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## Interventions for atypical haemolytic uraemic syndrome (Review)

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[Intervention Review]

# Interventions for atypical haemolytic uraemic syndrome

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## ABSTRACT

### Background

Atypical haemolytic uraemic syndrome (aHUS) is a rare disorder characterised by thrombocytopenia, microangiopathic haemolytic anaemia, and acute kidney injury. The condition is primarily caused by inherited or acquired dysregulation of complement regulatory proteins with ~40% of those affected aged < 18 years. Historically, kidney failure and death were common outcomes, however, improved understanding of the condition has led to discovery of novel therapies.

### Objectives

To evaluate the benefits and harms of interventions for aHUS.

### Search methods

We searched the Cochrane Kidney and Transplant Register of Studies for randomised controlled studies (RCTs) up to 3 September 2020 using search terms relevant to this review. Studies in the Register are identified through searches of CENTRAL, MEDLINE, and EMBASE, conference proceedings, the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov. MEDLINE(OVID) 1946 to 27 July 2020 and EMBASE (OVID) 1974 to 27 July 2020 were searched for non-RCTs.

### Selection criteria

All randomised and non-randomised clinical trials comparing an intervention with placebo, an intervention with supportive therapy, or two or more interventions for aHUS were included. Given the rare nature of the condition in question, prospective single-arm studies of any intervention for aHUS were also included.

### Data collection and analysis

Two authors independently extracted pre-specified data from eligible studies and evaluated risk of bias using a newly developed tool based on existing Cochrane criteria. As statistical meta-analysis was not appropriate, qualitative analysis of data was then performed.

### Main results

We included five single-arm studies, all of which evaluated terminal complement inhibition for the treatment of aHUS. Four studies evaluated the short-acting C5 inhibitor eculizumab and one study evaluated the longer-acting C5 inhibitor ravulizumab. All included studies within the review were of non-randomised, single-arm design. Thus, risk of bias is high, and it is challenging to draw firm conclusions from this low-quality evidence. One hundred patients were included within three primary studies evaluating eculizumab, with further data reported from 37 patients in a secondary study. Fifty-eight patients were included in the ravulizumab study. After 26 weeks of eculizumab therapy there were no deaths and a 70% reduction in the number of patients requiring dialysis. Complete thrombotic microangiopathic (TMA) response was observed in 60% of patients at 26 weeks and 65% at two years. After 26 weeks of ravulizumab therapy four patients

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had died (7%) and complete TMA response was observed in 54% of patients. Substantial improvements were seen in estimated glomerular filtration rate and health-related quality of life in both eculizumab and ravulizumab studies. Serious adverse events occurred in 42% of patients, and meningococcal infection occurred in two patients, both treated with eculizumab.

### Authors' conclusions

When compared with historical data, terminal complement inhibition appears to offer favourable outcomes in patients with aHUS, based upon very low-quality evidence drawn from five single-arm studies. It is unlikely that an RCT will be conducted in aHUS and therefore careful consideration of future single-arm data as well as longer term follow-up data will be required to better understand treatment duration, adverse outcomes and risk of disease recurrence associated with terminal complement inhibition.

## PLAIN LANGUAGE SUMMARY

### What is the most effective treatment for atypical haemolytic uraemic syndrome?

#### What is the issue?

Haemolytic uraemic syndrome (HUS) is a condition involving blockages in small blood vessels leading to destruction of blood cells and dysfunction of several organs, most notably the kidneys. It is commonly caused by infections, often *E.Coli*, and can be associated with diarrhoea. A rare form of HUS known as atypical HUS (aHUS) is a more aggressive form of the disease caused by inherited or acquired abnormalities of proteins involved in controlling an aspect of our immune system known as "complement". Almost half of cases involve patients aged less than 18 years. In the past a diagnosis of aHUS was associated with a poor prognosis with patients often progressing to kidney failure and death. More recently, an improved understanding of the condition has led to better treatments. This review aims to evaluate the usefulness of these treatments by systematically examining the available evidence in order to find out the most effective treatments available for aHUS.

#### What did we do?

We searched the literature extensively and found five studies which tested therapies for aHUS. In four studies the treatment used was eculizumab and in one study the treatment was ravulizumab. Both of these recently developed drugs act in a similar way and have shown promise in other medical conditions.

#### What did we find?

The included studies demonstrated that the majority of patients treated with either eculizumab or ravulizumab showed improvements in kidney function with a large proportion improving enough to stop dialysis treatment. Markers of disease activity in the blood also improved significantly. Over the course of 26 weeks of treatment, no patients given eculizumab died, although two patients did contract meningococcal infections, a likely consequence of the treatment. Although four patients treated with ravulizumab died, none of these deaths were thought to be caused by the drug. The quality of life of patients treated with both drugs was improved significantly.

#### Conclusions

aHUS is an extremely rare condition and without treatment is often fatal. For this reason, we found no studies which were able to compare one treatment with another, or one treatment with no treatment. Instead, the included studies gave all participants either eculizumab or ravulizumab, with results only comparable with historical data obtained before these drugs were available. This introduces substantial bias into the review, and therefore limits the confidence of any recommendations which stem from it. Nevertheless, the best available evidence suggests that treatment with either eculizumab or ravulizumab is effective in patients with aHUS and appears superior to previous therapies.

## SUMMARY OF FINDINGS

### Summary of findings 1. Eculizumab versus placebo or alternative treatment for children and adults with atypical haemolytic uraemic syndrome (aHUS)

#### Eculizumab versus placebo or alternative treatment for children and adults aHUS

**Patient or population:** children and adults with aHUS

**Settings:** inpatient

**Intervention:** eculizumab

**Comparison:** placebo or alternative treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Risk with placebo or alternative treatment	Risk with eculizumab treatment				
Death	N/A	1/100	N/A	100 (4 single-arm studies)	⊕○○○ <b>very low</b>	All 100 patients were alive at 26 weeks. There was 1 death in the 37 patients who were subsequently followed up over 2 years
Requirement for KRT	N/A	N/A	N/A	100 (4 single-arm studies)	⊕○○○ <b>very low</b>	37/100 were undergoing dialysis at initiation of eculizumab therapy. Of these patients, 11 (30%) continued to require regular dialysis after 26 weeks of treatment representing a 70% reduction in dialysis requirement. At 2 years, 3/37 patients included within the secondary study remained dialysis-dependent compared with 7 at baseline (57% reduction)
Disease remission	N/A	60/100	N/A	100 (4 single-arm studies)	⊕○○○ <b>very low</b>	60/100 patients treated with eculizumab achieved complete TMA response after 26 weeks of treatment. Median time to complete TMA response was 56 - 60 days. In a cohort of patients followed up for 2 years, 65% maintained complete TMA response at this time point

Change in eGFR	N/A	N/A	N/A	88 (3 single-arm studies)	⊕○○○ <b>very low</b>	In patients treated with eculizumab, mean change in eGFR over 26 weeks was 33 ± 34 mL/min/1.73 m <sup>2</sup> . At 2 years, eGFR had improved by ≥ 15 mL/min/1.73 m <sup>2</sup> in 37 patients (49%)
HRQoL	N/A	N/A	N/A	100 (4 single-arm studies)	⊕○○○ <b>very low</b>	In 49 patients aged ≥ 12 years treated with eculizumab, 67% demonstrated a clinically significant improvement in EQ-5D score. In 22 paediatric patients treated with eculizumab the mean improvement in FACIT-F score was 19.7 (improvement of > 4.7 considered clinically meaningful)
Adverse events	N/A	100/100	N/A	100 (4 single-arm studies)	⊕○○○ <b>very low</b>	Adverse events occurred in 100% of patients treated with eculizumab. Serious adverse events occurred in 37% of patients. The most commonly reported events included diarrhoea (23%), fever (21%), headache (19%), upper respiratory tract infection (19%), cough (17%) and urinary tract infection (10%)
Meningococcal infection	N/A	2/100	N/A	100 (4 single-arm studies)	⊕○○○ <b>very low</b>	Meningococcal infection occurred in 2 patients (2%) treated with eculizumab

\*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio; **N/A:** not applicable; **KRT:** Kidney replacement therapy; **TMA:** Thrombotic microangiopathy; **eGFR:** Estimated glomerular filtration rate; **HRQoL:** health-related quality of life; **FACIT-F:** Functional assessment of chronic illness therapy - fatigue.

GRADE Working Group grades of evidence

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** We are very uncertain about the estimate.

## Summary of findings 2. Ravulizumab versus placebo or alternative treatment for adults with atypical haemolytic uraemic syndrome (aHUS)

### Ravulizumab versus placebo or alternative treatment for adults with aHUS

**Patient or population:** adults with aHUS

**Settings:** inpatient

**Intervention:** ravulizumab

**Comparison:** placebo or alternative treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Risk with placebo or alternative treatment	Risk with ravulizumab treatment				
Death	N/A	4/58	N/A	58 (1 single-arm study)	⊕○○○ <b>very low</b>	Four deaths occurred, including one in a patient ultimately excluded based on eligibility criteria but who had received one dose of ravulizumab. No deaths were considered treatment-related by the study investigators
Requirement for KRT	N/A	N/A	N/A	56 (1 single-arm study)	⊕○○○ <b>very low</b>	29/56 were undergoing dialysis at initiation of ravulizumab therapy. Of these patients, 12 (41%) continued to require regular dialysis after 26 weeks of treatment representing a 59% reduction in dialysis requirement
Disease remission	N/A	30/56	N/A	56 (1 single-arm study)	⊕○○○ <b>very low</b>	30/56 patients treated with ravulizumab achieved complete TMA response after 26 weeks of treatment. Median time to complete TMA response was 86 days
Change in eGFR	N/A	N/A	N/A	56 (1 single-arm study)	⊕○○○ <b>very low</b>	In patients treated with ravulizumab, mean change in eGFR over 26 weeks was 35 ± 35 mL/min/1.73 m <sup>2</sup>
HRQoL	N/A	N/A	N/A	44 (1 single-arm study)	⊕○○○ <b>very low</b>	A clinically meaningful improvement in FACIT-F score (≥ 3-point increase) was observed in 84% of patients treated with ravulizumab
Adverse events	N/A	58/58	N/A	58 (1 single-arm study)	⊕○○○ <b>very low</b>	Adverse events occurred in 100% of patients treated with ravulizumab. Serious adverse events occurred in 52% of patients. The most commonly reported events included headache (36%), diarrhoea (31%), vomiting (26), hypertension (22%), nausea (22%) and urinary tract infection (17%)
Meningococcal infection	N/A	0/58	N/A	58 (1 single-arm study)	⊕○○○ <b>very low</b>	No patients treated with ravulizumab developed meningococcal infection

\*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk Ratio; **N/A:** not applicable; **KRT:** Kidney replacement therapy; **TMA:** Thrombotic microangiopathy; **eGFR:** Estimated glomerular filtration rate; **HRQoL:** Health-related quality of life; **FACIT-F:** Functional assessment of chronic illness therapy - fatigue.

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GRADE Working Group grades of evidence

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** We are very uncertain about the estimate.

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## BACKGROUND

### Description of the condition

Haemolytic uraemic syndrome (HUS) is a form of thrombotic microangiopathy (TMA) which affects adults and children and is characterised by thrombocytopenia, microangiopathic haemolytic anaemia and acute kidney injury (AKI) (Noris 2009). The term HUS encompasses several different disease processes which can be broadly divided into infection-induced HUS, HUS secondary to a pre-existing condition, or atypical HUS (aHUS) (Loirat 2016).

Around 90% of cases of HUS are considered infection-induced and are most typically associated with either Shiga toxin-producing *Escherichia coli* (STEC) or *Streptococcus pneumoniae* (Ariceta 2009). STEC-associated cases are often (but not always) preceded by the onset of bloody diarrhoea (Besbas 2006). Pre-existing conditions leading to the development of HUS include autoimmune diseases, stem cell or solid organ transplantation, and certain malignancies. This category of HUS can also be associated with certain drugs and with pregnancy (Fakhouri 2017).

The remainder of cases fall into the category of aHUS. Classically this term has been used to describe HUS associated with dysregulation of the alternative complement pathway due to either inherited or acquired dysfunction of complement regulatory proteins (Noris 2009). Further subdivision of this group is now possible, including recognition of those with anti-factor H autoantibodies (a subgroup which accounts for ~10% of paediatric aHUS) (Fremeaux-Bacchi 2013). More recently the definition of aHUS has been broadened to include other rare forms of HUS including diacylglycerol kinase E and Cobalamin C deficiency, as well as HUS with no clear precipitant (Loirat 2016).

The incidence of aHUS based on this broader classification is 0.23 to 0.42 cases/million population/year, with around 35% to 42% of cases occurring in children under the age of 18 (Fremeaux-Bacchi 2013; Sheerin 2016).

Diagnosis is based on the presence of thrombocytopenia, microangiopathic haemolysis, and kidney injury and the exclusion of other forms of HUS or thrombotic thrombocytopenic purpura (TTP). A genetic or acquired abnormality of complement regulation can be identified in around 50% of cases, however therapeutic interventions are often required before this information is available (Sheerin 2016).

Historically up to 25% of people die during the acute illness (Kaplan 2014). Of those surviving, 50% require acute kidney replacement therapy (KRT) of whom a significant proportion never recover native kidney function and require long-term KRT (Constantinescu 2004; Noris 2009).

### Description of the intervention

Plasma exchange and plasma infusion have been the main treatments for aHUS since the early 1990s and work by replacing absent or removing abnormal complement proteins within the body. Although death rates decreased significantly following the introduction of plasma therapies a proportion of patients struggle to tolerate regular plasma therapy and relapse following discontinuation of treatment (Lara 1999; Noris 2005). Various other agents including corticosteroids, antiplatelet agents and thrombolytics have been studied with varying results. Liver

transplantation has also been used as a treatment for aHUS in a small number of patients with known genetic complement factor deficiencies (Saland 2009). As certain complement factors such as factor H and factor I are produced in the liver successful transplantation, either alone or with combined kidney transplant, has the potential to cure aHUS in this subset of patients (Coppo 2016). However, this intervention is not without significant risk of morbidity and death and is not available in all centres (Remuzzi 2005).

Eculizumab, a humanised monoclonal antibody, targets complement component C5 in an attempt to halt the dysregulated activation of the complement pathway, reducing endothelial injury and subsequent organ dysfunction. Eculizumab is now recognised as the treatment of choice for paroxysmal nocturnal haemoglobinuria (PNH), a condition which also involves dysregulated terminal complement activation. Several studies have shown it to be effective for this indication with an acceptable safety profile (Hillmen 2013; Kanakura 2011). More recently, a longer-acting C5 inhibitor, ravulizumab, has demonstrated non-inferiority to eculizumab for the treatment of PNH with the additional benefit of reduced dosing frequency (Lee 2019; Kulasekararaj 2019). Both eculizumab and ravulizumab may therefore be superior to plasma therapy in the treatment of aHUS due to the ability to “switch off” abnormal complement activity.

### Why it is important to do this review

A previous Cochrane Review has identified and evaluated interventions for HUS but this was not specific to aHUS (Michael 2009). Importantly, this review was conducted prior to the widespread use of eculizumab for the treatment of aHUS. We therefore considered it important to carry out this review in order to identify and evaluate emerging interventions for aHUS given the recent advances in our understanding of disease pathogenesis and directed treatment.

## OBJECTIVES

This review aims to evaluate the benefits and harms of interventions for aHUS.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

All randomised controlled trials (RCTs), quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) and non-randomised studies which compare an intervention with placebo, an intervention with supportive therapy, or two or more interventions for aHUS were included. Given the rare nature of the condition in question, prospective single-arm studies of any intervention for aHUS were also included.

#### Types of participants

##### Inclusion criteria

Studies including patients of all ages with a confirmed diagnosis of aHUS. This diagnosis is defined as all three of:

- Evidence of kidney impairment (raised serum creatinine (SCr) or equivalent biomarker which meets local criteria for AKI)
- Evidence of thrombocytopenia (platelet count < 150 x 10<sup>9</sup>/L)
- Evidence of haemolysis (lactate dehydrogenase (LDH) above upper limit of normal, haptoglobin count below the lower limit of normal, evidence of fragmented red blood cells in a peripheral blood smear, or presence of schistocytes)

### Exclusion criteria

The following patient groups were excluded.

- Patients with evidence of STEC infection
- Patients with evidence of Streptococcus pneumoniae infection
- Patients with evidence of ADAMTS-13 deficiency (level at or below 10% in plasma)
- Patients with evidence of HUS as a consequence of a pre-existing condition or disease including malignancy, haematopoietic stem cell transplantation, solid organ transplantation, infections, autoimmune conditions, malignant hypertension, and drug-induced HUS
- Patients with pregnancy-associated HUS.

### Types of interventions

Any intervention for aHUS was considered including, but not limited to, eculizumab, ravulizumab, plasma exchange, plasma infusion, anti-platelet agents, thrombolytics, immunosuppressants, corticosteroids, and liver transplantation.

### Types of outcome measures

#### Primary outcomes

- Death (any cause)
- Requirement for KRT
- Successful remission as defined independently by each study. This may involve normalisation or stabilisation of platelet count, resolution of haemolysis, or resolution of AKI.

#### Secondary outcomes

- Change in SCr or glomerular filtration rate (GFR)
- Persistent requirement for plasma therapy
- Degree of proteinuria: as evidenced by urinalysis, urine protein:creatinine ratio (UPCR), or 24-hour urine protein measurement
- Presence of hypertension: as evidenced by the need for, and number of, antihypertensive agents
- Kidney biopsy changes: as there is no standardised system for reporting the varied biopsy changes associated with aHUS, we planned to report subjective scales as presented in each paper individually, e.g. mild/moderate/severe, an estimation of severity such as presence/percentage of crescents, an estimation of acute activity if provided- for example by endothelial cell swelling, lumen narrowing or thrombi formation in the interlobular arteries, arterioles and glomerular capillaries as well as information on chronicity by evaluating the extent of glomerulosclerosis, tubular atrophy and interstitial fibrosis present on the biopsy
- Health-related quality of life (HRQoL): as no disease specific tools exist, currently validated tools such as questionnaires like the 36 Item Short-Form Survey, EuroQoL 5 Domain

tool, Consensus-based Standards for the selection of health status Measurement Instruments (COSMIN) and the Evaluating Measures of Patient-Reported Outcomes (EMPRO) are appropriate

- Adverse events
- Meningococcal infection.

### Search methods for identification of studies

#### Electronic searches

We searched the [Cochrane Kidney and Transplant Register of Studies](#) up to 3 September 2020 through contact with the Information Specialist using search terms relevant to this review. The register contains studies identified from the following sources.

1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL)
2. Weekly searches of MEDLINE OVID SP
3. Searches of kidney and transplant journals, and the proceedings and abstracts from major kidney and transplant conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected kidney and transplant journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Studies contained in the register are identified through searches of CENTRAL, MEDLINE, and EMBASE based on the scope of Cochrane Kidney and Transplant. Details of search strategies, as well as a list of handsearched journals, conference proceedings and current awareness alerts, are available on the Cochrane Kidney and Transplant website under [CKT Register of Studies](#).

MEDLINE(OVID) 1946 to 27 July 2020 and EMBASE (OVID) 1974 to 27 July 2020 were searched for non-RCTs.

See [Appendix 1](#) for search terms used in strategies for this review.

#### Searching other resources

1. Reference lists of review articles, relevant studies, and clinical practice guidelines.
2. Letters seeking information about unpublished or incomplete studies to investigators known to be involved in previous studies.

### Data collection and analysis

#### Selection of studies

The search strategy described was used to obtain titles and abstracts of studies relevant to the review. The titles and abstracts were screened independently by two authors, who discarded studies that were not applicable; however studies and reviews that included relevant data or information on studies were retained initially. Two authors then independently assessed retrieved abstracts and, if necessary, the full text of these studies, to determine which studies satisfied the inclusion criteria.

#### Data extraction and management

Data extraction was carried out independently by two authors using standardised data extraction forms. Studies reported in non-English language journals were translated before assessment.

Where more than one publication of one study existed, reports were grouped together and the publication with the most complete data was used in the analyses.

### Assessment of risk of bias in included studies

Three independent risk of bias assessment tools were assigned to analyse risk of bias in RCTs, non-randomised studies and single-arm studies. For each included study, two authors independently assessed risk of bias using the assigned tool. It was our intention, where possible, to evaluate risk of bias in RCTs using the Cochrane risk of bias tool (Appendix 2), in non-RCTs (where there was direct comparison between two or more treatment arms, or with a historical or external comparator) using the ROBINS-I tool (Sterne 2016), and in single-arm studies using a newly developed tool designed specifically for this purpose (Appendix 3).

The recently designed tool for assessing risk of bias in single-arm studies considered the following items.

- Selection bias
- Lead time bias/immortal time bias
- Confounding by indication
- Misclassification bias/information bias
- Bias from natural recovery/regression to the mean
- Bias due to adjunctive therapies
- Attrition bias
- Selective reporting of outcomes.

### Measures of treatment effect

For dichotomous outcomes results were to be expressed as risk ratio (RR) with 95% confidence intervals (CI). Where continuous scales of measurement were used to assess the effects of treatment the mean difference (MD) was to be used, or the standardised mean difference (SMD) if different scales were used. Due to the nature of the included studies these analyses were not possible.

### Unit of analysis issues

There were no unit of analysis issues.

### Dealing with missing data

Any further information required from the original author was requested by written correspondence (e.g. emailing corresponding author). Evaluation of important numerical data such number of patients screened, randomised as well as intention-to-treat, as-treated and per-protocol population was carefully performed. Attrition rates, for example drop-outs, losses to follow-up and withdrawals were investigated. Issues of missing data and imputation methods (for example, last-observation-carried-forward) were critically appraised (Higgins 2011).

### Assessment of heterogeneity

If suitable studies were identified, we planned to first assess heterogeneity by visual inspection of the forest plot and subsequently quantify statistical heterogeneity using the  $I^2$  statistic, which describes the percentage of total variation across studies that is due to heterogeneity rather than sampling error (Higgins 2003). Due to the nature of the included studies no such assessment was possible. Due to the inclusion of non-randomised and single-arm studies, it was anticipated that a greater degree of

heterogeneity would be apparent among included studies and this was taken into account when considering potential sources of bias.

### Assessment of reporting biases

If possible, funnel plots were to be used to assess for the potential existence of small study bias (Higgins 2011).

### Data synthesis

Unadjusted data from included RCTs were to be pooled using the random-effects model or the fixed-effect model however this was not possible. It was our intention to combine data from non-randomised studies for meta-analysis only when such data were considered to be significantly free from bias and heterogeneity as assessed independently by two authors, however again this was not possible. In such circumstances, consideration would be given to analyse adjusted, rather than unadjusted, effect estimates as an inverse-variance weighted average. Where pooling of data was not appropriate then qualitative data synthesis only was performed.

### Subgroup analysis and investigation of heterogeneity

Subgroup analysis was to be used to explore possible sources of heterogeneity (e.g. participants or interventions). Heterogeneity among participants could be related to their age, whether they were being treated for a first presentation or relapse of aHUS, specific complement mutations identified, whether they required acute KRT, or whether or not they had developed aHUS after a kidney transplant. Heterogeneity in interventions could be related to the dosage and duration of therapies used, as well as co-interventions and previous treatments.

### Sensitivity analysis

If suitable data were acquired, we planned to perform sensitivity analyses in order to explore the influence of the following factors on effect size.

- Repeating the analysis excluding unpublished studies
- Repeating the analysis taking account of risk of bias, as specified
- Repeating the analysis excluding any very long or large studies to establish how much they dominate the results
- Repeating the analysis excluding studies using the following filters: diagnostic criteria, language of publication, source of funding (industry versus other), and country.

### Summary of findings and assessment of the certainty of the evidence

We planned to present the main results of the review in 'Summary of findings' tables. These tables present key information concerning the quality of the evidence, the magnitude of the effects of the interventions examined, and the sum of the available data for the main outcomes (Schunemann 2011a). The 'Summary of findings' tables also include an overall grading of the evidence related to each of the main outcomes using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach (GRADE 2008). The GRADE approach defines the quality of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the true quantity of specific interest. The quality of a body of evidence involves consideration of within-trial risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates

and risk of publication bias (Schunemann 2011b). We planned to present the following outcomes in the 'Summary of findings' tables.

- Death (any cause)
- Requirement for KRT
- Disease remission
- Persistent elevation of SCr and/or GFR of < 60 mL/min/1.73 m<sup>2</sup>
- Persistent requirement for plasma therapy
- Adverse events due to treatment.

## RESULTS

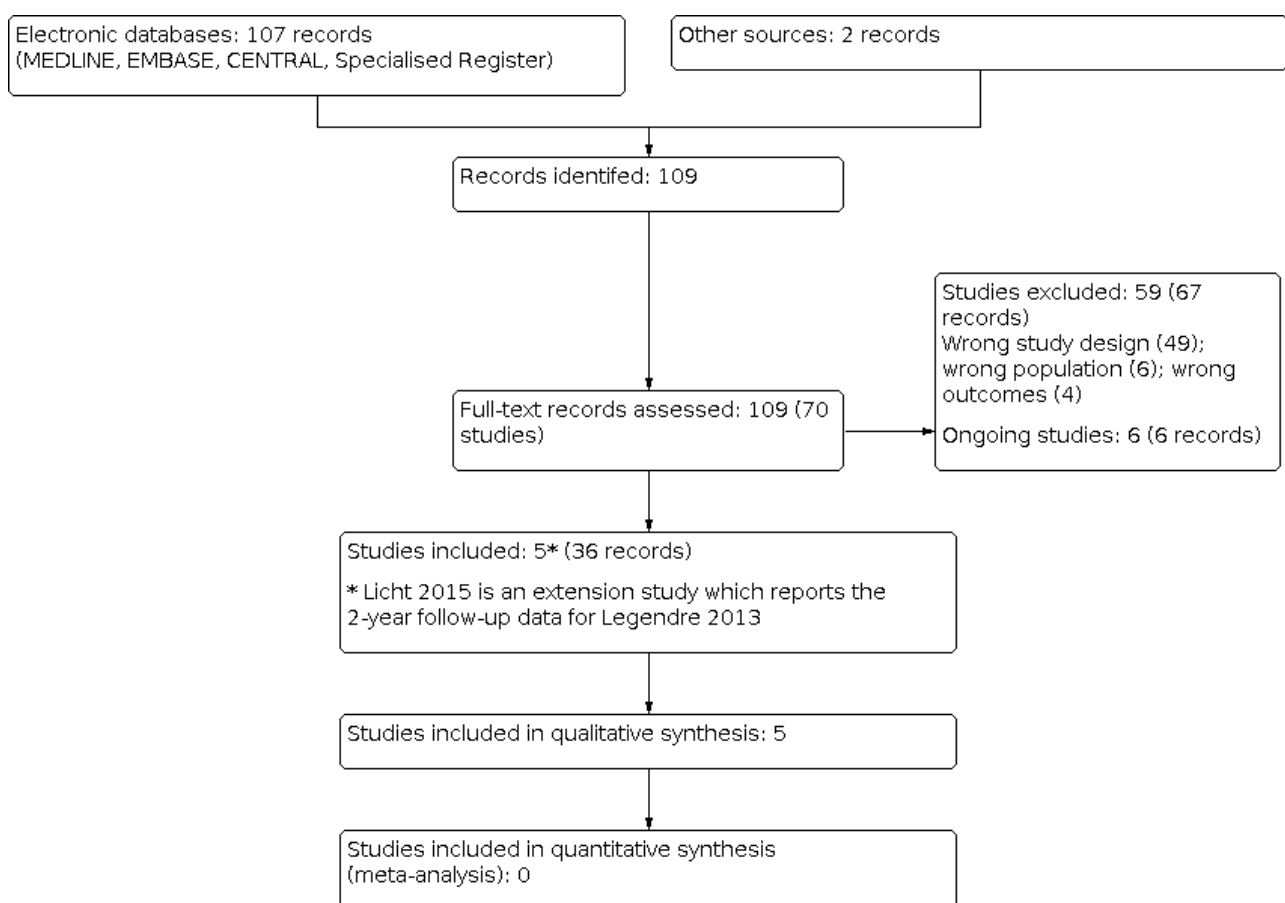
### Description of studies

See [Characteristics of included studies](#); [Characteristics of excluded studies](#); [Characteristics of ongoing studies](#).

### Results of the search

We performed an initial search of Cochrane Kidney and Transplant's Specialised Register (including CENTRAL, MEDLINE and EMBASE) in November 2017. From this initial search we identified 81 records. Further searches were conducted in February 2019 (yielding a further six records) and September 2020 (yielding a further 20 records) providing a total of 107 records. Two records were identified through additional searching of record references. After screening titles and abstracts and full-text review, five studies (36 reports) were included, 59 studies (67 reports) were excluded, and six ongoing studies were identified (EUCTR2017-001082-24; EudraCT2014-001032-11; NCT01757431; NCT03131219; NCT03205995; UMIN000014869) These six studies and will be assessed in a future update of this review (Figure 1).

**Figure 1. Study flow diagram.**



### Included studies

All five included studies were of non-randomised, single-arm design and evaluated terminal complement inhibition in patients with aHUS without a comparator group. Four studies evaluated eculizumab, a short-acting C5 inhibitor (Fakhouri 2016; Greenbaum 2016; Legendre 2013; Licht 2015), and one study evaluated ravulizumab, a longer-acting C5 inhibitor (Rondeau 2020). More information is presented in the [Characteristics of included studies](#) section. Licht 2015 reported two-year extension data from Legendre 2013 and thus describes the same patient population.

It has therefore been described as a secondary study, with the remainder of the included studies described as primary studies. All included studies were sponsored by Alexion Pharmaceuticals who are responsible for manufacturing both eculizumab and ravulizumab.

Given the rare nature of the condition in question all four primary studies recruited patients from multiple sites. Two studies (Fakhouri 2016; Legendre 2013) included patients from Europe and North America. Greenbaum 2016 included patients from Europe,

North America, and Australia, and [Rondeau 2020](#) included patients from Europe, North America, Australia, and Asia.

All included patients had a diagnosis of aHUS with similar diagnostic criteria used within each study ([Characteristics of included studies](#)). [Legendre 2013](#) subdivided participants into two sub-studies; those with progressive TMA with resistance to plasma therapy, and those with a chronic aHUS phenotype receiving maintenance plasma therapy. In all other primary studies there was no such subdivision. Of note, [Rondeau 2020](#) was the only study to exclude patients requiring chronic haemodialysis at baseline.

[Greenbaum 2016](#) focused on the paediatric aHUS population, including patients aged one month to 18 years. [Legendre 2013](#) included adolescent and adult patients ( $\geq 12$  years) in both sub-studies, and [Fakhouri 2016](#) and [Rondeau 2020](#) included only adult patients ( $\geq 18$  years). As [Licht 2015](#) is an extension of [Legendre 2013](#), this study also involved adolescent and adult patients.

There were 158 patients included in the four primary studies with further data reported from 37 patients in the secondary study. The age range was five months to 80 years with 28 of the 158 included primary patients under the age of 18 years (18%). Total duration of therapy was 26 weeks in all four primary studies. Two studies ([Fakhouri 2016](#); [Legendre 2013](#)) used a dosing regimen of intravenous eculizumab 900 mg once/week for 4 weeks, 1,200 mg at week 5, and then 1,200 mg every 2 weeks. Paediatric dosing of eculizumab ([Greenbaum 2016](#)) was based upon weight with dosing sufficient to ensure that  $> 95\%$  of patients had complete and sustained terminal complement inhibition and to provide peak plasma concentrations within a target range of 50 to 700 mg/mL. Ravulizumab dosing was based upon weight with an initial intravenous loading dose of 2400 to 3000 mg followed by maintenance doses of 3000 to 3600 mg on day 15 and every 8 weeks thereafter.

Plasma therapy and/or plasma exchange was used as additional therapy in the eculizumab studies where required ([Fakhouri 2016](#); [Greenbaum 2016](#); [Legendre 2013](#); [Licht 2015](#)), however was not permitted in the ravulizumab study ([Rondeau 2020](#)).

### Excluded studies

We excluded 59 studies (67 records). Reasons for exclusion included retrospective study design, incorrect patient population, duplicate data, and incorrect study outcomes.

We contacted two authors to enquire about unpublished data discussed in abstracts, and to seek clarification where data discussed in papers appeared to represent a subgroup of a larger published study. One author confirmed that the data represented analysis of patient cohorts published elsewhere and the study was grouped accordingly ([Van De Kar 2014](#)). The other author confirmed that the study did not meet our inclusion criteria ([Khandelwal 2016](#)).

### Risk of bias in included studies

All included studies within the review were of non-randomised, single-arm design. Thus, the overall risk of bias is high, limiting the confidence in the results of this review. Despite this, some single-arm studies are subject to higher degrees of bias than others, and certain forms of bias can largely be eliminated with effective single-arm study design. The following assessment was compiled using

the Cochrane risk of bias in single-arm studies assessment tool ([Appendix 3](#)).

As all included studies were non-randomised, single-arm studies, there was no blinding of participants or investigators. It was therefore clear which patients were receiving either eculizumab or ravulizumab (all included patients) and this will have influenced results.

Eligibility criteria were clearly described and were similar in all studies thus reducing the possibility of selection bias. However, as all included studies were of single-arm design it was not possible to compare eligibility criteria with studies with comparator groups. The process of patient recruitment was not clearly defined in any of the included studies. Given the rarity of the condition it is likely that all eligible participants encountered during the recruitment period were recruited, but this is not specifically reported.

In three of the four primary studies ([Fakhouri 2016](#); [Greenbaum 2016](#); [Rondeau 2020](#)) the time between recruitment and initiation of therapy was minimal. In [Legendre 2013](#) participants in the first sub-study were treated within 3 days, however those in the second sub-study underwent an eight-week observation period following recruitment and prior to initiation of treatment which may have increased the potential for lead time bias.

Eculizumab and ravulizumab dosing and outcome measures were clearly defined at the outset in all studies reducing the potential for misclassification or information bias.

Outcome variables were generally measured at outset and at end-point in all studies (e.g. requirement for dialysis, degree of kidney impairment, requirement for plasma therapy). Previous studies of aHUS have demonstrated that prior to the advent of effective therapies the natural course of the condition if untreated is likely to be death. It is likely, therefore, that bias from natural recovery was negligible in all studies.

The requirement for plasma therapy (the main adjunctive therapy used) both before, during and after the treatment period was well described in all studies where it was permitted.

All four primary studies clearly documented reasons for participant withdrawal, which was uncommon. Three primary studies were analysed based on an intention to treat basis ([Fakhouri 2016](#); [Greenbaum 2016](#); [Legendre 2013](#)). [Rondeau 2020](#) included all initially enrolled and treated participants in their safety analysis, however, excluded two participants from their full analysis on the basis of ineligibility.

There was no evidence of selective reporting in any of the included studies.

### Effects of interventions

See: [Summary of findings 1 Eculizumab versus placebo or alternative treatment for children and adults with atypical haemolytic uraemic syndrome \(aHUS\)](#); [Summary of findings 2 Ravulizumab versus placebo or alternative treatment for adults with atypical haemolytic uraemic syndrome \(aHUS\)](#)

Either eculizumab or ravulizumab therapy was the sole intervention in all five included studies with no comparator groups.

Meta-analysis was therefore not feasible, and a descriptive analysis was performed.

### Death (any cause)

#### *Eculizumab*

All 100 patients included within the three primary studies were alive at 26 weeks (completion of initial eculizumab treatment period). Of the 37 patients included in [Licht 2015](#), one patient (3%) had died at two years. This was as a result of complications of intestinal haemorrhage which were thought to be unrelated to eculizumab therapy.

#### *Ravulizumab*

Of the 58 patients included within the safety analysis, four patients (7%) had died by 26 weeks. None of these deaths were thought to be related to the study drug and were caused by septic shock (2), intracerebral haemorrhage, and cerebral artery thrombosis.

### Requirement for kidney replacement therapy

#### *Eculizumab*

There were 37/100 patients included in the primary studies who were undergoing dialysis at initiation of eculizumab therapy. Of these patients, 26 discontinued regular dialysis after 26 weeks of treatment representing a 70% reduction in dialysis requirement. At two years, 3/37 patients included within the secondary study remained dialysis-dependent compared with 7/37 at baseline (57% reduction) ([Licht 2015](#)).

#### *Ravulizumab*

Unlike the eculizumab studies, patients undergoing chronic haemodialysis for established end-stage kidney disease (ESKD) at baseline were excluded from [Rondeau 2020](#), although patients undergoing haemodialysis due to AKI as a result of aHUS were included. Dialysis was discontinued in 17/29 patients who required dialysis at baseline (59%).

### Disease remission

#### *Eculizumab*

Disease remission, or complete TMA response, was defined similarly by each of the three included primary eculizumab studies. In all three studies the definition included haematological normalisation (platelet count maintained  $\geq 150 \times 10^9/L$  and LDH maintained below the upper limit of normal on two separate measurements  $\geq$  four weeks apart) and either improvement ( $\geq 25\%$  reduction in SCr from baseline) ([Greenbaum 2016](#); [Legendre 2013](#)) or preservation ( $< 25\%$  increase in SCr from baseline) ([Fakhouri 2016](#)) of kidney function. Sixty percent of patients achieved complete TMA response after 26 weeks of eculizumab treatment. Median time to complete TMA response was 56 days in one study involving adult patients ([Fakhouri 2016](#)) and 60 days in a study involving patients  $< 18$  years ([Greenbaum 2016](#)). Follow-up data from [Licht 2015](#) showed that 65% of patients (37) had achieved complete TMA response at two years.

#### *Ravulizumab*

Complete TMA response was defined by [Rondeau 2020](#) as platelet count normalisation ( $\geq 150 \times 10^9/L$ ), LDH normalisation ( $< 246 U/L$ ), and  $\geq 25\%$  improvement in SCr from baseline at two separate

assessments obtained at least 28 days apart. Fifty-four percent of patients achieved complete TMA response during the 26-week treatment period. The median time to complete TMA response was 86 days.

### Kidney function

#### *Eculizumab*

Mean increase in eGFR over 26 weeks was  $33 \pm 34$  mL/min/1.73 m<sup>2</sup> for patients in the three primary studies (88 patients). Baseline eGFR was not reported. eGFR improved by  $\geq 15$  mL/min/1.73 m<sup>2</sup> in 50% of patients at 26 weeks. At two years, eGFR had improved by  $\geq 15$  mL/min/1.73 m<sup>2</sup> in 37 patients (49%) ([Licht 2015](#)).

#### *Ravulizumab*

Mean increase in eGFR over 26 weeks in those treated with ravulizumab was  $35 \pm 35$  mL/min/1.73 m<sup>2</sup> (56 patients). eGFR improved by at least one eGFR category in 47 patients with available data (68%).

### Requirement for plasma therapy

#### *Eculizumab*

Prior to the widespread use of eculizumab, treatment of aHUS largely depended upon regular plasma therapy (including plasma exchange). At initiation of eculizumab 81 patients (81%) were receiving plasma therapy. After 26 weeks of treatment, two patients (2%) remained reliant upon plasma therapy, representing a 98% reduction in requirement for this time- and labour-intensive treatment.

#### *Ravulizumab*

Plasma therapy was not permitted as an adjunctive treatment in the ravulizumab study.

### Proteinuria

#### *Eculizumab*

Change in degree of proteinuria was only assessed by one primary study ([Legendre 2013](#)) and by the secondary study ([Licht 2015](#)). At baseline, 26 patients (70%) had  $\geq 1+$  proteinuria on dipstick urinalysis. Of this group, 18 patients (69%) had a reduction of  $\geq 1$  proteinuria 'grade' (as assessed by dipstick urinalysis) after 26 weeks. This figure increased to 85% at two years ([Licht 2015](#)). Baseline UPCr was  $2.46 \pm 1.74$  g/mmol with a mean reduction in UPCr of  $0.74 \pm 0.75$  g/mmol after 26 weeks (37 patients).

#### *Ravulizumab*

Proteinuria was not assessed by [Rondeau 2020](#).

### Blood pressure

This outcome was not reported by any of the included studies.

### Renal biopsy change

This outcome was not reported by any of the included studies.

### Health-related quality of life

#### *Eculizumab*

HRQoL was measured in all studies using a variety of tools including EQ-5D, 36-Item Short Form Health Survey (SF-36), and Functional

Assessment of Chronic Illness – Fatigue (FACIT-F) (adult and paediatric versions). Of the adult and adolescent population (age  $\geq$  12 years), 67% demonstrated a clinically meaningful improvement ( $> 0.06$ ) in EQ-5D score (49 patients). [Greenbaum 2016](#) used a paediatric FACIT-F tool to demonstrate a mean improvement in score of 19.7, with an improvement of  $> 4.7$  considered clinically meaningful (22 patients) ([Lai 2007](#)).

### **Ravulizumab**

[Rondeau 2020](#) assessed HRQoL using the adult FACIT-F score at baseline and at 26 weeks. A clinically meaningful improvement ( $\geq$  3-point increase) was observed in 44 patients with available data (84%).

### **Adverse events**

#### **Eculizumab**

Serious adverse events occurred in 37% of patients included within the primary eculizumab studies. Adverse events occurred in 100% of patients. The most commonly reported events included diarrhoea (23%), fever (21%), headache (19%), upper respiratory tract infection (19%), cough (17%), and urinary tract infection (10%). Reporting of adverse events was incomplete in two of three primary studies ([Fakhouri 2016](#); [Greenbaum 2016](#)). [Fakhouri 2016](#) reported all serious adverse events and adverse events occurring in  $> 15\%$  of patients. [Greenbaum 2016](#) reported all adverse events but only serious adverse events occurring in  $\geq 2$  patients. All serious adverse events and adverse events were clearly reported by [Legendre 2013](#).

#### **Ravulizumab**

Although only 56 patients with confirmed eligibility were included within the complete analysis for this study, all patients (58) treated with at least one dose of ravulizumab were included within the safety analysis. At least one adverse event occurred in all patients, and serious adverse events occurred in 52%. The most frequent adverse events observed were headache (36%), diarrhoea (31%), vomiting (26%), hypertension (22%), nausea (22%), and urinary tract infection (17%). The most common serious adverse events (occurring in  $\geq 3\%$  of patients) included malignant hypertension (3%) and infections including pneumonia (5%), and septic shock (3%).

### **Meningococcal infection**

#### **Eculizumab**

Meningococcal infection occurred in two patients (2%) in the primary studies. One patient developed meningococcal meningitis which led to permanent discontinuation of eculizumab therapy. A second patient developed meningococcal sepsis and was hospitalised but was able to continue eculizumab. In both cases the patients recovered. Both patients had received meningococcal vaccination against serogroups A, C, W, and Y but had not been prescribed long-term antibiotics.

#### **Ravulizumab**

No episodes of meningococcal infection were reported within the ravulizumab study.

## **DISCUSSION**

### **Summary of main results**

This review evaluates the best available evidence for current interventions for aHUS. In four single-arm studies, terminal complement inhibition (either eculizumab or ravulizumab) was used to treat 158 patients over a period of 26 weeks with no comparator groups. A fifth study described two-year follow-up data from a subset patients treated with eculizumab.

Death at 26 weeks was zero in each of the eculizumab studies, and of the selected 37 patients which formed the two-year follow-up only one died. In the ravulizumab study death was 7% at 26 weeks. Plasma exchange/infusion has been the historical standard of care for aHUS prior to the introduction of C5 inhibitors. Observational data of patients with aHUS treated with plasma exchange/infusion describe death rates of up to 8% at first presentation and 11% at three years in one series ([Noris 2010](#)), and 4% after median follow-up of 45 months in another ([Fremeaux-Bacchi 2013](#)). While longer term data are lacking, reported death rates for eculizumab in particular are notably improved.

Substantial improvements were seen in kidney function, haematological parameters, and quality of life after 26 weeks of therapy in all studies. All studies showed an overall reduction in the number of patients with a requirement for KRT following treatment, ranging from a reduction of 57% ([Legendre 2013](#)) to 82% ([Greenbaum 2016](#)). At 26 weeks, 35% of patients who were KRT-dependent at baseline and treated with either eculizumab or ravulizumab remained KRT-dependent. Historically, patients treated with plasma therapies have demonstrated rates of KRT dependency of up to 67% ([Noris 2010](#)). Haematological remission was achieved in 58% of patients at 26 weeks. Longer term data are limited, but effects with eculizumab appear to be maintained at two years with 65% of patients in the secondary study achieving complete TMA response by this time point. Again, this compares favourably with observational data of patients treated with plasma therapies with one series reporting partial or complete response in  $\sim 50\%$  of those treated with plasma exchange or infusion, but with fewer patients maintaining this response in the long term ([Noris 2010](#)).

Adverse events were common in all included studies. [Licht 2015](#) identified four patients (11% of that study group) undergoing extended therapy who suffered serious adverse events (accelerated hypertension, asymptomatic bacteriuria, and hypertension). Less serious adverse events were common, and most often occurred during the first six months of treatment. [Legendre 2013](#) reported that, while there were no “infection related” events, all patients had at least one serious adverse event in their first sub-trial, while 50% had serious adverse events in their second sub-trial. While the authors do not ascribe all of these events directly to eculizumab, they included hypertension, peritonitis, influenza, and a venous disorder not otherwise specified. All events resolved within 26 weeks of treatment and did not necessitate interruption to the treatment regime. [Greenbaum 2016](#) reported similarly high levels of treatment-emergent adverse events in 20/22 patients, the most common being fever, cough, abdominal pain, diarrhoea, and upper respiratory tract infection. The most serious events occurred in an infant and child less than 12 years of age – viral induced bone marrow suppression (parainfluenza type 3), wrist fracture and acute respiratory failure. Fifty nine percent of patients

reported one or more serious adverse event, one of which led to treatment discontinuation. All patients included within the safety analysis of [Rondeau 2020](#) suffered at least one adverse event and > 50% suffered a serious adverse event. Three patients discontinued ravulizumab because of a serious adverse event. Despite this, the authors report that none of the serious adverse events observed were considered 'unexpected'. All patients were vaccinated against meningococcal infection. Despite this, two patients treated with eculizumab developed meningococcal infections, both of whom recovered.

The included studies offer little evidence to guide discontinuation of C5 inhibitor therapy. Eculizumab and ravulizumab are both expensive, and thus guidance on when, if at all, these drugs can be safely withdrawn in patients with aHUS without risking relapse is an important consideration.

Thirty-four patients included within the four primary studies had previously undergone kidney transplantation with recurrence of aHUS post-transplant and outcomes following treatment with either eculizumab or ravulizumab in this setting suggest efficacy. Several retrospective case-series have suggested positive outcomes with eculizumab following kidney transplantation in patients with aHUS as a measure to maintain remission, rather than treat recurrent disease ([Alpay 2019](#); [Bhalla 2019](#)), but this was not assessed in this review. Similarly, our search strategy did not identify any studies which prospectively evaluated liver transplantation (either combined or in associated with kidney transplantation) as a treatment for aHUS. Although this treatment is likely to decline further following the widespread adoption of C5 inhibitor therapy as the mainstay of aHUS treatment, case report data suggests there may still be a role for liver transplantation in select cases where treatment with C5 inhibitors has failed ([Coppo 2016](#)).

### Overall completeness and applicability of evidence

All studies were well conducted and data were largely complete. However, follow-up is limited and kidney biopsy data, which would have been a useful supplementary measure of kidney outcomes, is absent. We assessed the risk of bias as being high due to the single-arm nature of the studies and as a result the certainty of the evidence is low. This is primarily due to study limitation biases detected with the risk of bias in single-arm studies assessment tool ([Appendix 3](#)).

### Quality of the evidence

We conducted this review according to the processes described in the Cochrane Handbook for Systematic Reviews of Interventions ([Higgins 2011](#)), however, deviated when assessing risk of bias in single-arm studies, instead using a new tool developed by Cochrane for this purpose.

This review is limited by the sole inclusion of single-arm studies which presents a number of important confounders. The lack of an internal control leaves all studies open to bias and misinterpretation making any inference about intervention effect much less powerful, with conclusions drawn based upon comparisons with historical registry data of aHUS outcomes.

### Potential biases in the review process

While this review was conducted according to methods developed by the Cochrane Collaboration, some bias may be present in the review process. We searched for all relevant studies using sensitive and validated strategies in major medical databases and grey literature sources. However, it is possible that some studies (such as unpublished data and studies with negative or no effects) were not identified. There is extensive multicentre collaboration in the field and a number of patient cohorts reappear in multiple abstracts and papers. Every effort was taken to ensure no patients have been included more than once or inadvertently excluded.

### Agreements and disagreements with other studies or reviews

No previous Cochrane reviews have specifically evaluated interventions for aHUS. [Michael 2009](#) previously published *Interventions for haemolytic uraemic syndrome and thrombotic thrombocytopenic purpura*, however this was prior to the advent of C5 inhibitor therapy for aHUS and did not include non-randomised or single-arm studies. It therefore did not include any studies examining interventions for aHUS.

To our knowledge, this is the only systematic review of interventions for aHUS to have been published since the majority of the landmark C5 inhibitor studies were published. A previous review by [Rathbone 2013](#) was conducted in 2013 and includes results from [Legendre 2013](#) as well as several retrospective studies. Our review is largely in agreement with this review.

## AUTHORS' CONCLUSIONS

### Implications for practice

In patients with aHUS, terminal complement inhibition with either eculizumab or ravulizumab appears to offer favourable outcomes in terms of death, disease remission, requirement for KRT and quality of life when compared with historical data obtained prior to the use of these treatments. This is based upon data from five single-arm, non-comparative studies which represents very low-quality evidence. The lack of any RCT impacts significantly upon the quality of evidence generated and limits the strength of any conclusions drawn from this review. Adverse events are common with both eculizumab and ravulizumab, but rarely necessitate drug discontinuation. It seems unlikely that an RCT will be conducted given the apparent improvement in outcomes associated with C5 inhibitor use, and so careful consideration of future single-arm data and longer term follow-up data will be required to better understand treatment duration, adverse outcomes, and risk of disease recurrence.

All of the included studies were conducted in highly specialist centres with strict inclusion criteria which should be taken into account when considering the logistics of treatment and patient selection and extrapolating results to other patient populations.

### Implications for research

Despite the very low-quality evidence presented here, an RCT investigating the efficacy of terminal complement inhibitor therapy for aHUS is unlikely to be feasible or warranted. Any future single-arm studies of interventions for aHUS should consider the potential sources of bias outlined in this review in order to produce



evidence of as high a quality as possible (specifically, dealing with selection bias, lead time bias, selective reporting of outcomes and attrition bias). It would be important for future studies to have a thoughtfully designed comparison group. It might be useful to compare the estimated risk/effect size with a historical or external comparator. Alternatively, a comparative study could be designed (i.e. measuring symptoms in a single group of individuals before and after intervention).

The authors are aware of several studies of other novel therapies for aHUS currently under investigation, the results of which should be compared to both historical data and eculizumab/ravulizumab where possible ([EUCTR2017-001082-24](#); [EudraCT2014-001032-11](#); [NCT01757431](#); [NCT03131219](#); [NCT03205995](#); [UMIN000014869](#)).

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**Schunemann 2011b**

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**CHARACTERISTICS OF STUDIES**
**Characteristics of included studies** [ordered by study ID]

**Fakhouri 2016**
**Study characteristics**

Methods	<ul style="list-style-type: none"> <li>• Study design: single-arm study</li> <li>• Country: multicentre (North America, Europe)</li> <li>• Recruitment: not reported</li> <li>• Intention to treat: yes</li> <li>• Follow-up: 26 weeks with optional 2-year extension period</li> </ul>
Participants	<ul style="list-style-type: none"> <li>• Total number: 41</li> <li>• Age range: ≥18 years</li> <li>• Inclusion criteria: ≥ 18 years; diagnosis of aHUS; platelet count &lt; 150 x 10<sup>3</sup>/μL; Hb ≤ lower limit of normal range; LDH ≥ 1.5 times the upper limit of normal range; SCr ≥ the upper limit of normal range at screening; vaccinated against <i>Neisseria meningitidis</i></li> </ul>

**Interventions for atypical haemolytic uraemic syndrome (Review)**

**Fakhouri 2016** (Continued)

- Exclusion criteria: ADAMTS13 activity  $\leq$  5% in plasma; evidence of STEC infection; prior eculizumab exposure

Interventions	Intervention group <ul style="list-style-type: none"> <li>• Eculizumab therapy: 900 mg once a week for 4 weeks, 1,200 mg at week 5, and then 1,200 mg every 2 weeks. The dosing regimen was designed to ensure that <math>\geq</math> 95% of patients had complete and sustained terminal complement inhibition (including at times of increased complement activity, e.g. infection or surgery) and to provide peak concentrations (50 to 700 <math>\mu</math>g/mL) within the target range</li> </ul> Control group <ul style="list-style-type: none"> <li>• Not applicable</li> </ul>
Outcomes	Primary outcomes <ul style="list-style-type: none"> <li>• Complete TMA response: defined as haematologic normalisation (platelet count <math>\geq</math> 150 <math>\times 10^9/\mu</math>L and LDH <math>&lt;</math> upper limit of normal range) and preservation of kidney function (SCr <math>&lt;</math> 25% increase from baseline), confirmed by 2 or more consecutive measurements obtained 4 or more weeks apart</li> </ul> Secondary outcomes <ul style="list-style-type: none"> <li>• Modified complete TMA response</li> <li>• TMA event-free status</li> <li>• TMA intervention rate</li> <li>• Hematologic normalisation</li> <li>• Improvements in hematologic parameters and kidney function measures</li> <li>• Change in HRQoL</li> </ul>
Notes	<ul style="list-style-type: none"> <li>• Study sponsored by Alexian Pharmaceuticals, the manufacturer of eculizumab</li> </ul>

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	All subjects treated with eculizumab. Given the rarity of the condition it is likely that all eligible participants encountered during the recruitment period were recruited, but this is not specifically reported. There is no reporting of how participants were selected for the study. Eligibility criteria clearly described.
Allocation concealment (selection bias)	High risk	Not randomised
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Little or no missing outcome data
Selective reporting (reporting bias)	Low risk	All expected outcomes published

**Fakhouri 2016** (Continued)

Other bias	Low risk	<b>See below for single-arm study bias assessment</b>
<i>Lead time bias / immortal time bias</i>	Low risk	The time between recruitment and initiation of therapy was minimal (maximum seven days)
<i>Confounding by indication</i>	Low risk	Given the rarity of the condition participants at all stages of the disease were included with similar prognostic factors as compared with other studies
<i>Misclassification bias / information bias</i>	Low risk	Clear dosing regimen and outcome reporting
<i>Bias from natural recovery / regression to the mean</i>	Low risk	Given the severe nature of the condition and historical data it is unlikely that there was no significant bias from natural recovery observed
<i>Bias due to adjunctive therapies</i>	Low risk	The need for plasma therapy (the main adjunctive therapy) was well described

**Greenbaum 2016**
**Study characteristics**

Methods	<ul style="list-style-type: none"> <li>• Study design: single-arm study</li> <li>• Country: multicentre (North America, Europe, Australia)</li> <li>• Recruitment: not reported</li> <li>• Intention to treat: yes</li> <li>• Follow-up: 26 weeks of treatment plus optional 2-year continuation phase</li> </ul>
Participants	<ul style="list-style-type: none"> <li>• Total number: 22</li> <li>• Age range: 1 month to 18 years</li> <li>• Inclusion criteria: 1 month to 18 years with aHUS; weight <math>\geq 5</math> kg; platelet count <math>&lt;</math> lower limit of normal; LDH level <math>\geq 1.5</math> times the upper limit of normal; Hb <math>&lt;</math> lower limit of normal; fragmented RBC with a negative Coombs test result; SCr <math>\geq 97</math>th percentile for age; patients with or without identified complement gene mutation, autoantibody or polymorphism were included regardless</li> <li>• Exclusion criteria: HUS of other causes; ADAMTS13 deficiency; PE/PI for <math>&gt; 5</math> weeks before enrolment; chronic dialysis for ESKD; previous use of eculizumab; hypersensitivity to components of eculizumab</li> </ul>
Interventions	<p>Intervention group</p> <ul style="list-style-type: none"> <li>• Eculizumab therapy: given by weight, with an induction phase followed by maintenance phase, to ensure that 95% of patients had complete and sustained terminal complement inhibition (including at times of increased complement activity, e.g. infection or surgery) and to provide peak concentrations (50 to 700 mg/mL) within the target range</li> </ul> <p>Control group</p> <ul style="list-style-type: none"> <li>• Not applicable</li> </ul>
Outcomes	<p>Primary outcomes</p> <ul style="list-style-type: none"> <li>• Complete TMA response: defined as haematologic normalisation (platelet count <math>\geq 150 \times 10^9/L</math>, LDH levels <math>&lt;</math> upper limit of normal) and improvement in kidney function (SCr <math>\geq 25\%</math> decrease from baseline) on 2 consecutive measurements obtained <math>\geq 4</math> weeks apart</li> </ul> <p>Secondary outcomes</p>

**Greenbaum 2016** (Continued)

- TMA event-free status
- TMA intervention rate
- Haematologic normalisation
- Hb increase  $\geq 2$  g/dL
- SCr  $\geq 25\%$  decrease
- Improvement in eGFR by  $\geq 15$  mL/min/1.73 m<sup>2</sup>
- Improvement in CKD by  $\geq 1$  stage
- Change in HRQoL

## Notes

- Study sponsored by Alexian Pharmaceuticals, the manufacturer of eculizumab

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	All subjects treated with eculizumab. Given the rarity of the condition it is likely that all eligible participants encountered during the recruitment period were recruited, but this is not specifically reported. There is no reporting of how participants were selected for the study. Eligibility criteria clearly described.
Allocation concealment (selection bias)	High risk	Not randomised
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Very little missing outcome data
Selective reporting (reporting bias)	Low risk	All expected outcomes published
Other bias	Low risk	<b>See below for single-arm study bias assessment</b>
<i>Lead time bias / immortal time bias</i>	Low risk	The time between recruitment and initiation of therapy was minimal (maximum seven days)
<i>Confounding by indication</i>	Low risk	Given the rarity of the condition participants at all stages of the disease were included with similar prognostic factors as compared with other studies
<i>Misclassification bias / information bias</i>	Low risk	Clear dosing regimen and outcome reporting
<i>Bias from natural recovery / regression to the mean</i>	Low risk	Given the severe nature of the condition and historical data it is unlikely that there was no significant bias from natural recovery observed
<i>Bias due to adjunctive therapies</i>	Low risk	The need for plasma therapy (the main adjunctive therapy) was well described

**Interventions for atypical haemolytic uraemic syndrome (Review)**

## Legendre 2013

### Study characteristics

Methods	<ul style="list-style-type: none"> <li>• Study design: 2 single-arm studies</li> <li>• Country: multicentre (North America, Europe)</li> <li>• Recruitment: not reported</li> <li>• Intention to treat: yes</li> <li>• Follow-up: 26 week study period and optional extension period</li> </ul>
Participants	<ul style="list-style-type: none"> <li>• Total number: study 1 (17); study 2 (20)</li> <li>• Age range: <math>\geq 12</math> years</li> <li>• Inclusion criteria           <ul style="list-style-type: none"> <li>* Study 1: weight <math>\geq 40</math> kg; confirmed diagnosis of aHUS; evidence of haemolysis; evidence of kidney impairment; evidence of progressive TMA after 4 or more sessions of PE/PI in the prior week</li> <li>* Study 2: Weight <math>\geq 40</math> kg; confirmed diagnosis of aHUS; evidence of haemolysis; evidence of kidney impairment; no decrease in the platelet count <math>&gt; 25\%</math> for at least 8 weeks before receipt of first dose of eculizumab and treated with PE/PI at least once every 2 weeks but no more than 3 times/week</li> </ul> </li> <li>• Exclusion criteria: ADAMTS13 activity at or below 5% in plasma; evidence of STEC infection; prior eculizumab exposure</li> </ul>
Interventions	<p>Intervention group</p> <ul style="list-style-type: none"> <li>• Eculizumab therapy: 900 mg/week (IV) for 4 weeks, a dose of 1200 mg 1 week later, and a maintenance dose of 1200 mg every 2 weeks</li> </ul> <p>Control group</p> <ul style="list-style-type: none"> <li>• Not applicable</li> </ul>
Outcomes	<p>Primary outcomes</p> <ul style="list-style-type: none"> <li>• Study 1           <ul style="list-style-type: none"> <li>* Inhibition of complement-mediated TMA, as indicated by a change in the platelet count and normalisation of haematologic values (normal platelet count and LDH level) sustained for at least 2 consecutive measurements over a period of at least 4 weeks</li> </ul> </li> <li>• Study 2           <ul style="list-style-type: none"> <li>* Inhibition of complement-mediated TMA, as indicated by TMA event-free status for at least 12 weeks (no decrease in the platelet count of <math>&gt; 25\%</math>, no PE/PI, and no initiation of dialysis) and normalisation of haematologic values (normal platelet count and LDH level), sustained for at least 2 consecutive measurements over a period of at least 4 weeks</li> </ul> </li> </ul> <p>Secondary outcomes</p> <ul style="list-style-type: none"> <li>• Study 1           <ul style="list-style-type: none"> <li>* TMA event-free status</li> <li>* Measures of kidney function</li> <li>* Changes in HRQoL</li> <li>* Pharmacokinetics and pharmacodynamics</li> <li>* Safety and tolerability</li> </ul> </li> <li>• Study 2           <ul style="list-style-type: none"> <li>* Measures of kidney function</li> <li>* Changes in HRQoL</li> <li>* Pharmacokinetics and pharmacodynamics</li> <li>* Safety and tolerability</li> </ul> </li> </ul>
Notes	<ul style="list-style-type: none"> <li>• Study sponsored by Alexian Pharmaceuticals, the manufacturer of eculizumab</li> </ul>

**Legendre 2013** (Continued)

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	All subjects treated with eculizumab. Given the rarity of the condition it is likely that all eligible participants encountered during the recruitment period were recruited, but this is not specifically reported. There is no reporting of how participants were selected for the study. Eligibility criteria clearly described.
Allocation concealment (selection bias)	High risk	Not randomised
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Very little missing outcome data
Selective reporting (reporting bias)	Low risk	All expected outcomes published
Other bias	Low risk	<b>See below for single-arm study bias assessment</b>
<i>Lead time bias / immortal time bias</i>	Unclear risk	Participants in the first sub-study were treated within 3 days, however those in the second sub-study underwent an eight-week observation period following recruitment and prior to initiation of treatment which may have increased the potential for lead time bias
<i>Confounding by indication</i>	Low risk	Given the rarity of the condition participants at all stages of the disease were included with similar prognostic factors as compared with other studies
<i>Misclassification bias / information bias</i>	Low risk	Clear dosing regimen and outcome reporting
<i>Bias from natural recovery / regression to the mean</i>	Low risk	Given the severe nature of the condition and historical data it is unlikely that there was no significant bias from natural recovery observed
<i>Bias due to adjunctive therapies</i>	Low risk	The need for plasma therapy (the main adjunctive therapy) was well described

**Licht 2015**
**Study characteristics**

Methods	<ul style="list-style-type: none"> <li>Study design: 2 single-arm studies</li> <li>Country: multicentre (North America, Europe)</li> </ul>
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**Licht 2015** (Continued)

	<ul style="list-style-type: none"> <li>Recruitment: not reported</li> <li>Intention to treat: yes</li> <li>Follow-up: 26-week treatment period and 2-year extension period</li> </ul>
Participants	<ul style="list-style-type: none"> <li>Total number: study 1 (17); study 2 (20)</li> <li>Age range: <math>\geq 12</math> years</li> <li>Inclusion criteria           <ul style="list-style-type: none"> <li>* Study 1: weight <math>\geq 40</math> kg; confirmed diagnosis of aHUS; evidence of haemolysis; evidence of kidney impairment; evidence of progressive TMA after 4 or more sessions of PE/PI in the prior week</li> <li>* Study 2: weight <math>\geq 40</math> kg; confirmed diagnosis of aHUS; evidence of haemolysis; evidence of kidney impairment; no decrease in the platelet count of <math>&gt; 25\%</math> for at least 8 weeks before receipt of first dose of eculizumab and treated with PE/PI at least once every 2 weeks but no more than 3 times/week</li> </ul> </li> <li>Exclusion criteria: ADAMTS13 activity at or below 5% in plasma; evidence of STEC infection; prior eculizumab exposure</li> </ul>
Interventions	<p>Intervention group</p> <ul style="list-style-type: none"> <li>Eculizumab therapy: 900 mg/week (IV) for 4 weeks, a dose of 1200 mg 1 week later, and a maintenance dose of 1200 mg every 2 weeks. During the extension, patients received a maintenance dose of 1200 mg eculizumab every 2 weeks</li> </ul>
Outcomes	<p>Primary outcomes</p> <ul style="list-style-type: none"> <li>Study 1           <ul style="list-style-type: none"> <li>* Platelet count increase: change in platelet count from baseline to week 26 and the proportion of patients with platelet count normalisation (<math>\geq 150 \times 10^9/L</math>); proportion of patients with platelet count normalisation sustained for at least 2 consecutive measurements for <math>\geq 4</math> weeks was an additional analysis</li> <li>* Haematologic normalisation: platelet count normalisation (<math>\geq 150 \times 10^9/L</math>) and LDH <math>&lt;</math> upper limit of normal sustained for at least 2 consecutive measurements, which span a period of <math>\geq 4</math> weeks</li> </ul> </li> <li>Study 2           <ul style="list-style-type: none"> <li>* TMA event-free status: absence of all the following for <math>\geq 12</math> consecutive weeks               <ul style="list-style-type: none"> <li><input type="checkbox"/> Decrease in platelet count of <math>&gt; 25\%</math></li> <li><input type="checkbox"/> PE/PI</li> <li><input type="checkbox"/> New dialysis</li> </ul> </li> <li>* Haematologic normalisation: platelet count normalisation (<math>\geq 150 \times 10^9/L</math>) and LDH <math>&lt;</math> upper limit of normal sustained for at least 2 consecutive measurements, which span a period of <math>\geq 4</math> weeks</li> </ul> </li> </ul> <p>Secondary outcomes</p> <ul style="list-style-type: none"> <li>TMA event-free status (study 1 only)</li> <li>TMA intervention rate: number of PE/PIs and new dialysis (interventions/patient/day); rate during the pre-eculizumab period compared with the rate during eculizumab treatment period</li> <li>Complete TMA response: haematologic normalisation plus improvement in kidney function (25% reduction from baseline in SCr in 2 consecutive measurements for <math>\geq 4</math> weeks)</li> <li>Change in Hb <math>\geq 20</math> g/L from baseline</li> <li>LDH <math>&lt;</math> upper limit of normal</li> <li>eGFR increase <math>\geq 15</math> mL/min/1.73 m<sup>2</sup></li> <li>SCr decrease <math>\geq 25\%</math></li> <li>Improvement in proteinuria by <math>\geq 1</math> grade</li> <li>CKD improvement of <math>\geq 1</math> stage</li> <li>Change in HRQoL</li> <li>Peak and minimum serum eculizumab concentrations</li> <li>Proteinuria: change in grade according to dipstick measurement and urine PCR</li> </ul>

**Licht 2015** (Continued)

## Notes

- Study sponsored by Alexian Pharmaceuticals, the manufacturer of eculizumab

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	All subjects treated with eculizumab. Given the rarity of the condition it is likely that all eligible participants encountered during the recruitment period were recruited, but this is not specifically reported. There is no reporting of how participants were selected for the study. Eligibility criteria clearly described.
Allocation concealment (selection bias)	High risk	Not randomised
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Very little missing outcome data
Selective reporting (reporting bias)	Low risk	All expected outcomes published
Other bias	Low risk	<b>See below for single-arm study bias assessment</b>
<i>Lead time bias / immortal time bias</i>	Unclear risk	Participants in the first sub-study were treated within 3 days, however those in the second sub-study underwent an eight-week observation period following recruitment and prior to initiation of treatment which may have increased the potential for lead time bias.
<i>Confounding by indication</i>	Low risk	Given the rarity of the condition participants at all stages of the disease were included with similar prognostic factors as compared with other studies
<i>Misclassification bias / information bias</i>	Low risk	Clear dosing regimen and outcome reporting
<i>Bias from natural recovery / regression to the mean</i>	Low risk	Given the severe nature of the condition and historical data it is unlikely that there was no significant bias from natural recovery observed
<i>Bias due to adjunctive therapies</i>	Unclear risk	The need for plasma therapy (the main adjunctive therapy) was well described

**Rondeau 2020**
**Study characteristics**

## Methods

- Study design: single-arm study

**Interventions for atypical haemolytic uraemic syndrome (Review)**



**Rondeau 2020** (Continued)

- Country: multicentre (North America, Europe, Australia, Asia)
- Recruitment: not reported
- Intention to treat: safety analysis was conducted based upon intention to treat, however all other analyses were based upon only those with confirmed eligibility
- Follow-up: 26 weeks with optional 4.5-year extension period

**Participants**

- Total number: enrolled (58); safety analysis (56); all other analyses (56)
- Age range:  $\geq 18$  years
- Inclusion criteria:  $\geq 18$  years; weight  $\geq 40$  kg; evidence of TMA (platelet count  $< 150 \times 10^3/\mu\text{L}$ ; LDH  $\geq 1.5$  times the upper limit of normal range); SCr  $\geq$  upper limit of normal range at screening; among patients with onset of TMA postpartum, persistent evidence of TMA for  $> 3$  days after the day of childbirth; vaccinated against *Neisseria meningitidis* or treated with appropriate prophylactic antibiotics until 2 weeks after meningococcal vaccination; if previous kidney transplantation: 1) known history of aHUS prior to current kidney transplant, or 2) no known history of aHUS, and persistent evidence of TMA at least 4 days after modifying the immunosuppressive regimen (e.g. suspending or reducing the dose) of CNI or mTORi
- Exclusion criteria: ADAMTS13 activity at or below 5% in plasma; evidence of STEC infection; evidence of *S. pneumoniae* infection; prior eculizumab exposure; receiving immunosuppression unless they were part of an established post-transplant antirejection regimen, the patient had confirmed anti-complement antibodies, or if steroids were being used for a different condition; receiving PE/PI for a period of 28 days or longer before screening; receiving chronic dialysis at screening (defined as dialysis on a regular basis for ESKD)

**Interventions**
**Intervention group**

- Ravulizumab therapy: IV loading dose of 2400 mg, 2700 mg, and 3000 mg administered in patients at least 40 to  $< 60$  kg, at least 60 to  $< 100$  kg, and 100 kg or more, respectively, on day 1 and maintenance doses of 3000 mg, 3300 mg, and 3600 mg, respectively, on day 15, and then every 8 weeks thereafter

**Outcomes**
**Primary outcomes**

- Complete TMA response: defined as platelet count normalisation ( $\geq 150 \times 10^9/\text{L}$ ), LDH normalisation ( $< 246$  U/L), and 25% or better improvement in SCr from baseline at 2 separate assessments obtained at least 28 days apart, and at any measurement in between

**Secondary outcomes**

- Requirement for dialysis
- Time to complete TMA response
- Change in eGFR
- eGFR category (as evaluated by eGFR at select target days)
- Change in haematologic variables (platelets, LDH, Hb)
- Change in QoL (as measured by the Functional Assessment of Chronic Illness Therapy–Fatigue version 4)

**Notes**

- Study sponsored by Alexian Pharmaceuticals, the manufacturer of ravulizumab

**Risk of bias**
**Bias**
**Authors' judgement**
**Support for judgement**

Random sequence generation (selection bias)

High risk

All subjects treated with ravulizumab. Given the rarity of the condition it is likely that all eligible participants encountered during the recruitment period were recruited, but this is not specifically reported. There is no reporting of how participants were selected for the study. Eligibility criteria clearly described.

**Rondeau 2020** (Continued)

Allocation concealment (selection bias)	High risk	Not randomised
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Very little missing outcome data
Selective reporting (reporting bias)	Low risk	All expected outcomes published
Other bias	Low risk	<b>See below for single-arm study bias assessment</b>
<i>Lead time bias / immortal time bias</i>	Low risk	The time between first disease symptom and initiation of therapy was minimal (median 0.28 months)
<i>Confounding by indication</i>	Low risk	Given the rarity of the condition participants at all stages of the disease were included with similar prognostic factors as compared with other studies
<i>Misclassification bias / information bias</i>	Low risk	Clear dosing regimen and outcome reporting
<i>Bias from natural recovery / regression to the mean</i>	Low risk	Given the severe nature of the condition and historical data it is unlikely that there was no significant bias from natural recovery observed
<i>Bias due to adjunctive therapies</i>	Low risk	Plasma therapy (the main adjunctive treatment used in the other included studies) was not permitted in this study

CKD - chronic kidney disease; CNI - calcineurin inhibitor; ESKD - end-stage kidney disease; (e)GFR - (estimated) glomerular filtration rate; (a)HUS - (atypical) haemolytic uraemic syndrome; Hb - haemoglobin; HRQoL - health-related QoL; IV - intravenous/ly; LDH - lactate dehydrogenase; mTORi - mammalian target of rapamycin inhibitor; QoL - quality of life; PCR - protein:creatinine ratio; PE/PI - plasma exchange/plasma infusion; RBC - red blood cell; STEC - Shiga toxin-producing *E. coli* infection; TMA - thrombotic microangiopathy

**Characteristics of excluded studies** [ordered by study ID]

Study	Reason for exclusion
<a href="#">Aigner 2018</a>	Wrong study design: observational
<a href="#">Aigner 2020</a>	Wrong study design: retrospective analysis
<a href="#">Al-Akash 2012</a>	Wrong study design: subgroup analysis
<a href="#">Alpay 2019</a>	Wrong study design: retrospective analysis
<a href="#">Alsakran 2019</a>	Wrong study design: retrospective analysis

Study	Reason for exclusion
<a href="#">Bhalla 2019</a>	Wrong study design: retrospective analysis
<a href="#">Bohl 2016</a>	Wrong study population: haematopoietic stem cell transplantation-associated TMA
<a href="#">Cao 2018</a>	Wrong study design: retrospective analysis
<a href="#">Cataland 2014</a>	Wrong study design: subgroup analysis
<a href="#">Cofiell 2015</a>	Wrong study outcomes: study designed to monitor the effect of eculizumab on multiple physiologic pathways affected by complement dysregulation in aHUS but does not measure the clinical outcomes included within this review
<a href="#">Escribano 2017</a>	Wrong study design: retrospective analysis
<a href="#">Favi 2018</a>	Wrong study population: transplant recipients
<a href="#">Fremeaux-Bacchi 2015</a>	Wrong study design: review
<a href="#">Frykman 2016</a>	Wrong study design: observational
<a href="#">Galbusera 2019</a>	Wrong study design and outcomes: case-series evaluating the efficacy of an ex-vivo test for disease activity in aHUS during treatment
<a href="#">Gavriilaki 2015</a>	Wrong study design and outcomes: pre-clinical study designed to develop a novel cell assay to distinguish aHUS from other TMA
<a href="#">Gomez-Alvarez 2016</a>	Wrong study design: retrospective analysis
<a href="#">Gruppo 2011</a>	Wrong study design: retrospective analysis
<a href="#">Han 2019</a>	Wrong study design: case report
<a href="#">Hanes 2019</a>	Wrong patient population: healthy volunteers
<a href="#">Ito 2019</a>	Wrong study design: observational
<a href="#">Jozsi 2007</a>	Wrong study design and outcomes: pre-clinical study examining the role of factor-H autoantibodies in aHUS
<a href="#">Kant 2020</a>	Wrong study design: retrospective analysis
<a href="#">Kato 2019</a>	Wrong study design: observational
<a href="#">Khandelwal 2016</a>	Wrong study design: retrospective analysis
<a href="#">Khandelwal 2019</a>	Wrong study design: retrospective analysis
<a href="#">Khursigara 2014</a>	Wrong study design: retrospective analysis
<a href="#">Kumar 2019</a>	Wrong study design: retrospective analysis
<a href="#">Lappegard 2015</a>	Wrong study design: review
<a href="#">Legault 2009</a>	Wrong study design: case study

Study	Reason for exclusion
<a href="#">Levi 2016</a>	Wrong patient population: transplant recipients
<a href="#">Mazo 2017</a>	Wrong study design: retrospective analysis
<a href="#">Menne 2019</a>	Wrong study design and patient population: observational study reporting long-term outcomes for patients previously treated with eculizumab in prospective studies. Participants not required to fulfil TMA criteria at enrolment in this trial
<a href="#">Monet-Didailler 2020</a>	Wrong patient population: Shiga toxin-producing <i>E. coli</i> HUS
<a href="#">Nayer 2016</a>	Wrong study design: review
<a href="#">Nester 2013</a>	Wrong study design: review
<a href="#">Nilsson 2007</a>	Wrong study design and outcomes: observational study designed to understand the role of factor I in complement regulation in patients with aHUS
<a href="#">Noris 2014</a>	Wrong study outcomes: designed to test new assays of complement activation and identify a tool for eculizumab titration
<a href="#">Pape 2016</a>	Wrong study design and patient population: observational study reporting long-term outcomes for patients previously treated with eculizumab in prospective study. Participants not required to fulfil TMA criteria at enrolment in this trial
<a href="#">Pape 2017</a>	Wrong study design and patient population: observational study reporting long-term outcomes for patients previously treated with eculizumab in prospective study. Participants not required to fulfil TMA criteria at enrolment in this trial
<a href="#">Picard 2015</a>	Wrong study design: review
<a href="#">Raina 2018</a>	Wrong study design: retrospective analysis
<a href="#">Siedlecki 2019</a>	Wrong study design: retrospective analysis
<a href="#">Simonetti 2011</a>	Wrong study design: retrospective analysis
<a href="#">Socie 2019</a>	Wrong study design: retrospective analysis
<a href="#">Taylor 2010</a>	Wrong study design: guideline
<a href="#">Ubago 2014</a>	Wrong study design: review
<a href="#">Uriol 2018</a>	Wrong study design: retrospective analysis
<a href="#">Vakiti 2019</a>	Wrong study design and patient population: case series; drug induced aHUS
<a href="#">Vilalta 2012</a>	Wrong study design: retrospective analysis
<a href="#">Vivarelli 2014</a>	Wrong study design: review
<a href="#">Volokhina 2016</a>	Wrong study outcomes: pharmacodynamics
<a href="#">Volokhina 2016a</a>	Wrong study outcomes: pharmacodynamics
<a href="#">Walle 2017</a>	Wrong study design: observational

Study	Reason for exclusion
<a href="#">Walle 2017a</a>	Wrong study design: retrospective analysis of pooled data
<a href="#">Weston-Davies 2013</a>	Wrong patient population: healthy volunteers
<a href="#">Wijnsma 2016</a>	Wrong study design: case series
<a href="#">Wong 2015</a>	Wrong study design: review
<a href="#">Wuhl 2020</a>	Wrong study design: retrospective analysis

aHUS - atypical haemolytic uraemic syndrome; TMA - thrombotic microangiopathy

### Characteristics of ongoing studies *[ordered by study ID]*

#### [EUCTR2017-001082-24](#)

Study name	A phase 2, open label, multicenter study of ALN-CC5 administered subcutaneously in adult patients with atypical hemolytic uremic syndrome
Methods	Open-label multicentre study of investigational medicinal product
Participants	Aged >18 years with diagnosis of aHUS
Interventions	Cemdisiran
Outcomes	To evaluate the effect of ALN-CC5 on platelet response in adult patients with aHUS
Starting date	20/06/2017
Contact information	clinicaltrials@alnylam.com
Notes	<b>Trial terminated prematurely</b>

#### [EudraCT2014-001032-11](#)

Study name	A Phase 2, uncontrolled, three-stage, dose-escalation cohort study to evaluate the safety, pharmacokinetics, pharmacodynamics, immunogenicity, and clinical activity of OMS721 in adults with thrombotic microangiopathies
Methods	Open-label ascending-dose-escalation study
Participants	Age >18 years and diagnosis of aHUS, HSCT-associated TMA, or TTP
Interventions	OMS721
Outcomes	Primary end points: <ul style="list-style-type: none"> <li>Safety as assessed by adverse effects, vital signs, and clinical laboratory tests</li> <li>Clinical activity as assessed by platelet count</li> </ul>
Starting date	02/06/2014
Contact information	Omeros Corporation, Pawel.Szczesniak@psi-cro.com

### Interventions for atypical haemolytic uraemic syndrome (Review)

**EudraCT2014-001032-11** (Continued)

Notes

**NCT01757431**

Study name	The safety and efficacy of eculizumab in Japanese patients with atypical hemolytic uremic syndrome (aHUS)
Methods	Open-label single-arm study
Participants	Age > 1 month with confirmed diagnosis of aHUS
Interventions	Eculizumab
Outcomes	Adverse events and serious adverse events and their severity and relationship to the drug
Starting date	31/12/2012
Contact information	Alexion Pharmaceuticals

Notes

**NCT03131219**

Study name	A phase 3, open-label, multicenter study of ALXN1210 in children and adolescents with atypical hemolytic uremic syndrome (aHUS)
Methods	Open-label, single-arm
Participants	Age < 18 years with diagnosis of aHUS
Interventions	ALXN1210
Outcomes	Complete TMA response
Starting date	27/04/2017
Contact information	Alexion Pharmaceuticals

Notes

**NCT03205995**

Study name	A phase 3 study to evaluate the safety and efficacy of OMS721 for the treatment of atypical hemolytic uremic syndrome (aHUS) in adults and adolescents
Methods	Open-label, single-arm
Participants	Age > 12 years with diagnosis of aHUS
Interventions	OMS721

**Interventions for atypical haemolytic uraemic syndrome (Review)**

**NCT03205995** (Continued)

Outcomes	The effect of OMS721 as measured by platelet count change from baseline
Starting date	02/07/2017
Contact information	Omeros Corporation
Notes	

**UMIN000014869**

Study name	Observational study of atypical hemolytic uremic syndrome in Japan
Methods	Observation study
Participants	All patients with diagnosis of aHUS
Interventions	Nil
Outcomes	To recognize the morbidity, genetic abnormalities, prognosis, and outcomes of treatment in aHUS
Starting date	01/09/2014
Contact information	mnangaku-ky@umin.ac.jp
Notes	

aHUS - atypical haemolytic uraemic syndrome; HSCT - haematopoietic stem cell transplant; TMA - thrombotic microangiopathy; TTP - thrombotic thrombocytopenic purpura

## APPENDICES

### Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. MeSH descriptor: [Atypical Hemolytic Uremic Syndrome] this term only 2. "atypical hemolytic uremic syndrome":ti,ab,kw (Word variations have been searched) 3. "atypical haemolytic uraemic syndrome":ti,ab,kw (Word variations have been searched) 4. "atypical hemolytic uraemic syndrome".tw:ti,ab,kw (Word variations have been searched) 5. ahus:ti,ab,kw (Word variations have been searched) 6. {or #1-#5}
MEDLINE	1. Atypical Hemolytic Uremic Syndrome/ 2. atypical h?emolytic ur?emic syndrome*.tw. 3. ahus.tw. 4. or/1-3
EMBASE	1. hemolytic uremic syndrome/

(Continued)

2. atypical haemolytic uraemic syndrome\*.tw.
3. ahus.tw.
4. or/1-3

## Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria
<b>Random sequence generation</b>  Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	<p><i>Low risk of bias:</i> Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimisation (minimisation may be implemented without a random element, and this is considered to be equivalent to being random).</p> <p><i>High risk of bias:</i> Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention.</p> <p><i>Unclear:</i> Insufficient information about the sequence generation process to permit judgement.</p>
<b>Allocation concealment</b>  Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	<p><i>Low risk of bias:</i> Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes).</p> <p><i>High risk of bias:</i> Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.</p> <p><i>Unclear:</i> Randomisation stated but no information on method used is available.</p>
<b>Blinding of participants and personnel</b>  Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	<p><i>Low risk of bias:</i> No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.</p> <p><i>High risk of bias:</i> No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.</p> <p><i>Unclear:</i> Insufficient information to permit judgement</p>
<b>Blinding of outcome assessment</b>  Detection bias due to knowledge of the allocated interventions by outcome assessors.	<p><i>Low risk of bias:</i> No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.</p> <p><i>High risk of bias:</i> No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.</p> <p><i>Unclear:</i> Insufficient information to permit judgement</p>
<b>Incomplete outcome data</b>	<p><i>Low risk of bias:</i> No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across</p>



(Continued)

Attrition bias due to amount, nature or handling of incomplete outcome data.

groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods.

*High risk of bias:* Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.

*Unclear:* Insufficient information to permit judgement

### Selective reporting

Reporting bias due to selective outcome reporting

*Low risk of bias:* The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).

*High risk of bias:* Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. sub-scales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.

*Unclear:* Insufficient information to permit judgement

### Other bias

Bias due to problems not covered elsewhere in the table

*Low risk of bias:* The study appears to be free of other sources of bias.

*High risk of bias:* Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem.

*Unclear:* Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias.

## Appendix 3. Risk of bias in single arm studies assessment tool

Domain	Signalling Questions	Yes	No	Can't tell / not reported / not applicable	Quote or reason for judgement
Selection bias	1. Was the selection of participants either consecutive, or randomly selected from the population?				
	2a. Were the eligibility criteria clearly described?				

(Continued)

	2b. If yes, were the eligibility criteria similar to the other studies in the review that had a control group?
Lead time bias / immortal time bias	3. Was the time between starting follow-up for outcomes (recruitment) and starting the intervention of an appropriately short duration?
	4. Was it similar to other studies in the review that had a control group?
Confounding by indication	5. Are those in the study at a similar stage/severity of their disease and have similar prognostic factors to other studies in the review that had a control group?
Misclassification bias / information bias	6. Was dose (or other details) of intervention, both planned and given, clearly described?
	7. Was measurement of outcome made by a reliable and valid method (e.g. objective measure)?
Bias from natural recovery / regression to the mean	8. Were outcome variables measured pre-intervention (i.e. interrupted time series design with multiple measurements, of before-after design)?
Bias due to adjunctive therapies	9. Is there adequate reporting of adjunctive therapies both before and during the study period?
Attrition bias	See Cochrane RoB tool
Selective reporting of outcomes	See Cochrane RoB tool

## HISTORY

Protocol first published: Issue 11, 2017

Review first published: Issue 3, 2021

## CONTRIBUTIONS OF AUTHORS

1. Draft the protocol: DP, EDO
2. Study selection: DP, EDO
3. Extract data from studies: DP, EDO
4. Enter data into RevMan: DP, EDO
5. Carry out the analysis: EDO, FAID, PM
6. Interpret the analysis: EDO, FAID, PM
7. Draft the final review: DP, EDO, FAID, PM, DK
8. Disagreement resolution: DK, PM
9. Update the review: DP, EDO

## Interventions for atypical haemolytic uraemic syndrome (Review)

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## DECLARATIONS OF INTEREST

- D Pugh has declared that they have no conflict of interest
- ED O'Sullivan has declared that they have no conflict of interest
- FAI Duthie has declared that they have no conflict of interest
- P Masson has declared that they have no conflict of interest
- D Kavanagh: Newcastle University has received funding from Biomarin, Gyroscope Therapeutics and Alexion Pharmaceuticals for consultancy work undertaken by DK. DK is scientific advisor to Gyroscope Therapeutics, London.

## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Removal of secondary outcome "Persistent requirement for, and duration of, RRT" as duplication of primary outcome "Requirement for RRT". Removal of secondary outcome "Extra-renal manifestations of disease" as considered too vague.

Rather than using the standard risk of bias assessment tool we adopted a newly created risk of bias tool developed specifically for single-arm studies ([Appendix 3](#)). This allowed a more accurate assessment of the risk of bias in included studies.

## INDEX TERMS

### Medical Subject Headings (MeSH)

Antibodies, Monoclonal, Humanized [adverse effects] [\*therapeutic use]; Atypical Hemolytic Uremic Syndrome [\*drug therapy] [mortality]; Bias; Complement Inactivating Agents [adverse effects] [\*therapeutic use]; Glomerular Filtration Rate; Non-Randomized Controlled Trials as Topic; Quality of Life; Thrombotic Microangiopathies [drug therapy]

### MeSH check words

Humans