INSTITUT DE CARDIOLOGIE
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Intravenous immunoglobulin and plasmapheresis : a strategy to prevent antibody mediated rejection in patients with pretransplant DSA

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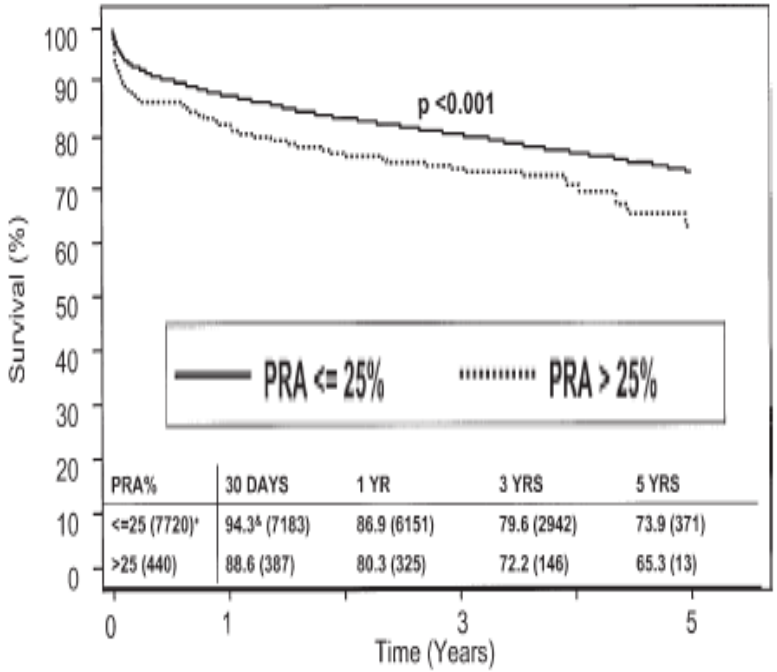
ngrès SFH dec 2014

Influence of pretransplant PRA on outcomes of 8,160 Htx patients



Risk Factor[a]	Hazard Ratio	95% Confidence Interval	*p* Value
PRA (continuous variable)	1.005	1.002–1.009	<0.001
PRA 1%–10%[b]	1.17	0.96–1.42	0.12
PRA 11%–25%[b]	0.94	0.99–1.00	0.73
PRA >25%[b]	1.4	1.09–1.77	0.007

Nwakanma et al .human Immunology 2007

PRE-transplant desensitization: IVIg + plasmapheresis

Pisani, *J Heart Lung Tranpl* 1999

- 102 Patients PRA < 10% : standard tt
- 16 Patients PRA > 10% : EP + Ig IV

⇒ **No difference**

1 year mortality (87% vs 84%)

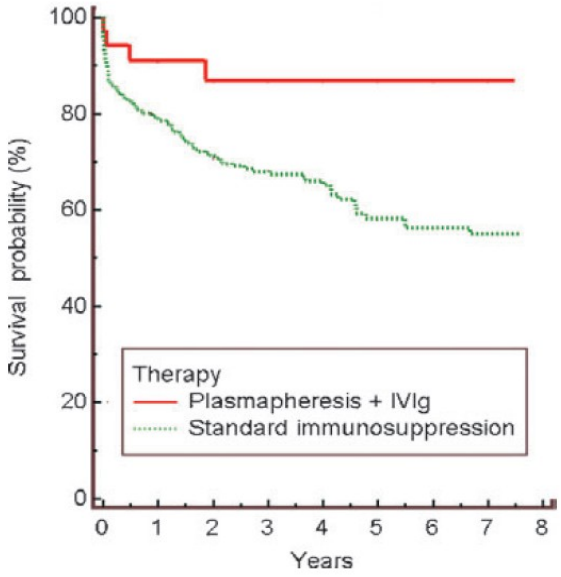
ISHLT	0 (%)	1A/1B (%)	2 (%)	3A/3B (%)	4 (%)	BSI	HR
Group 1	57.9	27.9	6.0	1.6	0	7.7	1
Group 2	64.9	30.9	5.2	1.4	0	8.1	10
p-value	NS	NS	NS	NS	NS	NS	NS

BSI (Bx Score Index), HR, Humoral rejection.

Pisani, 1999

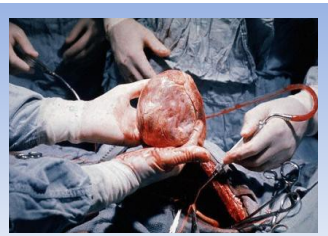
Leech, *Clin Tranplant* 2006

- 276 Patients PRA < 10% : standard tt
- 35 Patients PRA > 10% : EP + Ig IV



Leech, 2006

Purpose of study



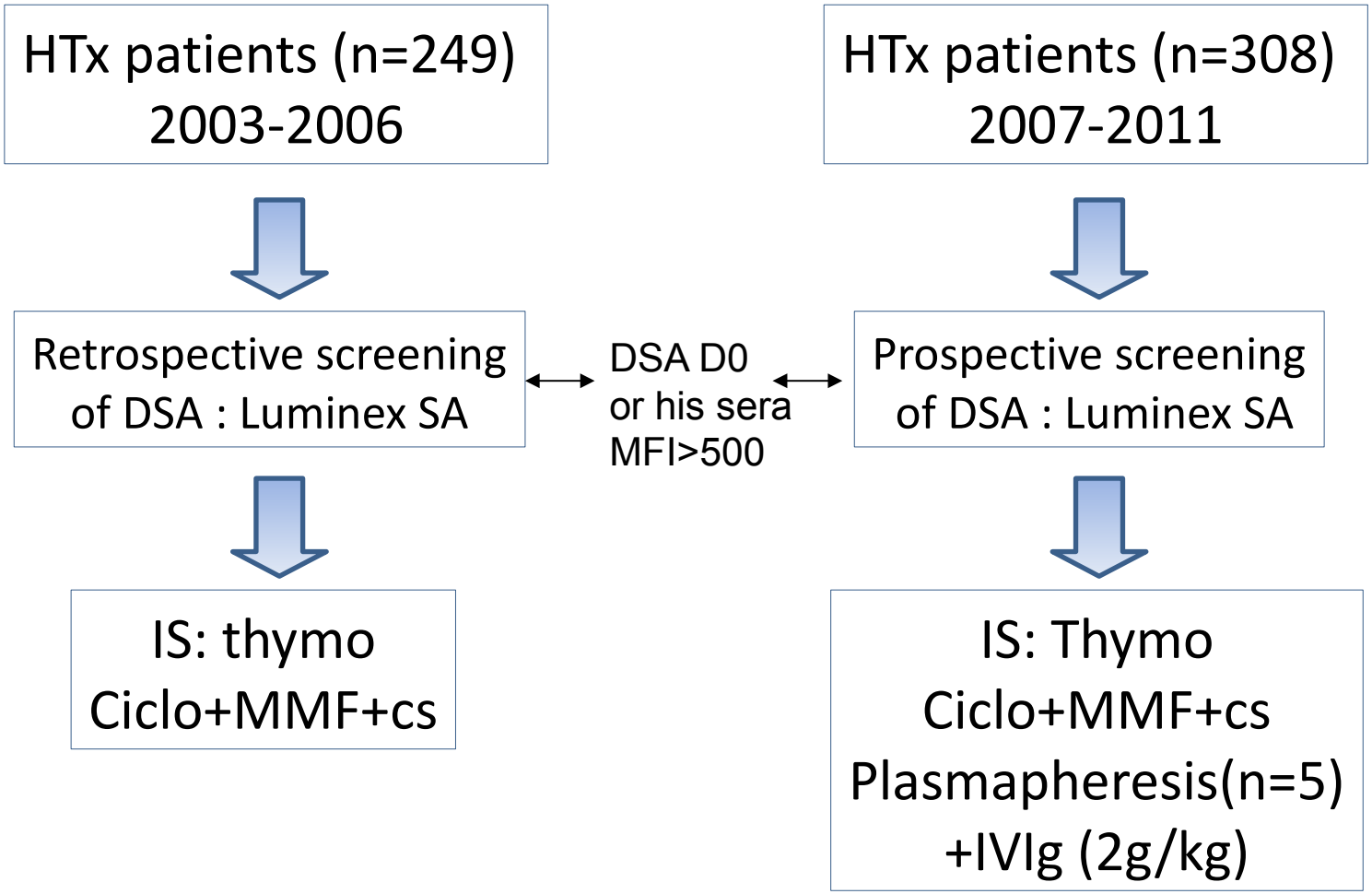
- purpose of this study was to find out if the plasmapheresis + IgIV can be effective at per transplant desensitization and improve heart transplant outcomes

- « case – control » study treatment study:

Prospective group of sensitized patients with desensitization therapy was compared to a historical group without treatment

- desensitization started at the time of transplantation in treated group

Study design



Historical no treated group:

Control (n= 35, 14%)

Prospective treated group:

Cases (n= 47,15%)

Endpoints

- Primary outcome:

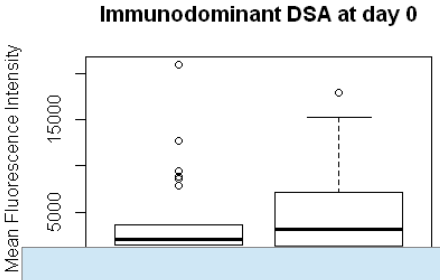
  3 years survival

- Secondary outcomes:
  - Occurrence of Antibody-mediated rejection (12 months)
  - Allograft function at 3 years
  - Cardiac allograft vasculopathy at 3 years

Characteristics of patients at time of transplantation

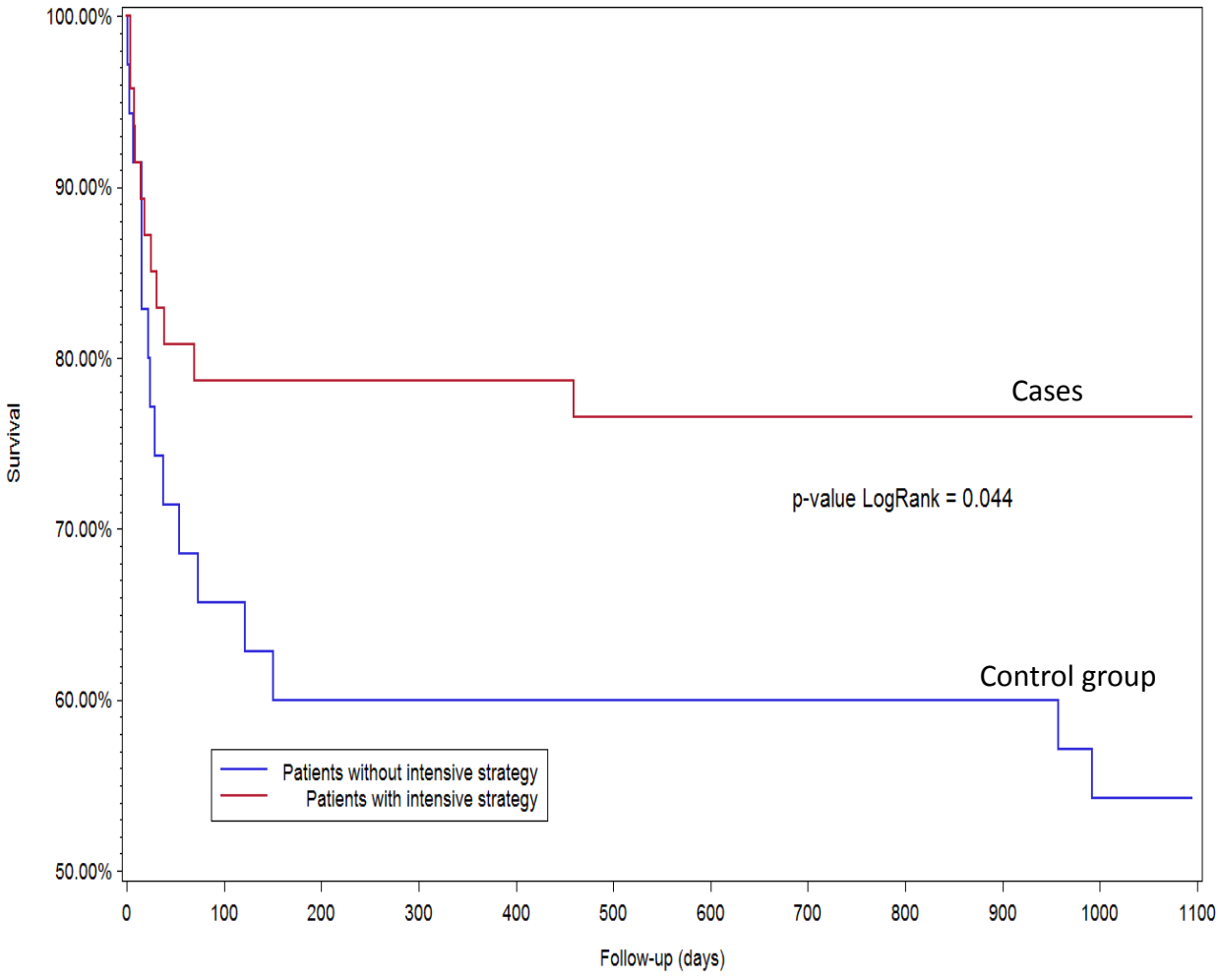
	Total n=82	Treated group n=47	Historical group n=35	p value
Recipient age (years, mean ±SEM)	45.3±14.5	45.1±14	45.1±14.9	0.85
Gender (male, n, %)	48 (58.5%)	29 (61.7%)	19 (54.3%)	0.53
Primary heart disease				
Dilated cardiomyopathy (n, %)	36 (43.9%)	20 (42.6%)	16 (45.7%)	0.8
Ischemic cardiomyopathy (n, %)	26 (31.7%)	15 (31.9%)	11 (31.4%)	0.96
Retransplantation (n, %)	5 (6.1%)	4 (8.5%)	1 (2.9%)	0.55
Other (n, %)	15 (18.3%)	8 (17%)	7 (20%)	0.73
Donor				
Donor Gender (male, n, %)	48 (58.5%)	29 (61.7%)	19 (54.3%)	0.26
Donor age (years, mean±SEM)	49.8±10.2	49.4±10.6	50.4±9.9	0.51
Mismatch Gender D/R (n,%)	34 (41.5%)	20 (42.6%)	9 (25.7%)	0.18
Cold Ischemia time (minutes, mean ± SEM)	190.3±57.1	202.9±56.4	173.4±54.3	0.01
Preoperative ECMO n(%)	15 (18.3%)	12 (25.5%)	3 (8.6%)	0.09
Crossmatch at Day 0	15/39 (38.5%)	12/34 (35.3%)	3/5 (60%)	0.33

Immunological parameters



	Total n=82	Treated group n=47	Historical group n=35	p
Class 1 DSA (n, %)	52 (63.4%)	36 (76.6%)	16 (45.7%)	0.67
Class 2 DSA (n, %)	62 (75.6%)	38 (80.9%)	24 (68.6%)	0.60
Class 1 Immunodominant DSA (n, %)	32 (39.0%)	18 (43.9%)	9 (34.6%)	0.27
Class 2 Immunodominant DSA (n, %)	50 (61.0%)	31 (66.0%)	19 (54.3%)	0.61
Immunodominant DSA MFI (peak)				
Mean (±SEM)	4536 (± 4761)	4824 (±4853)	4153 (±4674)	0.45
Cumulated MFI				
Mean (±SEM)	6936 (± 8761)	7522 (±8256)	7169 (± 9687)	0.74

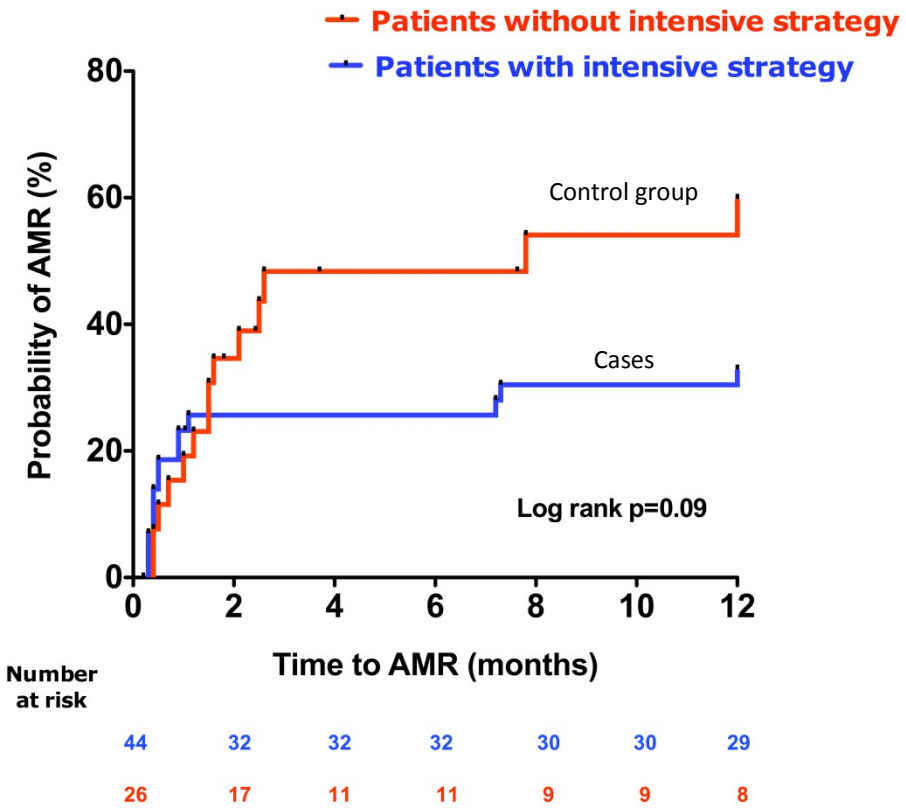
Primary outcome: 3 years survival



47	37	36	36
35	21	21	18

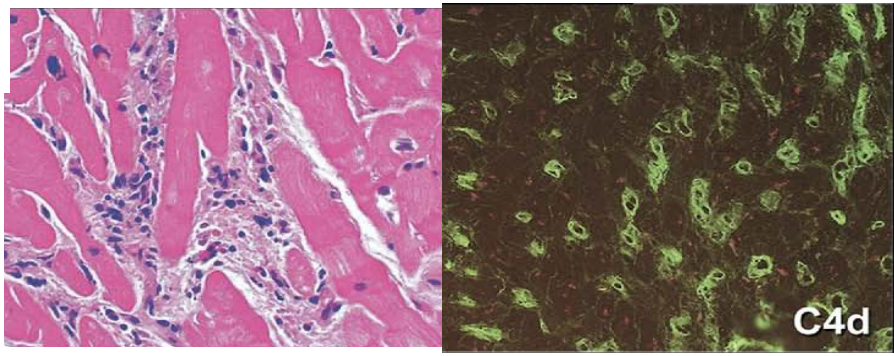
Antibody mediated rejection

(n=70 pts with EMB available)

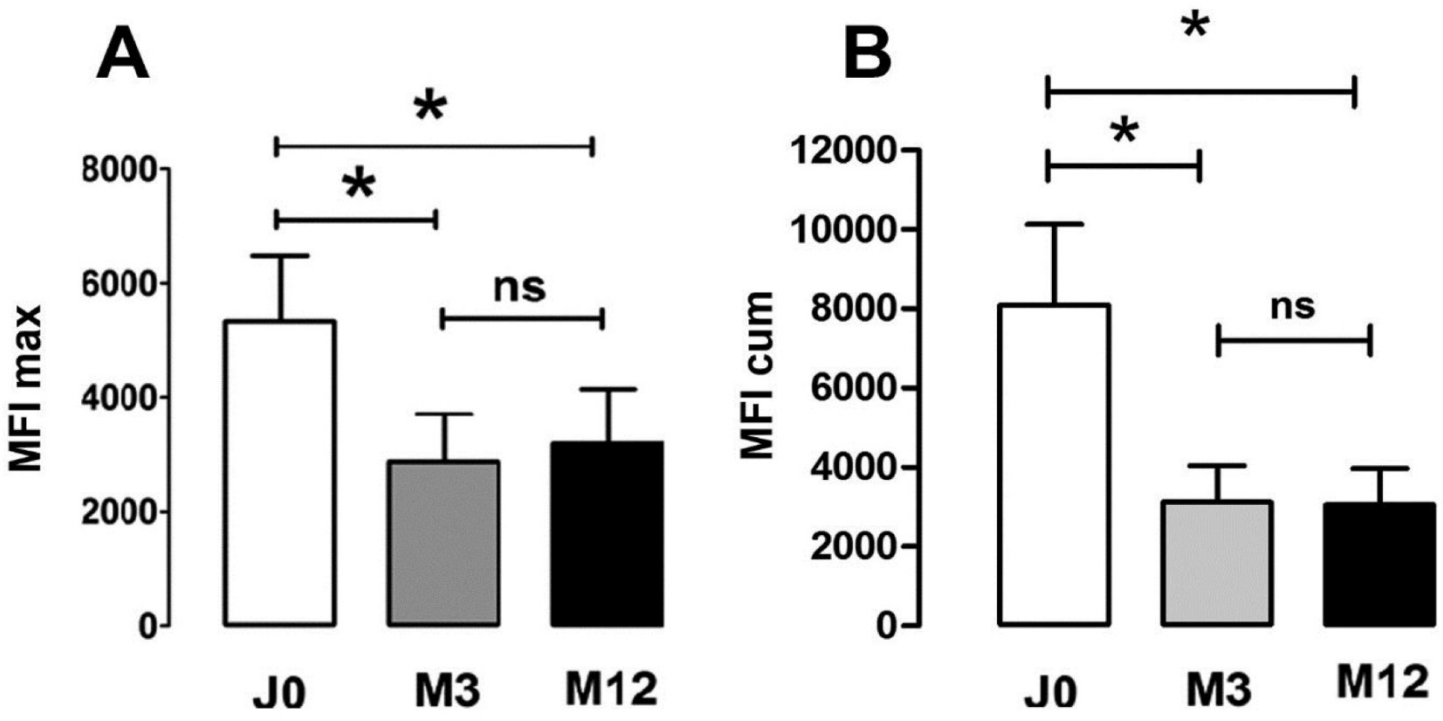


Grade	Pathologic features of AMR[1]
pAMR 0 Negative for pathologic AMR	Negative histologic and immunopathologic findings
pAMR 1 (H+): Histopathologic AMR	Positive histologic findings alone
pAMR 1 (I+): Immunopathologic AMR	Positive immunopathologic findings alone
pAMR 2 Pathologic AMR	Both histologic and immunopathologic findings
pAMR 3 Severe pathologic AMR	Interstitial hemorrhage, edema, capillary fragmentation, mixed inflammatory infiltrates, endothelial cell pyknosis/karyorrhexis

[1]Histologic features of AMR: endothelial swelling, macrophage infiltration, interstitial hemorrhage and edema. Immunopathologic features of AMR: C4d, C3d, CD68 and Ig.



DSA (MFI) after prophylactic strategy



* P value = 0.04

LIMITATIONS

- small size of study population
- No randomized study
- comparison to an historical cohorte (2003-2006)

Conclusion & perspective

- With this prophylactic strategy, heart transplantation in sensitized patients should be considered with acceptable results and may contribute to decrease the mortality

- Safety evaluation of this strategy in a larger cohort of patients
- Definition of the cutoff points of MFI
- To identify a better risk stratification with complement binding anti HLA antibodies (C1q)

L’équipe de chirurgie cardiaque-GHPS
L’équipe de réanimation chirurgicale- GHPS
L’équipe de réanimation médicale-GHPS
L’équipe de biothérapie et et de plasmaphérèse – GHPS
L’équipe d’anatomopathologie – GHPS et HEGP
Le PARCC

Merci

Immunosuppressive regimen and postoperative management

Immunosuppressive regimen at Day 0	**Total n=82**	**Intensive strategy group n=47**	**Control group n=35**	**p value**
Corticosteroids	82	47	35	
Thymoglobulins (1.5 mg/kg/jour during 5 days) (n)	79	47	32	
Basiliximab (20 mg at day 0 and 4) (n)	3	0	3	
Calcineurin inhibitors (n)	82	47	35	
Mycophenolate mofetil (n)	82	47	35	
Intensive prophylactic therapeutic strategy in postoperative period				
Intravenous Immunoglobulins (n)	47	45	2	
Plasmapheresis (n)	47	47	0	
Anti-CD20 (Rituximab, 375mg/m^2) (n)	3	3	0	
Immediate postoperative graft function				
Postoperative ECMO n (%)	28 (34.1%)	16 (34%)	12 (34.3%)	0.98
Primary graft dysfunction (n,%)	*23 (32,9%)*	*15 (34,1%)*	*8 (30,8%)*	*0.57*

Mortality at 3 years

	Total (n=25/82)	Treatment group (n = 11/47)	Historical group (n = 14/35)
Sepsis	12	6	6
Stroke	3	1	2
Primary graft dysfunction	2	1	1
Acute rejection	1	1	0
Cardiogenic shock	1	1	0
Bleeding	1	0	1
Unknown	5	1	4