

Hypersensitivity transfusion reactions to platelet concentrate: a retrospective analysis of the French hemovigilance network

Paul M. Mertes,¹ Charles Tacquard,¹ Georges Andreu,² Daniel Kientz,³ Sylvie Gross,⁴ Lucile Malard,⁴ Christian Drouet,⁵ Monique Carlier,⁶ Christian Gachet,³ Imad Sandid,⁷ and Karim Boudjedir⁷

BACKGROUND: Among labile blood products, platelet concentrates (PCs) are the leading cause of hypersensitivity transfusion reactions (HTRs). These reactions often lead to interruption of PC transfusion and can result in a prolonged transfusion process leading to significant morbidity and use of premedication and close monitoring for patients with a history of allergic transfusion reactions. The French hemovigilance database is one of the largest standardized databases providing information on HTRs following administration of labile blood products. In this study, we analyzed this database to assess the relative risk of HTR for each type of PC.

STUDY DESIGN AND METHODS: HTRs following PC transfusion were retrospectively extracted from the e-Fit Hemovigilance database of the French National Agency for Medicines and Health Products Safety (ANSM). Frequencies were calculated using the number of specific PCs transfused.

RESULTS: Between 2008 and 2014, the overall estimated incidence of HTRs following PC administration was calculated at 232 HTRs per 100,000 PCs transfused. The rate of HTRs was significantly higher with apheresis PC (337/100,000) than with buffy-coat PC (94/100,000). Platelets in additive solutions (PAS) were associated with a significantly lower frequency of HTRs when compared with PCs in native plasma.

Amotosalen/UVA- PCs (APCs and BCPCs) which are always in PAS in France, exhibited the lowest frequency of HTRs when compared with their corresponding PCs in native plasma or in PAS ($p < 10^{-7}$ in all comparisons).

CONCLUSION: Our results showed that the type of PC and its processing may have an impact on the risk of HTR.

Hypersensitivity transfusion reactions (HTRs) are defined as reactions with suggestive clinical signs of allergy that appear during or within 4 hours of a transfusion. This definition does not presuppose the mechanism of the reaction, which can be either immune-mediated or not.¹ HTRs account for a large share of adverse transfusion reactions. In comparison with other labile blood products (LBPs), platelet concentrates (PCs) used to correct a defect in the quality/quantity of blood platelets are associated with the highest rate of HTRs. The estimated frequency of these reactions is at least 1.72% of all PCs transfused but this depends on the reporting system and the type of PC.^{2,3} The pathophysiology of PC-related HTRs is not fully understood, insufficiently investigated and complicated by its multifaceted nature. The underlying mechanisms may be recipient-related, donor-related, and/or storage-related. For example, recipient atopy, especially hay fever, has been identified as a risk factor for HTR to PCs.⁴ While recipient and donor-related factors are difficult

From the ¹Department of Anesthesia and Intensive Care, Nouvel Hôpital Civil, Hôpitaux Universitaires de Strasbourg; the ³Etablissement Français du Sang Grand Est, Strasbourg; ²Institut National de Transfusion Sanguine; the ⁵INSERM U1016, CNRS UMR8104, Institut Cochin, Université Paris-Descartes, Paris; ⁴Etablissement Français du Sang, La Plaine Saint-Denis; ⁶Agence Régionale de Santé Grand Est, Châlons en Champagne, and the ⁷French National Agency for Medicines and Health Products Safety (ANSM), Saint Denis, France.

Address reprint requests to: Paul M. Mertes, Service d'anesthésie-réanimation chirurgicale, Hôpitaux Universitaires de Strasbourg, Nouvel Hôpital Civil, 1 Place de l'Hôpital - BP 426 67091 Strasbourg Cedex, France; e-mail: paul-michel.mertes@chru-strasbourg.fr.

Unfunded study, carried out voluntarily by all the authors and co-authors and the French National Agency for Medicines and Health Products Safety. CD has been granted by a program conducted within the Etablissement Français du Sang (EFS call 2016; coordinator: Frank Cognasse).

Received for publication July 10, 2018; revision received February 19, 2019, and accepted February 19, 2019.

doi:10.1111/trf.15275

© 2019 AABB

TRANSFUSION 2019;99:999;1–6

to control, factors linked to PC processing or storage could be targeted to reduce the rate of HTR. Although severe reactions are rare, the occurrence of HTRs often leads to interruption of PC administration, resulting in a delay in treatment with a prolonged transfusion process and significant morbidity.¹

PCs can be processed by different methods in order to reduce the risk of infection, HTRs, and graft-versus-host disease (GvHD). Platelets are prepared from apheresis (APC) or whole blood-derived pooled buffy coats (BCPC). They can be suspended either in native plasma or in additive solution (PAS). A pathogen reduction method using Amotosalen and exposure of PC always prepared in PAS before treatment to Ultraviolet A light (Amotosalen/UVA) has been generalized in France since November 2017. Until this date, gamma-irradiation was still commonly used to prevent GvHD, while a small region (Alsace) and overseas French territories already used Amotosalen/UVA treated PCs since 2007.^{5,6}

The French hemovigilance database of the French National Agency for Medicines and Health Products Safety (ANSM) is one of the largest databases providing information on HTRs following administration of LBPs. ANSM has developed a standard reporting protocol and the reporting of HTRs is mandatory in France.⁷ We retrospectively analyzed this database to assess the relative risk of HTR for each type of PC between 2008 and 2014 in France.

METHODS

HTRs following PC transfusion between 2008 and 2014 were retrospectively extracted (all severities, causality defined as possible, likely or definite) from the e-Fit Hemovigilance database of the ANSM. Transfusion reactions were considered as HTRs by the local hemovigilance correspondents when they met ANSM's criteria (allergy factsheet).⁸ These criteria include the occurrence of mucocutaneous signs (morbilliform rash with pruritus, urticaria, angioedema, edema of lips, tongue and uvula, conjunctival edema), cardiovascular signs (hypotension, tachycardia, syncope, anaphylactic reaction), or respiratory signs (dyspnea, cough, wheezing/bronchospasm, hypoxemia) occurring during the transfusion or within 4 hours of transfusion. An increased histamine or tryptase plasma level during the reaction was also an argument for HTR. When different types of labile blood products were transfused, the attending clinician determined the suspected component(s) according to the temporal relationship between transfusion of each product and the first clinical signs. The severity of the reaction was graded according to the Ring and Messmer classification (Table 1).⁸ HTRs were graded as 1 (mild), 2 (severe), 3 (life-threatening), or 4 (death).

Once the investigation of the transfusion was completed, causality was assessed as follows:

- Non-assessable (NA): When there are insufficient data for causality assessment.
- Excluded/Unlikely: When there is conclusive evidence beyond reasonable doubt for attributing the HTR to

TABLE 1. The Ring and Messmer classification. e-Fit: Hemovigilance database of the French National Agency for Medicines and Health Products Safety (URL ansm.sante.fr/Services/E-FIT)

Grade	Symptoms	e-fit grade
I	Cutaneous signs: erythema, urticaria with or without angioedema	1
II	Presence of measurable but not life-threatening symptoms: cutaneous effects, arterial hypotension, cough or difficulty in mechanical ventilation	2
III	Presence of life-threatening symptoms: cardiovascular collapse, tachycardia or bradycardia, arrhythmia, severe bronchospasm	3
IV	Circulatory failure, cardiac and/or respiratory arrest	3 if the patient is still alive 4 if the patient deceased

alternative causes. Or, when the evidence is clearly in favor of attributing the HTR to causes other than the blood or blood components.

- Possible: When, more than 4 hours after the transfusion, the evidence is indeterminate for attributing the HTR either to the blood or blood component or to alternative causes.
- Likely/Probable: When the evidence is clearly in favor of attributing the HTR to the blood or blood component but without confirmation by a specific test of the responsibility of the transfused blood components.
- Definite/Certain: When there is conclusive evidence beyond reasonable doubt for attributing the HTR to the blood or blood component (such as confirmation by a specific test).

Frequencies were calculated using the number of specific PCs transfused (source: *Etablissement Français du Sang (EFS), National blood service*).

Statistical analysis

Fisher or χ^2 tests were used to compare incidence data. For all comparisons, the results were considered significant at $p < 0.05$. We used the online statistical software provided by Pierre and Marie Curie University.⁹

RESULTS

Between 2008 and 2014, 1,965,318 platelet units, corresponding to 1,119,036 APCs and 843,905 BCPCs were transfused. The various subsets of platelets are shown in Table 2. PCs without plasma or PAS (APCs $n = 14,103$; BCPCs $n = 2,272$) and PCs used for clinical trials (2,377) were excluded from this analysis due to limited data.

During the same period, 4,567 platelet-related HTRs (male = 2,586, female = 1,981) were reported by the French

TABLE 2. Distribution of platelet concentrates transfused in France between 2008 and 2014

	APC	BCPC	Total
Platelets in native plasma	412,413	46,988	459,401
Platelets in PAS	621,473	704,285	1,325,758
Platelets in PAS treated with Amotosalen/UVA	71,047	90,360	161,407
Total	1,104,933	841,633	1,946,566

APC = apheresis platelet concentrate; BCPC = buffy-coat-derived platelet concentrate; PAS = platelet additive solution; UVA = ultraviolet A.

hemovigilance network, corresponding to an estimated incidence of 232 HTRs per 100,000 PCs transfused.

Ninety-five percent of these reactions were observed in a hematology-oncology setting. Transfusion causality was graded as level 1 (possible) in 1,249 cases (27.3%), level 2 (likely/probable) in 2,981 cases (65.3%), and level 3 (definite/certain) in 337 cases (7.4%). In most cases (91%) the reaction occurred after a single PC transfusion, 5% after more than one transfusion, and the remaining 4% after transfusion with various blood products. Most of these reactions were mild (grade 1, $n = 4,172$; 91%), 243 were grade 2 (5.3%), 151 were grade 3 (3.3%), and 1 was grade 4.

The median storage time of the PCs was 3 days (0–4 days) across all types of PC and technical processing.

In terms of HTR incidence rates per 100,000 PCs transfused, significant differences were observed between the various types of PC, with a significantly higher rate for APCs (337/100,000) compared with BCPCs (94/100,000) ($p < 0.0001$).

These differences were still observed when the various subsets of APCs and BCPCs were compared (Table 3). Platelets in PAS, whether APC or BCPC, were associated with a significantly lower frequency of HTRs when compared with PCs in native plasma ($p < 0.001$).

PCs treated with Amotosalen/UVA exhibited the lowest rate of HTRs when compared with their corresponding PCs in native plasma or in PAS (Supplementary data Table S1).

Irradiated PCs ($n = 3,243$) had a higher rate of HTRs than non-irradiated PCs ($n = 1,324$). Table 4 presents the incidence rates for the different types of PCs according to irradiation status.

DISCUSSION

Based on our results, the risk of HTR following PC transfusion appears to be strongly influenced by the type of platelet

concentrate and its processing. This risk is higher with APC than with BCPC. The use of PAS reduces the risk of HTR in comparison with native plasma while irradiation is associated with a higher risk of HTR in the case of APCs. Pathogen-reduced PCs in PAS treated by the Amotosalen/UVA method, which combines the advantage of reducing the infectious risk and avoiding irradiation, exhibit the lowest risk of HTR when compared with other preparations.

The incidence of HTRs was estimated at 232 per 100,000 PCs transfused in our study. In comparison, on the same period, the incidence of febrile nonhemolytic transfusion reactions (FNHTR) was estimated at 82 per 100,000 PCs transfused. These results are consistent with the one recently published by Van Hout et al.¹⁰ Between 2006 and 2015, their incidence of HTR and FNHTR were respectively estimated at 210 and 150 per 100,000 PCs transfused.¹⁰ These results confirm that HTR are the main cause of adverse transfusion reaction.

Our results suggest that the risk of HTR is significantly higher with APCs than with BCPCs (337 vs. 94 per 100,000 PCs transfused, $p < 0.0001$) regardless of the type of processing. These results are consistent with previously published studies on smaller series. In 2008, Rebibo et al. reported that APCs were associated with a higher risk of HTR (345 vs. 124 HTR per 100,000 LBP transfused).¹¹ In a US healthcare safety network hemovigilance survey between 2010 and 2012 on 393,375 PCs transfused, the rate of adverse reactions was higher with APCs than with BCPCs (538 vs. 101 adverse reactions per 100,000 LBP).¹² Only one small study conducted in two academic hospitals showed discordant results with a risk of HTR that was higher with pooled platelets than with APCs (0.41% vs. 0.24%, $p = 0.0029$).¹³ However, these results were obtained on a small number of reactions and no difference was observed when the first academic hospital involved in the study was considered. Furthermore, this increased risk was observed with pooled platelets prepared with the platelet-rich plasma (PRP) method while the pooled platelets in our study were prepared from pooled buffy-coats (BC). This may account for the difference, as the volume of plasma from each individual donor of the pool is constantly lower with BC than with the PRP method.

PCs can be prepared either from whole blood donation (mainly buffy-coat methods in Europe) or by an apheresis procedure. These two methods are considered equivalent in terms of efficacy and risk of HLA allo-immunization. Although APCs and BCPCs may be considered equivalent in the absence of HLA allo-immunization,¹⁴ compatible APCs are preferably used in patients

TABLE 3. Number of HTRs and estimated incidence of HTR per 100,000 units transfused according to PC type in France between 2008 and 2014

	APC N (incidence/100,000)	BCPC N (incidence/100,000)	OR (95%CI)
Platelets in native plasma	2,063 (500)	80 (170)	2.94 (2.35–3.72)
Platelets in PAS	1,638 (264)	677 (96)	2.74 (2.51–3.00)
Platelets in PAS treated with Amotosalen/UVA	71 (100)	38 (42)	2.38 (1.38–3.62)

N = number of HTRs; OR = odds ratio; UVA = ultraviolet A; APC = apheresis platelet concentrate; BCPC = buffy-coat-derived platelet concentrate.

TABLE 4. Number of HTRs and estimated incidence of HTR per 100,000 units transfused of non-irradiated and irradiated platelet concentrates in France between 2008 and 2014

	Non-irradiated N (incidence /100,000)	Irradiated N (incidence /100,000)	OR (95% CI)
APC in native plasma	575 (435)	1,488 (531)	1.22 (1.11–1.35)
APC in PAS	303 (200)	1,335 (284)	1.42 (1.25–1.61)
APC in PAS treated with Amotosalen/UVA*	71 (100)	-	-
BCPC in native plasma	33 (244)	47 (140)	0.57 (0.36–0.93)
BCPC in PAS	304 (98)	373 (94)	0.96 (0.82–1.12)
BCPC in PAS treated with Amotosalen/UVA*	38 (42)	-	-

N = number of HTRs; OR = odds ratio; UVA = ultraviolet A; APC = apheresis platelet concentrate; BCPC = buffy-coat-derived platelet concentrate; PAS = platelet additive solution.

* Amotosalen-inactivated platelets were never irradiated.

with HLA/HPA allo-immunization with platelet transfusion inefficacy and in pediatric preparations.

In our study, the rate of HTR following PC transfusion was 36–48% lower when using PAS. Although the reason for these beneficial effects is not fully understood, our findings are in line with previous reports.^{10,11,15,16} Several hypotheses have been proposed to explain this, including a reduction in plasma protein concentration with the use of PAS.^{3,17} Indeed, plasma accumulation of inflammatory proteins (C5a, brain-derived neutrophilic factor and CCL5) and mitochondrial DNA have been found to be associated with a higher risk of HTR.^{18,19} It is important to note that PCs in PAS accounted for more than 98% of PCs transfused since 2012 versus less than 50% in 2008–2009. This evolution is a result of ANSM recommendations for the prevention of Creutzfeldt-Jakob disease transmission by blood transfusion and the observation that the use of a PAS was associated with a reduction of HTR. Between 2008 and 2014, four types of PAS were used in France: T-Sol, Intersol, SSP, and SSP+. Data from in our study were too limited to analyze each type of PAS independently. However, in their study, Van Hout et al. reported a lower risk of HTR with Intersol when compared with T sol PAS (relative risk 0.58; CI95 0.40–0.82).¹⁰ By reducing the use of premedication to prevent HTR, the use of PAS was even found to be cost-effective.¹⁵

In our study, the incidence of HTRs was 72–80% lower with Amotosalen/UVA-treated PCs in PAS compared with PCs in plasma and 56–61% lower when compared with PCs in PAS.

These results are similar to those of a prospective cohort in 2015, which reported a reduction in the rate of adverse reactions using Amotosalen/UVA-pathogen reduction.²⁰ In the EFFIPAP study, a randomized controlled trial comparing PCs in plasma, in PAS or inactivated using Amotosalen/UVA, the rate of allergic reaction was also found to be lower in the group of Amotosalen/UVA inactivated PCs. Their hemostatic efficacy was non-inferior when compared with PCs in PAS but slightly reduced in comparison with PCs in native plasma.²¹ However, due to the global benefice of PCs in PAS, PCs in native plasma are almost no longer used in France.

Amotosalen/UVA is a pathogen reduction method using a combination of a synthetic psoralen Amotosalen and UVA. It was found to be effective in preventing a wide spectrum of bacterial,

viral, and protozoal infections.^{22,23} Briefly, on illumination with UVA, Amotosalen forms covalent interstrand cross-links with DNA or RNA, preventing DNA replication and RNA transcription. In this process, platelets are first suspended in a mix of plasma and PAS (Intersol, T-Sol, or SSP+) in the same proportion as the standard use of these PAS, i.e., 50–70% of the initial plasma volume in replaced by the PAS. After illumination, residual Amotosalen is absorbed before storage. At the end of the process, the final volume of plasma remains unchanged. Storage lesions have been considered as acceptable for transfusion up to 7 days by some authors.²⁴ This extension of the storage time to 7 days was recently authorized by the ANSM.

As the Amotosalen/UVA pathogen reduction method targets nucleated leukocytes, it is also effective at preventing transfusion-related graft-versus-host disease.²⁵ Therefore, Amotosalen/UVA-treated PCs do not require gamma-irradiation. The molecular and cellular mechanisms of the protective effect of Amotosalen/UVA-treated PCs on HTRs are not fully understood. However, Amotosalen/UVA treatment prevents white cell cytokine synthesis, which could reduce cytokine accumulation in PCs.²⁶

Our results indicate that irradiation of APCs is associated with an increased risk of HTR. The effect of gamma-irradiation on PCs is not well understood and further studies are required. Irradiation is used to prevent transfusion-related graft-versus-host disease (TR-GvHD) in immunocompromised patients by inhibiting T-cell activation.¹⁷ Irradiation alone is not sufficient to prevent bacterial growth, as the total dose of irradiation to prevent TR-GvHD (25–45 Gray) is 1,000-fold lower than the dose used for sterilization.²⁷ In this regard, the use of Amotosalen/UVA treated PCs can not only reduce the infectious risk, but also suppress the need for irradiation.

Our study suffers from several limitations:

- During the considered period, only two French regions (Alsace and overseas territories) used Amotosalen/UVA treated PCs. Overseas territories are known to have a lower notification rate for adverse transfusion reactions and this could induce a bias in the interpretation of our results. Amotosalen/UVA pathogen reduction method has now been generalized in France and further studies are required to confirm our results.

- Data on the type of PCs used in different recipient populations (e.g., oncology-hematology setting) were not recorded. In France, APCs and irradiated PCs were preferentially used in onco-hematology patients and these patients are more likely to be exposed to PCs than patients receiving BCPCs, non-irradiated PCs, or Amotosalen/UVA treated PCs. An increased exposition might increase the risk of sensitization although the relation between exposure and sensitization is not linear. Therefore, this could act as a confounding factor, especially when considering the difference of HTR incidence between APCs and BCPCs and between non-irradiated, irradiated PCs, and Amotosalen/UVA treated PCs.

In conclusion, this large-scale retrospective study involving almost two millions of PCs transfusions confirms that the type of PC (APC vs pooled BCPC) and their further processing (PC in native plasma, PC in PAS, Amotosalen/UVA-treated PCs, gamma irradiation) impact the risk of HTR. Further random controlled trials are necessary to confirm our findings.

CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

DISCLAIMER

None.

REFERENCES

1. Mertes PM, Bazin A, Alla F, et al. Hypersensitivity reactions to blood components: document issued by the allergy committee of the French medicines and healthcare products regulatory agency. *J Investig Allergol Clin Immunol* 2011;21:171-8.
2. Savage WJ, Tobian AA, Fuller AK, et al. Allergic transfusion reactions to platelets are associated more with recipient and donor factors than with product attributes. *Transfusion* 2011; 51:1716-22.
3. Hirayama F. Current understanding of allergic transfusion reactions: incidence, pathogenesis, laboratory tests, prevention and treatment. *Br J Haematol* 2013;160:434-44.
4. Savage WJ, Hamilton RG, Tobian AA, et al. Defining risk factors and presentations of allergic reactions to platelet transfusion. *J Allergy Clin Immunol* 2014;133:1772-5 e9.
5. Cazenave JP, Isola H, Waller C, et al. Use of additive solutions and pathogen inactivation treatment of platelet components in a regional blood center: impact on patient outcomes and component utilization during a 3-year period. *Transfusion* 2011;51: 622-9.
6. Rasongles P, Angelini-Tibert MF, Simon P, et al. Transfusion of platelet components prepared with photochemical pathogen inactivation treatment during a Chikungunya virus epidemic in Ile de La Reunion. *Transfusion* 2009;49:1083-91.
7. Andreu G, Morel P, Forestier F, et al. Hemovigilance network in France: organization and analysis of immediate transfusion incident reports from 1994 to 1998. *Transfusion* 2002;42:1356-64.
8. ANSM. Fiche technique des effets indésirables receveurs - Allergie [monograph on the internet]. 2015 [cited 2015, december 15]. Available from: ansm.sante.fr
9. (UPMC) IaPMCU. Statistical software developed by the Pierre Louis Institute of epidemiology and public health UMR 1136 [monograph on the internet]. 2018 [cited 2017, november 29]. Available from: <http://marne.u707.jussieu.fr/biostatgv/>
10. van Hout FMA, van der Meer PF, Wiersum-Osselton JC, et al. Transfusion reactions after transfusion of platelets stored in PAS-B, PAS-C, or plasma: a nationwide comparison. *Transfusion* 2018;58:1021-7.
11. Rebibo D, Simonet M, Hauser L. Introduction of platelet additive solution in platelet concentrates: towards a decrease of blood transfusion reactions. *Transfus Clin Biol* 2008;15:289-93.
12. Harvey AR, Basavaraju SV, Chung KW, et al. Transfusion-related adverse reactions reported to the National Healthcare Safety Network Hemovigilance Module, United States, 2010 to 2012. *Transfusion* 2015;55:709-18.
13. Xiao W, Tormey CA, Capetillo A, et al. Allergic transfusion reactions to platelets are more commonly associated with prepoolled than apheresis components. *Vox Sang* 2013;105:334-40.
14. Hess JR, Trachtenberg FL, Assmann SF, et al. Clinical and laboratory correlates of platelet alloimmunization and refractoriness in the PLADO trial. *Vox Sang* 2016;111:281-91.
15. Kacker S, Ness PM, Savage WJ, et al. The cost-effectiveness of platelet additive solution to prevent allergic transfusion reactions. *Transfusion* 2013;53:2609-18.
16. de Wildt-Eggen J, Nauta S, Schrijver JG, et al. Reactions and platelet increments after transfusion of platelet concentrates in plasma or an additive solution: a prospective, randomized study. *Transfusion* 2000;40:398-403.
17. Tynngard N. Preparation, storage and quality control of platelet concentrates. *Transfus Apher Sci* 2009;41:97-104.
18. Savage WJ, Savage JH, Tobian AA, et al. Allergic agonists in apheresis platelet products are associated with allergic transfusion reactions. *Transfusion* 2012;52:575-81.
19. Yasui K, Matsuyama N, Kuroishi A, et al. Mitochondrial damage-associated molecular patterns as potential proinflammatory mediators in post-platelet transfusion adverse effects. *Transfusion* 2016;56:1201-12.
20. Knutson F, Osselaer J, Pierelli L, et al. A prospective, active haemovigilance study with combined cohort analysis of 19,175 transfusions of platelet components prepared with amotosalen-UVA photochemical treatment. *Vox Sang* 2015;109:343-52.
21. Garban F, Guyard A, Labussiere H, et al. Comparison of the hemostatic efficacy of pathogen-reduced platelets vs untreated platelets in patients with thrombocytopenia and malignant hematologic diseases: a randomized clinical trial. *JAMA Oncol* 2018;4:468-75.
22. Benjamin RJ, Brachler T, Weingand T, et al. Hemovigilance monitoring of platelet septic reactions with effective bacterial protection systems. *Transfusion* 2017;57:2946-57.

23. Kaiser-Guignard J, Canellini G, Lion N, et al. The clinical and biological impact of new pathogen inactivation technologies on platelet concentrates. *Blood Rev* 2014;28: 235-41.
24. Lozano M, Knutson F, Tardivel R, et al. A multi-centre study of therapeutic efficacy and safety of platelet components treated with amotosalen and ultraviolet A pathogen inactivation stored for 6 or 7 d prior to transfusion. *Br J Haematol* 2011;153: 393-401.
25. Cid J. Prevention of transfusion-associated graft-versus-host disease with pathogen-reduced platelets with amotosalen and ultraviolet A light: a review. *Vox Sang* 2017;112:607-13.
26. Hei DJ, Grass J, Lin L, et al. Elimination of cytokine production in stored platelet concentrate aliquots by photochemical treatment with psoralen plus ultraviolet A light. *Transfusion* 1999;39:239-48.
27. Huston BM, Brecher ME, Bandarenko N. Lack of efficacy for conventional gamma irradiation of platelet concentrates to abrogate bacterial growth. *Am J Clin Pathol* 1998;109:743-7. 

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

Table S1. Comparison of the estimated incidence of HTR per 100,000 units transfused between Amotosalen/UVA PCs and their corresponding PCs in plasma or in PAS.

	Amotosalen/UVA N (incidence/100,000)	Other PCs N (incidence/100,000)	OR (95%CI)	p
APC Amotosalen/UVA vs. APC in plasma	71 (100)	2,063 (500)	0.2 (0.16 – 0.25)	$9 \cdot 10^{-8}$
APC Amotosalen/UVA vs. APC in PAS	71 (100)	1,638 (264)	0.38 (0.29 – 0.48)	$1.8 \cdot 10^{-20}$
BCPC Amotosalen/UVA vs. BCPC in plasma	38 (42)	80 (170)	0.25 (0.16 – 0.37)	$1.3 \cdot 10^{-13}$
BCPC Amotosalen/UVA vs. BCPC in PAS	38 (42)	677 (96)	0.44 (0.31 – 0.61)	$3.3 \cdot 10^{-8}$

Table S1: Comparison of the estimated incidence of HTR per 100,000 units transfused between Amotosalen/UVA PCs and their corresponding PCs in plasma or in PAS

N: number of HTRs; OR: Odds ratio; UVA: Ultraviolet A

APC: Apheresis Platelet Concentrate; BCPC: Buffy-Coat-derived Platelet Concentrate;