measures such as 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. Follow-up of the cases outlined in this evidence summary varied between 3 months and 3 years. A conference abstract has described 5-year follow-up of the patient reported by Vivarelli et al. (2012). Although the patient's renal function remained normal, renal biopsies showed deterioration. The authors concluded that eculizumab did not appear to have modified disease progression in the kidney (Vivarelli et al. 2015). More information is needed on the longer-term efficacy of eculizumab on patient-oriented outcomes such as need for dialysis and kidney transplantation.

Bomback et al. (2012) proposed that normalisation of elevated sC5b-9 might be a marker of eculizumab's ability to improve disease parameters. However, not all data support this (see Oosterveld et al. 2015) and it has been suggested that, although eculizumab inhibits production of C5b-9, dysregulation of the alternative complement pathway can remain (Gurkan et al. 2013). Le Quintrec et al. (2015) proposed that, as well as elevated sC5b-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. Oosterveld et al. (2015) also note that sC5b-9 may not reflect disease levels in the kidney. As alternative suggestions, they propose that sC5b-9 measurement may be inaccurate, and eculizumab may not block the uncontrolled activation of the alternative complement pathway underlying C3 glomerulopathy as a whole.

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. Oosterveld et al. (2015) also

consider that ongoing production of C3 degradation products may lead to chronic inflammatory changes and, in the long run, renal injury.

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.

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. Six cases reported by Bomback et al. (2012), Oosterveld et al. (2015) (3 cases), Payette et al. (2015) and Vivarelli et al. (2012) experienced recurrence of C3 glomerulopathy soon after stopping eculizumab treatment. 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 dosage of eculizumab that was used in most of the cases was the dosage that is licensed for aHUS. However, 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, in terms of outcomes such as the need for dialysis or kidney transplantation, 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, MIMS, November 2015), 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 (2015) 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 (2013) NICE guideline CG169.

References

Alexion Pharma UK Limited (2015) Soliris summary of product characteristics. [online; accessed 16 September 2015]

Barbour S and Gill JS (2015) Advances in the understanding of complement mediated glomerular disease: implications for recurrence in the transplant setting. American Journal of Transplantation 15: 312–9

Berthe-Aucejo A, Sacquepee M, Fila M et al. (2014) Blockade of alternative complement

pathway in dense deposit disease. Case Reports in Nephrology 2014: 201568

Besbas N, Gulhan B, Gucer S et al. (2014) A novel CFHR5 mutation associated with C3 glomerulonephritis in a Turkish girl. Journal of Nephrology 27: 457–60

Bomback AS (2014a) Eculizumab in the treatment of membranoproliferative glomerulonephritis. Nephron Clinical Practice 128: 270–6

Bomback AS (2014b) Anti-complement therapy for glomerular diseases. [Review]. Advances in Chronic Kidney Disease 21: 152–8

Bomback AS, Smith RJ, Barile GR et al. (2012) Eculizumab for dense deposit disease and C3 glomerulonephritis. Clinical Journal of the American Society of Nephrology 7: 748–56

Daina E, Noris M, Remuzzi G (2012) Eculizumab in a patient with dense-deposit disease. New England Journal of Medicine 366: 1161–3

Gurkan S, Fyfe B, Weiss L et al. (2013) Eculizumab and recurrent C3 glomerulonephritis. Pediatric Nephrology 28: 1975–81

Haffner K, Michelfelder S and Pohl M (2015) Successful therapy of C3Nef-positive C3 glomerulopathy with plasma therapy and immunosuppression. Pediatric Nephrology 30: 1951–9

Inman M, Prater G, Fatima H et al. (2015) Eculizumab induced reversal of dialysis-dependent kidney failure from C3 glomerulonephritis. Clinical Kidney Journal 8: 445–8

Kerns E, Rozansky D, Troxell ML (2013) Evolution of immunoglobulin deposition in C3-dominant membranoproliferative glomerulopathy. Pediatric Nephrology 28: 2227–31

Le Quintrec M, Lionet A, Kandel C et al. (2015) Eculizumab for treatment of rapidly progressive C3 glomerulopathy. American Journal of Kidney Diseases 65: 484–9

Oosterveld MJS, Garrelfs MR, Hoppe B et al. (2015) Eculizumab in pediatric dense deposit disease. Clinical Journal of the American Society of Nephrology doi: 10.2215/CJN.01360215

Ozkaya O, Nalcacioglu H, Tekcan D et al. (2014) Eculizumab therapy in a patient with

dense-deposit disease associated with partial lipodystropy. Pediatric Nephrology 29: 1283–7

Payette A, Patey N, Dragon-Durey MA et al. (2015) A case of C3 glomerulonephritis successfully treated with eculizumab. Pediatric Nephrology 30: 1033–7

Pickering MC, D'Agati VD, Nester CM et al (2013) C3 glomerulopathy: consensus report. Kidney International 84: 1079–89

Rousset-Rouviere C, Cailliez M, Garaix F et al. (2014) Rituximab fails where eculizumab restores renal function in C3nef-related DDD. Pediatric Nephrology 29: 1107–11

Vivarelli M, Pasini A, Emma F (2012) Eculizumab for the treatment of dense-deposit disease. New England Journal of Medicine 366: 1163–5

Vivarelli M, Diomedi-Camassei F, Pasini A et al. (2015) Long-term follow-up with repeat biopsy of 5-year treatment with eculizumab for dense deposit disease. Molecular Immunology 67: 193

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

Professor Matthew Pickering has acted as a consultant for Achillion Pharmaceuticals. He has received speakers' fees from Alexion Pharmaceuticals, and funding for pre-clinical

testing of complement therapeutic agents.

Dr Stephen Kardasz declared no relevant interests.

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**.

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