Innocuité et efficacité du plasma inactivé par amotosalen-UVA pour traiter le purpura thrombotique thrombocytopénique par échange plasmatique thérapeutique

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Update article

Plasma for direct therapeutic use, for today and tomorrow: A short critical overview

Un état des lieux et les nouvelles questions à propos du plasma à usage thérapeutique direct

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Available online 26 July 2018

Unitaire minipool

Pool+++

Souplesse, réactivité

Lié aux performances individuelles

Pas de risque de propagation virale à grande échelle

Dilution des paramètres (-)

Homogénéisation / Standardisation

Mais risque de propagation virale à grande échelle

Sécurité « industrielle »

→ Procédés d'inactivation

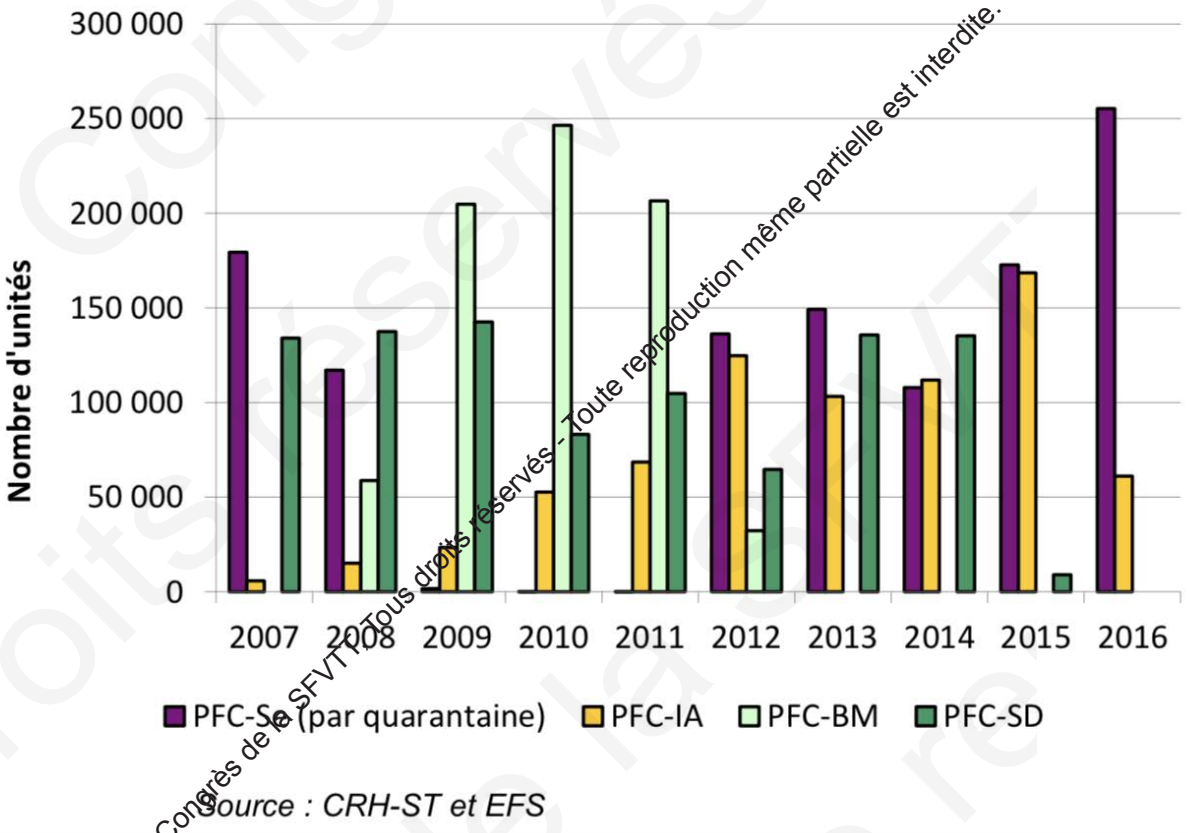
Supplemental Table 1: Types of plasma for direct therapeutic use issued in France 2008-2016

Types of fresh frozen plasma in use in France (2008-2016)

	Solvent-Detergent inactivated plasma	Quarantine plasma	Methylene Blue inactivated plasma	Amotosalen-HCl-UVA inactivated plasma
2008	+	+	+	-
2009	+	discontinued	+	-
2010	+	-	+	+
2011	+	-	+	+
2012	+	+	discontinued	+
2013	+	+	-	+
2014	-	+	-	+
2015	-	+	-	+
2016	-	+	-	+

Considered Period

Figure 7 : Evolution du nombre de plasmas thérapeutiques cédés, 2007-2016



Source : ANSM, 2017

Source: FDA, 2014

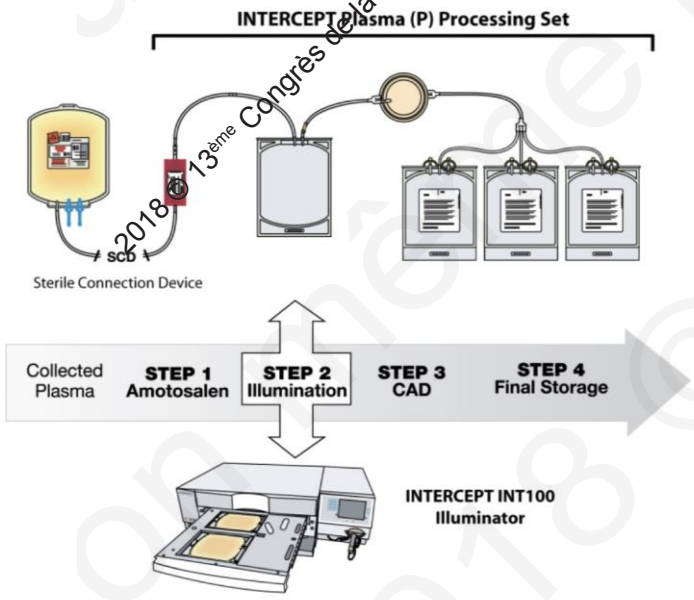
J. Irsch et al Vox Sang 2009,
DOI: 10.1111/j.1423-0410.2009.01224.x

Study method: This study was conducted at two blood centers. Test samples were derived from whole blood plasma, which was processed and frozen within 24 hours. Sixty two pools, (186 total units) of plasma were collected. A portion of each pool was separated, frozen and tested as the untreated control. The remaining portion of each pool was processed using the INTERCEPT system, frozen, and then tested in parallel with untreated control samples. A summary of study results is presented in the table below.

In Vitro Study Results

Test	IBS processed plasma		Control plasma	
	Mean±SD	Range	Mean±SD	Range
pH	7.38±0.03	7.35 – 7.45	7.41±0.05	7.34 – 7.58
Osmolality (mOsm/kg)	308±5	294 –321	309±5	295 – 322
PT (s)	14.4±0.7	12.7 – 16.9	13.1±0.3	11.6 – 15.3
aPTT (s)	27.0±1.7	23.1 – 31.3	24.2±1.4	20.4 – 27.6
Fibrinogen (g/L)	2.43±0.37	1.70 – 3.74	2.81±0.36	2.28 – 4.10
Prothrombin (IU/mL)	0.93±0.09	0.72 – 1.14	1.03±0.10	0.85 – 1.28
Factor V (IU/mL)	0.82±0.11	0.51 – 1.19	0.91±0.13	0.56 – 1.27
Factor VII (IU/mL)	0.81±0.13	0.60 – 1.22	0.99±0.14	0.71 – 1.41
Factor VIII (IU/mL)	0.73±0.20	0.35 – 1.21	0.91±0.25	0.44 – 1.52
Factor IX (IU/mL)	0.93±0.17	0.58 – 1.56	1.12±0.19	0.71 – 1.66
Factor X (IU/mL)	0.83±0.13	0.53 – 1.18	0.95±0.14	0.62 – 1.33
Factor XI (IU/mL)	0.90±0.13	0.66 – 1.28	1.02±0.14	0.77 – 1.43
vWF R:Co (IU/mL)	0.97±0.24	0.46 – 1.55	1.01±0.25	0.51 – 1.56
ADAMTS-13 antigen (%)	128.8±20.6	94.0 – 181.4	124.7±17.9	90.4 – 173.4
ADAMTS-13 activity (%)	87.5±11.0	64.0 – 114.8	93.4±10.3	68.0 – 114.8
Antithrombin III (IU/mL)	0.93±0.06	0.73 – 1.07	0.98±0.06	0.76 – 1.11
Protein C (IU/mL)	0.86±0.09	0.67 – 1.01	0.95±0.10	0.79 – 1.20
Protein S (IU/mL)	1.04±0.10	0.84 – 1.26	1.08±0.11	0.84 – 1.30
Alpha-2-plasmin Inhibitor (IU/mL)	0.85±0.07	0.63 – 1.02	1.00±0.08	0.72 – 1.18
TAT (IU/mL)	2.3±0.8	2.0 – 6.3	2.4±0.8	2.0 – 6.7
Factor VIIa (ng/mL)	<3.6	<3.6	<3.6	<3.6
NAPTT (s)	91.8±11.4	70.3 – 121.9	91.8±10.6	69.9 – 118.4
C3a (ng/mL)	50.4±38.4	13.0 – 216.2	134.7±57.0	66.8 – 359.0

Illustration of the IBS for Plasma



Marqué CE, 2006

INTERCEPT Plasma Clinical Development Efficacy and Safety

Phase I/II, 2 trials
42 healthy subjects

Phase II/III, 4 trials
203 patients / 5,000 units

Phase 1
Amotosalen Kinetics
N = 15

Phase 2 Acquired Coagulopathy –Pilot
N = 13

Phase 2
Warfarin Reversal
N = 27

Phase 3A
Congenital Coagulopathy
N = 34

Phase 3B
Acquired Coagulopathy
N = 121

Phase 3C
TPE – TTP
N = 35

Post Marketing

Acquired Coagulopathy
Liver Transplant
N = 427

Acquired Immune TTP
N = 31

Hambleton et al: Transfusion 2002; 42:1302-1307
De Alarcon et al: Transfusion 2005;45:1362-1372
Mintz et al: Blood 2006;107:3753-3760
Mintz et al: Transfusion 2006;46:1693-1704

IX. SUMMARY OF PRIMARY CLINICAL STUDIES

The safety and effectiveness of IBS processed plasma were investigated in eight clinical studies summarized in the table below (N=704).

Clinical Trials of IBS Processed Plasma

Trial	Phase	Design	Clinical Setting	N	Objectives
C-001-97	1	Randomized Crossover Blinded	Healthy Subjects	15	Amotosalen kinetics Safety
C-002-97	2	Randomized Crossover Blinded	Anticoagulated Healthy Subjects	27	Warfarin reversal Factor kinetics Safety
C-002-98	2	Randomized Parallel Group Blinded	Acquired Coagulopathy Liver Disease	13	Pilot study Logistics Clinical response
F3A99UC*	3	Single Group Open Label	Congenital Coagulopathy	34	Factor kinetics Clinical response Safety
F3B99	3	Randomized Parallel Group Blinded	Acquired Coagulopathy Liver Disease	121	Clinical response to invasive surgery Safety
F3C99	3	Randomized Parallel Group Blinded	TTP with therapeutic plasma exchange	35	Clinical response Safety
CLI 00080	Post marketing in Europe	Retrospective Cohort Controlled Comparative Efficacy	TTP	31	Clinical response
EFS Alsace/ Strasbourg University	Post marketing in Europe	Retrospective Cohort Controlled Comparative Efficacy	Liver Transplant	427	Clinical response Safety

*Not discussed in detail as the data are not adequate to support the indication

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DOI: 10.1111/vox.12007

ORIGINAL PAPER

A regional haemovigilance retrospective study of four types of therapeutic plasma in a ten-year survey period in France

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Background and objectives Our objective was to compare the frequency of adverse events (AEs) due to any of the 4 types of fresh-frozen plasma (FFP) prepared and delivered by the French Blood Establishment (EFS) over a 10-year period. Surveillance of AEs and vigilance was performed according to a homogeneous policy. The four types of FFP comprised of one type (methylene blue [MB]) that was stopped since then and of another type [amotosalen (AI)] that was recently introduced, along with two conventional products [quarantine (Q) and solvent–detergent (SD)].

Materials and Methods This is a retrospective study based on the national AE reporting database and on the regional database system for deliveries. AEs recorded after the delivery of 1 of the 4 types of FFP were pairwise compared, with appropriate statistical corrections.

Results 105 964 FFP units were delivered (38·4% Q, 17·9% SD, 9·7% MB and 34% AI).

Statistical comparisons of AEs identified only a difference in AE rates between quarantine and solvent–detergent plasma.

Conclusions FFP was confirmed to be extremely safe in general, especially if one considers 'severe' AEs. All types of FFP were associated with extremely low occurrences of AEs. Q, SD, MB and AI led, respectively, to 7·14, 4·86, 1·05 and 4·16 AEs per 10 000 deliveries.

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Key words: adverse events, fresh-frozen plasma, haemovigilance, therapeutic plasma, transfusion safety.

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Vox Sanguinis (2015)

DOI: 10.1111/vox.12300

SHORT REPORT

Independent evaluation of tolerance of therapeutic plasma inactivated by amotosalen-HCl–UVA (Intercept™) over a 5-year period of extensive delivery

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Amotosalen-HCl–UVA (AI) is a process to inactivate pathogens in therapeutic plasma (FFP). Tolerance is the main residual issue in FFP transfusion, and only large series observations are powered enough to identify significantly elevated levels of hazards. We report here on 15 133 new transfusions of AI-FFP, over the previously published 36 035, which in all represents one of the largest series observed by means of a highly standardized surveillance (51 168 observations). There is no noticeable difference in terms of tolerance of AI-FFP compared to 5875 transfusions of Quarantine (Q)-FFP. There was no significant difference in terms of advance events, between the two types of FFP ($P = 0{\cdot}98$); further, no difference was recorded either when the total number of AI-FFP (51 168) was compared to the corresponding number of Q-FFP (5875; $P = 0{\cdot}62$).

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Key words: amotosalen, haemovigilance, pathogen reduction, safety, therapeutic plasma.

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ORIGINAL PAPER

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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Comparative effectiveness of plasma prepared with amotosalen-UVA pathogen inactivation and conventional plasma for support of liver transplantation

Jacques Cinqualbre,[1] Daniel Kientz,[2] Emilie Remy,[2] Norman Huang,[3] Laurence Corash,[3] and Jean Pierre Cazenave[4]

TRANSFUSION 2015;55;1710–1720

AI-FFP

cnr-mat
Centre de référence des microangiopathies thrombotiques

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

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Table 1: Demographics of Test and Control patients

	Test group: Amotosalen-inactivated plasma (n=48)	Control group: Solvent-Detergent plasma (n=40)	P value (test versus control)
1a: Demographics			
Age (years; mean ± SD)	44.8 ± 15.7	39.2 ± 16.3	0.110
Female Gender; number (%)	34 (70.8)	30 (70.0)	1.000
Weight (kg)	75.8 ± 16.9	79.6 ± 18.3	0.330
Elapsed time (days) from diagnosis to TPE (mean± SD; [median])	1.9 ± 3.3 [1.0]	9.5 ± 48.1 [1.0]	0.324
1b: Clinical Presentation			
Baseline platelet count (10^9/L; mean ± SD; [median])	22.5 ± 28.2 [12.5]	13.3 ± 11.9 [10.0]	***0.041***
Hemoglobin (g/L)	87 ± 19	85 ± 21	0.571
Reticulocyte count (10^9/L)	160 ± 92	191 ± 129	0.326
Lactate De-Hydrogenase (LDH), Units/L	550 ± 340*	490 ± 340*	0.468
Anti-ADAMTS13 antibody levels (units/mL)	83.2 ± 55.2	73.3 ± 33.5	0.328
N of patients presenting with cardiac lesions (%) based on elevated troponin levels >0.02 ng/mL;	21 (43.8)	13 (32.5)	0.221
Mean level ±SD	0.51 ± 1.22	0.59 ± 0.81	0.826
N of patients presenting with renal lesions (%) based on creatinine levels**	14 (29.2)	10 (25.0)	0.811
N of patients presenting with cerebral lesions (clinical reports) (%)***	25 (52.1)	26 (65)	0.280

*: For LDH levels, data were available from 45 out of 48 test patients and 32 out of 40 control patients. **: Serum/plasma creatinine levels were assessed from gender adapted abacuses. ***Cerebral lesions were determined either from clinical symptoms or MRI-CAT scans upon availability.

Supplemental Table 2. Definitions of patients' outcome.

Complete remission	Full resolution of the neurologic manifestations (or stabilization of neurologic abnormalities in patients considered as having permanent sequels) and renal failure and recovery of normal platelet count (≥150x10^9/L) for at least two days.
Durable remission	Complete response with no further thrombocytopenia, renal failure or clinical worsening for more than 30 consecutive days from the first day of platelet count recovery. At this step, the episode is considered as ended.
Exacerbation	Worsening of neurologic manifestations and/or a recurrence of thrombocytopenia (<100x10^9/L ≥ 2 days) and/or a worsening of thrombocytopenia (a decrease of more than one-third the highest count, for at least 2 days) with no other identifiable cause, before achieving durable remission.
Relapse	Reappearance of neurological manifestations, renal failure and/or thrombocytopenia (<100x10^9/L for at least two days) with no other identifiable cause after durable remission.
Refractoriness	Platelet count after 4 days of standard intensive treatment less than double the initial, together with persistently elevated LDH levels.
Suboptimal response	Exacerbation or refractory disease under standard treatment.

Garraud O…. Coppo P. (submitted)

Table 2: Therapeutic interventions

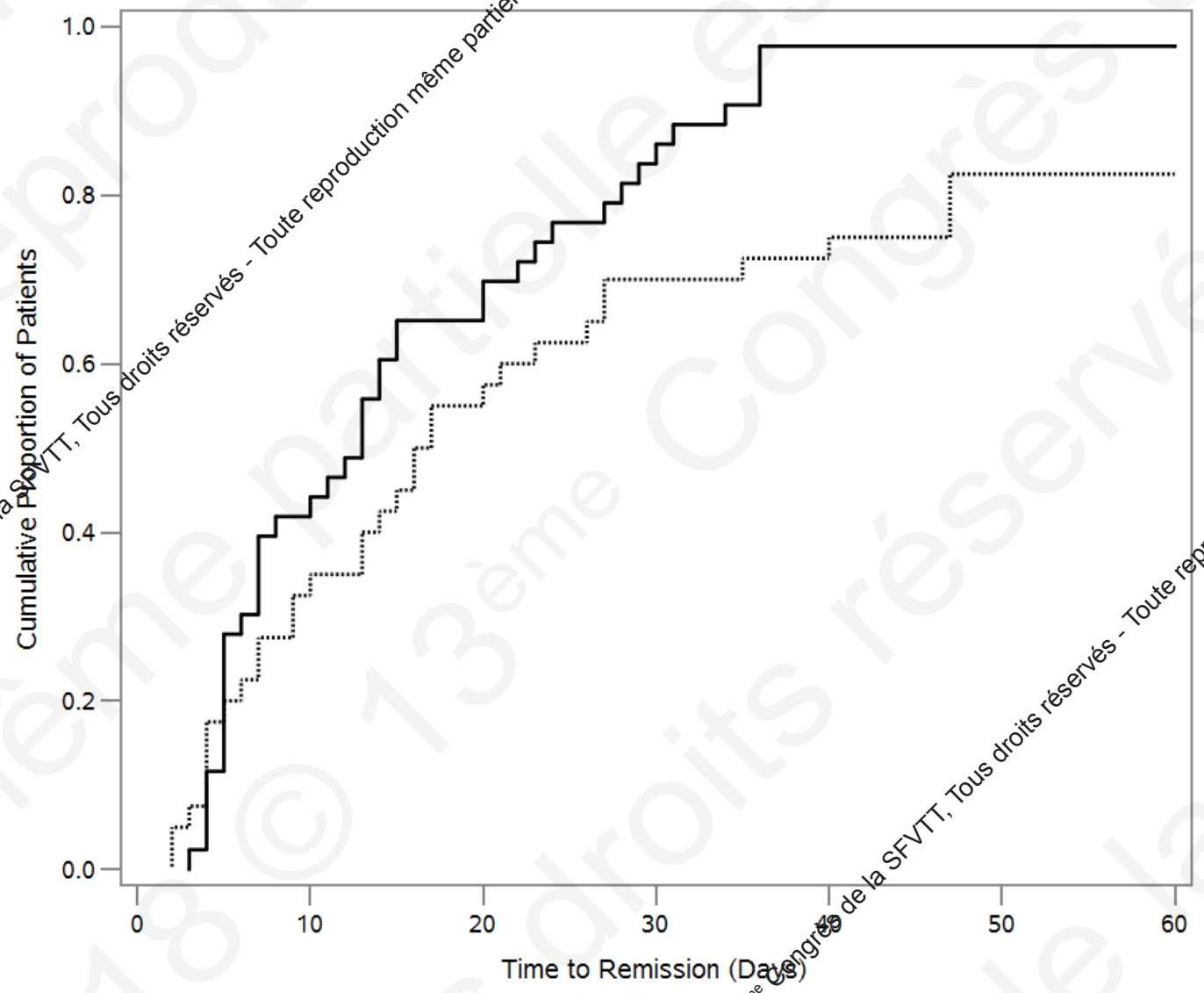
	Test (n=48)	Control (n=40)	P value
2a: Therapeutic Plasma Exchange			
Number of Plasma Components *(200 mL; mean ± SD [median])*	271.8 ± 178.9 [248.8]	381.6 ± 292.7 [293.0]	***0.043***
Total volume plasma *(L; mean ± SD [median])*	54.6 ± 36.0 [49.8]	76.3 ± 58.5 [58.6]	***0.045***
Days between admission and fist TPE	2.1 ± 3.7	2.1 ± 5.3	1.000
2b: Adjunctive therapy			
Patients treated with Corticosteroids, N (%)	41 (85.4)	35 (89.7)	0.748
Corticosteroids: dose *(mg/kg; mean ± SD, median)*	1.16 ± 0.32 (1.00)	1.01 ± 0.10 (1.00)	***0.007***
Corticosteroids: treatment duration *(mean ± SD, median)*	39.6 ± 32.4 (25.5)	16.6 ± 9.4 (21)	0.088
Rituximab*; N (%)	24 (50)	27 (67.5)	0.130

**: 375 mg/m², 3 injections within 4 days followed by a 4th injection 15 days after [29]*

Table 3: Outcome of Test and Control Cohorts (Thrombotic Thrombocytopenic Purpura Patients)

	Test group: Amotosalen-inactivated plasma (n=48)	**Control group: Solvent-Detergent plasma (n=40)**	**Test versus Control**
3a: Primary outcome			
Median days to remission	13.0	16.5	***0.025***
3b: Secondary outcome			
Refractoriness, N (%)	3/47 (6.4)	7/39 (17.9)	0.174
Exacerbation, N (%)	22/46 (47.8)	23/38 (60.5)	0.278
Relapse, N (%)	13/47 (27.7)	10/32 (31.3)	0.803
Death up to 60 days post first therapeutic plasma exchange, N (%)	2/47 (4.2)	5/40 (12.5)	0.238

Proportion of Patients Achieving Remission with Therapeutic Plasma Exchange Using Amotosalen-inactivated Plasma or SD Plasma



Test _____

Control .....

Note: Kaplan Meier graph illustrating the cumulative percentage of patients achieving remission; Test group (Amotosalen-inactivated plasma, N=48) in solid line and Control group (SD plasma, N=40) in dotted line.

Table 4: 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

	Test group: Amotosalen-inactivated plasma (n=48)	**Control group: Solvent-Detergent plasma (n=40)**	**Test versus Control**
All declared reactions, of severity 2 and 3*; imputability* 1 to 3; N (%)	20 (41.7)	15 (37.5)	0.827
Reactions attributable to plasma, of severity 2 and 3; imputability 1 to 3; N (%)	12 (25.0)	12 (30.0)	0.637
Other side effects	8 (16.7)	7 (17.5)	1.000

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

Type of plasma preparation used for plasma exchange and clinical outcome of adult patients with acquired idiopathic thrombotic thrombocytopenic purpura: a French retrospective multicenter cohort study

Marie Toussaint-Hacquard,[1] Paul Coppo,[2,3,4] Marc Soudant,[5] Lysiane Chevreux,[1] Suzanne Mathieu-Nafissi,[1] Thomas Lecompte,[1,6] Sylvie Gross,[1] François Guillemin,[5] and Thierry Schneider[7]

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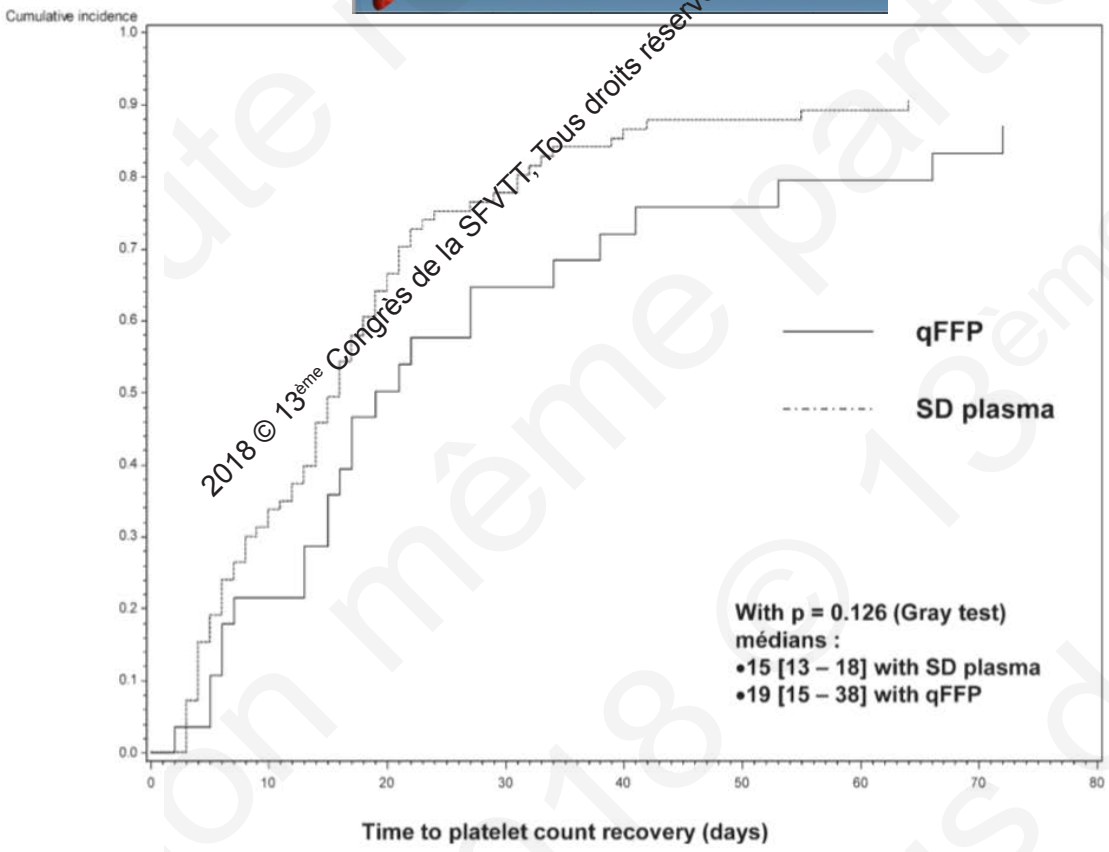

BACKGROUND: Plasma exchange (PE) is the first-line therapy of acquired thrombotic thrombocytopenic purpura (TTP). Several plasma preparations have been available; their equivalence in terms of outcome remains uncertain.

STUDY DESIGN AND METHODS: We performed a retrospective analysis of the cases prospectively reported from 2005 to 2010 to the national registry established by the thrombotic microangiopathies French reference center. We analyzed 108 initial episodes of acquired idiopathic TTP in adults treated with PE, 81 with solvent/detergent (S/D) plasma, and 27 with quarantine fresh-frozen plasma (qFFP). The primary endpoint was the time to platelet (PLT) count recovery.

RESULTS: Time to PLT count recovery was not significantly different with S/D plasma versus qFFP (median, 15 days vs. 19 days, respectively; $p = 0.126$). Complete remission rates, exacerbations, and survival were comparable. By multivariate competitive risk (Fine-Gray) analysis, the only significant association with a shorter time to PLT count recovery was the absence of additional treatment (hazard ratio, 2.06; 95% confidence interval [CI], 1.39-3.05; $p < 0.001$). There was a significant interaction between type of plasma and age, and for patients less than 40 years old, the use of S/D plasma was associated with a shorter time to PLT count recovery versus qFFP (median, 13 [95% CI, 9-16] days vs. 20 [95% CI, 16-64] days, respectively; $p = 0.004$).

CONCLUSION: The outcomes of acquired TTP treated with S/D plasma or qFFP seem similar and therefore both preparations can be used safely for PE in this indication. The faster response of S/D plasma observed in younger patients warrants confirmation in prospective studies.

Pas de différence majeure entre les ≠ types de plasma

Pas de perte de chance thérapeutique dans un l'autre groupe

Quelques différences mineures peu explicites (à investiguer le cas échéant)

Taille relativement petite des groupes de patients

Grande variabilité des volumes de plasma échangé/apporté

Hétérogénéité clinique

Merci