BMC Nephrology

REVIEW

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Ten tips for managing complement-mediated thrombotic microangiopathies (formerly atypical hemolytic uremic syndrome): narrative review

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Abstract

Complement-mediated thrombotic microangiopathies (CM-TMA) are rare and life-threatening disorders characterized by microangiopathic hemolytic anemia, thrombocytopenia, and organ damage. These conditions result from dysregulation of the alternative complement pathway, often due to genetic variants or autoantibodies. The clinical spectrum is broad, comprising varied presentations and triggers, including infections, malignancies, and pregnancy-related complications. Advances in understanding the genetic and immunological basis of CM-TMA have improved diagnosis and treatment. Diagnosis requires exclusion of other thrombotic microangiopathies like thrombotic thrombocytopenic purpura and secondary causes, with genetic testing recommended to identify underlying susceptibilities. The introduction of C5 inhibitors has transformed the management of CM-TMA, significantly improving outcomes compared to the pre-2011 era when therapeutic plasma exchange was the primary therapy. Despite these advances, challenges remain in determining the optimal duration of therapy. Prophylactic measures against infections, particularly meningococcal disease, are mandatory for patients receiving C5 inhibitors. This article underscores the need for a personalized, multidisciplinary approach in the diagnosis and management of CM-TMA. Advances in genetics and complement biology have led to improved therapeutic strategies, however ongoing research is essential to address unanswered questions regarding relapse risk, treatment duration, and long-term outcomes.

Keywords Thrombotic microangiopathy, Complement-mediated thrombotic microangiopathy, Atypical hemolytic uremic syndrome, Anti-complement therapies, Complement

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Introduction

Thrombotic microangiopathies (TMA) are a group of clinical disorders characterized by the presence of microangiopathic hemolytic anemia, thrombocytopenia, and multisystem organ damage. These conditions encompass various entities, such as thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS) secondary to infections (often associated with Shiga toxin-producing Escherichia coli [STEC] infection), and atypical HUS, now referred to as complement-mediated thrombotic microangiopathy (CM-TMA).

In recent years, advances in understanding the complement system, along with improvements in genetic diagnostic techniques and the development of novel therapeutic agents for TMA, have significantly enhanced the knowledge and management of these complex diseases.

1. Evolution of nomenclature

The current nomenclature has evolved significantly as the understanding of the underlying pathophysiology of thrombotic microangiopathies has deepened. The term HUS was traditionally classified into two entities:

"Typical" HUS or STEC-HUS This term refers to the condition that predominantly affects children under five years, typically presenting bloody diarrhea after the first days of exposure to STEC. Shiga toxin induces endothelial damage, leading to the manifestations of thrombotic microangiopathy. Approximately 5% of cases are associated with invasive pneumococcal disease [1]. Management is primarily supportive, ensuring adequate hydration, blood pressure control, correction of electrolyte imbalances, and transfusion of hemocomponents. Renal replacement therapy is required in up to 45% of cases and is associated with a 3–4% mortality rate during the acute phase [2]. Long-term follow-up reveals evidence of chronic kidney damage in up to one-third of patients [3].

Typical HUS can also affect adults, particularly in the context of outbreaks of foodborne poisoning, such as the one that occurred in Germany in 2011 due to an unusual Escherichia coli O104:H4 strain [4].

CM-TMA (formerly atypical HUS) This term initially referred to TMA manifestations not preceded by diarrhea, typically occurring in older patients (adolescents or young adults). In some cases, there was history of prior TMA episodes or a family history of TMA [5]. It was later identified as a condition mediated by uncontrolled activation of the alternative complement pathway, leading to the formation of membrane attack complexes (C5b-9) that damage vascular endothelium. Unlike typical HUS, this form has a severe clinical course, with a high rate of progression to kidney failure and mortality if not treated promptly [1].

With the growing understanding of the mechanisms underlying alternative complement pathway dysfunction, the need for more precise terminology emerged. New expert consensus has highlighted the importance of renaming atypical HUS to CM-TMA to specifically describe forms of TMA in which complement dysfunction is the primary pathogenic factor. This updated nomenclature is expected to optimize clinical research and therapeutic management, allowing for a more targeted approach, particularly with C5 inhibitors [6, 7].

2. Etiology of TMAs

CM-TMA arise specifically from dysregulation of the alternative complement pathway, secondary to pathogenic variants in complement-related genes or the presence of autoantibodies against complement factor H. This condition is often triggered by environmental factors, as will be discussed in section #5 [8].

Pathogenic gene variants in complement factors can result in either loss-of-function of regulatory proteins (e.g., Factor H, Factor I, CD46, among others) or gain-of-function variants (e.g., C3 or Factor B). Factor H variants are the most common, occurring in 20–30% of cases, and carry the highest risk of recurrence. MCP/CD46 variants are the second most frequent (10–15%) and are associated with a moderate risk of recurrence. Variants in Factor I, C3, and Factor B account for 4–8%, 2–10%, and 1–2% of cases, respectively [9].

Approximately 6% of CM-TMA are secondary to the presence of anti-Factor H autoantibodies, most observed in pediatric populations (up to 25% of cases). Its development has been associated with deletions of complement factor H-related proteins 1 and 3 (CFHR1-3), although the underlying mechanism remains unclear [10]. Initial treatment involves therapeutic plasma exchange, followed by immunosuppressive therapy to suppress antibody production [11].

3. How to suspect CM-TMA?

CM-TMA presents the three classic features of thrombotic microangiopathies: microangiopathic hemolytic anemia, thrombocytopenia, and organ damage, with certain specific characteristics. These clinical manifestations typically develop rapidly and may progress to organ failure and death if not adequately treated [12].

Microangiopathic hemolytic anemia

Non-immune microangiopathic hemolytic anemia is a hallmark of TMA, characterized by erythrocyte destruction in the microcirculation due to endothelial damage. It is identified by the following laboratory findings: elevated lactate dehydrogenase (LDH), indirect bilirubin,

reticulocyte count, and free hemoglobin; decreased haptoglobin; and the presence of schistocytes on peripheral blood smear [12, 13]. The direct coombs test is negative, except in TMA secondary to *Streptococcus pneumoniae* infection, where up to 90% of cases may present with a positive result, because it detects the binding of anti-T antibodies to recently exposed Thomsen-Friedenreich antigen on the red blood cell membrane. In such cases, if therapeutic plasma exchange is indicated, the exchange should be performed with 5% albumin [14], because fresh frozen plasma contains pre-formed antibodies anti Thomsen-Friedenreich antigen IgM, that may worsen the disease process [15].

Thrombocytopenia

Thrombocytopenia is defined as a platelet count below 150,000/mm^3 or a 25% decrease from baseline levels. This reduction occurs due to platelet consumption in microthrombi formed within small vessels [13]. Thrombocytopenia severity in CM-TMA is generally less pronounced than in TTP [16].

Organ damage

Organ damage is multisystemic. Renal involvement, characterized by the formation of microthrombi in glomerular capillaries that impair glomerular filtration, is distinctive of CM-TMA and uncommon in TTP [17]. About 50–60% of patients require renal replacement therapy, and malignant hypertension is frequently observed [1, 18]. Neurologic manifestations include encephalopathy, focal deficits, seizures and coma, but are considerably less frequent than in TTP [19]. Skin, cardiovascular, respiratory and gastrointestinal systems involvement are described in small number of case reports.

Attention should be drawn to the fact that approximately 25% of patients with CM-TMA may present with renal-limited TMA [20]. A kidney biopsy is essential for early detection. Morphological findings alone do not allow for the identification of the underlying etiology; therefore, patients should be screened for complement dysregulation [21]. Renal-limited TMA is associated with less severe renal dysfunction and a lower risk of death compared to cases with hematological involvement. The effect of anti-C5 therapy in renal-limited TMA remains unclear [20].

4. How to diagnose CM-TMA?

The diagnosis of CM-TMA is one of exclusion during the acute phase of the disease, requiring the rule out of TTP and secondary causes of TMA. It is important to note that C3 levels are decreased in fewer than 50% of patients [8].

Thrombotic thrombocytopenic purpura

While the gold standard for diagnosing TTP is measuring the activity of von Willebrand factor-cleaving protease (ADAMTS13), this test may be unavailable or take several days. Therefore, clinical prediction scores, such as the French score and the PLASMIC score, have been developed to assess the likelihood of TTP. The French score was published in 2010 and includes platelet count, creatinine level and antinuclear antibodies, and assumes that there is no history or clinical evidence of cancer, transplantation or disseminated intravascular coagulopathy. Creatinine level < 2.26 mg/dL and platelet count $< 30 \times 10^9$/L had the stronger association with a severe ADAMTS13 deficiency [16].

The PLASMIC score is based on seven clinical and laboratory parameters: platelet count, hemolysis markers, mean corpuscular volume, prothrombin time-INR, creatinine level, and history of active cancer or transplantation [22]. In cases with an intermediate or high risk (PLASMIC score ≥ 5), initiating therapy with fresh frozen plasma is recommended, ideally as therapeutic plasma exchange (TPE) or, alternatively, plasma infusion [22, 23]. It is important to note that a score ≤ 4 does not rule out TTP but makes it less likely. The definitive diagnosis requires ADAMTS13 activity measurement. This score has been validated in adults, and a pediatric adaptation, PLASMICkid, is available [24].

Before starting TPE, it is critical to collect a sample for ADAMTS13 activity testing (using a citrate tube, as EDTA inhibits enzymatic activity), broad immunological studies and quantitative analysis of complement proteins. Once TPE begins, ADAMTS13, complement proteins and autoantibodies will be replenished or removed, potentially preventing a definitive diagnosis. An ADAMTS13 activity level $\geq 10\%$, combined with the absence of an anti-ADAMTS13 inhibitor (autoantibody), excludes TTP [9].

Secondary causes of TMA

Identifying secondary causes of TMA is crucial in managing these patients. Studies suggest that up to 94% of TMA cases have an identifiable secondary cause [9]. A wide range of underlying conditions can trigger TMA, including infections, malignant hypertension, autoimmune diseases, malignancies, medications, solid organ and hematopoietic stem cell transplants, and pregnancy complications (Fig. 1). Therefore, a comprehensive evaluation for secondary causes is essential [13].

As mentioned in section #1, STEC-HUS is the primary differential diagnosis in pediatric patients. The confirmation of the diagnosis is based on a combination of clinical clues (Hemorrhagic diarrhea that typically develops around three days after exposure to STEC, with a range of 1 to 10 days) [25], laboratory elements of TMA

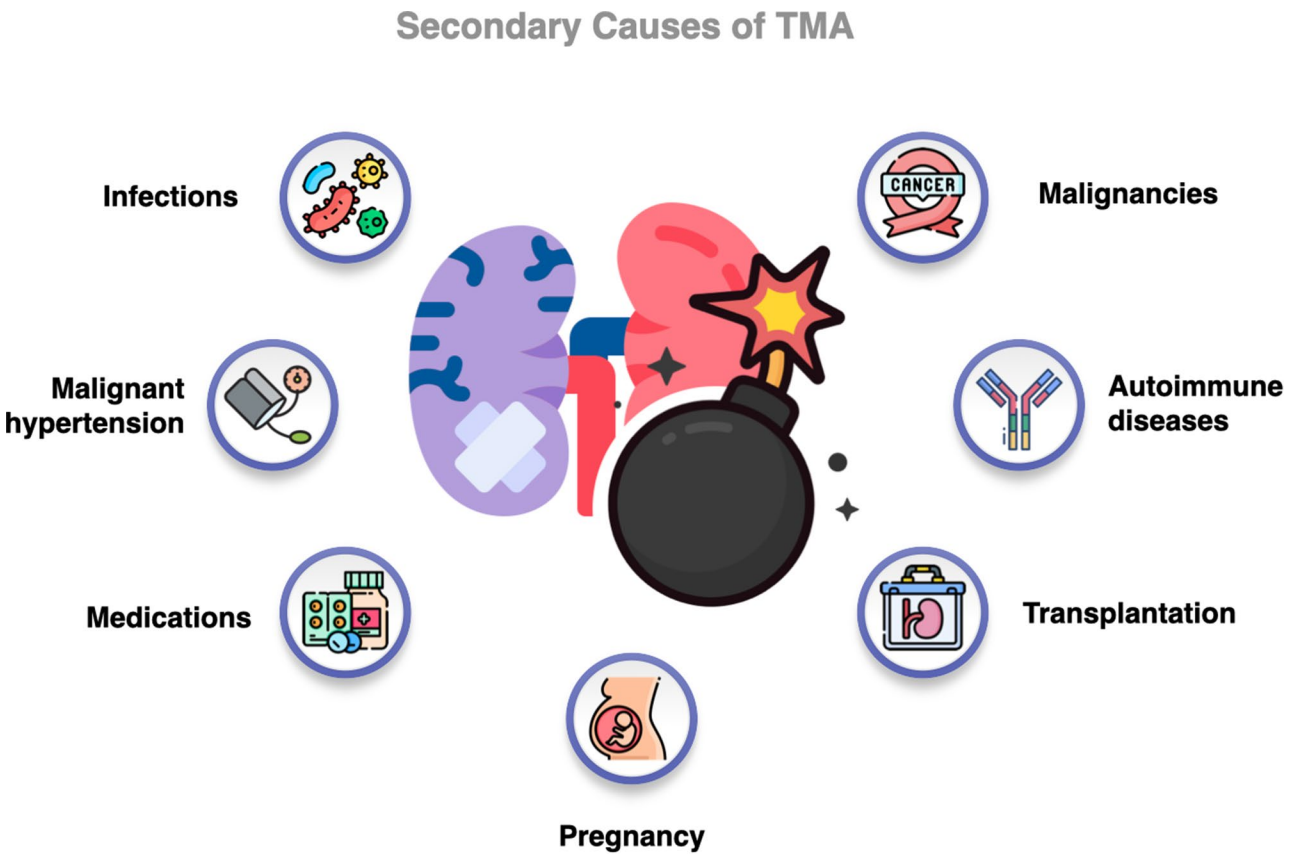

Fig. 1 Secondary causes of thrombotic microangiopathies. TMA: Thrombotic Microangiopathies

(described in section #3) and stool tests that confirm de infection. The latter include selective cultures (such as sorbitol-MacConkey agar) that identify STEC and molecular assays (polymerase chain reaction) that detect genes encoding Shiga toxins 1 and 2 [26].

Malignant hypertension and TMA have a complex interrelationship, where each can act as both a cause and a consequence of the other. It is characterized by a severe elevation in blood pressure that causes diffuse microvascular injury [27]. In the kidneys, reduced glomerular perfusion activates the renin-angiotensin system, further worsening hypertension and creating a vicious cycle [28]. Manifestations of TMA secondary to malignant hypertension should resolve with aggressive blood pressure control. When it does not occur, CM-TMA should be considered and treatment with complement inhibitors initiated [29].

TMA can manifest de novo in solid organ transplant recipients, affecting 3–14% of kidney transplant cases and may result from several factors, including medications such as calcineurin inhibitors and mammalian target of rapamycin inhibitors, infections like cytomegalovirus and BK virus, antibody-mediated rejection or as a recurrence of an undiagnosed pre-transplant CM-TMA [30]. Hematopoietic transplantation is associated with TMA through multiple endothelial-damaging mechanisms, ranging from intensive conditioning regimens, immunosuppressive therapy, infections to graft-versus-host disease [31].

If TMA manifestations persist despite treatment of an identified secondary cause, underlying alternative complement pathway dysfunction should be suspected. In such cases, the use of C5 complement inhibitors has been reported while awaiting results from genetic complement studies, as discussed below [32].

TMA during pregnancy and postpartum will be discussed in the next section.

5. How to suspect CM-TMA during pregnancy and postpartum?

The most common TMA during pregnancy is the HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets), which usually occurs in the presence of preeclampsia and is associated with high maternal and fetal morbidity and mortality. Treatment involves pregnancy termination, after which most patients recover within 48–72 h [33].

Pregnancy appears to have a protective effect against CM-TMA, likely due to the placenta's reliance on CD59 and Decay Accelerating Factor (DAF) to regulate the

alternative complement pathway. These membrane proteins negatively regulate complement activation, compensating for deficiencies in other regulatory proteins involved in this condition. However, during the postpartum period, the protection afforded by the overexpression of CD59 and DAF is lost with placental expulsion, increasing the risk of CM-TMA onset [34, 35].

CM-TMA should be suspected if hemolytic manifestations persist and progressive acute kidney injury develops despite pregnancy termination. A recent study demonstrated that the combination of serum creatinine ≥ 1.9 mg/dL and LDH ≥ 600 U/dL has a specificity of 100% and a sensitivity of 97% for diagnosing postpartum CM-TMA [36]. Early treatment with C5 complement inhibitors is indicated in cases that do not improve within 48–72 h from delivery, with extensive literature supporting the use of eculizumab and some case reports documenting the use of ravulizumab.

6. Secondary cause does not exclude the presence of a genetic variant

The development of CM-TMA requires a factor causing significant vascular injury in a genetically susceptible host [37]. In most cases, an environmental trigger reveals an underlying, previously asymptomatic variant in the alternative complement pathway, most often associated with infectious or neoplastic events [8, 38], though any of the triggers described in the previous section may be involved. Pathogenic or likely pathogenic variants can be present in 3–19% of cases, therefore, the presence of a secondary cause does not rule out a genetic cause [38, 39].

If CM-TMA occurs following a common event that causes limited and transient endothelial damage (e.g., mild viral infection), the patient is presumed to have a significant genetic predisposition to the disease. Conversely, if endothelial damage is intense and prolonged, as in hematopoietic stem cell transplantation, a minor genetic susceptibility factor may suffice to contribute to CM-TMA development [37].

Screening for variants and hybrid genes in CFH, CFI, CD46/MCP, C3, CFB, CFHR1-5, MMACHC and DGKE (the two latter primarily in young children) using next-generation sequencing and multiplex ligation-dependent probe amplification is recommended [40, 41]. Additionally, analysis of copy number variations in the CFH/CFHRs genomic region is particularly advised in cases of CM-TMA secondary to anti-CFH antibodies [41].

7. What should we know about treatment?

Plasma therapy

Prior to 2011, the only available treatment for CM-TMA was plasma therapy, either through therapeutic plasma exchange (PLEX) or fresh frozen plasma infusion when PLEX was not available. However, outcomes in the pre-C5 inhibitor era were catastrophic, with mortality rates of 6.7% and end-stage renal disease (ESRD) rates of 46% at one year in adult patients [42]. PLEX aimed to remove mutated complement factors or anti–Factor H antibodies while supplying functional plasma regulatory proteins [43] and is still used with suboptimal results in areas where C5 inhibitors are not available.

Complement inhibitors

The introduction of complement C5 inhibitors, such as eculizumab and ravulizumab, has revolutionized the treatment of atypical HUS. Initially developed for paroxysmal nocturnal hemoglobinuria, these drugs block terminal complement activation, preventing the formation of C5b-9 complexes that drive endothelial damage.

The first reported case of CM-TMA successfully treated with eculizumab was published in 2009, involving a refractory CM-TMA following kidney transplant. The patient exhibited rapid recovery of platelet count and improved renal function, marking a turning point in disease management [28]. Subsequently, two pivotal clinical studies were presented at the 16th European Hematology Congress in 2011, showing groundbreaking results [44, 45]. These findings led to the accelerated approval of eculizumab for CM-TMA treatment by regulatory agencies, with official publication in 2013 [46].

Ravulizumab, developed through targeted substitution of four amino acids in eculizumab's structure, enhances endosomal dissociation of C5 and facilitates more efficient recycling through the neonatal Fc receptor pathway. This modification extends the terminal half-life of ravulizumab to approximately four times that of eculizumab, allowing for less frequent dosing (every 8 weeks versus every 2 weeks with eculizumab) [47]. The extended dosing interval significantly improves patients' quality of life by reducing infusion frequency while maintaining disease control [33]. Both drugs have demonstrated long-term clinical benefits, including improved platelet counts, reduced hemolysis, and stabilized renal function in patients with CM-TMA [48–50].

Studies evaluating the transition from eculizumab to ravulizumab have shown stable renal function and hematologic parameters without new cases of dialysis, renal transplantation, or TMA recurrence. These findings support ravulizumab as an effective and safe long-term option for CM-TMA patients switching from eculizumab [51, 52].

New molecules targeting other components of the complement system are being studied as potential treatments for this disease (Fig. 2). BCX9930, which targets Factor D, is in phase 2 trials. Iptacopan, a Factor B inhibitor, is in phase 3, while Ruxoprubart, acting on Factor Bb, is in phase 2. Pegcetacoplan, which targets C3, is

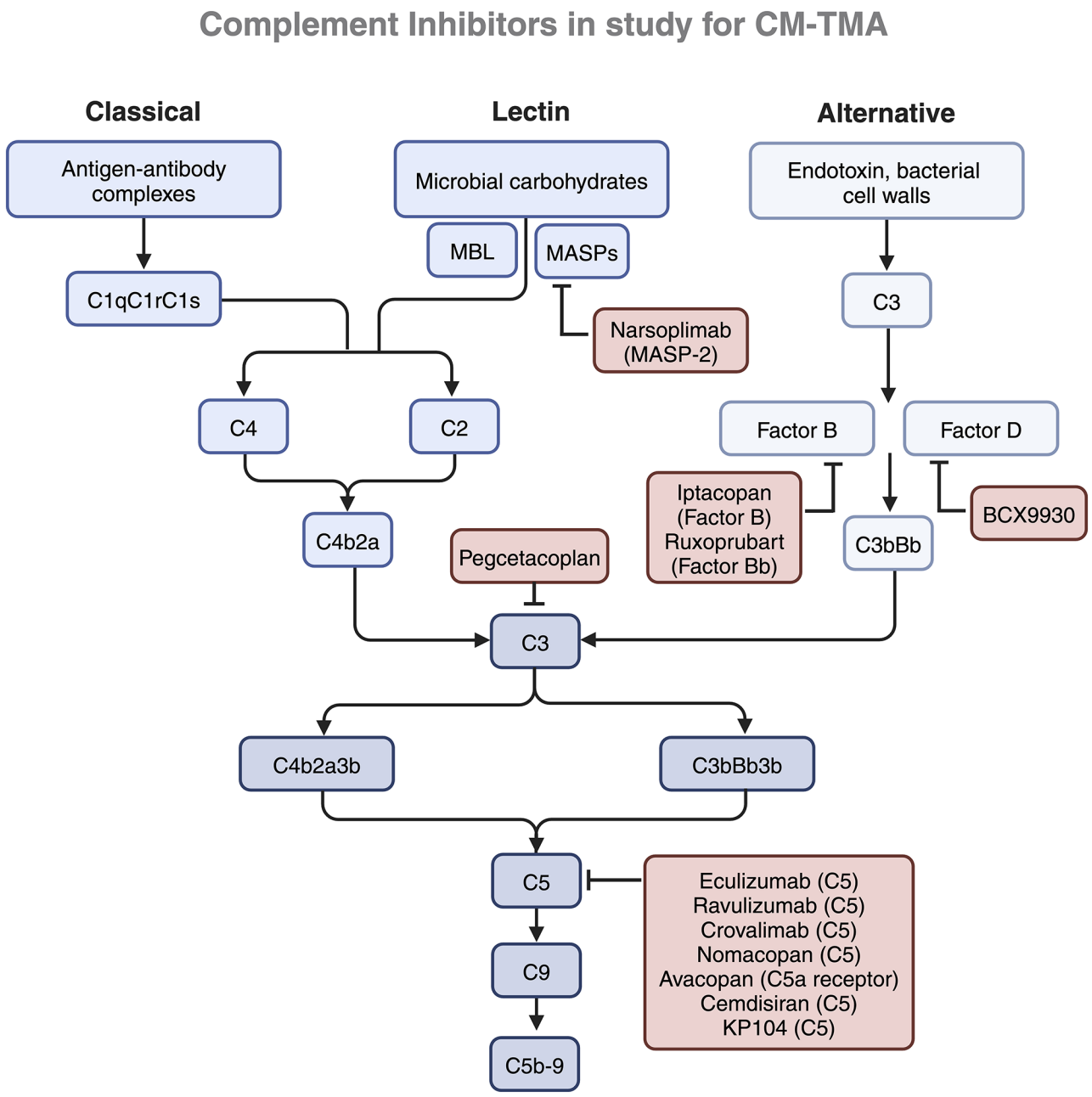

Fig. 2 Complement Inhibitors in study for Complement-Mediated Thrombotic Microangiopathies. CM-TMA: Complement-Mediated Thrombotic Microangiopathies; MBL: Mannose-Binding Lectin; MASPs: Mannan Binding Lectin Serine Peptidase

undergoing phase 2 trials. Several drugs targeting C5 are in different phases of development: Crovalimab, Nomacopan, and Avacopan (the latter a C5a receptor inhibitor) are in phase 3, whereas Cemdisiran and KP104 are in phase 2. Narsoplimab, which inhibits MASP-2, is in Phase 3. These drugs represent promising therapeutic options for complement-mediated diseases.

8. Never forget meningococcal infection prophylaxis

The complement system is critical for defending against encapsulated pathogens, such as *Neisseria meningitidis* and *Streptococcus pneumoniae*. It achieves this through membrane attack complex formation and enhanced opsonization [53]. Patients undergoing treatment with complement inhibitors face an estimated 2,000-fold increased risk of meningococcal infections [54].

Patients scheduled to receive C5 inhibitors must be vaccinated against meningococcal infections, including a serogroup B vaccine and a quadrivalent vaccine (A, C, W, Y) [55] (Table 1). However, due to the time required to develop an adequate immune response post-vaccination, antibiotic prophylaxis with penicillin or macrolides

Table 1 Immunization schedule against *Neisseria meningitidis*

Vaccine	Number of doses	Interval of administration	Booster according to age
Tetravalent vaccine (Serogroups A, C, W-135 and Y)	2	0–8 weeks	< 7 years: At 3 years, and then every 5 years. ≥ 7 years: Every 5 years
Serogroup B Vaccines (according to availability)			
MenB-4 C	2	0–4 weeks	≥ 10 years: At one year and then every 2–3 years
MenB-FHbp	3	0-2-6 months	≥ 10 years: At one year and then every 2–3 years

Table 2 Frequency of genetic variants in patients with CM-TMA

Complement protein gene	Frequency
Factor H	20–30%
MCP/CD46	10–15%
Factor I	4–8%
C3	2–10%
Factor B	1–2%
Not identified	30–55%

should be initiated and continued for at least two weeks following immunization. Despite complete vaccination, cases of meningococcal infections have been reported [56, 57]. Consequently, some experts recommend indefinite antibiotic prophylaxis throughout the duration of C5 inhibitor therapy to mitigate this persistent risk [58].

9. The absence of a pathogenic gene variants does not rule out CM-TMA diagnosis

Several studies across different populations have reported a pathogenic variant detection rate of 45–70% [42, 43, 59, 60], so it is crucial to understand that the absence of a detectable pathogenic gene variants does not exclude the diagnosis of CM-TMA (Table 2).

Advances in genetic testing technologies and the growing availability of patient registry databases have led to the identification of new pathogenic variants over time [61], principally structural rearrangements of the CFH gene cluster and variants in vitronectin gene [62, 63].

If genetic testing was performed many years ago, it is advisable to repeat the analysis because enhanced detection capabilities may reveal previously not detected variants.

10. How long should C5 inhibitor therapy be maintained?

Given the adverse effects and high costs associated with C5 inhibitor therapy, several studies have evaluated the optimal treatment duration for CM-TMA. The presence of pathogenic genetic variants increases the likelihood of relapse upon treatment discontinuation. Pathogenic gene variants in Factor H and CD46/MCP are particularly associated with higher relapse risks. Elevated levels of soluble C5b-9 (≥ 300 ng/mL) have been shown to significantly correlate with relapse, with an odds ratio of 20.96 (1.76–250, $p = 0.0162$) [64–66]. Serial measurements showing a progressive decline in sC5b-9 have supported safe discontinuation in case reports [30].

The decision to continue or discontinue therapy should be made by the treating medical team and tailored to each patient's unique circumstances. Key considerations include severity of the initial presentation, identification of genetic variants and capacity for close patient follow-up. Incorporating the patient and/or their caregivers in the decision-making process is essential for shared understanding and compliance.

Final considerations

CM-TMA represent a group of complex disorders whose identification and management have advanced significantly due to detailed knowledge of the alternative complement pathway and progress in genetic diagnostics. The introduction of C5 inhibitors has revolutionized treatment, improved survival rates and reduced progression to chronic kidney disease.

However, the genetic heterogeneity of CM-TMA presents ongoing challenges, emphasizing the importance of comprehensive diagnostic approaches that consider both genetic and environmental factors. Long-term C5 inhibitor therapy requires meticulous monitoring and prophylactic measures against meningococcal infections, along with careful evaluation of when discontinuation is feasible.

A multidisciplinary and personalized approach is essential to optimize patient outcomes and guide future research in this evolving field of Nephrology and Hematology.

Acknowledgements
We thank Fundación Pro Salud Renal and AstraZeneca for their financial support in covering the publication fee of this manuscript. They had no role in its development, writing, or content. We thank FlatIcon and BioRender for providing the platforms used to create the figures in this work.

Author contributions
Pilar Musalem wrote and reviewed the main manuscript text and designed the figures and tables.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethical approval
Not applicable.

Consent to Participate
Not applicable.

Consent to Publish
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 20 February 2025 / Accepted: 18 March 2025
Published online: 27 March 2025

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