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Thrombocytopenia-Associated Multiple Organ Failure and Acute Kidney Injury

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INTRODUCTION

Thrombocytopenia-associated multiple organ failure (TAMOF) is a clinical phenotype that encompasses a spectrum of syndromes associated with disseminated microvascular thromboses, such as the thrombotic microangiopathies (TMAs) thrombotic thrombocytopenic purpura/hemolytic uremic syndromes (TTP/HUS) and disseminated intravascular coagulation (DIC). TAMOF is characterized by new-onset thrombocytopenia with progression to multiple organ failure (MOF) in critically ill patients. The decrease in platelet counts reflects their involvement in causing disseminated microvascular thromboses, which lead to organ ischemia and dysfunction. Autopsy studies from patients who died with TAMOF reveal widespread microvascular thromboses in all organs.[1–4] With the current management strategy, mortalities from TAMOF remain high, ranging from 5% to 80%.[5–13]

The past decade has brought significant advances in our knowledge of the pathophysiologic processes of TTP, HUS, and DIC. Von Willebrand factor (VWF) and ADAMTS-13 (also known as VWF-cleaving protease) play a central role in TTP.[14,15] Shiga toxins and the complement pathway are vital in the development of HUS.[15,16] Tissue factor is the major protease that drives the pathology of DIC.[17]

Acute kidney injury (AKI) is a common feature in patients with TAMOF with incidences as high as 58% in TTP, 100% in HUS, and 42% in DIC.[18–20] Because of the progress made in the field, we have better insight into the development of AKI in patients with TAMOF and, it is hoped, better innovative approaches to reverse their pathologic consequences.

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THROMBOTIC THROMBOCYTOPENIA PURPURA

In 1924 Dr Moschowitz[21] was the first to describe a case of TTP in a girl who suddenly died with petechiae, paralysis, and coma. Autopsy findings revealed that she had disseminated occlusions of her terminal arterioles and capillaries with hyaline thrombi. For decades, the diagnosis of TTP remained a clinical diagnosis with the classic clinical pentad of thrombocytopenia, hemolytic anemia, fever, and neurologic and renal involvement. In 1982 Dr Moake and colleagues[22] identified ultralarge VWF (ULVWF) as the "powerful poison which had both agglutinative and hemolytic properties"[22] that caused disseminated microvascular thromboses in TTP. Not until 1998 did Dr Tsai and Lian[23] and Dr Lammle, from 2 different laboratories, simultaneously report that ADAMTS-13 (also known as VWF-cleaving protease) deficiency was the underlying pathophysiologic process in TTP.[24] With ADAMTS-13 deficiency, the ULVWF and large plasma VWF remained uncleaved and maintain their prothrombotic properties in the blood.

TTP is divided into 2 categories: congenital and acquired. In both categories, the ADAMTS-13 activity level is less than 10%. In congenital TTP, more than 80 mutations of the *ADAMTS13* gene have been identified.[25,26] In acquired TTP, ADAMTS-13 inhibitors, such as immunoglobulin G (IgG) autoantibodies to ADAMTS-13 have been reported.[23,24] Autopsies in patients who have died with TTP reveal characteristic VWF/platelet-rich microthrombi in all organs.[1,2,4,27]

Von Willebrand Factor and ADAMTS-13 in Thrombotic Thrombocytopenic Purpura

VWF is the largest multimeric glycoprotein in plasma with a molecular weight ranging from 500 to 20,000 kDa.[28] VWF mediates platelet adhesion to sites of vascular damage by binding to the platelet receptor glycoprotein Ib-IX-V (GP Ib-IX-V) complex and to exposed subendothelial collagen. VWF is synthesized by endothelial cells and megakaryocytes as monomers with subsequent dimerization and multimerization in the endoplasmic reticulum and Golgi apparatus, respectively. After synthesis, VWF is secreted by either the constitutive pathway of lower molecular mass (~500 kDa) dimers or the inducible pathway of larger VWF and ULVWF.[28,29] The inducible pathway is induced by inflammation.[30–32] VWF adhesiveness is associated with its larger size. Thus, ULVWF is extremely large and hyperadhesive. ULVWF can spontaneously aggregate platelets by forming high-strength bonds with the platelet receptor GP Ib-IX-V complex.[33] This ULVWF is rapidly and partially cleaved by ADAMTS-13 before being released into the plasma. Consequently, plasma VWF binds and aggregates platelets only in the presence of modulators, such as ristocetin, or *at high shear stress*.[34,35] Deficiency of ULVWF proteolysis results in the accumulation of ULVWF in plasma and on endothelial surfaces as observed in patients with TTP.

ADAMTS-13 is a member of the ADAMTS family of proteases (*A D*isintegrin *A*nd *M*etalloproteinase with *T*hrombo*S*pondin motifs).[25] The *ADAMTS13* gene encodes a protein with 1427 amino acids, and its mRNA is detected in hepatic stellate cells, endothelial cells, platelets, and glomeruli podocytes.[25,36–39] ADAMTS-13 cleaves VWF at a single peptide bond Tyr842-Met843 in the VWF A2 domain. This cleavage reduces the ULVWF, which spontaneously aggregates platelets, to smaller plasma forms that bind to platelets only

with modulators or high fluid shear stress. The cleaved VWF is no longer prothrombotic but maintains hemostatic functions.

Thrombotic Thrombocytopenic Purpura and Acute Kidney Injury

Before the widespread measurement of ADAMTS-13 in patients with TMAs, AKI and neurologic injury were used to discriminate between the TMAs, HUS, and TTP. Severe AKI was sufficient to diagnosis HUS, and severe neurologic injury was sufficient to diagnosis TTP in patients with TMA. This simple clinical differentiation may have led to the underestimation of the incidence of TTP or AKI-associated TTP. Furthermore, old definitions of kidney injury were more restrictive, which might have led to the underdiagnosis of AKI. Thus, with the current use of the ADAMTS-13 assay and a new standardized AKI definition, investigators are now reporting that AKI is much more prevalent in patients with TTP, with up to 58.7% of patients presenting with AKI compared with approximately 20.0% in older studies.[20,40,41]

In a retrospective study, Zafrani and colleagues[20] reported that by using the Kidney Disease–Improving Global Outcomes 2012 guidelines, 54 (58.7%) out of 92 patients with TTP (ADAMTS-13 <10%) presented with AKI, including 46.3% of patients with stage 3 AKI. Renal replacement therapy was required in 25.9% of patients. Mild or moderate chronic renal disease occurred in 42.6% of the patients with AKI. These investigators also found that patients with TTP-induced AKI had lower serum levels of C3 compared with patients with TTP without AKI. C3 deposition in the kidney was observed in all 4 of their patients who underwent kidney biopsy and 3 of whom had low serum C3 levels. These findings suggested that the alternative complement pathway is activated in TTP-induced patients with AKI. In another study, investigators reported 2 sisters who presented with congenital TTP with one presenting with severe renal failure and the other presenting with exclusive neurologic injury. Both had heterozygous mutations of the *ADAMTS13* gene. However, the sister who developed renal failure also had a heterozygous mutation in factor H of the complement gene.[42] These two studies suggest that patients with TTP-induced AKI may have a genetic disposition to complement pathway hyperactivation.

Manea and colleagues[39] revealed that glomeruli podocytes synthesized and secreted ADAMTS-13 into the glomerular circulation. They described 2 patients with congenital TTP-induced AKI with *ADAMTS13* mutations that impaired the secretion of synthesized ADAMTS-13. They proposed that ADAMTS-13 in the glomeruli protected VWF/platelet-rich microthrombi formation in the *high-shear glomerular circulation*. Thus, a defect in ADAMTS-13 secretion could explain a subset of patients with TTP who are predisposed to develop AKI.

Acquired TTP can be a manifestation of autoimmune diseases, such as systemic lupus erythematosus.[41,43,44] These autoimmune diseases with their associated glomerulopathies and interstitial nephropathies can rapidly worsen the already fragile renal function during an acute TTP episode and manifest as TTP-induced AKI.

Managing Thrombotic Thrombocytopenic Purpura

The clinical pentad of TTP (thrombocytopenia, hemolytic anemia, fever, neurologic, and renal injuries) will trigger the clinicians to work up TMA. ADAMTS-13, VWF, and complement assays should be sent. Elevated lactate dehydrogenase and the presence of schistocytes would suggest the pathophysiologic process of TMA. The confirmatory diagnosis of TTP will be made with ADAMTS-13 activity less than 10%, the presence of ULVWF, and clinical signs/symptoms of TTP. The therapeutic strategies for TTP are (1) replenish ADAMTS-13 activity, (2) remove ADAMTS-13 inhibitors, and (3) remove ULVWF. Transfusion with fresh frozen plasma (FFP), which contains ADAMTS-13, addresses the first strategy. The second strategy is addressed by steroids and/or rituximab (anti-CD20 on B-lymphocytes), which can be given to reduce the synthesis of IgG inhibitory autoantibodies to ADAMTS-13.[45] The third strategy is addressed by therapeutic plasma exchange, which is now the standard therapy for newly diagnosed TTP. It has decreased TTP mortality from 100% down to less than 20%.[7,9]

The recognition that AKI is prevalent in TTP is important. TTP and HUS need to be differentiated by molecular diagnosis because they have potentially different management strategies. Plasma therapies including therapeutic plasma exchange (TPE) are best for TTP, whereas TPE is not recommended for infection-induced HUS. If uncontrolled complement pathway activation is involved as reported in some patients with TTP-induced AKI earlier, anti-C5 monoclonal antibody eculizumab may also have a role. A multidisciplinary approach is warranted including early involvement from hematology, transfusion medicine, nephrology, and immunology.

HEMOLYTIC UREMIC SYNDROME

The clinical triad of HUS is thrombocytopenia, hemolytic anemia, and AKI. Most cases require only supportive care and do not progress into MOF. However, cases with brain injuries, such as coma, seizures, and stroke, are more likely to develop TAMOF and are associated with higher mortality.[11] HUS is divided into 2 major clinical phenotypes: infection-induced HUS and atypical HUS with complement dysregulation. Autopsies in patients who have died with HUS reveal disseminated fibrin-rich microthrombi in most cases, but a subset of patients do have VWF/platelet-rich microthrombi.[1,27] These HUS autopsies reveal that the kidneys are markedly involved compared with other organs, contrasting with TTP and DIC whereby all organs are involved.[1]

Infection-induced HUS accounts for 90% of all HUS cases; most cases (~85%) are caused by Shiga toxin-producing *Escherichia coli* (STEC) and several other bacteria, including *Streptococcus pneumonia*.[13,46] HUS develops in 6% to 15% of the infected patients 2 to 10 days after bloody diarrhea.[46] STEC-HUS has commonly been affecting children until the recent 2011 outbreak in Germany that affected mostly adults.[10] Mortality for STEC-HUS ranges from 5% to 9%.[11]

Atypical HUS accounts for approximately 10% of all HUS cases.[13] The complement pathway genetic mutations account for 50% to 60%, and thrombomodulin mutations account

for 5% of atypical HUS cases. Mortality is approximately 25% for all atypical HUS but is 50% to 80% for the familial form of atypical HUS.[12,13]

Shiga Toxins and Complement Pathway in Hemolytic Uremic Syndrome

Shiga toxins produced by enterohemorrhagic *Escherichia coli* bind to the glycosphingolipid surface receptor globotriaosyl ceramide expressed on the renal microvascular endothelium. The toxins are then internalized leading to protein synthesis inhibition and cell death.[47] In addition, Shiga toxins can cause a prothrombotic state in a host by activating monocytes to release inflammatory cytokines,[48] activating platelets,[49] increasing tissue factor activity on glomerular endothelial cells,[50] inhibiting ADAMTS-13, stimulating ULVWF release from glomerular endothelial cells,[51] and activating the complement alternative pathway.[52] Recently, investigators proposed a link between the ULVWF and the alternative complement pathway in HUS. They showed that the endothelial cells can synthesize the alternative complement components that are assembled and activated on the endothelial cells-secreted ULVWF.[53] The activated complement complex on ULVWF could then cause local endothelial damage.

The complement system is essential for immune surveillance and homeostasis.[54] The complement genetic mutations associated with atypical HUS allow for the tightly regulated complement pathway to become unregulated and hyperactive after an inflammatory trigger. This process leads to inflammation and, if severe, will lead to uncontrolled systemic inflammation, disseminated microvascular thromboses, and MOF. More than 120 complement genetic mutations have been linked to atypical HUS.[16] Autoantibodies to factor H, a regulatory complement protein, can also cause HUS.[55]

Hemolytic Uremic Syndrome and Acute Kidney Injury

Shiga toxins directly bind to the renal microvascular endothelium, as described earlier, to cause renal damage. All STEC-HUS manifest some renal impairment. About 30% to 40% of cases require renal support therapy for an average of 10 days, and 25% of cases have long-term renal sequelae.[11,56] Complement regulatory factors are expressed on or bound to the endothelium. These regulatory factors protect the endothelium from complement-induced damage. In atypical HUS, the genetic mutations to these complement regulatory factors lead to uncontrolled complement activation and endothelial damage. Certain vascular beds are at increased risk for hyperactive complement activation. In particular, the glomerular capillary bed has a fenestrated endothelium, which continually exposes the subendothelial matrix to circulating proteins and peptides and, thus, is very vulnerable to complement attack. Overall, atypical HUS has worse morbidities and mortality than STEC-HUS. The severity depends on the underlying complement abnormality. Up to 70% of patients with complement mutations die or progress to end-stage renal disease.[13]

Managing Hemolytic Uremic Syndrome

Complement pathway interrogation and a genetic workup should be initiated in patients with the clinical triad of HUS. ADAMTS-13 and VWF assays should be sent to rule out TTP. For most STEC-HUS, supportive care is the current recommendation. The American Society for Apheresis (ASFA) gives a category I recommendation (“apheresis [i.e. TPE] is accepted as a

first line therapy")[7] for atypical HUS caused by autoantibody to factor H. ASFA gives TPE a category II recommendation ("apheresis is accepted as a second-line therapy"[7]) for atypical HUS caused by complement factor gene mutation. Currently, TPE is not recommended for STEC-HUS (category IV recommendation). Direct complement inhibition with monoclonal antibody eculizumab should be considered for atypical HUS.[57,58]

Diarrhea/infection-associated HUS with brain injuries and/or rapid progression into TAMOF poses a significant therapeutic strategy dilemma for intensivists. These patients may have a mixture of pathologic mechanisms involving Shiga toxins, VWF, ADAMTS-13, platelets, complements, fibrin, and endothelium. Until clinicians have the ability to rapidly tease out the exact pathologic mechanism, there is a biological plausibility for the benefit of TPE with the aim of restoring the homeostatic milieu of the plasma. More recent case series have highlighted the benefit of TPE in severe diarrhea/infection-associated HUS.[59,60] Eculizumab also has recently been suggested to be beneficial in STEC-HUS.[19,61]

DISSEMINATED INTRAVASCULAR COAGULATION

The consensus definition of DIC by the Scientific Subcommittee on DIC of the International Society of Thrombosis and Hemostasis is "an acquired syndrome characterized by the intravascular activation of coagulation with loss of localization arising from different causes. It can originate from and cause damage to the microvasculature, which if sufficiently severe, can produce organ dysfunction."[62] Conditions that can trigger DIC include sepsis, cancer, trauma/burns, obstetric complications, toxin exposure, and vascular abnormalities. DIC can occur in 39% of patients with severe sepsis, with a mortality of up to 50%.[5,6] Clinically, the patients present with shock caused by poor perfusion of the organs and petechiae and purpura on the skin. Autopsies in patients who have died with DIC reveal fibrin-rich microthrombi in small and midsize vessels in all organs.[2,4,27]

Tissue Factor in Disseminated Intravascular Coagulation

Tissue factor plays a key role in the initiation and propagation of DIC. The tissue factor is expressed from 2 major sources: the vessel wall and hematopoietic cells. When the vascular wall is injured, the extravascular tissue factor is exposed. Monocytes will express and release the tissue factor after stimulated by inflammatory cytokines or endotoxins during systemic inflammation, such as infection.[17,63,64] After expression, the tissue factor complexes with factor VIIa. This complex then activates factors IX and X, eventually leading to thrombin generation. As the tissue factor propagates thrombin formation, the endogenous anticoagulants in the body, such as antithrombin III, protein C, and tissue factor pathway inhibitor, are all found to be impaired during DIC. Decreased synthesis, increased consumption and degradation, and the development of inhibitors all contribute to the depletion of anticoagulants activities.[65] Finally, the body's natural fibrinolytic system that is responsible for the breakdown of clots during a prothrombotic state is also impaired. Plasminogen-activator inhibitor type-1, a potent inhibitor of the fibrinolytic pathway, is pathologically elevated in DIC and MOF.[66–68]

Disseminated Intravascular Coagulation and Acute Kidney Injury

The overall incidence of AKI is lower in DIC (up to 48%) than TTP or HUS.[18] Unlike TTP and HUS in which the kidneys are specifically at risk for injury, the DIC pathologic mechanism does not specifically target the kidneys compared with other organs. Of note, Ono and colleagues[69] found that 28% of patients with sepsis-induced DIC had evidence of AKI. In particular, those patients with ADAMTS-13 activity less than 20% had a significantly higher incidence of AKI compared with those with ADAMTS-13 activity greater than 20% (41% vs 15% respectively). In additions, these patients' plasma contained granulocyte elastase, a protease released by activated granulocytes during sepsis that can proteolyze ADAMTS-13 into inactive fragments. This study suggests that patients with DIC with low ADAMTS-13 activity may be prone to AKI because of the risk of the high-shear-dependent platelet/VWF-mediated thrombosis in the glomerular circulation.

Managing Disseminated Intravascular Coagulation

In 2013, the Scientific Subcommittee on DIC of the International Society of Thrombosis and Haemostasis published a guideline combining the recommendations from the British, Japanese, and Italian DIC treatment guidelines.[70] In summary, this subcommittee recommends the following: (1) There is no gold standard for the diagnosis of DIC, and no single test is capable of diagnosing DIC. (2) The key in DIC treatment is treating the underlying condition. (3) The transfusions of platelets, FFP, fibrinogen, and prothrombin complex concentrate is recommended in actively bleeding patients with low platelet counts, prolonged prothrombin time/activated partial thromboplastin time, hypofibrinogenemia, or contraindicated FFP-transfusion, respectively. (4) Therapeutic doses of low-molecular-weight heparin (LMWH) should be considered if thrombosis predominates. (5) Prophylaxis for venous thromboembolism with prophylactic doses of unfractionated heparin or LMWH is recommended in nonbleeding patients. (6) The administration of antithrombin III, recombinant thrombomodulin, or activated protein C may be considered. (7) Generally, antifibrinolytic agents should not be used. (8) Patients with severe bleeding characterized by a marked hyperfibrinolytic state, such as leukemia and trauma, could be treated with antifibrinolytic agents.

THROMBOCYTOPENIA-ASSOCIATED MULTIPLE ORGAN FAILURE

In the intensive care unit (ICU), overt DIC has been observed in 40% of patients with new-onset thrombocytopenia.[71–73] TTP and HUS are rare diagnoses in the ICU. The mechanism of the other 60% of patients with new-onset thrombocytopenia in the ICU is of great interest because new-onset thrombocytopenia has been associated with significantly higher mortality.[73–75] Investigators studying MOF have observed that pediatric patients with TAMOF defined as platelet counts less than 100,000/mm^3 and at least 2 failing organs have clinical, biomarkers, and histologic evidences of a thrombotic microangiopathic process.[76] Only 46% of these patients with TAMOF have evidence of an activated fibrin-mediated pathway as in DIC with prolonged prothrombin time. None of these patients with TAMOF have classic TTP, but 89% of the patients have evidence of increased VWF-mediated thrombosis similar to TTP pathophysiology. The mean ADAMTS-13 activity level is 39%, which is abnormally low but not less than 10% as in patients with classic TTP. ULVWF is

observed in 53% of these patients. Histopathologic findings in these patients with TAMOF reveal VWF/platelet-rich and fibrin-rich microthrombi in the brain, lungs, and kidneys. Of note, all of these pediatric patients with TAMOF have concurrent sepsis. These investigators suggest that more than half of critically ill children with TAMOF have an acquired ADAMTS-13 deficiency leading to a thrombotic microangiopathic process.

Other investigators have reported that acquired ADAMTS-13 deficiency associated with systemic inflammation has higher morbidity and mortality.[69,77–80] Many molecules associated with systemic inflammation or activated coagulation can inhibit ADAMTS-13. Interleukin 6 can inhibit ADAMTS-13 from cleaving ULVWF.[30] Plasma-free hemoglobin, which is released during hemolysis, can inhibit ADAMTS-13.[81,82] Plasmin and thrombin, products of activated coagulation and inflammation, can proteolyze and inactivate ADAMTS-13.[83] Released by activated neutrophils during systemic inflammation, granulocyte elastase and reactive oxygen species that oxidize VWF can inhibit ADAMTS-13-mediated cleavage.[69,84] VWF proteolytic fragments seem to provide a negative feedback loop by inhibiting ADAMTS-13.[85] Neutralizing IgG autoantibodies to ADAMTS-13 are the first described inhibitors of ADAMTS-13.[23,24]

Thrombocytopenia-Associated Multiple Organ Failure and Acute Kidney Injury

In patients with TAMOF but who do not have overt DIC, TTP, or HUS, evidences suggest that these patients have a thrombotic microangiopathic process that leads to disseminated microvascular thromboses. Similar to the incidence of TTP-induced AKI, a large US multicenter pediatric TAMOF registry and a pediatric Turkish TAMOF network reported that 56.8% and 47.6% of patients with TAMOF, respectively, have AKI requiring renal replacement therapy.[86,87] These studies suggest that platelet/VWF-mediated thrombosis might be the underlying pathophysiologic process.

Managing Thrombocytopenia-Associated Multiple Organ Failure (Not Overt Disseminated Intravascular Coagulation, Thrombotic Thrombocytopenic Purpura, and Hemolytic Uremic Syndrome)

Mounting evidence suggests that a nonspecific plasma therapeutic strategy, such as TPE, may have a role in reversing MOF and improving outcomes in patients with TAMOF. Of note, all of these patients with TAMOF have concurrent sepsis as a diagnosis.[76,86–88] Currently, the ASFA gives a category III recommendation (“Optimum role of apheresis therapy is not established. Decision making should be individualized”[7]) for TPE in sepsis with MOF. A randomized controlled trial for TPE in TAMOF is warranted.

Currently, there is no monotherapy for DIC and TTP. Various agents have been tried without success, such as heparin, antithrombin III, recombinant tissue factor pathway inhibitor, recombinant activated protein C, protein C concentrate, and recombinant soluble thrombomodulin.[89–96] Eculizumab, an anti-C5 monoclonal antibody, is a promising drug for atypical HUS and possibly for STEC-HUS with MOF.[19,57,58,61,97]

Investigators continue to search for effective therapeutic strategies for a TAMOF clinical phenotype. A phase I recombinant ADAMTS-13 for congenital TTP is ongoing (ClinicalTrials.gov; NCT02216084). An anti-VWF nanobody trial for acquired TTP has

been completed and preliminarily reported at the American Society of Hematology meeting in 2014 “Caplacizumab improved standard of care of patients affected with acquired TTP by a more rapid achievement of platelet normalization and lower number of exacerbations with manageable side effects and bleeding episodes” (ClinicalTrials.gov; NCT01151423). N-acetylcysteine has been shown to reduce the size of VWF in human plasma and mice.[98] Recently, N-acetylcysteine was used successfully to treat a case of refractory TTP.[99] The authors have recently reported using a recombinant VWF A2 polypeptide that inhibits platelet-fibrin (estropipate [Ogen]) interaction to reduce disseminated microvascular thromboses and mortality in an endotoxemia-induced DIC murine model.[100]

Armed with a better understanding of the mechanisms of a TAMOF clinical phenotype, innovative therapeutic strategies are being tried to improve the high morbidity and mortality associated with TAMOF.

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KEY POINTS

- Thrombocytopenia-associated multiple organ failure (TAMOF) is a clinical phenotype that encompasses a spectrum of syndromes associated with disseminated microvascular thromboses, such as thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), and disseminated intravascular coagulation.
- Acute kidney injury (AKI) is a common finding in patients with TAMOF, especially those with TTP and HUS.
- Patients with TAMOF with genetic predisposition leading to dysregulation of the complement pathway and/or Von Willebrand factor/platelet-mediated microvascular thrombosis may be more at risk to develop AKI.
- There are sufficient preliminary data to support the design of randomized controlled trials to evaluate the role of therapeutic plasma exchange in patients with TAMOF.