bjh research paper

# Impact of severe ADAMTS13 deficiency on clinical presentation and outcomes in patients with thrombotic microangiopathies: the experience of the Harvard TMA Research Collaborative

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Received 25 April 2015; accepted for publication 23 July 2015

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## Summary

The Harvard TMA Research Collaborative is a multi-institutional registry-based effort to study thrombotic microangiopathies (TMA). Laboratory and clinical parameters were recorded for 254 cases of suspected autoimmune thrombotic thrombocytopenic purpura (TTP). Patients with severe ADAMTS13 deficiency (activity ≤10%, $N = 68$) were more likely to be young, female and without a history of cancer treatment or transplantation. While all patients with severe deficiency were diagnosed with autoimmune TTP, those without severe deficiency frequently had disseminated intravascular coagulation, drug-associated TMA and transplant-related TMA. Patients with severe ADAMTS13 deficiency had superior overall survival at 360 d compared to those without severe deficiency (93·0% vs. 47·5%, $P < 0·0001$). Almost all patients with severe deficiency received therapeutic plasma exchange (TPE), but the use of TPE in patients with ADAMTS13 activity >10% varied significantly across the institutions in our consortium (13·2–63·8%, $P < 0·0001$). Nevertheless, 90-d mortality was not different in patients with ADAMTS13 activity >10% between the three hospitals ($P = 0·98$). Our data show that patients with severe ADAMTS13 deficiency represent a clinically distinct cohort that responds well to TPE. In contrast, TMA without severe ADAMTS13 deficiency is associated with increased mortality that may not be influenced by TPE.

**Keywords:** thrombotic microangiopathy, plasma exchange, ADAMTS13, autoimmune thrombotic thrombocytopenic purpura.

Thrombotic microangiopathies (TMAs) are a group of uncommon but serious disorders that result from abnormal coagulation in the microvasculature (Moake, 2002; Sadler, 2008; George & Nester, 2014). TMAs, characterized clinically by microangiopathic haemolytic anaemia (MAHA) and thrombocytopenia, are associated with a broad range of conditions, including infection, malignancy, solid organ or haematopoietic stem cell transplantation, autoimmune disease and pregnancy, or may be seen following exposure to certain medications. Thrombotic thrombocytopenic purpura (TTP) is a distinct form of TMA that represents a haematological emergency and, if left untreated, can rapidly lead to end organ damage, cardiovascular collapse and death in approximately 90% of patients (Amorosi & Ullman, 1966).

Scientific advances since the 1990s have improved our understanding of the pathophysiology underlying TTP, emphasizing the role of the enzyme ADAMTS13 (a disintegrin and metalloprotease with thrombospondin type 1 motif, member 13) in the disease process. ADAMTS13 functions as a negative regulator of thrombosis by cleaving the Tyr1605-Met1606 bond in the A2 subunit of von Willebrand factor (VWF), thereby generating shorter, less active multimers of VWF (Furlan *et al*, 1996; Levy *et al*, 2001). TTP results from a congenital or acquired deficiency in ADAMTS13 activity, which leads to the accumulation of ultra-large VWF multimers and subsequent uncontrolled platelet thrombus formation in the microvasculature (Furlan *et al*, 1998; Tsai & Lian, 1998). This sequence of events in turn is thought to explain both the major clinical manifestations of TTP and the effectiveness of therapeutic plasma exchange (TPE).

Though it preceded our understanding of the role of ADAMTS13 in the disease process, the introduction of TPE

  doi: 10.1111/bjh.13658

as a therapy marked a significant advance in therapeutic interventions used to manage TTP (Bukowski *et al*, 1977). TPE has reduced the mortality rate to approximately 20% (Rock *et al*, 1991). In fact, this dramatic response has led to the recognition that acquired autoimmune TTP is a subtype of TMA that generally has excellent clinical outcomes when treated promptly and appropriately. These patients typically have a severe deficiency in ADAMTS13 activity (i.e. ≤10%) and circulating ADAMTS13-specific inhibitory antibodies that can be removed by TPE. However, the precise positive and negative predictive values of the ADAMTS13 assay remain uncertain for the diagnosis of TTP (Kremer Hovinga *et al*, 2010).

The rarity of TTP has made registry-based methods an important tool for studying this disease (Vesely *et al*, 2003; Coppo *et al*, 2010). These registries have helped address important questions in the diagnosis, management and follow up of TTP patients. Here we report the experience of the Harvard TMA Research Collaborative registry, a cohort of all consecutive suspected TTP cases at three academic medical centres over the last 10 years.

## Methods

### *The Harvard TMA Research Collaborative Registry*

Our registry aimed to capture all suspected cases of TTP regardless of ADAMTS13 activity levels. We included all consecutive patients admitted with suspected TTP at three academic medical centres in Boston (Beth Israel Deaconess Medical Center, Brigham and Women's Hospital, Massachusetts General Hospital) between 8 January 2004 and 6 August 2013. Suspected cases were defined as individuals admitted with thrombocytopenia (platelet count range: 5·0–149 × $10^9$/l) and schistocytes indicative of MAHA for whom an ADAMTS13 assay was sent. Patients were excluded if they were seen as outpatients, were less than 18 years old, had a total bilirubin >342 μmol/l, had a haemolysed specimen, or if the ADAMTS13 assay specimen was sent less than 24 h after the administration of plasma or initiation of TPE. In addition to the results of ADAMTS13 testing, 29 different demographic, clinical and laboratory parameters were recorded for each patient (Table I). Schistocytes were documented as either present or absent, based on manual review of the peripheral blood smear either by the haematology consultation service or by haematology laboratory personnel. Clinical parameters included the presence of neurological symptoms (defined as new altered mental status, seizure, stroke or vertigo), fever (subjective or a temperature ≥100·4°F documented in the medical record), diarrhoea, a history of treatment for cancer within the preceding year (excluding basal and squamous skin cancers) and a history of either bone marrow or solid organ transplantation. In cases where the ADAMTS13 assay was sent within 3 d of admission, we selected the earliest available laboratory or clinical information from the day of admission. Data from up to 3 d after admission were recorded in the event that a specific test was not performed on the date of admission. In patients for whom the ADAMTS13 test was sent after 3 d of hospitalization, the earliest laboratory or clinical data from the date of the ADAMTS13 assay were selected, and values taken within 5 d of this date were used when data from the

**Table I.** Data collected in the Harvard TMA Research Collaborative Registry.

| |
|---|
| Demographic information |
| Age |
| Sex |
| Ethnicity (African American, Asian, Caucasian, Hispanic) |
| Clinical information |
| Timing of ADAMTS13 testing (sent at initial presentation or after 3 d of hospitalization) |
| Symptoms present at the time of ADAMTS13 testing |
| Neurological symptoms (altered mental status, seizure, stroke, vertigo) |
| Fever (subjective or objective temperature ≥38·5°C) |
| Diarrhoea |
| Prior history |
| Cancer treatment within the preceding year (excluding basal and squamous cell skin cancers) |
| History of bone marrow or solid organ transplantation |
| Treatment with therapeutic plasma exchange (TPE) during the index hospitalization (yes or no) |
| Laboratory parameters |
| Haematology data |
| Complete blood count |
| Haemoglobin |
| Haematocrit |
| Platelet count |
| Mean corpuscular volume (MCV) |
| Red blood cell distribution width (RDW) |
| Reticulocyte count |
| Schistocytes (present or absent) |
| Haptoglobin |
| Chemistries |
| Blood urea nitrogen (BUN) |
| Creatinine |
| Lactate dehydrogenase |
| Alanine transaminase (ALT) |
| Aspartate transaminase (AST) |
| Total bilirubin |
| Coagulation testing |
| International Normalized Ratio (INR) |
| Partial thromboplastin time (PTT) |
| D-dimer |
| ABO typing |
| Direct antiglobulin test (DAT) |
| Treatment and outcomes data |
| Survival |
| Hospital length of stay |
| Days until platelet count recovery |
| Number of TPE treatments |
| Number of units of plasma transfused |


 

date of the ADAMTS13 assay were unavailable. Outcomes data, with the exception of length of hospital stay, were calculated using the date the ADAMTS13 test was sent as day 0. Data were collected retrospectively until May 2012 and prospectively thereafter. The registry has been approved by the institutional review boards of all three members of the consortium.

### *Clinical diagnostic categories*

Patients were assigned to one of 11 clinical diagnoses based on predefined criteria and without regard to ADAMTS13 activity level except in situations where it was necessary to distinguish autoimmune TTP from haemolytic-uremic syndrome (HUS) (Table II). During this process, relevant clinical and laboratory data from the patient's electronic medical record proximate to the date of the ADAMTS13 test were reviewed by at least two of the study authors and the diagnostic category was assigned by consensus.

### *ADAMTS13 assay*

All ADAMTS13 testing was performed at the Blood Center of Wisconsin or the Mayo Clinic Laboratories with a fluorogenic assay utilizing the FRETS-VWF73 substrate (Kokame *et al*, 2004). Given that bilirubin and free haemoglobin are known to inhibit detection of ADAMTS13 activity by this assay, patients with hyperbilirubinaemia (total bilirubin >342 μmol/l) or those in whom ADAMTS13 activity was measured in a haemolysed sample were excluded from analysis. A reflex assay for an ADAMTS13 inhibitor was performed when ADAMTS13 activity was less than 30%. Inhibitors were detected using mixing studies with the patient specimen and normal pooled plasma in the FRETS-VWF73 assay (Kokame *et al*, 2004). Inhibitor titres were reported in Bethesda Units (BU). An inhibitor level ≥0·4 BU was deemed a positive result.

### *Clinical outcomes and survival analysis*

Clinical endpoints of interest included use and response to TPE, platelet count recovery, hospital length of stay and overall survival. Platelet count recovery was defined as the achievement of a platelet count $>150 \times 10^9$/l for two consecutive days. Platelet count recovery was not achieved if the patient died prior to reaching a platelet count of $>150 \times 10^9$/l or if recovery occurred more than 1 month after hospital discharge. In those who had received TPE, the number of sessions of TPE and number of plasma units used were calculated until cessation of TPE treatment. Hospital length of stay was calculated using the index admission and discharge dates regardless of the date of ADAMTS13 testing. For survival analysis, the study start date was defined by the date that the ADAMTS13 assay was sent regardless of TPE

**Table II.** Diagnostic categories and definitions.

| Diagnosis | Definitions |
|---|---|
| Autoimmune TTP | TMA (MAHA and thrombocytopenia) without an alternative explanation |
| HUS | TMA and ADAMTS13 activity >10% PLUS at least ONE of the following:<br>1) Serum creatinine >176 μmol/l<br>2) Stool culture positive for shiga toxin-producing organism<br>3) Mutations identified in complement regulatory proteins |
| DIC | Laboratory evidence of overt DIC with a clear precipitant, including:<br>1) Sepsis and multiorgan failure<br>2) Cancer<br>3) Pancreatitis<br>4) Other |
| Drug-associated | TMA in the setting of a drug previously associated with TMA not used in solid organ or bone marrow transplant |
| Transplant-related | TMA and solid organ or haematopoietic stem cell transplant with or without immunosuppressive drugs known to be associated with TMA |
| Cancer | Disseminated cancer without laboratory evidence of overt DIC |
| Hypertensive emergency | TMA and documented systolic blood pressure >180 mmHg and alternative cause excluded |
| Autoimmune-associated | TMA and documented active autoimmune disease process that provides a plausible explanation for the TMA (e.g. systemic lupus erythematosis, antiphospholipid antibody syndrome) |
| Pregnancy-related | TMA in association with pregnancy |
| Other | TMA related to a well-defined precipitant not listed above |
| Multifactorial | TMA and more than one well-described precipitant listed above (e.g. Transplant-related and DIC) |

TTP, thrombotic thrombocytopenic purpura; TMA, thrombotic microangiopathy; MAHA, microangiopathic heamolytic anaemia; HUS, haemolytic uremic syndrome; DIC, disseminated intravascular coagulation.

initiation. Patients were censored if they remained alive or were lost to follow-up prior to study end date (2 August 2014).

### *Statistical analysis*

The Fisher exact test was used to compare categorical variables. The chi-square test was used to compare data in a 2 × 3 array. Continuous variables were compared using the Mann–Whitney *U* test. Multiple comparisons were performed using the Kruskall–Wallis test. Reported *P* values were calculated for two-tails and were considered statistically significant when <0·05. No correction for multiple comparisons was made. Statistical analysis was performed using MedCalc vs15.2.2 (Ostend, Belgium).

## Results

### *Patients*

A total of 440 patients had an ADAMTS13 assay sent from the three participating hospitals between 8 January 2004 and 6 August 2013 (Fig 1). Of these, 58 were excluded because they were not thrombocytopenic or lacked platelet data, and 106 were excluded because they lacked evidence of schistocytes. Of the remaining 276 patients, exclusions were made for age <18 years ($n = 4$), total bilirubin >342 μmol/l ($n = 9$), plasma exposure prior to the ADAMTS13 assay being sent ($n = 7$), haemolysed specimen ($n = 1$) and the same patient being seen at multiple hospitals within the consortium ($n = 1$). This left 254 patients in the analysis cohort.

Overall, values for ADAMTS13 activity demonstrated a bimodal distribution (Fig 2). Sixty-eight patients had an ADAMTS13 activity level ≤10% (severe deficiency) and 186 had a level >10%. The median (interquartile range, IQR) ADAMTS13 activity in the latter group was 56% (42–68%). A comparison of key demographic features and presenting clinical and laboratory data for these two cohorts is shown in Table III. A higher proportion of non-Caucasians who received the ADAMTS13 test had a level ≤10% (24/57, 42·1%) compared with Caucasians who were tested (42/187, 22·5%) ($P = 0·006$). Similarly, a larger fraction of women (50/146, 34·2%) tested for ADAMTS13 activity were found to have severe deficiency as compared with men (18/108, 16·7%) ($P = 0·002$). In contrast, a history of treatment for malignancy within the preceding year and prior history of solid organ or haematopoietic stem cell transplantation were both strongly associated with ADAMTS13 activity >10%. Neither neurological symptoms at presentation nor fever distinguished between severe deficiency and an ADAMTS13 activity >10%. However, patients with severe deficiency had a lower platelet count and either normal or minimally impaired renal function at presentation compared to those with an ADAMTS13 activity >10%. Similarly, the presence of an inhibitor also discriminated between patients with severe deficiency and those with an ADAMTS13 activity >10%. In the group with severe ADAMTS13 deficiency, 82·4% had a positive inhibitor level, compared with only 0·5% of patients with an ADAMTS13 activity >10% ($P < 0·0001$). The median inhibitor titre among patients with severe ADAMTS13 deficiency was 1·4 BU (0·6–2·0 BU). The only patient with a positive inhibitor test in the group with an ADAMTS13 activity level >10% had an inhibitor titre of 0·7 BU and an ADAMTS13 activity of 15%. During the time period studied, an average of 7·3 ± 2·9 patients were diagnosed with autoimmune TTP per year at the three participating institutions.

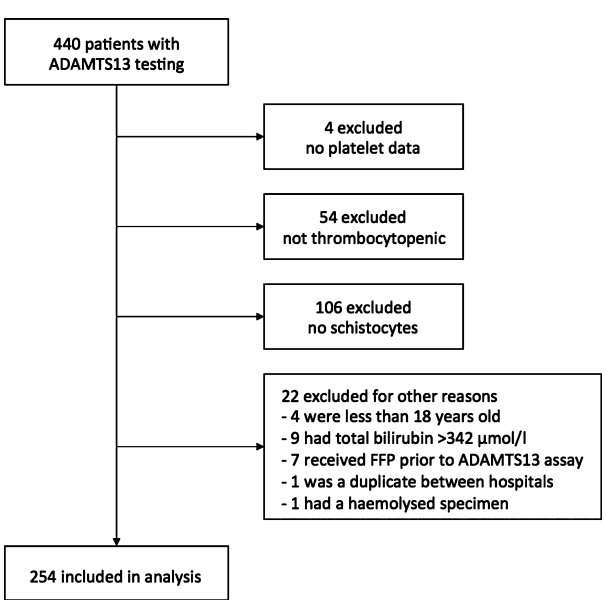


**Fig 1.** Patient enrolment in the registry.

### *Clinical diagnostic categories*

We reviewed patients' medical records and assigned each patient to one of 11 diagnostic categories based on the registry's predefined criteria (Table II). Of the 254 patients included in the registry dataset, 68 had an ADAMTS13 activity level of ≤10%, comprising 26·8% of patients, all of whom were determined to have autoimmune TTP. The remaining 186 patients carried a range of diagnoses (Table IV), with disseminated intravascular coagulation (DIC; 43%), transplant-associated TMA (14%) and drug-associated TMA (8·1%) being the most common. HUS cases (both diarrhoea-associated and atypical) comprised 6·5% of cases. Two patients with ADAMTS13 activity of >10% were classified as autoimmune TTP. One was a previously healthy 45-year-old female who presented with fatigue and dark urine and had an ADAMTS13 activity level of 15% with an associated inhibitor titre of 0·7 BU. Her platelet count increased during treatment with TPE. The other patient, a 21-year-old male with a history of intravenous drug use, presented after a 4 d prodrome of non-bloody diarrhoea with fatigue and new onset dark urine consistent with haemolysis. His creatinine


 

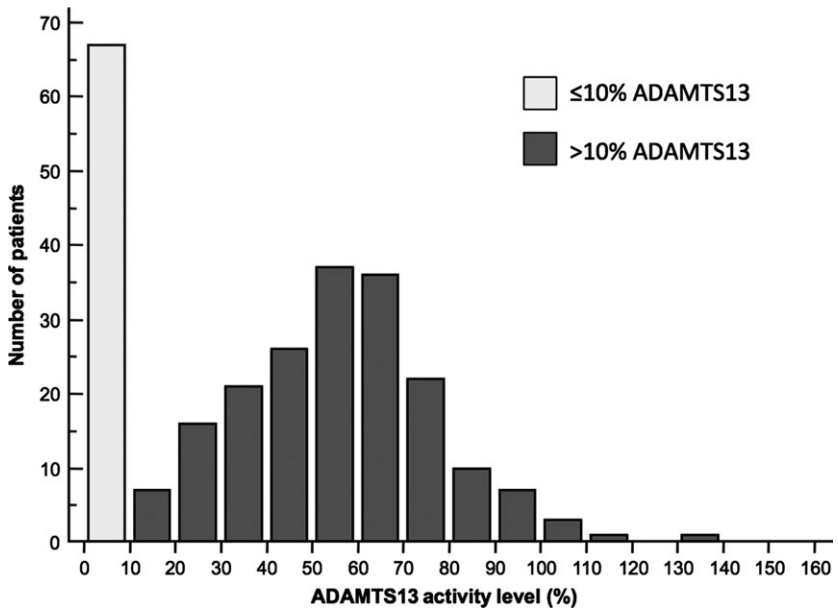


**Fig 2.** Distribution of ADAMTS13 activity levels within the Harvard TMA Research Collaborative registry.

was 106 μmol/l, lactate dehydrogenase 1705 iu/l and bilirubin 61·6 μmol/l. Haptoglobin was undetectable. He had started omeprazole approximately 1 week prior to presentation. ADAMTS13 activity level returned at 92% without detectable inhibitor, and he received a total of six sessions of TPE over 7 d, during which time his platelet count rose from $10 \times 10^9$/l to $252 \times 10^9$/l.

### *Treatment and outcomes*

Treatments and outcomes for patients in our dataset are outlined in Tables IV and V. Among patients with an ADAMTS13 >10%, the most common diagnostic categories treated with TPE were DIC, drug-associated TMA, transplant-related TMA and HUS (Table IV). Overall, 95·6% of patients with severe ADAMTS13 deficiency received TPE compared to 38·2% of patients with an ADAMTS13 level >10% ($P < 0{\cdot}0001$, Table V). Both the median number of TPE treatments and units of plasma transfused were significantly higher in the group with severe ADAMTS13 deficiency compared to the group with an ADAMTS13 activity level of >10%: 11 *versus* 5 treatments ($P < 0{\cdot}0001$) and 125 *versus* 51 units ($P < 0{\cdot}0001$), respectively.

We also examined a number of outcome indicators for our patients. The median follow-up period was 1310 d, with 23, 29 and 37 patients cumulatively lost to follow-up at 90, 180 and 360 d, respectively. Patients with severe ADAMTS13 deficiency had significantly shorter hospitalization periods (9 d vs. 14 d, $P < 0{\cdot}002$) and more rapid platelet count recovery to $>150 \times 10^9$/l (4 d vs. 6 d, $P = 0{\cdot}01$) (Table V). Patients with severe deficiency were also more likely to be alive at both 90 and 360 d ($P < 0{\cdot}0001$) and had longer median overall survival compared to those without severe deficiency (1384 d vs. 126 d, $P < 0{\cdot}0001$) (Table V).

Interestingly, we observed significant variation in the utilization of TPE for patients with an ADAMTS13 activity level >10% across the three institutions (designated A, B, and C) participating in this registry. Whereas only 13·2% of patients at Site A with TMA and an ADAMTS13 activity >10% received at least one session of TPE, 39·5% and 63·8% of patients meeting this description received TPE at sites B and C, respectively ($P < 0{\cdot}0001$ for TPE use across the three institutions) (Table VI). Additionally, those patients with ADAMTS13 activity >10% who received TPE at Site A were given a shorter treatment course, 3·0 (1·3–4·0) TPE sessions (median (IQR)) compared with 5·5 (4·0–8·0) TPE sessions at Site B and 5·0 (4·0–8·0) TPE sessions at Site C ($P = 0{\cdot}02$ for number of sessions across the three institutions). Nevertheless, there was no significant difference in 90-d mortality across the three sites for patients without severe ADAMTS13 deficiency ($P = 0{\cdot}98$). In addition, the distribution of diagnostic categories associated with 90-d mortality (≥50%, between 11–49% and ≤10%) (Table IV and data not shown) was not different between the three institutions ($P = 0{\cdot}57$). These data imply that TPE may not benefit patients with suspected TTP and an ADAMTS13 activity level >10%. All three institutions utilize ABO-compatible fresh frozen plasma (FFP) as their standard product, with cryoprecipitate-poor plasma being used in the event that insufficient inventory of ABO-compatible FFP is available.

## Discussion

The Harvard TMA Research Collaborative is a multicentre disease registry approach to studying TTP and other TMAs. Consistent with previous reports (Zheng *et al*, 2004; Coppo *et al*, 2010; Kremer Hovinga *et al*, 2010), the population of patients in our dataset with an ADAMTS13 activity level of

**Table III.** Comparison of demographic, clinical, and laboratory features of patients with ADAMTS13 activity ≤10% *versus* >10%.

| | ADAMTS13 ≤10% | ADAMTS13 >10% | *P* |
|---|---|---|---|
| Demographic features | | | |
| Age, years | 40 (29–53) | 58 (45–67) | <0·0001 |
| | *N* = 68 | *N* = 186 | |
| Sex, female (%) | 50 (73·5) | 96 (51·6) | 0·002 |
| | *N* = 68 | *N* = 186 | |
| Race | | | |
| Caucasian (%) | 42 (63·6) | 145 (81·5) | 0·006 |
| | *N* = 66 | *N* = 178 | |
| Non-Caucasian (%) | 24 (36·4) | 33 (19·5) | |
| | *N* = 66 | *N* = 178 | |
| Asian (%) | 1 (1·5) | 5 (2·8) | |
| | *N* = 66 | *N* = 178 | |
| Black (%) | 13 (19·7) | 22 (12·4) | |
| | *N* = 66 | *N* = 178 | |
| Hispanic (%) | 10 (15·2) | 6 (3·4) | |
| | *N* = 66 | *N* = 178 | |
| Clinical findings | | | |
| Neurological symptoms (%) | 27 (39·7) | 68 (37·4) | 0·77 |
| | *N* = 68 | *N* = 182 | |
| Fever symptoms (%) | 24 (35·3) | 63 (34·1) | 0·88 |
| | *N* = 68 | *N* = 185 | |
| History of cancer (%) | 0 (0) | 73 (39·2) | <0·0001 |
| | *N* = 68 | *N* = 186 | |
| History of transplant (%) | 0 (0) | 40 (21·5) | <0·0001 |
| | *N* = 68 | *N* = 186 | |
| Laboratory findings | | | |
| Haematocrit, % | 27 (23–31) | 26 (23–29) | 0·50 |
| | *N* = 68 | *N* = 186 | |
| Platelet count, $\times 10^9$/l | 17 (12–23) | 45 (27–76) | <0·0001 |
| | *N* = 68 | *N* = 186 | |
| Serum creatinine, μmol/l | 97·2 (70·7–132·6) | 212·2 (123·8–442·0) | <0·0001 |
| | *N* = 68 | *N* = 186 | |
| Lactate dehydrogenase, iu/l | 1107 (797–1349) | 879 (539–1613) | 0·17 |
| | *N* = 68 | *N* = 184 | |
| Inhibitor positive (%) | 56 (82·4) | 1 (0·5) | <0·0001 |
| | *N* = 68 | *N* = 186 | |
| Blood group | | | |
| O (%) | 35 (52·2) | 94 (51·1) | 0·89 |
| | *N* = 67 | *N* = 184 | |
| Non-O (%) | 32 (48·8) | 90 (48·9) | |
| | *N* = 67 | *N* = 184 | |
| A (%) | 22 (32·8) | 57 (31·0) | |
| | *N* = 67 | *N* = 184 | |
| B (%) | 9 (13·4) | 23 (12·5) | |
| | *N* = 67 | *N* = 184 | |
| AB (%) | 1 (1·5) | 10 (5·4) | |
| | *N* = 67 | *N* = 184 | |

Relevant clinical features and laboratory findings proximate to the time of ADAMTS13 testing are reported. A positive inhibitor is defined as a titre >0·4 Bethesda Units. Continuous variables are reported as median (interquartile range) and statistical comparisons made using the *U* test. Categorical variables are reported as number (%) and statistical comparisons were made using the Fisher exact test. *P* values reported are for 2 tails. The *N* evaluable for each parameter is also reported beneath the variable (*N*=).

≤10% was highly enriched for patients with detectable inhibitor and clinical features of autoimmune TTP. Patients with severe ADAMTS13 deficiency were also more likely to be younger and female than those with other TMAs. Additionally, severe deficiency was observed more frequently among non-Caucasians enrolled in the registry as compared with Cau-


 

**Table IV.** Diagnoses, use of therapeutic plasma exchange (TPE) and associated 90-d mortality among the 186 patients with an ADAMTS13 activity >10%.

| | Number (%)* | Number (%) receiving TPE† | Number (%) dead at 90 d‡ |
|---|---|---|---|
| Disseminated intravascular coagulation | 80 (43) | 20 (25) | 45 (60) *N* = 75 |
| Sepsis/multi-organ failure | 47 (25·3) | 10 (21·3) | 26 (59·1) *N* = 44 |
| Cancer | 23 (12·4) | 6 (26·1) | 17 (73·9) *N* = 23 |
| Pancreatitis | 7 (3·8) | 3 (42·9) | 2 (33·3) *N* = 6 |
| Other | 3 (1·6) | 1 (33·3) | 0 (0) *N* = 2 |
| Transplant-related | 26 (14) | 8 (30·8) | 9 (36·0) *N* = 25 |
| Drug-associated | 15 (8·1) | 9 (60·0) | 6 (42·9) *N* = 14 |
| Multifactorial | 14 (7·5) | 7 (50) | 7 (50) *N* = 14 |
| Autoimmune | 13 (7) | 7 (53·8) | 4 (33·3) *N* = 12 |
| Haemolytic-uraemic syndrome | 12 (6·5) | 8 (66·7) | 1 (10) *N* = 10 |
| Hypertensive emergency | 10 (5·4) | 2 (20) | 0 (0) *N* = 9 |
| Other thrombotic microangiopathy | 9 (4·8) | 6 (66·7) | 0 (0) *N* = 5 |
| Pregnancy-related | 3 (1·6) | 1 (33·3) | 0 (0) *N* = 2 |
| Autoimmune thrombotic thrombocytopenic purpura | 2 (1·1) | 2 (100) | 0 (0) *N* = 2 |
| Disseminated cancer | 2 (1·1) | 1 (50) | 1 (100) *N* = 1 |

The number (%) of patients, the number (%) treated (received) with TPE, and death at 90 d are reported for each diagnosis.
*Percentage is calculated using *N* = 186 as the denominator.
†Percentage is calculated using the number of patients within the specific diagnostic category as the denominator.
‡The number of patients with the diagnosis and not lost to follow-up is indicated (*N*=) and is used to calculate per cent mortality. Diagnoses in the category 'Other thrombotic microangiopathy' include heparin-induced thrombocytopenia, drug-associated haemolytic anaemia, haemolytic-uraemic syndrome not meeting criteria, and nonspecific thrombotic microangiopathies.

**Table V.** TPE and clinical outcomes of patients with ADAMTS13 activity ≤10% *versus* >10%.

| | ADAMTS13 ≤10% | ADAMTS13 >10% | *P* |
|---|---|---|---|
| Received TPE | 65 (95·6) *N* = 68 | 71 (38·2) *N* = 186 | <0·0001 |
| Number of TPE treatments | 11 (5–19) *N* = 65 | 5 (3–7) *N* = 71 | <0·0001 |
| Plasma transfused, units | 125 (46–233) *N* = 65 | 62 (39–86) *N* = 71 | <0·0001 |
| Hospital length of stay, days | 9 (7–17) *N* = 68 | 14 (8–27) *N* = 186 | <0·002 |
| Days to normal platelet count | 4 (4–6) *N* = 66 | 6 (4–9) *N* = 87 | 0·01 |
| Alive at 90 d | 60 (95·2) *N* = 63 | 96 (57·1) *N* = 168 | <0·0001 |
| Alive at 360 d | 53 (93·0) *N* = 57 | 76 (47·5) *N* = 160 | <0·0001 |
| Overall survival, days | 1384 (513–2293) *N* = 68 | 126 (13–1044) *N* = 186 | <0·0001 |

Continuous variables are reported as median (interquartile range) and statistical comparisons made using the *U* test. Categorical variables are reported as number (%) and statistical comparisons made using the Fisher exact test. *P* values reported are for 2 tails. The *N* evaluable for each parameter is reported beneath the variable.
TPE, therapeutic plasma exchange.

casians. This agrees with the findings of the Oklahoma TTP Registry (Kremer Hovinga *et al*, 2010) and suggests that these features of TTP are consistent across geographically disparate patient populations. We also confirmed previous findings showing no association between ABO blood group and TTP (Staropoli *et al*, 2009).

Our study has a number of limitations inherent to the nature of retrospective review. For example, we were not able to reliably document TTP relapses that may have been treated at institutions outside of the consortium; consequently, we have not reported relapse data here. Follow-up data were available on 84·6% of patients at 360 d, allowing us to report survival data in this timeframe with a high degree of confidence. Another concern is that suspected cases of TTP for which an ADAMTS13 assay was not sent would not have been captured in the dataset.

We observed substantial variation between the hospitals in our consortium in the use of TPE for patients with an ADAMTS13 activity level >10%. We attribute this variation to the broad discretion allowed by current treatment guidelines and to differences in the willingness of clinicians to withhold TPE in cases for which an alternative cause for TMA is present. Nevertheless, survival in patients without severe deficiency of ADAMTS13 did not differ between the three institutions, despite the disparity in utilization of TPE. To study the impact that variation in disease acuity could have had on this finding, we determined the proportion of patients at each institution with diagnoses associated with low, moderate and high 90-d mortality. No significant difference was found in this metric between the three sites. Our data imply that, compared to patients with autoimmune TTP and severe ADAMTS deficiency, patients with TMA and ADAMTS13 levels >10% have reduced survival that may not be improved by TPE. In contrast, other investigators have reported therapeutic responses to TPE in cases of TMA without severe ADAMTS13 deficiency (Vesely *et al*, 2003), but these findings

**Table VI.** Use of therapeutic plasma exchange (TPE) in patients with an ADAMTS13 activity >10% across institutions.

| | Participating institutions | | |
|---|---|---|---|
| | A | B | C |
| Number (%) of patients treated with TPE* | 7 (13·2) *N* = 53 | 34 (39·5) *N* = 86 | 30 (63·8) *N* = 47 |
| Number of TPE treatments† | 3·0 (1·3–4·0) | 5·5 (4·0–8·0) | 5·0 (4·0–8·0) |
| Number (%) dead at 90 d‡ | 21 (42·0) *N* = 50 | 34 (43·6) *N* = 78 | 18 (43·9) *N* = 41 |
| Number (%) dead at 90 d among patients treated with TPE§ | 2 (33·3) *N* = 6 | 9 (31·0) *N* = 29 | 7 (28·0) *N* = 25 |

The number of TPE treatments is reported as median (interquartile range) and statistical comparison made using the Kruskall–Wallis test; pairwise comparisons employed the *U* test. Categorical variables are reported as number (%) and statistical comparisons made using the chi-square test; pairwise comparisons used the Fisher exact test. *P* values reported are for 2 tails. The *N* evaluable for each parameter is also reported beneath the variable (*N*=).

*$P < 0{\cdot}0001$ for use of TPE across the three institutions. $P = 0{\cdot}001$ for the comparison between institutions A and B, $P < 0{\cdot}0001$ for the comparison between A and C and $P = 0{\cdot}01$ for the comparison between B and C.

†$P = 0{\cdot}02$ for number of TPE treatments across the three institutions. $P = 0{\cdot}005$ for the comparison between institutions A and B, $P = 0{\cdot}02$ for the comparison between A and C and $P = 0{\cdot}59$ for the comparison between B and C.

‡$P = 0{\cdot}98$ for death at 90 d across the three institutions.

§$P = 0{\cdot}95$ for death at 90 d across the three institutions among patients treated with TPE.

are limited by the absence of comparison to a similar cohort of patients not treated with TPE. Therefore, the variation in clinical practice we observed within our consortium constitutes a 'natural experiment' that may permit a rigorous assessment of TPE in patients with TMA and an ADAMTS13 >10%.

Our registry allowed analysis of different types of TMA that are commonly considered in the differential diagnosis for TTP. TMAs other than autoimmune TTP comprised 73·2% of cases. A further 164 patients of the 440 screened for enrolment in the registry (37·2%) were evaluated for ADAMTS13 activity but were excluded due to absence of schistocytes and/or thrombocytopenia. Of these 164 patients, five had an ADAMTS13 activity level of ≤10%. These five included two outpatients with a diagnosis of congenital ADAMTS13 deficiency, one patient with a total bilirubin of 354 μmol/l, resulting in a falsely low ADAMTS13 level, and two outpatients who were being followed up for recently treated autoimmune TTP. The fact that only 68 of 440 (15·5%) patients who received ADAMTS13 testing had a result ≤10% and met inclusion criteria suggests a need to examine the policies governing the cost-effective utilization of this test.

In this dataset, an ADAMTS13 activity level of ≤10% demonstrated excellent sensitivity (97%) and specificity (100%) in identifying cases of autoimmune TTP. By comparison, the fraction of autoimmune TTP with ADAMTS13 activity levels <5% that is reported in the literature varies from 33% to 100% (Furlan *et al*, 1998; Tsai & Lian, 1998; Veyradier *et al*, 2001; Vesely *et al*, 2003; Kremer Hovinga *et al*, 2004; Matsumoto *et al*, 2004; Zheng *et al*, 2004; Bohm *et al*, 2005; Sadler, 2008). The high sensitivity reported in this study probably reflects the stringency of our clinical definitions and our careful attention to secondary causes of TMA. The fact that all three institutions employed the same laboratory, which used the same ADAMTS13 assay during the study interval, probably minimized variability attributable to testing differences.

Patients with severe ADAMTS13 deficiency represent a subgroup that demonstrates excellent outcomes, with a 1-year survival of 94·6%. This survival rate compares favourably to experiences reported previously (Vesely *et al*, 2003; Zheng *et al*, 2004), which may reflect the rapidity of diagnosis and institution of TPE at our centres. Unfortunately, in most clinical contexts, the ADAMTS13 assay remains a send-out test with turnaround times ranging from 24 h to 7 d. As a result, the French TMA Reference Centre has proposed a simple diagnostic approach consisting of three clinical criteria: platelet count $<30 \times 10^9$/l, creatinine ≤200 μmol/l and the presence of detectable antinuclear antibodies. When any one of these criteria is met in a case of suspected TTP, the sensitivity and specificity to identify cases with severe ADAMTS13 deficiency were 98·8% and 48·1%, respectively. When all three criteria were met, sensitivity declined to 46·9% while specificity increased to 98·1% (Coppo *et al*, 2010). This effort highlights the need for a more sophisticated, externally validated, and bedside-deployable clinical risk scoring system to rapidly identify patients with severe ADAMTS13 deficiency who would benefit from prompt treatment with TPE. Further, a reliable scoring system with high predictive value could assist in improving the cost effectiveness of ADAMTS13 testing.

In summary, we have reported the experience of a large, multi-institutional effort aimed at studying TTP and other TMAs. The demographic, clinical and laboratory features and clinical outcomes of our patients are largely consistent with previously published registries. We observed variable use of TPE among TMA patients without severe ADAMTS13 deficiency but no associated difference in mortality. Additionally, our work underscores the need for a clinical scoring tool to assist in the rapid identification of patients with severe ADAMTS13 deficiency so that these cases can quickly move on to receive lifesaving care.

## Acknowledgements

This work was generously supported by the Luick Family Fund of the Massachusetts General Hospital.

## Author contributions

P.K.B., R.S.M., L.U., R.K., C.S. and W.D. conceived of and designed the study. P.K.B., A.L. and A.H. collected the data. P.K.B., A.L. and R.S.M. analysed the data. P.K.B. and R.S.M. wrote the manuscript.

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