

Aphérèses et désimmunisation avant greffe rénale

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Indications

1. Greffes rénales ABO incompatibles

- Quand titres des isoagglutinines (IgG et/ou IgM) sup à 1/8

2. Greffes rénales HLA incompatibles

- Quand existent avant greffe un ou des anticorps anti-HLA spécifiques contre le donneur (donor-specific alloantibody) pour lesquels l'intensité de fluorescence moyenne (MFI) est supérieure à 3000

Quelles sont les techniques disponibles?

Trois techniques:

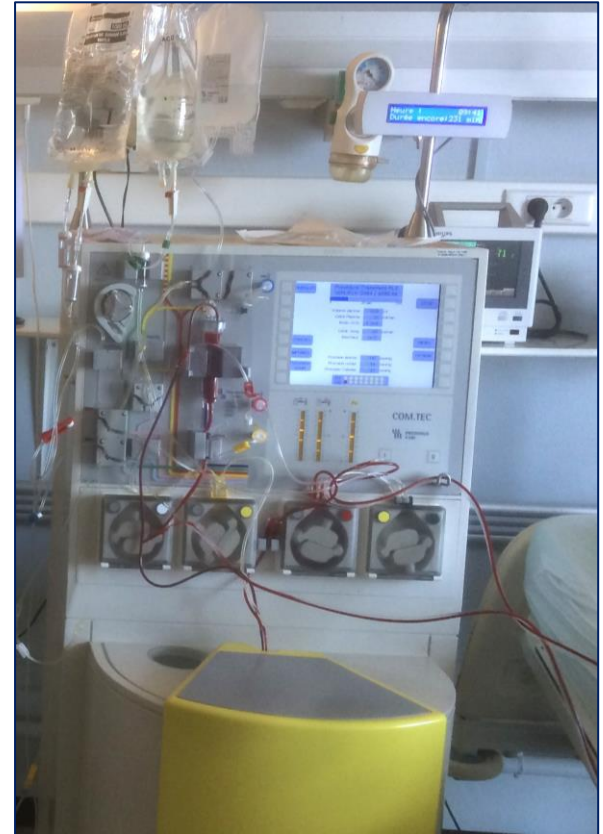
- **Plasma apheresis** : plasma removal and substitution
- **Membrane filtration (DFPP)** : plasma filtration and removal of molecules based on « size », e.g. immunoglobulins, α_2 macroglobulin, fibrinogen, etc...
- **Immunoabsorption** : removal of immunoglobulins (mainly IgG) from plasma. NOT adapted for IgM isoagglutinin removal

Plasmaphérèse

Plasma exchange:

Plasma removal (by centrifugation or by filtration) and substitution with :

- plasma
- albumin



Plasmaphérèse + filtration par membrane

Plasma separation + Membrane filtration

- Removing from plasma molecules that are filtered according to pore size



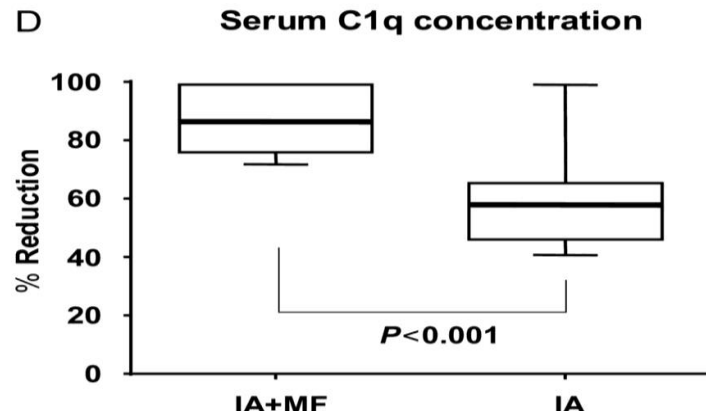
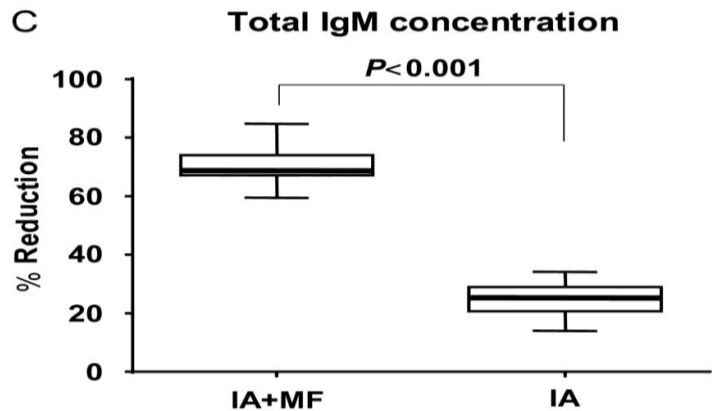
Immunoadsorption



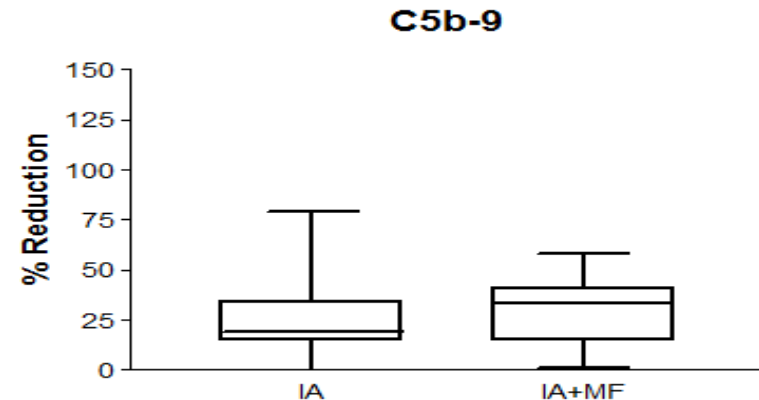
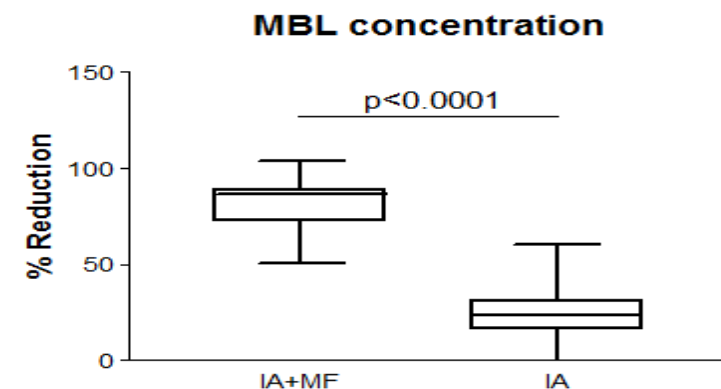
Immuno-
adsorption
(IA)

±
membrane
filtration
(MF)

Immunoadsorption : efficacy

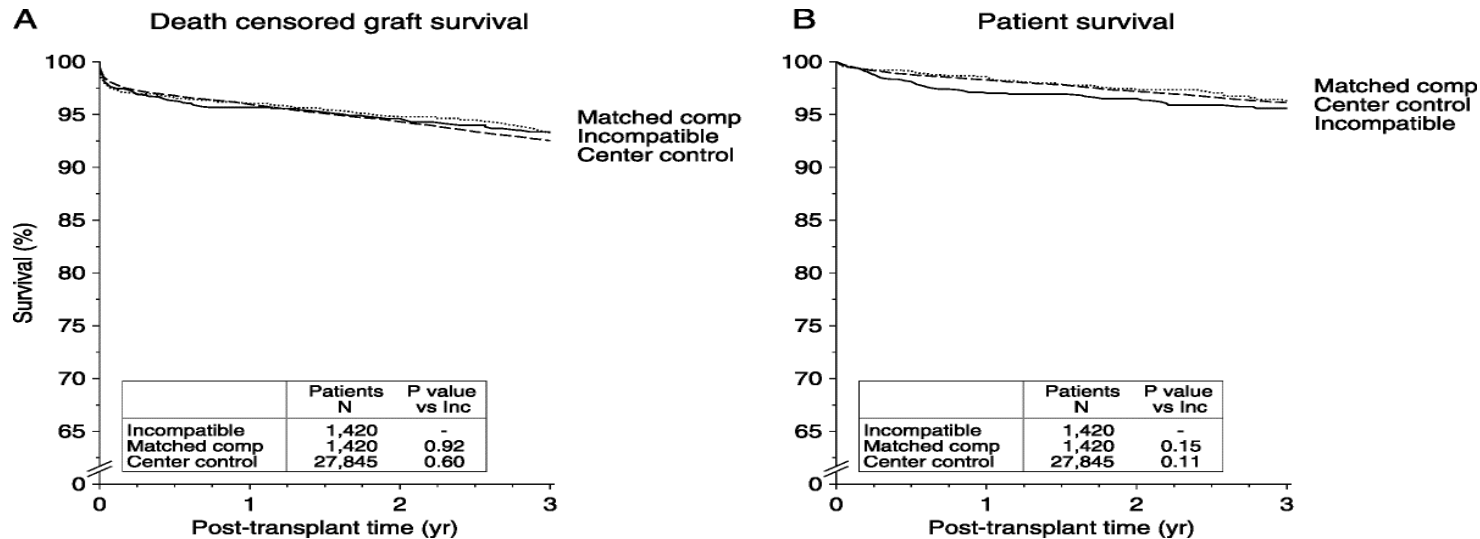


Eskandary F, et al.
NDT 2014;29(3):706-14.



ABO incompatible transplantation

Three-year outcomes following 1420 ABO-incompatible living-donor kidney transplants performed after ABO antibody reduction : results from 101 centers (1)

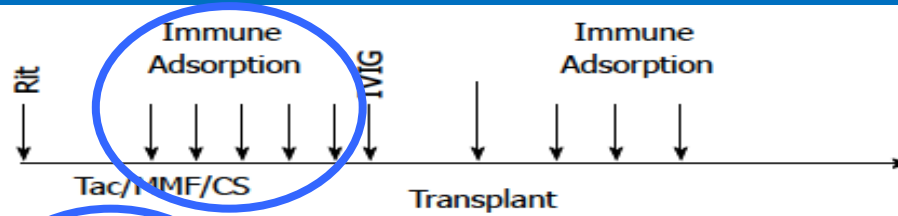


Cumulative incidence of (A) death-censored graft survival and (B) patient death in living-donor recipients of an ABO-incompatible graft, matched controls receiving an ABO-compatible graft, or all ABO-compatible transplants from centers that performed at least five ABO-incompatible grafts during the study period ('center control' group) (Kaplan-Meier estimates). P values according to the log-rank test.

Different ABOi KTx protocols

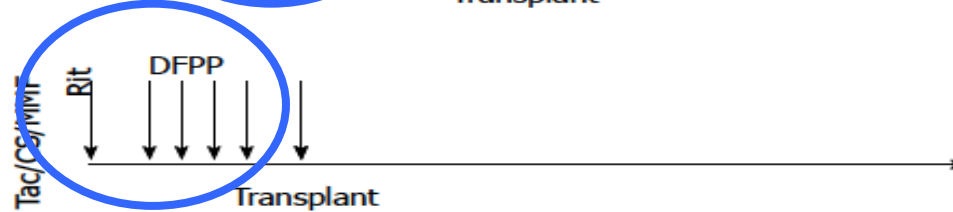
A

Karolinska University
Hospital,
Sweden



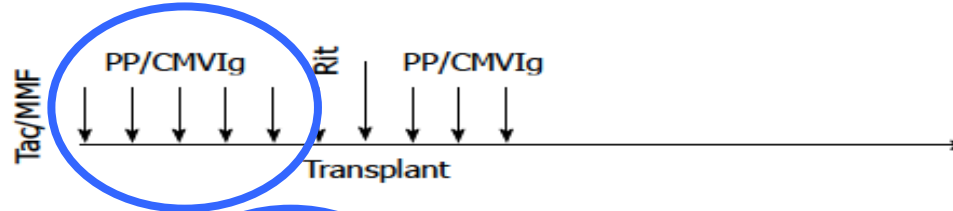
B

Tokyo Women's Medical
University,
Tokyo, Japan



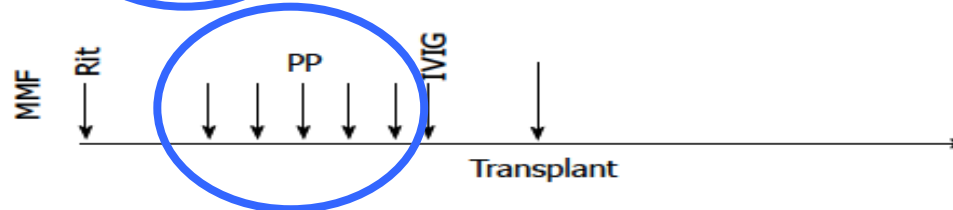
C

Johns Hopkins University,
Baltimore, United States



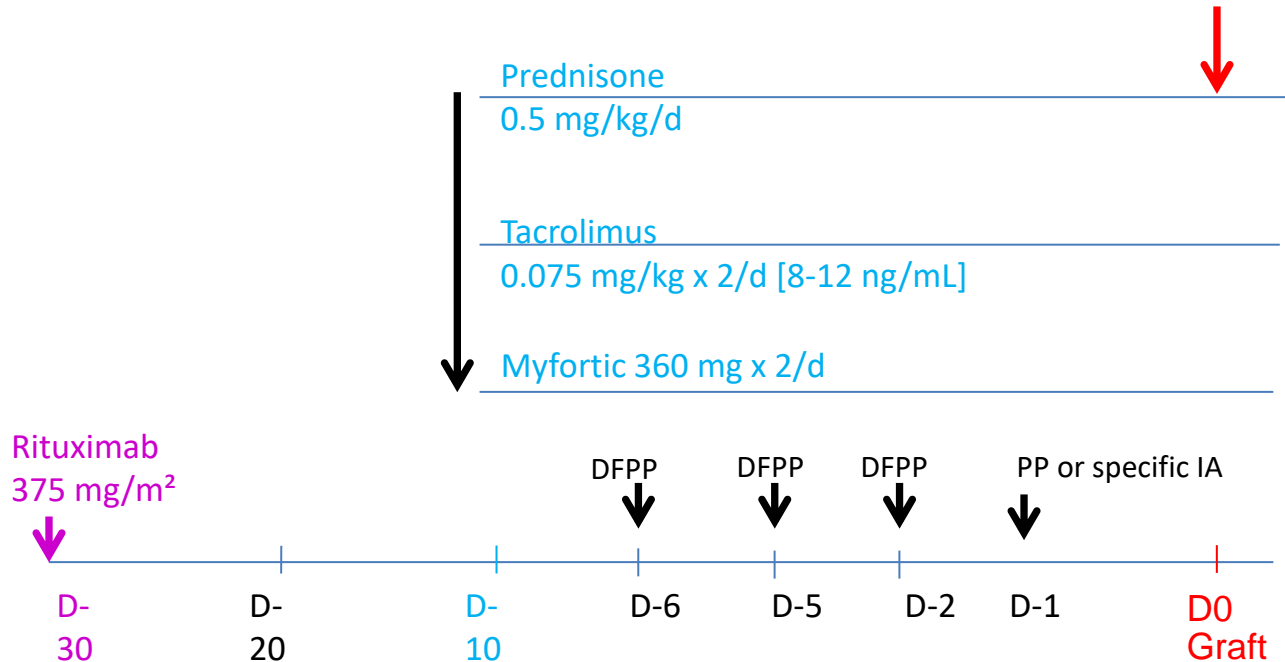
D

Cedars-Sinai Medical Center,
Los Angeles, United States



ABOi protocol in Grenoble

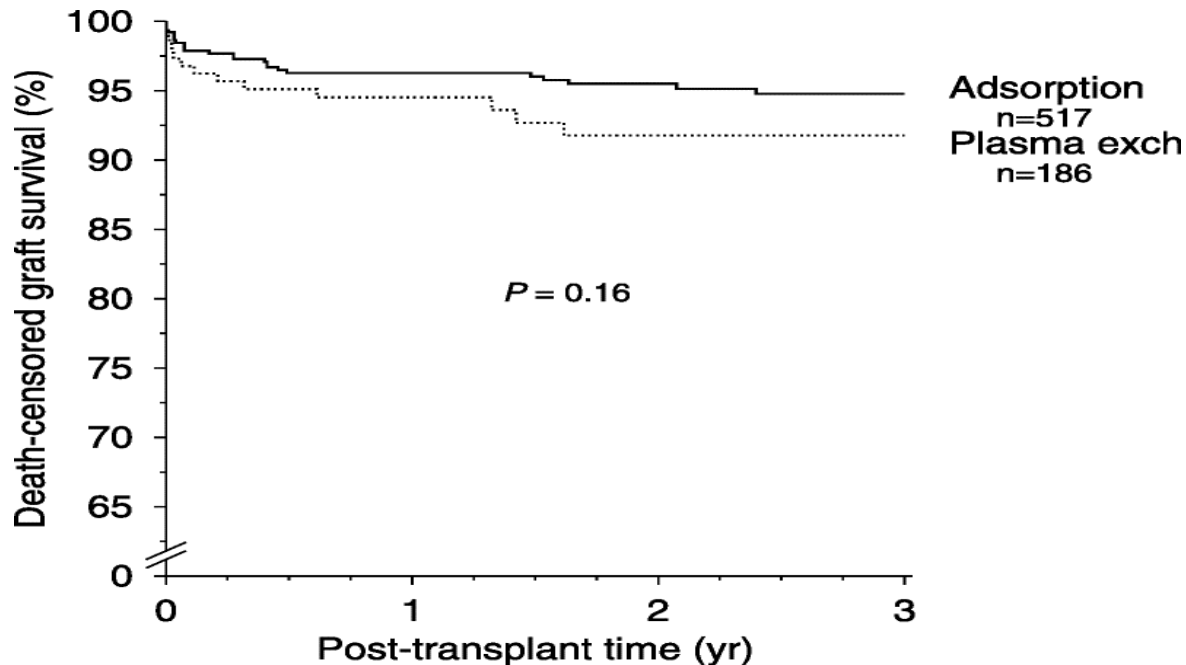
Basiliximab 20 mg D0 and D4



The number of DFPP sessions can be increased according to the pre-desensitization isoagglutinin titer

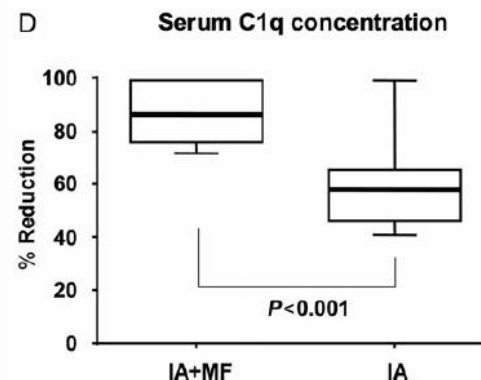
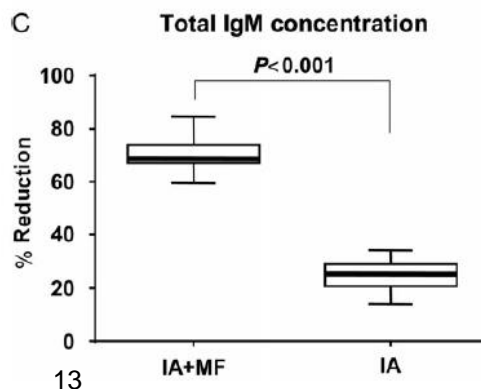
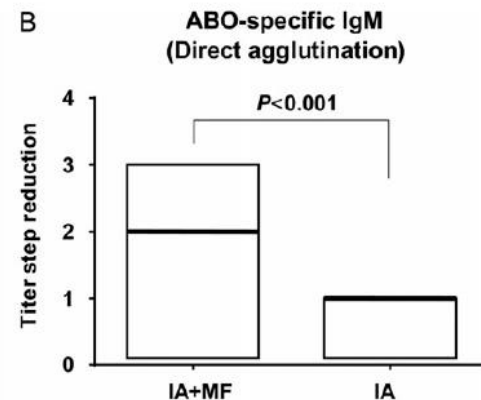
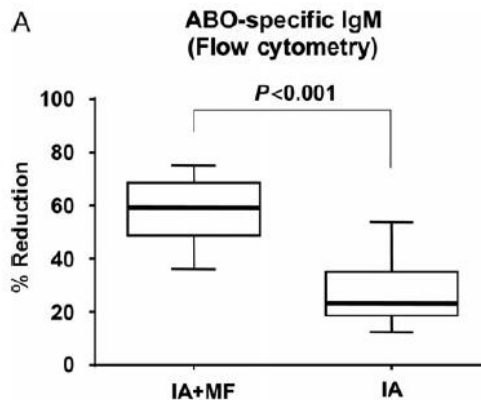
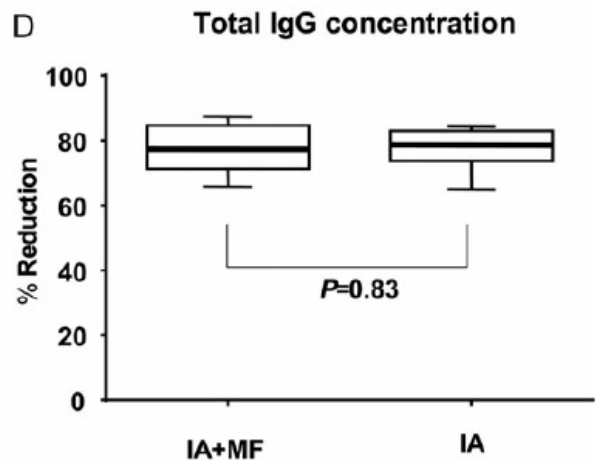
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Three-year outcomes following 1420 ABO-incompatible living-donor kidney transplants performed after ABO antibody reduction : results from 101 centers (2)



Cumulative incidence of death-censored graft survival in living-donor recipients of an ABO-incompatible graft according to whether ABO antibody reduction was performed by adsorption columns or plasma exchange (Kaplan-Meier estimates). P values according to the log-rank test.

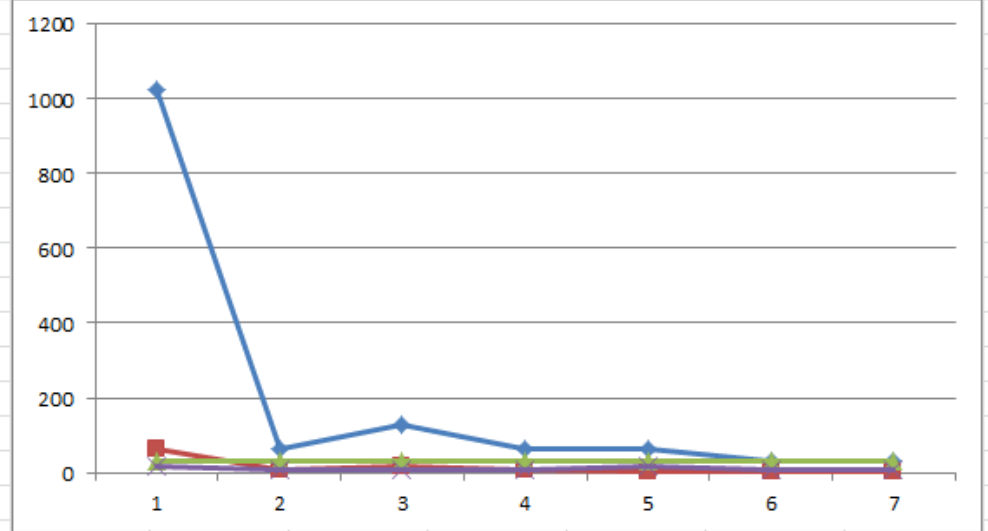
Isoagglutinins and semi-specific IA+ Membrane Filtration



Isoagglutinin removal by specific IA (anti-A or anti-B columns)

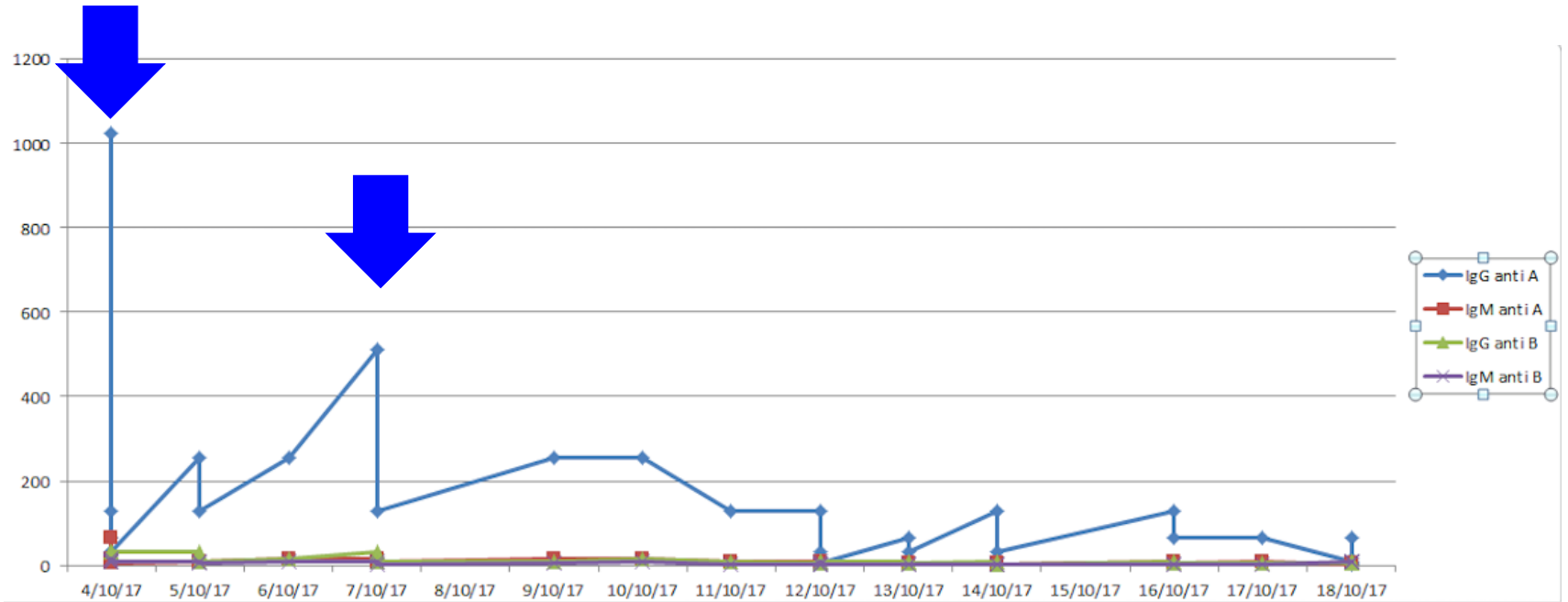


	4/10/17	4/10/17	4/10/17	4/10/17	4/10/17	4/10/17	4/10/17
IgG anti A	1024	64	128	64	64	32	32
IgM anti A	64	8	16	8	4	4	4
IgG anti B	32	32	32	32	32	32	32
IgM anti B	16	8	8	8	16	8	8



Personal data

Specific IA (blue arrows) –long sessions when isoagglutinin titers are high

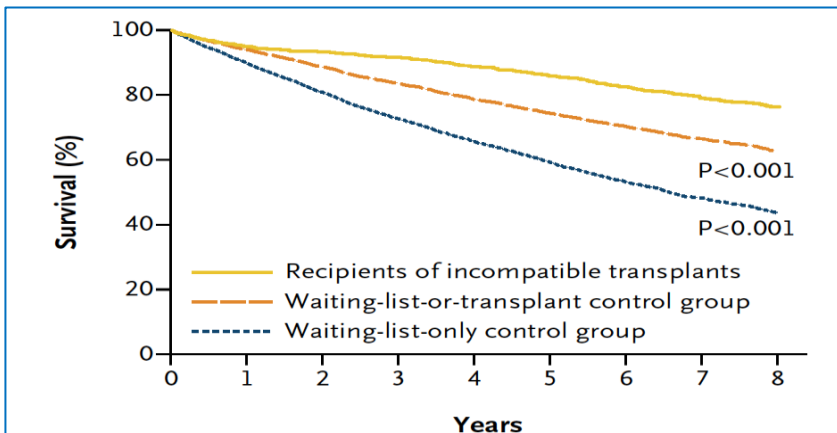


Personal data

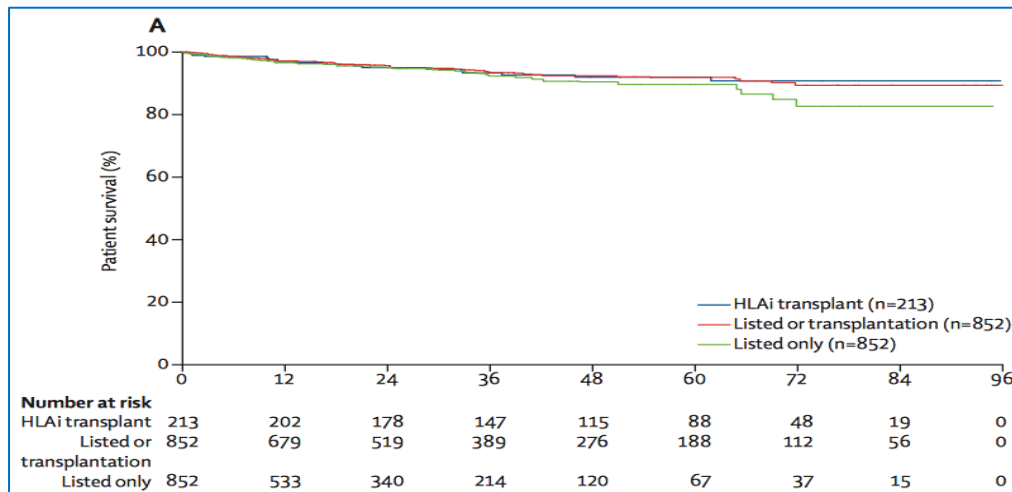
HLA incompatible transplantation

Role of plasmapheresis

Patient survival in the setting of HLA incompatible transplantation

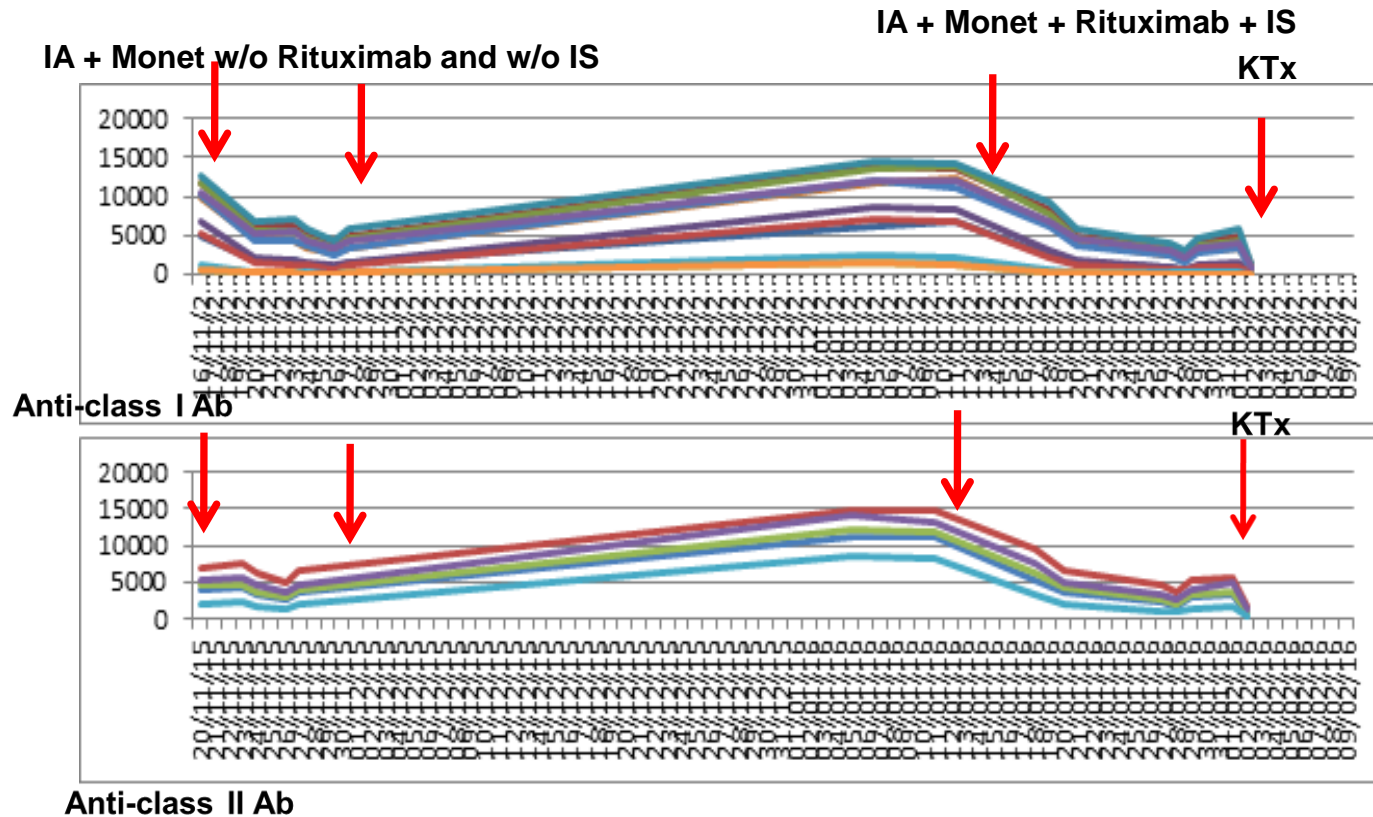


Orandi et al. NEJM 2016



Manook M et al. Lancet 2017

IA + Monet : anti-HLA alloantibodies (class I; II)



Isolated (no IS) IA + membrane filtration

5 sessions : effect on anti-HLA alloantibody MFIs

Before					After				
A/B/Cw	BCM	Assign	BCM	Assign	A/B/Cw	BCM	Assign	BCM	Assign
A*33:03	13545	Positive	2548	Positive	A*33:01	11102	Positive	2180	Positive
A*33:01	11102	Positive	2180	Positive	A*31:01	9087	Positive	1733	Positive
A*31:01	9087	Positive	1733	Positive	A*34:02	10778	Positive	1468	Positive
A*34:02	10778	Positive	1468	Positive	A*68:01	10474	Positive	1305	Positive
A*68:01	10474	Positive	1305	Positive	B*57:01	13929	Positive	1098	Positive
B*57:01	13929	Positive	1098	Positive	A*30:01	5474	Positive	938	Positive
A*30:01	5474	Positive	938	Positive	A*66:02	7807	Positive	862	Positive
A*66:02	7807	Positive	862	Positive	A*74:01	5963	Positive	799	Positive
A*74:01	5963	Positive	799	Positive	A*02:05	10430	Positive	760	Positive
A*02:05	10430	Positive	760	Positive	A*29:02	4274	Positive	754	Positive
A*29:02	4274	Positive	754	Positive	A*68:02	8970	Positive	719	Positive
A*68:02	8970	Positive	719	Positive	B*58:01	11367	Positive	719	Positive
B*58:01	11367	Positive	719	Positive	A*02:02	9998	Positive	691	Positive
A*02:02	9998	Positive	691	Positive	A*66:01	7158	Positive	657	Positive
A*66:01	7158	Positive	657	Positive	A*24:02	3864	Positive	581	Positive
A*24:02	3864	Positive	581	Positive	A*69:01	6573	Positive	575	Positive
A*69:01	6573	Positive	575	Positive	A*02:01	7162	Positive	551	Positive
A*02:01	7162	Positive	551	Positive	A*23:01	3453	Positive	512	Positive
A*23:01	3453	Positive	512	Positive	A*03:01	4622	Positive	493	Positive
A*03:01	4622	Positive	493	Positive	A*02:03	7734	Positive	492	Positive
A*02:03	7734	Positive	492	Positive	A*24:03	3639	Positive	444	Positive
A*24:03	3639	Positive	444	Positive	A*11:01	4453	Positive	441	Positive
A*11:01	4453	Positive	441	Positive	A*80:01	2491	Positive	297	Positive
A*80:01	2491	Positive	297	Positive	A*11:02	3191	Positive	167	Negative
A*11:02	3191	Positive	167	Negative	A*26:01	4265	Positive	72	Negative
A*26:01	4265	Positive	72	Negative	B*08:01	6069	Positive	64	Negative
B*08:01	6069	Positive	64	Negative	A*25:01	4454	Positive	23	Negative
A*25:01	4454	Positive	23	Negative	B*82:02	1531	Positive	-54	Negative
B*82:02	1531	Positive	-54	Negative	B*54:01	2095	Positive	-57	Negative
B*54:01	2095	Positive	-57	Negative					

Antibody-mediated rejection

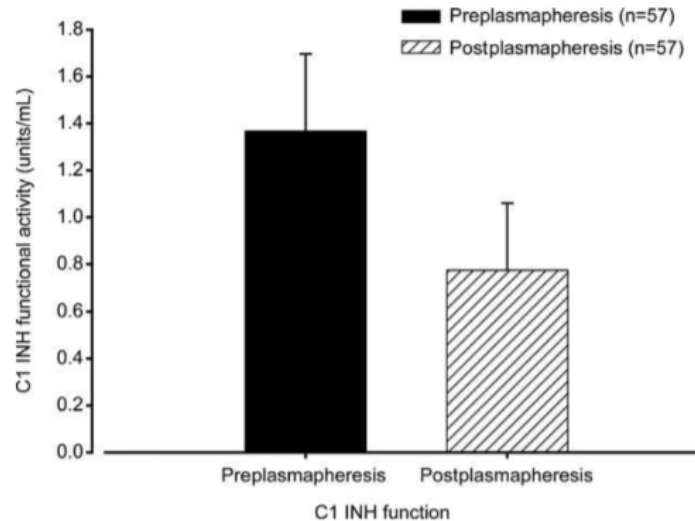
Role of apheresis

Very few randomized trials

Patient number	IA after index Bx	IA rescue	'Anti-cellular' treatment	Allograft function/serum creatinine (mg/dL) after randomization				
				Index Bx	21 days	6 months	12 months	24 months
Group A								
2	Yes	-	-	Dialysis	1.3	1.5	1.5	2.3
4	Yes	-	ATG	Dialysis	2.2	2.7	2.1	1.9
5	Yes	-	-	Dialysis	1.6	1.2	1.1	1.7
7	Yes	-	Steroids	Dialysis	2.9	¹	-	-
9	Yes	-	Steroids	Dialysis	4.9	1.2	²	-
Group B								
1	No	No ³	ATG/Steroids	Dialysis	Dialysis	Dialysis	Dialysis	Dialysis
3	No	Yes	Steroids	Dialysis	Dialysis	Dialysis	Dialysis	Dialysis
6	No	Yes	-	Dialysis	Dialysis	Dialysis	Dialysis	Dialysis
8	No	-	-	5	2.1	1.6	1.6	²
10	No	Yes	-	Dialysis	Dialysis	Dialysis	²	-

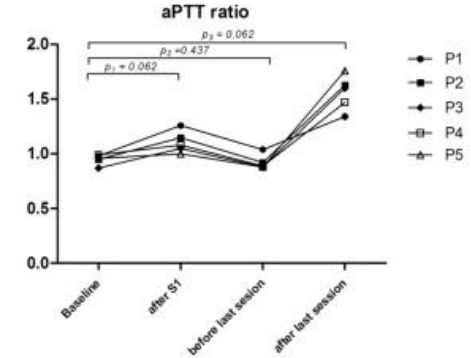
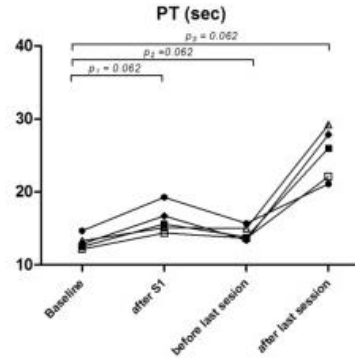
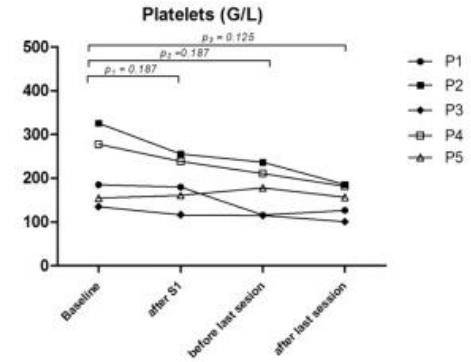
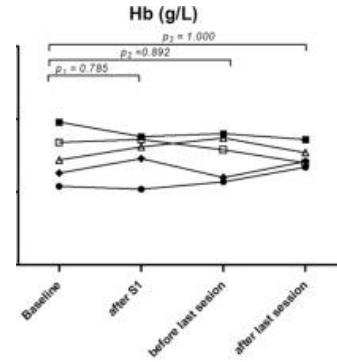
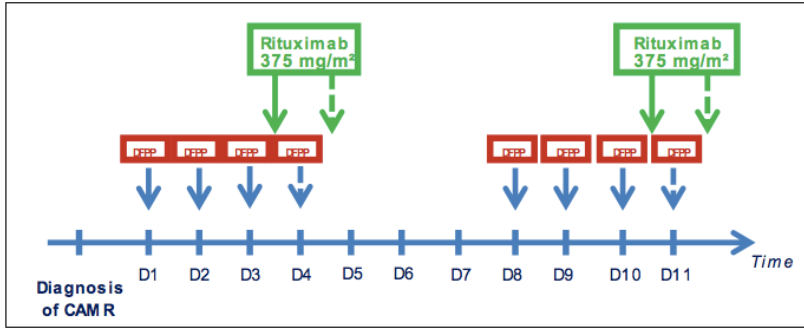
Apheresis and antibody-mediated rejection

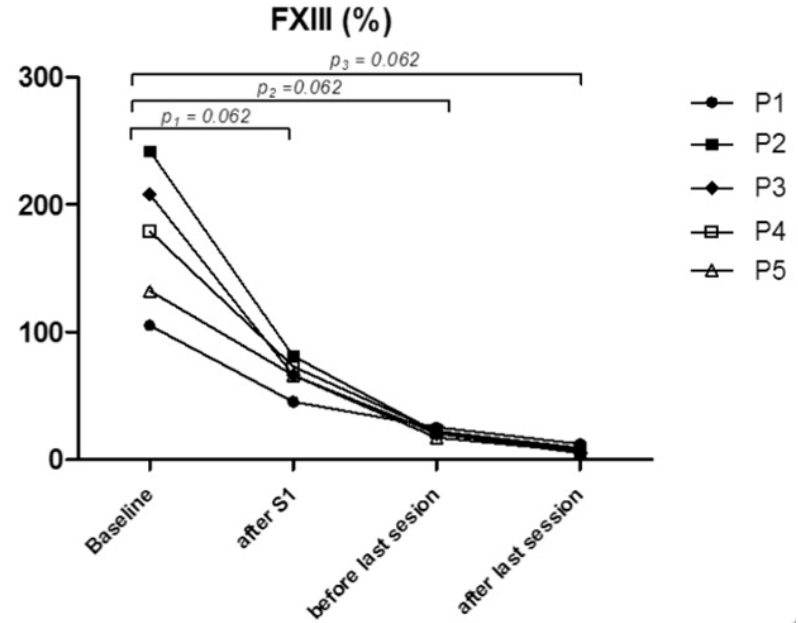
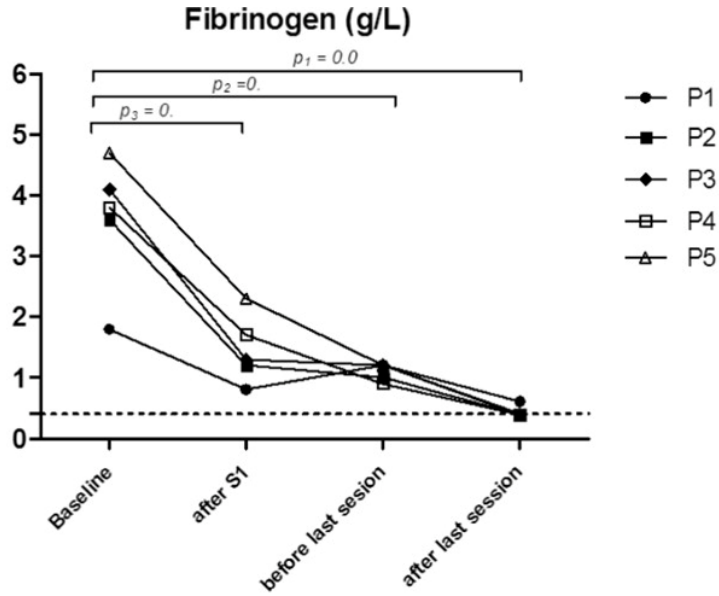
- Apheresis certainly reduces circulating antibody titers
- But...
- It may also deplete all drugs that are used to treat rejection



Paramètres de la COAGULATION

DFPP et coagulation





- Membrane filtration (DFPP) depletes coagulation factors with high molecular weights (e.g. fibrinogen).
- Repeated sessions cause very important depletion of those factors that have a long half-life (e.g. factor XIII).

In conclusion

- Apheresis **in all its forms** is a useful tool in the kidney transplant setting :
 - To deplete antibodies
 - To deplete other potentially dangerous molecules
 - But also:
 - Needs to be **wisely** used because may cause deep depletion of coagulation factors
 - May deplete other large molecules : EPO, vitamins (C) drugs (mAb, etc)
- ↪ **Apheresis treatment protocols must be adapted to the clinical situation of each patient.**

Special thanks:



Transplant nephrologists:

- Pr L Rostaing
- Dr P Malvezzi
- Dr B Janbon
- Dr T Jouve
- Dr J Noble
- Dr E Chevallier



Apheresis Group:

- Dr H Naciri Bennani
- Dr F Terrec
- L Motte

Transplant surgeons:

- Pr JJ Rambeaud
- Dr N Terrier

Immunologists :

- Dr D Masson
- Dr B Bardy
- Dr C Dard
- Dr C Lathuile
- A Bourdin



Thank you for your attention

