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# Amotosalen-Inactivated Fresh Frozen Plasma Is Comparable to Solvent-Detergent Inactivated Plasma to Treat Thrombotic Thrombocytopenic Purpura

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## Conflicts of interest

-The French Reference Center for Thrombotic Microangiopathies ([www.cnr-mat.fr](http://www.cnr-mat.fr)) is in part supported by the French Ministry of Health (Plan National Maladies Rares, Direction Générale de l'Offre de Soins) and the Programme Hospitalier de Recherche Clinique (PHRC 2012 P120118, Clinicaltrials.gov identifier NCT02134171).

-OG has received invitations from Cerus-Europe, Terumo-BCT-Europe, MacoPharma-France and Octapharma-France to attend key opinion leader meetings; he declares no further link of interest.

-PC is member of the Advisory Boards of Ablynx for the development of caplacizumab, Alexion for the development of eculizumab and Shire for the development of Bax930. He has received funds from Ablynx, Alexion, Octapharma and Roche.

-AV is member of the Advisory Boards of Ablynx for the development of caplacizumab.

-MOU has had a clinical research funded by Cerus.

-RH has received honoraria from Cerus.

-LC, JMP, KL, and JSL are employees of Cerus Corporation US/Europe and beneficial holders of Cerus stock.

**Key words:** Thrombotic thrombocytopenic purpura, ADAMTS13, plasma, rituximab, plasma exchange

**Running head:** Amotosalen- versus solvent-detergent-inactivated plasma in TTP

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## **Abstract**

**Background:** Therapeutic Plasma Exchange (TPE) is the primary therapy of immune-mediated Thrombotic Thrombocytopenic Purpura (iTTP). Efficacy and safety data for TPE of iTTP have been assessed with Quarantine and Solvent-Detergent inactivated (SD) plasma. Here, amotosalen-UVA pathogen inactivated (AI) plasma, also in routine use, was evaluated in iTTP.

**Methods:** We conducted a retrospective review of iTTP cases prospectively reported to the French national registry (2010-2013). Cases reviewed underwent TPE with  $\geq 70\%$  of either AI or SD plasma. The primary endpoint was time to platelet count recovery; secondary endpoints were related to follow-up (sustained remission, relapses, flare-ups and refractoriness).

**Results:** 30 Test patients were identified in the AI group which could be timely matched to 40 Control patients in the SD group. The groups were fairly comparable for clinical presentation. Major findings were: (i) iTTP patients were exposed to lower plasma volumes in the AI group than in the SD group; (ii) Recovery rates were comparable between the groups. Median time to platelet count recovery ( $>150 \times 10^9/L$ ) trended to be shorter in the AI group though non significantly. Tolerance of AI vs SD plasma was of comparable frequency and severity in either group.

**Conclusion:** TPE with Amotosalen-inactivated plasma demonstrated therapeutic efficacy and tolerability for iTTP patients. In view of the retrospective design, confirmation of these results is required in larger prospective studies.

## Introduction

Immune mediated Thrombotic thrombocytopenic purpura (iTTP) almost invariably results in death from organ failure in the absence of effective treatment; it is specifically mediated by autoantibodies to ADAMTS13, the metalloproteinase that cleaves the large multimers of von Willebrand factor [1,2], leading to a severe deficiency in this essential factor [3]. The first-line therapy for acute iTTP still relies on emergent daily therapeutic plasma exchange (TPE) [4] replacing ADAMTS13 and removing anti-ADAMTS13 autoantibodies and proaggregant substances [5,6]. In most cases, TPE is complemented by steroids [7]. Although additional and promising bioactive compounds have been recently added to the therapeutic arsenal for iTTP [8-11], TPE remains indispensable. ADAMTS13 is thus provided in sufficient amounts by fresh plasma. In France, all forms of plasma for direct therapeutic use are fresh frozen plasma (FFP) leukoreduced, frozen at -30°C, and kept at -25°C for less than a year; FFP is thawed by a validated procedure immediately prior to use (and within 6 h) [12].

FFP carries moderate risk of intolerance for patients exposed to large volumes of plasma [13-19]. The risk of virus transmission by transfusion has been largely reduced by multiple additive measures [20]; however, as emergent virus infection may still occur [21], solutions such as pathogen-inactivation have been considered a major step forward to either limit or eradicate those risks [22,23].

The most studied plasma categories used in iTTP series are: (i) Solvent-Detergent-(SD) FFP, produced by industrial pooling of plasma sources from pools of 100 to 1.500 individual plasma collections or more, depending on the manufacturer, with pathogen inactivation by solvent and detergent treatment; and (ii) Quarantine- (Q) FFP, that has not been modified apart from freezing, thawing and retesting for a limited number of pathogens [19,24]. More recently, new forms of FFP have been made available, including individual or mini-pools of therapeutic plasma pathogen inactivated by Amotosalen-UVA [25]. [Uses of different plasma categories in France has varied over time as recently discussed in \[26\].](#)

We thus aimed to evaluate the efficacy and tolerance of Amotosalen-pathogen inactivated FFP in iTTP patients undergoing TPE, in comparison with SD-plasma which has

been used previously as a standard of care in France, and in many other countries. Due to the low frequency of iTTP, we designed a retrospective study using data acquired from routine practice in multiple centers prospectively entered into a national reference center database (French National Network for TMAs/French National Reference Center Registry: CNR-MAT, Paris: <http://www.cnr-mat.fr>).

## **Patients and Methods**

### *Patients, study design and objectives*

This non-randomized, retrospective, multi-center, cohort study compared the clinical outcomes in adult patients supported with AI- or SD-FFP for TPE in iTTP cases prospectively reported to the CNR-MAT over a period of 4 years (2010 to 2013); subsequent cases were disregarded as TPE were principally processed with one type of plasma only (AI-plasma up to 2017, or Quarantine plasma or imported SD plasma after that period). The considered period was the only one when either type of plasma (AI or SD) was used to treat [similar] patients, allowing comparisons as adjunctive therapies were also similar [7]. Patient cohorts were identified in the national reference center database for TMA study centers within the collaborative network.

Inclusion criteria were those of the French Register [7]: a diagnosis of iTTP and TPE treatment with  $\geq 70\%$  of either AI- or SD-FFP, both licensed plasma products, during this period. All patients had a severe acquired ADAMTS13 deficiency (activity  $< 10\%$ ; anti-ADAMTS13 antibodies present or ADAMTS13 recovery after the acute episode). Patients with multifactorial causes of thrombocytopenia were excluded as previously defined [27].

The study identified patients treated by TPE with predominantly ( $\geq 70\%$  of the total volume used) of AI-FFP (Test) or SD-FFP (Control). As FFP was issued by the blood bank based upon availability, a bias of selection was not relevant. All FFP components were adjusted to 200-210 mL each by the manufacturer (regional EFS: AI-plasma; Aquitaine-EFS: SD-plasma). The primary endpoint was the time to sustained remission, measured by platelet count recovery ( $> 150 \times 10^9/L$  for 2 days), defined as the time elapsed from the first

session to a complete response [4,28]. We also assessed secondary endpoints: sustained remission proportions and survival, exacerbations and refractoriness, plasma volumes needed to achieve remission, relapse rate, and adverse reactions.

### *Plasma preparations*

Both types of FFP were produced and provided by the French Blood Establishment (Établissement Français du Sang; EFS). (i) AI plasma consisted of individual apheresis plasma collections (using different apheresis devices as previously reported [29]); plasma was leukodepleted to a level below  $10^4$  leukocytes/L, and then subjected to the inactivation process as prescribed by the supplier (Cerus, Amersfoort, NL). AI-FFP units were processed by regional blood establishments into ~200-210 mL components and frozen ( $-30^{\circ}\text{C}$ ) within 8 h after collection (before 2013) or within 18 h (after 2013). AI plasma was stored for up to one year at  $\leq -25^{\circ}\text{C}$ . (ii) SD-plasma was obtained from apheresis collections leukodepleted to below  $10^4$  residual leukocytes/L, frozen to  $-30^{\circ}\text{C}$  before 6 h following collection, and subsequently manufactured in one regional blood establishment with the solvent detergent process by pooling 100 units with processing into individual plasma components (200 mL). SD-FFP was stored for up to one year at  $\leq -25^{\circ}\text{C}$ . (iii) Quality control for both types of plasma was performed by the EFS according to specifications of the notified body ANSM (Agence Nationale de Sécurité du Médicament et des Produits de Santé), the French Drug Agency. The affect of safety chemical and physical treatment on fresh plasma was evaluated by Hacquart et al. [30], showing that either Amotosalen or SD interventions did not alter ADAMTS13 activity even minimally. Further, Amotosalen treatment was shown to preserve the vWF-Ag and vWF activity for as long as 12 months [25,31]. SD-inactivated plasma was found having reduced levels of the highest molecular weight vWF multimers [6] compared to untreated or MB-treated plasma; Amotosalen has not been documented—to our knowledge—for the highest molecular weight vWF multimer distribution.

### *Therapeutic plasma exchange regimens*

The recommended treatment was in conformity with the French guidelines [7]. Briefly, patients received daily TPE with therapeutic plasma units, starting as soon as possible after the diagnosis of iTTP was established. The daily FFP exchange volume targeted

1.5 times the predicted patient plasma volume, approximately 60 mL/kg, until remission. TPE sessions were then usually tapered over 3 weeks (maintenance treatment: 3 TPEs on week one, then 2 TPEs on week 2 and 1 TPE on week 3) and finally stopped. Exacerbation or relapse led to resumption of daily TPE sessions. Patients without active infection received corticosteroid therapy (prednisone), 1 mg/kg daily for 3 weeks. For patients who met the criteria for a suboptimal response to the above-described standard treatment, 4 infusions of Rituximab were prescribed within 15 days (day 1, day 4, day 8 and day 15) [32]. Patients with an undetectable ADAMTS13 activity (< 10%) and otherwise in remission were usually treated preemptively with rituximab [33,34].

### *Definitions*

Response criteria followed the definitions provided elsewhere [7; 28,33].

Definitions for imputability and severity of adverse reactions and events were based on the International Haemovigilance Network Database ISTARE [36].

### *Statistical comparisons*

The data from the CNR-MAT database were extracted and transferred in an Excel file format to Cerus, Concord, CA for data analysis. Patients' characteristic and plasma usage data were summarized descriptively by patient cohort (AI plasma vs. SD plasma). Comparisons between the two patient cohorts (AI plasma vs. SD plasma) were performed using 2-sample t test with unequal variances for continuous variables, Fisher's exact test for binary outcome, and Cochran–Mantel–Haenszel Row Mean Scores Differ test for ordinal categorical variables. For continuous variables with skewed distributions (e.g., baseline platelet count), the Wilcoxon rank-sum test was also conducted. For time-to-event variables (e.g. time from the first AI or SD plasma transfusion to platelet count recovery), the median time was estimated by Kaplan-Meier curves, and the log-rank test (with or without adjusting for patient age at admission and baseline platelet count as covariates) was used to assess the differences between the two patient cohorts. All statistical analyses were performed using SAS® software (Version 9.4) and/or the R programming language.



## Results

### *Patient Demographics*

To avoid confounding events, of the 48 cases having benefitted PE with AI-plasma, for whom data were recorded by the Reference Center, 30 were considered for the present survey, that were treated with AI-plasma during the period when other patients (40) were treated by SD-plasma. The demographics and clinical presentation of patients, 30 in the test (AI) group compared to 40 in the control (SD), were comparable and not statistically significantly different between the groups with respect to the duration between admission and diagnosis and prognostic factors such as age, LDH level and neurological and cardiac involvement (including cardiac failure and increased cardiac troponin). The mean baseline platelet count was close in Control patients and in Test patients (13.3 vs 16.0 x 10<sup>9</sup>/L respectively) (**Table 1**).

### *Overall exposure to plasma (therapeutic plasma exchange)*

All patients received TPE: 100% of patients in the Test group (AI-FFP) were treated with AI-FFP; and 100% of patients in the Control (SD-FFP) group were treated with SD-FFP. However, 6 patients in the Test (AI-FFP) group received small amounts of SD-FFP; and 2 patients within the Control (SD-FFP) group received small amounts of AI-FFP in (<30% of the total plasma volume used). In addition, 11 patients in the SD-FFP group received Methylene Blue (MB)-FFP in small amounts (<15% of the total plasma volume used). Lastly, 15 patients within the AI-FFP group received small amounts of Q-FFP (<15% of the total plasma volume used), compared to 6 in the SD group. Volumes of off-protocol plasma types in all combinations ranged from 5% to 22.5% (mean, ≤15%; **Table 2**).

The duration between admission and first TPE was comparable between both groups (**Table 3a**). iTTP patients in the Test (AI-FFP) group were exposed to a lower number of units, than patients in the SD-FFP group to achieve sustained remission (p=0.012 from the t test). The total volume exchanged paralleled this finding: iTTP patients in the AI-FFP group received an inferior volume of plasma than the SD-FFP group (p=0.013 from the t test) (**Table 3a**).

### *Adjunctive therapies*

27 patients in the Test group (AI-FFP) received corticosteroids (90%), and 35 in the control (SD-FFP) group (90%). The mean dose was slightly higher in the AI-FFP group ( $p=0.008$  from the t test;  $0.010$  from the Wilcoxon rank-sum test); the duration of corticotherapy could not be validly compared as many data were actually missing, respectively and numbers were too low to allow valid comparison. Numbers of patients in each group received rituximab (46.7% and 67.5% for Test and Control cohorts, respectively) were non significantly different; **Table 3b**).

### *Patient outcomes*

Median time to sustained platelet count recovery (the primary efficacy endpoint) tended to be shorter in the AI-FFP group compared to the SD-FFP-group: 11.0 vs 16.0 days, respectively, though non significantly ( $p=0.099$  by log-rank test, without any covariate adjustment). Consistent results were observed with or without age group and/or baseline platelet count included in the model as covariate adjustments ( $p\leq 0.029$  for treatment effect from the Cox proportional hazards model). Survival, exacerbation, refractoriness and relapse, were comparable between both groups (**Table 4**). Causes of deaths in the control group were reported to be consequent to neurovascular stroke; in the test group, they all occurred in complex situations: one severe bleeding; two pneumopathies and sepsis; one cardiogenic shock (perhaps after neurovascular stroke); and one myocardial infarction and cardiogenic shock. [None died at the onset of the treatment in either group and they received highly variable amounts of plasma, allowing no statistical comparison at this stage.](#)

### *Adverse reactions*

Approximately one fourth of patients in each group had adverse reactions (imputability score of 2 to 3) during of after the procedure: 11 patients (36.7%) in the AI-FFP group and 15 patients (37.5%) in the SD-FFP group. A comparable number of adverse reactions that were actually attributable to plasma (imputability 2 and 3) were found in either group: 5 patients (16.7%) in the AI-FFP group and 7 patients (17.5%) in the SD-FFP group ( $p=1.000$ ) (**Table 5**). Of note, only severe cases scored 2 (immediate intervention required) or 3 (vital threat) were reported; no lethal cases attributable to either type of FFP

were recorded. Transfusion complications all comprised allergic-type reactions (rashes, urticaria, bronchospasm); according to the French procedures, patients having manifested a severe allergic reaction (score 3) clearly attributable to plasma (scores 2-3) were exchanged with another type of plasma thereafter.

## **Discussion**

Based on the primary outcome for efficacy evaluation of plasma types (time to platelet count recovery), the main findings of this study were: (i) an equivalent time to platelet count recovery and a trend to shorter recovery though non significant, (ii) a lower plasma volume for patients in the Test cohort (AI-FFP) compared to the Control cohort (SD-FFP) and (iii) otherwise comparable outcome parameters including survival, exacerbation, refractoriness, long-term outcome and relapse in the acute phase between groups. Although the study was retrospective and not designed as a non-inferiority study [38-40], the data indicate that the test plasma (AI-FFP) compares well to SD-FFP [41-43]. Two and half times more Test group patients than Control group patients received another type of plasma; in spite of these numbers, unique patients in a given group received maximum volumes of reciprocal plasma (15.8% of total exchanged plasma in the test group and 27.2% of total exchanged plasma in the control group); the vast majority of either Test or Control patients received small amounts of any other type of plasma in total. This situation was unavoidable for two reasons: the main one was due to inventory management limitations within a national blood service, but calls for caution in concluding that AI-FFP was superior to SD-FFP; the other one—as was specified—was related to the plasma type change in case an adverse reaction was reported.

Our study is confirmatory of other two studies evaluating the safety of AI-plasma in TPE for TTP: one compared AI-FFP to unmanipulated FFP in a small (17 in the test versus 18 in the control) group TTP patients, with no clinically significant differences in safety and efficacy (bearing in mind the low number of test and control patients). This study was part of the Phase III clinical development program for AI-FFP registration [44]. Another recent study

carried out by our group reported comparable efficacy between AI-FFP and Q-FFP in iTTP [45].

Of note, the frequency of refractoriness, exacerbation and relapses (**Table 4**) appears quite large; however, it seems consistent with data from others considering the treatment period; since then, regimens with preemptive Rituximab have allowed a reduction in complications; the new era of Caplacizumab will likely give a new twist in the iTTP outcome. [Death occurrences could not be further explored in this retrospective, multisite survey; they were ascribed to as the most likely cause; though they were all strokes in the test group and more diversified in the control group. Death aetiology would perhaps be of interest to better care patients and set up preventive strategies, and that particular issue would deserve specific examination in an prospective study.](#)

The tolerance of AI-FFP was excellent in all studies, including the present one, as it is consistent with the extended surveillance surveys of plasma transfusions (>100.000 components in one study [14], including AI-plasma [15] and including TPE in TMA patients [18;46]).

In conclusion, this study has validated, on a larger scale than the previous ones, the safe and effective use of AI-plasma for TPE in iTTP patients. AI-plasma is as safe as SD-plasma, which is comparable to unmanipulated plasma according to our previous investigation [42]. In France, AI-plasma has been delivered on a large basis after 2016 and—retrospectively, as newer diagnosed iTTP have been exchanged with AI-plasma—it can be considered that those patients received an appropriate regimen, comparable to the state of the art type of plasma used to TPE those patients. Moreover, TPE with AI-plasma trends to show superior performance; this would deserve prospective investigation before concluding superiority. Eighteen more cases have been investigated since then, all enduring TPE with AI-FFP, with excellent performance (not shown); cases were not included in this survey as the comparators (TPE with SD-plasma) were not overlapping regarding timeframe, which might affect other parameters in the overall healthcare (time to treatment, adjunctive therapy etc.). This is encouraging data as blood banks producing only one type of plasma due to national regulations—and having not access to commercial SD-FFP—can safely issue it for TPE programs, with no need of a separate inventory.

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**Table 1:** Demographics of Test and Control patients

	<b>Test group: Amotosalen- inactivated plasma (n=30)</b>	<b>Control group: Solvent- Detergent plasma (n=40)</b>	<b>P value (test versus control)</b>
<b><u>1a: Demographics</u></b>			
<i>Age (years; mean ± SD)</i>	41.1 ± 13.7	39.2 ± 16.3	0.603
<i>Female Gender; number (%)</i>	24 (80)	30 (70.0)	0.415
<i>Weight (kg)</i>	76.8 ± 18.8	79.6 ± 18.3	0.542
<b><u>1b: Clinical Presentation</u></b>			
<i>Baseline platelet count (10<sup>9</sup>/L; mean ± SD; [median])</i>	16.0 ± 10.9 [ 11.5]	13.3 ± 11.9 [10.0]	0.325
<i>Hemoglobin (g/L)</i>	89 ± 20	85 ± 21	0.373
<i>Reticulocyte count (10<sup>9</sup>/L)</i>	158 ± 84	191 ± 129	0.313
<i>Lactate De-Hydrogenase (LDH), Units/L</i>	600 ± 376	490 ± 340*	0.246
<i>Anti-ADAMTS13 antibody levels (units/mL)</i>	73.7 ± 38.0	73.3 ± 33.5	0.966
<i>N of patients presenting with cardiac lesions (%) based on elevated troponin levels &gt;0.02 ng/mL**</i>	8 (80)	10 (76.9)	1.000
<i>N of patients presenting with renal involvement (%) based on creatinine levels***</i>	7 (23.3)	10 (25.0)	1.000
<i>N of patients presenting with cerebral lesions (clinical reports)****(%)</i>	15 (50.0)	26 (65)	0.230

\*: For LDH levels, data were available from 45 out of 48 test patients and 32 out of 40 control patients. \*\*: n=8 patients for the Test group and n=10 patients for the Control group with measured troponin levels \*\*\*: Serum/plasma creatinine levels were assessed from gender adapted abacuses. \*\*\*\*Cerebral lesions were determined either from clinical symptoms or MRI-CAT scans upon availability.

**Table 2:** Volume of alternative exchanged therapeutic plasma among patients with use of a given type of plasma

<i>Groups</i>	<i>Variable: Type of therapeutic plasma</i>	<i>Number of individuals</i>	<i>Mean</i>	<i>SD</i>	<i>Median</i>	<i>Minimum (L)</i>	<i>Maximum (L)</i>
<b>Control</b>	Amotosalen-inactivated (AI)	2	5.5	3.5	5.5	3.0	8.0
	<b>Solvent-Detergent (SD)</b>	<b>40</b>	71.1	52.9	58.0	4.8	236.0
	Methylene Blue (MB)	11	8.9	5.9	8.4	0.8	18.0
	Quarantine (Q)	6	16.6	23.8	7.0	2.0	64.2
<b>Test</b>	<b>Amotosalen-inactivated (AI)</b>	<b>30</b>	50.3	32.5	49.8	3.2	187.6
	Solvent-Detergent (SD)	6	6.0	3.3	5.8	1.6	11.0
	Methylene Blue (MB)	0	0.0	0.0	0.0	0.0	0.0
	Quarantine (Q)	15	7.8	7.7	5.2	0.4	29.8

**Table 3:** Therapeutic interventions

	Test (n=30)	Control (n=40)	P value
<b><u>3a: Therapeutic Plasma Exchange</u></b>			
<i>Number of Plasma Components (200 mL; mean <math>\pm</math> SD [median])</i>	245.4 $\pm$ 139.2 [246.3]	381.6 $\pm$ 292.7 [293.0]	<b>0.012</b>
<i>Total volume plasma (L; mean <math>\pm</math> SD [median])</i>	49.2 $\pm$ 27.7 [49.3]	76.3 $\pm$ 58.5 [58.6]	<b>0.013</b>
<i>Days between admission and first TPE</i>	1.6 $\pm$ 2.7	2.1 $\pm$ 5.3	0.614
<b><u>3b: Adjunctive therapy</u></b>			
<i>Patients treated with Corticosteroids, N (%)</i>	27 (90.0)	35 (89.7)	1.000
<i>Corticosteroids: dose (mg/kg; mean <math>\pm</math> SD, median)</i>	1.20 $\pm$ 0.35 (1.00)	1.01 $\pm$ 0.10 (1.00)	<b>0.008</b>
<i>Rituximab*; N (%)</i>	14 (46.7)	27 (67.5)	0.150

\*: 375 mg/m<sup>2</sup>, 3 injections within 4 days followed by a 4<sup>th</sup> injection 15 days after [29]



**Table 4:** Outcome of Test and Control Cohorts (Thrombotic Thrombocytopenic Purpura Patients)

	<b>Test group: Amotosalen- inactivated plasma (n=30)</b>	<b>Control group: Solvent- Detergent plasma (n=40)</b>	<b>Test versus Control</b>
<b><u>4a: Primary outcome</u></b>			
<i>Median days to sustained remission</i>	11.0	16.0	<i>0.099</i>
<b><u>4b: Secondary outcome</u></b>			
<i>Refractoriness, N (%)</i>	3/30 (10.0)	7/39 (17.9)	0.500
<i>Exacerbation, N (%)</i>	12/30 (40.0)	23/38 (60.5)	0.227
<i>Relapse, N (%)</i>	9/30 (30.0)	10/32 (31.3)	1.000
<i>Death up to 60 days post first therapeutic plasma exchange, N (%)</i>	1/30 (3.3)	5/40 (12.5)	0.228

**Table 5:** Tolerance to plasma and reported adverse transfusion reactions of Thrombotic Thrombocytopenic Purpura patients undergoing Therapeutic Plasma exchange with either Amotosalen- or Solvent-Detergent-inactivated plasma

	<b>Test group: Amotosalen- inactivated plasma (n=30)</b>	<b>Control group: Solvent- Detergent plasma (n=40)</b>	<b>Test versus Control</b>
<b><i>All declared reactions, of severity 2 and 3*; imputability* 1 to 3; N (%)</i></b>	11 (36.7)	15 (37.5)	1.000
<b><i>Reactions attributable to plasma, of severity 2 and 3; imputability 1 to 3; N (%)</i></b>	5 (16.7)	12 (30.0)	0.264
<b><i>Other side effects</i></b>	6 (20.0)	7 (17.5)	0.720

\*Severity and imputability were scored according to the International Haemovigilance Network Database [33].