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Efficacy and safety of novel complement inhibitors in atypical haemolytic uremic syndrome: a protocol for systematic review and meta-analysis

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ABSTRACT

Background Atypical Haemolytic Uremic Syndrome (aHUS) is a rare but life-threatening thrombotic microangiopathy. If inadequately managed, aHUS can lead to progressive kidney failure, cardiovascular complications and multiorgan dysfunction, resulting in high healthcare costs and a substantial impact on patients' quality of life. Novel complement inhibitors offer potential advantages, yet comprehensive evidence comparing their efficacy and safety is limited. This protocol elaborates the systematic review plans to evaluate the effectiveness and the drug safety of complement inhibitors in aHUS.

Methods A systematic search will be conducted across PubMed, Embase, Cochrane Library, Web of Science and Scopus to identify relevant studies. Eligible studies include randomised controlled trials (RCTs), observational studies and case series with at least three aHUS patients treated with novel complement inhibitors. Two independent reviewers will perform data extraction and quality assessment using standardised tools, including the Risk of Bias Tool 2 for RCTs and the Newcastle-Ottawa Scale for observational studies. A meta-analysis will be conducted if feasible, utilising a random-effects model to account for study heterogeneity.

Ethics and dissemination Ethical approval is not required as only previously published data will be used. Results will be disseminated via peer-reviewed journals and conferences, targeting healthcare professionals and policymakers to support evidence-based decision-making in aHUS management.

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STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ A predefined PICOTS framework is used to guide eligibility criteria and ensure consistency in data extraction.
⇒ Both randomised controlled trials and observational studies will be included to enhance the comprehensiveness of evidence synthesis.
⇒ This review protocol follows Preferred Reporting Items for Systematic reviews and Meta-Analyses for Protocols (PRISMA) and PRISMA-P guidelines and has been registered in PROSPERO.
⇒ The risk of bias will be rigorously assessed using validated tools specific to each study design (Risk of Bias Tool 2 and Newcastle-Ottawa Scale).
⇒ Study heterogeneity may limit the feasibility of quantitative synthesis and affect the interpretation of pooled estimates.

INTRODUCTION

Atypical Haemolytic Uremic Syndrome (aHUS) is a rare but life-threatening thrombotic microangiopathy (TMA). The triad of thrombocytopenia, microangiopathic haemolytic anaemia and acute kidney injury characterises this syndrome.[1 2] Unlike typical haemolytic uremic syndrome (HUS), often associated with Shiga toxin-producing *Escherichia coli*, AHU is primarily driven by uncontrolled complement system activation due to genetic mutations or acquired autoantibodies affecting regulatory proteins.[1 2] The annual incidence of aHUS is ranging from 0.23 to 1.9 cases per million individuals, with prevalence estimates varying between 2.2 and 9.4 per million population in those aged 20 years or younger.[3] If left untreated or inadequately managed, aHUS can lead to progressive kidney failure, cardiovascular complications and multiorgan dysfunction, resulting in high healthcare costs and a substantial impact on patients' quality of life.[4] Despite advances in supportive care, AHU remains a serious condition with a high rate of recurrence and a poor prognosis in untreated individuals.[4]

Complement inhibition with C5 inhibitors such as eculizumab and ravulizumab is now the standard treatment for atypical haemolytic uremic syndrome (aHUS), directly addressing the underlying dysregulation of the complement system. Supportive measures like plasma exchange and renal replacement therapy may still be used in selected cases but are no longer considered definitive therapy. The introduction of complement inhibitors,

particularly eculizumab, has revolutionised the management of aHUS by specifically targeting the dysregulated complement pathway and reducing TMA.[5–7] However, despite these advancements, challenges remain, including the burden of biweekly intravenous administration, potential long-term adverse events (AEs) and substantial treatment costs.[5–7]

Ravulizumab, a second-generation C5 inhibitor engineered for extended half-life, has demonstrated comparable efficacy and improved convenience with less frequent dosing. In phase 3 trials and long-term follow-ups, ravulizumab achieved complete TMA response rates of 53.6%–61% in adults and up to 90% in paediatric patients, alongside significant improvement in kidney function and haematologic parameters.[8 9] Real-world evidence supports these findings, showing that switching from eculizumab to ravulizumab maintained clinical stability without new safety concerns.[10] Moreover, registry-based analyses highlight variability in treatment practices and outcomes across Europe, with discontinuation strategies increasingly explored in clinical settings.[11] Novel complement inhibitors targeting different components of the complement cascade have emerged as promising alternatives that may offer improved efficacy, better safety profiles and more personalised therapeutic options.[12 13] Despite the growing body of clinical data, no systematic comparison has yet comprehensively evaluated the safety and efficacy of these agents across different patient populations and clinical scenarios. A systematic review is therefore warranted to synthesise current evidence, assess comparative outcomes and identify knowledge gaps to inform future research and optimise individualised therapy for aHUS.

A previous Cochrane systematic review evaluated the benefits and harms of interventions for aHUS, primarily focusing on terminal complement inhibitors such as eculizumab and ravulizumab.[14] However, their analysis was limited to five non-randomised, single-arm studies, and meta-analysis was not conducted due to study design heterogeneity and lack of comparative data.[14] Our review aims to build on this foundation by expanding the evidence base to include recent randomised controlled trials (RCTs) and comparative observational studies, where available, and by conducting a quantitative meta-analysis where appropriate.

This systematic review and meta-analysis aims to evaluate the efficacy and safety of complement inhibitors—particularly eculizumab, ravulizumab and other novel agents—in patients with aHUS, across both adult and paediatric populations. We aim to synthesise data from RCTs, observational studies and eligible case series to compare treatment outcomes, including haematologic and renal responses, relapse rates, AEs and treatment durability. Our findings will inform clinical decision-making, highlight areas for future research and contribute to optimising therapeutic strategies for aHUS.

METHODS AND ANALYSIS

Protocol and registration

This protocol will follow the Preferred Reporting Items for Systematic reviews and Meta-Analyses for Protocols (PRISMA-P).[15] PRISMA-P checklist is attached in online supplemental table 1. The registration ensures that the research objectives, inclusion criteria and planned methodology are predefined and publicly accessible, promoting research integrity and minimising the risk of duplication. Any protocol amendments will be documented and justified within the final publication to maintain transparency.

Patient and public involvement

Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Eligibility criteria

Study design/characteristics

This systematic review will include studies that meet specific inclusion criteria to ensure a comprehensive evaluation of the efficacy and safety of novel complement inhibitors in patients with aHUS. Eligible studies will include RCTs that assess the therapeutic effectiveness and safety profile of complement inhibitors in aHUS patients. Additionally, non-randomised studies, such as observational cohort studies (both prospective and retrospective) and case–control studies, will be included to complement the evidence from RCTs by providing real-world clinical data, especially on long-term safety and outcomes across diverse patient populations. We also include case series with at least three patients to ensure the inclusion of relevant early-phase or rare disease data, as aHUS is a rare condition and high-quality RCTs may be limited. Including these various study designs allows for a more comprehensive synthesis of the available evidence, improves external validity and helps identify knowledge gaps for future research.

Studies will be excluded if they do not meet the predefined criteria. Specifically, case reports with fewer than three patients will not be considered, as they may lack sufficient generalisability. Furthermore, review articles, commentaries, editorials and opinion pieces that do not present original patient data will be excluded to maintain the focus on primary research evidence. Preclinical or animal studies will also be excluded, as they do not provide direct clinical applicability to human populations.

There will be no restrictions based on the study location, publication date or language, provided the study meets the inclusion criteria. Studies published in languages other than English will be translated as necessary to ensure a comprehensive synthesis of available evidence. Relevant studies from peer-reviewed journals, conference proceedings and grey literature will also be considered to minimise publication bias and provide a holistic view of the current landscape of complement inhibitor therapy in aHUS. We included the PICOTS framework in table 1.

Table 1 PICOTS framework

Element	Description
Population (P)	Patients diagnosed with atypical haemolytic uremic syndrome (aHUS) based on clinical, laboratory or genetic criteria includes both paediatric and adult populations.
Intervention (I)	Novel complement inhibitors such as eculizumab, ravulizumab or other complement pathway-targeting therapies, administered as monotherapy or in combination with supportive treatments.
Comparator (C)	Placebo, standard care (eg, plasma exchange, supportive management without complement inhibitors) or other pharmacological treatments for aHUS.
Outcome (O)	*Efficacy outcomes*: resolution of thrombotic microangiopathy (TMA), renal function improvement (eGFR, serum creatinine), survival rate, reduction in complement activity (CH50 assay).
	Safety outcomes: incidence of adverse events (AEs), serious adverse events (SAEs) and treatment discontinuation.
Study design (S)	Randomised controlled trials (RCTs), observational studies (cohort and case–control studies) and case series with at least five patients.
Timing (T)	Outcomes will be assessed at the end of treatment or the longest follow-up period available. Longitudinal studies reporting at multiple time points will also be considered.
Setting (S)	No restrictions on geographic location, study setting (hospital or community-based) or publication language, with non-English studies translated as needed.

aHUS, Atypical Haemolytic Uremic Syndrome.

Population

This systematic review will include studies involving patients diagnosed with aHUS based on clinical, laboratory or genetic criteria. Eligible participants will consist of individuals from all age groups, encompassing paediatric and adult populations, to ensure a comprehensive analysis of treatment outcomes across different demographics. The included studies must evaluate patients receiving treatment with novel complement inhibitors such as eculizumab, ravulizumab or other agents targeting the complement pathway. These therapies are particularly interesting due to their potential to improve clinical outcomes by addressing the underlying complement dysregulation in aHUS.

Studies will be excluded if they involve patients diagnosed with typical HUS, such as those cases caused by *Shiga toxin-producing E. coli* (STEC-HUS) or other secondary forms of HUS, including pregnancy-related or drug-induced HUS. Furthermore, studies focusing on other thrombotic microangiopathies, such as thrombotic thrombocytopenic purpura, will be excluded unless they provide separate data specific to aHUS patients. Additional exclusions include case reports, editorials and review articles that do not present original data, animal studies or preclinical research, which do not directly contribute to the clinical understanding of aHUS management.

Intervention

The systematic review will focus on novel complement inhibitors used in treating aHUS. These therapies specifically target the complement system to prevent uncontrolled complement activation, which leads to endothelial damage and thrombus formation—key pathological mechanisms in aHUS. The primary interventions of interest include eculizumab, ravulizumab and other complement pathway inhibitors currently in clinical use or under investigation.

Eculizumab, a monoclonal antibody that inhibits complement component C5, is widely used to prevent the membrane attack complex formation, thereby reducing complement-mediated endothelial injury. Ravulizumab, a long-acting C5 inhibitor, provides an extended dosing interval compared with eculizumab, potentially improving treatment adherence and reducing healthcare burdens. In addition to these established agents, other emerging complement inhibitors targeting various components of the complement cascade will also be considered to provide a comprehensive overview of available therapeutic options for aHUS.

The included studies may assess these interventions as monotherapy or in combination with other supportive treatments, such as plasma exchange and renal replacement therapy, often employed in the acute management of aHUS. The review will evaluate various aspects of intervention use, including dosage regimens, routes of administration and treatment duration, as reported in the selected studies. This approach aims to provide a thorough analysis of the efficacy and safety of complement inhibitors, facilitating evidence-based recommendations for clinical practice.

Comparators/controls

In this systematic review, the comparator groups will include placebo, standard care and other pharmacological treatments used for aHUS. Standard care typically encompasses supportive management strategies such as

plasma exchange and renal replacement therapy, which aim to mitigate disease progression and manage complications without complement inhibitor therapy. These conventional approaches have historically been the cornerstone of aHUS management before the advent of targeted complement inhibition.

Additionally, studies comparing novel complement inhibitors with other pharmacological treatments for aHUS will be included to assess the efficacy and safety of different therapeutic approaches. Comparisons against alternative treatment strategies will provide valuable insights into the effectiveness of complement inhibitors in improving clinical outcomes compared with existing options.

Outcomes

The primary outcomes of this systematic review will focus on both efficacy and safety parameters related to the use of novel complement inhibitors in aHUS. Efficacy outcomes will include the resolution of TMA, defined by normalising key laboratory parameters such as platelet count, lactate dehydrogenase levels and the absence of new TMA events. Renal function improvement will also be assessed through changes in estimated glomerular filtration rate (eGFR), serum creatinine levels and dialysis independence as indicators of therapeutic effectiveness. Additionally, the survival rate, measured as the proportion of patients surviving throughout the study period, will provide insight into the long-term benefits of complement inhibition. Reduction in complement activity, evaluated using biomarkers such as the CH50 and C3 assay, and biochemical markers of haemolysis (eg, haptoglobin, haemoglobin and haematocrit) will serve as a surrogate measure of the pharmacodynamic response to therapy. We will also include relapse following discontinuation of complement inhibitors, defined as recurrence of TMA or aHUS-related clinical deterioration after cessation of therapy, as reported by individual studies.

Safety outcomes will include the incidence of AEs, capturing the frequency and severity of treatment-related complications such as infections and infusion reactions. Serious adverse events (SAEs) will also be evaluated, defined as life-threatening conditions, hospitalisations or any events leading to treatment discontinuation. Furthermore, treatment discontinuation rates will be analysed to determine the number of patients who stopped therapy due to adverse effects or lack of efficacy, which can provide valuable information about the tolerability and sustainability of these treatments in real-world clinical settings.

The timing of outcome measurement will be considered at the end of the treatment period or the longest available follow-up duration reported in the included studies. For longitudinal studies, outcomes reported at multiple time points will also be analysed to capture trends over time and provide a comprehensive understanding of both the short-term and long-term effects of novel complement inhibitors in aHUS management.

Data source and search strategy

A comprehensive literature search will be conducted across multiple electronic databases to identify relevant studies evaluating the efficacy and safety of novel complement inhibitors in aHUS. The primary databases to be searched include PubMed, ScienceDirect, Google Scholar and Scopus. In addition, grey literature sources will be reviewed, including ClinicalTrials.gov and WHO International Clinical Trials Registry Platform (ICTRP), to capture ongoing, unpublished or non-indexed studies that meet the inclusion criteria.

The search strategy will be developed using a combination of Medical Subject Headings (MeSH) terms and relevant keywords related to aHUS, complement inhibitors and therapeutic outcomes. The key terms will include but are not limited to ‘atypical hemolytic uremic syndrome’, ‘aHUS’, ‘complement inhibitors’, ‘eculizumab’, ‘ravulizumab’, ‘C5 inhibitors’, ‘thrombotic microangiopathy’ and ‘treatment outcomes’. Boolean operators will be used to refine search results and maximise sensitivity and specificity. The search strategy will be tailored to each database to ensure comprehensive coverage of relevant studies. A detailed database search strategy is attached in table 2.

No restrictions will be placed on language, publication date, or study location to minimise selection bias and capture the most comprehensive evidence base. Non-English studies will be translated if necessary. The final search results will be documented in a Preferred Reporting Items for Systematic reviews and Meta-Analyses for Protocols (PRISMA) flow diagram to ensure transparency and reproducibility of the search process.

Data management and study selection

The retrieved studies will be managed using Zotero, a reference management software, to organise citations, remove duplicates and facilitate efficient data handling. All search results from the selected electronic databases will be imported into Zotero, where duplicates will be identified and removed systematically. After deduplication, the remaining citations will be transferred to Rayyan, a web-based tool designed to streamline the screening process for systematic reviews. Rayyan will enable an efficient, blinded screening process by multiple reviewers, helping to minimise bias and ensure a thorough selection of relevant studies.

The study selection process will be conducted in two phases: screening titles and abstracts and a full-text review. During the initial screening phase, two independent reviewers will evaluate the titles and abstracts of all identified studies based on predetermined inclusion and exclusion criteria. Studies not fulfilling the eligibility requirements will be excluded, while those deemed potentially relevant will advance to the full-text review stage. In the subsequent phase, the full texts of the selected studies will be independently assessed by the same reviewers to verify their eligibility. Any disagreements with the reviewer will be resolved through discussion or, if needed, by consulting a third reviewer.

Table 2 Search Strategies

Database	Search terms	Filters applied
PubMed	('atypical hemolytic uremic syndrome'(MeSH Terms) OR 'aHUS'(All Fields) OR 'hemolytic uremic syndrome, atypical'(All Fields)) AND ('complement inhibitor'(All Fields) OR 'eculizumab'(All Fields) OR 'ravulizumab'(All Fields))	No language restriction; all years.
ScienceDirect	TITLE-ABSTR-KEY('atypical hemolytic uremic syndrome' OR 'aHUS') AND TITLE-ABSTR-KEY('complement inhibitor' OR 'eculizumab' OR 'ravulizumab')	Articles only; no language restriction.
Google Scholar	'atypical hemolytic uremic syndrome' OR 'aHUS' AND 'complement 'inhibitor' OR 'eculizumab' OR 'ravulizumab'	Custom range: all years; sorted by relevance.
Scopus	(TITLE-ABS-KEY('atypical hemolytic uremic syndrome' OR 'aHUS') AND TITLE-ABS- KEY('complement inhibitor' OR 'eculizumab' OR 'ravulizumab'))	No filters applied.

aHUS, Atypical Haemolytic Uremic Syndrome.

The final selection of studies will be documented in a PRISMA flow diagram, detailing the number of records identified, screened, excluded and included in the systematic review. The reasons for exclusion during the full-text review will be recorded to ensure transparency and reproducibility. This structured approach to data management and study selection aims to maintain methodological rigour and reduce the risk of selection bias.

Data extraction and quality assessment

Data extraction will be conducted systematically using a standardised data extraction form to ensure accuracy and consistency. The extracted data will include study characteristics (eg, study design, setting and sample size), participant demographics (eg, age, gender and disease severity), intervention details (eg, type of complement inhibitor, dosage and duration), comparators and key outcomes related to efficacy and safety. Where reported, we will extract data on relapse incidence, time to relapse, severity of relapse and the outcomes following reinitiation of therapy. Information on the risk of bias and study limitations will also be collected. Two independent reviewers will extract the data. Any discrepancies will be resolved through discussion or consultation with a third reviewer. All extracted data will be recorded in a structured spreadsheet or data management tool to facilitate further analysis and synthesis.

The quality assessment of included studies will be performed using appropriate tools based on study design. For RCTs, the Cochrane Risk of Bias Tool (RoB 2) will be applied to assess bias related to randomisation, deviations from intended interventions, missing data, outcome measurement and selective reporting.[16] For observational studies, the Newcastle-Ottawa Scale will be used to evaluate study selection, comparability of cohorts and outcome assessment.[17] Key aspects of quality assessment will include the adequacy of study design and conduct, such as randomisation methods, allocation concealment, blinding (if applicable) and data completeness, including how missing data and loss to follow-up were handled. The objectivity and consistency of outcome assessments will also be evaluated to identify any potential measurement bias. Additionally, studies will be assessed for selective reporting bias by comparing reported outcomes with study protocols or pre-specified objectives.

The risk-of-bias assessment will be conducted independently by two reviewers, with any disagreements resolved through discussion or involving a third reviewer. The quality assessment results will be summarised in a risk-of-bias table, which will inform the interpretation of findings and contribute to the overall strength of the evidence synthesised in this systematic review.

Data synthesis and statistical analysis

The data synthesis will include quantitative and qualitative approaches to comprehensively evaluate the efficacy and safety of novel complement inhibitors in aHUS. Given the expected clinical and methodological heterogeneity across studies, a random-effects model will be used for meta-analysis. This approach accommodates variability in study populations, interventions and outcome definitions and provides more conservative pooled estimates. Subgroup analyses will be performed by age group (paediatric vs adult) to account for differences in disease presentation and treatment outcomes. Separate analyses will be conducted if sufficient data are available for each group. For dichotomous outcomes, such as resolution of TMA and incidence of AEs, pooled effect estimates will be expressed as relative risks or ORs with corresponding 95% CIs. For continuous outcomes, including changes in eGFR, mean differences or standardised mean differences with 95% CIs will be calculated. Statistical analyses will be conducted using RevMan or R software, utilising appropriate meta-analysis packages to ensure robust and reproducible results.

The I^2 statistic and χ^2 test will be employed to assess statistical heterogeneity among studies, with a significance threshold of $p<0.1$ indicating substantial heterogeneity.[18] In cases where significant heterogeneity is detected, potential sources will be explored through subgroup

analyses based on population characteristics (eg, paediatric vs adult patients), intervention type (eg, eculizumab vs ravulizumab) and study design. Sensitivity analyses will assess the robustness of findings by excluding studies deemed at high risk of bias or by employing alternative statistical models to validate the consistency of results.

A qualitative narrative synthesis will be performed if a meta-analysis is not feasible due to substantial heterogeneity or insufficient data. This will involve a structured summary of the results, emphasising patterns, trends and key findings across the included studies. The narrative synthesis will comprehensively describe the available evidence and identify gaps in the literature that require further investigation.

If at least 0 studies are included in the meta-analysis, publication bias will be assessed through visual inspection of funnel plots. Additionally, statistical tests like Egger's test will detect potential asymmetry and small-study effects that may indicate bias.[19] Findings from this analysis will be considered in interpreting results and formulating recommendations for clinical practice and future research.

ETHICS AND DISSEMINATION

This systematic review and meta-analysis aim to comprehensively evaluate the efficacy and safety of novel complement inhibitors in managing aHUS. Given the critical role of complement dysregulation in the pathophysiology of aHUS, understanding the effectiveness of emerging therapeutic agents is essential for optimising patient outcomes. This review will contribute to the existing body of evidence by synthesising data from diverse study designs, identifying gaps in the current literature and offering insights for future research and clinical practice. Additionally, the review will address the variability in treatment responses across different populations and explore the long-term implications of complement inhibitor therapy on patient prognosis and quality of life.

This systematic review does not require ethical approval, as it will utilise data from previously published studies without directly involving human participants. All included studies will be assessed for ethical compliance as reported by the original authors, and no personal or identifiable patient data will be used in the analysis. The review process will adhere to rigorous methodological standards and ethical guidelines, ensuring transparency and integrity in data collection, synthesis and reporting. Any potential conflicts of interest and funding sources for the included studies will be disclosed to maintain objectivity and reduce bias in interpreting results.

The results of this systematic review will be disseminated through peer-reviewed publications in high-impact scientific journals and presented at relevant conferences and academic forums. Additionally, the findings will be shared with healthcare professionals, policymakers and patient advocacy groups to support evidence-based decision-making in managing aHUS. Open-access publication will be pursued to maximise accessibility and facilitate the broad dissemination of knowledge to stakeholders across different regions and healthcare settings. Furthermore, efforts will be made to communicate key findings through educational materials and clinical guidelines to enhance awareness and implement effective treatment strategies for aHUS.

Contributors ME played a key role in conceiving and developing the research protocol. RJ and MNY will be responsible for conducting the literature search and screening process. ME will oversee data extraction. Both ME and AB contributed significantly to the study design, provided methodological guidance and thoroughly reviewed the protocol manuscript. ME also supervised the overall development of the research protocol. All authors actively participated in drafting, revising and refining the manuscript and have approved the final version for submission. ME serves as the guarantor of the study. We use AI to detect and correct grammar and spelling errors.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

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