Methylene blue-photoinactivated plasma vs quarantine fresh frozen plasma in thrombotic thrombocytopenic purpura: a multicentric, prospective cohort study

Julio del Río-Garma, ¹ Alberto Alvarez-Larrán, ² Clara Martínez, ³ Josep Muncunill, ⁴ Dolors Castellà, ⁵ Javier de la Rubia, ⁶ Concepción Zamora, ⁷ Mercedes Corral, ⁸ Aurora Viejo, ⁹ Francisco Peña, ¹⁰ Pilar Rodríguez-Vicente, ¹¹ Enric Contreras, ¹² Cristina Arbona, ¹³ Consuelo Ramírez, ¹⁴ José A. García-Erce, ¹⁵ Adrián Alegre, ¹⁶ José Mateo and Arturo Pereira ¹⁷

¹Service of Haematology, Complexo Hospitalario, Ourense, ²Service of Haematology, Hospital del Mar, Barcelona, ³Unit of Haemostasis & Thrombosis, Hospital de la Santa Creu i Sant Pau, Barcelona, ⁴Service of Haematology, Hospital Son Dureta, Palma de Mallorca, ⁵Banc de Sang i Teixits, Hospital Vall d’Hebron, Barcelona, ⁶Service of Haematology, Hospital La Fe, Valencia, ⁷Service of Haemotherapy, Hospital Ramón y Cajal, Madrid, ⁸Service of Haematology, Hospital Clínic, Salamanca, ⁹Service of Haematology, Hospital La Paz, Madrid, ¹⁰Service of Haematology, Hospital de Meixoeiro, Vigo, ¹¹Service of Haematology, Hospital Central de Asturias, Oviedo, ¹²Banc de Sang i Teixits, Hospital Juan XXIII, Tarragona, ¹³Service of Haematology, Hospital Clínico, Valencia, ¹⁴Service of Haematology, Hospital Juan Canalejo, A Coruña, ¹⁵Service of Haematology, Hospital Miguel Servet, Zaragoza, ¹⁶Service of Haematology, Hospital la Princesa, Madrid, and ¹⁷Service of Haemotherapy & Haemostasis, Hospital Clinic, Barcelona, Spain

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Correspondence: Dr Arturo Pereira, Service of Haemotherapy and Haemostasis, Hospital Clinic, Villarroel 170, 08036 Barcelona, Spain.
E-mail: apereira@clinic.ub.es

*Julio del Río-Garma and Alberto Alvarez-Larrán contributed equally to this article.

Summary

Plasma exchange (PE) with plasma infusion is the treatment of choice for thrombotic thrombocytopenic purpura (TTP) but doubts remain as to whether all kinds of plasma are equally effective. A multicentric cohort study was conducted to compare methylene blue-photoinactivated plasma (MBPIP) with quarantine fresh frozen plasma (qFFP) in the treatment of TTP. One hundred and two episodes of idiopathic TTP were included; MBPIP was used in 63 and qFFP in 39. The treatment schedule consisted of daily PE and corticosteroids, and the main end-point was remission status on day 8. Patients treated with MBPIP required more PEs (median: 11 vs. 5, P = 0.002) and a larger volume of plasma (median: 485 ml/kg vs. 216 ml/kg, P = 0.007) to achieve a remission, and presented more recrudescences while on PE therapy (29 of 63 vs. 8 of 39, P = 0.02) than those receiving qFFP. After adjustment for possible confounding factors, the use of MBPIP was associated with a lower likelihood of remission on day 8 [Odds ratio (OR): 0.17; 95% confidence interval (CI): 0.06–0.47] and a higher risk of recrudescence while on treatment (OR: 4.2; 95% CI: 1.6–10.8). In conclusion, MBPIP is less effective than qFFP in the treatment of TTP.

Keywords: methylene blue-photoinactivated plasma, plasma exchange, thrombotic thrombocytopenic purpura, ADAMTS13.
Plasma exchange (PE) with massive plasma infusion is the treatment of choice for thrombotic thrombocytopenic purpura (TTP) because it produces disease remission in more than 80% of patients (Rock et al., 1991, 2000). The high remission rate and the subsequent decrease in mortality observed with PE is presumably due to replacement of the ADAMTS13 von Willebrand factor protease, which is defective in many patients, and/or the removal of inhibitory autoantibodies (Bianchi et al., 2002). However, massive plasma infusion has the drawback of exposing patients to a great number of plasma donors, which increases the risk of transfusion-transmitted infections despite the improved safety associated with the current methods of blood donor screening and testing.

Several strategies aimed at further reducing the risk of viral infection by plasma transfusion have been implemented over the past decade. One of them is to quarantine the donated FFP unit (qFFP) for a period longer than the window-period for human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) until the donor is confirmed to be seronegative for these transfusion-transmitted viruses. Other approaches include chemical inactivation of viruses with solvent-detergent (S/D) (Hellstern, 2004; Solheim & Seghatchian, 2006), methylene blue and light (Lambrecht et al., 1991), or psoralens and ultraviolet light (Wollowitz, 2001). All these methods are highly effective against blood-borne infections but chemical manipulation of plasma may result in the decreased concentration or functional impairment of plasmatic proteins, which reduces the therapeutic efficacy of transfused plasma (Haubelt et al., 2002; Murphy et al., 2003; Williamson et al., 2003; Singh et al., 2006). On the contrary, qFFP, which is not submitted to any chemical treatment, retains the protein contents and therapeutic efficacy of FFP (McCarthy et al., 2000).

In the setting of TTP, the published experience with chemical-inactivated plasma is limited to one study involving 16 patients who were exchanged with S/D plasma (Horowitz & Pehta, 1998), one prospective, randomised study in which 17 patients received plasma inactivated with amotosalen and ultraviolet light (Mintz et al., 2006), and two retrospective studies accounting for a total of 31 patients treated with methylene blue-photoinactivated plasma (MBPIP) (de la Rubia et al., 2001; Alvarez-Larrán et al., 2004). It is worth noting that these two latter studies, conducted in Spain, showed that TTP patients receiving MBPIP required larger volumes of plasma and more PE sessions to achieve a remission, and experienced more recrudescences while on PE treatment than historical controls treated with FFP (de la Rubia et al., 2001; Alvarez-Larrán et al., 2004).

We undertook the present study in order to confirm the above preliminary results in a larger, prospectively followed cohort of TTP patients exchanged with either qFFP or MBPIP. The results from this study may aid decisions regarding the introduction of virus-inactivated plasma.

**Design and methods**

**Patients and study design**

All patients with idiopathic TTP, consecutively seen at 31 Hospitals in Spain and treated by PE according to a homogeneous protocol, were included in a prospective cohort study. Subjects were recruited over a 3-year period, between October 2004 and October 2007. Informed consent for the scientific use of the patients’ clinico-haematological data and biological samples was obtained at diagnosis according to each centre’s ethical committee. The diagnosis of idiopathic TTP was based on the presence of haemolytic anaemia with schistocytes in the blood smear and consumptive thrombocytopenia in the absence of renal failure (creatinine >221 μmol/l), a positive antiglobulin test, disseminated intravascular coagulation, malignant hypertension, neoplasm, stem cell transplantation, concurrent infection or positive HIV serology. Disease severity at presentation was evaluated using the score described by the Canadian Apheresis Group (Wyllie et al., 2006). Neurological involvement at diagnosis was assessed according to Rose and Eldor (1987). The date of the patient’s first medical attendance was used as a proxy of TTP debut. Blood samples taken before PE on day 1 were evaluated in a central laboratory (Hospital de Sant Pau, Barcelona, Spain) for ADAMTS13 activity and inhibitory autoantibodies by the collagen-binding affinity method, as described previously (Gerritsen et al., 1999).

The treatment schedule consisted of daily PE with infusion of at least 30 ml of plasma per kg of body weight (goal: 40 ml/kg) and prednisone (1.5 mg/kg/d) until the platelet count was above 150 × 10^9/l for three consecutive days, at which time the frequency of PE was reduced to one every 2 d for 1–2 weeks before being stopped. All the patients were treated according to this schedule for the first 7 d. Thereafter, if the patient had not attained a response, the attending physicians could use any complementary treatment at their discretion. The cut-off for response evaluation was set at the 8th day for two reasons. First, previous experiences by our group (Pereira et al., 1995; Alvarez-Larrán et al., 2004) and others (Henon, 1991) had shown that, in many patients who eventually achieve a sustained remission with PE alone, the response started in the first week of treatment. Second, many participating haematologists were reluctant to postpone complementary treatments (e.g. vincristine) in patients who had not responded by the 8th day.

At each hospital, the type of plasma used for PE (MBPIP or qFFP) was provided by the regional blood bank according to the local policy for viral safety of transfused plasma. MBPIP was produced by either the ‘in house’ Macopharma method or the Springe method (Pereira, 2007). Quarantine FFP was produced at the regional blood bank according to the local policy for viral safety of transfused plasma. MBPIP was produced by either the ‘in house’ Macopharma method or the Springe method (Pereira, 2007). Quarantine FFP was produced at the regional blood bank according to the local policy for viral safety of transfused plasma. MBPIP was produced by either the ‘in house’ Macopharma method or the Springe method (Pereira, 2007). Quarantine FFP was produced at the regional blood bank according to the local policy for viral safety of transfused plasma. MBPIP was produced by either the ‘in house’ Macopharma method or the Springe method (Pereira, 2007). Quarantine FFP was produced at the regional blood bank according to the local policy for viral safety of transfused plasma. MBPIP was produced by either the ‘in house’ Macopharma method or the Springe method (Pereira, 2007). Quarantine FFP was produced at the regional blood bank according to the local policy for viral safety of transfused plasma. MBPIP was produced by either the ‘in house’ Macopharma method or the Springe method (Pereira, 2007).
subsequently sent to the study co-ordinators who reviewed the diagnoses and procedures for compliance with the established protocol and the admission criteria.

Response to treatment was defined as a platelet count of $>150 \times 10^9/l$ for more than three consecutive days, normal serum lactate dehydrogenase (LDH) activity and absence of any TTP-related symptom or sign. Recrudescence was defined as a decrease in platelet count below $50 \times 10^9/l$ (or below 50% of the highest platelet count previously achieved) while on PE treatment or after a response had been achieved. Responses that eventually lasted for longer than 30 d after withdrawal of PE therapy were considered as remissions. Relapse was defined as disease reappearance after a remission had been achieved.

The primary end-point of the study was remission status on day 8 of treatment. Secondary end-points included recrudescence while on PE therapy and the number of PE sessions and total volume of plasma infused to remission. Events occurring after remission (i.e. frequency of relapse) were not analysed because post-remission management varied slightly across the participating hospitals (number of additional PE sessions and whether or not splenectomy or rituximab were used to prevent relapses).

In order to account for the possibility that treatment outcomes were influenced by the experience of the clinical team at each participating hospital, we distinguished between experienced and less experienced teams according to whether they reported more than one case per year (11 teams) or less (20 teams) over the 3-year period under study.

**Results**

**Patient recruitment**

A total of 117 TTP episodes were evaluated for inclusion in this study. Ten of the 117 episodes were excluded due to protocol violations (a mixture of MBPIP and qFFP was used in the first 7 d of treatment or the volume of infused plasma was below 30 ml/kg/d). Five additional patients were excluded because the diagnosis of idiopathic TTP was doubtful due to concomitant renal failure (1 case), neoplasm (2), amoebic infection (1) or lack of sufficient data (1). In the remaining 102 TTP episodes that were finally analysed, MBPIP was used for fluid replacement in 63 (62%) and qFFP in 39 (38%). These 102 episodes corresponded to 90 patients because 12 patients each presented with two episodes.

**Patients characteristics**

Table I summarises the main clinical and laboratory data at presentation of the 102 TTP episodes according to the type of plasma used for exchange. Six out of the 63 cases treated with MBPIP were switched to qFFP owing to lack of response after a median of 13 (range: 8–19) PE sessions whereas two out of the 39 cases treated with qFFP were switched to MBPIP due to exhaustion of plasma stocks after 11 and 14 PE sessions respectively. They were analysed in the treatment group corresponding to the type of plasma used in the first instance. Seventy of the 102 episodes that were analysed were initial episodes of newly diagnosed TTP and 32 were relapses or non-initial episodes of a previously known TTP. The latter episodes were more frequent in the MBPIP group than in the qFFP group; 24 of the 32 non-initial episodes (75%) were treated with MBPIP and eight (25%) with qFFP ($P = 0.06$). These non-initial episodes corresponded to a second TTP episode in 15 cases, a third episode in seven cases, a fourth episode in four cases, and a fifth episode in six cases.

As some patients suffered more than one episode, the logistic model was clustered at the patient level. The adjusted odds ratio for each binary variable was obtained by exponentiating the $\beta$ coefficient of that variable. All independent variables were forced to stay in the logistic model. Calculations were carried out using the Statistical Package for the Social Sciences (SPSS) software, version 12.0 (SPSS Inc, Chicago, IL, USA). $P$-values $<0.05$ were considered significant.
### Table I. Clinical and laboratory features at presentation in 102 episodes of idiopathic thrombotic thrombocytopenic purpura according to the type of plasma employed for plasma exchange.

<table>
<thead>
<tr>
<th>Variable</th>
<th>MBPIP (N = 63)</th>
<th>qFFP (N = 39)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>40 (18–79)</td>
<td>39 (19–73)</td>
<td>0.9</td>
</tr>
<tr>
<td>Female gender</td>
<td>43 (68)</td>
<td>31 (79)</td>
<td>0.2</td>
</tr>
<tr>
<td>CNS involvement, n (%)</td>
<td>27 (43)</td>
<td>25 (64)</td>
<td>0.04</td>
</tr>
<tr>
<td>Fever, n (%)</td>
<td>7 (11)</td>
<td>11 (28)</td>
<td>0.03</td>
</tr>
<tr>
<td>Hb, g/l</td>
<td>97 (44–162)</td>
<td>87 (58–159)</td>
<td>0.3</td>
</tr>
<tr>
<td>Platelet count, x10⁹/l</td>
<td>15 (4–129)</td>
<td>12 (2–79)</td>
<td>0.4</td>
</tr>
<tr>
<td>Serum creatinine, μmol/l</td>
<td>79.6 (26.5–221)</td>
<td>88.4 (44.2–212.2)</td>
<td>0.3</td>
</tr>
<tr>
<td>Serum LDH* ≥430 U/l</td>
<td>3.6 (1.1–15.4)</td>
<td>4.0 (1.1–13.4)</td>
<td>0.5</td>
</tr>
<tr>
<td>Severity score†</td>
<td>2 (0–6)</td>
<td>2 (0–6)</td>
<td>0.2</td>
</tr>
<tr>
<td>ADAMTS13 &lt;5%</td>
<td>22/27</td>
<td>19/28</td>
<td>0.2</td>
</tr>
<tr>
<td>ADAMTS13 inhibitor</td>
<td>25/27</td>
<td>22/28</td>
<td>0.2</td>
</tr>
<tr>
<td>Days until treatment</td>
<td>1 (0–34)</td>
<td>1 (0–9)</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Continuous variables expressed as median (range).
MBPIP, methylene blue-photoinactivated plasma; qFFP, quarantine fresh frozen plasma; CNS, central nervous system.
*LDH observed in the patient/upper limit of normality of the corresponding laboratory.
†According to the score by the Canadian Apheresis Group.

### Table II. Intensity of initial treatment and response to plasma exchange therapy in 102 episodes of idiopathic thrombotic thrombocytopenic purpura according to the type of plasma used for fluid replacement.

<table>
<thead>
<tr>
<th>Variable</th>
<th>MBPIP (N = 63)</th>
<th>qFFP (N = 39)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma infused in the first 3 d, ml/kg</td>
<td>132 (91–239)</td>
<td>140 (95–198)</td>
<td>0.6</td>
</tr>
<tr>
<td>Plasma infused in the first 7 d, ml/kg</td>
<td>300 (213–507)</td>
<td>309 (217–415)</td>
<td>0.7</td>
</tr>
<tr>
<td>Remission on day 8, n (%)</td>
<td>24 (38)</td>
<td>27 (69)</td>
<td>0.002</td>
</tr>
<tr>
<td>Recrudescence, n (%)</td>
<td>29 (46)</td>
<td>8 (20)</td>
<td>0.02</td>
</tr>
<tr>
<td>Mortality, n (%)</td>
<td>2 (3)</td>
<td>2 (5)</td>
<td>0.6</td>
</tr>
<tr>
<td>No. of PE to remission</td>
<td>11 (2–52)</td>
<td>5 (2–25)</td>
<td>0.002</td>
</tr>
<tr>
<td>Plasma infused to remission, ml/kg</td>
<td>485 (93–3108)</td>
<td>216 (75–1224)</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Continuous variables expressed as median (range).
MBPIP, methylene blue-photoinactivated plasma; qFFP, quarantine fresh frozen plasma.

### Treatment intensity and complementary therapy

The intensity of initial treatment with PE, as measured by the total volume of plasma infused in the first 3 and 7 d of treatment, was comparable between the two groups of patients (Table II). After the 8th day of treatment and because of lack of response to PE, vincristine was added to the therapeutic schedule in 20 patients (12 and eight patients in the MBPIP and qFFP groups, respectively) and rituximab in 10 patients (eight and two patients in the MBPIP and qFFP groups respectively). Four additional patients received rituximab as a consolidation therapy after remission (three and one patients in the MBPIP and qFFP group respectively). Four patients underwent splenectomy after 10, 13, 26, and 34 PE sessions respectively (all in the MBPIP group).

### Treatment outcomes

A remission was eventually achieved in 61 (97%) episodes treated with MBPIP and 37 (95%) episodes treated with qFFP. Two out of 63 patients (3%) in the MBPIP group and two out of 39 (5%) in the qFFP group did not attain a remission and died from progressive TTP after 8, 11, 20 and 22 PE sessions respectively.

As it can be seen in Table II, the primary end point (disease remission on day 8 of treatment) was significantly more frequently achieved in the qFFP group than in the MBPIP group (69% vs. 38%, P = 0.002). Twenty-nine patients (46%) in the MBPIP group experienced one or more recrudescences while on PE therapy, whereas only eight patients (20%) in the qFFP group showed this pattern of response (P = 0.02).

Primary end point achievement was comparable between experienced and less experienced teams (27 out of 34 cases and 20 out of 21, respectively; P = 0.68).

In the 98 patients who eventually achieved a remission, this was obtained after a median of 11 (range: 2–52) PE sessions in the group treated with MBPIP and 5 (range: 2–25) sessions in those treated with qFFP (P = 0.002). The volume of plasma infused to remission was significantly larger in the MBPIP group (median: 485 ml/kg vs. 216 ml/kg, P = 0.007).

Table III shows the main treatment outcomes according to the type of plasma after adjustment for the effect of potential confounder variables. As can be seen, patients treated with MBPIP were less likely to have attained remission on the 8th
day of treatment [adjusted odds ratio (OR) = 0·17; 95% confidence interval (CI): 0·06–0·47] and more prone to TTP recrudescence while on PE therapy (adjusted OR = 4·2; 95% CI: 1·6–10·1). Non-initial episodes were more likely to have remitted on day 8 of treatment than de novo episodes (adjusted OR = 7·8; 95% CI: 2·0–30·2).

### Discussion

The present study compared MBPIP with qFFP as replacement fluids in patients with TTP treated by PE. The effect of the type of plasma on the response to PE was assessed on the 8th day, after the patients were treated according to a homogenous protocol over the preceding 7 d. After statistical adjustment for possible confounding variables, patients treated with MBPIP were sixfold less likely to attain a remission by day 8 of treatment and had a fourfold greater risk of TTP recrudescence while on PE therapy. The results from this study, which is one of the largest ever conducted on the efficacy of virus-inactivated plasma in TTP, confirm the findings from two previous, retrospective and substantially smaller studies (de la Rubia et al, 2001; Alvarez-Larrán et al, 2004).

The MBPIP arm included a higher proportion of non-initial episodes, a finding that deserves some comment. First, in order to prevent a confounding effect on the study primary endpoint, the type of episode (initial versus non-initial) was included as a covariate in the logistic model, and non-initial episodes were found to be independently associated with a higher remission rate by the 8th treatment day. Therefore, the better response of non-initial episodes to PE may have contributed to improve the overall remission rate observed in the MBPIP group. Second, since the frequency of non-initial episodes would be expected to be similar in both groups; the fact that most such episodes (77%) were seen in centres using MBPIP suggests a higher incidence of TTP relapse associated with this kind of plasma, an issue that warrants further exploration.

Chemical inactivation of plasma with methylene blue and light leads to free-oxygen radical formation, in which leads to the destruction of lipid-enveloped viruses, such as HIV, HCV and HBV. The reason why MBPIP is less effective than FFP in TTP remains unclear because ADAMTS13 activity seems to be conserved in MBPIP (Furlan et al, 1998; Cardigan et al, 2002; Yarranton et al, 2004). The reduced activity of several coagulation factors in MBPIP and the impaired fibrin polymerisation due to photo-oxidation of some histidin residues in the fibrinogen molecule (Inada et al, 1978; Zeiler et al, 1994; Henschen-Edman, 1997) makes it plausible for similar alterations to operate in TTP. Since the functional activity of ADAMTS13 is highly dependent on the intravascular flow conditions (Shim et al, 2008), subtle changes in ADAMTS13 as a result of photo-oxidative damage might impair the in vivo function or half-life while passing undetected by the current laboratory assays. In this regard, the impressive incidence of TTP recrudescence while on PE treatment observed in the MBPIP group strongly suggest that some kind of exhaustion of the therapeutic factor supplied by the infused plasma takes place with MBPIP but not with FFP. Alternatively, since not all patients with idiopathic TTP have a severe ADAMTS13 deficiency, the photo-oxidative damage of other, hitherto-unidentified plasmatic proteins involved in the pathogenesis of TTP can be entertained (Veyradier et al, 2001; Vesely et al, 2003; Coppo et al, 2004).

In Spain, the Health Authority of each of the 17 Autonomous Regions can decide between qFFP and MBPIP as the preferred method for reducing the risk of virus transmission by plasma transfusion. Hospitals within each Autonomous Region are forbidden from arranging the supply of blood products with blood banks outside their region, so that clinical teams have a very limited influence on the kind of plasma they use. At the national level, MBPIP accounts for 63% of transfused plasma and qFFP for 37% (Pereira, 2007), a distribution that was mirrored in our series, where 63 out of 102 (62%) TTP patients were treated with MBPIP.

Although the ideal study design for comparing MBPIP to qFFP would be a randomised, controlled trial, there were logistic and ethical reasons precluding us from undertaking such a study. First, it could be reasonably argued that randomisation would violate the equipoise principle (Freedman, 1987) because previous reports have suggested that MBPIP could be inferior to FFP in the treatment of TTP (de la Rubia et al, 2001; Alvarez-Larrán et al, 2004). Second, the regional-based policy of plasma safety prevailing in Spain would pose an insurmountable logistic problem for a
randomised trial, since not enough qFFP would be available in areas where only MBPIP is supplied by the regional blood bank. Despite this methodological drawback, the distribution of patients between both treatment groups in our study, which exactly mirrors the usage of each kind of plasma at the national level, suggests that no strong bias other than the geographical location of the participating hospital has influenced the type of plasma used.

The introduction of MBPIP to further improve the safety of transfused plasma has had a paradoxical effect in TTP patients. These patients can obtain a large potential benefit from reducing the risk of blood-borne infections since they are exposed to a large number of plasma donors. However, since more PE sessions and a larger amount of MBPIP (often complemented with expensive additional treatments) are necessary to achieve TTP remission, the increased exposure to the non-infectious risks of plasma transfusion and the longer and costlier hospital stay probably offset any benefit derived from virus inactivated plasma.

In conclusion, our results show that MBPIP is associated with a worse outcome in TTP patients as it requires more PE sessions, greater plasma usage, and entails a higher patient exposure to the non-infectious risks of plasma transfusion.

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Author contribution
J.D.R-G, A.A-L and A.P. designed the study, managed the data, performed the statistical analysis and drafted the article; C.M., J.M., J.D.R. and C.Z. designed the study, managed the clinical data, revised and approved the final version of the article; D.C., M.C., A.V., F.P., P.R.V., E.C., C.A., C.R., J.A.G-E. and A.A. managed the clinical data, revised and approved the final version of the article. J.M. performed the ADAMTS13 assays.

Conflict-of-interest disclosure
The authors declare no competing financial interests.

Study group members
The following investigators participated in the Spanish Apheresis Study Group:
M. Pujol, Hospital Vall d’Hebron, Barcelona; F. Moscardó, Hospital La Fe, Valencia; J.R. González-Porrás, Hospital Clínico Universitario, Salamanca; J.M. García-Gala, Hospital Central de Asturias, Oviedo; L. Enríquez, Hospital do Meixoeiro, Vigo; R. González, Hospital Juan Canalejo, A Coruña; M.A. Canales, Hospital La Paz, Madrid; M. Hernández-Jodra, Hospital Ramón y Cajal, Madrid; V. Callao, Hospital Joan XXIII, Tarragona; A. Galmés, Hospital Son Dureta, Palma de Mallorca; A. García-Noblejas, Hospital de la Princesa, Madrid; E. Gómez-Arteta, Hospital San Pedro de Alcántara, Cáceres; E. Teruel, Hospital Clínico Universitario, Valencia; A. Vidaller and J. Muñoz, Hospital de Bellvitge, Hospitallet de Llobregat; A. INSUNZA and I. ROMÓN, Hospital Marqués de Valdecilla, Santander; M.J. Muñoz, Hospital de Móstoles, Madrid; C. Paniagua, Fundación Jiménez Díaz, Madrid; D. Gutiérrez and A. Rodríguez, Hospital Virgen de la Macarena, Sevilla; J.R. Grifols and A. Serrano, Hospital Germans Trias i Pujol, Badalona; A. Campos and M. Villamayor, Hospital Clínico Universitario, Santiago de Compostela; A. de Andréis, Hospital Xeral Calde, Lugo; J.M. Jiménez, Hospital Virgen del Rocío, Sevilla; J. Plaza, Hospital Xeral-Cíes, Vigo; A. García-Coca, Hospital Clínico Universitario, Valladolid; M. Casanueva, Hospital 12 de Octubre, Madrid; M.J. Uriz and M.L. Antelo, Hospital de Navarra, Pamplona; E. Carreter, Hospital General, Lanzarote; A. Peña and L. Llorente, Hospital Clínico San Carlos, Madrid; A. Gómez-Pineda and J. Anguita, Hospital Gregorio Marañón, Madrid; R. López and J.A. Muñoz, Hospital Virgen del Mar, Cádiz.

References
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