Désimmunisation HLA périopératoire en transplantation pulmonaire Quelle place pour l'IA ?

F Parquin
Groupe de Transplantation pulmonaire
Hôpital Foch
Suresnes

Pas de conflit d’intérêt

Hyperacute rejection

Fulminant allograft dysfunction
Within mn or hours after lung implantation
Severe gas exchange impairment, hemorrhagic pulmonary edema, diffuse infiltrates
Neutrophilic infiltration of the alveolar septae, fibrinoid necrosis and hemorrhagic infarction, C4d + immunostaining

Table 1: Clinical cases

Author	Sex/age	Indication Tx	PRA	Crossmatch	Evolution
Frost *et al.* [3]	Female/48	COPD	33%	+: Anti-B8	Died: 13th DPO
Choi *et al.* [6]	Female/50	COPD	Negative	+: unidentified	Died: 4 h
Bittner *et al.* [8]	Female/57	COPD	33%	+: Anti-A2	Survives
Scornik *et al.* [10]	Female/?	Not available	Negative	+: Anti-DR11	Died: 48 h
de Jesus Peixoto Camargo *et al.* [9]	Female/53	COPD	Negative	+: Anti-A2	Died: 24 h
Masson *et al.* [7]	Female/60	COPD	Negative	+: Anti-B7-B81	Died 9th DPO
[redacted] Campo C	Male/62	COPD	5%	+: Anti-DQA1	Died: 77 h
Dawson et al	Female/56	fibrosis	cPRA 99%	+B DR8, DR14,DR52DQ7	Alive A1

Early acute AMR

- 4 case report
- Onset : very acute D15 (2 cases) D 30, D90
- Preformed and or de novo DSA
- Good response to different treatment
  - PP, IvIg Bortezomib
  - MP, Rituximab
  - MP, PE, IvIg rituximab
  - MP, PE IvIg rituximab and thereafter bortezomib
- 4 pts cured
  - *Astor AJT 2009 9 409-12*
  - *Morrel JHLT 2009 28 96-100*
  - *Baum JHLT 2013 1270*
  - *Stuckey The annals of Pharmacotherapy 2012 46 e2*

Lung Transplantation in Patients with Pretransplantation Donor-Specific Antibodies Detected by Luminex Assay

Olivier Brugière,[1,4] Caroline Suberbielle,[2] Gabriel Thabut,[1] Elodie Lhuillier,[1] Gaelle Dauriat,[1] Anne-Cecile Metivier,[1] Chantal Gautreau,[2] Dominique Charron,[2] Herve Mal,[1] François Parquin,[3] and Marc Stern[3]

Transplantation • Volume 95, Number 5, March 15, 2013

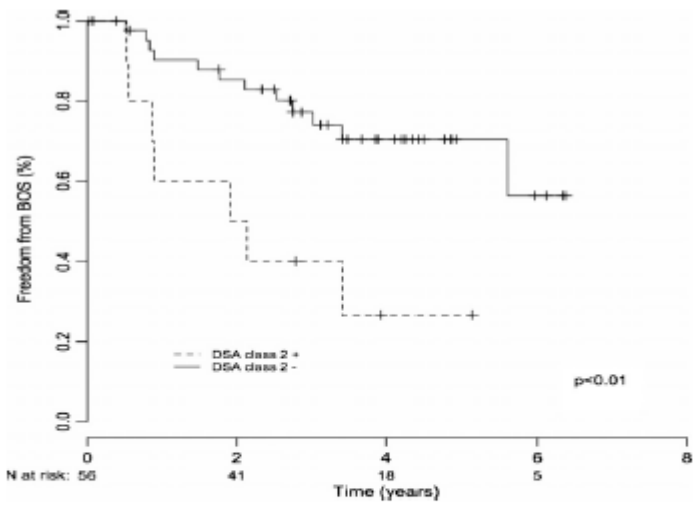

FIGURE 2. Freedom from bronchiolitis obliterans (BOS) in patients with or without pre–lung transplantation (LTx) single-antigen flow bead (SAFB) Luminex positivity for donor-specific antibodies (DSA) class II. A significant lower freedom from BOS was observed in patients with pre-LTx SAFB Luminex-positive DSA class II compared with those without pre-LTx SAFB Luminex-positive DSA class II (P=0.004).

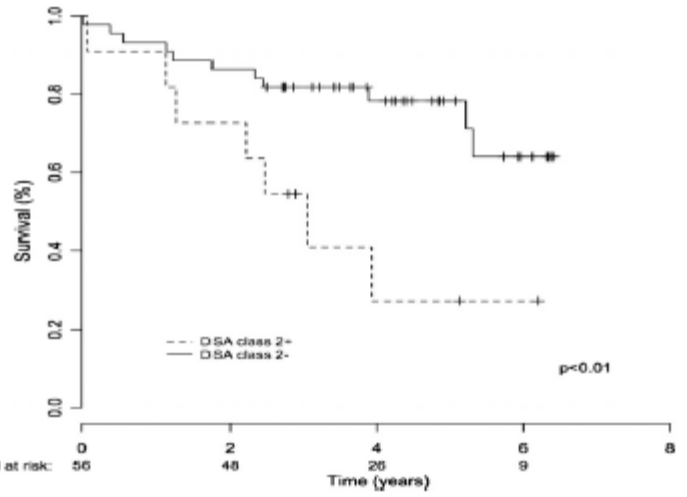

FIGURE 3. Survival curves in patients with or without pre–lung transplantation (LTx) single-antigen flow bead (SAFB) Luminex Luminex positivity for donor-specific antibodies (DSA) class II. A significant lower survival was observed in patients with pre-LTx SAFB Luminex-positive DSA class II compared with those without pre-LTx SAFB Luminex-positive DSA class II (P=0.007).

DSA préformé: quel niveau de MFI ?

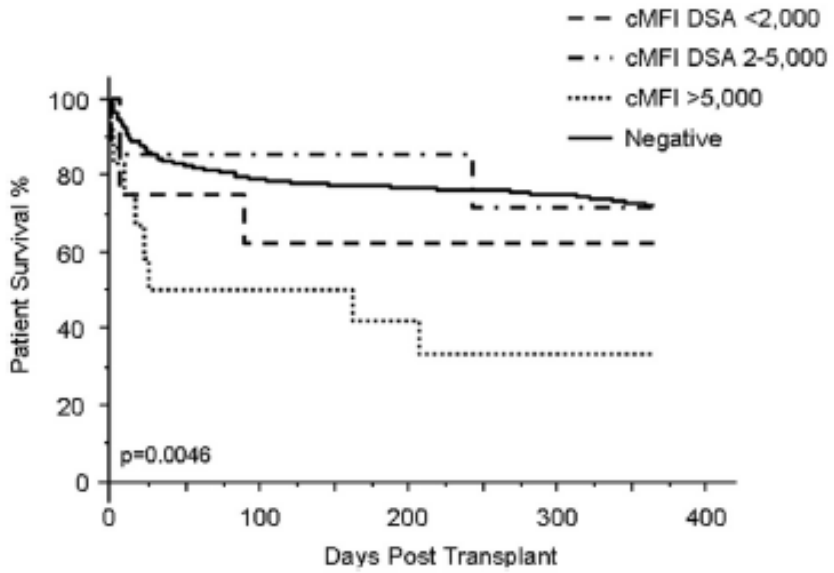

Figure 3 Effect of cMFI DSA on patient survival. Actuarial patient survival according to cMFI levels of DSA in pre-transplant sera, with the sera containing DSA with cMFI >5,000 ($n = 12$); cMFI 2,000 to 5,000 ($n = 7$); cMFI <2,000 ($n = 8$); and no DSA ($n = 398$) ($p < 0.0001$). DSA with cMFI >5,000 had reduced 1-year survival (33.3%) compared with DSA of cMFI 2,000 to 5,000 and DSA <2,000 (62.5%) and in patients with no DSA (72.4%).

Smith J et al JHLT 2014

I L'approche classique « relookée »

- Repose sur
  - Identification des DSA
  - Détermination des ag interdits
  - cross match virtuel négatif
    - *Appel et al .Transplantation .2006 81; 1049-56*
- Avantage
  - Pas de cross prospectif
- *Mais*
  - Non applicable aux patients hyperimmunisés
    - Trop peu de donneurs possibles (simulation sur les 2 ou 3 années précédentes)
    - longue durée d'attente et risque de décès sur liste
  - Quel seuil de positivité retenir pour les DSA ?
    - <1000 or <500

II

Antibody Desensitization Therapy in Highly Sensitized Lung Transplant Candidates

American Journal of Transplantation 2014; XX: 1–8

L. D. Snyder[1,*], A. L. Gray[1], J. M. Reynolds[1], G. M. Arepally[1], A. Bedoya[1], M. G. Hartwig[2],

Day 1	Plasmapheresis	Methylprednisolone 100mg IV	Bortezomib 1.3 mg/m^2 SQ	Rituximab 375 mg/m^2 IV
Day 4	Plasmapheresis	Methylprednisolone 100mg IV	Bortezomib 1.3 mg/m^2 SQ	
Day 8	Plasmapheresis	Methylprednisolone 50mg IV	Bortezomib 1.3 mg/m^2 SQ	
Day 11	Plasmapheresis	Methylprednisolone 50mg IV	Bortezomib 1.3 mg/m^2 SQ	
Day 14	Plasmapheresis			
Day 17	Plasmapheresis			
Day 19	Plasmapheresis			Rituximab 375 mg/m^2 IV
Day 26	IVIG 500mg/kg, continuing monthly			

: **Desensitization pretransplant protocol.** IV, intravenous; IVIG, intravenous immunoglobulin; SQ, subcutaneous.

Antibody Desensitization Therapy in Highly Sensitized Lung Transplant Candidates

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A J T 2014 4:849-56

18 pts hyperimmunisés

9 pts transplantés (69 jours)

- 4 avec cross match virtuel nég (Jo et historique)
- 2 avec cross match virtuel nég (Jo)
- 3 avec cross match virtuel pos de bas niveau, cross match prospectif neg

PRA calculés class I or class II non modifiés par la désensibilisation

Diminution statistiquement significative des MFI seulement dans le groupe 5000-10000 (class I or II) : pertinence clinique ?

III

Utility of Peritransplant and Rescue Intravenous Immunoglobulin and Extracorporeal Immunoadsorption in Lung Transplant Recipients Sensitized to HLA Antigens

James Z. Appel III, Matthew G. Hartwig, R. Duane Davis, and Nancy L. Reinsmoen

Human Immunology 66, 378–386 (2005)

1992-2003
380 LT pts
35 pts avec anti HLA ac non DSA
12 traités, 23 non traités

Elimination des Class I Ab plus facile que Class II

TABLE 1 Peritransplant desensitization regimen for lung transplant recipients sensitized to third-party HLA antigens[a]

Time	Regimen
At transplant	IVIG (2g/kg) + ECI
Posttransplant week 1	IVIG (500mg/kg) + daily ECI
Posttransplant weeks 2–4	IVIG (500mg/kg) + weekly ECI
Posttransplant weeks 5–24	IVIG taper

Abbreviations: ECI = extracorporeal immunoadsorption; IVIG = intravenous immunoglobulin.

[a] ECI withheld in some patients with lower pretransplant percentages of panel-reactive antibodies.

TABLE 2 Impact of peritransplant desensitization therapy on class I and class II anti-HLA antibodies

Patient	Pretransplant PRA[a] (class I/class II)	Time until AB elimination[b] (days)
1	89%/0%	62
2	29%/0%	55
3	86%/0%	—
4	11%/0%	116
5	32%/22%	1/–
6	27%/0%	105
7	0%/26%[c]	NA
8	9%[c]/0%	NA
9	29%/0%	107
10	0%/14%	—
11	0%/7%	185
12	12%[c]/18%[c]	NA/NA

Utility of Peritransplant and Rescue Intravenous Immunoglobulin and Extracorporeal Immunoadsorption in Lung Transplant Recipients Sensitized to HLA Antigens

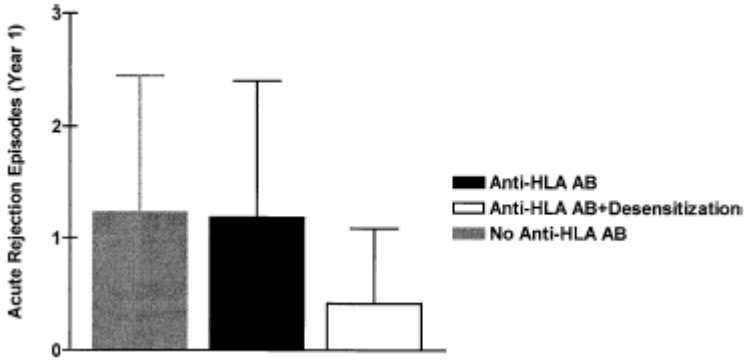


FIGURE 2 Mean number of acute rejection episodes during the first year after transplantation. Frequency of acute rejection episodes among lung transplant recipients presensitized to third-party human leukocyte antigens (HLA) was significantly lower for those who received peritransplant desensitization therapy compared with those who did not ($p = 0.05$ based on Student's t-test) or compared with nonsensitized patients ($p = 0.02$ based on Student's t-test, $p = 0.07$ overall based on analysis of variance). Frequency of acute rejection events was comparable among nonsensitized recipients and presensitized recipients who did not receive peritransplant desensitization therapy ($p = 0.86$ based on Student's t-test). AB = antibodies.

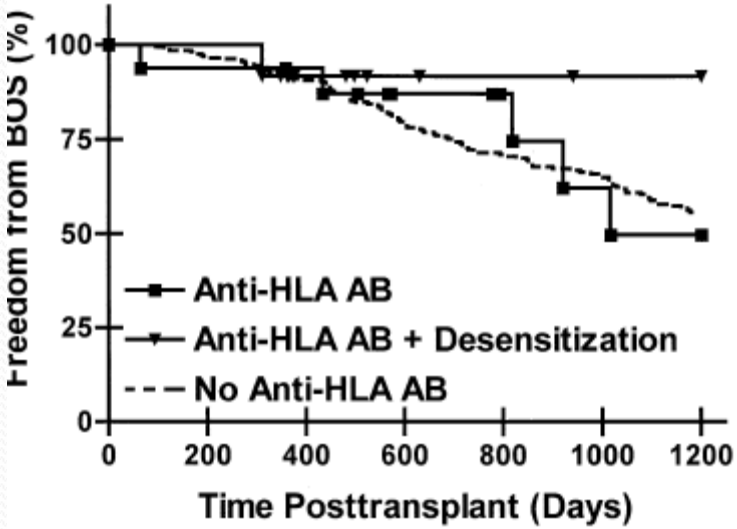


FIGURE 1 Freedom from bronchiolitis obliterans syndrome (BOS) Kaplan-Meier curves. Freedom from BOS over 3 years of follow-up was higher among lung transplant recipients presensitized to third-party human leukocyte antigens (HLA) who received peritransplant desensitization therapy compared with those who did not receive therapy or compared with nonsensitized recipients ($p = 0.32$ based on log-rank analysis). AB = antibodies.

Survival in Sensitized Lung Transplant Recipients With Perioperative Desensitization

K. J. Tinckam[2], S. Keshavjee[1], C. Chaparro[1], D. Barth[2,3], S. Azad[1], M. Binnie[1], C. W. Chow[1], M. de Perrot[1], A. F. Pierre[1], T. K. Waddell[1], K. Yasufuku[1], M. Cypel[1] and L. G. Singer[1,*]

American Journal of Transplantation 2015; 15: 417–426
Wiley Periodicals Inc.

Table 1: Toronto lung transplant sensitized recipient protocol 2008–2011*

Clinical status		Likelihood of future DSA-negative transplant		Decision
Part 1: Transplant decision strategy for DSA-positive recipients				
1		Acceptable – cPRA < 30%		Wait – use alternate recipient
1		Lower – cPRA > 30%		Proceed with transplant
2/3		Any		Proceed with transplant
Risk Group	**PRA**	**DSA**	**AHG CDC XM**	**Treatment**
Part 2: Treatment determined by risk group				
High	Pos	Pos	Pos	ATG 5 mg/kg, PLEX, IVIg (1 g/kg), MPA
High	Pos	Pos	Neg	ATG 3 mg/kg, PLEX, IVIg (1 g/kg), MPA
Mod	Pos	Neg	Neg	MPA
Low	Neg	Neg	Neg	Standard care including azathioprine

All subjects received cyclosporine and prednisone. See Supplemental Appendix for current iteration of this protocol.

Survival in Sensitized Lung Transplant Recipients With Perioperative Desensitization

Table 4: Outcomes by sensitization group

	DSA positive ($n=53$)	PRA no DSA ($n=93$)	Unsensitized ($n=194$)	p-Value
Any PGD 3 at 48 or 72 h, *n* (%)	11 (21)	19 (21)	35 (18)	0.82[1]
Cardiopulmonary bypass, n (%)	40 (75)	35 (38)	59 (30)	<**0.0001**[1]
ICU days (Med [IQR])	6 [3–22]*	4 [2–17]	3 [2–10]	**0.0079**
Hospital LOS	29 [20–45] *	29 [15–62] *	21 [16–35]	**0.0127**
Infections *n* (%)				
CMV	18 (34)	30 (32)	60 (30)	0.9[1]
Fungal	11 (21)	25 (27)	52 (26)	0.65[1]
Rejection and function				
Acute >=A2 rejection	5 (9.4)	8 (8.6)	36 (18.6)	**0.048**[1]
Max %pred FEV_1	76 ± 22	74 ± 25	80 ± 23	0.10[2]
Max %pred FVC	79 ± 19	77 ± 22	81 ± 20	0.4[2]
CLAD *n*(%)	4 (7.6)	8 (8.6)	25 (12.9)	0.43[1]

PGD, Primary graft dysfunction; ICU, intensive care unit; Med, median; IQR, interquartile range; LOS, length of stay; CMV, cytomegalovirus; Max, maximum; %Pred, percent predicted; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; CLAD, chronic lung allograft dysfunction.

Survival in Sensitized Lung Transplant Recipients With Perioperative Desensitization

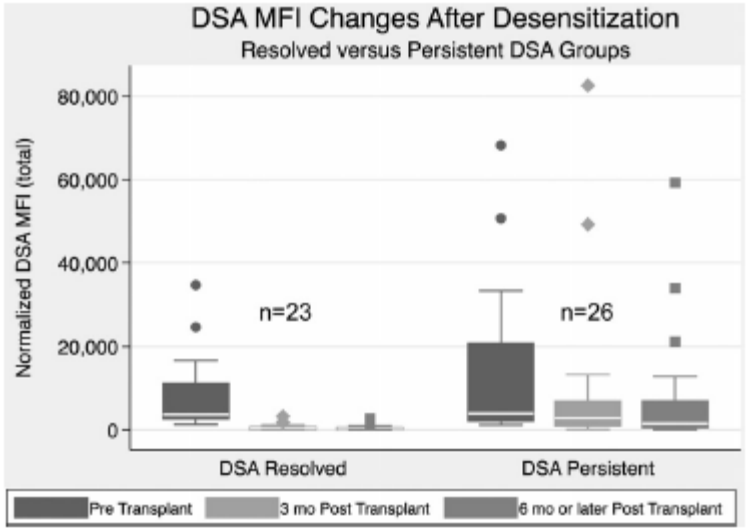


Figure 1: Overall, DSA MFI were reduced following desensitization. DSA MFI (sum) at three time points: Immediate pretransplant serum drawn on day of transplant (in $n=49$ with at least one posttransplant test), 3 months posttransplant and 6 months (posttransplant or later if 6 month data not available) in groups defined by DSA resolved ($n=23$; no pretransplant DSA detected >1200 MFI on any posttransplant serum) versus DSA persisted ($n=26$; DSA detected >1200 MFI at least one time posttransplant during follow up). MFI were significantly reduced, even in those recipients where DSA persisted (p = 0.001, DSA Resolution group and p = 0.05, DSA Persistent group).

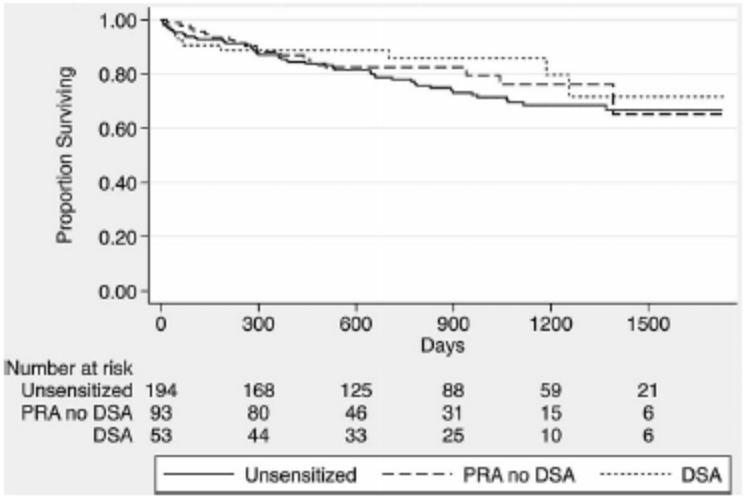


Figure 2: Unadjusted Kaplan–Meier survival estimates by pretransplant sensitization status (defining the intended antibody treatment group) (p = 0.47).

A peritransplant strategy in LT recipients with preformed anti HLA DSA Foch Lung Transplant Group ISHLT 2014 P 514 Etude pilote

	DSA + pts (n=17)	DSA - pts (n=82)	*p-value*
Age (y)	41 [29; 47]	37 [27; 51]	*0.6*
Men (n)	7 (41%)	37 (45%)	*0.8*
Underlying disease Cystic fibrosis	10 (59%)	47 (57%)	*1*
Time on waiting list (d)	72 [5; 124]	18 [5; 38]	*0.02*
Graft ischemic time (mn)	360 [330; 455]	330 [300; 393]	*0.3*
Red packed cells (unit)	6 [5; 9]	5 [4; 8]	*0.1*
Post operative ECMO (n)	6 (35%)	17 (21%)	*0.2*
Induction therapy (n)	4 (24%)	24 (29%)	*0.7*
Extubation in OR (n)	5 (29%)	31 (38%)	*0.6*
Cellular rejection D7 (n)	2 (12%)	21 (26%)	*0.3*
Cellular rejection M1 (n)	3 (18%)	15 (18%)	*1*
Mechanical ventilation (d)	11 [0; 21]	4.5 [0; 21]	*0.7*
Bacterial pneumonia in ICU (n)	9 (53%)	45 (55%)	*0.9*
ICU LOS (d)	15 [6; 19]	8 [5; 17]	*0.3*
Follow up (d)	655 [482;1012]	555 [306;824]	*0.2*
Death (07/13) (n)	2 (12%)	20 (24%)	*0.3*

Etude Foch

- Etude rétrospective
- 440 Patients TP d'avril 2011 à avril 2018
- 39 patients immunisés HLA
  - Cross match virtuel pos
  - Ac Anti HLA MFI >1000
  - Protocole désimmunisation périopératoire
- Recherche DSA J0 fin EP et M1
- 27 femmes, 12 hommes
- TBP 36, TMP 2 TBP foie 1
- Age 45+- 13
- Muco 16, emphyseme BPCO 9, PID fibrose 8, autres 3

Patients DSA préformés + cross match « virtuel » pos

DSA Scores 6-8 (MFI <5000)

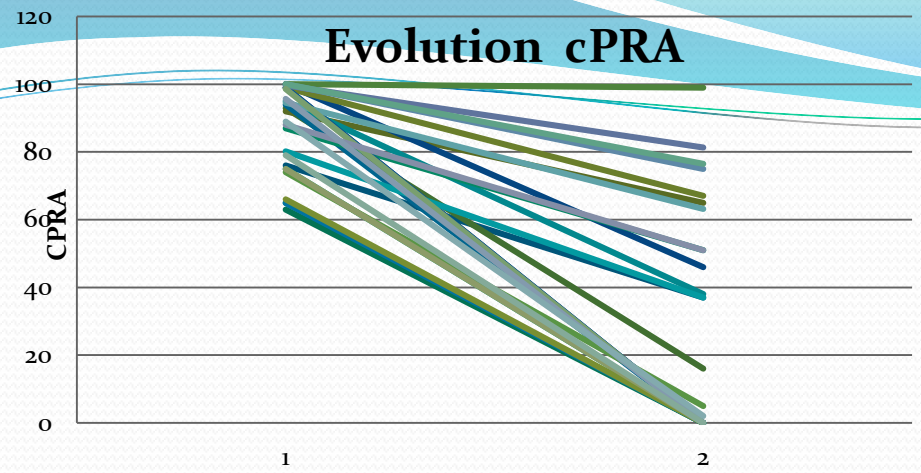
- Si accès très limité et /ou détérioration fonctionnelle rapide
  - Pré op: 1 EP
  - Post op : 5EP (Jo-J5)
    - Contrôle DSA J5
      - Si diminution DSA > 20 %, IvIg 2g/kg+- rituximab
      - Si pas de diminution poursuite EP
  - Cellcept 1000 mg*3 /j

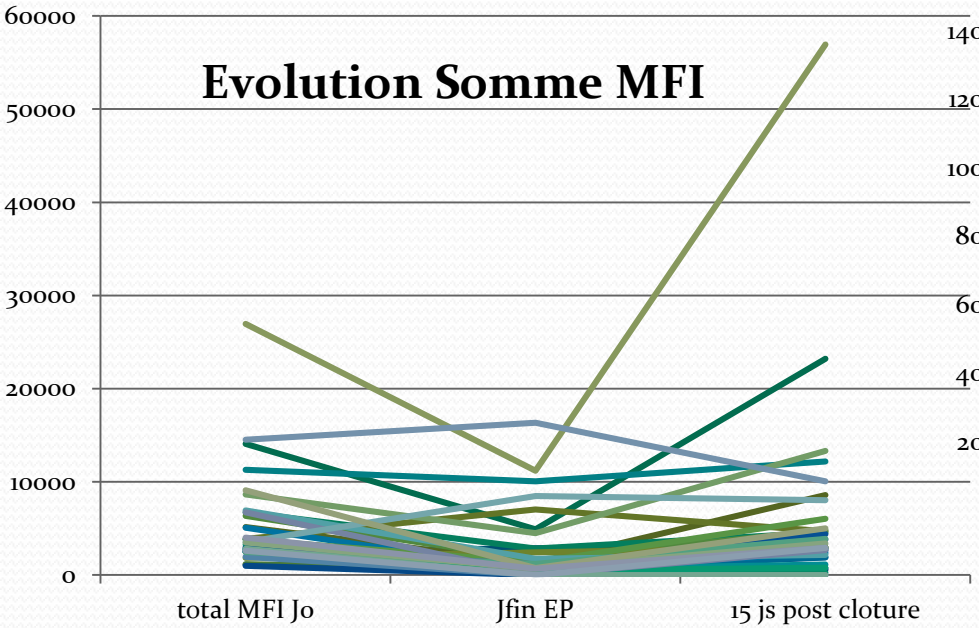
EP

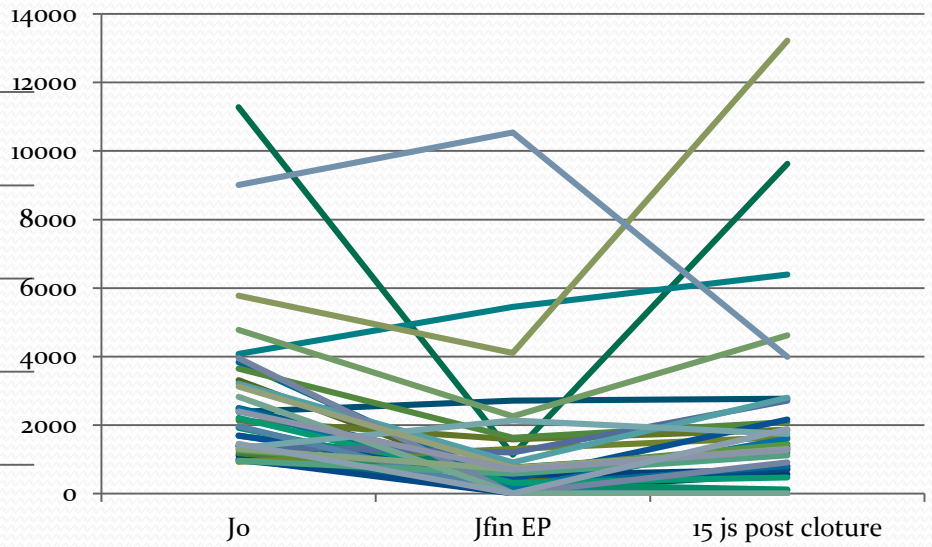
- Centrifugation Optia
- Voie d'abord KT fémoral gauche
- 1,2 MP
- PFC pour pré op et post op immédiat puis Albumine 4% PFC
- Anticoagulant citrate
- réchauffeur ligne de retour
- Calcium

Données immuno

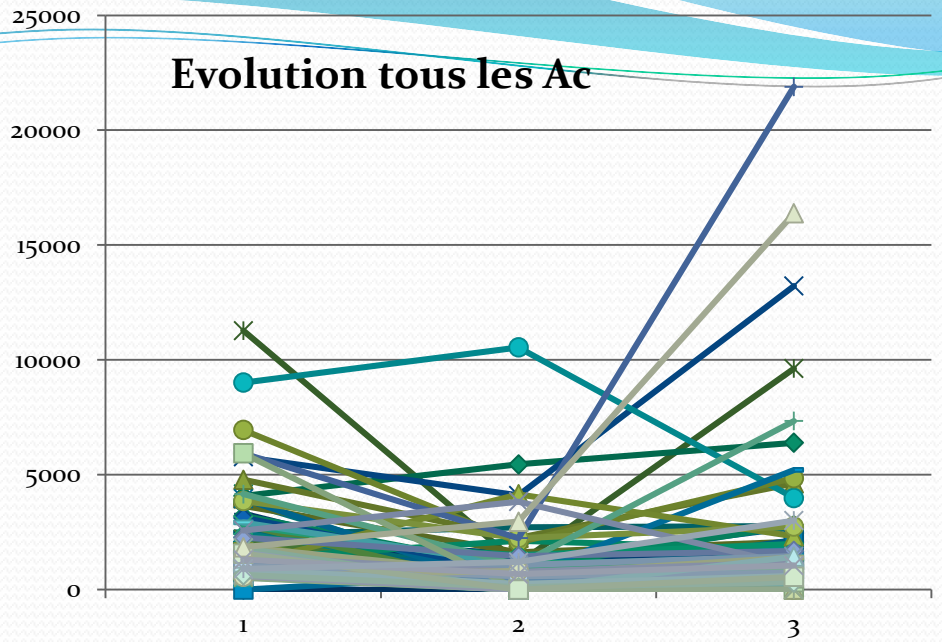
- cPRA
- Ac
  - Classe I seul n=9
  - Classe II seul n= 16
  - Classe 1-2 n=14
  - MFI
    - > 10000 n = 2
    - 5000<MFI<10000 n= 2
    - 3000<MFI<5000 n= 9
    - 1000<MFI<3000 n=26
  - Ac dominant
    - Classe 1 n=16
    - Classe2 n=23
- Cross match 5 pos/38 IgM
  - 1 pt sous ritux
  - 1 PR facteur rhumatoide ?
  - 3 pts muco

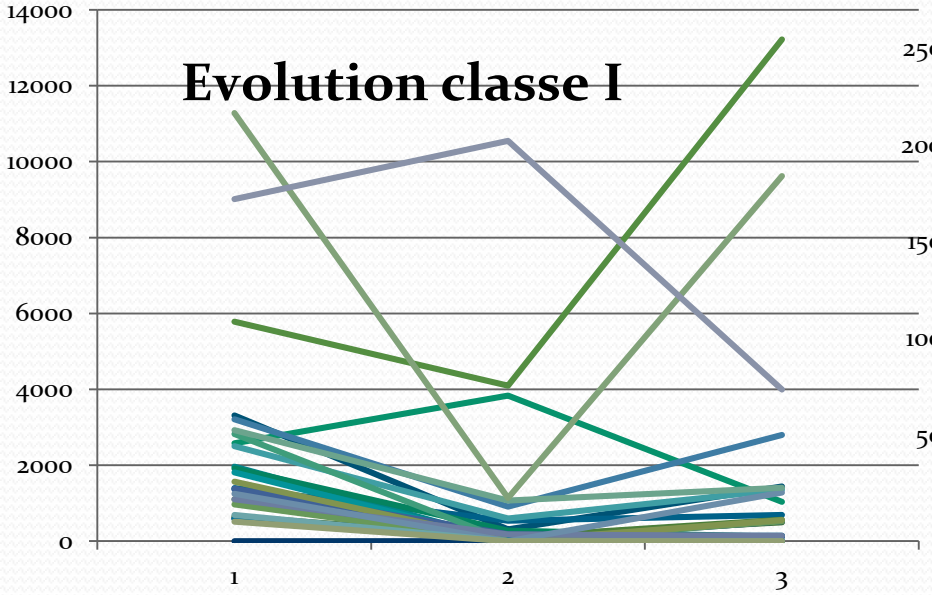


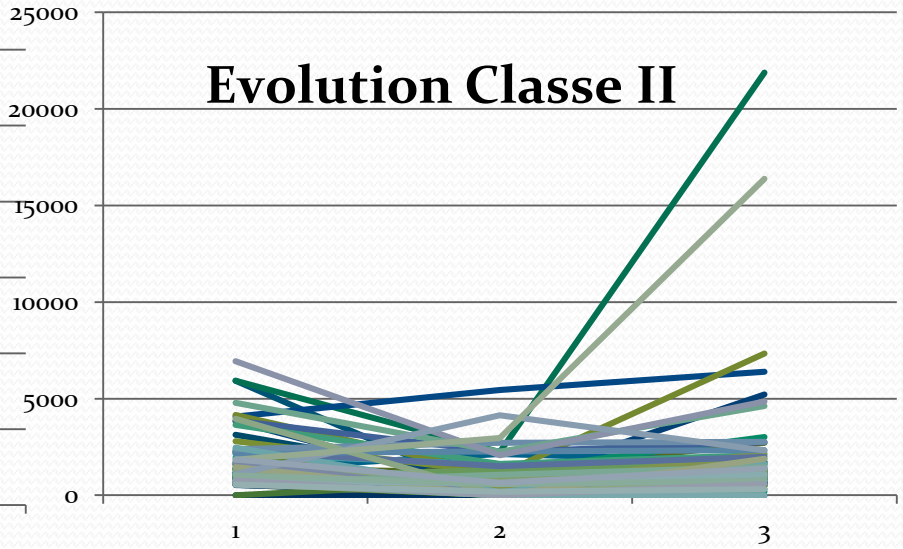




Evolution Ac dominant


Evolution tous les Ac
25000
20000
15000
10000
5000
0
1
2
3


Evolution classe I
14000
12000
10000
8000
6000
4000
2000
0
1
2
3

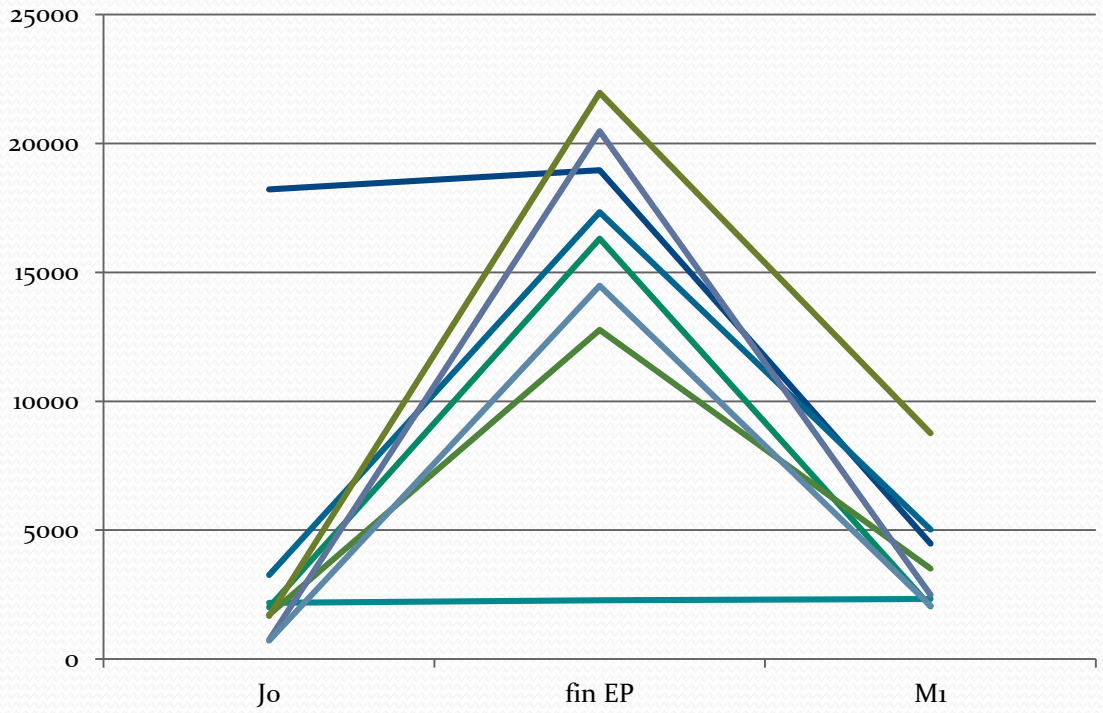

Evolution Classe II
25000
20000
15000
10000
5000
0
1
2
3

Scores MFI exprimés en médiane [IQ] Comparés par un test non paramétrique (Wilcoxon)

	Jo	Après EP	P (Test Wilcoxon)
CPRA	94 [76-99]	3 [0-63]	< 0,001
Ac dominant	1968 [1299-3310]	610 [219-1302]	< 0,001
Total MFI	3512 [2507-6729]	902 [497-2843]	< 0,001
Tous Ac	1335 [882-2278]	420 [0-1070]	< 0,001
Ac Classe 1	1481 [898-2847]	127 [0-677]	< 0,001
Ac Classe 2	1279 [878-2190]	580 [0-1169]	< 0,001

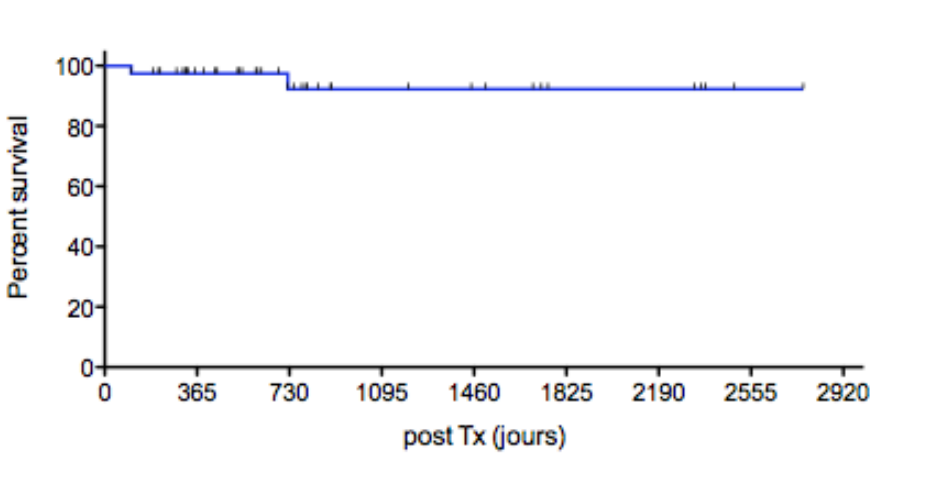
Comparaison des taux d'Ac de classe 1 et 2 à Jo : NS (p=0,22)
Comparaison des taux d'Ac de classe 1 et 2 après EP : p=0,04)

Pourcentage de diminution des Ac Classe 1 = 90% [75-100]
Pourcentage de diminution des Ac Classe 2 = 64% [35-100]
Comparaison : p=0,003

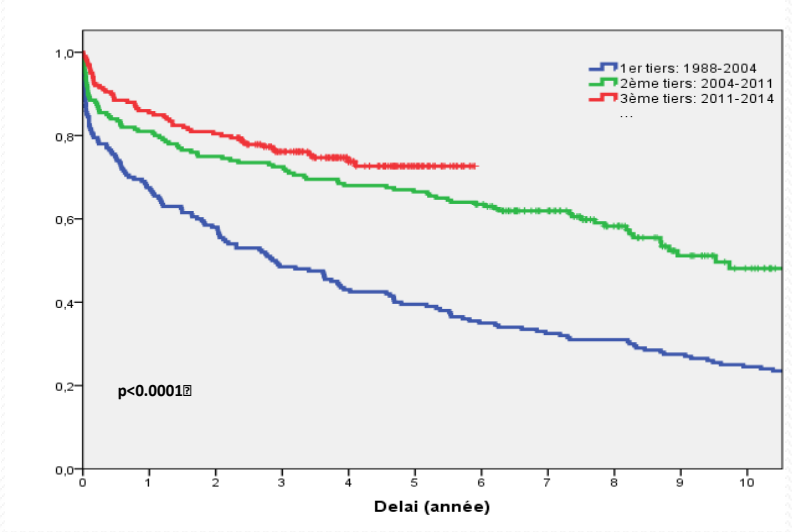


Mme S polyimmunisée cross LCT nég, FCM pos

Evolution à long terme



Désimmunisation periopératoire



Cohorte Foch

1 rejet aigu grave très précoce
9/39 épisode AMR, 2 CLAD part humorale
15/39>= 1 épisode de rejet cellulaire

Place IA

- Ac élevés pré TP
  - Essayer 1 IA pour évaluer réponse et définir une limite d'efficacité éventuelle
  - Pré op immédiat pas d'IA
    - Organisation
    - Temps ++
  - Post opératoire
    - > 5000
    - Non réponse au traitement standart

Conclusion

- Désimmunisation périopératoire efficace en TP
- Pas de sur morbidité infectieuse post opératoire
- Bons résultats à long terme
- Intérêt du dosage de fin d'échange
- Pb des hyperimmunisés avec MFI hautes >15000 ?
- Place pour des techniques IA seules ou combinées

Remerciements

- A Braconnier et A Lamarche
- A G Si Larbi pour les statistiques