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Apheresis for desensitization in the setting of HLA incompatible kidney transplantation: efficacy and at what cost?

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**APHERESIS FOR DESENSITIZATION IN THE SETTING OF HLA INCOMPATIBLE
KIDNEY TRANSPLANTATION: EFFICACY AND AT WHAT COST?**

THÈSE
PRÉSENTÉE POUR L'OBTENTION DU TITRE DE DOCTEUR EN MÉDECINE,
DIPLOME D'ÉTAT

Antoine METZGER

[Données à caractère personnel]

THÈSE SOUTENUE PUBLIQUEMENT À LA FACULTÉ DE MÉDECINE DE
GRENOBLE

Le : 20/10/2020

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aux opinions émises dans les thèses ; ces opinions sont considérées comme propres
à leurs auteurs.*

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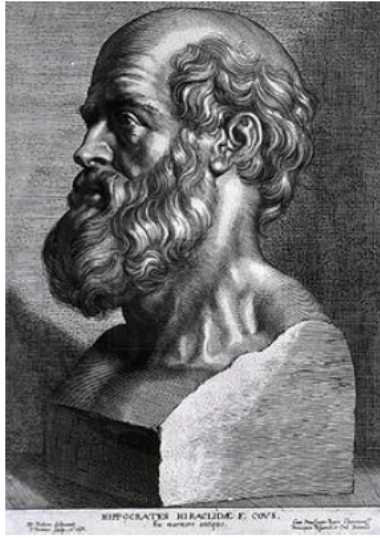
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SERMENT D'HIPPOCRATE

En présence des Maîtres de cette Faculté, de mes chers condisciples et devant l'effigie d'HIPPOCRATE,

Je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuitement à l'indigent et n'exigerai jamais un salaire au dessus de mon travail. Je ne participerai à aucun partage clandestin d'honoraires.

Admis dans l'intimité des maisons, mes yeux n'y verront pas ce qui s'y passe ; ma langue taira les secrets qui me seront confiés et mon état ne servira pas à corrompre les mœurs, ni à favoriser le crime.

Je ne permettrai pas que des considérations de religion, de nation, de race, de parti ou de classe sociale viennent s'interposer entre mon devoir et mon patient.

Je garderai le respect absolu de la vie humaine.

Même sous la menace, je n'admettrai pas de faire usage de mes connaissances médicales contre les lois de l'humanité.

Respectueux et reconnaissant envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

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Abbreviations:

ABOi: ABO incompatible

ABM: Agency of Biomedicine

ABMR: Antibody-mediated rejection

BMI: Body-Mass index

CKD: Chronic Kidney Disease

CMV: Cytomegalovirus

cPRA: Calculated Panel Reactivity Antibodies

CNIL: French National Committee for data protection

DFPP: Double-Filtration Plasmapheresis

DSA: Donor-Specific Alloantibody

ESKD: End-Stage Kidney Disease

FFP: Fresh Frozen Plasma

HD: Hemodialysis

HLA: Human Leucocyte Antigen

HLAi: Human Leucocyte Antigen Incompatible

IA: Immuno-Adsorption

IgA: Immunoglobulins A

IgG: Immunoglobulins G

IgM: Immunoglobulins M

IV: Intravenous

IVIG: Intravenous Immunoglobulins

KT: Kidney Transplantation

MFI: Mean Fluorescence Intensity

PCR: Polymerase Chain Reaction

PE: Plasma Exchange

PRA: Panel-Reactivity Antibody

SA: Single Antigen

SD: Standard Deviation

TGI: Incompatible Graft Rate

THÈSE SOUTENUE PAR : Metzger Antoine

TITRE :

APHERESIS FOR DESENSITIZATION IN THE SETTING OF HLA INCOMPATIBLE KIDNEY TRANSPLANTATION: EFFICACY AND AT WHAT COST?

CONCLUSION :

Introduction: Between 2013 and 2018, nearly 18% of patients on the waiting-list for kidney transplantation (KT) are highly sensitized. Despite the priority allocation system, highly sensitized patients remain on waiting list two to three times longer than non-sensitized candidates. We assessed in this study the efficacy, cost and tolerance of different technic (i.e. plasma exchanges (PE), double-filtration plasmapheresis (DFPP) and immunoadsorption (IA)) to remove anti-HLA priori to HLA incompatible (HLAi) KT.

Methods: All patients who underwent apheresis for HLAi KT in the University Hospital of Grenoble were included. Data of apheresis parameters, biology, tolerance and cost of each session was assessed.

Results: A total of 881 apheresis sessions were performed for 45 patients in the setting of HLAi KT: 107 DFPP, 54 PE, 720 IA. Patients were women in 55.6 %. Mean age at KT was 53 ± 13 years. The procedure led to HLAi KT in 39 patients (87%) after 51 days [24-86]. Mean relative reduction of total IgG post session was significantly different for each technique ($p < 0.001$) (40 % in DFPP, 61% in PE and 60% in IA). Maximum DSA MFI decrease after desensitization from 7993 to 198 at transplant. Safety was good: hypotension occurred 154 sessions (17.5%), more frequently in DFPP versus IA or PE. Leucocytes count increase from 9.5 to 16.8 G/L post DFPP sessions only. Severe adverse events defined by discontinuation of session or hospitalization occurred in 17 sessions (1.9%) and more frequently in DFPP (6.5% of sessions) versus IA (1.9%) or PE (1.2%). Transfusion occurred in 9.3% of the apheresis sessions. Mean cost (in

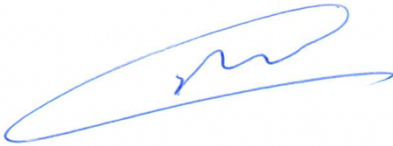
euros) was 998 ± 357 for EP, 690 ± 133 for DFPP and 1554 ± 369 for IA. Patients have needed 15 [5-92] sessions to be eligible for KT, i.e. a mean cost of 21 225 euros. According to ABM data, highly sensitized patients are transplanted after a median time of 35 months later than non-sensitized patients (i.e. 233 000 euros per patients).

Conclusion: Apheresis technics are effective to remove HLA antibodies for HLAi KT, well tolerated (IA and PE > DFPP) and provide a financial benefit compared to hemodialysis.

VU ET PERMIS D'IMPRIMER

Grenoble, le : 30/9/20

LE DOYEN



Pr. Patrice MORAND

Pour le Président
et par délégation
—
Le Doyen de Médecine
Pr. Patrice MORAND

LE PRÉSIDENT DE LA THÈSE

Pr. Lionel ROSTAING



RÉSUMÉ :

Introduction : Entre 2013 et 2018, environ 18 % des patients inscrits sur la liste d'attente nationale de transplantation rénale (TR) étaient hyperimmunisés. Malgré la mise en place de systèmes d'attributions prioritaires, les patients hyper immunisés restent sur la liste d'attente deux à trois fois plus longtemps que les candidats non immunisés. Dans cette étude nous avons évalué les différentes techniques d'aphérèse : échanges plasmatiques (EP), plasmaphérèse-double-filtration (DFPP) et immunoadsorption (IA), employées en vue d'une greffe HLA incompatible (HLAi).

Méthodes : Tous les patients ayant bénéficiés d'aphérèse au CHU de Grenoble en vue d'une TR HLAi ont été inclus. Les paramètres, la tolérance et le coût par séance ont été recueillis.

Résultats : 881 séances d'aphéreses ont été réalisées pour 45 patients : 107 DFPP, 54 EP, 720 IA. L'âge moyen à la TR était de 53 ± 13 ans. 55.6% des patients étaient des femmes. Le programme de désimmunisation a permis une TR HLAi pour 39 patients (87%) après 29 [15 - 51] jours. La baisse des IgG après séance était significativement différente pour chaque technique ($p < 0,001$) (42 % en DFPP, 70 % en EP et 69 % en IA). En analyse multivariée, l'augmentation du nombre de séance était associée à une plus grande baisse des MFI inter-séances des DSA classe 1 ($p=0.029$). L'IA, les EP et une MFI maximale basse du DSA étaient associés à un pourcentage de baisse plus importante des MFI intra-séances des DSA classe 2 ($p<0.001$, $p=0.001$ and $p<0.001$ respectivement). Des effets indésirables graves (arrêt séance ou hospitalisation) sont survenus pour 17 séances (1,9 %); plus fréquemment pour la DFPP (6,5 % des séances) par rapport à l'IA (1,9 %) ou l'EP (1,2 %). Une transfusion sanguine a été nécessaire après 82 (9,3 %) séances. Le coût moyen par séances (Euros) était de 998 ± 357 pour l'EP, 690 ± 133 pour la DFPP, 1554 ± 369 pour l'IA. 15 [5-92] séances ont été nécessaire avant la TR: soit un coût moyen de 21 225

euros. Selon l'ABM, les hyperimmunisés sont transplantés 35 mois plus tard que les non immunisés (soit 233 000 euros/patient).

Conclusion : L'aphérèse est efficace pour enlever les anticorps anti-HLA et permet l'accès à la greffe de patients immunisés. Les séances ont bien été tolérées (IA et PE > DFPP) et la désimmunisation apporte un avantage financier par rapport à l'hémodialyse.

MOTS CLÉS : Transplantation rénale, HLA incompatible, Aphérèse, Désimmunisation, Immunoabsorption, Échange plasmatique, Plasmaphérèse par double filtration.

FILIÈRE : Néphrologie, Transplantation rénale

APHERESIS FOR DESENSITIZATION IN THE SETTING OF HLA INCOMPATIBLE KIDNEY TRANSPLANTATION: EFFICACY AND AT WHAT COST?

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Introduction

Chronic kidney disease and end-stage renal disease (ESRD) are a global public health problem. In France in 2018, 89 692 patients were undergoing kidney replacement therapy: 49 271 (55%) on dialysis and 40 421 (45%) with a functional kidney transplant. Kidney transplantation (KT) provides the best results in terms of survival, quality of life and health care savings as compared to haemodialysis (HD) ⁽¹⁻³⁾. Currently, access to KT is becoming more and more difficult due to an ever-increasing number of people on waiting lists but a graft shortage. In 2018, 5 269 new patients were added to the French national waiting list for KT. 19 625 candidates were waiting for kidney transplants while only 3567 were transplanted. The number of new registrants has increased by 35% in 10 years and the number of candidates by 82% in 10 years ⁽⁴⁾. A major cause of restricting access to KT is recipient Human Leukocyte Antigen (HLA) sensitization. Between 20 and 50% of patients waiting for KT are sensitized to HLA

antigens, depending on the detection technique ⁽⁵⁾. The rate of sensitized patients in France is approximately 30% and 15% are highly sensitized ⁽⁶⁾. Sensitized patients may have Donor-Specific Antibody (DSA) prior to transplantation. DSA prevent access to living donor transplants or delay access to deceased donor KT ⁽⁷⁾. Highly sensitized patients remain on waiting list two to three times longer than non-sensitized candidates⁽⁸⁾. Some priorities have been made to promote KT access for highly sensitized patients in France: national highly sensitized patients' priority, national full match priority (for sensitized patients) and expert committee request to graft with a different compatible blood group. Alternative ways to transplant highly sensitized patients are the national "permitted antigen program", living cross donation or desensitization ⁽⁹⁾.

Desensitization significantly improves access to deceased or living donor KT ⁽¹⁰⁾. The goal of desensitization therapy is to reduce DSA to the lowest levels at the time of transplantation in order to obtain a negative crossmatch. HLAi KT may be considered in case of negative complement-dependent cytotoxic crossmatch (which corresponds to DSA MFI Luminex measurement <5000 in our center). Various desensitization protocols have been used for HLAi KT. Most of the desensitization regimens involve plasmapheresis, followed by low (100 mg/kg) or high-dose intravenous immunoglobulin (2 g/kg) and/or B-cell depletion ⁽¹¹⁾. Plasmapheresis includes several types of extracorporeal therapies that can be used to reduce or remove circulating HLA antibodies. Methods available are plasma exchange (PE), double-filtration plasmapheresis (DFPP) and immunoadsorption (IA). To date, there is no evidence of superiority of one technique to another and very few studies have compared the different apheresis techniques in the indication of HLA desensitization ⁽¹²⁾. The aim of this study was to assess the efficacy, safety, tolerance and cost of each apheresis technique in the setting of HLAi KT desensitization.

Study population and definition

Patient and methods

All adult patients who underwent a desensitization programme for the purpose of HLAi KT in the University Hospital of Grenoble since January 2016 were included in this study. For an HLAi KT with deceased donors, patients had to be on the waiting list for at least 3 years and had to have a TGI >80%. To be defined as HLAi, all patients had to have a pre-existing DSA > 1500 MFI.

All medical data were collected from our database [CNIL (French National committee for data protection) approval number 1987785v0]. Patients agreed with written consent for this data to be used for research purposes.

Endpoints

The primary outcome was comparison of efficacy to remove HLA antibodies and DSA between three apheresis techniques. The screening for pretransplant immunization was performed using a bead assay (Luminex Single Antigen assay, Immucor, USA). DSA were monitored at least once a week during the desensitization period until KT. “Inter-session DSA reduction” was defined as the absolute reduction of two consecutive immunodominant DSA MFI for each patient measured at the beginning of an apheresis session. “Intra-session DSA reduction” was defined as the percentage of reduction between pre and post-apheresis session for the immunodominant DSA MFI of the patient.

The secondary endpoints were the comparison of safety between the three apheresis techniques, based on the number of severe adverse events, haemodynamic tolerance and the evolution of several biological parameters (platelet, haemoglobin, leukocyte and fibrinogen). Severe adverse events were defined in this study as an event

occurring during the apheresis session and leading to session discontinuation or hospitalisation. Technical issues were defined as the need of nurse intervention for the continuation of the session. We also assessed the cost of the sessions for each technique including the cost of apheresis itself, nursing time, the cost of haemodialysis, the cost of filters or columns (depending on the technique) and the cost of blood and derived products (IVIg, FFP, Fibrinogen, Albumin) provided by the hospital and the apheresis service.

Procedures

The aim of the desensitization was to obtain negative complement-dependent cytotoxic crossmatch on transplantation day (DSA MFI <5000). All patients received prophylactic antibiotherapy with penicillin V and sulfamethoxazole-trimethoprim. Vaccines were updated according to the current recommendations and were performed 3 months before the beginning of desensitization. Converting enzyme inhibitor therapies, incompatible with some apheresis techniques were replaced by angiotensin II receptor antagonists or stopped if possible. The apheresis sessions were carried out in parallel with the haemodialysis sessions (tandem procedure) to limit constraints to the patient. Every patient had vascular access that could be used in bi-puncture, necessary for apheresis techniques and acceptable session time. The use of arteriovenous fistula was possible and did not compromise its lifespan. In other cases, double-lumen catheter was used. Two IV Rituximab injection were given (375 mg/m²) at 30 and 15 day before living donor KT or at the beginning (day 5 and 12) of desensitization for KT with deceased donor. Immunosuppression therapy was started 10 days before the living KT or at beginning of desensitization for deceased donor. The immunosuppressive regimen consisted in Prednisone (0.5 mg/kg), Mycophenolate Mofetil (500 mg x 2 per day) and Tacrolimus (0.1 mg/kg/day, with a target trough

concentration between 8 and 10 ng/ml). Apheresis were performed either by IA, PE or DFPP.

The amount of total plasma volume (TPV) exchanged/treated was set at 1.5 x PV for DFPP and PE, and 100 ml x body weight (kg) for IA. Plasma volume (PV) was calculated according to the Kaplan formula: $PV = 0.065 \times \text{weight (kg)} \times (1 - \text{hematocrite})$ (13).

- PE was performed by centrifugation on Spectra Optia® (Terumo) or Comtec® (Fresenius). Filtration was carried out on a PlasautoΣ™ with a Plasmaflo™ OP-08W (Asahi Kasei Medical, Tokyo, Japan). Blood flow was 80 ml/min. Plasma was replaced by human albumin (4%). One PE with plasma substitution was performed the day before KT to restore clotting factors and reduce risk of bleeding post-surgery.
- DFPP was performed by PlasautoΣ™ (Asahi Kasei Medical, Tokyo, Japan), equipped with 2 filters in series. A primary filter with large pores (Plasmaflo™ OP-08W) separate cells and plasma, followed by a specific secondary filter (Cascadeflo™ EC-20W) for immunoglobulins filtration. Substitution liquid was composed of 100ml of Albumin 20% or 500 ml of Albumin 4% according to the volume required. Volume of rejection and therefore substitution varied according to membrane pressures. Blood flow was 150 ml/min and plasma separation was 25% of maximum blood-flow rate.
- For IA, plasma was separated from blood cells using centrifugation with Spectra Optia® or Comtec® monitors. Plasma was passed through two adsorber Globaffin columns (Fresenius Medical Care, Bad-Homburg, Germany) working in tandem (ie, one was rinsed while the other filtered the plasma). The Globaffin uses synthetic peptide GAM ligands to bind with strong affinity for the constant (Fc) section of subclasses 1, 2, and 4 IgG antibodies. Peptide GAM also binds with lower affinity to IgG subclass 3 as well as to IgM and IgA antibodies.

A porous polysulfone membrane optional filter (Monet, Fresenius Medical Care, Bad-Homburg, Germany) was placed after centrifugation before Globaffin columns, to purify the plasma of macromolecules (LDL-cholesterol, fibrinogen, FXIII, IgM ...) that saturate Globaffin columns quickly. We used it punctually according to the monitoring of the various parameters. Substitution liquid was 100 ml of Albumin 20% to compensate for the avoid hemodynamic instability created by loss of immunoglobulin (Ig) during sessions. Blood flow was 50-60 ml/min and a plasma flow was 35 ml/min. In France, GLOBAFFIN® columns must be reused at least 12 times to make them financially profitable. However, the decision to change the columns was based on elevated transmembrane pressures during the IA session.

All three apheresis techniques required anticoagulation, carried out with ACD-A anticoagulant citrate dextrose solution (Macopharma, Mouvoux, France). Calcium was infused on the venous (return) line, one bolus of 1 g and then 1,0 – 1,5 g/h according to ionized calcium. In the case of apheresis and hemodialysis coupling, anticoagulation of the extracorporeal circuit was done with IV sodium heparin.

If the replacement fluid was Fresh Frozen Plasma (FFP), pre-emptive allergy treatment with 2 mg of Dexchlorpheniramine was given. If allergic manifestations appeared, the patient received an injection of 100 mg of methyl-prednisolone.

If plasma IgG levels fell below 2 g/L, 100 mg/kg of intra venous immunoglobulins (IVIg) were infused after last apheresis session. If fibrinogen levels fell below 1 g/L, apheresis sessions were spaced or human fibrinogen was infused after the last apheresis session.

Desensitization protocol

For living donor KT, the protocol consisted in 4-5 apheresis sessions per week. If DSA MFI was > 12,000, IA were performed daily with a weekly MFI assessment. Monet filter

was left free to prescribers depending on the level of DSA MFI, its evolution, and the loss of coagulation factors or IgG/IgM. If DSA MFI was <6000, IA could be replaced by DFPP or PE to achieve a threshold of MFI <3000 before transplant.

For deceased donor KT, IA was performed five consecutive days. If a significant decrease in HLA antibody was observed, the program was pursued. To facilitate purification of high MFIs HLA antibodies, some patients get Tocilizumab injections (anti-IL6 antibody) before the start of apheresis. The technique of apheresis and frequency were dependent on HLA antibodies MFIs monitored every week. Once a week, a multidisciplinary discussion took place in order to remove HLA incompatibility for those antibodies whose MFI was under 3000. Apheresis sessions were pursued to maintain these results until KT was performed. If no national graft were proposed within 45 days after the beginning of desensitization, the first local, ABO-compatible graft matched to age and weight was proposed.

Statistical analyses

Quantitative data are presented with mean \pm standard deviation (SD) or median [Q1 – Q3] according to their distribution. Qualitative data are presented with number of patients and percentages. The Chi-squared test was used for categorical variables, the Wilcoxon or the Kruskal-Wallis tests were used for continuous variables to compare the three apheresis techniques. A multiple linear regression analysis was performed to identify the independent factors associated with inter-session and intra-session immunodominant DSA evolution. A p-value < 0.05 was considered to be statistically significant.

Results

Population included

Between 2016 and 2020, 45 patients have been desensitized in the purpose of HLAi KT at Grenoble University Hospital. Baseline characteristics of these patients are summarized in Table 1. Patients were 53 ± 13 years old and 25 (55.6%) were women. Seventeen patients (44%) were desensitized in a perspective of a living donor KT. Eight patients (20.5%) were desensitized due to both HLA and ABO incompatibility. Primary glomerulonephritis was the leading cause of ESRD in 14 patients (31%), including 3 (6.7%) IgA nephropathy and 3 (6.7%) membranous nephropathy. Other causes of graft loss were malformative uropathy in 4 patients (8.9%) and hypertensive nephropathy in 3 patients (6.7%) .

One patient (2.2%) started the desensitization protocol without prior dialysis, for a pre-emptive KT project. At the beginning of desensitization, median of immunodominant class I DSA MFI was at 2458 [0 – 10548] and 2079 [0 – 7238] for class II DSA. Retrospectively, 27 (60%) patients had more than one DSA. 16 (37.4%) patients had more than one class I DSA and 11 (28%) had more than one class II DSA. Regarding to class I DSA, anti HLA-A was present in 77.7% of patients, anti HLA-B in 63% of patients and anti HLA-C in 15%. Regarding to class II DSA, anti HLA-DP was present in 28% of patients, anti-HLADQ in 36% and anti HLA-DR in 44%. At the time of KT, most of recipients had 3 class I mismatches (17 patients: 45.9%) and 2 class II mismatches (15 patients: 40.5%).

Table 1. Baseline characteristics of desensitized patients

		Total (N=45)
Age of recipients (year)	Mean \pm SD	53 \pm 13
BMI (Kg/m ²)	Mean \pm SD	24 \pm 4
Female gender	N (%)	25 (55.6%)
Deceased donor	N (%)	22 (56.4%)
Recipient group	N (%)	
A		16 (35.6%)
AB		2 (4.4%)
B		10 (22.2%)
O		17 (37.8%)
Donor group	N (%)	
A		18 (46.2%)
AB		1 (2.6%)
B		7 (17.9%)
O		13 (33.3%)
No of kidney transplant	N (%)	
1		16 (41.0%)
2		19 (48.7%)
3		4 (10.3%)
Haemodialysis duration	(months)	
Median	[IQ]	65 [16.5 – 110]
TGI	(%)	
Mean \pm SD		84.6 \pm 26.3
DSA MFI class I at transplant		
Median	[IQ]	234 [0 – 1387]

DSA MFI class II at transplant

Median [IQ]

161 [0 – 773]

ABOi : ABO incompatible; BMI : Body Mass Index ; DSA :Donor Specific Antibody ;
TGI : Incompatible Graft Rate

Apheresis and course of the sessions:

We carried out from January 2016 to January 2020, 881 apheresis sessions. Number of sessions carried out per patient was 15 [10 – 24]. IA was the most performed technique with 720 (81.7%) sessions. Time between first and last session was 29 [15 - 51] days. Median duration of one session was 3.2 hours [2.6 - 3.9] and IA sessions were significantly longer (3.5 hours) as compared to DFPP and PE ($p < 0.001$) (Table 2). Most of the sessions 657 (74.6%) were performed on arteriovenous fistula and 853 (96,8%) sessions were carried out in tandem with haemodialysis.

Number of IA sessions per patient was 9 ± 6 , PE sessions 2 ± 1 and DFPP sessions 3 ± 2 . 155 sessions (13%) were performed by filtration (8 PE and 107 DFPP). The Monet filter was added in 340 of IA sessions (47.2%). Thirteen patients (28.9%) had received Tocilizumab prior to apheresis desensitization. They received 4 [4 — 5] injections of Tocilizumab at the dose of 8mg/kg. FFP was used as replacement fluid in 35 (64.8%) of PE sessions. 19 (42.2%) patients received IVIG injections post apheresis at a mean dose of 9.5 ± 7 g. Fibrinogen was infused after 51 sessions at a mean dose of 1.8 ± 0.8 g.

The volume of plasma purified was consistently higher in IA: 6641 mL [5520 - 7523] compared to DFPP 3675 mL [3000 - 4200] and PE 4200 mL [2564 -3685] ($p < 0.001$). The mean volume of plasma lost was 212 ± 789 mL. The technique with the highest plasma loss was PE: 2973 ± 917 mL followed by DFPP 328 ± 209 mL and IA 2 ± 64 mL ($p < 0.001$). Blood flow rates were 145 ± 14 mL/min in DFPP; 63 ± 37 mL/min in PE

and 54 ± 7 mL/min in IA ($p < 0.001$). The ratio of plasma volume prescribed over effectively treated plasma volume was satisfactory for all three types of sessions: 99 ± 12 %.

Table 2. Characteristics of sessions according to apheresis technique

	DFPP (N=107)	PE (N=54)	IA (N=720)	Total (N=881)	P value
Duration of session (hour)					< 0.001
Median [IQ]	2 [1.8 – 2.3]	1.7 [1.5 – 2.0]	3.5 [2.9 – 4.0]	3.2 [2.6 – 3.9]	
Treated plasma volume (mL)					< 0.001
Median [IQ]	3675.0 [3000 – 4200.0]	4200 [2564 – 3685.0]	6641 [5520 – 7523]	6035.0 [4803 – 7286.0]	
Blood flow (mL/min)					< 0.001
Mean \pm SD	146 \pm 14	63 \pm 38	54 \pm 7	65 \pm 32	
Substitution volume (mL)					< 0.001
Mean \pm SD	259 \pm 224	2857 \pm 750	104 \pm 53	295 \pm 717	
Substitution fluid N (%)					< 0.001
- Albumine 20%	10 (9.3%)	0 (0%)	720 (100%)	730 (83%)	
- Albumine 20% + Saline serum	88 (82.2%)	0 (0%)	0 (0%)	88 (10%)	
- Albumine 4%	9 (8.4%)	20 (37%)	0 (0%)	29 (3.2%)	
- FFP	0 (0%)	34 (63.0%)	0 (0%)	34 (3.9%)	

DFPP : Double Filtration Plasmapheresis ; PE : Plasmatic Exchange ; IA : Immunoabsorption FFP : Fresh Frozen Plasma

Primary endpoint: apheresis efficacy

Regarding access to KT, 39 (87%) patients were transplanted after the desensitization protocol. Six desensitized patients were not transplanted because of failure of HLA antibodies removal (8.3%) or intercurrent events during the desensitization period (8.3%) (myocardial infarction, pulmonary infection and digestive perforation). One patient died during the desensitization protocol period because of acute coronary syndrome.

We assessed factors associated with inter- and intra-session DSA evolution. For inter-session analyses, we grouped sessions that were performed with the same technique (IA, DFPP or PE) and for which we had immunodominant DSA MFI measurement at the beginning of two consecutive sessions. A total of 161 groups of sessions in class I (including a total of 417 sessions) and 129 in class II (including a total of 315 sessions) was established and used for the analyses. For intra-session analysis, we assessed MFI measurements before and after sessions when available.

Inter-session analyses (Table 3) : For class I DSA, in univariate analyses, the volume of purified plasma and the number of sessions were significantly associated with inter-sessions MFI decrease. In multivariate analyses, only the number of sessions remains significantly associated with the inter-session MFIs decrease ($p=0.029$). For class II DSA, in univariate analyses, the volume of purified plasma, the number of sessions and the shorter delay between two sessions were significantly associated with inter-sessions MFI decrease. In multivariate analyses, although close to significance, none of those criteria were significantly associated with MFI reduction.

Table 3. Uni and multivariate analyses of factors associated with reduction of inter-session MFI of immunodominant DSA

	DSA class I		DSA Class II	
	Univariate	Multivariate	Univariate	Multivariate
Volume of treated Plasma	< 0.001	0.143	0.002	0.527
Technique of apheresis (IA and PE versus DFPP)	0.642	-		
Delay between sessions	0.068	0.170	0.012	0.072
Number of sessions	0.001	0.029	0.001	0.065
Duration of session	0.929	-	0.678	-

DFPP : Double Filtration Plasmapheresis ; DSA : Donor Specific Antibody ; IA : Immunoabsorption ; PE : Plasma Exchange

Intra-session analyses (Table 4): For class I DSA, in univariate analyses, neither the volume of purified plasma, the technique of apheresis, the duration of session or the maximal MFI were significantly associated with intra-sessions MFI decrease of class I DSA. For class II DSA, in univariate analyses, IA and PE were significantly associated with inter-sessions MFI decrease as compared to DFPP as well as lower maximal DSA MFI. In multivariate analyses, those factors remained significantly associated with class II DSA decrease post session.

Table 4. Uni and multivariate analyses of factors associated with reduction of intra-session MFI of immunodominant DSA

	DSA class I		DSA Class II	
	Univariate	Multivariate	Univariate	Multivariate
Volume of treated plasma	0.806	-	0.072	-
Technique of apheresis (IA and PE versus DFPP)	0.149	-	EP: 0.019 IA: 0.013	EP: 0.001 IA: <0.001
Duration of session	0.887	-	0.097	-
Max MFI of DSA	0.395	-	0.002	<0.001

DFPP : Double Filtration Plasmapheresis ; DSA : Donor Specific Antibody ; IA : Immunoabsorption ; MFI: Mean Fluorescence Intensity ; PE : Plasmatic Exchange

Finally, efficacy on sub-type of immunoglobulins are summarized in Table 5. The best reduction rate of IgG was - 70.1% [-57.3 ; -74.1] for PE session, followed by - 69.2 [-63.6 ; -74.5] for IA and - 41.7 [-35.6 ; -52.5] for DFPP ($p < 0.001$). The increase of the percentage of IgG reduction post apheresis was significantly associated with the increase of plasma treated volume (Figure 1). Figure 2 show these results according to apheresis techniques.

Table 5. Effectiveness and biological impact according to apheresis techniques.

	DFPP (N=107)	PE (N=54)	IA (N=720)	Total (N=881)	P value
Pre-post IgA evolution					< 0.001
(%)					
Median [IQ]	- 54.8 [-45 ; -62.7]	- 69.5 [-52 ; -74.9]	- 14.1 [-6.6 ; - 21.3]	- 17.1 [-7.8 ; - 29.3]	
Pre-post IgG evolution					< 0.001
(%)					
Median [IQ]	- 41.7 [-35.6 ; -52.5]	- 70.1 [-57.3 ; -74.1]	- 69.2 [-63.6 ; - 74.5]	- 66.7 [-57.8 ; - 73.3]	
Pre-post IgM evolution					0.096
(%)					
Median [IQ]	- 37.5 [0 ; -58.3]	- 71.6 [52.3, 77.0]	- 16.7 [0 ; - 54.5]	- 16.7 [0 ; -57.1]	
Pre-post Alb evolution					0.730
(%) Median [IQ]	1.1 [14.7 ; 2.4]	9.8 [13.6 ; -2.6]	9.4 [13.9 ; -1.3]	9.2 [14.7 ; 0]	
Pre-post Fibrinogens evolution (%)					< 0.001
Median [IQ]	- 61.5 [-55.6 ; -69.2]	-33.3 [-28.6 ; -64.3]	-42.9 [-22.2 ; - 57.4]	-46.7 [23.1 ; -60]	
Pre-post Haemoglobin evolution (%)					< 0.001
Median [IQ]	15.5 [21.9 ; -8.2]	2.0 [10.2 ; -2.1]	2.4 [8.6 ; -2]	3.4 [11.2 ; - 1.8]	
Pre-post Leukocytes Evolution (%)					< 0.001
Median [IQ]	64.9 [96.5 ; 33.5]	22.2 [60.4 ; 4.7]	4.1 [18.4 ; 7.9]	8.5 [27.2 ; 5.9]	
Pre-post Platelets evolution (%)					0.008
Median [IQ]	7.4 [-1.1 ; 16.7]	14.3 [2.0 ; 21.1]	12.3 [3.1 ; 21.2]	11.6 [2.5 ; 20.8]	

DFPP : Double Filtration Plasmapheresis ; PE : Plasmatic Exchange ; IA : Immunoadsorption

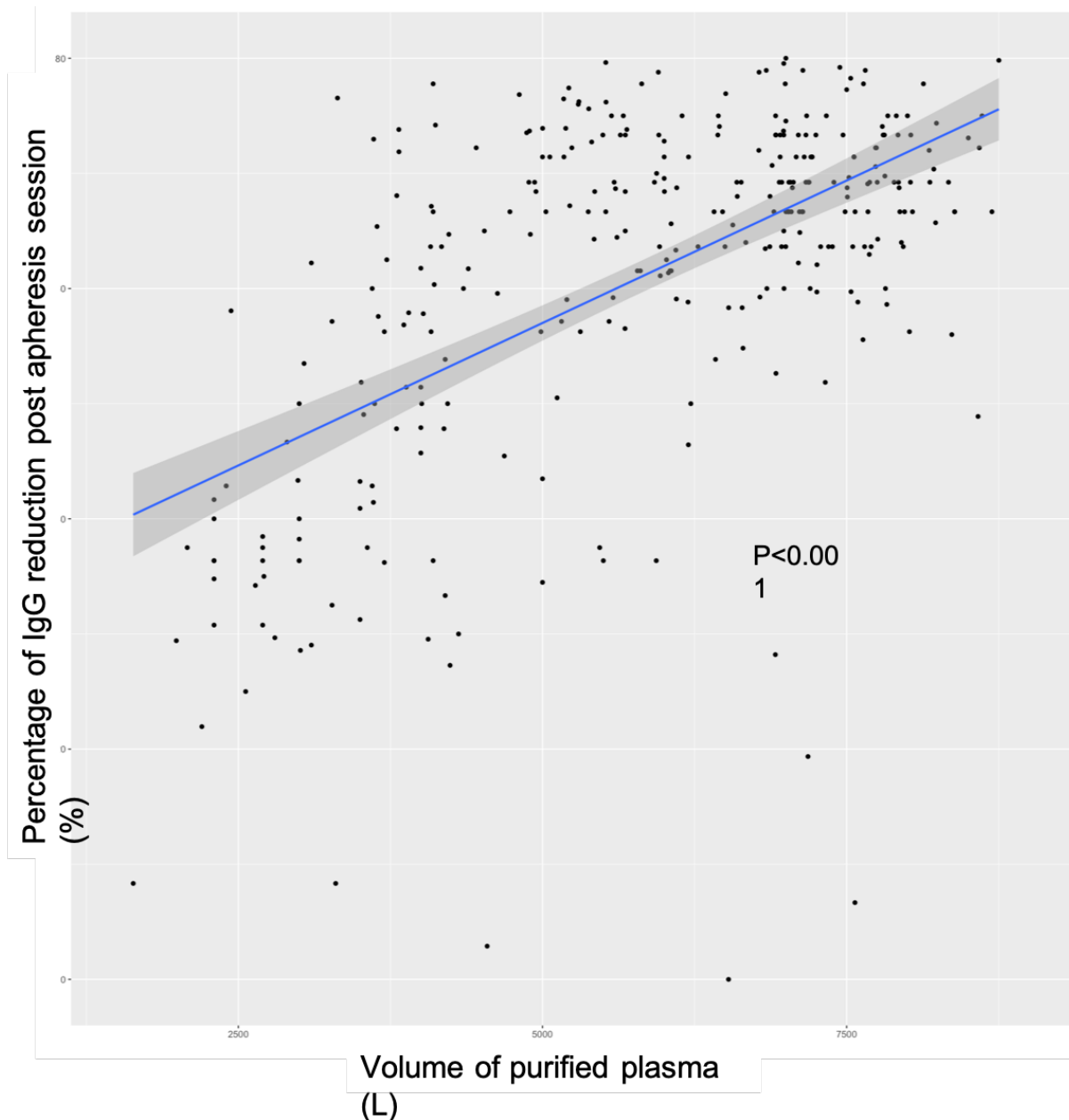


Figure 1: Reduction of IgG according to volume of purified plasma, all techniques combined. IgG stands for Immunoglobulin subtype G.

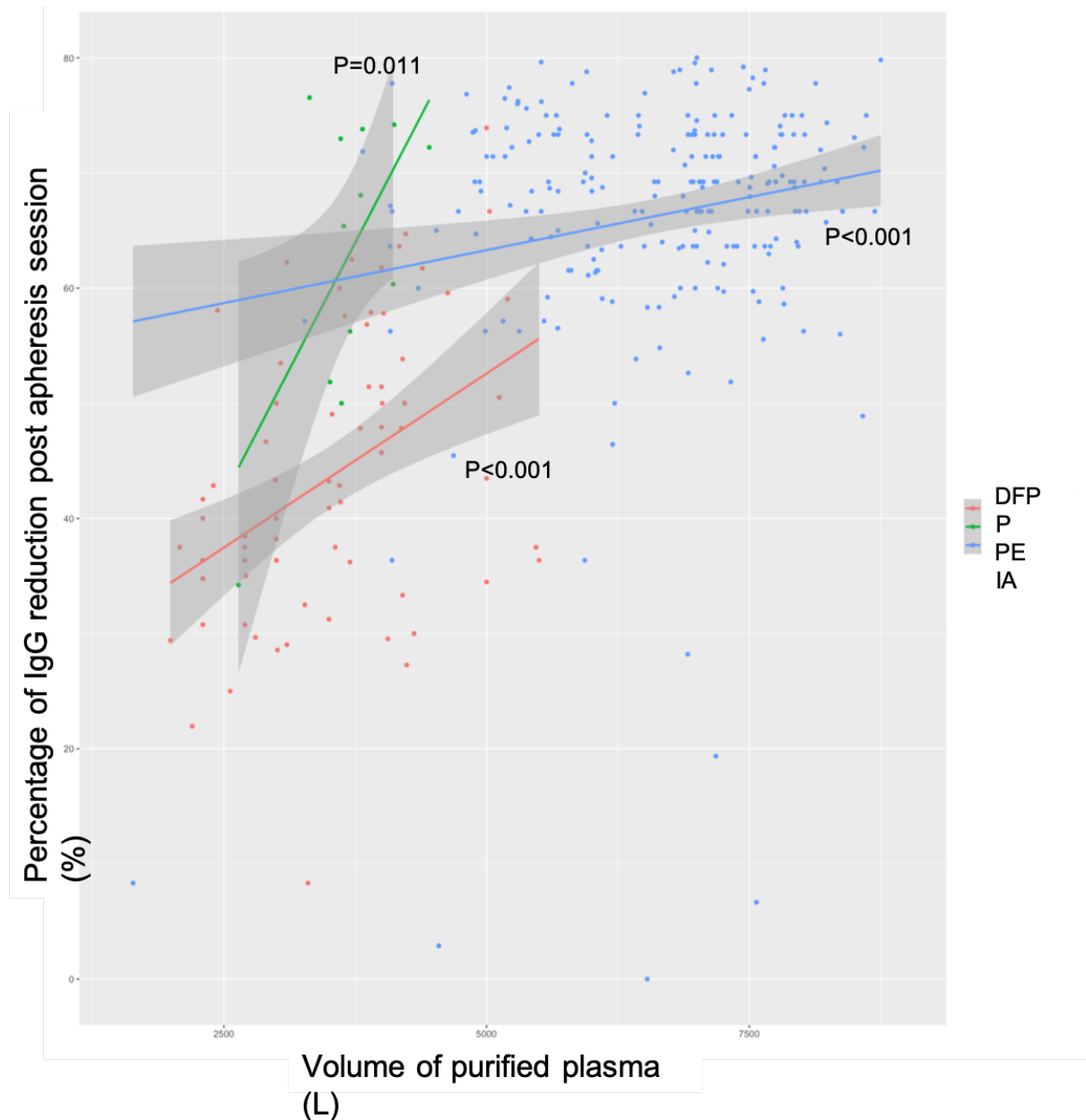


Figure 2 : Reduction of IgG according to apheresis techniques. DFPP stands for Double-filtration plasmapheresis, PE stands for plasma exchange, IA stands for Immunoabsorption, IgG stands for Immunoglobulin subtype G.

The use of Monet filter associated with IA permitted to improve the reduction of IgG, IgA and IgM reduction post apheresis (Figure 3). IgG reduction was 46.4% ± 29 without Monet as compared to 53.1% ± 30 when the Monet filter was used.

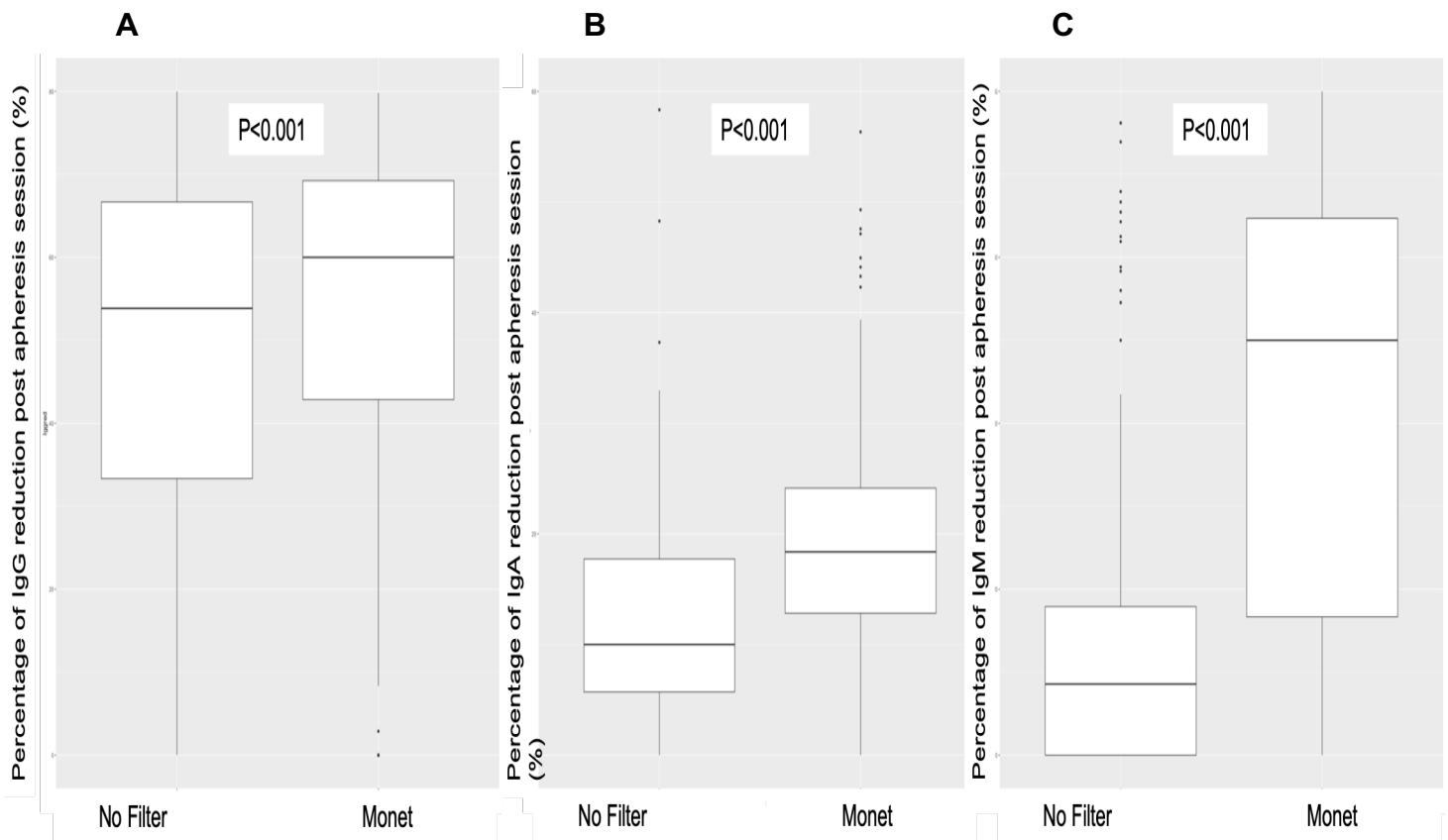


Figure 3 : Reduction of Ig according to the use of Monet filter. Boxplots represent the percentage of immunoglobulin reduction post apheresis session (IgG : panel A, IgA : panel B and IgM : panel C). IgG stands for Immunoglobulin subtype G. IgA stands for Immunoglobulin subtype A. IgM stands for Immunoglobulin subtype M.

Adverse event

Serious adverse events as described in the method section occurred in 17 sessions (1.9%) (Table 6). Haemodynamic intolerance occurred in 154 (17.5%) sessions. DFPP was correlated with higher numbers of serious adverse events in 7 (6.5%) sessions and hypotension in 42 (39.3%) sessions as compared to IA and PE ($p < 0.001$). Fibrinogen decreased by -46.7 % [-23; -60] with a higher loss with DFPP - 61.5 % [-55; -69] versus PE and IA: -33.3% [-28; -64] and -42.9% [-22; -57] respectively ($p < 0.001$). Post session fibrinogen was lower with DFPP: 0.6g/L \pm 0.4 as compared to other techniques ($p < 0.01$). Twenty-one (46.7%) patients were deficient in vitamin C

during desensitization (defined as vitamin C concentration <14 µmol/L). Five (11.1%) patients presented a Cytomegalovirus (CMV) DNAemia and 9 (20%) an Epstein-Barr Virus DNAemia during the desensitization period. One patient developed CMV disease with digestive involvement. Red-blood cell transfusion was performed in 82 (9.3%) sessions. Finally, the 3 techniques were comparable in terms of technical issue (p = 0.533).

Table 6. Costs and undesirable effects associated with apheresis technique

	DFPP (N=107)	PE (N=54)	IA (N=720)	Total (N=881)	P value
Severe adverse event	7 (6.5%)	1 (1.9%)	9 (1.2%)	17 (1.9%)	0.001
N (%)					
Hypotension N (%)	42 (39.3%)	11 (20.4%)	101 (14.0%)	154 (17.5%)	< 0.001
Technical issue N (%)	11 (10.3%)	3 (5.6%)	74 (10.3%)	88 (10%)	0.533
Cost of the session €					< 0.001
Mean ± SD	690 ± 133	998 ± 357	1554 ± 369	1415 ± 460	

DFPP : Double Filtration Plasmapheresis ; PE : Plasmatic Exchange ; IA : Immunoabsorption

Cost-benefit analyses

We finally tried to assess the cost of apheresis in regard of the cost of hemodialysis. The mean total cost of an apheresis session was 1415 ± 460 €. IA was the most expensive technique 1554 ± 369 € compared to DFPP 690 ± 13 € and PE 998 ± 357€. Patients needed 15 [5-92] sessions to be eligible for a KT: i.e., average cost of 21,225 Euros for a patient. When we add the cost of 1 month of hemodialysis (mean duration of desensitization), this brings the total cost at 27,891 Euros. On the other hand, according to ABM data, highly sensitized patients are transplanted at a median time of

35 months longer than non-sensitized patients which represents a cost of 233,000 Euros per patient.

Discussion

In this study, we showed the efficacy of apheresis techniques to perform desensitization prior to HLAi KT. Intra-session class II MFI DSA removal was more significant when we used IA or PE versus DFPP and when the maximal MFI DSA was lower. Inter-session DSA decrease was associated with the number of sessions in multivariate analyses. We also showed the tolerance and the cost of each apheresis techniques.

First plasmapheresis technique was performed on dogs experiments in 1914 by J.-J. Abel *et al.* ⁽¹⁴⁾. The first therapeutic application of plasma exchange was the treatment of hyperviscosity syndrome in Waldenström macroglobulinemia disease in the 1960s. Various plasmapheresis techniques are now part of the therapeutic arsenal to improve patient care in several areas of medical specialties. In solid organ transplantation, diseases concerned by plasmapheresis are antibody mediated rejection, recurrence of Focal Segmental Glomerulosclerosis and desensitization ⁽¹⁵⁾. Highly sensitized patients without HLA compatible donors are difficult to manage. These patients have to wait for a long period for a compatible deceased donor; they are often on hemodialysis, and have an increased morbi-mortality ⁽¹⁶⁾. Desensitization significantly improves access to transplantation from deceased and living donors ^(10,17).

The goal of desensitization is to obtain a sustained drop in MFI DSA and allow KT under acceptable immunological risk. In desensitization, plasmapheresis has shown best results as compared to repeated IVIG with a better success rate and lower antibody mediated rejection rates ⁽¹⁸⁾. Already in the 1970s, Cardella *et al.* considered that PE were able to purify DSA involved in acute humoral rejection ⁽¹⁹⁾. Anti-HLA

antibodies are IgG, whose half-life approaches 21 days, molecular weight about 160,000 Daltons and vascular distribution about 40% ⁽²⁰⁾. For these reasons, apheresis is a relevant technique for purifying DSA from plasma. To date, there are 3 different apheresis techniques used in our centre on a routine basis: PE, DFPP and IA. PE is a non-selective technique that purifies all patient plasma which is replaced by albumin or FFP. PE could be carried out by filtration or centrifugation. In our center, PE was mainly performed by centrifugation, which allowed a decrease in blood flow and session time reduction compared to filtration ⁽²¹⁾. DFPP and IA are more recent techniques that allow selective or semi-selective plasma purification. Selective plasma purification avoids unnecessary plasma proteins loss (coagulation factors, non-pathogenic immunoglobulins, albumin), reduces need for liquid replacement and increases efficiency of purification ⁽²²⁾.

In our study, the most effective apheresis technique in IgG purification was PE and IA. The first use of IA in kidney transplantation for highly sensitized dates from 1989 ⁽²³⁾. IA has since been used successfully in desensitizing therapy by many teams ^(24,25). The most commonly IA column used in our centre was a Globaffin® column. Globaffin® uses a synthetic peptide with a high affinity for the constant fraction (Fc) of IgG antibodies of subclass 1, 2 and 4 ⁽²⁶⁾. By purifying a high plasma volume with IA, Belàk *et al.* showed a 87% drop in the initial IgG level and show a good affinity bound for IgG 2 and 4 ⁽²⁷⁾. IA and DFPP allow higher plasma volumes to be processed without excessive loss of plasma ^(28,29) whereas the main constraint of PE remains the necessary use of a substitution solution due to extensive purification of the plasma components.

To the best of our knowledge, only few studies with small population have compared apheresis techniques in the setting of HLAi KT. None have compared all 3 together

(27,30). Zhang *and al.* found a higher IgG decrease with IA vs DFPP (83.5% vs 62.7%, $p = 0.002$). DFPP had the worse results in term of IgG epuration but had good results in term of IgA and IgM reduction with low level of IgA post session (data not shown). PE showed best results to remove IgM followed by DFPP (data not shown). This is partly due to the pore size of DFPP filters, which allows good elimination of IgA and IgM but low elimination of IgG to avoid loss of albumin with close molecular weight (31). When the Monet filter was added before the IA columns, the purification of IgM and IgA was significantly increased: IgM reduction was $4.2\% \pm 35$ without Monet as compared to $35.1\% \pm 41$ when the Monet was used.

Apheresis is not a harmless therapy. It requires both medical and paramedical expertise with a team well trained in the different techniques. Plasmapheresis may be complicated by cardio-vascular (32), haemorrhagic (33,34) or allergic (35) complications. In our centre, the technique with the most undesirable effects was DFPP. Regarding to worse tolerance of DFPP, we found a significant increase in the numbers of leukocytes during the DFPP session. This may be explained by the bio-incompatibility of the membranes and the frictional forces imposed on blood through these membranes (36). This activation of the inflammatory system may be partly responsible for the excess risk of hypotension during DFPP sessions. The majority of PE sessions with plasma substitution were complicated by symptoms of pruritus-type anaphylaxis.

Apheresis unit staff consisted of 14 full-time equivalent nurses, 5 hospital service staff, 1 full-time equivalent hospital practitioners, 1 clinical assistant and 1 resident.

The evaluation of an apheresis session cost took into account: nursing time, cost of hemodialysis, cost of filters or columns (depending on the technique) and cost of substitute products (IVIg, FFP, fibrinogen, albumin) provided by the hospital and the apheresis service : IVIg (174 E per 5g), FFP (87 E per per bag: 280 mL), (Albumin 47

E per 20g) and fibrinogen (692 E per 1.5g). Simultaneous apheresis and haemodialysis sessions limit the constraints for dialysis patients and avoid to saturate dialysis planning ^(37,38).

IA was the most expensive technique in our study. The columns were generally used 10 sessions. The Monet filter increased cost of the session. Substitute products increased greatly the cost of PE with a large use of FFP pre-KT to improve coagulability pre-operatively. The cost of an albumin-PE session without FFP was 550 E.. Desensitization, even if expensive in the initial phase, allows consequent health and cost savings by reducing the number of years on the waiting list and therefore in dialysis ⁽³⁹⁾. Finally, even if not assessed in this study, we may suspect an improvement of quality of life in those patients that were transplanted post desensitization as compared to remaining on dialysis ^(2,3).

Conclusion:

Desensitization by apheresis is effective to remove HLA antibodies in the setting of HLAi KT. IA and EP were more effective, especially for class II DSA, and were better tolerated than DFPP. In spite of an extra cost in the initial period, apheresis desensitization achieves a financial benefit as compared to remaining on haemodialysis.

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