Blood Reviews xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Blood Reviews

journal homepage: www.elsevier.com/locate/blre

REVIEW

De novo thrombotic microangiopathy after non-renal solid organ transplantation

Annelies Verbiest [a,1], Jacques Pirenne [b,2], Daan Dierickx [c,*]

[a] Department of General Internal Medicine, University Hospitals Leuven, Campus Gasthuisberg, Herestraat 49, 3000 Leuven, Belgium
[b] Department of Abdominal Transplant Surgery and Transplant Coordination, University Hospitals Leuven, Campus Gasthuisberg, Herestraat 49, 3000 Leuven, Belgium
[c] Department of Hematology, University Hospitals Leuven, Campus Gasthuisberg, Herestraat 49, 3000 Leuven, Belgium

ARTICLE INFO

Available online xxxx

Keywords:
Thrombotic microangiopathy
Calcineurin inhibitor
mTOR inhibitor
Plasma exchange
ADAMTS13
von Willebrand Factor
Organ transplantation
Liver transplantation
Lung transplantation
Intestinal transplantation
Heart transplantation

ABSTRACT

Thrombotic microangiopathy (TMA) is a rare but serious complication of organ transplantation. This article presents the first literature review on TMA following non-renal solid organ transplantation (SOT). Ischemia–reperfusion, immunosuppressive drugs, acute interfering disease and a relative deficiency of the von Willebrand factor (vWF) cleaving protease (ADAMTS13) appear to play a major role in its pathogenesis. De novo TMA occurs in 4.0% of liver and 2.3% of lung transplant recipients, whereas the incidence remains unknown after intestinal transplantation. The median time of onset is 2, 37 and 8 weeks after liver, lung and intestinal transplantations respectively, with a three month survival of about 70%. In heart transplantation TMA is rare, occurrence is late and prognosis is poor. In TMA early after liver transplantation an elevated vWF/ADAMTS13 ratio may show diagnostic value. Early withdrawal of calcineurin inhibitors (CNI) proves to be lifesaving. Conversion to another CNI and rechallenge after resolution are generally safe, except after heart transplantation. The value of plasma exchange therapy remains controversial.

1. Introduction

TMA is a potentially fatal disorder characterized by formation of platelet rich thrombi in the microcirculation, thrombocytopenia and non-immune hemolytic anemia. The term thrombotic microangiopathy encompasses a spectrum of diseases, all defined by the same histopathological lesions of the vessel wall, mainly arterioles or capillaries and especially those in the glomeruli. The lesions are characterized by a patchy distribution and consist of vessel wall widening with swelling and detachment of the endothelial cells from the basement membrane and the accumulation of fluffy material in the subendothelium. This causes intravascular platelet aggregation with subsequent formation of platelet rich thrombi within the microcirculation and obstruction of vessel lumina. The consumption of platelets combined with mechanical damage of red blood cells, reflected by the presence of fragmented red blood cells, results in the typical biochemical hallmark of thrombocytopenia and microangiopathic hemolytic anemia. The classic pentad of signs, although rarely all present, is further completed by the presence of fever, renal failure and neurological symptoms [1].

TMAs, though uncommon, are of considerable clinical importance because of their abrupt onset and high morbidity and mortality when left untreated. Especially in the post-transplant setting, clinicians should be aware of the risk of patients developing TMA. Early recognition and therapeutic intervention can be lifesaving.

After giving a brief overview of the classification, clinical presentation and diagnosis of TMAs, we review the literature on non-renal SOT associated TMA and review its pathogenesis and treatment in light of these findings. Transplantation associated TMA (TA-TMA) after renal and hematopoetic stem cell transplantation has already been described extensively in literature and will be discussed only briefly [2–5].

1.1. Classification of thrombotic microangiopathies

Historically TMAs were largely considered to be two separate disorders: thrombotic thrombocytopenic purpura (TTP) and hemolytic–uremic syndrome (HUS). Idiopathic TTP is a condition characterized by a deficiency of ADAMTS13, the vWF cleaving protease. This results in the formation of ultralarge vWF multimers, leading to profound platelet consumption, fragmentation of red blood cells and occlusion of small vessels. Neurological signs and purpura are often more remarkable than renal failure. The ADAMTS13 deficiency may be genetic, but it is attributed to an autoimmune mechanism in a majority of patients. These patients respond well to therapeutic plasma exchange (PEX) which removes anti-ADAMTS13 antibodies and provides new ADAMTS13. The introduction of PEX has improved survival from 10% to over 80% in this population [6].

* Corresponding author. Tel.: +32 16 34 09 37, +32 16 34 68 80 (secr.); fax: +32 16 68 81.
E-mail addresses: Annelies.Verbiest@uzleuven.be (A. Verbiest), Jacques.Pirenne@uzleuven.be (J. Pirenne), Daan.Dierickx@uzleuven.be (D. Dierickx).
[1] Tel.: +32 16 34 42 75 (secr.); fax: +32 16 34 42 30.
[2] Tel.: +32 16 34 06 03, +32 16 34 87 27 (secr.); fax: +32 16 87 43.

http://dx.doi.org/10.1016/j.blre.2014.09.001
0268-960X/

Table 1
Classic classification of the thrombotic microangiopathies.

Category	Specific clinical features	Etiology	Treatment
Idiopathic TTP	Often neurological signs. Severe renal failure is uncommon. Sometimes associated with specific conditions.	ADAMTS13 deficiency, mostly autoimmune.	>80% response to plasma exchange. Corticosteroids, rituximab.
Secondary TTP	Associated with cancer, infection, hematopoietic stem cell transplantation, solid organ transplantation, chemotherapy, certain drugs.	Mostly unknown. ADAMTS13 deficiency is rare.	Dependent on the associated condition.
Diarrhea-associated HUS	Bloody diarrhea followed by acute renal failure.	Endothelial damage by Shiga toxin producing bacteriae.	Supportive care.
Atypical HUS	Acute renal failure.	Complement regulatory protein defects in at least 50% of patients.	Supportive care. Sometimes kidney or liver–kidney transplantation. Specific therapy according to the specific defect (e.g. eculizumab).

TTP: thrombotic thrombocytopenic purpura. ADAMTS13: a disintegrin and metalloprotease with a thrombospondin type 1 motif, member 13. HUS: hemolytic–uremic syndrome.

HUS, on the other hand, is recognized as a disorder in which renal failure dominates the clinical picture, caused by endothelial damage by Shiga toxin producing bacteriae. It is generally preceded by bloody diarrhea and PEX has proven not to be beneficial [7].

However, both conditions have turned out to share the same hallmark of thrombocytopenia and non-immune microangiopathic hemolytic anemia, caused by identical endothelial lesions. Moreover a multitude of other conditions characterized by the same pathological mechanism has emerged. These were classified as either atypical HUS (aHUS), in which acute renal failure is not associated with diarrheal illness but mostly with complement regulatory protein defects, and secondary TTP, associated with a variety of precipitating factors like organ transplantation, drugs, infection, pregnancy, autoimmune diseases and cancer (Table 1) [8,9] Consensus grew that all of these disorders are best described with the general histopathological term thrombotic microangiopathy.

In clinical practice the terms TTP, secondary TTP, HUS and aHUS are commonly used, sometimes leading to misunderstandings about their exact etiology and appropriate treatment. In 2006 Besbas et al. proposed a novel classification, based on etiology rather than clinical presentation [10].

1.2. Clinical presentation and differential diagnosis

In contrast to TMA after hematopoetic stem cell transplantation (HSCT) uniform diagnostic criteria for TMA after SOT do not exist. This not only complicates clinical practice, but also severely impedes analysis of the literature.

In general, the presence of thrombocytopenia and Coombs negative hemolytic anemia with no other cause in a SOT recipient is considered to be TA-TMA. Early recognition is of major importance given its poor prognosis without treatment.

TA-TMA can be restricted to the native kidneys, to the graft or manifest systemically [11]. The presence of thrombocytopenia is mandatory but is frequent after transplantation for various reasons. A sharp drop in the platelet count however is rather typical of TMA and is often the first sign [12,13]. The presence of Coombs negative anemia is also mandatory and is recognized by the presence of schistocytes on the peripheral blood smear, elevated lactate dehydrogenase (LDH), reticulocytes and bilirubin, and low haptoglobin levels. Impaired renal function or failure is present in most cases. Some patients also present with fever, although high spiking fevers are not typical and rather suggest sepsis. Neurological symptoms may be present.

The clinical manifestation of TA-TMA is extremely variable, but often the diagnosis is made purely based on biochemical findings and oliguria, with patients being asymptomatic or presenting with aspecific complaints like malaise or headache [14]. Possible symptoms and biochemical findings are summarized in Table 2. Patients with TA-TMA are almost always receiving a CNI-based immunosuppressive regimen. ADAMTS13 levels are not diagnostic, as will be discussed later.

The differential diagnosis is extensive, as shown in Table 3. Especially, although beyond the scope of this article, TA-TMA after kidney transplantation is difficult to differentiate from acute rejection or recurrence of aHUS. Renal biopsy is warranted if the platelet count allows so. In other SOT recipients, it is recommended to measure at least the prothrombin time, activated partial thromboplastin time and fibrinogen levels, which ought to be normal. Cytomegalovirus (CMV) serology must be obtained, since CMV can cause a TMA-like condition characterized by thrombocytopenia but without hemolysis. The need for further diagnostic tests like anti-cardiolipins, lupus anti-coagulants, renal biopsy, coagulation factors, extended serological testing or others, is based on clinical judgment. Heparin-induced thrombocytopenia (HIT) does not cause hemolysis. It must be noted that the presence of schistocytes is not pathognomonic, as they may also be found in

Table 2
Possible clinical and biochemical presentations of TMA.

Hallmark	Clinic	Biochemy
Non-immune hemolytic anemia	Fatigue, pallor, icterus	Low hemoglobin and haptoglobin High reticulocytosis, LDH and indirect bilirubin Schistocytes Negative Coombs test
Thrombocytopenia	Mucosal bleeding, purpura	Thrombocytopenia
Microvascular thrombosis		
▪ Renal	▪ Oliguria, hypertension	▪ High creatinin
▪ Cerebral	▪ Focal neurological deficit, confusion	
▪ Retinal	▪ Visual disturbances	
▪ Coronary	▪ Chest pain, conduction defects	
▪ Pulmonary	▪ Diffuse alveolar hemorrhage	
▪ Mesenteric	▪ Abdominal pain	

LDH: lactate dehydrogenase.

Please cite this article as: Verbiest A, et al, De novo thrombotic microangiopathy after non-renal solid organ transplantation, Blood Rev (2014), http://dx.doi.org/10.1016/j.blre.2014.09.001

Table 3
Differential diagnosis of thrombocytopenia and microangiopathic hemolytic anemia.

- TMA
  - Evan's syndrome
  - Disseminated intravascular coagulation
  - Preeclampsia, eclampsia
  - Malignant hypertension
  - Systemic vasculitis
  - Anti-phospholipid syndrome
  - Sepsis
  - Viral infections (CMV, adenovirus, herpes simplex virus)
  - Malignancy
  - Drugs (CNI, ticlopidine, clopidogrel, simvastatin, interferon, quinine)

TMA: thrombotic microangiopathy. CMV: cytomegalovirus. CNI: calcineurin inhibitor.

malignant hypertension, renal failure, neoplasm and other pathological conditions [15]. Since they often become detectable only several days after the onset of TMA, clinicians should not wait for their presence to make the diagnosis and initiate treatment.

Despite the general definition of TMA, it is of interest that TMA-lesions in the kidneys have also been found in lung transplant patients with isolated renal dysfunction [16]. This suggests the need for a low threshold for renal biopsy in transplant recipients with progressive renal dysfunction, in whom a change in immunosuppressive regimen is possible.

2. TA-TMA after different organ transplants

2.1. Methods

PubMed and Google Scholar were searched for combinations of the following terms: "thrombotic microangiopathy", "thrombotic thrombocytopenic purpura" or "hemolytic–uremic syndrome", combined with "liver transplantation", "lung transplantation", "heart transplantation", "cardiac transplantation", "visceral transplantation", "intestinal transplantation", "multivisceral transplantation" or "pancreas transplantation". For the search of PubMed, MESH-terms were used. The last search was May 29th, 2014. We withheld every case series and sufficiently documented case report in English describing patients with TA-TMA after non-renal SOT. Reports of multi-organ transplantation however were not included, except for intestinal transplant recipients. Upon finding different reports from the same center and period in time, we included only the one with the largest number of patients. No cases of TA-TMA after pancreas transplantation were found, except for three cases after combined kidney–pancreas transplantation. These are not discussed. Statistical analysis was not possible because of the heterogeneity and scarceness of reported data. The incidence rates were calculated based on the number of cases and total number of patients described in case series. The median times of onset and survival rates were calculated based on the times of onset and outcomes reported in both case series and case reports. Since the only published case series covering TMA after intestinal transplantation was published by our group, intestinal transplantation associated TMA is reviewed in more detail, including one new case report and an overview of the intestinal transplantations performed at our center. TMA after kidney and hematopoietic stem cell transplantation will be mentioned briefly. Results are summarized in Table 4.

2.2. Results

2.2.1. Liver transplantation

Four case series and 18 case reports were found, including a total of 69 adult liver transplant recipients. Two case series and 1 case report including a total of 5 pediatric patients were found as well [12,17–42].

TMA occurred at a median interval of 2 weeks post-transplantation (range 0–448). This unusually early onset might be explained by an imbalance of the vWF/ADAMTS13 ratio the first weeks post-transplantation, as will be discussed in the section "Pathogenesis of TMA after solid organ transplantation". Two authors have described an elevated ratio of vWF/ADAMTS13 as a potential diagnostic tool [32,43]. However, this ratio changes depending on the interval after transplantation and presence of other factors like splenectomy, and their real significance and reference values still need to be determined in prospective studies [43–46].

The incidence was 4.0% (range 0–7.6%) in adults and 2.4% (range 0–3.9%) in children. These numbers however are of doubtful value since hemolysis and thrombocytopenia due to other causes are frequent after liver transplantation and no uniform criteria for the diagnosis of TA-TMA exist [37]. This may cause overdiagnosis or, maybe even more likely, underdiagnosis.

There was a 73.6% survival rate after three months in adults and 57.1% in children. Long term survival was worse after an episode of TMA, with a 5 year survival rate of 47.7% after TMA versus 87.3% in controls in one series [12]. One case series found a strong correlation between change of immunosuppression (conversion of CNI) and survival, whereas PEX was not effective [18]. In another series however, there was no difference between change of immunosuppression (conversion or elimination of CNI) and PEX [12].

Risk factors for the development of TMA withheld after multivariate analysis were cessation of plasma infusion less than a week after transplantation (OR 2.6, 95% CI 1.1–6.6) and preexisting HLA-sensitization (OR 16.1, 95% CI 1.7–133). The following risk factors were clinically

Table 4
Comparison of TA-TMA in different organ transplant recipients.

	Liver	Lung	Visceral	Heart	Kidney	HSCT
Incidence	4.0%	2.3%	?	'Rare'	0.8–14.0%	8.2%
Onset*	2 weeks	37 weeks	8 weeks	2 years	<3 months	7 weeks
Survival**	73.6%	71.4%	66.7%	40.0%	80% graft recovery	25–39%
Risk factors***	Stop PI < 1 week post transplantation HLA-sensitization ABO-incompatibility HCV Splenectomy Transplantation for FHF Longer anhepatic phase	History of TMA Female gender CNI + mTORi Concurrent disease	Acute rejection		CMV, parvovirus 19 Deceased donor Anti-phospholipid antibodies	Female gender Older age Unrelated or HLA-mismatched donor GVHD Systemic infection Advanced or refractory disease for which the transplant was done

PI: plasma infusion; HLA: humane leukocyte antigens; HCV: hepatitis C virus; FHF: fulminant hepatic failure; GVHD: graft versus host disease.
* Median time of onset after transplantation.
** Three month survival rate.
*** Risk factors as identified in the individual transplantations, yet many may be generalized: female gender, concurrent disease, combination of a CNI + mTORi, history of TMA, anti-phospholipid antibodies.

Please cite this article as: Verbiest A, et al, De novo thrombotic microangiopathy after non-renal solid organ transplantation, Blood Rev (2014), http://dx.doi.org/10.1016/j.blre.2014.09.001

significant but not withheld after multivariate analysis: hepatitis C virus (HCV) infection, longer anhepatic phase and splenectomy. Transplantation for fulminant hepatic failure and ABO-incompatibility were strong risk factors, not tested by multivariate analysis. Perioperative infusion of a protease inhibitor via the portal vein was suggested to prevent TMA in ABO-mismatched transplants, but not tested in a controlled trial [13]. Receptor blood group O was a risk factor as well, which might be explained by the higher risk to receive an ABO-incompatible graft. ABO-incompatible transplantation has become rare though in countries where mainly deceased donor grafts are used. There was a trend towards increased risk for female gender, mean portal vein flow <60 cm/s, anhepatic phase >180 min and Model for End-stage Liver Disease score >14. The use of tacrolimus versus cyclosporin A, age, blood loss, elevated liver enzymes, CMV infection, acute rejection and small for size syndrome did not increase the risk [12,13,18,23].

Ten out of 18 cases of TMA described in case reports occurred during a concurrent acute event like infection or acute rejection. We did not withhold this because of the high prevalence of such events early after transplantation. Acute rejection was no risk factor in Shindoh's series. A decrease in ADAMTS13 has been reported to accompany graft dysfunction so the risk may be elevated in the setting of graft dysfunction [44].

The following risk factors for poor outcome were withheld after multivariate analysis: longer interval after transplantation, blood urea nitrogen before start of treatment, HLA-sensitization and younger age [12,24]. The importance of a longer interval after transplantation may be explained by a delay in diagnosis, again stressing the need for high clinical awareness. Elevated liver enzymes, CMV-positivity and acute rejection had no prognostic value [12,18].

From a pathophysiological point of view, TMA following liver transplantation is different from other SOTs because the vWF/ADAMTS13 ratio is disturbed the first weeks post-transplantation and CNIs are cleared by the liver. This will be discussed in the section "Pathogenesis of TMA after solid organ transplantation" in more detail.

Because the liver synthesizes ADAMTS13 and clears CNIs, many authors believe TMA to be more prevalent after LDLT where smaller grafts are used in adult recipients. It was not possible to deduct this from the published literature, since all series covered LDLT. Yet it must be mentioned that in clinical practice living donor grafts generally show superior function immediately post-operative in comparison to deceased donor grafts, except in small for size syndrome, but Shindoh did not withhold small for size syndrome as a significant risk factor for TA-TMA [12]. Moreover, as discussed below, consumption of ADAMTS13 by vWF rather than decreased synthesis may be the main problem and deceased donor grafts after cold preservation could yield more vWF than living donor grafts. Therefore LDLT may as well not be a risk factor for the development of TMA. On the other hand, as also discussed in the section "Pathogenesis of TMA after solid organ transplantation", endothelial damage is the key event in the development of TMA. This damage may be caused by ischemia–reperfusion injury, as is the case after deceased donor transplantation, but perhaps also by higher stress on the endothelium of a smaller graft, as is the case after LDLT in adults. It is therefore uncertain whether a living or rather a deceased donor graft poses the highest risk, but we believe ischemia–reperfusion or higher stress on the endothelium to be the main contributing factor rather than decreased synthesis of ADAMTS13.

2.2.2. Lung transplantation

Four case series and 10 case reports were found, including a total of 63 adult lung transplant recipients [14,47–56].

TMA occurred at a median interval of 37 weeks post-transplantation (range 0–134). The incidence was 2.3% (range 0.5%–9.7%), with a three month survival of 71.4%. Female gender (OR 4.09, 95% CI 1.37–12.2) and a history of TMA (OR 6.72, 95% CI 2.16–20.9) were significant risk factors. CMV positivity and the use of tacrolimus versus cyclosporin A did not elevate the risk [14].

Fifty percent of the cases occurred during concurrent disease, their survival rate was only 38.9%. In one series, 13 out of 24 cases occurred during concurrent disease, but 7 out of 9 deaths occurred in patients with concurrent disease.

The combination of a CNI and a mammalian target of rapamycin inhibitor (mTORi) is sometimes used in lung transplantation. Clinicians must be aware of the highly elevated risk in comparison to treatment with CNI alone, the incidence appearing to be 6 to 7 times higher [14,57].

It is hard to explain why TMA generally occurs late after lung transplantation, in contrast to TMA after other transplants. One hypothesis could be the frequent association with mTORis in the reported cases. These drugs are not used in the immediate post-transplant period because of their adverse effect on wound healing. Since the immediate danger of TMA after transplantation has passed at the time of their association, the onset of TMA might be quite variable. It was not possible to derive a trend confirming or denying this hypothesis from the published literature.

In case reports, TMA after lung transplantation has been noted to be associated with the start of macrolide antibiotics and is sometimes present as diffuse alveolar hemorrhage [49,51].

2.2.3. Cardiac transplantation

Only 5 case reports of TMA after heart transplantation were found [27,58–60]. Median time of onset was 2 years after transplantation. Three out of 5 patients died, the other 2 suffered terminal renal failure and remained hemodialysis dependent. In 3 patients the precipitating factor seemed an acute disease, in 2 the only identified risk factor was a change from Sandimmun ® to Neoral ® about six months earlier, while they had done well for 7 years [60]. Two patients who were rechallenged with a CNI after resolution of TMA developed recurrent TMA. No incidence rates were reported. Parissis reported no cases of TMA occurring after 680 heart and 65 heart-lung transplants, but the method of retrospective review was not reported [49].

Thus, occurrence of TMA after heart transplantation is extremely rare, but its onset can be surprisingly late and the prognosis is poor.

2.2.4. Intestinal transplantation

Intestinal transplantation is by now established as a standard procedure in patients with life-threatening complications due to intestinal failure and total parenteral nutrition, though results remain inferior to those of other SOTs [61]. Eight cases of TA-TMA after intestinal or multivisceral transplantation have been published, one yet unpublished case occurred at our center [62–65]. Detailed data are provided in Table 5, which shows a rather strong link with acute rejection.

Median time of onset is 8 weeks post-transplantation. Three month survival is 66.7%, although all patients who had a fatal outcome succumbed after resolution of TMA. Eight out of 9 patients suffered from concurrent disease: acute rejection in 7 and infection in 1. All patients were treated with tacrolimus, 4 were treated with sirolimus and tacrolimus. Levels of immunosuppressive drugs were high in 7, due to increased dosing for acute rejection.

Seven had renal failure, only one patient presented with neurological symptoms. In one patient, TMA-lesions were manifest in the small intestine.

At our center, 12 visceral or multivisceral transplantations were performed between 2000 and 2011, including 2 pediatric patients. All patients were administered an initial immunosuppressive regimen consisting of corticosteroids, tacrolimus and azathioprin. Four of these patients developed TMA. This high number may be explained by high clinical awareness and a predisposing condition in 2 patients, who suffered from preexisting anti-phospholipid syndrome and Churg–Strauss vasculitis.

Short term survival was only 50%. One other patient lost her graft and died 5 years post transplantation. Four of the 12 patients transplanted since 2000 have died, 3 of them had a history of TMA.

Please cite this article as: Verbiest A, et al, De novo thrombotic microangiopathy after non-renal solid organ transplantation, Blood Rev (2014), http://dx.doi.org/10.1016/j.blre.2014.09.001

Table 5
Cases of TMA after intestinal transplantation.

	Age	Gender	Reason of transplantation	Type of transplantation	CNI or mTORi	Onset (weeks)	Concurrent disease
H	34	M	Crohn, short bowel syndrome	Intestinal	Tacrolimus	8	Acute rejection
H	6	F	Short bowel syndrome	Intestinal + liver	Tacrolimus	4	Acute rejection
B	32	F	Carcinoid tumor	Multivisceral	Tacrolimus	5	No
P	36	M	Desmoid tumor	Multivisceral	Tacrolimus + sirolimus	8	Acute rejection
P	44	M	Crohn, short bowel syndrome	Intestinal	Tacrolimus + sirolimus	158	Acute rejection
D	43	M	Anti-phospholipid syndrome	Multivisceral	Tacrolimus + sirolimus	13	Infection
D	34	F	Churg Strauss vasculitis	Intestinal	Tacrolimus + sirolimus	8	Acute rejection
D	41	F	Bowel ischemia, post thrombosis	Intestinal	Tacrolimus	24	Acute rejection
New	48	F	Bowel ischemia, post torsion	Intestinal + renal	Tacrolimus	207	Acute rejection

	Hemoglobin (g/dl)	Platelet count (/μl)	Lactate dehydrogenase (IU/l)	Schistocytes	Creatinin ↑	ADAMTS13	Neurological signs
H	7.4	36	1920	++	Yes	*NR*	*NR*
H	*NR*	26	4990	++	Yes	*NR*	*NR*
B	'low'	'low'	9105	++	Yes	*NR*	*NR*
P	5.8	66	1493	++	Yes	*NR*	*NR*
P	10	78	180	++	Yes	*NR*	*NR*
D	7.5	89	5277	<30	Yes	60%	Yes
D	8.6	37	1420	12–15	No	>100%	No
D	7.1	23	975	>20	No	40%	No
New	8.9	121	832	>15	Yes	*Not measured*	No

	Plasma level tacrolimus	Plasma level sirolimus	Change of immunosuppression	Plasma infusion or exchange	Resolution	Complication	Outcome
H	*NR*	–	Conversion CNI ➔ mTORi	Yes	Yes	Hemodialysis	Died, suicide
H	*NR*	–	Dose reduction	No	Yes	No	Alive
B	24.9 μg/l	–	Stop CNI	Yes	Yes	No	Alive
P	15–20 μg/l	5–10 μg/l	CNI + PSI ➔ conversion CNI ➔ stop both	Yes	Yes	Acute rejection	Alive
P	26.1 μg/l	9.3 μg/l	CNI + PSI ➔ dose reduction CNI, stop PSI	Yes	Yes	No	Alive
D	<2 μg/l	16.6 μg/l	Stop CNI	Yes	Yes	Acute rejection	Died, rejection and infection
D	15 μg/l	'normal'	Stop CNI	Yes	Yes	Graft loss	Alive
D	27 μg/l	–	No change (acute rejection)	No	Yes	No	Died, infection
New	10 μg/l	–	No change (mild form, acute rejection)	Yes	Yes	No	Alive

References: H: Humar; B: Banerjee; P: Paramesh; D: Dierickx.
M: male; F: female; NR: not reported.

Male to female ratio was the same in TMA and non-TMA patients. ADAMTS13 activity was measured in 3 patients and was normal in all.

2.2.5. Kidney transplantation

Diagnosis of TA-TMA after kidney transplantation is difficult since it can mimic acute vascular rejection, recurrence of aHUS or de novo HUS.

De novo TMA after kidney transplantation occurs in 0.8% according to the United States Renal Data System, but single center studies report incidences of 4–14%. Graft recovery rate is 80%. Reported risk factors are CMV-infection, parvovirus 19 infection, deceased donor kidney transplantation, female gender, anti-phospholipid antibodies in HCV-positive patients and drugs associated with TMA like valacyclovir and clopidogrel [2,66]. Clopidogrel however is an independent cause of TMA, not associated with organ transplantation.

2.2.6. Hematopoietic stem cell transplantation

TMA after HSCT can hardly be compared to TMA after SOT. The etiology is different, with hematologic malignancy and treatment with chemo- and radiotherapy being important precipitating factors. Moreover it concerns a vulnerable population, suffering from severe immunosuppression and other poor prognostic factors. Two sets of consensus diagnostic criteria have been published, yet the existence of TMA as a distinct pathologic entity after HSCT has even been doubted because of the severe confounding factors in diagnosis [3–5].

The incidence is 8.2% with a median time of onset 44 days after transplantation. Immediate mortality rate is 61–75%, with an elevated long term mortality as well. Female gender is often reported as a risk factor. Other risk factors, although reports are contradictive, are graft versus host disease, advanced or refractory disease for which the transplant is done, systemic infections, unrelated or HLA-mismatched donor and older age. PEX seems to have no proven therapeutic value albeit randomized controlled trials (RCTs) are lacking. It is therefore not recommended as a standard of care, but should not be withheld in patients with poor prognostic factors [3,5].

3. Pathogenesis of TMA after solid organ transplantation

As mentioned in the Introduction, consensus has grown that endothelial damage is the key event in all forms of TMA, which was suggested as early as 1942 [68]. This concept was clearly demonstrated by Galbusera, who showed plasma samples of patients with acute TTP induce cytotoxicity and apoptosis of human endothelial cells from the microvasculature [8].

Among others, nitric oxide (NO) and vascular endothelial growth factor (VEGF) are of particular importance in protecting endothelial integrity. It has been shown that mice deficient of endothelial NO develop TMA-like lesions when aging. In mice-models of HUS, administration of NO and VEGF has beneficial effects [69].

In this view Goldberg hypothesized how the underlying health of the endothelium could predispose patients to develop TMA when exposed to other precipitating events [69]. Therefore maybe not only treatment by stopping further endothelial damage during TMA may be warranted, but preventive measures by promoting endothelial health should be considered as well. Possible drugs exerting this effect could be ACE-inhibitors, vitamin C, statins, allopurinol or NO-producing drugs.

Please cite this article as: Verbiest A, et al, De novo thrombotic microangiopathy after non-renal solid organ transplantation, Blood Rev (2014), http://dx.doi.org/10.1016/j.blre.2014.09.001

The exact pathogenesis of TMA after SOT remains unresolved. The heterogeneity of clinical presentation and moment of onset, ranging from days to several years after transplantation, indicates the presence of several pathological mechanisms. Factors being linked with TA-TMA are the event of transplantation itself, the use of immunosuppressive drugs, noxious events like acute rejection or infection and a non-immune relative deficiency of ADAMTS13.

3.1. Transplantation surgery

It seems logical that transplantation surgery itself causes direct endothelial damage. However, this intuitive suggestion does not explain why TMA occurs only after transplantation and not after other surgery. It seems that there must be a specific noxious event. Ischemia–reperfusion injury is the likely culprit, due to both ischemic and inflammatory mechanisms.

Apoptotic endothelium has indeed been demonstrated to become pro-coagulative for non-activated platelets, with not only ischemia but inflammation as well promoting endothelial apoptosis [70]. The most direct evidence in TA-TMA comes from studies on liver transplantation: the vascular endothelium turned out to be the primary target for ischemia–reperfusion injury, with massive platelet adhesion to the sinusoidal endothelium and increased production of vWF accompanied by consumption of ADAMTS13 following reperfusion, especially after cold preservation [45]. Likewise a case of TMA 6 weeks after renal artery thrombosis has been reported, also suggesting a possible link with ischemia–reperfusion [71].

Land showed how reactive oxygen species in the allograft, resulting from brain death and reperfusion injury, turn it into an inflammatory organ which activates the host's immune system, probably contributing to acute and chronic rejection [72]. Moreover, this mechanism not only seems to be important in the immediate post-transplant period, but even for years after [73]. These findings could explain why unmatched living renal allografts yield better results than matched deceased donor allografts [74]. TA-TMA in renal transplant patients also appears to be more frequent after deceased donor allograft transplantation, with its prognosis being more severe [75]. In light of these findings one can reason that the inflammatory response triggered by ischemia–reperfusion injury contributes not only to graft dysfunction and rejection, but to TA-TMA as well. A link between inflammation and TMA is indeed plausible, since the inflammatory cytokines interleukin (IL) 8 and tumor necrosis factor alpha (TNA-α) stimulate the release of ultralarge vWF multimers whereas IL-6 inhibits their cleavage [76]. In sepsis related thrombocytopenia, severity of inflammation and thrombocytopenia are correlated with an imbalance between ADAMTS13 and vWF [44]. So even without severe ADAMTS13 deficiency this might result in TMA in inflammatory circumstances. The frequent occurrence of TA-TMA during concurrent acute events like infection or acute rejection further supports this hypothesis.

3.2. Calcineurin inhibitors

Shortly after the introduction of the CNIs cyclosporin A and tacrolimus, a link between their use and the occurrence of TMA was recognized. CNIs, though indispensable in current practice, exert their possibly deleterious effects on the endothelium through various mechanisms, including both direct and indirect endothelial injuries and platelet aggregation. They cause a decrease in vasodilating agents (NO, prostacyclin), an increase in vasoconstricting agents (endothelin, thromboxane A2, activation of the renin–angiotensin system), a decrease in the formation of activated protein C and increased production and release of high molecular weight vWF multimers. Cyclosporin A also increases plasma levels of plasminogen activator inhibitor and possibly disturbs the function of complement regulatory proteins [2,66,69].

Since tacrolimus and cyclosporin A are metabolized in the liver, there is an elevated risk of toxic levels in the case of graft dysfunction or inadequate dosing when a small graft is used. The clearance of tacrolimus depends on the graft size, its levels being higher for the same dose after LDLT. The optimal dose of tacrolimus can be calculated based on the graft volume versus standard liver volume ratio [28].

Some have reported the risk of TA-TMA in renal transplants to be higher for cyclosporin A compared to tacrolimus, but this has not been observed by others [77,78]. In liver and lung transplantation, there seems to be no difference [14,24].

Importantly, supratherapeutic levels of CNIs have been reported in only a minority of the cases we analyzed.

Apart from causing TA-TMA, CNIs also exert a direct nephrotoxic effect. Ten percent of non-renal SOT patients develop end-stage renal disease within 10 years after transplantation [79]. Lefaucheur reported a series of 15 lung transplant patients, 93.3% of whom had signs of CNI-toxicity on renal biopsy. Moreover, in 46.7% renal biopsy showed TMA-lesions even though none of the patients developed hemolysis or thrombocytopenia [16].

3.3. mTOR inhibitors

TA-TMA has been reported in patients receiving mTORis alone as well as in combination with CNIs. Several studies have shown the risk of TA-TMA to be remarkably higher when a combination of an mTORi and a CNI is used, with many reports originating from series of lung transplant recipients [14,55,79–81].

The most important mechanism probably is mTORi-induced down-regulation of VEGF, which may directly cause TMA or impair the repair of endothelial damage caused by CNIs. This is supported by the finding that administration of bevacizumab, a monoclonal anti-VEGF antibody, causes severe thrombotic glomerular damage in mice [69]. In humans, 6 cases of bevacizumab associated TMA have been reported [82]. Furthermore, mTORis also cause direct endothelial damage and platelet aggregation, though not as markedly as cyclosporin A [80,83].

3.4. Interfering disease

In a considerable proportion of patients with TA-TMA, the condition developed during the course of another stressful event like acute rejection or infection, or was associated to the administration of certain medications.

The same mechanism of endothelial damage through inflammatory conditions, as discussed above, seems to apply, in combination sometimes with a more specific pathological effect. The presence of antibodies and immune complexes for example, as in acute rejection, can induce endothelial injury and trigger massive sequestration of platelets and polymorphonuclear leukocytes in the microcirculation [8].

As observed in several case reports, a typical case of TA-TMA is a patient on an immunosuppressive regimen containing a CNI and perhaps an mTORi, who experiences an episode of acute rejection or infection in the first weeks post-transplantation. Thus, in most patients several risk factors are present at the same time when TA-TMA develops.

3.5. Relative ADAMTS13 deficiency

Primary TTP is caused by autoantibodies against ADAMTS13, resulting in an increase in ultralarge vWF multimers. PEX removes these antibodies and substitutes ADAMTS13, thereby increasing survival from 10% to 80% [6]. For this reason a deficit of ADAMTS13, immune or non-immune, has been hypothesized to be responsible for TA-TMA as well. However, no convincing evidence is present and RCTs measuring ADAMTS13 activity or investigating the effect of PEX are warranted.

In our literature search of TMA after non-renal SOT, we found 11 cases in which ADAMTS13 activity was reported. It was normal in 8, temporarily reduced without correlation to the clinic in 1 and <5% with the presence of an inhibitor in 2 [14,23,25,51,63]. One of these two patients was treated with PEX but did not respond and succumbed,

Please cite this article as: Verbiest A, et al, De novo thrombotic microangiopathy after non-renal solid organ transplantation, Blood Rev (2014), http://dx.doi.org/10.1016/j.blre.2014.09.001

whereas the other responded to PEX and discontinuation of tacrolimus, but relapsed when cyclosporin A was introduced, this time with normal activity of ADAMTS13 without inhibitor. Pham described a case of TMA in a renal transplant patient with undetectable ADAMTS13 levels and presence of an inhibitor, who responded to PEX and discontinuation of cyclosporin A [84].

The observation that only a minority of patients presents low ADAMTS13 activity and an inhibitor when measured, suggests another pathological mechanism in TA-TMA compared to primary TTP. It is possible that in the few cases reported, inhibitors had been present even before transplantation, but increased due to the inflammatory-enhancing effect of transplantation surgery. Notably all three cases occurred in the first days after transplantation.

In contrast to an autoimmune mediated absolute deficit of ADAMTS13, a relative deficit has also been suggested to contribute to the pathogenesis of TA-TMA. Several arguments support this hypothesis. It is well known that endothelial injury may result in a widespread release of unusually large vWF multimers, thus causing a relative deficiency of ADAMTS13 [11]. We already mentioned how inflammatory cytokines contribute to the formation of ultralarge vWF multimers as well. Moreover, 10% of TMAs in general occur during pregnancy or in the postpartum period, when an increase in vWF and a decrease in ADAMTS13 are noted [69].

This relative ADAMTS13 deficiency seems to be of special importance in TMA after liver transplantation. Patients with liver dysfunction suffer from dysregulation of the hemostatic system, with among others a decrease in ADAMTS13 and increase of vWF [46]. Low levels of ADAMTS13, which is synthesized in the stellate cells of the liver, are known to be a marker of liver disease [85]. Moreover, a decreased ADAMTS13 level after liver transplantation has been shown to be a marker of graft dysfunction and correlated with prolonged thrombocytopenia [44].

Several authors have reported a decrease of ADAMTS13 and, to a lesser extent, an increase in vWF after liver transplantation, thus leading to an imbalance in the vWF/ADAMTS13 ratio and possibly a hypercoagulable state. The responsible mechanism seems to be the massive release of hyperactive vWF by the injured sinusoidal endothelium after reperfusion and parallel consumption of ADAMTS13. This may lead to a "local TMA", with thrombocytopenia but without systemic hemolysis or renal failure [43–46].

It is plausible that patients with such a pronounced "local TMA" are at risk for developing a full blown systemic TA-TMA, whereas it could be a self-limiting phenomenon in others. In one small series and one prospective study, patients experiencing TMA after liver transplantation had a markedly more elevated vWF/ADAMTS13 ratio compared to others and the authors postulated this ratio to be of diagnostic value [32,43]. Moreover, the median time of occurrence of TMA after liver transplantation, as we found in the literature, is at two weeks post-transplantation, the moment when the vWF/ADAMTS13 ratio is highest [43].

Is this mechanism really much more important in liver transplant patients than in others? It must be noted that the vWF/ADAMTS13 ratio has, to our knowledge, not yet been investigated in other transplants. This is a research topic that certainly deserves attention in the future. Yet, the fact that TMA tends to occur early after liver transplantation, which is only the case in a minority of patients after other SOTs, supports the idea that this imbalance is more important in liver transplant recipients. Why would this be? After all, one would expect that vWF release by ischemic endothelium, with consumption of ADAMTS13, could occur after any SOT — perhaps even more so after lung transplantation where deceased donor grafts are used, whereas the reports in liver transplantation are mainly from LDLT series. There are several possible reasons. Firstly, an imbalance between vWF and ADAMTS13 is present in patients with liver dysfunction even before transplantation, which could augment the effect post-transplantation. Secondly, ADAMTS13 is synthesized in the liver, so graft dysfunction could lead to decreased levels (there are several strong arguments, beyond the scope of this review, that stress extensive consumption as the main contributing factor, but this is especially the case immediately post-operative) [45]. A third possibility could be that the endothelium of the liver is more prone to ischemia–reperfusion injury than that of other organs, thus releasing more vWF. The finding of massive platelet aggregation in the microcirculation shown after liver transplantation strongly supports this hypothesis [45]. Moreover smaller grafts are used in adults receiving living donor grafts, thus causing higher stress on the endothelium. Finally, since hemolysis and thrombocytopenia are frequently seen shortly after liver transplantation for various reasons, TA-TMA may be overdiagnosed. This last possibility is far from certain however, it could just as well be a reason for underdiagnosis.

4. Prevention and therapy

4.1. Prevention

In general, the use of statins, ACE-inhibitors, vitamin C or other medications with stabilizing effects on the endothelium might reduce the incidence of TMA, but no studies addressing this question are available. In light of the findings discussed above, prevention by careful surgery and anesthesia, tight control of CNI levels, prevention of acute rejection and infection, especially HCV in liver transplants, are important.

As for liver transplantation, we hypothesized above how a decrease in ADAMTS13 probably plays a major role in the development of TA-TMA early after liver transplantation. The level of ADAMTS13 was correlated with the risk of TA-TMA [43]. Substituting ADAMTS13 can be done by administering plasma derivates. Indeed, the cessation of fresh frozen plasma (FFP) therapy within one week post-transplantation was a risk factor for TA-TMA after multivariate analysis in one series [12]. In one series of 20 liver transplant patients, the 3 with low ADAMTS13 had been transfused with packed red cells instead of FFP. Interestingly, the one with lowest ADAMTS13 on day 1 post-operatively, developed hepatic artery thrombosis on day 2 [46].

Although plasma derivates are rarely used after surgery the first week, TA-TMA may be prevented by continuing plasma infusion for at least a week after transplantation. Perioperative infusion of a protease inhibitor via the portal vein might be useful in ABO-incompatible transplants, but this has not been validated in clinical practice.

4.2. Change of immunosuppression

Since CNIs and less frequently mTORis constitute the most important risk factor for TA-TMA, change of immunosuppressive regimen is pivotal in its treatment. This change may be discontinuation of CNIs, dose reduction or conversion.

If possible, the CNI should be substituted by an immunosuppressive agent not linked with TMA, like mycophenolate mofetil (MMF), azathioprin or cyclophosphamide. MMF and azathioprin have the important advantage of being not nephrotoxic.

If maintenance of strong immunosuppression is needed, for example in the case of acute rejection, temporary administration of high doses of corticosteroids is often successful. In mild forms of TA-TMA where discontinuation of the CNI is not feasible, dose reduction may suffice in selected patients [64,65].

An alternative approach when continuation of a CNI is needed is conversion from tacrolimus to cyclosporin A or vice versa. In 63 of the cases after non-renal SOT we analyzed, patients were converted to the other CNI. Sixty of them had good outcomes, which is even higher than average, possibly because mainly patients with a mild form of TMA were converted.

After resolution of TMA, the causative CNI may be reintroduced safely if needed. In a series of kidney transplant patients, 19 out of 20 rechallenges proved successful [86]. There still remains a risk

Please cite this article as: Verbiest A, et al, De novo thrombotic microangiopathy after non-renal solid organ transplantation, Blood Rev (2014), http://dx.doi.org/10.1016/j.blre.2014.09.001

of recurrence however, especially in heart transplant patients. Two out of 5 heart transplant patients we analyzed, developed recurrent TMA at rechallenge [27,58–60].

In cases where the immunosuppressive regimen is not altered, due to late recognition or unfavorable circumstances, prognosis is poor. Twelve patients of the cases we analyzed were treated with PEX alone, but only 6 survived. Notably only 3 out of 12 experienced concomitant acute rejection impeding stop of CNI, but 2 out of 3 survived. Thus, the presence of acute rejection does not seem to be the major cause of poor outcome in patients without adaptation of immunosuppression.

In patients treated with the combination of a CNI and an mTORi it seems safe to discontinue only the mTORi when TMA develops shortly after its introduction [14,79].

4.3. Therapeutic plasma exchange

Historically, PEX has grown to be a standard of care in TMA, because of its superiority in the treatment of primary TTP. By now however, the lack of its effect in HUS has long been shown and it has become clear that the etiology of TA-TMA as well is very different from that of TTP [7]. Since autoantibodies against ADAMTS13 are not present in TA-TMA, there seems to be no rationale for the systematic use of PEX. Unfortunately, RCTs in this rare condition are lacking and clinicians are reluctant not to administer a possibly useful therapy in such a serious condition. Yet one must keep in mind the potential adverse effects of PEX in these already seriously ill patients: thrombosis, bleeding, infection, anaphylaxis, pneumothorax or hypotension [87]. George reported that 24% of patients treated with PEX suffered a major complication. Although this number tended to decrease over the years, this was only the case for patients with primary TTP. In those with a normal ADAMTS13 level, the complication rate remained unchanged. He attributed this to the fact that patients with normal ADAMTS13 do not clearly respond to PEX and thus receive more sessions [88].

According to the American Society for Apheresis guidelines, the role of apheresis for CNI-associated TMA is not established and its initiation should be based on individualized decision making. Moreover, the evidence to support this guideline is weak [89].

In HSCT, although RCTs are lacking, large series have not shown a beneficial effect of PEX and it is not considered standard therapy [4]. In renal transplantation, an advantage of PEX has been reported sporadically in small series [86]. In our analysis of non-renal SOT, data are too heterogeneous to draw firm conclusions. Some observed that conversion of CNI is the key to resolution, whereas others found no difference between PEX or CNI conversion [12,18,32]. In 12 case reports of patients treated only with PEX, outcome was worse. Of 2 patients with low ADAMTS13 level and an anti-ADAMTS13 inhibitor at presentation, one was treated with PEX and conversion and survived; the other was treated only with PEX but died [51]. Lovric treated every patient with a sudden decrease in renal function or TMA-lesions on renal biopsy with PEX and all patients experienced at least a temporary improvement of renal function [79].

Theoretically, PEX could have beneficial effects through the substitution of ADAMTS13 or a yet unknown plasma factor, or by removing a noxious factor like angiopoietin-2 [57].

Early after liver transplantation, when ADAMTS13 deficiency appears to play a major role, administration of FFP should be an integral part of the therapeutic approach in our opinion, though this has not yet been tested in RCTs. PEX is known to improve prognosis of post-operative liver failure and may prove advantageous to prevent volume overload or renal failure by removing bilirubin when this is severely elevated. One should be cautious though since severe hepatic sinusoidal damage could facilitate PEX-mediated induction of hypercoagulopathy in a setting where coagulation is already disturbed. Two case reports have been published describing patients without TMA who suffered lethal hepatic artery thrombosis after initiation of PEX for post-operative hepatic failure [90].

4.4. Supportive care

Apart from treating precipitating factors like infection, TA-TMA may be managed by transfusion of packed red cells, folic acid supplementation during hemolysis and low molecular weight heparin when platelet count exceeds 50000/μl.

Platelet transfusion is generally not recommended in the absence of active bleeding or a planned invasive procedure, as this might increase the risk of thrombosis. However a recent review of platelet transfusion in TTP did not show an adverse effect [91]. Splenectomy is not useful and has even been reported to increase the risk of TA-TMA [12].

4.5. Experimental therapies

Alternative drugs when substituting CNIs could be monoclonal antibodies like the anti-CD25 antibodies dacliximab or basiliximab or the anti-CD52 antibody alemtuzumab. These antibodies are not directly cytotoxic to the endothelium, so they may be an option when classic immunosuppressive therapy is not possible. Wolff treated 13 patients who developed TMA after HSCT with daclizumab and discontinuation of CNIs. Nine of these patients obtained complete remission and 2 partial response [92]. Togashi reported 3 patients with TMA after LDLT who responded well to substitution of CNIs with basiliximab [93].

Eculizumab, an anti-C5 antibody, is useful in aHUS associated with mutations in complement regulating genes and its recurrence after transplantation. There is no rationale for using it in TA-TMA, although one case has been reported with resolution of kidney transplantation associated TMA after eculizumab therapy [94]. This patient did not have any mutations associated with aHUS and had not responded to PEX or conversion of CNI.

Rituximab, an anti-CD20 antibody, is often used in primary TTP to halt production of anti-ADAMTS13 antibodies, but has no theoretical advantage in TA-TMA [95]. One case report has suggested the possibility of belatacept, a selective T-cell activation blocker, as an alternative immunosuppressive drug [96]. Furthermore defibrotide, which possesses profibrinolytic, anti-thrombotic, anti-inflammatory and anti-ischemic properties, is used in sinusoidal obstructive syndrome. In one series, 12 patients suffering from TA-TMA after HSCT were treated with defibrotide. Nine of them responded. Some other small series in HSCT have reported positive results [87]. Theoretically, an advantage of VEGF, TNF-α blockers or NO-donors could be expected.

5. Discussion

TMA is a histopathological term referring to a whole spectrum of diseases with endothelial damage as the common etiological factor. This results in typical endothelial lesions and formation of platelet rich thrombi in the microvasculature, especially in the glomeruli. The specific etiology of TA-TMA remains unresolved but is associated with endothelial damage and inflammation due to ischemia–reperfusion, immunosuppressive drugs and certain other precipitating events like infection or acute rejection. A relative deficit of ADAMTS13 for various reasons, especially early after liver transplantation, may as well play a causative role but needs further investigation by studies measuring the vWF/ADAMTS13 ratio in transplant patients with and without TA-TMA. TA-TMA seems to occur in about 2–4% of solid organ recipients and 8% of HSCT. Survival is about 70% for liver, lung and intestinal transplant recipients,>80% after kidney transplantation but only 25–39% after HSCT. Patients often do not die directly from TMA, but from other complications. In pediatric liver transplantation, the incidence seems to be lower but the prognosis is worse. The most important complications in survivors are graft loss and terminal renal failure. Moreover long term survival is significantly worse in patients with a history of TMA.

TA-TMA generally occurs within the first 3 months after transplantation but the risk remains present for years afterwards. It occurs particularly early after liver transplantation, with a median time of onset after

Please cite this article as: Verbiest A, et al, De novo thrombotic microangiopathy after non-renal solid organ transplantation, Blood Rev (2014), http://dx.doi.org/10.1016/j.blre.2014.09.001

2 weeks, probably due to an imbalance in the vWF/ADAMTS13 ratio. It occurs rather late after lung and heart transplantations, maybe because of the immunosuppressive regimen used in lung transplantation and its very rare occurrence after heart transplantation.

Uniform diagnostic criteria are lacking, yet early diagnosis and treatment determine prognosis. In general, the presence of thrombocytopenia and Coombs negative hemolytic anemia without other explanation in a SOT recipient, is considered to be TA-TMA. Most patients suffer from renal insufficiency as well. Clinical symptoms like fever, neurological signs, visual disturbances or abdominal pain may be variably manifest but often are not present at all. Only a minority of patients presents with supratherapeutic levels of immunosuppressive drugs. Differential diagnosis is extensive, especially acute vascular rejection or HUS after kidney transplantation or DIC and CMV-infection after any transplantation should be excluded. Further diagnostic testing depends on the clinicians' best judgment. A sharp drop in platelet count is rather suggestive of TMA. An elevated vWF/ADAMTS13 ratio shows diagnostic value early after liver transplantation, but still needs validation and reference values have not yet been determined.

Acute disease like infection or acute rejection increases the risk of TA-TMA and worsens its prognosis. Therefore clinicians should be extra alert for signs of TMA in this setting. The only exception seems liver transplantation, where the occurrence of TMA and its prognosis were not associated with acute rejection [12]. This might be explained by the early onset after liver transplantation, when such acute events are common in control patients as well.

Important other risk factors for TA-TMA are the combination of CNIs with an mTORi and predetermining conditions like a history of TMA or anti-phospholipid antibodies. Female gender slightly increases the risk. Importantly, CMV-positivity was never withheld as a risk factor after non-renal SOT, although it has been reported to increase the risk after kidney transplantation. In liver transplantation, specific risk factors are cessation of plasma infusion within one week after transplantation, HLA-sensitization, ABO-incompatibility, HCV-infection, transplantation for fulminant hepatic failure and splenectomy. LDLT has been hypothesized to be a risk factor because of a smaller size of the graft, but no comparison with deceased donor liver transplantation could be made and there are several arguments against this idea as well. Theoretically, graft dysfunction could be a risk factor but this has not yet been assessed.

Early recognition and treatment are of vital importance for survival, with the most important factor in treatment being change of immunosuppression. This includes cessation of CNIs when possible. A valid alternative is conversion to another CNI when cessation is impossible, in the cases we analyzed 60 out of 63 patients treated with conversion had good outcomes. For mild forms dose reduction may suffice in selected patients. When onset is clearly associated with start of an mTORi, cessation of the mTORi may be sufficient as well. After the resolution of TA-TMA, rechallenge with a CNI is generally safe, except maybe in heart transplant recipients.

PEX is the standard of care in acquired TTP, but has no proven value in TA-TMA. RCTs are lacking and sporadic case reports and small series often report contradictive results. In the cases we analyzed, patients treated with PEX alone had poorer outcomes except in one series. Moreover the potential adverse effects of PEX should be kept in mind. In HSCT it is no longer recommended as a standard of care. We would therefore recommend starting PEX only in those SOT recipients with poor prognostic factors. The presence of an ADAMTS13 inhibitor should be ruled out though, since it is present in some patients with seemingly transplant associated TMA. Early after liver transplantation, where TMA is associated with early stop of plasma infusion after transplantation and a decrease of ADAMTS13, we would recommend FFP-infusion and PEX if needed as a standard of care in the absence of further studies.

Prevention of TMA by careful surgery and anesthesia, tight control of CNI levels, prevention of acute rejection and infection, especially HCV in liver transplants, and administration of FFP after liver transplantation are important. Further study is needed for optimization of underlying endothelial health by drugs like statins, NO-donors, ACE-inhibitors or vitamin C and for prevention of oxide free radicals mediated damage by perioperative treatment with a superoxide scavenger.

6. Conclusion

TA-TMA is a rare but serious complication of organ transplantation and its early recognition and treatment are of vital importance. Diagnosis is made based upon the presence of thrombocytopenia and Coombs negative hemolytic anemia without a more likely explanation in a SOT recipient. The most important therapeutic intervention is a rapid change of immunosuppressive therapy. RCTs are needed to evaluate the value of PEX, but currently we would only recommend it as a standard of care early after liver transplantation and in patients with poor prognostic factors. Further studies for interventions that could reduce the risk of TA-TMA and for investigation of the diagnostic value of the vWF/ADAMTS13 ratio in different transplants and at different intervals after transplantation are needed.

Practice points

- Thrombocytopenia and Coombs-negative hemolytic anemia in a SOT recipient without a more likely explanation is considered to be TA-TMA. Apparition of schistocytes may be delayed. Renal dysfunction is present in most patients, clinical symptoms are not.
- TA-TMA mostly occurs in the first 3 months post-transplantation, after liver transplantation even during the first weeks, but the risk remains present for several years.
- Acute events like infection or acute rejection elevate the risk of TA-TMA and may mask its diagnosis.
- CNIs are the most important risk factor, association of an mTORi elevates the risk.
- Early treatment is important.
- Change of CNI (discontinuation, dose reduction, conversion) and mTORi treatment is the most important therapeutic factor.
- We recommend the infusion of FFP or PEX as a standard of care in TMA early after liver transplantation, in other settings the value of PEX is controversial.

Research agenda

- Determination of the therapeutic value of PEX.
- Determination of the prophylactic and therapeutic value of FFP in TA-TMA early after liver transplantation.
- Search for CNI-saving immunosuppressive protocols, for example using monoclonal antibodies.
- Determination of the diagnostic value of the vWF/ADAMTS13 ratio for TA-TMA after liver transplantation and determination of reference levels at different intervals post-transplantation.
- Investigating the vWF/ADAMTS13 ratio in TA-TMA after non-liver SOT.

Conflict of interest statement

None.

References

[1] Moschcowitz E. Hyaline thrombosis of the terminal arterioles and capillaries: a hitherto undescribed disease. Proc NY Pathol Soc 1924;24:21–4.
[2] Ponticelli C, Banfi G. Thrombotic microangiopathy after kidney transplantation. Transpl Int 2006;19(10):789–94.
[3] Ho VT, Cutler C, Carter S, Martin P, Adams R, Horowitz M, et al. Blood and marrow transplant clinical trials network toxicity committee consensus summary: thrombotic microangiopathy after hematopoietic stem cell transplantation. Biol Blood Marrow Transplant 2005;11(8):571–5.

Please cite this article as: Verbiest A, et al, De novo thrombotic microangiopathy after non-renal solid organ transplantation, Blood Rev (2014), http://dx.doi.org/10.1016/j.blre.2014.09.001

[4] Ruutu T, Barosi G, Benjamin RJ, Clark RE, George JN, Gratwohl A, et al. Diagnostic criteria for hematopoietic stem cell transplant-associated microangiopathy: results of a consensus process by an International Working Group. Haematologica 2007; 92(1):95–100.
[5] Kojouri K, George JN. Thrombotic microangiopathy following allogeneic hematopoietic stem cell transplantation. Curr Opin Oncol 2007;19(2):148–54.
[6] Rock GA, Shumak KH, Buskard NA, Blanchette VS, Kelton JG, Nair RC, et al. Comparison of plasma exchange with plasma infusion in the treatment of thrombotic thrombocytopenic purpura. Canadian Apheresis Study Group. N Engl J Med 1991; 325:393–7.
[7] Michael M, Elliott EJ, Ridley GF, Hodson EM, Craig JC. Interventions for haemolytic uraemic syndrome and thrombotic thrombocytopenic purpura. Cochrane Database Syst Rev 2009;1:CD003595.
[8] Galbusera M, Noris M, Remuzzi G. Thrombotic thrombocytopenic purpura — then and now. Semin Thromb Hemost 2006;32(2):81–9.
[9] Sadler JE. Thrombotic thrombocytopenic purpura: a moving target. ASH education program book, 1; 2006 415–20.
[10] Besbas N, Karpman D, Landau D, Loirat C, Proesmans W, Remuzzi G, et al. A classification of hemolytic uremic syndrome and thrombotic thrombocytopenic purpura and related disorders. Kidney Int 2006;70(3):423–31.
[11] Elliott M, Nichols W. Thrombotic thrombocytopenic purpura and hemolytic uremic syndrome. Mayo Clin Proc 2001;76(11):1154–62.
[12] Shindoh J, Sugawara Y, Akamatsu N, Kaneko J, Tamatsu S, Yamashiki N, et al. Thrombotic microangiopathy after living-donor liver transplantation. Am J Transplant 2012;12(3):728–36.
[13] Miyata R, Shimazu M, Tanabe M, Kawachi S, Hoshino K, Wakabayashi G, et al. Clinical characteristics of thrombotic microangiopathy following ABO incompatible living donor liver transplantation. Liver Transpl 2007;13(10):1455–62.
[14] Hachem RR, Yusen RD, Chakinala MM, Aloush AA, Patterson GA, Trulock EP. Thrombotic microangiopathy after lung transplantation. Transplantation 2006;81(1): 57–63.
[15] Scully M, Hunt BJ, Benjamin S, Liesner R, Rose P, Peyvandi F, et al. Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies. Br J Haematol 2012;158(3):323–35.
[16] Lefaucheur C, Nochy D, Amrein C, Chevalier P, Guillemain R, Cherif M, et al. Renal histopathological lesions after lung transplantation in patients with cystic fibrosis. Am J Transplant 2008;8(9):1901–10.
[17] Turner D, Schreiber R, Grant D, Hebert D, Sherman PM. Hemolytic uremic syndrome after pediatric liver transplantation. J Pediatr Gastroenterol Nutr 2006;43(7): 109–12.
[18] Tamura S, Sugawara Y, Matsui Y, Kishi Y, Akamatsu N, Kaneko J, et al. Thrombotic microangiopathy in living-lonor liver transplantation. Transplantation 2005;80(2): 169–75.
[19] Shimazu M, Kitajima M. Living donor liver transplantation with special reference to ABO-incompatible grafts and small-for-size grafts. World J Surg 2004;28(1):2–7.
[20] Rerolle JP, Akposso K, Lerolle N, Mougenot B, Ponnelle T, Rondeau E, et al. Tacrolimus-induced hemolytic uremic syndrome and end-stage renal failure after liver transplantation. Clin Transplant 2000;14(3):262–5.
[21] Ramasubbu K, Mullick T, Koo A, Hussein M, Henderson JM, Mullen KD, et al. Thrombotic microangiopathy and cytomegalovirus in liver transplant recipients: a case-based review. Transpl Infect Dis 2003;5(2):98–103.
[22] Piscitelli D, Fiore MG, Rossi R, Casiello M, Sanguedolce F. Unusual case report of thrombotic microangiopathy of the small bowel following liver transplantation, a possible immunosuppressant-induced disease with histological and ultrastructural findings. Sci World J 2009;9:1031–4.
[23] Nwaba A, MacQuillan G, Adams LA, Garas G, Delriviere L, Augustson B, et al. Tacrolimus-induced thrombotic microangiopathy in orthotopic liver transplant patients: case series of four patients. Intern Med J 2013;43(3):328–33.
[24] Nishi H, Hanafusa N, Kondo Y, Nangaku M, Sugawara E, Makuuchi M, et al. Clinical outcome of thrombotic microangiopathy after living-donor liver transplantation treated with plasma exchange therapy. Clin J Am Soc Nephrol 2006;1(4):811–9.
[25] Nakazawa Y, Hashikura Y, Urata K, Ikegami T, Terada M, Yagi H, et al. Von Willebrand factor-cleaving protease activity in thrombotic microangiopathy after living donor liver transplantation: a case report. Liver Transpl 2003;9(12):1328–33.
[26] Matsusaki T, Morimatsu H, Sato T, Sato K, Mizobuchi S, Morita K. Thrombotic microangiopathy after living-donor liver re-transplantation. J Anesth 2010; 24(4):614–7.
[27] Mach-Pascual S, Samii K, Beris P. Microangiopathic hemolytic anemia complicating FK506 (Tacrolimus) therapy. Am J Hematol 1996;52(4):310–2.
[28] Luo Y, Zhang A, Huang H, Zheng S. Haemolytic uraemic syndrome after living-donor liver transplantation: is small-for-size graft a potential risk factor? J Int Med Res 2008;36(3):599–604.
[29] Lo CM, Liu CL, Lau GK, Chan SC, Ng IO, Fan ST. Liver transplantation for chronic hepatitis B with lamivudine-resistant YMDD mutant using add-on adefovir dipivoxil plus lamivudine. Liver Transpl 2005;11(7):807–13.
[30] Lee CH, Chen CL, Lin CC, Yang CH, Cheng YF, Wang MC, et al. Plasma exchange therapy for thrombotic thrombocytopenic purpura in pediatric patients with liver transplantation. Trans Proc 2008;40(8):2554–6.
[31] Saland JM, Ruggenenti P, Remuzzi G. Liver-kidney transplantation to cure atypical hemolytic uremic syndrome. J Am Soc Nephrol 2009;20(5):940–9.
[32] Hori T, Kaido T, Oike F, Ogura Y, Ogawa K, Yonekawa Y, et al. Thrombotic microangiopathy-like disorder after living-donor liver transplantation: a single-center experience in Japan. World J Gastroenterol 2011;17(14):1848–57.
[33] Czubkowski P, Pawłowska J, Jankowska I, Teisseyre M, Kaminska D, Marciewicz M, et al. Successful sirolimus rescue in tacrolimus-induced thrombotic microangiopathy after living-related liver transplantation. Pediatr Transplant 2012;16(6):261–4.
[34] Akamatsu N, Sugawara Y, Tamura S, Togashi J, Kaneko J, Makuuchi M. Late mortality from thrombotic microangiopathy after liver transplantation: report of a case. Surg Today 2007;37(4):345–8.
[35] Sekido H, Matsuo KI, Takeda K, Morioka D, Kubota T, Tanaka K, et al. Successful adult ABO-incompatible liver transplantation: therapeutic strategy for thrombotic microangiopathy is the key to success. Transplantation 2003;75(9):1605–7.
[36] Furmanczyk A, Komuda-Leszek E, Durlik M. Atypical calcineurin inhibitor-induced haemolytic uremic syndrome after liver transplantation. Ann Transpl 2009;14(4): 47–51.
[37] Valbonesi M, Valente U, Pellicci R, Piri C, Ferrari M, Frisoni R, et al. Thrombotic microangiopathy of the miscellaneous secondary type responding to plasma exchange in a liver transplant recipient. Int J Artif Organs 1988;11(2):131–3.
[38] Bonser RS, Adu D, Franklin I, McMaster P. Cyclosporin-induced haemolytic uraemic syndrome in liver allograft recipient. Lancet 1984;12(2):1337.
[39] McCauley J, Bronsther O, Fung J, Todo S, Starzl TE. Treatment of cyclosporin-induced haemolytic uraemic syndrome with FK506. Lancet 1989;12(2):8678–9.
[40] Dzik WH, Georgi BA, Khettry U, Jenkins R. Cyclosporin-associated thrombotic thrombocytopenic purpura following liver transplantation — successful treatment with plasma exchange. Transplantation 1987;44(4):570–2.
[41] Yamazaki S, Takayama T, Inoue K, Higaki T, Makuuchi M. Transplantation-related thrombotic microangiopathy triggered by preemptive therapy for hepatitis C virus infection. Transplantation 2008;86(7):1010–1.
[42] Matsuda D, Toshima T, Ikegami T, Harimoto N, Yamashita YI, Yoshizumi T, et al. Thrombotic microangiopathy caused by severe graft dysfunction after living donor liver transplantation: report of a case. Clin J Gastroenterol 2014;7(2):159–63.
[43] Kobayashi T, Wada H, Usui M, Sakurai H, Matsumoto T, Nobori T, et al. Decreased ADAMTS13 levels in patients after living donor liver transplantation. Thromb Res 2009;124(5):541–5.
[44] Nobuoka Y, Wada H, Mizuno S, Kishiwada M, Usui M, Sakurai H, et al. Prolonged thrombocytopenia after living donor liver transplantation is a strong prognostic predictor irrespective of history of splenectomy: the significance of ADAMTS13 and graft function. Int J Hematol 2014;99(4):418–28.
[45] Ko S, Okano E, Kanehiro H, Matsumoto M, Ishizashi H, Uemura M, et al. Plasma ADAMTS13 activity may predict early adverse events in living donor liver transplantation: observations in 3 cases. Liver Transpl 2006;2(12):859–69.
[46] Pereboom IT, Adelmeijer J, van Leeuwen Y, Hendriks HG, Porte RJ, Lisman T. Development of a severe von Willebrand factor/ADAMTS13 dysbalance during orthotopic liver transplantation. Am J Transplant 2009;9(5):1189–96.
[47] Shitrit D, Starobin D, Aravot D, Fink G, Izbicki G, Kramer M. Tacrolimus-induced hemolytic uremic syndrome case presentation in a lung transplant recipient. Transplant Proc 2003;35(2):627–8.
[48] Roberts P, Follette D, Allen R, Katznelson S, Albertson T. Cyclosporine A-associated thrombotic thrombocytopenic purpura following lung transplantation. Transplant Proc 1998;30(4):1512–3.
[49] Parissis H, Gould K, Dark J. Dangerous drug interactions leading to hemolytic uremic syndrome following lung transplantation. J Cardiothorac Surg 2010;5(1):70.
[50] Myers JN, Shabshab SF, Burton NA, Nathan SD. Successful use of cyclosporine in a lung transplant recipient with tacrolimus-associated hemolytic uremic syndrome. J Heart Lung Transplant 1999;18(10):1024–6.
[51] Mal H, Veyradier A, Brugière O, Da Silva D, Colombat M, Azoulay E, et al. Thrombotic microangiopathy with acquired deficiency in ADAMTS 13 activity in lung transplant recipients. Transplantation 2006;81(12):1628–32.
[52] Butkus DE, Herrera GA, Raju SS. Successful renal transplantation after cyclosporine-associated hemolytic–uremic syndrome following bilateral lung transplantation. Transplantation 1992;54(1):159–62.
[53] Go O, Naqvi A, Tan A, Amzuta I, Lenox R. The spectrum of thrombotic thrombocytopenic purpura: a clinicopathologic demonstration of tacrolimus-induced thrombotic thrombocytopenic purpura in a lung transplant patient. South Med J 2008;101(7): 744–7.
[54] Boyer NL, Niven A, Edelman J. Tacrolimus-associated thrombotic microangiopathy in a lung transplant recipient. BMJ Case Rep 2013. http://dx.doi.org/10.1136/bcr-2012-007351.
[55] Scheed A, Jaksch P, Klepetko W. Thrombotic microangiopathy after lung transplantation. J Heart Lung Transplant 2014;33(4):186.
[56] Panchabhai T, Beauclair A, Akindipe O, Budev MM. Thrombotic micro-angiopathy associated with sirolimus — de'fragmenting' the story. Am J Respir Crit Care Med 2014. http://dx.doi.org/10.1164/ajrccm-conference.2014.189.1_MeetingAbstracts.A1582.
[57] Lovric S, Lukasz A, Hafer C, Kielstein J, Haubitz M, Haller H, et al. Removal of elevated circulating angiopoietin-2 by plasma exchange — a pilot study in critically ill patients with thrombotic microangiopathy and anti-glomerular basement membrane disease. Thromb Haemost 2010;104(5):1038–43.
[58] Galli FC, Damon LE, Tomlanovich J, Keith F, Chatterjee K, DeMarco T. Cyclosporine-induced hemolytic uremic syndrome in a heart transplant recipient. J Heart Lung Transplant 1993;12(3):440–4.
[59] Walder B, Ricou B, Suter PM. Tacrolimus (FK 506)-induced hemolytic uremic syndrome after heart transplantation. J Heart Lung Transplant 1998;17(10):1004–6.
[60] Mercadal L, Petitclerc T, Assogba U, Beaufils H, Deray G. Hemolytic and uremic syndrome after heart transplantation. Am J Nephrol 2000;20(5):418–20.
[61] Pirenne J. Intestinal failure: autologous reconstruction, intestinal transplantation and intestinal ischemia reperfusion injury. Curr Opin Organ Transplant 2013;18(3):285.
[62] Banerjee D, Kupin W, Roth D. Hemolytic uremic syndrome after multivisceral transplantation treated with intravenous immunoglobulin. J Nephrol 2002; 16(5):733–5.
[63] Dierickx D, Monbaliu D, De Rycke A, Wisanto E, Lerut E, Devos T, et al. Thrombotic microangiopathy following intestinal transplantation: a single center experience. Transplant Proc 2010;42(1):79–81.

Please cite this article as: Verbiest A, et al, De novo thrombotic microangiopathy after non-renal solid organ transplantation, Blood Rev (2014), http://dx.doi.org/10.1016/j.blre.2014.09.001

[64] Humar A, Jessurun J, Sharp HL, Gruessner RW. Hemolytic uremic syndrome in small-bowel transplant recipients: the first two case reports. Transpl Int 1999;12(5):387–90.
[65] Paramesh AS, Grosskreutz C, Florman SS, Gondolesi G, Sharma S, Kaufman S, et al. Thrombotic microangiopathy associated with combined sirolimus and tacrolimus immunosuppression after intestinal transplantation. Transplantation 2004;77(1):129–31.
[66] Caires RA, Marques IDB, Repizo LP, Sato VAH, Carmo LPF, Machado DJB, et al. De novo thrombotic microangiopathy after kidney transplantation: clinical features, treatment and long-term patient and graft survival. Transplantation Proceedings 2012;44:2388–90.
[67] Altschule MD. A rare type of acute thrombocytopenic purpura: widespread formation of platelet thrombi in capillaries. N Engl J Med 1942;227(13):477–9.
[68] Goldberg RJ, Nakagawa T, Johnson RJ, Thurman JM. The role of endothelial cell injury in thrombotic microangiopathy. Am J Kidney Dis 2010;56(6):1168–74.
[69] Bombeli T, Schwartz BR, Harlan JM. Endothelial cells undergoing apoptosis become proadhesive for nonactivated platelets. Blood 1999;93(11):3831–8.
[70] Cailhier JF, Nolin L, Hébert MJ. Thrombotic microangiopathy following renal ischaemia and revascularization: apoptosis of endothelial cells in action. Nephrol Dial Transplant 2001;16(8):1725–6.
[71] Land WG. Emerging role of innate immunity in organ transplantation: part I: evolution of innate immunity and oxidative allograft injury. Transplant Rev (Orlando) 2012;26(2):60–72.
[72] Land W, Schneeberger H, Schleibner S. The beneficial effect of human recombinant superoxide dismutase on acute and chronic rejection events in recipients of cadaveric renal transplants. Transplantation 1994;57(2):211–7.
[73] Matzinger P. The evolution of the danger theory. Expert Rev Clin Immunol 2012;8(4):311–7.
[74] Wiener Y, Nakhleh RE, Lee MW, Escobar FS, Venkat KK, Kupin WL, et al. Prognostic factors and early resumption of cyclosporin A in renal allograft recipients with thrombotic microangiopathy and hemolytic uremic syndrome. Clin Transplant 1997;11(3):157–62.
[75] Bernardo A, Ball C, Nolasco L, Moake JF, Dong J. Effects of inflammatory cytokines on the release and cleavage of the endothelial cell-derived ultralarge von Willebrand factor multimers under flow. Blood 2004;104(1):100–6.
[76] Reynolds JC, Agodoa LY, Yuan CM, Abbott KC. Thrombotic microangiopathy after renal transplantation in the United States. Am J Kidney Dis 2003;42(5):1058–68.
[77] Noris M, Remuzzi G. Thrombotic microangiopathy after kidney transplantation. Am J Transplant 2010;10(7):1517–23.
[78] Lovric S, Kielstein JT, Kayser D, Bröcker V, Becker J, Hiss M, et al. Combination of everolimus with calcineurin inhibitor medication resulted in post-transplant haemolytic uraemic syndrome in lung transplant recipients — a case series. Nephrol Dial Transplant 2011;26(9):3032–8.
[79] Saikali JA, Truong LD, Suki WN. Sirolimus may promote thrombotic microangiopathy. Am J Transplant 2003;3:229–30.
[80] Crew RJ, Radhakrishnan J, Cohen DJ, Stern L, Goldstein M, Hardy M, et al. De novo thrombotic microangiopathy following treatment with sirolimus: report of two cases. Nephrol Dial Transplant 2005;20(1):203–9.
[81] Eremina V, Jefferson JA, Kowalewska J, Hochster H, Haas M, Weisstuch J, et al. VEGF inhibition and renal thrombotic microangiopathy. N Engl J Med 2008;358(11):1129–36.
[82] Ramzy D, Rao V, Tumiati LC, Xu N, Miriuka S, Delgado D, et al. Role of endothelin-1 and nitric oxide bioavailability in transplant-related vascular injury: comparative effects of rapamycin and cyclosporine. Circulation 2006;114(1):214–9.
[83] Pham P-TT, Danovitch GM, Wilkinson AH, Gritsch H, Pham P-CT, Eric T, et al. Inhibitors of ADAMTS13: a potential factor in the cause of thrombotic microangiopathy in a renal allograft recipient. Transplantation 2002;74(8):1077–80.
[84] Uemura M, Fujimura Y, Ko S, Matsumoto M, Nakajima Y, Fukui H. Pivotal role of ADAMTS13 function in liver diseases. Int J Hematol 2010;91(1):20–9.
[85] Karthikeyan V, Parasuraman R, Shah V, Vera E, Venkat KK. Outcome of plasma exchange therapy in thrombotic microangiopathy after renal transplantation. Am J Transplant 2003;3(10):1289–94.
[86] Choi CM, Schmaier AH, Snell MR, Lazarus HM. Thrombotic microangiopathy in haematopoietic stem cell transplantation: diagnosis and treatment. Drugs 2009;69(2):183–98.
[87] George JN, Al-Nouri ZL. Diagnostic and therapeutic challenges in the thrombotic thrombocytopenic purpura and hemolytic uremic syndromes. ASH Education Program book, 1; 2012. p. 604–9.
[88] Schwartz J, Winters JL, Padmanabhan A, Balogun R, Delaney M, Linenberger M, et al. Guidelines on the use of therapeutic apheresis in clinical practice — evidence-based approach from the writing committee of the American Society for Apheresis: The Sixth Special Issue. 2013;284(7):145–284.
[89] Mizuno S, Wada H, Hamada T, Nobuoka Y, Tabata M, Nobori T, et al. Lethal hepatic infarction following plasma exchange in living donor liver transplant patients. Transpl Int 2011;24(7):57–8.
[90] Swisher KK, Terrell DR, Vesely SK, Kremer Hovinga JA, Lämmle B, George JN. Clinical outcomes after platelet transfusions in patients with thrombotic thrombocytopenic purpura. Transfusion 2009;49(5):873–87.
[91] Wolff D, Wilhelm S, Hahn J, Gentilini C, Hilgendorf I, Steiner B, et al. Replacement of calcineurin inhibitors with daclizumab in patients with transplantation-associated microangiopathy or renal insufficiency associated with graft-versus-host disease. Bone Marrow Transplant 2006;38(6):445–51.
[92] Togashi J, Sugawara Y, Akamatsu N, Tamura S, Tanaka T, Kaneko J, et al. A single-center experience of the use of interleukin-2 receptor antagonists for various situations in liver transplant recipients. Transplant Proc 2014;46(3):739–43.
[93] Wilson CH, Brown AL, White SA, Goodship THJ, Sheerin NS, Manas DM. Successful treatment of de novo posttransplant thrombotic microangiopathy with eculizumab. Transplantation 2011;92(8):42–3.
[94] Mörtzell M, Berlin G, Nilsson T, Axelsson EG, Efvergren M, Audzijoni J, et al. Thrombotic microangiopathy. Transfus Apher Sci 2011;45(2):119–23.
[95] Ashman N, Chapagain A, Dobbie H, Raftery MJ, Sheaff MT, Yaqoob MM. Belatacept as maintenance immunosuppression for postrenal transplant de novo drug-induced thrombotic microangiopathy. Am J Transplant 2009;9(2):424–7.

Please cite this article as: Verbiest A, et al, De novo thrombotic microangiopathy after non-renal solid organ transplantation, Blood Rev (2014), http://dx.doi.org/10.1016/j.blre.2014.09.001