Characterization of efficacy and safety of pathogen inactivated and quarantine plasma in routine use for treatment of acquired immune thrombotic thrombocytopenic purpura

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Background Auto-immune thrombotic thrombocytopenic purpura (TTP) is a morbid multi-organ disorder. Cardiac involvement not recognized in initial disease descriptions is a major cause of morbidity. Therapeutic plasma exchange (TPE) requires exposure to multiple plasma donors with risk of transfusion-transmitted infection (TTI). Pathogen inactivation (PI) with amotosalen-UVA, the INTERCEPT Blood System for Plasma (IBSP) is licensed to reduce TTI risk.

Methods An open-label, retrospective study evaluated the efficacy of quarantine plasma (QP) and IBSP in TTP and defined treatment emergent cardiac abnormalities. Medical record review of sequential patient cohorts treated with QP and IBSP characterized efficacy by remission at 30 and 60 days (d) of treatment, time to remission, and volume (L/kg) of plasma required. Safety outcomes focused on cardiac adverse events (AE), relapse rates, and mortality.

Results Thirty-one patients (18 IBSP and 13 QP) met study criteria for auto-immune TTP. The proportions (%) of patients in remission at 30 d (IBSP = 61/1, QP = 46/2, P = 0.570) and 60 d (IBSP = 77/8, QP = 76/9, P = 1.00) were not different. Median days to remission were less for IBSP (15.0 vs. 24.0, P = 0.003). Relapse rates (%) 60 d after remission were not different between cohorts (IBSP = 7/1, QP = 40/0, P = 0.150). ECG abnormalities before and during TPE were frequent; however, cardiac AE and mortality were not different between treatment cohorts.

Conclusions Cardiac and a spectrum of ECG findings are common in TTP. In this study, IBSP and QP had similar therapeutic profiles for TPE.

Key words: cardiac diseases, infection, plasmapheresis, thrombotic thrombocytopenic purpura, transfusion medicine, transfusion reaction.

Introduction

Idiopathic auto-immune thrombotic thrombocytopenic purpura (TTP) is a highly morbid disorder with an estimated annual frequency of 4 per 10^6 persons [1]. The current standard of care for TTP utilizes therapeutic plasma exchange (TPE) to achieve remission in 80%–90% of patients with mortality of less than 20%–10% [2]. However, TPE requires repeated exposure to multiple allogeneic plasma donors with increased risk of transfusion-transmitted infection (TTI) due to pathogens undetected by current tests or emerging pathogens for which tests...
are not routinely available [3–6]. Pathogen inactivation treatment of plasma with amotosalen and UVA light (INTERCEPT Blood System for Plasma-IBSP, Cerus, Concord, CA, USA) has been licensed in multiple countries [7], and offers the potential to reduce the risk of TTI associated with repeated plasma donor exposures [8–11]. However, sporadic cases of TTI due to hepatitis E virus (HEV) have been reported after exposure to pathogen inactivated plasma [12].

Initial descriptions of TTP did not emphasize cardiac abnormalities as an essential component of the TTP syndrome [13]. Subsequently, cardiac involvement in TTP has been recognized [14–24]; and recommendations for electrocardiographic (ECG) monitoring and measurement of cardiac troponins have been advocated [20, 22–24]. A prospective randomized clinical trial conducted prior to 2006 to evaluate the safety and efficacy of IBSP for TPE to treat TTP did not utilize routine ECG monitoring [25]. Hawkins et al. [19] published a systematic review of cardiac abnormalities in TTP, but did not characterize the specific ECG changes during treatment. Hughes et al. [20] reported ECG abnormalities and cardiac troponin levels prior to treatment, but not sequentially during treatment. More recent studies have not reported ECG abnormalities in detail, but have corroborated the predictive value of troponin levels [20, 23]. In view of the variable reporting of ECG abnormalities in the past, and the recommendation to monitor cardiac abnormalities at initiation and during TPE, we conducted a retrospective review to define more completely the incidence and spectrum of ECG findings at baseline and associated adverse events during treatment. This study characterized further the efficacy and cardiac safety of IBSP and quarantine plasma (QP) in routine use.

Materials and Methods

General design

This was an open-label, non-randomized, retrospective, non-interventional, two-treatment period cohort study to assess the efficacy and safety of IBSP and QP for TPE of TTP.

Clinical data were extracted by review of primary medical records and blood centre production records (Établissement Français du Sang (EFS) Alsace, Strasbourg, France) for patients treated at two specialized TTP centres in Alsace, France (HUS Strasbourg and CH Mulhouse, France) between 1998 and 2013. From 1 January 1998 to 31 August 2007 only QP was used for TPE; and from 1 September 2007 to March 2013 IBSP was used exclusively for TPE. Both types of plasma were prepared as fresh frozen plasma (FFP) by a single regional blood centre (EFS Alsace, Strasbourg, France).

The study was conducted without patient informed consent, but with confidentiality, within the scope of the EFS hemovigilance program declared to the Commission Nationale de l’Informatique et des Libertés (CNIL). The study protocol was reviewed and approved by the Comité d’Ethique des Facultés de Médecine, d’Odontologie et de Pharmacie de Strasbourg. Patients were assigned study-specific identification codes, de-identified data were entered onto study-specific case report forms, submitted to a Data Coordinating Center (Axio Research, Seattle, WA, USA) for double entry into an electronic database and analysed according to a specified Statistical Analysis Plan.

Identification of patients for review

All patients from January 1998 to March 2013 with a suspected clinical diagnosis of primary, idiopathic autoimmune TTP with at least one assay for ADAMTS13 activity were identified from clinical laboratory records. Inclusion criteria for diagnosis of TTP were: platelet count <100 × 10^9/L, haemolytic anaemia with a negative Coombs test or clinical basis for non-immune haemolytic anaemia if no direct anti-globulin test was recorded, ADAMTS13 level <10%, serum creatinine <354 µmol/L, and age at enrolment of 2 years or greater. Exclusion criteria were as follows: congenital TTP, hematopoietic stem cell transplant within 1 year of onset of TTP, acute or chronic disseminated intravascular coagulation (DIC), metastatic or non-metastatic malignancy (isolated non-melanocytic skin tumours were not a basis for exclusion), collagen vascular/autoimmune disease unless demonstration of concurrent severe ADAMTS13 deficiency and the presence of an auto-antibody to ADAMTS13, HIV-AIDS, malignant hypertension (systolic pressure of >190 mm Hg and/or a diastolic pressure of >120 mmHg), micro-angiopathic syndrome other than primary autoimmune TTP (e.g. haemolytic uremic syndrome, or drug-induced micro-angiopathy). Assays for ADAMTS13 activity and antibodies to ADAMTS13 were performed in a central reference laboratory [26]. The limit of detection for ADAMTS13 activity was 5%, and samples with undetectable ADAMTS13 were reported as <5% and assigned an imputed value = 5% for statistical analyses. All patients who met the inclusion criteria, and without any of the exclusion criteria were selected for review.

Therapeutic plasma exchange

All plasma components were collected by apheresis and prepared according to standard procedures approved by the applicable national regulatory authority. During 1998–2013, no other forms of plasma were utilized other
than IBSP or QP in the respective review periods. In vitro analysis of IBSP demonstrates retention of coagulation factor activity including ADAMTS13 antigenic and functional activity (antigenic IU/dL: 118 ± 25; functional IU/dL: 90 ± 16) [7]. Conventional plasma contained similar levels (antigenic IU/dL = 116 ± 24; functional IU/dL = 97 ± 16).

The type of plasma used for each cohort was determined by the period in which patients were treated. The dose, frequency, and duration of TPE were determined by standard TTP patient management practices at HUS Strasbourg and CH Mulhouse. The minimal dose for each TPE was 40 mL/kg of patient body weight. A dose of 1.5 times the patient plasma volume, that is 60 mL/kg body weight was used depending on clinical conditions for progressive or unresponsive TTP. Patients were treated until clinical remission was achieved or an alternative therapy initiated. Remission was defined by: platelet count >150 × 10^9/L for 2 days, the absence of progression of neurologic deficits, and no other signs of persistent disease (new cardiovascular or other organ dysfunction related to TTP or an LDH level ≥1.5 times the upper limit of normal). Patients were treated for exacerbation or relapse as required. Exacerbation was defined as a recurrence of clinical signs and symptoms of TTP requiring re-initiation of TPE within 60 days after the most proximate remission. Relapse was defined as reappearance of clinical signs and symptoms of TTP requiring re-treatment with TPE more than 60 days after the last TPE of a prior TTP episode with remission.

**Outcome measures**

Efficacy outcomes included: the proportion of patients achieving remission within 30 and 60 days of the first TPE, days to remission, volume of plasma (L/kg patient body weight) required to achieve remission, number of TPEs to remission, proportion of patients with exacerbation of TTP, proportion of patients with relapse, and proportion of patients with refractoriness to treatment. Exacerbation with defined as need for re-treatment within 60 days of initial remission. Relapse was defined as need for re-treatment more than 60 days after initial remission. Refractoriness to TPE was defined by a decrease in platelet count after the initial response to TPE, or progression of disease signs and symptoms after an initial clinical response.

Safety outcomes included treatment emergent adverse events in the MedDRA (Medical Dictionary for Regulatory Activities) System Organ Class (SOC) of Cardiac Disorders during treatment and up to 7 days after the last TPE, treatment emergent abnormal ECG findings, incidence of all treatment emergent AEs during TPE and up to 7 days after the last study TPE, mortality up to 60 days after last TPE, health status at 60 days after the last TPE (remission, exacerbation, alive with treatment failure, or death), and the incidence of persistent, treatment emergent Grade 3 or Grade 4 hypokalemia up to 7 days after the last TPE of each episode by MedDRA Preferred Term of either “Hypokalemia” or “Low Potassium Level” defined by NCI CTCAE (version 4) Grade 3 or Grade 4 criteria (serum potassium level <3.0 mmol/L).

**Collection of data**

Clinical laboratory data in medical records were identified for assessment of serum chemistry and haematology parameters prior to the first TPE. Daily clinical assessments of haematologic parameters, clinical chemistry values, and the neurologic status of patients undergoing TPE were extracted from the primary care medical record. The date and volume of plasma administered for each TPE, as well as administration of other blood components, were obtained from plasmapheresis treatment records.

Follow-up data for health status during and after TPE were recorded from medical records, including after discharge from the treatment centre and upon subsequent clinic visits. Vital signs and AEs during plasma exchange were extracted from plasma-apheresis treatment records. All ECG recordings performed for routine care in the primary medical records were obtained, de-identified, copied, and submitted for interpretation by an external ECG consultant blinded to type of plasma (Cardiocore, South San Francisco, CA, USA). The ECG abnormalities were reported using uniform terminology. ECG consultants provided an integrated summary of findings to the Principal Investigators who correlated the ECG findings with each patient’s respective clinical course and classified treatment emergent cardiac AEs in association with ECG findings. The ECG findings by uniform terminology were not analysed for statistical significance by individual term, but were used for the analysis of treatment emergent cardiac AEs. The investigators included all treatment emergent cardiac AEs during TPE and up to 7 days after the last TPE based on signs, symptoms, progress notes, ECG recordings, and diagnoses recorded in primary medical records.

**Statistical methods and data analyses**

Data analysis was performed primarily with descriptive statistics. For categorical data, such as the proportion of patients achieving remission, Fisher’s exact test was used to test for statistical difference between the treatment cohorts. When modelling was required to compare proportions in the presence of confounders, a logistic
regression model was used to estimate the odds ratio between the treatment cohorts. For continuous data, analysis of variance (ANOVA) was used to compare the means; and if the parametric ANOVA procedure was deemed inappropriate, the non-parametric Wilcoxon rank sum test was used to detect a positional shift in distributions between treatment cohorts. Median time to remission was estimated using the Kaplan–Meier method, and an estimate of hazard ratio was obtained using a Cox proportional hazards model. Due to the limited size of the patient population, the study had insufficient power to support statistical conclusions, and multi-variate analyses for potential covariate factors were not conducted because of the study size limitation. P values are presented for informational purposes only.

Results

Baseline demographics and clinical status

Forty-nine patients were identified with a suspected clinical diagnosis of TTP from 1998 to 2013. Thirty-one patients (13 QP and 18 IBSP) met diagnostic inclusion criteria for idiopathic-autoimmune TTP. Five patients were treated for a second episode of TTP (1 IBSP, 4 QP). Because of the limited experience with a second TTP episode, only data for the first episode are presented. No patients were lost to follow up.

Baseline characteristics of patients included in the review demonstrated no substantial differences between cohorts except for median age and weight (Table 1). The baseline clinical laboratory characteristics immediately prior to the first TPE demonstrated severe TTP in both cohorts (Table 2).

Table 1 Study population baseline clinical characteristics

| Parameter                           | IBSP (n = 18) | QP (n = 13) |
|-------------------------------------|--------------|-------------|
| Median Age (years)                  | 47.0         | 38.0        |
| Proportion Male (%)                 | 50.0         | 46.2        |
| Blood Group %: A, B, AB, O          | 33/33/0/33   | 54/15/15/15 |
| Rh % : Negative, Positive           | 6/94         | 15/85       |
| Weight (kg)                         | 80.4 ± 17.3  | 74.9 ± 21.2 |
| Body Mass Index (BMI)               | 30.3 ± 6.6   | 28.9 ± 6.2  |
| DCT % (negative/unknown)            | 67/33        | 85/15       |
| Positive blood smear (%) a          | 78           | 85          |
| Fever Present (%)                   | 56           | 54          |
| Median ADAMTS13 level (%) b         | 5 (n = 18)   | 5 (n = 9)   |
| Initial/Relapsed TTP (%)            | 100/0        | 85/15       |

*Positive blood smear: micro-angiopathic red cell morphology.

ADAMTS13 levels reported as < 5% when < level of detection Two Reference patients had ADAMTS13 values > 5%. Baseline data not available for four patients, but subsequent levels were < 5%.

Similar proportions of patients in the QP and ISBP cohorts, respectively, had prior medical history of cardiac disorders (61.5–5%, 77.8–8%; P = 0.43). A smaller proportion of patients in the QP cohort had baseline ECGs than in the ISBP cohort (61.5–5%, 88.9–9%; P = 0.1). Among those with baseline ECGs, abnormalities by uniform terminology were observed in approximately 50% of patients in both cohorts prior to TPE (Table 3). The most prevalent abnormalities were non-specific T wave changes and sinus tachycardia. Physical examination prior to the first episode of TPE demonstrated expected and similar findings in both cohorts with the most frequent abnormalities involving cutaneous, neurologic, gastrointestinal, cardiac, and pulmonary system organ classes (SOC).

Efficacy outcomes

The proportions (% of patients in remission at 30 and 60 days after initiation of TPE were not substantially different between cohorts (Table 4). The median time to remission at day 60 was shorter for the IBSP cohort (Table 4). The hazard ratio derived from survival analyses adjusted for baseline platelet count, rituximab use, and age indicated that patients receiving IBSP were more likely to be in remission 60 days after initiation of TPE treatment than those receiving QP (4.9; 95% CI: 1.8–14.8). The number of TPE required for remission at day 30 and day 60 was similar between the cohorts; however,
the cumulative median plasma volume and median weight adjusted plasma volumes transfused to day 60 were larger for the IBSP cohort.

No patients in either group met the definition of exacerbation before a durable remission. Seven patients (4 IBSP and 3 QP) met criteria for refractoriness based on an initial response of the platelet count after initiation of TPE followed by clinical deterioration with either decline of the platelet count to <150 × 10^9/L or progression of TTP symptoms. Ultimately, with continued TPE, all refractory patients in both cohorts achieved durable remissions.

Five patients in remission at day 60 relapsed (1 IBSP and 4 QP). One IBSP patient was re-treated and achieved a second remission. One QP patient relapsed after 9/2007 and was re-treated with IBSP to remission. Three patients in the QP cohort relapsed and were re-treated with QP. Two of these patients achieved a second remission by day 60 with re-treatment, and one patient was a treatment failure at day 60 with a platelet count of 100 × 10^9/L. This patient had received 19 TPEs (total plasma volume of 900 L) and four doses of rituximab. After 9 TPE, the platelet count stabilized between 60 and 80 × 10^9/L after 3 doses of rituximab. This patient had an allogeneic HSCT more than 12 months before the onset of autoimmune TTP satisfying the inclusion criteria. Although the patient did not meet the remission platelet count criteria, the patient remained stable without other clinical signs of TTP. The sub-normal platelet count was attributed to persistent post HSCT bone marrow hypoplasia.

An extensive number of medications were prescribed during TPE treatment. Of specific interest was the use of steroids and rituximab. There was no substantial difference in the proportions of patients treated with rituximab (IBSP = 7, QP = 3), but the mean days of rituximab therapy were greater at day 60 for the IBSP cohort compared to the QP cohort (3.7 d; 1.7 d; P = 0.030). This difference likely reflected increased use of rituximab in later years as clinical practice evolved. The use of blood components other than the plasma for TPE was minimal.

### Safety outcomes

#### Adverse events

The proportions (%) of patients with treatment emergent AEs related to TPE were not substantially between the cohorts (ISBP = 88.9, QP = 84.6, P = 1.00). Similarly, the proportions of patients with treatment emergent SAEs related to TPE were not different between the cohorts (IBSP = 33.3, QP = 38.5, P = 1.00). The most frequent SAEs were in the Nervous System and Cardiac Disorders SOC. Six patients died during the study (3 IBSP, 3 QP). None of the deaths were related to TPE. The cause of death in one ISBP patient was attributed to pulmonary embolism with right bundle branch block and cardiac arrest. This patient had an abnormal ECG at baseline (sino-tachycardia, short PR interval and low voltage). The cause of death for one QP patient was ischaemic stroke associated with elevated baseline troponin, bradycardia, nodal rhythm and cardiac arrest after 10 TPE. No other deaths were attributed to cardiac adverse events.

Treatment emergent cardiac AEs were investigated in detail. Many patients had a baseline medical history of cardiac disease (ISBP = 77.8%, QP = 61.5%, P = 0.43). Similar proportions of ISBP and QP patients had ECG

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abnormalities by uniform ECG terminology prior to initiation of TPE (55.6%, 53.8%, \( P = 0.29 \)). The most frequent ECG abnormalities were non-specific T wave changes, sinus tachycardia, left axis deviation, atrial fibrillation with a spectrum of other infrequent abnormalities including: short PR interval, ST segment depression, inverted T wave, old septal myocardial infarction, left bundle branch block, premature atrial contraction, premature ventricular contraction, ST depression and biphasic T wave. Following initiation of TPE, the proportions of ISBP (66.7%) and QP patients (46.2%) with ECG findings by uniform terminology (Table 5) were not substantially different (\( P = 0.29 \)).

Clinically relevant treatment emergent Cardiac AEs were defined based on an integrated assessment of ECG recordings and clinical events reported in the medical record (Fig. 1). For the QP cohort, four of 13 (30.8%) patients had treatment emergent AEs. For the ISBP cohort, eight of 13 (61.5%) had a spectrum of treatment emergent AEs in association with ECG abnormalities (\( P = 0.48 \)). Of note the only Preferred Term approaching a significant difference was arrhythmia events with a higher frequency in the QP cohort (\( P = 0.06 \)). A spectrum of cardiac AE were observed, but there were no trends indicative of differences between ISBP (Test) and QP (Control) cohorts (Fig. 1).

Serious adverse events in the Cardiac SOC were distributed comparably between ISBP and QP cohorts (Fig. 2). Three SAEs, only in the QP cohort, were classified as related to treatment: cardiac arrest, bradycardia and nodal rhythm. Among the patients who died, one death in the QP cohort was possibly related to nodal rhythm and bradycardia.

### Discussion

This retrospective review evaluated the clinical efficacy of ISBP and QP in routine use for treatment of acquired autoimmune TTP. The size of the study population was limited by the low frequency of auto-immune TTP. Both types of plasma provided remission rates consistent with those reported for primary idiopathic TTP. Multiple secondary efficacy

*Table 5* Patients (%) with treatment emergent ECG abnormalities classified by uniform ECG reporting terminology

| Abnormality By Uniform Terminology | ISBP (n = 18)* | QP (n = 13)* |
|-----------------------------------|---------------|-------------|
| Any ECG Abnormal Finding          | 66.7          | 46.2        |
| Non-specific T wave changes       | 33.3          | 30.8        |
| Short PR interval                 | 0.0           | 15.4        |
| Sinus tachycardia                 | 38.9          | 15.4        |
| T wave flat                       | 5.6           | 15.4        |
| Bradycardia                       | 0.0           | 7.7         |
| Junctional rhythm                 | 0.0           | 7.7         |
| QTc interval prolongation         | 11.1          | 7.7         |
| T wave inverted                   | 0.0           | 7.7         |
| Left bundle branch block          | 5.6           | 0.0         |
| Left ventricular hypertrophy      | 5.6           | 0.0         |
| ST depression, ischaemia acute    | 5.6           | 0.0         |
| ST depression ischaemia chronic   | 5.6           | 0.0         |
| T wave biphasic                   | 5.6           | 0.0         |
| T wave change – ventricular conduction | 16.7       | 0.0         |

*Denominator based on total patient population.

Fig. 1 The proportions of patients with treatment emergent adverse events (AE) in the cardiac system organ class (SOC) are presented by preferred term. This analysis was based on ECG recording abnormalities and clinical assessments. Test = patients treated with IBSP and Control = patients treated with QP. The 95% confidence interval for the treatment difference in proportions is indicated.
outcomes were similar between treatment groups. The median time to remission at day 60 was shorter for IBSP compared to QP; but this may have been due to use of larger volumes of plasma for TPE due to practice evolution in later years as reported in other studies [28]. Increased use of rituximab in the second cohort was due to evolving therapeutic regimens with immune modulation agents [29]. While the proportions of patients treated with rituximab were not statistically different between the cohorts, the median days of use were different, but did not appear associated with shorter times to remission. No differences were detected in refractoriness to treatment between the cohorts. In both cohorts, patients who died had TTP unresponsive to TPE and in some cases unresponsive to immune modulation therapy as well. Cardiac adverse events were the antecedent cause of death in only one QP patient (nodal rhythm, bradycardia and cardiac arrest). Mortality was not substantially different from that reported in other studies [20, 23, 28, 30].

In the last decade, involvement and dysfunction of the cardiac microvasculature in TTP has received increased recognition [16, 18–20, 23, 24, 31]. Cardiac AEs may be under diagnosed unless rigorous ECG monitoring or cardiac troponin assays are utilized [20, 23]. Our retrospective review focused on ECG recording abnormalities as part of routine care, and AEs in the Cardiac SOC because routine measurement of cardiac troponin was evolving during the period of this study. A substantial proportion of patients had a history of cardiac disease prior to treatment. More than 60% of patients in each cohort had at least one ECG recording before initiation of TPE, and more than 80% had ECG recordings after initiation of TPE. The later cohort (IBSP) had more ECG recordings as physicians became increasingly aware of involvement of the myocardium in TTP. A broad spectrum of ECG abnormalities and cardiac AEs were observed in both treatment cohorts. The most frequent ECG abnormalities at baseline and during treatment were non-specific T wave changes and sinus tachycardia which were not considered clinically severe. Analysis of the cardiac AEs demonstrated that the most frequent were of low grade clinical severity and intermittent, primarily bradycardia and tachycardia.

The incidence of treatment emergent SAEs, including the Cardiac SOC, was similar in the cohorts, and mortality was not different between the cohorts. In both treatment cohorts, patients who died failed to respond to TPE, with and without use of adjuvant immune therapy, and died with complications of progressive, unresponsive TTP. Only one death in the QP cohort had a treatment emergent cardiac AE considered related to TPE. Despite limited size, this study provides a multi-year experience in the treatment of TTP using QP and IBSP with information regarding the spectrum of ECG abnormalities and cardiac AE. A systematic literature review by Hawkins et al. [19] of 111 patients, in which 47 had ECG abnormalities, found only sinus tachycardia in 16, ST segment elevation in eight, non-specific T wave changes in seven and other ischaemic changes in six patients. However, the review did not discuss these observations in relation to TPE. The study of Hughes et al. [20] focused on baseline troponin T levels and described baseline ECG abnormalities in 19 of 41 patients. Five patients had only sinus tachycardia and 13 had T wave abnormalities with a spectrum similar to the current study. A later study by Benhamou et al. focused on baseline troponin-I levels and reported a lower frequency of ECG abnormalities (12.5%) consisting primarily of negative T waves (13 patients) and three patients with ST elevation. The recent retrospective study of Toussaint-Hacquard et al. [28] compared two types of plasma for TPE of TTP, but did not report cardiac findings.

With increased awareness of cardiac involvement by TTP, the current study provides additional information about the frequency and types of ECG abnormalities at baseline, during treatment and treatment emergent cardiac AEs compared to the earlier study with IBSP [25]. The studies by Hughes et al. and Benhamou et al. suggest that baseline cardiac troponin is important for early recognition of patients at risk for cardiac involvement.
detection of severe cardiac disease to guide intensity of TPE or use of adjuvant immune therapy [20, 23]. While baseline troponin values may be predictive of disease severity and outcomes, monitoring of ECG abnormalities indicates a substantial frequency of abnormalities and provides additional information to identify cardiac abnormalities that may require treatment intervention other than TPE intensification or adjuvant immune therapy. The observations from our study support ECG monitoring periodically during treatment of TTP to identify new treatment emergent cardiac events that may not be detected by isolated troponin assays.

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Conflict of interest

J-S.L., C.E. and L.C. have a conflict of interest due to employment by Cerus and beneficial ownership of Cerus stock and/or stock options. Raoul Herbrecht and Mario Ojeda-Uribe received unrestricted research grants in support of this study. Emilie Remy received compensation from Association ARMESA for conduct of this study. Jean Pierre Cazenave and Raoul Herbrecht have received speaker honoraria for scientific presentations. All other authors have no conflict of interest.

Author Contributions

Raoul Herbrecht collaborated in study design, identified patients for inclusion in the study, reviewed medical records, directed the care of the patients at Hopitaux Universitaires de Strasbourg, edited, and reviewed the manuscript.

Mario Ojeda-Uribe collaborated in study design, identified patients for inclusion in the study, reviewed medical records, directed the care of the patients at Hospital Emile Muller, edited and reviewed the manuscript.

Daniel Kientz supervised the production and characterization of the plasma used for treatment of patients. He provided data on the volumes of plasma transfused and times of treatment. He reviewed the manuscript.

Cécile Fohrer, reviewed medical records, directed the care of the patients, and reviewed the manuscript.

Alain Bohbot directed the plasmapheresis at the Hopitaux Universitaires Strasbourg, directed care of the patients, and provided data for the apheresis procedures. He reviewed the manuscript.

Olivier Hinschberger directed the plasmapheresis at the Hospital Emile Muller, Mulhouse, directed care of the patients, and provided data for the apheresis procedures. He reviewed the manuscript.

Kun-Lun Liu reviewed medical records, directed the care of the patients, and reviewed the manuscript.

Emile Remy performed electronic data extraction and review of medical records.

Christine Ernst reviewed medical records and monitored extracted data against primary care medical records.

Jin Sying Lin supervised design of the database, wrote the statistical analysis plan, and performed the statistical analyses.

Laurence Corash designed the study, supervised the processes required for data extraction, reviewed the statistical analysis, and drafted the manuscript.

Jean Pierre Cazenave collaborated in study design and methods for data extraction and hemovigilance, supervised the collection and the production of plasma at the EFS Alsace during the entire study period.

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