Complement C5-inhibiting therapy for the thrombotic microangiopathies: accumulating evidence, but not a panacea

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Abstract

Thrombotic microangiopathy (TMA), characterized by organ injury occurring consequent to severe endothelial damage, can manifest in a diverse range of diseases. In complement-mediated atypical haemolytic uraemic syndrome (aHUS) a primary defect in complement, such as a mutation or autoantibody leading to over activation of the alternative pathway, predisposes to the development of disease, usually following exposure to an environmental trigger. The elucidation of the pathogenesis of aHUS resulted in the successful introduction of the complement inhibitor eculizumab into clinical practice. In other TMAs, although complement activation may be seen, its role in the pathogenesis remains to be confirmed by an interventional trial. Although many case reports in TMAs other than complement-mediated aHUS hint at efficacy, publication bias, concurrent therapies and in some cases the self-limiting nature of disease make broader interpretation difficult. In this article, we will review the evidence for the role of complement inhibition in complement-mediated aHUS and other TMAs.

Key words: atypical haemolytic uraemic syndrome, complement, eculizumab, thrombotic microangiopathy

Introduction

Thrombotic microangiopathy (TMA) is characterized by thrombocytopenia, microangiopathic haemolytic anaemia and organ injury [1], and can manifest in a diverse range of diseases. There is overlap in the pathogenic mechanisms involved in the different TMAs, and as a consequence classification is challenging. The introduction into clinical practice of complement-inhibiting therapy has stimulated particular interest into the role that complement plays. The prognosis of individuals with complement-mediated atypical haemolytic uraemic syndrome (aHUS), a term that we apply here specifically to individuals with TMA caused by a primary defect in the complement system that results in dysregulation, has been transformed by the terminal complement inhibitor eculizumab. This paradigm shift has understandably led to the question: who else with a TMA might benefit from this treatment? In this review, we will consider the contribution of complement dysregulation (resulting from a primary defect) and complement activation (as a secondary effect) to the pathogenesis of the different TMAs, and evaluate the strength of the evidence supporting clinical benefit of complement-inhibiting therapy. There has never been a randomized controlled trial (RCT) that demonstrates efficacy of complement-inhibiting therapy in any TMA. Complement has important physiological roles, for example in the immune system, which will be considered in this review.
defence against encapsulated organisms, so complement inhibition does not come without potential for significant harm; appropriate selection of individuals who are likely to benefit from therapy is therefore paramount.

Complement

The complement system comprises >30 plasma and cell surface-bound proteins that operate in a regulated network of signalling and amplification [2]. It functions to protect the host against infection, by stimulating the inflammatory response and opsonizing and lysing pathogens as a fundamental component of the innate immune system, as well as modulating the adaptive immune system; it also facilitates the disposal of damaged host cells and potentially injurious immune complexes [3]. Complement can be initiated by three pathways (Figure 1): in the classical pathway, pattern recognition molecules such as immunoglobulins are recognized by C1q, and in the lectin pathway mannose-binding lectin (MBL) recognizes pathogen-associated carbohydrates; these pathways generate the C3 convertase C4b2b. The alternative pathway can be initiated by pattern recognition molecules, but in addition is constitutively active, with spontaneous hydrolysis (tickover) of C3 leading to it interacting with factor B (FB) to generate the C3 convertase C3bBb, and the pathways converge in the amplification loop, in which C3 is cleaved and activated by C3bBb. This leads to C5 cleavage, and results in the production of anaphylatoxins and activation of the terminal pathway, which initiates the assembly of the cell-lysing membrane attack complex (MAC). The amplification loop allows for rapid response to pathogens, but leaves the host vulnerable to bystander damage if the tick over component is unchecked. The system is therefore tightly regulated by plasma and cell surface proteins; for the alternative pathway the most important are factor H (FH), factor I (FI) and membrane cofactor protein (MCP, CD46). Rarely, complement dysregulation due to a defect in a component or regulator can directly cause disease, and commonly, in many diseases, tissue damage activates complement, which intensifies the inflammation [4]. Consequently, there has been much interest and investment in developing complement-targeted therapy [5].

Complement-inhibiting therapy

The complexity of the complement system means that there are multiple potential therapeutic targets: drugs that target the activation pathways, the anaphylatoxins, the amplification loop and the terminal pathway have been developed and have entered preclinical and clinical trials [5]. Alexion Pharmaceuticals developed in the 1990s a recombinant humanized monoclonal antibody that functionally blocked C5 [6], and this agent, named eculizumab (Soliris), entered early clinical trials for a range of inflammatory conditions [5, 7]. Trials of eculizumab in patients with paroxysmal nocturnal haemoglobinuria (PNH), a disease characterized by complement-mediated intravascular haemolysis and caused by a somatic mutation that results in disruption of erythrocyte complement regulation, yielded the most impressive efficacy [8, 9] and eculizumab was approved for use in PNH in 2007 by the US Food and Drug Administration (FDA), and the European Medicines Agency (EMA) [10]. Because genetic and functional analysis had also identified aHUS as a disease caused by complement dysregulation, the PNH breakthrough encouraged the use of eculizumab in patients with complement-mediated aHUS; promising case reports [11, 12] were followed by successful clinical trials [13] and it was approved by the FDA and EMA for use in complement-mediated aHUS in 2011 [10].
Potential complications of complement-inhibiting drugs

The terminal complement pathway is fundamental to the immune response against encapsulated organisms, so the major concern with terminal complement inhibition is infection, and individuals deficient in terminal complement components are particularly susceptible to Neisseria infections [10, 14]. Disseminated gonococcal infection has been reported in patients treated with eculizumab, and the risk of meningococcal infection is increased by up to 10 000 times by treatment with eculizumab [14]. For this reason meningococcal vaccination and antibiotic prophylaxis is recommended in patients receiving eculizumab [15], though meningococcal infection can still occur despite these measures [16, 17].

There may be other infectious associations: respiratory tract infections are reported to be more common in patients on eculizumab compared with placebo [14], and a case of progressive multifocal leucoencephalopathy, an opportunistic infection of the CNS caused by reactivation of the polyomavirus JC, was recently reported in a patient treated with eculizumab, though they had also received multiple immunosuppressants [18].

In addition to infection complications, other concerns may emerge as use of complement-inhibiting therapy in clinical practice increases. Eculizumab-associated hepatotoxicity has been reported in children [19], and glomerular deposition of eculizumab in individuals with C3 glomerulopathy (C3G) [20], though not complement-mediated aHUS [21], has been reported although the long-term clinical consequences are as yet unclear.

TMAs

TMAs are the consequences of severe endothelial injury with pathological features representing the tissue response to injury [15]. TMAs are characterized by thrombocytopenia (due to aggregation and consumption of platelets), microangiopathic haemolytic anaemia (haemolysis consequent to mechanical injury to erythrocytes in partially occluded vessels) and organ injury (ischaemia) [1]. They can manifest in a diverse range of diseases and result in a range of clinical presentations, though they commonly comprise acute kidney injury (AKI) due to the apparent propensity of the glomerular circulation to endothelial damage and occlusion.

The classification and nomenclature of the TMAs can be challenging. Thrombotic thrombocytopenic purpura (TTP) refers to individuals with ADAMTS13 activity <5%, and Shiga toxin-producing Escherichia coli-associated HUS is defined as STEC-HUS. The term atypical haemolytic uraemic syndrome (aHUS) has broadly been used to describe any TMA that was not TTP or STEC-HUS, thus describing a heterogeneous mixture of conditions. There is a move towards using the term ‘complement-mediated aHUS’ to define those individuals with a complement abnormality as the primary underlying pathology, to distinguish them from individuals with TMA consequent to an underlying disorder; this is important because it may help guide therapeutic strategies [22, 23]. However, this distinction is not unequivocal: it is well recognized that complement gene mutations exhibit variable penetrance, and individuals with a genetic predisposition usually require an environmental trigger for TMA to manifest [3]. Conversely, in cases of TMA where no genetic or acquired complement abnormality is found, complement can be seen to be activated and may play a role in pathogenesis (Figure 2). TMA diagnosis, classification and treatment decisions are difficult; there may be no definitive diagnostic test, and no refined methods of monitoring disease activity or therapeutic response beyond crude tests of haemolysis parameters and organ recovery [24].

Evidence for the role of complement in the TMAs

Complement-mediated aHUS

The pathogenesis of complement-mediated aHUS is archetypal for diseases occurring due to over activation of the complement system. Ever since 1998, when genetic studies first produced molecular evidence that CFH mutations are associated with complement-mediated aHUS [25], there have been major advances in the understanding of the pathogenesis. Genetic studies and functional analysis in individuals, families and large cohorts [26, 27] have identified pathogenic activating mutations in the genes encoding the alternative pathway components C3 and CFH, and loss of function mutations in the genes encoding the alternative pathway regulators CFH, CFI and CD46 [3, 28–30]. A mutation is identified in ~60% of individuals [23]. Autoantibodies that bind to FH [31, 32] and FI [33] resulting in complement dysregulation [34] have also been identified in 5–56% of individuals with complement-mediated aHUS [35]. Even in those individuals with a complement mutation or autoantibody a trigger, for example infection or pregnancy, is frequently required for disease to manifest [3].

The evidence that this disease is mediated by a primary complement defect is strong, so there is mechanistic rationale for complement-inhibiting therapy, though there has never been an RCT. The landmark trials of eculizumab for complement-inhibiting therapy published in 2013 [13] were single-arm studies; however, given the high morbidity and mortality in individuals with complement abnormalities [3- to 5-year survival without established renal failure (ERF) of 52-64% in children and 33–36% in adults, even with plasma exchange (PEX) [26, 27]], it is accepted that comparison with historical controls is justified. The positive results (Table 1) paved the way for the first-line use of eculizumab in clinical practice, and its efficacy has been validated in subsequent prospective studies [37–39] and cohort analysis [42]. The prognosis of complement-mediated aHUS has been transformed: full recovery of renal function is now expected, other than in those who present late in the course of disease. Kidney Disease: Improving Global Outcomes (KDIGO) recommends that all patients with a clinical diagnosis of complement-mediated aHUS are eligible for treatment with a complement inhibitor [15]. International consensus recommendations are that in children with a clinical diagnosis of complement-mediated aHUS, eculizumab (or PEX if eculizumab is not available) should be started within 24–48 h (results of complement genetic tests are not required for this decision) [290].

More recently, with increased use in clinical practice, it has become clear that not all patients respond to eculizumab [94, 263]; in a non-randomized, uncontrolled trial of eculizumab in children, improvement in renal function was seen in all patients with a complement mutation or autoantibody, but not in 27% of those without an identified complement abnormality [39, 291]. The initial trials in adults included a higher proportion of patients with mutations than is seen in clinical practice. Further research is therefore required to inform a stratified approach to treatment [292] and it may be that the most clinically relevant classification would differentiate eculizumab responsive and eculizumab-resistant aHUS.

Prophylaxis and recurrence of complement-mediated aHUS after kidney transplantation

The outcomes of kidney transplantation in patients with complement-mediated aHUS were historically very poor: a retrospective
analysis reported recurrence of 68%, and 5-year death-censored graft survival of 51% [63]; even if patients with recurrence were treated with PEX, 59% of grafts failed [65]. The genetic background predicts the risk of recurrence and graft failure: rates of >70% have been reported in individuals with CFH mutations, but the risk is very low if the mutation is in CD46 [64, 293]. Some patients were therefore considered ‘untransplantable’. One option was combined liver and kidney transplantation, but experience is very limited internationally and short-term risk is significant: for 20 published cases, the success rate was 80% but the mortality rate was 15% [55]. There are no trials that specifically examine the use of eculizumab for prophylaxis or for treatment of recurrence in kidney transplantation, although the single-arm eculizumab trials included small number of adults [13, 37, 38] and children [39] with prior kidney transplant, and reported efficacy. Retrospective cohort analyses have reported successful use of eculizumab to facilitate transplantation [42–44] and to treat recurrence [43], and there are multiple case reports (Table 1). Again, despite the lack of RCT evidence, the favourable results with eculizumab compared with historical outcomes are felt to justify that prophylactic eculizumab is now the gold standard approach to kidney transplantation in those with a high-risk genetic background.

De novo TMA after transplantation

In kidney transplant recipients, the incidence of de novo TMA has been reported as 0.8% in the United States Renal Data System (USRDS) [294], but single-centre studies report incidences of up to 14% [295]. Multiple associations and risk factors have been observed, including viral infections such as cytomegalovirus (CMV), immunosuppressant drugs such as calcineurin inhibitors (CNIs) and sirolimus [295], and antibody-mediated rejection (AMR) [72]. These factors, together with ischaemia-reperfusion injury, create an ‘endothelial damaging milieu’ that transplant recipients are exposed to [296], and it is not clear to what extent complement is involved. Underlying complement mutations may play a role especially where the initial cause of end-stage renal failure was unclear. In one cohort analysis, mutations were identified in 29% of patients with de novo post-transplant TMA [66]. Evidence regarding management is also limited; good
### Table 1. Evidence for the role of complement in the TMAs

| TMA                      | Evidence for complement involvement in pathogenesis                                                                 | Evidence for complement-targeted therapy                                                                                     | Evidence for other management                                                                                     | High morbidity and mortality prior to eculizumab availability, best available treatment was PEX: |
|--------------------------|-----------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|
| Complement-mediated aHUS | • 2 large aHUS cohorts (>200 patients): complement gene mutation identified in 48–60% [26, 27]; functional significance of mutations in CFH, CFI, CD46, C3, CFB demonstrated [3].<br>• Anti-FH Ab identified in 5–25% of aHUS cohort in Europe, 56% in India [35]; functional analyses demonstrate pathogenicity of anti-FH Ab [36].<br>• No RCTs.<br>• 3 prospective, single-arm, phase 2 trials of eculizumab in adults: 88% TMA event-free status and 76% >25% improvement in sCr at 2 years in 17 patients with progressive TMA and renal impairment; complement mutation/anti-FH Ab in 76% [13, 37].<br>• 95% TMA event-free status and 55% >25% improvement in sCr at 2 years in 20 patients with stable TMA and renal impairment; complement mutation/anti-FH Ab in 70% [13, 37].<br>• Complete TMA response at 26 weeks in 73% in 41 patients.<br>• 2 cases of meningococcal infection.<br>• Complement mutation/anti-FH Ab in 49% [38].<br>• 1 prospective, single-arm, phase 2 trial of eculizumab in 22 children: complete TMA response in 64% at 26 weeks; >25% improvement in sCr in 73%; complement mutation/anti-FH Ab in 50%. No deaths/meningococcal infection [39].<br>• Successful use of eculizumab to facilitate transplantation without recurrence reported in retrospective cohort analyses [42–44].<br>• Case reports of successful use of eculizumab with [45, 46] and without [47–54] PEX. | • Kidney transplant<br>• Complement-mediated aHUS prophylaxis<br>• As above. | • High morbidity and mortality prior to eculizumab availability: Retrospective analysis of 2 large cohorts: 5-year survival without ERF 64% in children and 36% in adults (214 patients); worst prognosis with CFH mutations: 50% ERF at first episode despite high intensity PEX [26].<br>3-year survival without ERF 52% in children and 33% in adults (273 patients); 23% if CFH mutation, 6% if CD46 mutation. Complete remission with PEX in 5% with CFH mutation [27].<br>• Review of all published case series of patients (278 patients) with anti-FH Ab: ERF in 27–63% [40].<br>• 2 case reports of isolated liver transplant in patients with CFH mutation: 1 successful, 1 fatal [41]. | • Combined liver kidney transplantation: 20 published cases reviewed; success rate 80%, mortality 15% [55].<br>• 7 patients with ERF secondary to HUS (no genetic analysis or aetiology details reported) transplanted with preemptive CNI-free immunosuppression regimen, with no TMA recurrence [56].<br>• High rates of recurrence and graft loss prior to eculizumab availability:<br>• Retrospective review of 57 patients (71 transplants): 68% had a complement mutation. 68% aHUS recurrence. 7% mortality. 1- and 5-year post-transplantation death-censored graft survival were 76% and 51%. Preemptive PEX reduced graft loss but disease-driven PEX did not [63].<br>• Review of 100 kidney transplants: CFH mutation 73.7% recurrence, 77.8% graft failure; CFI mutation: 100% recurrence, 100% (continued) |
| TMA                     | Evidence for complement involvement in pathogenesis                                                                 | Evidence for complement-targeted therapy                                                                 | Evidence for other management                                                                 |
|------------------------|----------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
| **De novo TMA**        | • Genetic analysis in 24 patients with de novo TMA after transplantation identified CFH or CFI mutation in 29% [66].       | • 3 case reports of successful use of eculizumab for TMA following kidney transplantation [67, 68] and SPK transplantation [69–71], though in all cases eculizumab was used concurrently with other treatment (such as immunosuppression switch, PEX). | graft failure; CD46 mutation: no recurrence/graft failure [64].                                |
|                        |                                                                                                                      |                                                                                                          | 27 published cases of PEX for aHUS recurrence: only 41% of grafts survived [65].                |
|                        |                                                                                                                      |                                                                                                          | Case series: 29 patients with de novo TMA treated with discontinuation of CNI and PEX: graft salvage rate was 80% [72]. |
|                        |                                                                                                                      |                                                                                                          | Case reports of TMA resolution following immunosuppression switch, CNI to belatacept [73] or everolimus [74]. |
|                        |                                                                                                                      |                                                                                                          | 2 cases of TMA following PAK transplant successfully treated with PEX and immunosuppression switch [75]. |
| **AMR-associated TMA** | • No evidence specific to AMR with TMA.                                                                             | Case reports of eculizumab for AMR with TMA:                                                            | Therapeutic strategies for AMR (not specific to AMR with TMA) include PEX, IVIG and rituximab, but there is insufficient evidence to determine optimal treatment [92]. |
|                        | • C4d deposition in peritubular capillaries suggests classical complement pathway activation [76].                    | • TMA resolved, but graft failed of BKV nephropathy [77].                                                |                                                                                              |
|                        |                                                                                                                      | • TMA resolved but ongoing AMR [78].                                                                    |                                                                                              |
|                        |                                                                                                                      | • Successful use (concurrent with other treatment) [79, 80].                                             |                                                                                              |
|                        |                                                                                                                      | Trials of eculizumab for treatment of AMR (not specific to TMA related):                                 |                                                                                              |
|                        |                                                                                                                      | • Efficacy and safety of eculizumab for treatment of AMR following renal transplantation. Eculizumab versus PEX + IVIG. Terminated due to lack of efficacy. ClinicalTrials.gov Identifier NCT01895127 (unpublished). |                                                                                              |
|                        |                                                                                                                      | • Eculizumab to prevent AMR in patients with a positive cross match against their live donor: 26 patients compared with historical cohort of 51 patients; single-centre, open label. ClinicalTrials.gov Identifier: NCT006707. Eculizumab reduced acute AMR episodes but did not prevent chronic AMR [81, 82]. |                                                                                              |
|                        |                                                                                                                      | • Pilot RCT of eculizumab for chronic AMR: no significant difference, but underpowered [83].             |                                                                                              |
|                        |                                                                                                                      | • Case reports/series of successful [84–87], unsuccessful [88] and mixed success [89–91] in use of eculizumab for AMR (no TMA), concurrent with other treatment in most cases. |                                                                                              |
| TMA                      | Evidence for complement involvement in pathogenesis | Evidence for complement-targeted therapy | Evidence for other management |
|-------------------------|---------------------------------------------------|----------------------------------------|-------------------------------|
| DGKE-associated aHUS    | • No evidence for complement involvement in pathogenesis.  
• DGKE silencing in endothelial cells does not induce complement deposition in vitro [93]. | Only a small number of cases have been published:  
• Cohort of 13: 1/7 treated with eculizumab relapsed while on treatment. All developed progressive CKD/ERF [94].  
• 4 cases; 1 treated with eculizumab and responded—but had concomitant C3 mutation [95]. | • 5 patients; multiple relapses, treated supportively or with PI/PEX. Normal renal function in all at last follow-up [96].  
• 2 cases, responded to PI [97]. |
| TTP                     | • Mouse model: C3 deposition in kidneys [98].  
• In vitro: TTP serum caused C3 and MAC deposition on HMEC-1; cytotoxic effect was abolished by complement inhibition [99]. | Case report of efficacy of eculizumab in TTP case refractory to PEX, corticosteroids, rituximab, NAC and vincristine. However, a later update reported positive Anti-FH Ab, and ADAMTS13 not sufficiently low [106, 107].  
• Case report, efficacy of eculizumab in a child with congenital TTP (ADAMTS13 mutation) and no complement gene abnormality/anti-FH Ab [108]. | • American society of apheresis guidelines: grade IA evidence for PEX as first-line treatment: PEX decreased mortality from universally fatal to < 10%. 7 RCTs (301 patients) [109].  
• Phase 2 studies demonstrate efficacy of rituximab in preventing relapse in acquired TTP [110–112]: 10% relapse compared with 57% in historical controls [110].  
• Phase 2 study of caplacizumab (monoclonal antibody against vWF) versus placebo in addition to PEX + immunosuppression in acquired TTP more rapid resolution of TMA [113]. |
| Pregnancy associated    | Genetics: cohort of 21 females with pregnancy-associated aHUS (P-aHUS): 86% had a complement gene mutation [114]. | 2 case reports of successful use of eculizumab in P-aHUS in context of mutations in CFH [115] and CFI [116]. | In the cohort of 21 with P-aHUS, 83% were treated with PEX (none received eculizumab): 76% developed ERF [114].  
UK cohort of pregnancy-associated TTP. Congenital TTP: fetal survival 58% for index presentation, and 100% if actively managed. Acquired TTP: fetal survival 58% [117].  
Clinical studies have reported complete biochemical resolution rates of 29–43% with expectant management of severe pre-eclampsia/HELLP, but fetal/neonatal mortality of 14–20% [128]. |
| Complement-mediated aHUS| No evidence. | 75 pregnancies in 61 women on eculizumab for PNH: 8% developed pre-eclampsia [126].  
7 pregnancies in 3 women with complement-mediated aHUS on eculizumab: 2 women experienced pre-eclampsia and 1 HELLP despite complement inhibition [127].  
• Case report of eculizumab use in addition to expectant management for HELLP at 26 weeks gestation: delivery delayed until 29 weeks [128]. | |

| HELLP                   | In vitro: eculizumab plus HELLP serum resulted in less cell killing [118]. | 75 pregnancies in 61 women on eculizumab for PNH: 8% developed pre-eclampsia [126].  
5 pregnancies in 3 women with complement-mediated aHUS on eculizumab: 2 women experienced pre-eclampsia and 1 HELLP despite complement inhibition [127]. | |

Observational clinical data:  
• Reports of elevated C3a in HELLP [119]; elevated C3a and C5b-9 in pre-eclampsia [20]; elevated C3a, C5a, Bb and C5b-9 in pre-eclampsia [121].  
• But also report of no difference in C3 and FH levels in healthy pregnant women versus pre-eclampsia with and without HELLP [122].  
• 4/11 consecutive women with HELLP and renal impairment had a complement gene mutation [123].  
• 2/33 women with HELLP had a complement gene mutation (only 30% had renal impairment) [124].  
• 7/40 women with SLE and/or APS, and pre-eclampsia, had a complement gene variant [125]. |

(continued)
Table 1. (continued)

| TMA                  | Evidence for complement involvement in pathogenesis                                                                 | Evidence for complement-targeted therapy                                                                                                                                                                                                 | Evidence for other management                                                                 |
|----------------------|------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| Metabolic (cobalam in C deficiency) | • Genetics: Concomitant anti-FH Ab (patient died) and CFH mutation (patient responded to PEX) in one cohort with established cbC1 defect [129].
  • Child with aHUS attributed to CD46 mutation; died after renal transplantation from pulmonary veno-occlusive disease; subsequently found to have MMACHC mutation [130].
  • Case report: 2 sisters with cbC1 deficiency; 1 also had CFH mutation, and had more severe disease, though both responded to metabolic therapy [131]. |
| Infection associated | Mouse models: In vitro and in vivo experiments demonstrated Stx-induced complement activation and C3a-dependent microvascular thrombosis (via P-selectin) [133].
  • MBL2 inhibition protected against complement activation and renal injury induced by Stx-2 [134].
  • Stx-induced activation of the alternative complement pathway results in podocyte injury [135]. In vitro:
  • Stx2 binds to FH and delays cofactor activity [136].
  • Stx2 binds to CFHR1 and competes with FH for Stx2 binding, with resultant reduction in FH cofactor activity [137].
  • Stx and O157LPS induced the release of microparticles with surface-bound C3 and C9 [138].
  • Stx2-induced complement-mediated haemolysis [139].
  • Observational clinical data: elevated C5b-9 levels [140–142]. Genetics
  • Case reports of complement gene mutations in STEC HUS [140, 143–145].
  • Complement gene variant in 7/25 STEC HUS cases [146]. |
| STEC                 | • Case series of 36 patients: 2 received eculizumab and did not respond [129].
  • Case report: a dult presenting with TMA, dialysis dependent. No response to eculizumab. Subsequently found to have MMACHC mutation. Metabolic therapy resulted in resolution of TMA and renal recovery [132]. | • Case series of 36 patients: 54% had clinical recovery with metabolic therapy. Mortality 100% in untreated group, 44% overall, 79% in group with cardiopulmonary involvement [129]. |
| Pneumococcal        | • Mouse model: suggests that the interaction between pneumococcal surface protein C (PspC) and FH contributes to pneumococcal virulence [154].
  • Hypothesis: that the cleavage of sialic acid residues by pneumococcal produced neuraminidase results in disruption of the binding of FH/C3b, and therefore a function FH deficit at the cell surface [155]. |
|                      | • Case report: child with pneumococcal HUS treated with eculizumab due to lack of response to supportive care: recovered renal function (dialysis for 30 days) [156]. | • Natural history is of good prognosis. Long-term outcome data: 70% fully recover, 3% develop ESRD, 9–18% develop CKD [150].
  • American Society of Apheresis guidelines: PEX in STEC-HUS is grade 2C category III (and grade 1C category IV if absence of severe neurological symptoms) [109].
  • Prospective non-controlled trial: 12 patients in 2011 O104:H4 outbreak treated with IgG immunoadsorption and IgG replacement. 8 patients also received eculizumab. No deaths. Complete renal and neurological recovery in 10/12 [151].
  • 2009 systematic review: 7 RCTs in 476 children (no distinction between STEC-HUS and aHUS; >70%, were diarrhoea-associated cases). No advantage over supportive care identified for FFP, anticoagulation, steroids and Shiga toxin-binding agent [152].
  • Retrospective analysis of 90 children with STEC-HUS in the 2011 O104:H4 outbreak. 74% received supportive care only. 10 received PEX, 6 eculizumab and 7 received both. 71% required dialysis. Mortality was 1%. At 4 months follow-up 94% had normal renal function, 1% remained on dialysis and 3% had CKD3/4 [153].
  • Role of PEX controversial; theoretical risk of worsening the TMA with donor plasma because it may contain anti-T IgM [158].
  • American Society of Apheresis guidelines: PEX in pneumococcal HUS: grade 2C, category III recommendation [109]. |
|                      |                                                                                                                          |                                                                                                                          |                                                                                      |

(continued)
Table 1. (continued)

| TMA | Evidence for complement involvement in pathogenesis | Evidence for complement-targeted therapy | Evidence for other management |
|-----|--------------------------------------------------|----------------------------------------|-----------------------------|
| HIV | Observational clinical data: case reports/series have reported transient low C3 and complement gene mutations [156, 157]. | Case report: TMA in a patient non-compliant with HAART: treated with PEX and eculizumab and recovered (HAART also presum-ably restarted) [159]. | Death usually results from the complications of pneumococcal infection [155]. |
| CMV | No evidence. | Case report of de novo TMA after kidney transplant in the context of CMV infection, and recurrence of TMA with recurrence of CMV viraemia in the absence of CNI; successfully treated with valganciclovir and eculi-zumab [163]. | No evidence. |
| BMT | Mouse models: evidence that conditioning for BMT with radiation activates complement [164, 165] and treatment with a C5aR inhibitor reduced GvHD morbidity [165]. | Use of eculizumab: | Review of 5423 published cases: response to PEX reported in 0–80%, but mortality in those treated with PEX was 44–100% [181]. |
| | Observational clinical data: | No trials. | American Society for Apheresis guidelines: >300 reported patients (no trials): grade 2C, category III recommendation for PEX [109]. |
| | • Kidney C4d deposition in TMA in context of GvHD [166, 167]. | • Retrospective analysis: | • Mortality 50–60% despite treatment, with death due to complications of renal failure or GvHD, or infection [182]. |
| | • Proteinuria (>30 mg/dL) and elevated sC5b-9 associated with poor survival [168]. | 30 patients: 1 year survival 62% compared with 9% in 11 historical controls [172]. | • 20% response rate to PEX [173]. |
| | • Normal C3 and C4 levels [169]. | 12 patients: 50% haematological response, 33% mortality [173]. | • Response rate to PEX 55%, but mortality 80% [175]. |
| | Genetics: | • Case reports/series: | Retrospective analysis of 11 cases: treatment was with CNI withdrawal and PEX: 64% responded, but mortality 38% (versus 13% without TMA) [183]. |
| | • Heterozygous CFHR1/3 and CFHR1/4 deletion and detectable Anti-FH Ab [170]. | Good outcome [175–178]. | • Case reports of some response to rituximab, but mortality still high [184, 185]. |
| | • Genetic analysis of 34 patients with TMA after BMT: multiple complement gene variants of uncertain significance reported [171]. | Response but died [179]; 4/5 responded, 2/5 died [180]. | Case series of 7 patients with severe hypertension and TMA treated with anti-hypertensive medication: TMA resolved in all [190]. |
| | Severe hypertension | Mouse model of angiotensin II-induced hypertension: C5aR knock-out mice exhibited reduced cardiac remodelling and inflammation [186] and a C5aR antagonist reduced cardiomyocyte hypertrophy, cardiac inflammation and perivascular fibrosis [187]. | | Literature review: 19 cases with severe hypertension and TMA; all were treated with anti-hypertensive medication and 1/3 also had PEX: symptomatic improvement 100%, thrombocytopenia improvement in 84%, but significant sCr improvement in only 58% [191]. |
| | Observational clinical data: longitudinal cohort study (2178 males): higher plasma C3 levels associated with development of hypertension [188]. | Observation data suggest incidence of TMA in patients with HIV historically was 7% [160] and 35% if AKI [161], but has markedly reduced in HAART era to 0.3% [162]. | Case report: complete recovery of TMA and PRES with anti-hypertensive medication [192]. |
| | Genetics: population-based cohort study (3210 individuals): CFHR3/1 deletion and an AMD related CFH SNP were significantly associated with hypertension risk [189]. | | (continued) |
| TMA          | Evidence for complement involvement in pathogenesis | Evidence for complement-targeted therapy | Evidence for other management |
|-------------|----------------------------------------------------|----------------------------------------|-------------------------------|
| Drug mediated | • Genetics: CFH variants in 4 patients with ticlopidine-associated TMA (all had ADAMTS13 <5%) [193].  
• Case report: low C3 in a patient with clopidogrel-associated TMA (no genetic analysis) [194]. | Case reports/series of eculizumab:  
• Successful use reported in TMA associated with mitomycin C [195], gemcitabine [196–198], though given concurrently with other treatment (such as drug withdrawal, PEX); despite TMA response prognosis still poor due to malignancy [198].  
• 1 patient with proteasome inhibitor associated TMA had persistent TMA after eculizumab and died [199]. | • American Society for Apheresis guidelines: based on available evidence (no trials, only case series and reports) PEX recommended for ticlopidine-associated TMA (which should be considered TTP due to ADAMTS13 deficiency) but for all other drug-associated TMA the role of PEX has not been established and may be harmful [109].  
• 7 patients with TMA associated with ticlopidine and ADAMTS13 deficiency: all recovered with PEX and drug discontinuation [200].  
• Review of 44 patients with gemcitabine-associated TMA: worse outcome with PEX than drug withdrawal alone [201].  
• 2 cases of TMA associated with carfilzomib did not respond to PEX, but recovered with supportive care and drug discontinuation [202].  
• Case series of 10 patients thought to have TTP and so treated with PEX but subsequently found to have disseminated malignancy (only 1 received chemotherapy). Only 1 had a response to PEX, and all died soon after TMA diagnosis [203].  
• Registry report: 85 cases with malignancy-associated HUS. 99% received mitomycin C, 80% received 5-FU. 30% said to respond to PEX [204].  
• Registry report: 20 cases with malignancy-associated HUS. 50% 30-day mortality; chemotherapy associated with better outcome than PEX/PI [205]. | |
| Malignancy associated | No evidence. | Case reports of eculizumab use are all in the context of chemotherapy—see above. | |
| Autoimmune condition/glomerulopathy associated | | | |
| SLE | • Mouse model of SLE (not with TMA): C5 inhibition increased survival (80% versus ~5% at 40 weeks) [206].  
• Observational clinical data: correlation of hypocomplementaemia, secondary to complement activation and consumption, with disease activity [207].  
• Genetics: GWAS study identified association between CFHR3/1 deletion and susceptibility to SLE [208]. Mouse models: | | |
| APS | • Phase 1 trial: single dose of eculizumab in patients with SLE: pharmacokinetic and pharmacodynamics analysis [207].  
• Case reports of successful use of eculizumab in SLE with TMA (but no APS) [209–213].  
• No RCTs.  
• A prospective, single-arm, phase 2 trial is ongoing: eculizumab to enable renal | | |
| | | | |
Table 1. (continued)

| TMA | Evidence for complement involvement in pathogenesis | Evidence for complement-targeted therapy | Evidence for other management |
|-----|---------------------------------------------------|----------------------------------------|-------------------------------|
|     | • Complement-dependent and complement-independent pathways in a mouse model of TMA induced by aPL Ab [215].<br>• Passive transfer of human aPL Ab: complement activation plays a role in fetal loss and tissue injury [216].<br>• Factor B inhibitor prevented aPL Ab-induced pregnancy loss [217].<br>• C5 inhibitor rEV576 inhibits in vivo effects of aPL Ab [218].<br>Observational clinical data in APS:<br>• C5b-9 and C4d deposition in kidney allografts with TMA due to APS recurrence [219].<br>• (Not specific to APS with TMA): low C3 and C4, high C3a [220] and low C3 and C4 more frequent if renal involvement [221].<br>• anti-FH Ab in patients with APS, and association with VTE recurrence [222].<br>     | transplantation in patients with history of catastrophic antiphospholipid antibody syndrome. ClinicalTrials.gov Identifier: NCT01029587.<br>• Case reports/series of successful use of eculizumab:<br>CAPS [223–228].<br>CAPS recurrence in renal transplant [229, 230].<br>Prophylactic anticoagulation and eculizumab to enable renal transplantation in 3 patients [231].<br>3 cases with recurrence after kidney transplant: TMA resolved with eculizumab but chronic APS nephropathy not prevented [219].<br>     | eculizumab. Overall mortality 37% (no subgroup analysis according to treatment modality) [232].<br>• In kidney transplant recipients with APS: 7/10 treated with sirolimus had a functioning graft 144 months after transplantation versus 3/27 untreated patients [233].<br>     |     |
|     | IgA nephropathy<br>Observational clinical data:<br>• Mesangial C3 deposition in ~90% of patients [234].<br>• Glomerular deposition of MBL [235–237] observed, and associated with more severe renal disease [238].<br>• Normal FH levels and no mutations in CFH exons 18–23 in 46 patients [234].<br>• Low FH levels associated with IgA nephropathy in 2 families [239].<br>Genetics:<br>• GWAS identified association between CFHR3/1 deletion (protective) and IgA nephropathy [240].<br>• Rare variants in CFHR5 may contribute to genetic susceptibility to IgA nephropathy [241].<br>     | RCT of CCX168 (C5aR inhibitor) plus standard of care in AAV: results awaited. ClinicalTrials.gov Identifier: NCT02222155 (not specific to cases with TMA).<br>     |     |
|     | ANCA-associated vasculitis<br>Mouse models suggest complement important in pathogenesis of AAV [244, 245] and C5aR blockade protects against AAV [246].<br>Observational clinical data:<br>• Hypocomplementaemia in AAV associated with concurrent TMA and higher mortality [247] and poor renal prognosis [248].<br>• Majority of AAV renal biopsies are negative for immune complexes but are positive for C3d, C4d and C5b-9 staining [249].<br>     | • No trials specific to AAV with TMA.<br>• In AAV RCTs have demonstrated efficacy of cyclophosphamide and rituximab [250, 251].<br>     |     |

(continued)
| TMA | Evidence for complement involvement in pathogenesis | Evidence for complement-targeted therapy | Evidence for other management |
|-----|-----------------------------------------------|--------------------------------------|-------------------------------|
| Membranous | • Rat model of MN: C3 and C5b-9 co-localize with immune deposits, and urinary podocytes are coated in C5b-9 [252]. | • No evidence specific to MN with TMA. | • No trials specific to MN with TMA. |
| | • In vitro: anti-PLA2R IgG4 autoantibodies from MN patients can bind to C4 via MBL [252]. | • RCT of eculizumab in MN: 200 patients. Never published (abstract only). Negative results but inadequate dosing and short (16 weeks) follow-up [252]. | • RCT in MN demonstrated efficacy of cyclophosphamide and corticosteroids versus supportive treatment [256]. |
| | Observational clinical data: | | • Case reports/series of MN with TMA describe some response to FFP [257]; rituximab [258], together with corticosteroids [259] and PEX [260]. |
| | •glomerular deposition of FH and C3b [253], MBL and C5b-9 [254], and urinary C5b-9 excretion predicts poor prognosis [255]. | | |
| FSGS | Observational clinical data: | Case report: no response to eculizumab in a patient with TMA and INF2 mutation [263]. | No evidence specific to FSGS with TMA, and very limited trial evidence for FSGS. |
| SRC | • Peritubular capillary C4d score associated with non-recovery of renal function [264]. | Case reports of eculizumab use: | • Observational data: the use of ACE inhibitors has reduced mortality from ~85% at 6 months to 25–35% [268]. |
| | • C5b-9 deposition detected in skin biopsies of SSc patients but not in healthy subjects [265]. | • SRC with TMA in pregnancy; low C3 and C4, high C5b-9; no complement mutations. Management was Caesarean and an ACE inhibitor and eculizumab: haematological response but no renal recovery; died of heart failure [266]. | • Case series of 7 patients with SRC and TMA treated with PEX in addition to ACE inhibitors: 1 died, 1 ERF at 1 year [269]. |
| MPGN/C3G with TMA | • Mouse model of MPGN: lower creatinine and reduced mortality in C5−/− mice [270]. | • Trial: open-label, non-blinded, proof of concept efficacy and safety study of eculizumab in C3G. 6 adults (3 C3GN, 3 DDD): Renal function improved in 2, was stable in 2, and deteriorated in 2 (no TMA) [273]. | 3 cases of MPGN/C3GN with TMA: 2 (with MPGN I) received PEX + corticosteroids + cyclophosphamide and developed ERF, 1 (with C3GN) received corticosteroids + cyclophosphamide and developed CKD [258]. |
| | • In vitro: functional studies of anti-FH Ab; different binding epitopes compared with aHUS [34]. | • Review of 16 published cases with MPGN and TMA. 2 had anti-FH Ab, 6 had complement gene mutations. ERF/death in 9/16 [258]. 2 received eculizumab—TMA resolved in 1 [274], no long-term follow-up data [275]. | |
| | • Genetics: complement gene mutations in 17–20% [271, 272]. | | |
| | • C3NeF in 78–86% with DDD [271, 272]. | • Case reports/series (not specific to cases with TMA) have reported partial [276, 277] and good response to eculizumab in native kidneys [278–286] and in transplant recurrence [287, 288]. | |
| DIC | No evidence. | Speculation about use of eculizumab [289]. | |

anti-FH Ab, anti-factor H autoantibody; sCr, serum creatinine; PI, plasma infusion; HMEC, human microvascular endothelial cells; NAC, N-acetylcysteine; Stx, Shiga toxin; LPS, lipopolysaccharide; FFP, fresh frozen plasma; AMD, age-related macular degeneration; SNP, single nucleotide polymorphism; PRES, posterior reversible encephalopathy syndrome; GWAS, genome-wide association study; AC, anticoagulation; GC, glucocorticoids; AAV, ANCA-associated vasculitis; MN, membranous nephropathy; anti-PLA2R, anti-phospholipase A2 receptor; SRC, systemic sclerosis; SRC, scleroderma renal crisis; PM-Scl, polymyositis–scleroderma; MPGN, mesangio-proliferative glomerulonephritis; C3G, C3 glomerulopathy; C3NeF, C3 nephritic factor; DDD, dense deposit disease; CIGN, C3 glomerulonephritis; DKC, disseminated intravascular coagulation; 5-FU, fluorouracil; APS, anti-phospholipid syndrome; PAK, pancreas after kidney transplant.
outcomes with CNI withdrawal, with and without PEX, have been described in case reports and series [72, 74, 75]. A small number of case reports describe good outcomes with eculizumab for de novo TMA after kidney [67, 68] and simultaneous pancreas and kidney (SPK) [69–71] transplantation, but in all cases this was in combination with other strategies such as immunosuppression alteration and PEX. De novo TMA has also been reported to occur in 4% of liver transplant recipients and 2.3% of lung transplant recipients; the cause again is likely to be multifactorial [297].

For those carrying a complement mutation where the initial diagnosis may not have been made there is a clear rationale for eculizumab. In those without underlying complement abnormalities, the role of eculizumab is less clear and in many cases removal of CNIs or treatment of viral infections is sufficient to stop the TMA. Despite this, evidence of complement activation can be seen in these scenarios and it is unclear whether eculizumab would have an additional benefit to removal of the offending stimuli.

**Antibody mediated rejection**

TMA can manifest in the context of AMR; it was observed in 13.6% of C4d-positive biopsies in one large retrospective study [298]. There is no evidence for the role of complement in AMR triggering a TMA. The deposition of C4d in peritubular capillaries suggests classical complement pathway activation [76], though this feature is not requisite for the diagnosis of AMR according to the 2013 Banff criteria [299]. Therapeutic strategies for AMR (not specific to AMR with TMA) include PEX, intravenous immunoglobulin (IVIG) and rituximab, but there is insufficient evidence to determine the optimal treatment [92]. A trial of eculizumab for treatment of AMR was negative (unpublished; NCT01895127) and a non-randomized trial of eculizumab in sensitized recipients found that acute episodes were reduced but not chronic AMR [81]. Case reports of eculizumab for AMR with [77, 79, 80, 278] and without [84–91] TMA describe both good and poor outcomes. In summary, further research is required to define the role of eculizumab in TMA associated with AMR.

**DGKE-mediated renal disease**

Recessive mutations in the DGKE gene causing TMA were first reported in 2013 [94]. Genetic pleiotropism is also seen in DGKE-mediated renal disease with a separate report describing a membranoproliferative glomerulonephritis-like disease [300]. In vitro experiments suggest that the development of TMA due to loss of DGKE expression or activity is independent of complement activation [93]. Data regarding outcomes and treatment response are limited. Good outcomes have been reported with supportive treatment and PEX or plasma infusion [96, 97], but in the largest published cohort all patients developed progressive chronic kidney disease (CKD) or ERF regardless of treatment, and the single patient who received eculizumab relapsed on treatment [94]. One child with a DGKE mutation in the paediatric eculizumab trial did respond [39, 291] although given the relapsing/remitting nature of DGKE-mediated disease, attributing efficacy is difficult. In a separate case report of eculizumab response, the patient had a concomitant C3 mutation [95]. More data are required before the role of complement in the pathogenesis of DGKE-mediated aHUS and thus eculizumab treatment can be defined.

**Methylmalonic aciduria and homocystinuria, cobalamin C (cblC) type**

Homozygous or compound heterozygous mutations in the MMACHC gene result in a disorder of cobalamin (cbl; vitamin B12) metabolism. The severity of phenotype may vary but includes developmental, ophthalmological, neurological, cardiac and renal manifestations. TMA is associated with MMACHC mutations although the pathophysiological mechanisms that result in endothelial damage are unclear [129]. It can present in childhood or adulthood, and prognosis is very poor if untreated or if there is cardiopulmonary involvement; however, metabolic therapy with hydroxycobalamin is very effective [129]. The role of complement is not clear; there are isolated reports of concomitant complement gene mutations and polymorphisms that may modify the disease [129–131], but the small number of published reports of eculizumab use describe non-response [129, 132]. As such, treatment with metabolic therapy remains the gold standard.

**Thrombotic thrombocytopenic purpura**

TTP is a disease mediated by deficiency of ADAMTS13, a von-Willebrand factor (VWF)-cleaving protease, which can be hereditary (ADAMTS13 mutations) or acquired (anti-ADAMTS13 autoantibody), and is characterized by usually large VWF multimers and consequent occlusive microvascular platelet aggregation [22]. There is some evidence of complement involvement in a mouse model [98] and in vitro [99], and observational clinical data suggesting that the alternative complement pathway is activated [98, 100–103] (Table 1). One study analysed the complement genetics in patients with TTP and found no mutations [104]. The advent of PEX in the treatment of TTP decreased mortality to <10% from essentially universal fatality and numerous RCTs demonstrate its efficacy [109], and rituximab rituximab reduces the relapse rate in acquired TTP [110–112]. PEX is unquestionably the first-line treatment in TTP and should be instituted urgently once the diagnosis is suspected. There is speculation about an adjuvant role for complement inhibiting therapy in severe TTP [301], but there is only a single case report that describes a response to eculizumab in a patient with TTP and no complement mutation or FH autoantibody [108], so currently there is no evidence to support this.

**Pregnancy-associated TMAs**

**Pregnancy-associated complement-mediated aHUS**

Pregnancy appears to be the trigger for complement-mediated aHUS to manifest in ~20% of women, and this usually presents in the post-partum period [302]. In a pregnancy-associated aHUS cohort, complement mutations were identified in 86%, and though a high proportion were treated with PEX, 76% developed ERF [303]. Pregnancy-associated complement-mediated aHUS was not included in the initial trial of eculizumab, although good outcomes have been published in case reports [116, 117]. Given that pregnancy-associated aHUS appears to have a high incidence of complement mutations there is a good rationale for complement inhibition and, based on this, the authors’ opinion is that pregnancy-associated complement-mediated aHUS should be treated with eculizumab.

**Pregnancy-associated TTP**

It has been reported that 10–36% of women with TTP present during pregnancy [304], particularly during the second or third trimesters [303]; in normal pregnancy, there is increased release
of VWF, which consumes ADAMTS13, therefore its activity falls, and in women with a genetic predisposition it can fall low enough for TTP to manifest [303]. There is no evidence regarding complement and complement therapeutics in pregnancy-associated TTP.

**Syndrome of haemolysis, elevated liver enzymes and low platelets (HELLP)**
The HELLP syndrome is a TMA-like syndrome that occurs in 0.5–0.9% of all pregnancies, and complicates 5–10% of cases of severe pre-eclampsia [124]. The pathogenesis is poorly understood, though there is some evidence suggesting an association with increased circulating levels of the syncytiotrophoblast-derived antiangiogenic factors soluble endoglin and the soluble form of the vascular endothelial growth factor (VEGF) receptor (sFlt-1) [305, 306]. Unlike pregnancy-associated complement-mediated aHUS only a minority (8–10%) of patients with pre-eclampsia and HELLP syndrome harbour complement genes variants, mostly of unknown significance or non-pathogenic [125]. There is some observational data that suggests the alternative complement pathway is activated in HELLP [119] and pre-eclampsia [120, 121], and in vitro, eculizumab added to HELLP serum resulted in reduced cell killing [118]. Complete biochemical resolution has been observed with expectant management, which includes bed rest, sodium-restricted diet, antihypertensive treatment, anticonvulsant treatment and non-invasive monitoring, but fetal mortality is high [128]. The use of eculizumab (in addition to expectant management) to delay delivery in a patient with HELLP has been reported [128]. However, it is notable that in a cohort of women with PNH taking eculizumab, 8% still developed pre-eclampsia [126], and in a small case series of women with complement-mediated aHUS, both pre-eclampsia and HELLP occurred despite ongoing eculizumab treatment during pregnancy [127]. Although it is possible that complement does play a role in HELLP pathogenesis, the current available evidence does not support the use of complement-inhibiting therapy.

**Infection associated**

**STEC-HUS**
In STEC-HUS endothelial damage occurs following ribosomal inactivation, and inhibition of protein synthesis by Shiga toxin, which enters the cells after binding to the Gb3 receptor [22, 307]. In addition, Shiga toxin can activate signalling pathways inducing an inflammatory response in affected cells [308]. The prognosis is good compared with that of most other TMs; long-term outcome data suggest that 70% fully recover, 3% develop ERF and 9–18% develop CKD [150], and it is considered to be a self-limiting condition.

There is evidence suggesting that the lectin [134] and alternative [133, 135, 138, 139] complement pathways are activated or dysregulated [137] in in vitro and animal models of STEC-HUS [309]. In patients with STEC-HUS, increased levels of C5b-9 have been observed, suggesting that the terminal pathway is activated [140–142]. However, mutations in complement genes are only rarely detected in these patients, and in these cases the clinical picture is unusually severe [21, 140, 143–146].

A small case series published in 2011 first reported full renal and neurological recovery in three children with severe disease who were treated with eculizumab [149]. Subsequently, in the 2011 O104:H4 outbreak in Europe, which was characterized by severe disease in adults as well as children, a significant proportion were treated with eculizumab. The retrospective analyses did not demonstrate a beneficial role of eculizumab or PEX over supportive care [147, 148, 153], though direct comparison is difficult because the patients who were treated with eculizumab had more severe disease. A further case series of eculizumab use in STEC-HUS with neurological involvement has been published [310], and many unanswered questions remain regarding any potential role [311]. An RCT of eculizumab for STEC-HUS in children is ongoing (NCT02205541) and in such a self-limiting illness only this will define the role of complement inhibition.

**Pneumococcal HUS**
TMA is reported in association with Streptococcus pneumoniae infection; a hypothesized mechanism is that neuraminidase produced by pneumococci cleaves sialic acid residues from glycoproteins on erythrocyte, platelet and endothelial cell membranes, exposing the cryptic Thomsen-Friedenreich antigen (T-antigen) to which IgM in the plasma can then bind, resulting in cell damage and TMA [158]. Pneumococcal HUS is therefore Coombs test positive. The natural history is of poor prognosis, with high morbidity and mortality [312–315], usually reflecting the severity of the infection [155]. The role of complement is unclear although transient low serum C3 levels [156, 157] and rare complement gene mutations [129] have been reported. There is also speculation that neuraminidase may induce a functional FH deficit [155, 316]. A single case report describes a good outcome in a child treated with eculizumab after poor response to supportive care [156]. Currently, there is insufficient evidence to recommend eculizumab treatment in a situation where there is active infection.

**HIV**
Prior to the advent of highly active anti-retroviral therapy (HAART), TMA was not uncommon in people with HIV infection [317]: incidences of 7% [160], and 35% in those with AKI [161], have been reported. The pathogenic mechanisms remain undefined, despite investigation in Macaque models of HIV-associated TMA [318]. With the introduction of HAART the incidence has fallen to 0.3% [162]. There is a single case report describing good outcome with eculizumab in an individual who had been non-compliant with HAART, presumably concurrently with the reintroduction of anti-retrovirals [159]. Again, treatment of the underlying infection should remain the mainstay of treatment.

**Bone marrow transplant-associated TMA**
A multisystem TMA complications of 10–20% of allogeneic bone marrow transplants (BMTs) [175] although individual centres have reported an incidence as high as ~40% [171]. There are multiple risk factors, including CNIs, graft versus host disease (GVHD), HLA mismatch, chemotherapy, radiation therapy and infections [319]. In common with solid organ transplantation, it is likely that these factors contribute to an endothelial-damaging milieu. Prognosis is very poor, with mortality rates variously reported at 21–75% [168, 169, 181, 183]. There has been much interest in the possible role of complement. Mouse models suggest that complement is activated during radiation conditioning [164, 165] and observational data in humans suggest that complement may be activated [166–168]. Rare functionally significant variants in known aHUS-associated complement genetic risk factors [171] and factor H autoantibodies [170] have been reported rarely. There is no evidence that PEX results in reduced mortality [175, 181, 183] and its role has not been established [109]. There are no prospective trials of complement inhibiting therapy. In the largest retrospective analysis, 1-year survival (62%) was favourable in those treated with
eculizumab compared with historical controls [172]. In some case series and reports, mortality has been high despite a haematological response [179, 180], though in others the outcome was good [175–178]. Trial evidence will likely be required before a consensus on the role of complement-inhibiting therapy can be achieved.

**Severe hypertension**

Case series of patients with severe hypertension have identified TMA in 27–44% [190, 320–322]. The pathophysiology of severe hypertension is complex and not completely understood, and the role of complement has not been fully defined [323, 324]. Conversely, any patient with a TMA may have severe hypertension, and distinguishing between severe hypertension-associated TMA and complement-mediated aHUS at the time of the acute presentation to guide appropriate management strategy is a major challenge. In a retrospective case series, genetic analysis identified rare variants in complement genes in patients in whom TMA was initially attributed to severe hypertension; eight of nine patients progressed to ERF despite management of hypertension [324]. However, in the majority of patients with TMA associated with severe hypertension, renal function and microangiopathic haemolytic anaemia (MAHA) usually recover with the management of blood pressure [323, 325] and therefore in practice the failure of the TMA to respond to blood pressure control often informs the diagnosis and future investigation and management.

**Drug-mediated TMA**

There are many published reports that describe drug-mediated TMA, either by acute, immune-mediated reactions [326] or by dose-dependent toxicity [327–329]. A systematic review in 2015 found evidence of a definite association in only 28% of the 78 drugs reported, the most common of which included quinine (immune mechanism) and ciclosporin, tacrolimus, sirolimus and interferon, and chemotherapy agents such as gemcitabine and mitomycin (toxic mechanism) [326]. There is no strong evidence for the role of complement, and recovery has been reported following drug withdrawal [201, 202]. The only recognized role for PEX is in ticlopidine-associated TMA, which is associated with severe ADAMTS13 deficiency [109].

**Malignancy-associated TMA**

TMA can manifest in malignancy, though it can be challenging to differentiate between chemotherapy-induced TMA and malignancy-induced TMA [330]. One proposed mechanism for TMA is erythrocyte shearing following direct contact with microvascular embolic tumour cells [203, 331, 332], and when TMA is associated with disseminated malignancy the prognosis is predictably very poor regardless of treatment strategy [203–205].

Complement factor H autoantibodies have also been associated with malignancy, although not in the setting of TMA [333]. Case reports of eculizumab use in patients with cancer and treated with chemotherapy agents have suggested a TMA response [195–198], though in most cases the eculizumab was concurrent with drug withdrawal or PEX.

**TMAs associated with glomerular diseases**

Focal segmental glomerulosclerosis (FSGS) and INF2-mediated renal disease

TMA has been reported in patients with primary FSGS [258, 334–336], and FSGS is a frequent pathological sequelae of STEC-HUS [337]. There is some observational data suggesting that complement is activated in FSGS [261] and may be associated with worse outcomes [262]. Mutations in INF2 are the most common cause of familial autosomal dominant nephrotic syndrome; however, more recently it has also been associated with TMA [263]. In this report, all individuals with INF2 mutations presenting with a TMA also had complement-mediated aHUS risk haplotypes, potentially accounting for the genetic pleiotropy. Despite this eculizumab was ineffective in controlling the TMA, suggesting that the mechanism is not dependent on the terminal pathway of complement.

**IgA nephropathy**

Histopathological evidence of TMA has been reported in 2.3–53% [338, 339] of IgA nephropathy biopsies although few also had laboratory evidence of MAHA. In those with TMA a very high proportion had uncontrolled hypertension, so it is difficult to distinguish between TMA associated with severe hypertension and TMA associated with IgA nephropathy. There is some evidence that complement genetics are associated with IgA nephropathy: CFHR3/1 deletion may be protective [240, 340] and CFHR5 rare variants may contribute to genetic susceptibility [241]. Mesangial C3 deposition is seen in ~90% of patients [234], and deposition of MBL suggests the lectin pathway may be activated [235–237] and associated with more severe disease [238]. Two case reports describe the use of eculizumab for crescentic IgA nephropathy with TMA, there was a transient response, but it did not prevent progression to ERF [242, 243]. A single-arm trial of the C5a inhibitor CCX168 in IgA nephropathy (not restricted to cases with a TMA) is ongoing, but there is currently not strong evidence for complement-inhibiting therapy in cases with a TMA.

**ANCA-associated vasculitis**

Histopathological evidence of TMA has also been reported to occur in 14% of ANCA-associated vasculitis (AAV) biopsies [341], again without laboratory evidence of MAHA. Prognosis among those with concomitant TMA is poor: death or ERF occurs in up to 60% [258]. Mouse models suggest that complement is important in pathogenesis [244, 245] and C5aR blockade is protective [246]. In humans, the majority of AAV biopsies show deposition of C3d, C4d and C5b-9 [249], and hypocomplementaemia is associated with higher mortality [247] and worse renal prognosis [248]. There are no published reports of complement-inhibiting therapy in patients with AAV and TMA. An RCT of the C5aR inhibitor CCX168 in AAV (not restricted to cases with TMA) is ongoing.

**Membranous nephropathy**

There are case reports of TMA occurring with membranous nephropathy [257–260, 342, 343]. There is strong evidence that complement is activated in membranous nephropathy: in rat models [252], in vitro (lectin pathway) [252] and in observational clinical studies [253–255]. There is no evidence regarding management specific to membranous nephropathy with TMA, but an early trial of eculizumab in membranous nephropathy (presented in abstract form but never published) [252] was negative, though dosing was inadequate and follow-up was short.

**C3G/mesangio proliferative glomerulonephritis with TMA**

Both C3G and mesangio proliferative glomerulonephritis (MPGN) are complement-mediated diseases with autoimmune (C3 nephritic factor, factor H autoantibodies) and inherited (CFH, C3, CFHRs mutations) complement abnormalities [344–348] underlying many cases. Despite the role of complement in C3G, in a small
Successful use of eculizumab for SLE with TMA has been published. Concurrent TMA has been observed in 8–15% of systemic lupus erythematosus (SLE) biopsies and was reported to have no influence on outcome [352, 353] in some cohorts, but was associated with worse renal outcome in another [354]. In a mouse model of SLE, C5 inhibition increased survival [206]; in humans hypocomplementaemia correlates with disease activity [207], and CFHR3/1 deletion is associated with susceptibility to SLE [208]. Successful use of eculizumab for SLE with TMA has been published in case reports [209–213], but the only trial of eculizumab in SLE to date is a phase 1 study [207].

Antiphospholipid syndrome

The catastrophic antiphospholipid syndrome (CAPS) international registry reports the incidence of TMA to be 14% [232]. In a mouse model of antiphospholipid antibody (aPL Ab)-mediated TMA both complement-dependent and complement-independent pathways were described [215] and Cs blockade inhibited in vivo effects of aPL Ab [218]. There is observational data in humans suggesting that complement is activated [219–221]. Case reports and series describe the successful use of eculizumab for CAPS in native kidneys [223–228] and transplant kidneys [229–231]. There are no RCTs of complement-inhibiting therapy but the evidence supports the rationale, and a prospective, single-arm trial of eculizumab to enable renal transplantation in CAPS is ongoing (NCT01029587).

Scleroderma renal crisis

Scleroderma renal crisis (SRC) occurs in ~10% of people with systemic sclerosis, and TMA manifests in 45–50% [355]. The use of angiotensin-converting enzyme (ACE) inhibitors has transformed prognosis: from ~85% mortality at 6 months to 25–35% [268]. There is no strong evidence that complement is involved in the TMA. In two case reports eculizumab was used in addition to ACE inhibitors: there was haematological response in both, though one died [266, 267].

Summary

Ensuring that complement inhibitory therapy is used appropriately is critically important, principally to avoid exposing patients unnecessarily to the risks of terminal complement inhibition, but the financial implications to health services (eculizumab costs £327 600 per person per year in the UK [356]) also need to be considered.

In addition to its central role in the pathogenesis of complement-mediated aHUS, complement activation is seen in many other forms of TMA. Despite this, it is unclear if this is the primary event, a modifying event or has no contribution to the TMA whatsoever.

Although the seminal trial of eculizumab did not use a control arm to demonstrate efficacy, the high historical morbidity and mortality of aHUS in individuals with complement abnormalities suggested effectiveness. For other cases of TMA, the evidence for utility of eculizumab comes mainly from case reports with the inherent publication bias. Additionally, interpretation of available data in other TMA is difficult: some disorders are self-limiting (e.g. STEC-HUS); some have a clear precipitant that can be treated/removed (e.g. severe hypertension and drug-mediated TMA); some are complex and multifactorial (e.g. TMA occurring after bone marrow or solid organ transplantation); and in some the prognosis of the underlying disorder may be very poor (e.g. TMA associated with disseminated malignancy).

For those individuals with an established complement-mediated aHUS (mutation or autoantibody), treatment is not informed by RCTs, and while the current recommendation is for lifelong treatment with eculizumab there is no evidence that this is necessary. Research is needed to determine who can stop it and when, as well the appropriate monitoring strategy. A number of cases of eculizumab withdrawal have been published [23], and Alexion Pharmaceuticals are collecting data on individuals in whom eculizumab is stopped (EVIDENCE observational study), a trial is being conducted in France (NCT02574403) and a prospective trial of eculizumab withdrawal in complement-mediated aHUS is under way in the UK.

In summary, further research is needed to define the role of complement in the spectrum of TMAs, and complement C5-inhibiting therapy should not be considered a panacea.

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Conflict of interest statement

D.K. has received honoraria for consultancy work from Alexion Pharmaceuticals, and is a director of and scientific advisor to Gyroscope Therapeutics.

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