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# Transplant-Associated Thrombotic Microangiopathy (TA-TMA) and Consensus Based Diagnostic and Therapeutic Recommendations: Which TA-TMA Patients to Treat and When?

**Cornelio Uderzo C[1*], Sonata Jodele[2], Mohamed El Missiry[3], Fabio Ciceri[4], Alessandro Busca[5], Andrea Bacigalupo[6] and Selim Corbacioglu[7]**

[1]*Hematology Pediatrics DPT, Bone Marrow Transplantation Unit, S. Gerardo Hospital, Monza, University of Milan, Italy*

[2]*Division of Bone Marrow Transplantation and Immune Deficiency, Cincinnati Children's Hospital medical Center, Cincinnati Ohio, USA*

[3]*Hematology Research Unit, Division of Hematology, University Central Hospital, University of Helsinki, Finland*

[4]*Hematology and Bone Marrow Transplantation Unit, S. Raffaele Hospital, University of Milan, Italy*

[5]*Azienda Ospedaliera Universitaria S.Giovanni Battista, Molinette, Torino, Italy*

[6]*Hematology and Bone Marrow Transplantation Unit, Ospedale S. Martino, Genova, Italy*

[7]*DPT of Hematology Oncology and Stem Cell Transplantation, University Children's Hospital, Regensburg, Germany*

[*]**Corresponding author:** Cornelio Uderzo, Hematology Pediatrics DPT, Bone Marrow Transplantation Unit, S. Gerardo Hospital, Monza, University of Milan, Italy, Tel: +39-039-233-3523; E-mail: cornelio.uderzo@live.it or cornelio.uderzo@cure2children.org

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## Abstract

**Background:** Transplant-associated thrombotic microangiopathy (TA-TMA) is considered one of the most severe complications after hematopoietic stem cell transplantation. Unfortunately, controversial approaches on TA-TMA diagnostic criteria contribute to a delay in both diagnosis and treatment. Recommendations for TA-TMA based in the past on case reports or retrospective studies lack a reasonable level of evidence. One of the most promising drugs for TA-TMA likely induced by endothelium damage is Defibrotide, a polydisperse oligonucleotide. Auto-antibody depleting or complement blocking therapy has also emerged as new strategy to decrease TA-TMA-associated morbidity and mortality.

**Methods:** A joint study group of experts on TA-TMA met during the 2013 ASH Meeting (New Orleans, USA) and the 2014 EBMT Meeting (Milan, Italy) with the aim of proposing a reliable treatment for this complication. Common diagnostic criteria for TA-TMA have been discussed and are described in the review. Factors influencing the outcome of TA-TMA are also addressed.

**Results:** The panel agreed that an endothelial damage pathway is involved in the pathogenesis of TA-TMA. With emerging data, an updated version of TA-TMA diagnostic criteria is suggested. High or standard risk patients have been defined according to TA-TMA risk factors and a comprehensive therapeutic strategy for TA-TMA patients has been designed for a possible multicentre study.

**Conclusions:** The panel focused primarily on high level of awareness about an early TA-TMA diagnosis and treatment before a TA-TMA-induced multi-organ failure. An important consensus was obtained to investigate whether Defibrotide or Eculizumab can improve the outcome of TA-TMA in a multicentre study.

**Keywords:** Transplant-associated thrombotic microangiopathy; Hemolytic uremic syndrome; Defibrotide; Eculizumab; Endothelium damage

## Abbreviations:

aHUS: Acute Hemolytic Uremic Syndrome; ADAMTS 13: A Disintegrin and Metallo Protease with Thrombospondin-1-Like Domains 13; GVHD: Graft Versus Host Disease; HSCT: Hematopoietic Stem Cell Transplantation; TA-TMA: Transplant Associated Microangiopathy; TTPI: Thrombocytopenic Purpura Index; ULN: Upper Limit Of Normal; VOD: Veno-Occlusive Disease; TPE: Therapeutic Plasma-Exchange; Sc5b9: A Complement Lytic Complex

## Introduction

Transplant-associated thrombotic microangiopathy (TA-TMA) constitutes a form of microangiopathic haemolytic anemia and thrombocytopenia derived from a generalized endothelial dysfunction with intravascular platelet activation and formation of platelet-rich thrombi within the microcirculation. This occurs primarily in the kidneys and brain, as well as the gut, lung and liver until multiorgan failure for the majority of patients affected with TA-TMA [1-6].

Since these clinical features are common in several post hematopoietic stem cell transplantation (HSCT) complications such as capillary leak syndrome, engraftment syndrome, GVHD, diffuse alveolar hemorrhage and VOD [4], an initial diagnosis of TA-TMA is not always certain and this is a principal reason for the failure of proposed treatments in the past.

Despite this pessimistic panorama from the last decade, the concept that the diagnosis and treatment of TA-TMA shows real progress, or are we still waiting? [2] has been asserted. Our joint study group on TA-TMA met both during the 2013 ASH Meeting (New Orleans, USA) and the 2014 EBMT Meeting (Milan, Italy) with the aim of proposing a reliable treatment approach for this post-HSCT complication.

A number of clinical reviews have been published on TA-TMA covering this topic in detail [6-11]. In the current review, we elucidate the reasons why we could now be in the position to select the patients who are really affected by TA-TMA and to decide when they need to undergo the most reasonable treatment.

## TA-TMA Pathogenesis

In a relatively early post-HSCT phase, many factors (conditioning regimen, GVHD, 'cytokine storm', infectious diseases, calcineurin inhibitor toxicity, or alternative complement pathway alterations) can cause severe endothelial damage with a consecutive massive release of von Willebrand multimers factors, which cannot be cleared despite a normal or slightly decreased level of ADAMTS13 in transplanted patients [1,2,12].

Endothelial cell (EC) dysfunction is evident by the assessment of several markers of coagulation, adhesion molecules, circulating ECs and microparticles. This is also evident in the evaluation of morphologic and functional changes induced in cultured ECs [4,5,13-16] in an early post-transplant phase. The same injury has been linked to veno-occlusive disease (VOD) and TA-TMA, which are both based on an enhanced prothrombotic or proinflammatory response of a systemically altered endothelium [15].

A recent contribution strongly underlined the possibility of recognizing a new mechanism of TA-TMA pathophysiology where the kidney seems the most common organ affected by small vessels injury [17]. The evidence of resistant hypertension following vasoconstrictive properties of calcineurin inhibitors used in post-HSCT phase and the endothelium inflammation could constitute the evidence of kidney damage TA-TMA induced [8,17]. In this context, it has been outlined that the activation of the complement system (as demonstrated by elevated levels of sC5b-9) might contribute to an endothelium alteration and can precede the onset of TA-TMA in allogeneic HSCT patients. Important findings in patients with TA-TMA have revealed abnormalities in the gene-encoding proteins that control activation of the alternative complement pathway [18]. Similar genetic abnormalities are associated with the occurrence of atypical haemolytic uremic syndrome (aHUS), a disease that seems to benefit from novel terminal complement blockers that are able to bind with high affinity to C5 and are quite effective in disorders associated with abnormalities of the regulation of complement [19].

## TA-TMA Incidence and Outcome

TA-TMA has been considered one of the most frequent and severe post-HSCT complication occurring mainly in adults and preferentially in females with a variable incidence (6% to 20%) due in part to a lack of definitive diagnostic tools [8-11,17,20-23]. TA-TMA is often associated with GVHD, cytomegalovirus and other viral or fungal diseases, unrelated or mismatched donor HSCT [4,11,17,20,21], which are all factors that can influence the outcome of the microangiopathy. Median time to TA-TMA onset is approximately 30-45 days after HSCT, substantially later than VOD which peaks around day +12. The mortality rate is approximately 30–80% [9-11,17,19-23].

| Current diagnostic criteria for TA-TMA | | | |
|---|---|---|---|
| Category | BMT Clinical Trail Network Toxicity Committee (2005) | International Working Group (2007) | Probable TMA [6] |
| Schistocytes | >2 per high power field in peripheral blood | >4% in peripheral blood | >2 per high power field in peripheral blood |
| LDH | Increased above institutional baseline | Sudden and persistent increase | Increased |
| Renal function | Doubling of serum creatinine or 50% decreased of creatinine clearance from pre-HSCT baseline | | |
| Platelets | | Thrombocytopenia <50x$10^9$/L or a >50% decrease in PLT count | Thrombocytopenia <50x$10^9$/L or a >50% decrease in PLT count |
| Red Cells | | Decreased hemoglobin or increased red cell transfusion | Decreased hemoglobin |
| CNS | Unexplained neurological impairment | | |
| Coombs Test | Negative direct and indirect | | Negative |
| Haptoglobin | | Decreased | |
| Other | | | No coagulopathy |
| LDH = lactate dehydrogenase, HSCT = hematopietic stem cell transplantation, PLT = platelets | | | |

**Table 1**: TA-TMA Current Diagnostic Criteria

## TA-TMA Diagnostic Parameters and Associated Risk Factors

The diagnosis of TA-TMA is challenging, and at least three distinct sets of criteria have been published [3,7,6] with some consensus at least on elevated LDH levels, de novo anaemia, de novo thrombocytopenia, presence of schistocytes in the peripheral blood, the absence of coagulation alterations and a negative Coombs test (Table 1).

Deranged haptoglobin levels are poor markers since they can be elevated in many post-HSCT inflammatory conditions. The schistocytes count after HSCT can sometimes be misleading because a manual complete evaluation is not always carefully performed by laboratories [6,20,22]. Lactate dehydrogenase (LDH) as marker of acute haemolysis should also be assessed with caution because institutional normal ranges may vary. Severe renal or neurologic clinical impairment is also controversial because these conditions are rarely present at the onset of TA-TMA, but rather they appear more frequently in the overt phase of this complication [7,17,20]. In addition, two autopsy studies found renal histologic evidence in patients who died with no clinical signs of TA-TMA [24,25]. Jodele and colleagues in their single centre prospective study [17] showed that in the early post-HSCT phase, regular monitoring for proteinuria and a spot urine protein–to-creatinine ratio can offer diagnostic and prognostic information for those patients who are likely to develop TA-TMA. Significantly (even if in univariate analysis only ) more patients with TA-TMA compared to patients without TA-TMA, developed proteinuria with a higher random urine protein/creatinine ratio (2.9 vs. 0.89) and required more anti-hypertension medications (4 drugs vs. 2) [17] as diuretics to decrease steroid-induced sodium retention, vasodilators to antagonize steroids associated vasoconstriction, drugs capable to oppose the inhibitors of calcineurin, and finally angiotensin receptors blockers).This attitude in treating resistant hypertension is largely used in the majority of transplant centers.

In the same study, TA-TMA patients presenting with both proteinuria and an elevated sC5b-9 at diagnosis had a very low 1-year survival rate (16.7 +- 10.8%). Finally, one retrospective study [26] described severe pulmonary hypertension (PH) in five TA-TMA patients: the PH was diagnosed at a median of 76 days (range, 56-101 days) after a prolonged course of untreated TA-TMA, resulting in a 80% mortality.

Our joint study group agreed that TA-TMA may affect pulmonary, renal and brain vessels, but the exact incidence of this involvement is yet to be determined. The panel also emphasized that intestinal TA-TMA may sometimes be underestimated in HSCT patients with severe gastrointestinal symptoms because it is difficult to obtain an adequate tissue biopsy to evaluate TA-TMA vascular changes versus gut-GVHD [27]. With that regard histologic intestinal TA-TMA diagnostic criteria were proposed but should be validated in the future [28,29]. Other parameters for the diagnosis of TA-TMA, such as a high reticulocyte count and a so-called thrombotic thrombocytopenic purpura index (TTPI) >20 (i.e. ratio between LDH/ platelets count: 1000) have been described in the past [20,22,23]. The term TTPI was more recently substituted by TA-TMA index (TA-TMAI) which is more precise for transplanted patients who complain of thrombotic thrombocytopenic purpura associated to transplantation. An Italian cooperative study also showed that an elevated. TA-TMAI (>20) at the onset of the microangiopathy was statistically significant in multivariate analysis as a factor influencing the outcome of TA-TMA patients [20]. Considering the above findings, the panel suggests introducing modifications for classical diagnostic criteria to improve the sensitivity and specificity for the diagnosis of TA-TMA (Table 2).

| Parameters | References |
|---|---|
| **a) Haemoglobin: unexplained/rapid decreased value | [4,13-15,18-21,23,30,52] |
| **b) Platelets: unexplained/rapid decreased value | [4,13-15,18-20,23,52] |
| **c) LDH: above upper limit of normal range compared to normal institutional values | [4,13-21,23,30,52] |
| **d) Schistocytes: more than 1- 2% per high-power field on 2 or more consecutive peripheral blood smears | [4,13,14,18-23,30,52] |
| **e) Coombs test: negative | [4,13,14,17,20,22,23,30,52] |
| **f) TA-TMA Index (ratio between LDH/platelets:1000): = or >20 | [20,22,23] |
| °°g) Proteinuria: over 30 mg/dL | [11,19] |
| °°h) Unexplained Hypertension resistant to two or more drugs therapy | [11,19] |
| °°i) Serum sC5b-9: above normal range (i.e. 72-244 ng/mL) | [11,19] |

**Table 2:** Updated proposal of TA-TMA diagnostic parameters and optimal "timing" for TA-TMA treatment. The parameters** are sufficient for a diagnosis of "standard risk TA- MA" and if confirmed for at least 3 to 5 days from the onset of TA-TMA they call for a prompt TA-TMA treatment. The parameters°° (with or without all parameters**) are sufficient for a diagnosis of "high risk TA-TMA" and if confirmed at least twice or throughout 3 to 5 days from the onset of TA-TMA call for a rapid TA-TMA treatment.

## TA-TMA Treatment: Proposal Based on Risk Factors

Our proposal addressing a careful monitoring of clinical and laboratory TA-TMA markers for at least 3 to 5 consecutive days from the onset of the disease (Table 2) should permit a better evaluation of other concomitant and confounding complications, mainly engraftment syndrome, GVHD, infectious diseases, drug–related toxicity or any other cause of anemia and/or thrombocytopenia. On the other hand, the prognosis of TA-TMA is likely linked to a rapid diagnosis, which is a key point since TA-TMA that is treated early can

prevent a spiralling cascade of systemic endothelial damage. From our past experience, it has emerged that the TA-TMA outcome is better when available treatment is initiated within seven days from the diagnosis to avoid an increased disease-related toxicity [20,23,30].

Common toxicity criteria for TA-TMA were well described by Ho et al. [3] indicating grade 1-2 TA-TMA in the presence of schistocytosis and increased creatinine <3 times the upper limit of normal (ULN), and grade 3-4 TA-TMA when schistocytosis is combined with an increased creatinine >3 times ULN with or without the need for dialysis.

In the past TA-TMA was also classified as grade 0-2 [20,22] when there was an increased LDH (between 500 to 1000 IU/ml) that coexisted with a schistocytes count of <5%, and grade 3-4 (mortality rate=100%) whenever LDH increased beyond 1000 IU/ml with a coexistent increase in schistocytes (>5%).

Considering the established and more recently discovered TA-TMA risk factors [17] we would like to underline the opportunity for a more sensitive and specific early detection and treatment of TA-TMA patients in order to improve their outcome. In synthesis and according to diagnostic and/or risk factor criteria, TA-TMA patients could be divided into " standard risk" if they meet criteria a, b, c, d, e, f or "high risk " if they meet criteria g, h, and i (Table 2). The best available treatment should therefore be started without delay and the results should be confirmed in large prospective studies.

## TA-TMA Opportunities for Future Studies and Interventions

The primary intention of the panel is to encourage a multicenter TA-TMA prospective study to carefully evaluate the predictive value of the clinical and laboratory parameters preceding TA-TMA (Figure 1). We suggest to monitor since hematopoietic stem cells engraftment those TA-TMA diagnostic parameters (Table 2) that could also serve as TA-TMA "eligibility treatment criteria" for patients of any age, who are affected with hematological malignant or non-malignant diseases and undergo HSCT from any stem cells source. The discovery of the endothelium markers could probably help to both establish the onset of TA-TMA and to monitor the outcome of TA-TMA following treatment with Defibrotide, a drug capable of reducing the procoagulant activity and increasing the fibrinolytic properties of endothelial cells as demonstrated by Falanga et al. [15]. Defibrotide has been also shown to be capable of preventing the activation of microvascular and macrovascular endothelia caused by autologous HSCT [16].

Over the last decade, encouraging reports on the treatment of TA-TMA have included Defibrotide [20,30]. In animal models and human studies, this drug has been shown to affect platelet aggregation [31] and the plasma level of a number of proteins with antithrombotic activities, including t-PA and PAI-1, prostacyclin, thrombomodulin [32-35], thus reducing procoagulant activity [15]. In addition, Defibrotide has recently been demonstrated to protect endothelium from the deleterious effects of cyclosporine and tacrolimus or tacrolimus combined with sirolimus [36]. The same mechanism of action has been demonstrated in VOD [37-40]; therefore, Defibrotide is now used in first line therapy for this severe post-HSCT liver complication. The mechanism of action of Defibrotide as well as the common pathophysiology of diseases like VOD, TA-TMA and acute GVHD [4] could explain why this drug not only has decreased the incidence of VOD, but also how it has significantly prevented acute GVHD grades 2-4 in HSCT patients [39]. Two Italian multi-centre retrospective studies on TA-TMA [20,23] reviewed 551 transplanted patients in whom the diagnosis was made with homogeneous criteria similar to criteria adopted by the International Committees [3,6,7]. Seventy-six of the 551 patients (13.8 %) were affected with grade 3-4 TA-TMA due to a high TA-TMAI (median=50). Forty-two of the 76 patients treated with Defibrotide were alive and TA-TMA free (55%). No major adverse effects were recorded during the Defibrotide treatment whose efficacy was statistically significant in the univariate analysis only [20].

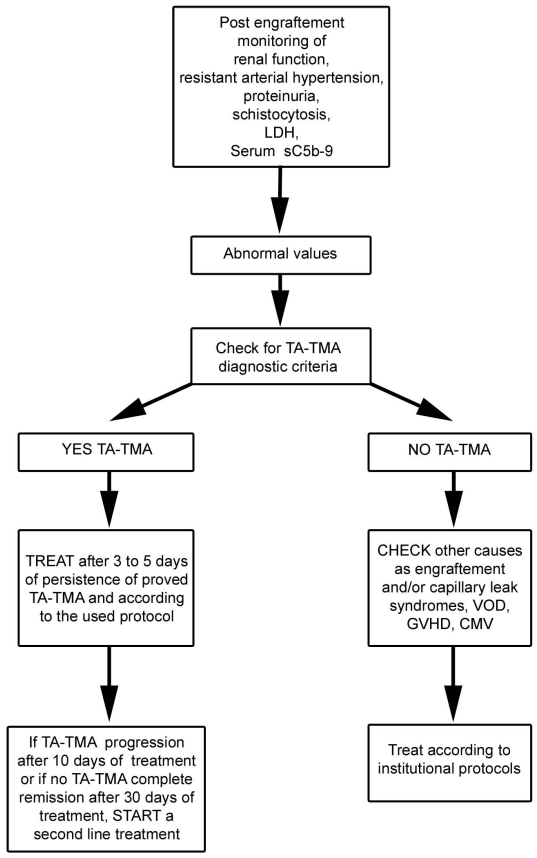


**Figure 1:** Treatment algorithm to establish when TA-TMA must be diagnosed (according to Table 2 parameters) and treated (according to Table 3 proposed treatment).

Auto-antibody complement blocking therapy such as Rituximab has recently emerged as another promising treatment for TA-TMA [8,41-44], even if the exact mechanism of action of this drug is unknown. Of the 15 cases published up to 2011 [8], 12 have shown a positive response to Rituximab as monotherapy or in combination with therapeutic plasma exchange (TPE) or Defibrotide. The Cincinnati HSCT team suggested a possible beneficial effect on the immunoregulation of Rituximab in those TA-TMA patients who have presented with detectable complement factor H (CFH) autoantibodies after HSCT [44].

Recently, Eculizumab, a novel complement blocker, was used in six children with severe TA-TMA; four of the six patients who were

treated promptly after the TA-TMA diagnosis achieved good disease control and recovery of their organ function. However, all of the transplanted children required higher doses or more frequent Eculizumab infusions to control TA-TMA than currently recommended for patients with aHUS [18], thus indicating that pharmacokinetics and/or pharmacodynamics therapy monitoring might be required after HSCT. Wolff et al. used Daclizumab in 13 patients and found that 9/13 attained a complete remission, however, some of the patients subsequently died from infections, GVHD or multi-organ failure [45].

Our proposal for conducting and monitoring the suggested treatments (Defibrotide or Eculizumab) is summarized in Table 3. While the dosage of Defibrotide is sufficiently standardized and similar to that used in post-transplant VOD [20,30], Eculizumab dosing may vary [18] to achieve and maintain an adequate through level capable to normalize sC5b-9 or CH50 values (Table 3). It is our intention to also evaluate if the discontinuation of calcineurin inhibitors at the onset of TA-TMA can improve the outcome of TA-TMA since it has not been well proven in the past retrospective or prospective studies [8,11,17,20,21].

Over the last 15 years, beneficial effects of TPE were reported in idiopathic TMA only [46-48], and not for TA-TMA where a poor response (median 36%) and a high mortality rate (80%, range 44%-100%) have been described [1,2,4,46,49]. Particular caution on TPE-related complications has been highlighted earlier [2,3,46,49] and one should also bear in mind the technical difficulties of this treatment especially in children. Should future studies confirm the role of complement, it may be that TPE can be employed in a selected set of TA-TMA patients to replace defective complement proteins or eliminate inflammatory cytokines. TA-TMA second line therapy could be based on drugs that modulate endothelial cell inflammatory responses, such as statins and antioxidant agents, but they need to be carefully tested in the future [9].

| **TA-TMA: treatment proposal** | |
|---|---|
| **Strategy** | All patients affected with “standard or high risk” TA-TMA according to TA-TMA diagnostic parameters (Table 2) are eligible for proposed treatments |
| **Aims** | Improve the outcome of TA-TMA in order to obtain a complete remission in about 60 to 70% of treated patients. “TA-TMA complete remission” is defined as normalization of TA-TMA clinical and Lab oratory parameters for at least 15 days<br>Assess if the outcome of TA-TMA in patients who undergo a discontinuation of “calcineurin inhibitors” is similar or not to the outcome obtained after the below proposed treatments |
| **Proposed treatments** | |
| A) Defibrotide Treatment | Induction: 25 mg/kg/day /iv. in 4 divided doses for at least 4 to 6 weeks ( i.e. until 2 weeks of “TA-TMA complete remission”)<br>Consolidation (beyond 6 weeks) for poor responders: should be discussed with the coordinating investigator |
| B) Terminal complement blocking therapy (Eculizumab) | Induction dose (i.e 300 mg iv.between 5 to 10 Kg /BW, until 900 mg iv. between 40 kg / BW and over),<br>Maintenance dose (i.e 300 mg iv. every 2 weeks if patient weight is between 5 to 10 Kg, until 1200 mg iv. every 2 weeks if patient weight is 40 kg or over) Eculizumab dosing schedule will be used with dose adjustments guided by pharmacodynamic monitoring of complement blockage and clinical response ( i.e. until 3-4 treatments with sC5b-9 and CH50 normalization) |
| **Treatment Monitoring** | All TA-TMA Lab and clinical parameters registered at the time of the TA-TMA diagnosis need to be monitored throughout the treatment<br>Monitoring of infectious diseases , GVHD and other adverse events is mandatory for the entire period of proposed treatments and up to six months after TA-TMA complete remission<br>Monitoring of renal function tests should be maintained up to second/third year after TA-TMA |
| **Ancillary studies** | Based on “ biological markers of endothelium damage” with the aim to give information about TA-TMA outcome<br>Based on the impact of Defibrotide, Eculizumab also on GVHD severity and outcome |
| **Second line treatment (if any)** | Should be started after failure of “first line treatment” |

**Table 3:** TA-TMA: treatment proposal

## Conclusions

If we think that in the 2013 EBMT report more than 35.000 HSCTs (40% allogeneic, 60% autologous) have been performed [50], it is really discouraging to believe that 3500 of those transplanted patients (i.e. 10%) could have diagnosed with TA-TMA with a potential mortality rate of 30 to 80% due to a delayed diagnosis and/or the futile believe that effective therapy is unavailable. As a matter of fact the

consolidated idea to consider TA-TMA as a life-threatening disease is no longer justified due to promising drugs available now .

Our proposal regarding novel diagnostic criteria and the optimal timing of TA-TMA treatment is based on physiopathologic considerations and could be applied in a larger and better defined set of TA-TMA patients who, treated promptly, could have a better outcome of this post-HSCT complication.

Measurements of sC5B9 (a novel diagnostic and prognostic parameter that is not easily evaluated in all laboratories), and proteinuria (rather a specific marker of renal disease due to TA-TMA), could both constitute a limitation. Assessment of endothelial injury biological markers [4,15,16] could represent another potential obstacle for our proposal in cases of laboratory difficulties. However, in our opinion, a more accurate TA-TMA diagnosis and early treatment should avoid a rapid increase or persistence of endothelium damage, which could greatly impair any further therapeutic attempt.

We no longer want to emphasize the message published years ago that urged large clinical trials on TA-TMA [2,51-53]. Rather, we are definitely in favour of them, whether they are randomized or observational. Prospective controlled studies with Defibrotide or Eculizumab (depending on the local availability of the two drugs) for patients affected with TA-TMA, should be conducted in order to validate their potential efficacy in reducing TA-TMA associated morbidity and mortality. A secondary objective of these trials should assess the role of Defibrotide or Eculizumab in protecting early post-HSCT endothelial damage and/or GVHD, which can trigger TA-TMA (Table 3).

In the absence of previous prospective studies, the length of the treatment should be established on the basis of the good response to the proposed drugs as defined after at least two weeks of achieved normalization of clinical and laboratory parameters (Table 3).

In the past, Defibrotide treatment has appeared to be sufficiently safe and promising in the treatment of VOD and TA-TMA [20,23,30,39,40].

The trial of Eculizumab therapy recently undertaken by the Cincinnati HSCT team in six patients [18] and more recently in another 14 patients (data not shown) could constitute an alternative approach due to the current tendency (mainly in USA) to explore the possible beneficial effect of drugs that control complement activation-mediated endothelial injury.

A possible delay in immunological recovery and associated post-HSCT infectious diseases could be one of major concern for complement inhibition therapy which should be assessed in a sufficiently large patient population in order to draw a reliable conclusion. An accurate surveillance of all adverse events throughout these trials should be created according to conventional rules and should provide useful information about the “pros and cons” of TA-TMA modern treatments.

Last but not least, even as we are aware of the high costs of the above treatments, we hope that scientific societies, public health authorities and companies involved both in the use and production of available TA-TMA drugs will be strongly sensitized and do their best to allow the startup of reliable clinical trials.

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