Durée de conservation des concentrés de plaquettes et risque d'Allo-immunisation

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Déclaration de liens d'intérêt

- Sur ces 5 dernières années,
  - Honorariums et invitations reçus de Cerus-Europe, Macopharma-France
  - Invitations reçues de Terumo-BCT

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Actualité quant aux concentrés de plaquettes ?

- En France
  - *Leucoréduction systématique in process*
  - *100% PAS*
  - **100% inactivées par l'Amotosalen-HCl-UVA (INTERCEPT®)**
  - **Durée de vie étendue à 7 j et non plus 5**
- Dans le monde
  - **Plaquettes à 4°C**

La question de la durée de conservation est-elle ainsi un sujet d'actualité ?

Actualité quant aux concentrés de plaquettes ?

OUI, au moins pour ces raisons relativement universelles…

- Appariement ABO (ABO compatible, ABO identique) pris en considération de façon variable
- Pas d'appariement HLA, HPA pour des raisons de logistique et de phéno(géno)typage des donneurs (et en particulier donneurs de sang total → MCPS)
- Sensibilité à l'alloimmunisation des polytransfusés et des femmes ayant été enceintes (multigestes, multipares)

Actualité quant aux concentrés de plaquettes ?

OUI, car l'application de PRT et l'extension de la durée de conservation peuvent modifier la donne initiale

- Des approches expérimentales relatives aux procédés de réduction de pathogènes affichent une réduction de l'allo-immunisation par les procédés et en particulier la Riboflavine-UVB
- Mais les premières données cliniques ne les confirment pas, au contraire !

Données anciennes

- Andreu G, Dewailly J, Leberre C, Quarre MC, Bidet ML, Tardivel R, Devers L, Lam Y, Soreau E, Boccaccio C, et al. Prevention of HLA immunization with leukocyte-poor packed red cells and platelet concentrates obtained by filtration. Blood. 1988 Sep;72(3):964-9.
- Andreu G, Boccaccio C, Kiaren J, Lecrubier C, Pirenne F, Garcia I, Baudard M, Devers L, Fournel JJ. The role of UV radiation in the prevention of human leukocyte antigen alloimmunization. Transfus Med Rev. 1992 Jul;6(3):212-24.
- Andreu G, Perrot JY, Pirenne F, Boccaccio C. The effect of ultraviolet B light on antigen-presenting cells: implications for transfusion-induced sensitization. Semin Hematol. 1992 Apr;29(2):122-31
- The Trial to Reduce Alloimmunization to Platelets Study Group. Leukocyte reduction and ultraviolet B irradiation of platelets to prevent alloimmunization and refractoriness to platelet transfusion. New Engl J Med 1997;337:1861-9.
- Slichter SJ, Fish D, Abrams VK, Gaur L, Nelson K, Bolgiano D. Evaluation of different methods of leukoreduction of donor platelets to prevent alloimmune platelet refractoriness and induce tolerance in a canine transfusion model. Blood. 2005 Jan 15;105(2):847-54
- Slichter JS, Bolgiano D, Kao JK, Kickler KS, McFarland J, McCullough J, Woodson Persistence Of Lymphocytotoxic Antibodies In Patients In The Trial To Reduce Alloimmunization To Platelets: Implications For Using Modified Blood Products. Transfus Med Rev. 2011 Apr; 25(2): 102–110.
- Slichter SL, Davis K, Enright H, Braine H, Gernsheimer T, Kao KJ, Kickler T, Lee E, McFarland J, McCullough J, Rodey G, Schiffer CA, Woodson R. Factors affecting posttransfusion platelet increments, platelet refractoriness, and platelet transfusion intervals in thrombocytopenic patients. Blood. 2005 May 15; 105(10): 4106–4114

Données plus récentes

- Slichter SJ, Pellham E, Bailey SL, Christoffel T, Gettinger I, Gaur L, Latchman Y, Nelson K, Bolgiano D. Leukofiltration plus pathogen reduction prevents alloimmune platelet refractoriness in a dog transfusion model. Blood. 2017 Aug 24;130(8):1052-1061
- van der Meer PF, Ypma PF, van Geloven N, van Hilten JA, van Wordragen-Vlaswinkel RJ, Eissen O, Zwaginga JJ, Trus M, Beckers EAM, Te Boekhorst P, Tinmouth A, Lin Y, Hsia C, Lee D, Norris PJ, Goodrich RP, Brand A, Hervig T, Heddle NM, van der Bom JG, Kerkhoffs JH. Hemostatic efficacy of pathogen-inactivated vs untreated platelets: a randomized controlled trial. Blood. 2018 Jul 12;132(2):223-231

Hypothèses sur l'allo-immunisation

- **Garraud O, Cognasse F, Moncharmont P.** Immunological features in the process of blood platelet-induced alloimmunization, with focus on platelet component transfusion. ***Diseases,*** 2019, *in press*

Recipient genetic condition and environment
-HLA genotype
-Environment and microbiota

Donor genetic background (blood and tissue [ABO, HLA])

Component condition
-Non-Leukoreduced
-Bedside filtered and leukoreduced
-Stringently leukoreduced in process after collection

Recipient medical and life history
-Antedecents of transfusion
-Pregnancies and multiparity

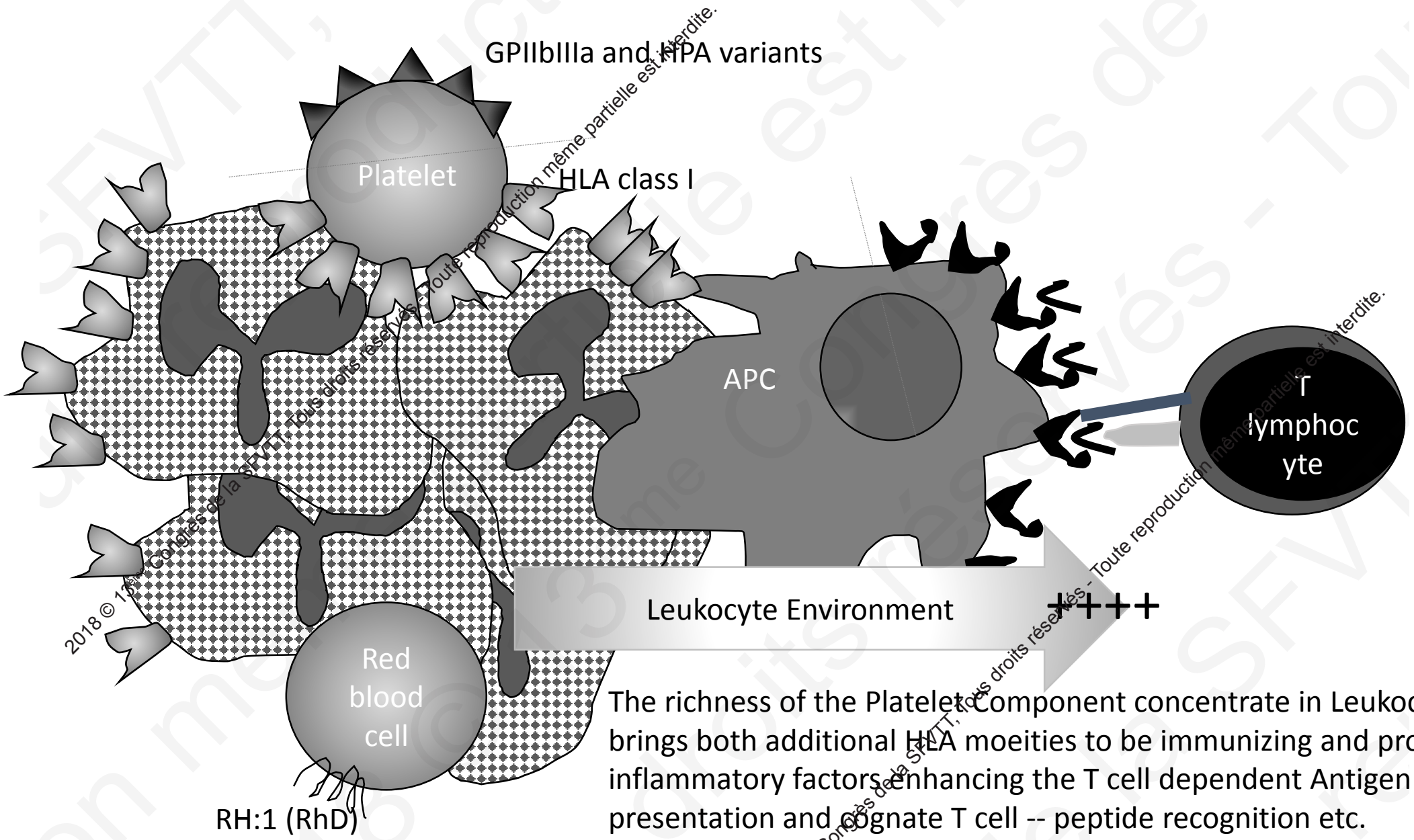
Mutual influence of parity on transfusion and vice-versa, with respect to alloimmunization

Alloimmunization

Recipient medical condition
-Causal disease
-Treatment and conditioning
Immunosuppressant

Recipient extrinsinc factors

Recipient intrinsinc factors



The richness of the Platelet Component concentrate in Leukocytes brings both additional HLA moeities to be immunizing and pro-inflammatory factors enhancing the T cell dependent Antigen presentation and cognate T cell -- peptide recognition etc.
All of the above favor the build up of a productive T cell help to B Lymphocytes and Antibody production

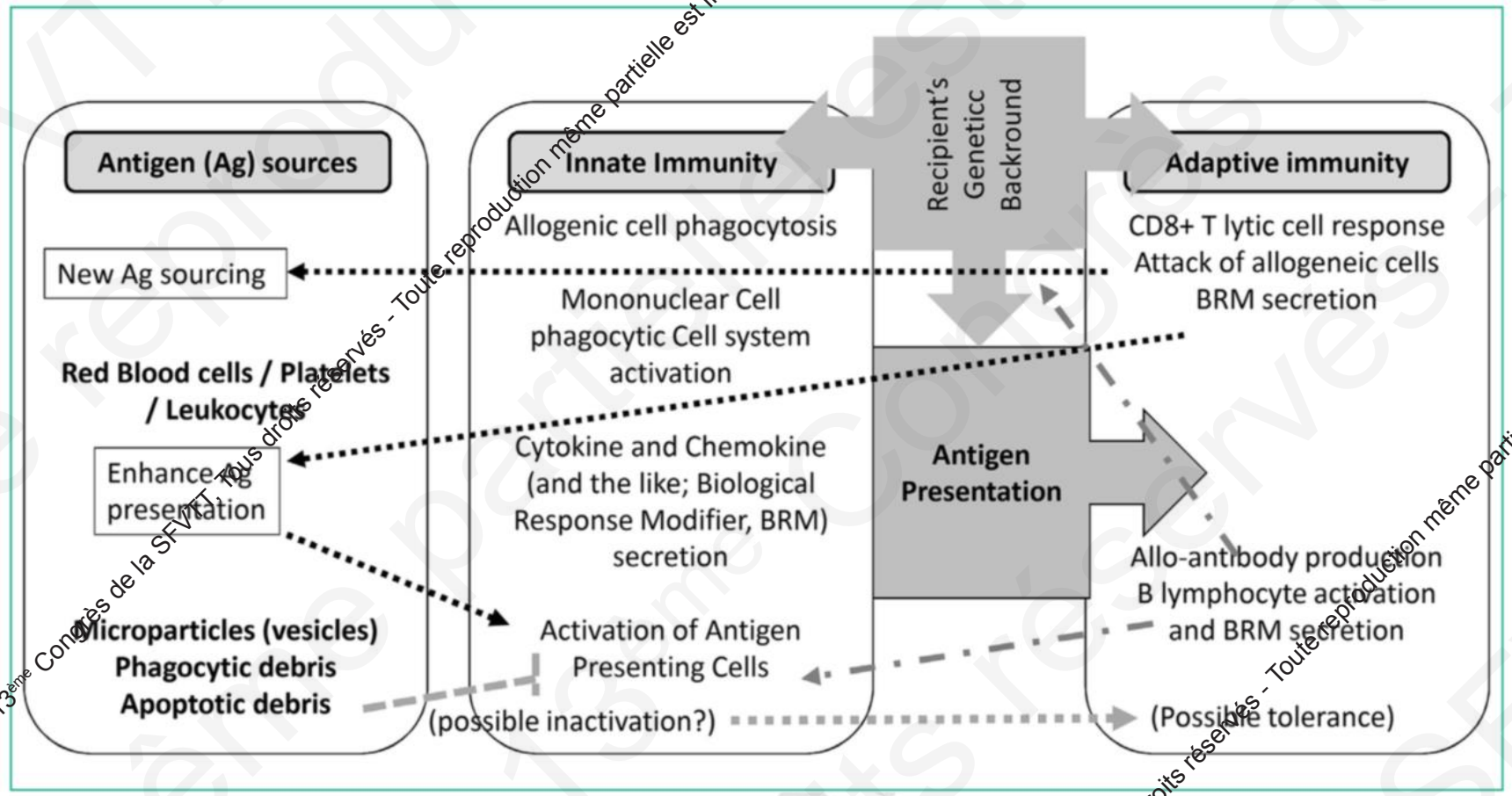


Fig. 1. Possible mechanisms of alloimmunization to red blood cell, platelet and human leukocyte antigens. The left panel indicates the main sources of allo-antigens after homologous transfusion; the main source of antigens derives from either fresh or aging cells emitting vesicles (and comprising the so-called storage lesions; indeed, blood components become non-natural by being outside of the [donor] body, refrigerated, processed and exposed to artificial elements such as plastics, etc.); the second source results from transfused cells specifically attacked by natural immune cells (from recipients): this is emphasized when the recipient recognizes recall antigens against which he/she has been sensitized or immunized by previous transfusions or pregnancies or – for certain antigens – grafts or transplantations. Most of the elements derived from the transfused cells are sensed as foreign by the recipient's innate (or natural) immune system, favoring phagocytosis (enhancing the source of antigens → left panel) and antigen presentation (plain arrow between the middle and right panels). Innate immunity (middle panel) enables either the destruction of foreign material by granulocytes and certain macrophages (not shown here) or the presentation of derived material therefore referred to as antigen when specifically bound to reacting T or B lymphocytes. This step requires that the recipient displays HLA moieties capable of presenting aligned peptidic antigens to CD4+ cytolytic T cells or CD4+ helper T lymphocytes, or that reactive B cells recognize conformational antigens on allogeneic red blood cells, platelets and leukocytes. The step consisting of specific T and B cell activities is now referred to as adaptive immunity (formerly specific immunity; right panel).

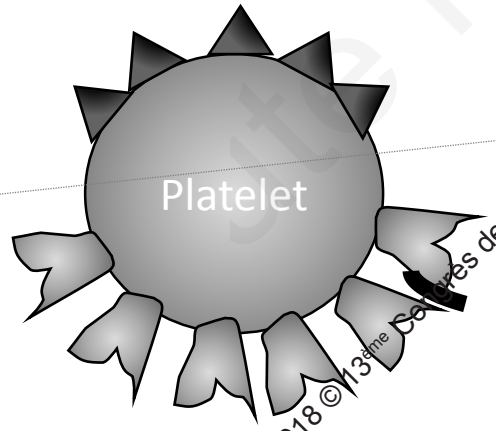
DONOR & COMPONENT

DONOR* OR RECIPIENT**

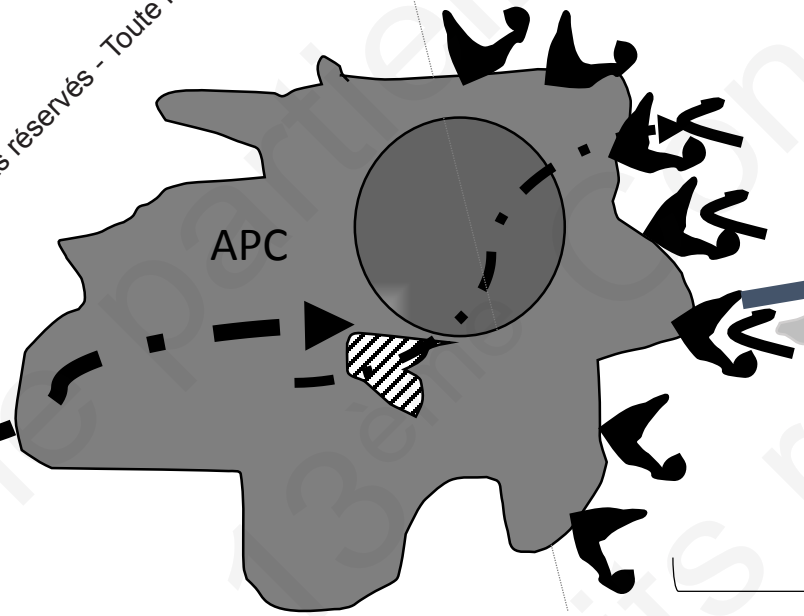
RECIPIENT

*Donor direct allorecognition
**Recipient indirect allorecognition

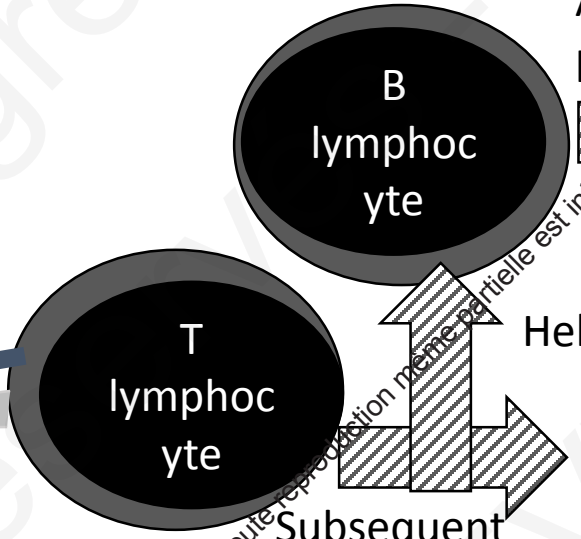
GPIIbIIIa and other adhesion molecules harbouring most HPA variants (antigens)



HLA class I molecules (with no firmly identified function on human platelets)



Platelet degradation and processing of peptides to be presented in HLA class II grooves



Cognate recognition of peptide
HLA class II restricted
Strengthened by adhesion molecules on Both APC and T lymphocyte (synapse)

Helper T cell help

Subsequent T cell activation and differentiation and B cell help

Antibody production

Not scaled up

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Transfusion and Apheresis Science xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Transfusion and Apheresis Science

journal homepage: www.elsevier.com/locate/transci

Pathogen reduction or inactivation technologies for platelet components: Does decision making have to await further clinical trials?

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What did the PREPAReS trial report [14]? This Dutch centralized but international investigation evaluated Mirasol™-treated platelets in 100% plasma against platelets in plasma (controls). In both approaches, intention to treat and per protocol, they found no non-inferiority regarding grade 2 bleeding, despite the fact that the CCI was lower in the test as compared to the control group (and also that there was a reduced interval between two transfusions in the intention to treat test group). They noticed a slight increase in bleeding in the test arm but the trial was not powered well enough to conclude adversely. In the "key point" section of their manuscript, the investigators further outlined that they did not observe a decrease in alloimmunization, in contrast with claims based on experimental models [15–18]. The Italian IPTAS trial on PI/PR (Mirasol™ vs Intercept™) failed to identify a reduction in alloimmunization as well, but this could be attributable to the sample size and a lack of power. Having extended their study in a 7d to 5d survey, the Dutch team revealed that after longer storage, the recipients' dendritic cells can pick up material derived from platelets—likely by apoptosis or the like—and enhance □-interferon secretion by CD4 + T cells and factors enhancing antigen presentation. This data is indeed impressive as it may reveal a propensity of longer stored platelets to favor alloimmunisation in genetically reactive recipients and even a reinforced propensity of PI/PR treated longer storage platelets to be immunizing [18].

I take this preliminary data very seriously as we have been claiming for more than a decade that, considering PCT, "the freshest the best", at least for tolerance [18,19]. There is thus accumulated evidence that 7-day platelets may be extremely useful to provide support to a needy patient in emergency situations but may be not good for routine management of the PC inventory [20]. In this case, further well powered clinical trials would be necessary before BEs operate routine inventory processing of 7d platelets when PI/PR treated (and the levels of other inflammatory reactions linked to transfusion would also be worth being examined as well [21,22]). Next, it must be noted that most clinical trials investigating PI/PR for PCT have been conducted in adult onco- or onco-hematological patients [23], while neonates, children, and females of childbearing age are also now exposed to PI/PR treated PCs. It would be particularly wise, in my opinion, to carry out reinforced hemovigilance and long-term observation of those populations.

In the aggregate, PI/PR technologies have allowed the near eradication of lethal complications of PC transfusion. A fine-tuned risk-benefit analysis has not yet been made fully available as illustrated by the possibility of enhanced alloimmunization in longer storage protocols. As extended storage is part of the benefit provided by BEs, this sheds light on possible conflicting values, to be evaluated as well.

Remerciements, crédits

- Collaborateurs dans l'EA_3064 (Lyon/Saint-Etienne) et en particulier Hind Hamzeh-Cognasse et Sandrine Laradi (PhD HDR) ; Dr Antoine Haddad MD (Beyrouth) ; Drs H Benamara et H Odent-Malaure, EFS
- CHU de Saint-Etienne et ICLN Saint-ETIENNE, en particulier Prs Denis Guyotat et Emmanuelle Tavernier, Drs Christiane Mounier et Dr Pascale Oriol
- Financements : EFS, Université de Saint-Etienne, INTS, ART, ANSM, ANRS, Association Amis de Rémi
- Organisateurs et comité scientifique SFVTT
- **Merci pour votre attention** → Questions ?
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