Journée Cochin d'Actualité Transfusionnelle et journée d'automne de la société Française d'Hémaphérèse, Paris, 24 novembre 2017

Evaluation de la tolérance du plasma sécurisé par Amotosalen/HCl/UVA dans les échanges plasmatiques pour MAT : une expérience régionale

O Garraud et al.

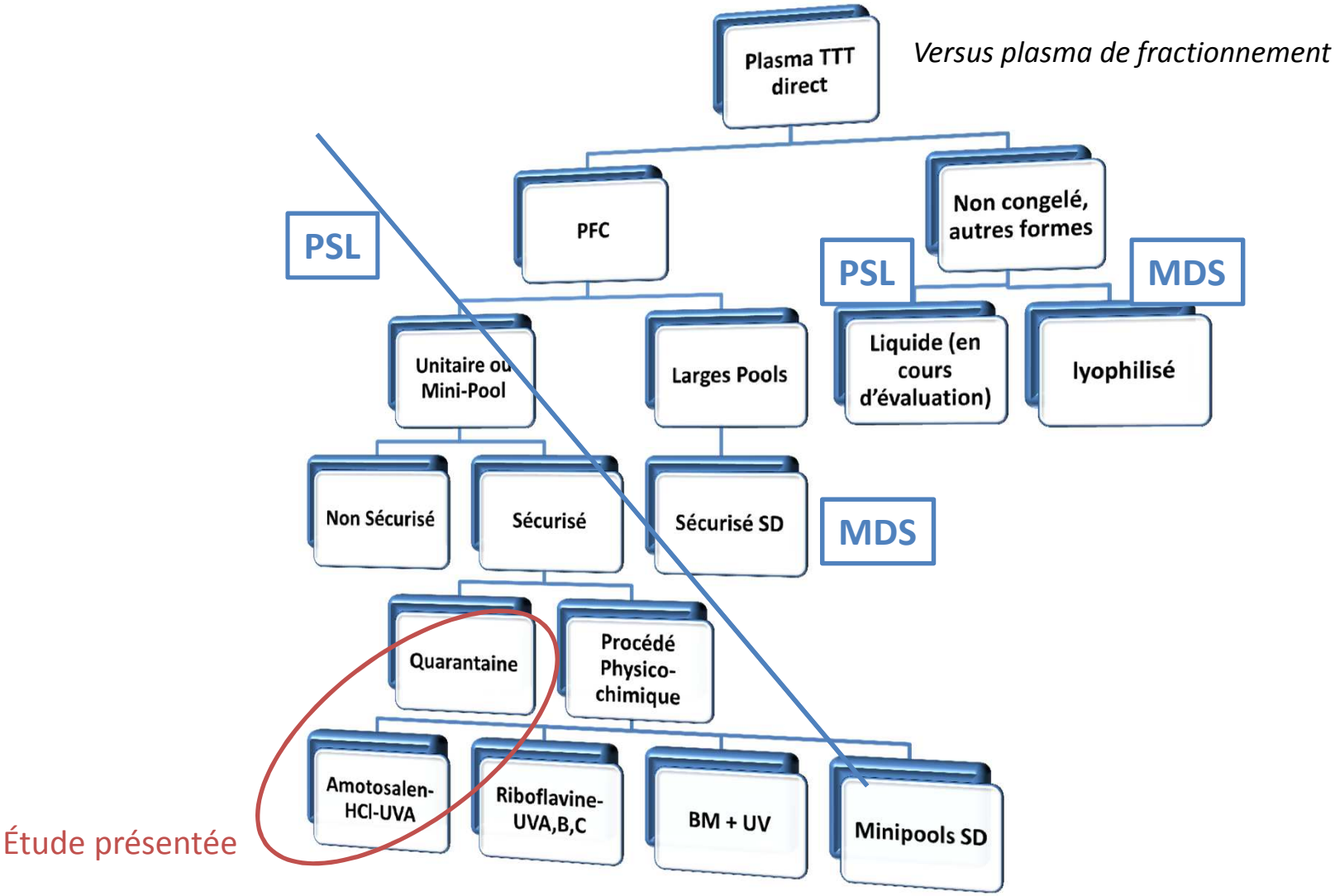
Liens d'intérêt

- Invitations reçues de MacoPharma-France, Terumo-BCT-Europe, Cerus-Europe (cinq dernières années)
- Visite usine OctaPharma, Suède (2016)
- Co-PI d'une étude d'efficacité du plasma Intercept (CNR MAT), prise en charge de frais d'études par Cerus-Europe
- Salarié INTS

Plan de la communication

1. Les différents types de plasma thérapeutiques
2. La tolérance « receveurs » au plasma thérapeutique, données de l'hémovigilance française
3. L'étude stéphanoise de la tolérance au plasma traité par Amotosalen/HCl/UVA vs Sécurisé par Quarantaine à propos de patients subissant des échanges plasmatiques de larges volumes
4. Perspectives et conclusions
5. À retenir dans la perspective d'une action DPC

Les différents types de plasma (directement) thérapeutique

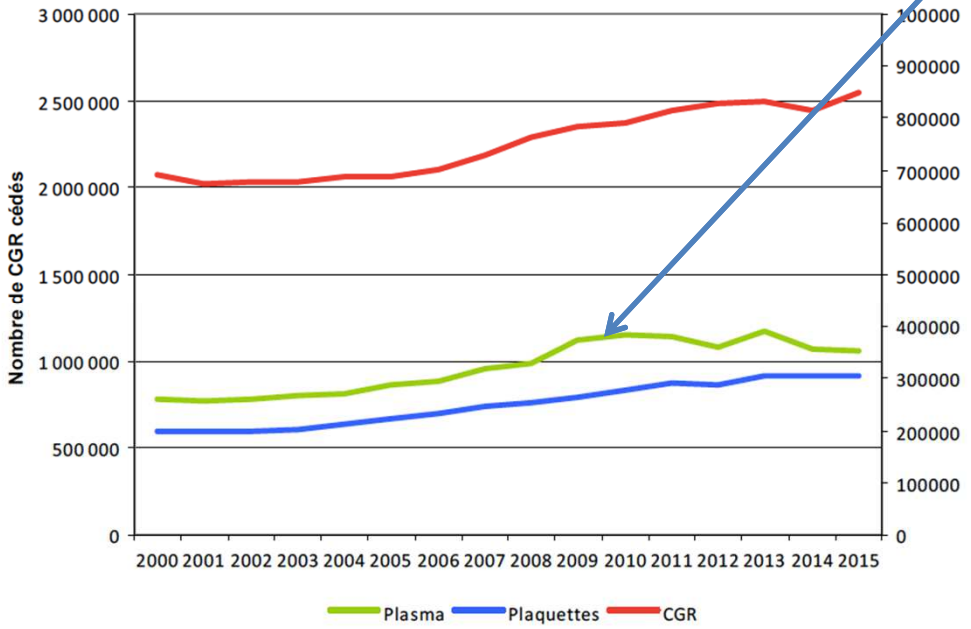


La tolérance « receveurs » au plasma thérapeutique, données de l'hémovigilance française

Données de délivrance

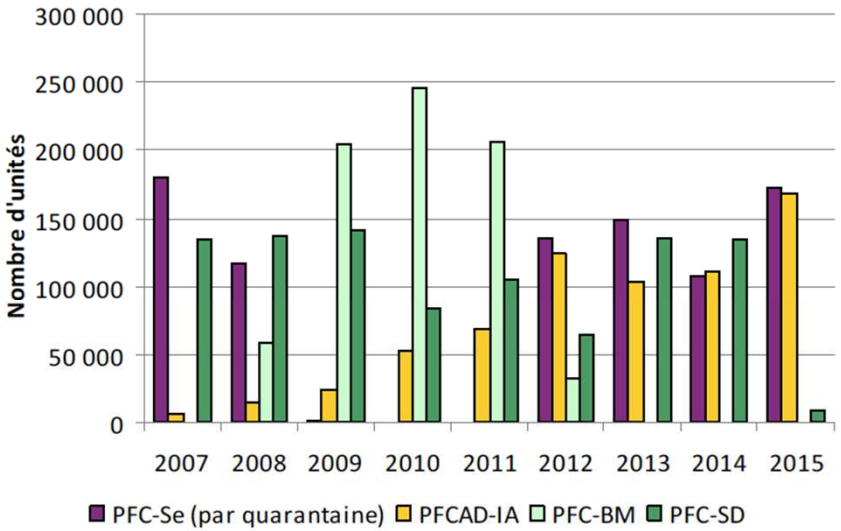
PFC

Figure 4 : Evolution de la consommation des différents types de PSL, 2000-2015



Source : CRH-ST

Figure 7 : Evolution du nombre de plasmas thérapeutiques cédés, 2007-2015



Source : CRH-ST et EFS

Données 2015 publiées en 2016 ; ANSM : Rapport annuel d'Hémovigilance

Tableau 13 : Taux de déclaration des EIR d'imputabilité probable ou certaine, par diagnostic et famille de PSL, enquête terminée, 2015

Diagnostic	Nombre EIR	Taux /100 000 PSL cédés			
		Tous PSL	CGR	Plasma	Plaquettes
Allo-immunisation isolée	2286	71,3	81,2	0,6	70,8
Allergie	634	19,8	3,9	58,0	106,7
Réaction fébrile non hémolytique (RFNH)	595	18,6	19,3	1,1	32,6
Incompatibilité immunologique	226	7,1	3,9	0,6	40,8
Oedème pulmonaire de surcharge	213	6,6	7,6	2,6	3,6
Réaction hypertensive	119	3,7	4,4	0,0	2,0
Inefficacité transfusionnelle	29	0,9	0,2	0,0	8,2
Hémosidérose		0,7	0,9	0,0	0,0
Réaction hypotens		0,5	0,5	0,0	1,0
Diagnostic non pré		0,5	0,2	0,3	3,3
Hémolyse drépano				0,0	0,0
Diagnostic non list				0,0	1,0
Hémolyse autre		0,3	0,4	0,0	0,0
Oedème pulmonai		0,2	0,2	0,0	0,3
Dyspnée non liée à un oedème pulmonaire		0,2	0,0	0,0	1,3
Infection bactérienne	5	0,2	0,1	0,0	0,7
Infection virale	3	0,1	0,0	0,0	1,0
Crise tétanique	1	0,0	0,0	0,3	0,0
Total	**4212**	**131,4**	**123,7**	**63,4**	**273,1**

PFC : EIR < 1 p.1000 imputabilité probable ou certaine

Tableau 15 : Répartition des diagnostics des EIR de grade 3 déclarés d'imputabilité 2 à 3 par PSL impliqué, 2015

Diagnostic	Famille de PSL				
	CGR	Plaquettes	Plasma	Total	%
Allergie	2	14	15	31	44,93%
Oe	3	3	5	31	44,93%
Hé		0	0	2	2,90%
Ine		2	0	2	2,90%
Inc			0	1	1,45%
Oe		0	0	1	1,45%
Ré		1	0	1	1,45%
To	9	20	20	69	100%
Taux / 100 000 PSL cédés	**1,1**	**6,5**	**5,7**	**2,2**	

PFC : EIGR (3) < 0,1 p.1000 imputabilité probable ou certaine

VoxSanguinis
The International Journal of Transfusion Medicine

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Vox Sanguinis (2013) 104, 337–341

ORIGINAL PAPER

DOI: 10.1111/vox.12007

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

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Vox Sanguinis

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 per-

>100.000 PFC sur 10 ans / expérience régionale / MB, SD, IA et SQ
Pas de différence S de tolérance et d'EIR

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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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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>50.000 PFC-IA sur 5 ans / expérience régionale vs SQ
Pas de différence S de tolérance et d'EIR

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; $P = 0{\cdot}62$).

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

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Accepted Manuscript

Title: Are all therapeutic plasma preparations the same: is it worth assessing them in clinical trials?

Author: Olivier Garraud

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DOI: https://doi.org/10.1016/j.transci.2017.11.023
Reference: TRASCI 2280

L'étude stéphanoise de la tolérance au plasma traité par Amotosalen/HCl/UVA vs Sécurisé par Quarantaine à propos de patients subissant des échanges plasmatiques de larges volumes

Thèse d'exercice de médecine (MG) de Charles GUIGNIER au CHU de Saint-Etienne

En collaboration avec :

- Le service de Néphrologie du CHU
- L'Hémovigilance hospitalière
- Le site EFS de Saint-Etienne, Saint-Priest-en Jarez (délivrance, hémovigilance)

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Short communication

Amotosalen-inactivated plasma is as equally well tolerated as quarantine plasma in patients undergoing large volume therapeutic plasma exchange

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Abstract

A retrospective – single center – survey compared tolerance of individual donor therapeutic plasma in a series of 88 patients principally presenting with thrombotic microangiopathy; all patients underwent therapeutic plasma exchange (TPE) performed with more than 90% of either of two types of plasma preparations. One plasma type used in TPE was prepared with pathogen reduction by amotosalen addition and UVA illumination, and the other one was non-manipulated (quarantine plasma). Both types of plasma were single donor. Occurrences of adverse reactions were equally low in either arm (amotosalen: 9 in 4689 bags of ~200 mL [0.019] versus quarantine: 2 in 828 bags [0.024]), confirming the safe use of amotosalen inactivated therapeutic plasma for TPE.

Keywords: Amotosalen; Fresh frozen plasma; Pathogen reduction technology; Total plasma exchange; Haemovigilance

Résumé

Cette étude est une observation rétrospective monocentrique de tolérance de séances d'échanges plasmatiques chez 88 patients présentant principalement une microangiopathie thrombotique. Les séances d'échanges plasmatiques ont été réalisées avec plus de 90 % d'un type de plasma frais congelé. Deux types de plasma ont été comparés : l'un est une préparation de plasma frais congelé monodonneur traité par amotosalen et suivie d'une illumination par des UVA ; l'autre est du plasma également monodonneur, mais sécurisé par quarantaine et non manipulé chimiquement. Les effets secondaires déclarés ont été également très bas, 0,019 (%) pour le groupe amotosalen contre 0,024 dans le groupe quarantaine. Cela suggère que le plasma amotosalen puisse être utilisé en toute sécurité dans les échanges plasmatiques pour microangiopathies thrombotiques.

The present survey was not designed for evaluating efficacy but – retrospectively – for examining tolerance of large volumes of plasma. A total number of 4689 units and 828 units of 200 ± 10 mL (on average) of AI- and Q-FFP, respectively, were issued for 88 patients reviewed during the survey period. Each patient was transfused with $\geq 90\%$ of either AI- or Q-FFP in sequences of daily sessions (Table 1); 7 patients were transfused with both types of plasma but in distinct sequences, spaced by a several month interval between TPE sequences. Those patients were considered being new patients in the present tolerance survey.

Table 1
Treatment protocols, mean volumes used to treat patients undergoing total plasma exchange related to pathology and adverse reactions.

Pathology	Amotosalen-inactivated FFP				Quarantine FFP			
	Patient characteristics	Mean volume exchanged per patient, (min.–max.) in mL	Number of sessions	Mean volume per session (of bag–equivalent 200 mL[c])	Patient characteristics	Mean Volume exchanged per patient, (min.–max.) in mL	Number of sessions	Mean volume per session (of bag–equivalent 200 mL[c])
TMA: TTP	$n=4$ 2 M; 2F	38,447 (6000–62,900)	7[b,1] 17; 20[b,2,c,5,d] 2	8–18 5–25 9–20 15	$n=2$ 2F	(11,262; 58,974)	16 3[d]	11–17 10–19
TMA: severe typical HUS	$n=8$ 3 M; 5F	14,472 (3780–30,810)	9 6 2; 3 4 7 5 2	2–21 2–10 5–13 15–18 15 19–20 18–20 6–18				
TMA: atypical HUS	$n=7$ 3 M; 4F	37,188 (14,200– 89,290)	25 + 7 + 32[a,d] 6 5; 8[b,3] 14 24 6	10–25 15–25 15 5–15 3–15 2–20 1–15	$n=1$ (F)	36,675	11[d]	10–18
TMA: others	$n=7$ 1 M; 7F	15,368 (3790–44,150)	6; 17[d] 1 1 3[b,4] 6 10	2–15 2–13 18 8 6–8 9–10 14–19	$n=1$ (F)	6330	4[d]	6–7
Vasculitis: AnCA + glomerulonephritis and vasculitis	$n=8$ 5 M; 3F	4358 (1050–7750)	3 9[b,5,c,5,d] 3 1 1 1 6 3	10–12 2–5 2–8 15 5 5 3 3	$n=7$ 4 M; 3F	5224 (2080–8452)	1[b,6] 1 5[d] 3 2 2[b,7,c,e]; 3	2 11 3–11 3–10 9 4 2–8
Glomerulonephritis and vasculitis: others	$n=4$ 1 M; 4F	37,967 (1920–129,100)	22 + 36 + 19 + 7[a,d] 2 9[d] 3	5–15 10 5–12 3	$n=2$ 2F	19,830 (16,760–32,670)	18 + 3[a,d] 7[d]	4–10 6–13

Table 1 (*Continued*)

Pathology	Amotosalen-inactivated FFP				Quarantine FFP			
	Patient characteristics	Mean volume exchanged per patient, (min.–max.) in mL	Number of sessions	Mean volume per session (of bag–equivalent 200 mL[c])	Patient characteristics	Mean Volume exchanged per patient, (min.–max.) in mL	Number of sessions	Mean volume per session (of bag–equivalent 200 mL[c])
Antibody mediated kidney rejection	$n = 20$ 11 M; 9F	6558 (420–13,160)	5[b,8,d]; 3 2 3 3 1 3 3 1 10 7 3 1 2 3 2[b,9] 1[b,10] 3 1 3	12–13 10 10–12 13 8 8 8–15 15 2 10–16 9–17 7 8 13 5 3–10 6 15–23 15 8–13	$n = 4$ 3 M; 1 F	(1190–3310)	3[d] 1 1 1	2–5 4 2 2
Prekidney graft desensitization	$n = 6$ 3 M; 3F	6316 (2110–5880)	3 1 5 1 3 1	2–8 10 2–7 5 3–10 12	$n = 3$ 2 M; 1F	10,770 (600–4510)	3 1 2	5–6 2 6
Segmental and focal hyalinosis	$n = 1$ (F)	12,490	8[b,11]	5–15	$n = 1$ (F)	1190	1	4

Severity scores were as follows (in accordance to the French haemovigilance organization): 1: absence of vital threat or long-term threat; 2: long-term morbidity; 3: immediate vital threat; 4: death. Imputability scores were as follows: 0: excluded; 1: doubtful; 2: possible; 3: likely and 4: unquestionable.

[a] Indicates that the patient underwent several sequences of TPE interrupted by several months, as a consequence of relapses.

[b] Indicates the occurrence of an adverse reaction (AR), numbered from 1 to 11 in superscript[1–11], as follows: [1,2,5,10,11] mild allergic type reactions (urticarial), severity grade 1, imputability 2; the exchange program has been pursued (severity and imputability scores are detailes at the bottom of the legends to this table). [3]Febrile non-hemolytic reaction, severity grade 1, accountability 3; the exchange program has been pursued. [6]Severe allergic type reaction (angioedema), severity grade 3, imputability 3; the exchange has been interrupted. [4,9]Moderate allergic type reaction (urticarial, pruritus), severity grade 3, imputability 2–3; the exchange program has been pursued. [7,8]Hypotensive reaction, severity grade 2, imputability 2; the exchange has been interrupted.

[c] Indicates that the patient has manifested an adverse reaction while having manifested no detectable reaction in previous TPE sessions using another plasma preparation: $ standing for previous quarantine plasma sessions and @ standing for previous solvent-detergent plasma sessions.

[d] Indicates that the patient has undergone TPE with either type of AI- or Q-FFP sequentially (after relapse): only one type of FFP within one series of TPE, however.

Among the treated patients, 17 had adverse reactions (ARs) that were notified to be in relation with the transfusion: 11 were declared attributable to FFP by haemovigilance consultants: 9 in the AI-FFP group and 2 in the Q-FFP group (the non-attributable ARs consisted of one transfusion associated cardiac overload (TACO), 1 catheter infection, 3 thrombotic events (unrelated to the TMA causality) and 1 hematoma. The severity of ARs was as follows: grade 1 (pruritus, urticarial reaction [$n = 5$] and febrile non-hemolytic reactions ($n = 1$]); grade 2 (hypotension [$n = 2$] and allergic (skin) reaction [$n = 2$]); grade 3 (angioedema [$n = 1$]); details are provided in Table 1. In total, 10 of 11 AEs were either of minor or moderate clinical severity (grade 1 or 2); 1 minor and 2 moderate ARs – manifesting as allergies – were seen in patients having already undergone TPE with another type of plasma in the present survey. A χ^2chi-square test with Yate's correction to protect against bias linked to discrepancies within categories was applied to test for any difference between occurrence frequencies of ARs in the AI- vs the Q-FFP treatment category; no significant difference was detected. The occurrences of adverse events were equally low in either arm (AI: 9 in 4689 bags of 200 mL [0.0192] versus Q: 2 in 828 bags [0.024]). Total volumes of FFP used in TPE were comparable in each diagnosis category, although they cannot be compared because patients were not randomized and presented with important pathogenic differences. Of note, a few patients received TPE with mixed volumes of AI-, Q and/or SD-FFP and have not been included in this series.

Cohérent avec les données françaises d'HV < attendu de la littérature ???

This tolerance survey indicates that AI-FFP, a type of plasma, which is not commonly used or reported to be used to perform TPE, is safe, as indicated in a previous survey though limited in size [12]. One may note however that, from the literature, near 5–10% of ARs should be reported. The discrepancy between this report and other haemovigilance reports may have two explanations: patients presented with severe conditions, associated pathology and complex treatment lines often comprising of glucocorticoids, known to mask some moderate ARs; further, due to the complexity of pathology and of the TPE procedure, it is not infrequent from the authors' and colleagues' experience that minor events are not considered worth to be reported; tough we pledge for a more comprehensive reporting and a compliance to the national regulation, we suspect some underreporting of minor reactions. ????

Perspectives et conclusions

In summary, this survey is the first to report on the large-scale use of AI-FFP in TPE sessions. It tends to show good tolerance for this type of plasma, comparable to usually reported TPE side effects in pathologies treated with TPE; indeed, it still appears not powered enough to evidence significant difference due to the very low number of notified reports. This survey precedes a retrospective – multicenter – analysis of clinical efficacy in progress to complement this tolerance study.

À retenir dans la perspective d'un DPC

- **Très grande sécurité générale de la transfusion de plasma dans les EP pour MAT** ; pas ≠ en France de la très bonne tolérance moyenne des transfusions de plasma thérapeutique
- Peut-être masquage thérapeutique et/ou **sous-déclaration des EIR mineurs** voire modérés ?
- **Pas de préférence actuelle pour un type de plasma thérapeutique donné par pathologie** mais cela pourrait changer
  - Avec l'offre et la mise à disposition de nouveaux types de plasma
  - Certains nouveaux plasmas pourraient être testés pour tel ou tel facteur d'intérêt par pathologie (par ex. ADAMTS13 pour PTT etc.)
  - Tolérance ≠ efficacité clinique → peu d'essais cliniques pour valider efficacité clinique « type de plasma par type de plasma » → à suivre…
- **Les recommandations "plasma" pourraient donc évoluer** avec
  - Les nouveaux plasmas
  - L'approche physiopathologique : effet trophique et cicatrisant du plasma sur les endothéliopathies → nouvelles indications ?

Merci

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- EFS Auvergne-Loire → Auvergne-Rhône-Alpes
- Université de Saint-Etienne

  - Prs C Mariat, E Alamartine
  - Drs N Maillard, P Oriol, A Benamara, Ch Guignier

- **Merci pour votre attention**
- **Questions ?**

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