CR2TI
UMR 1064
Centre de Recherche Translationnelle en Transplantation et Immunologie

CENTRE HOSPITALIER UNIVERSITAIRE DE NANTES

Greffe sous Imlifidase des patients hyperimmunisés

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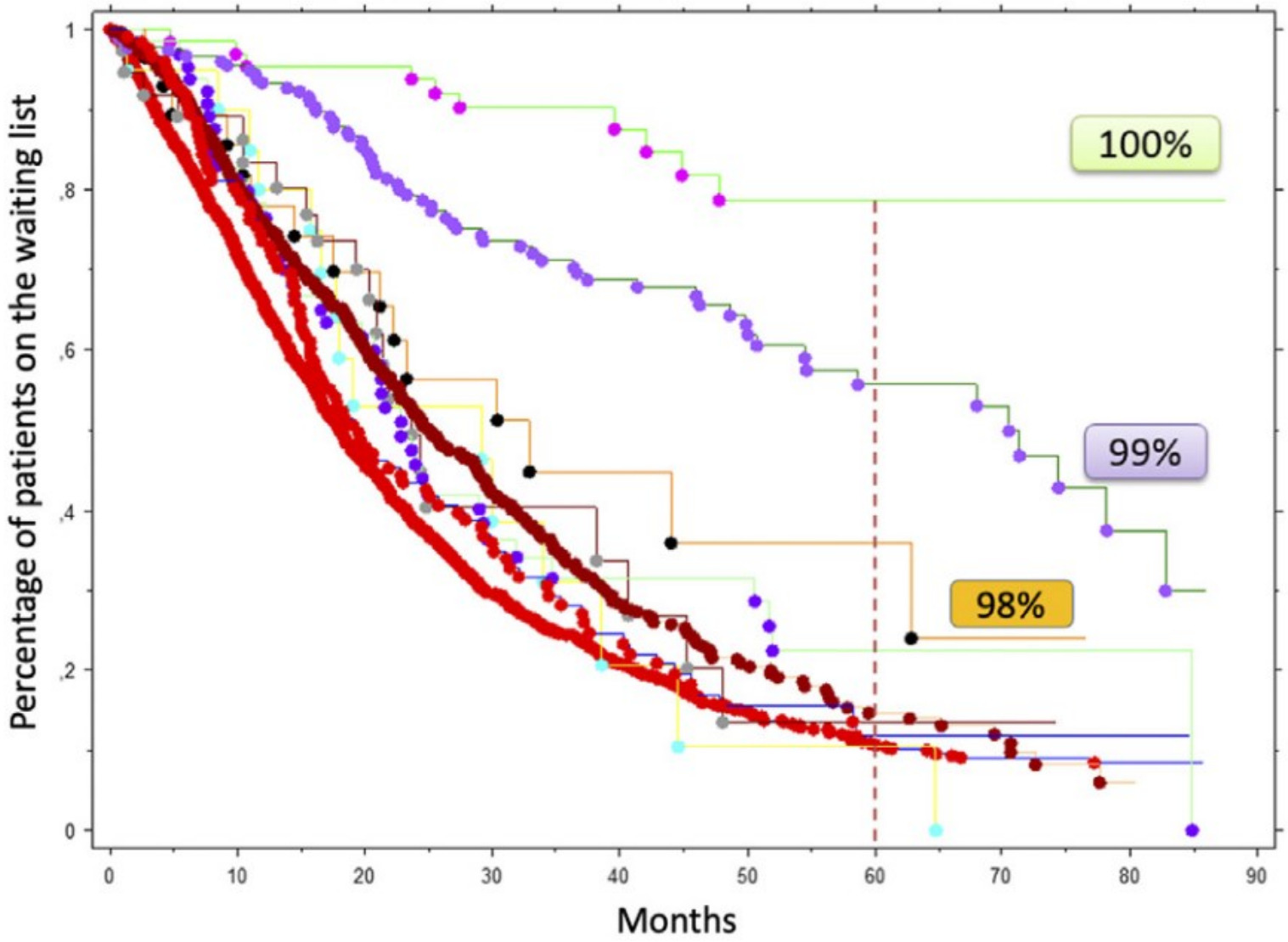
Disclosure

- Chiesi : Consulting fees
- **Hansa : Lecture fees**
- Sanofi : Consulting fees, Lecture fees

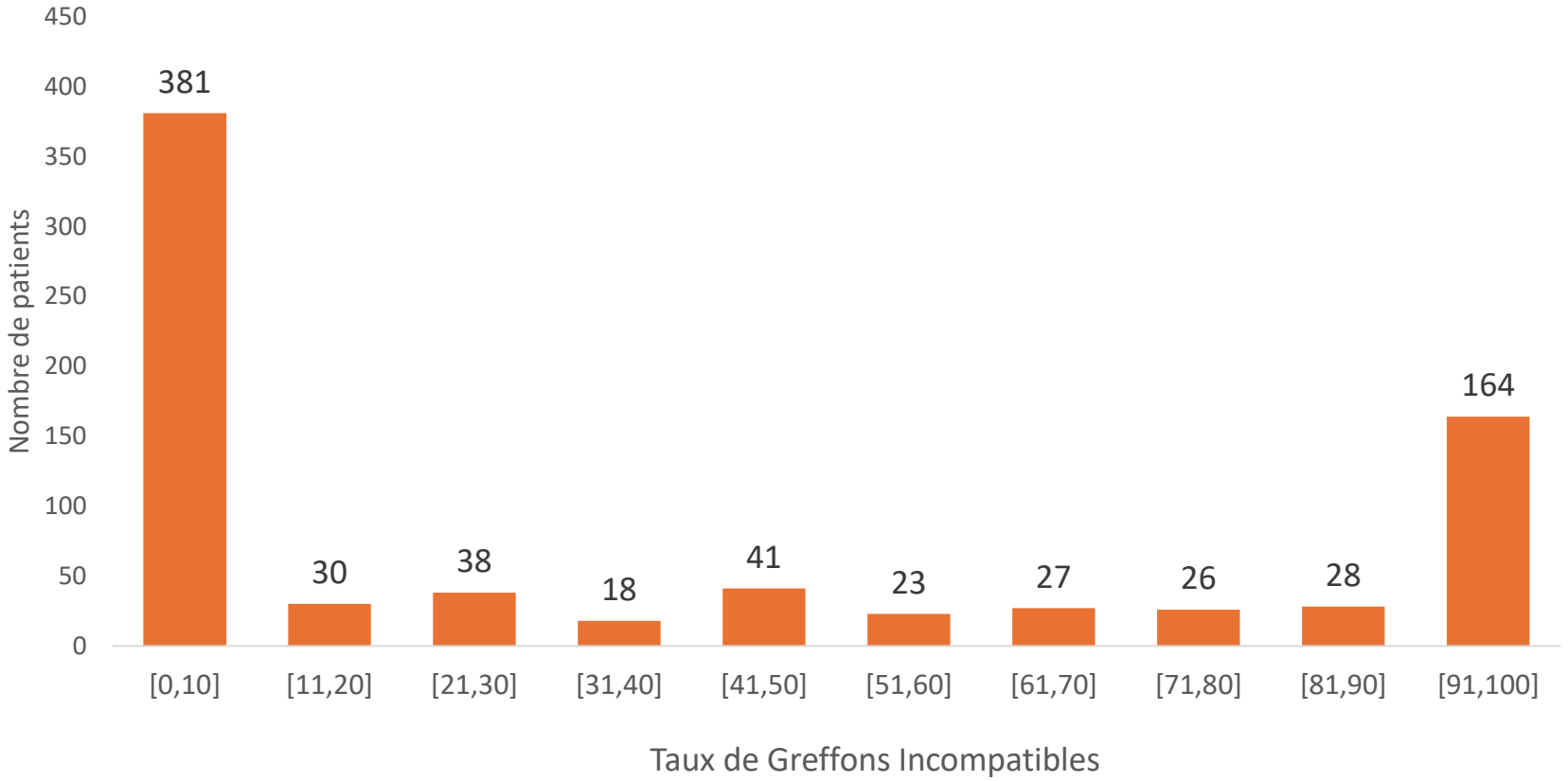
Access to kidney transplantation



Couzi et al, Transplant Int, 2024

Highly sensitized patients in Nantes

~800 patients in the waiting list for a kidney transplant (Nov 25)



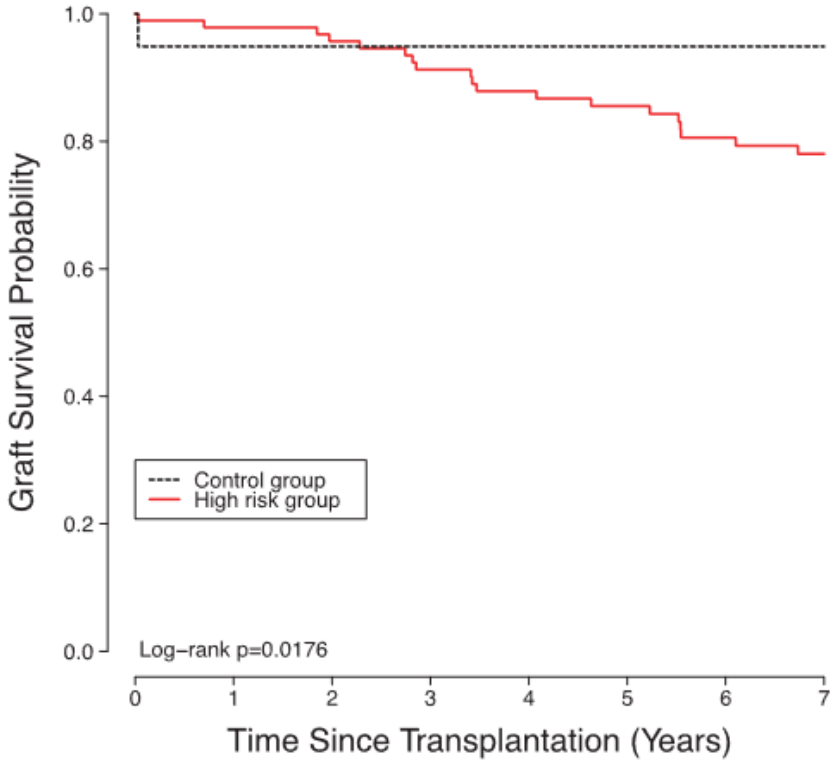
185 Highly sensitized patients (historical TGI ≥85%, last TGI ≥70%)

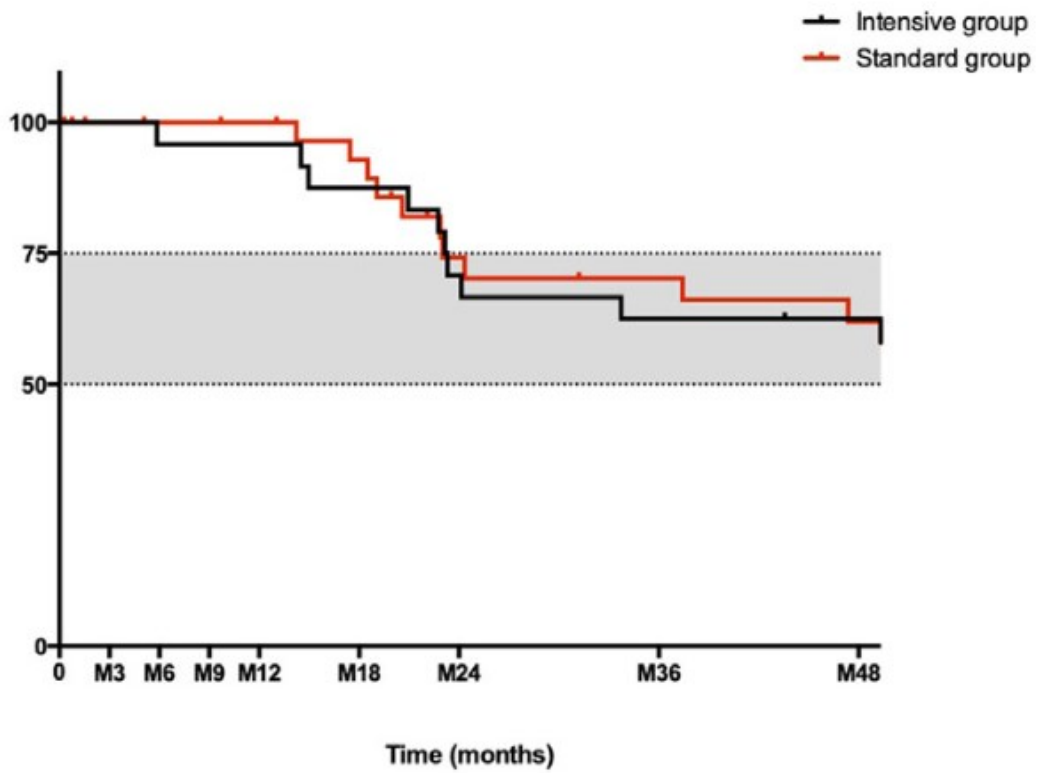
- 34 awaiting 1st transplantation
- **93 awaiting 2nd** transplantation
- **46 awaiting 3rd** transplantation
- **12 awaiting 4th** transplantation

~25% of our waiting list is considered Highly sensitized

TGI: Taux de greffons incompatibles. Data on file CHU Nantes

Desensitization strategies for highly sensitized patients: rituximab* + PLEX?





Kidney Transplantation with DSA > 3000 MFI and CDC neg

➥ **Poor mid-term allograft survival despite rituximab* + PLEX**

**Not approved in transplantation. DSA: Donor-specific antibodies. CDC: complement-dependent cytotoxicity crossmatch. PLEX: Plasma exchanges. IVIg: Intravenous immunoglobulin.*
Amrouche et al. Transplantation 2017, Mohamadou et al. Transplant Int 2023

Non-Active Desensitization (NAD, «Delisting »)

Local criteria protocol (called NAD – Non active desensitization)

- Age between 18 and 70 years old
- TGI ≥ 95%
- Minimum 5-year follow-up of anti-HLA antibodies with annual single antigen testing
- Whatever time on waiting list
- No living donor
- Written consent

Delisting

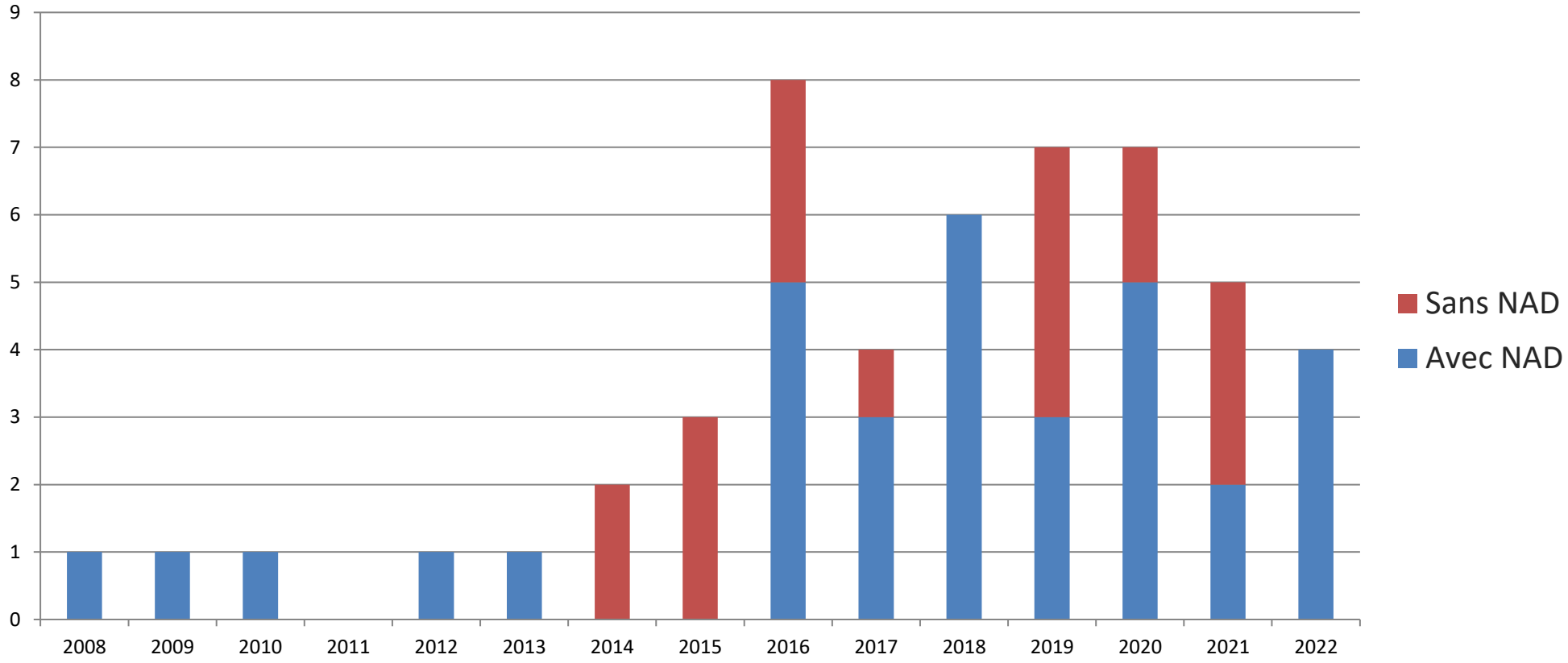
- **Anti HLA antibodies <3000 for 3 years and <10000 MFI for 5 years**
- **Whatever historical peak intensity**
- **Except antibodies directed against former grafts**

Proposal time / Day of transplant

- Verify that sum of DSA <6000 MFI in the last studied serum
- Wait for CDC crossmatch results before transplantation
- CDC crossmatch must be negative with sera of the last 3 years

MFI: Mean fluorescence intensity. CHU Nantes center protocol.

Non-Active Desensitization (NAD, «Delisting »)

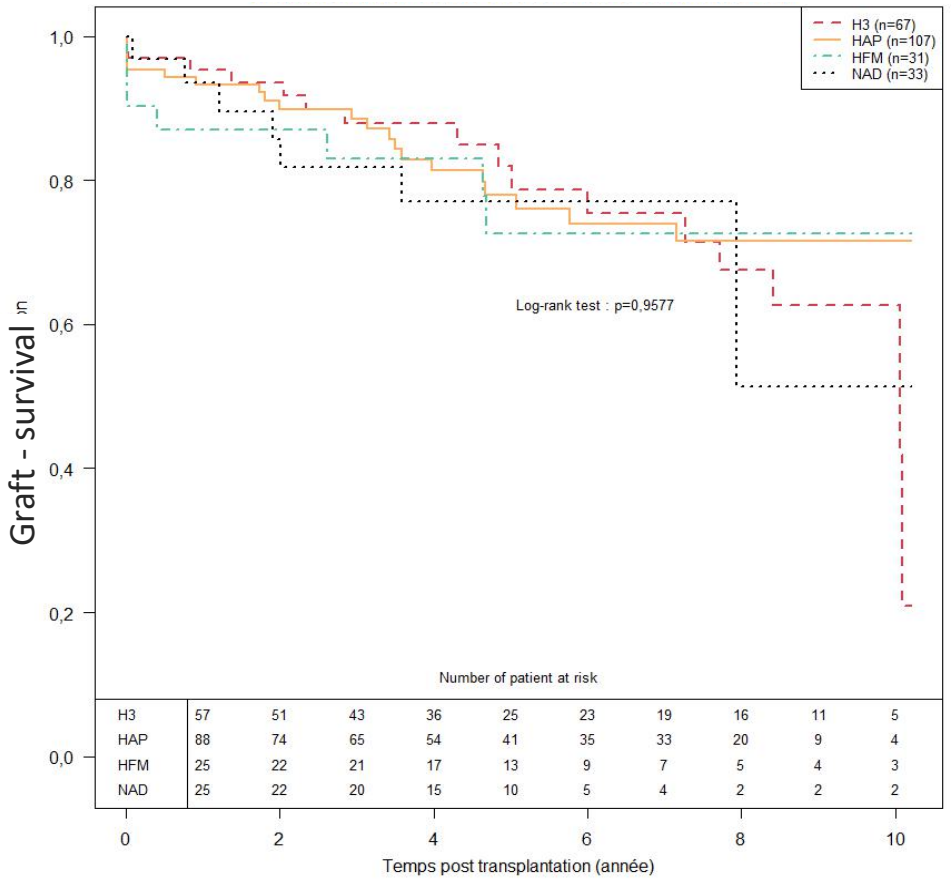


➥ **Since 2008, 53 patients included in the protocol have been transplanted**

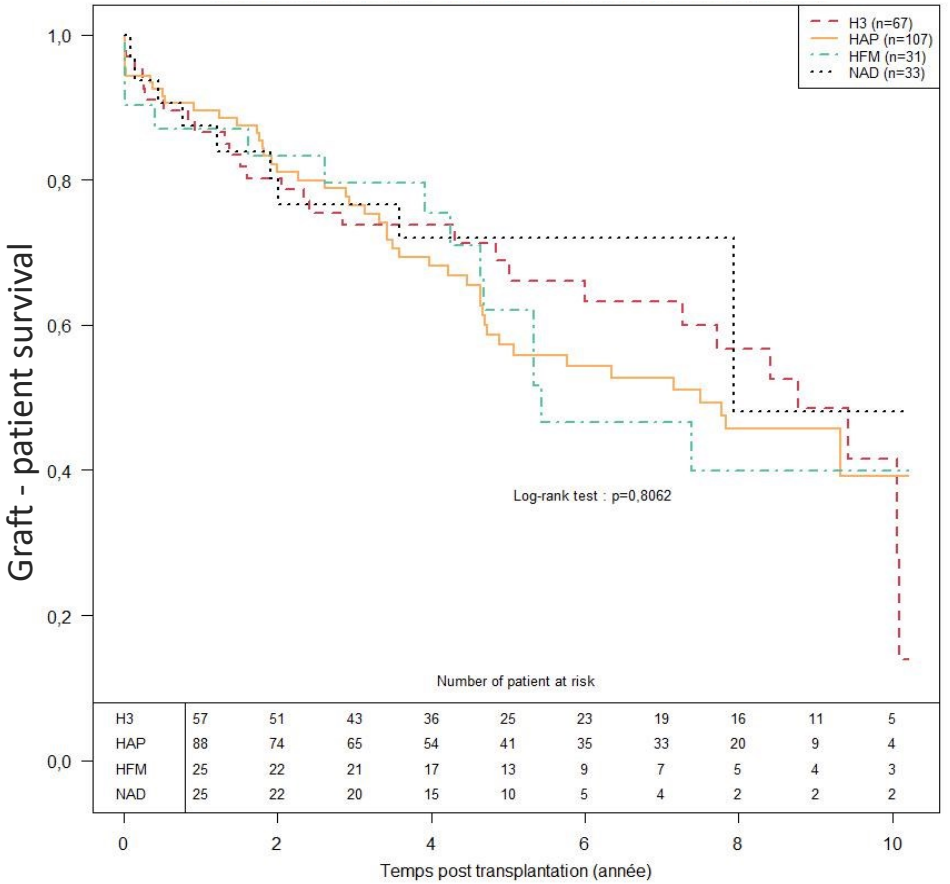
- **For 33 of them, the organ proposal is due to the protocol**

NAD transplantation: allograft and patient survival

Graft – survival depending on allocation protocol (n=238)



Graft- patient – survival depending on allocation protocol (n=238)

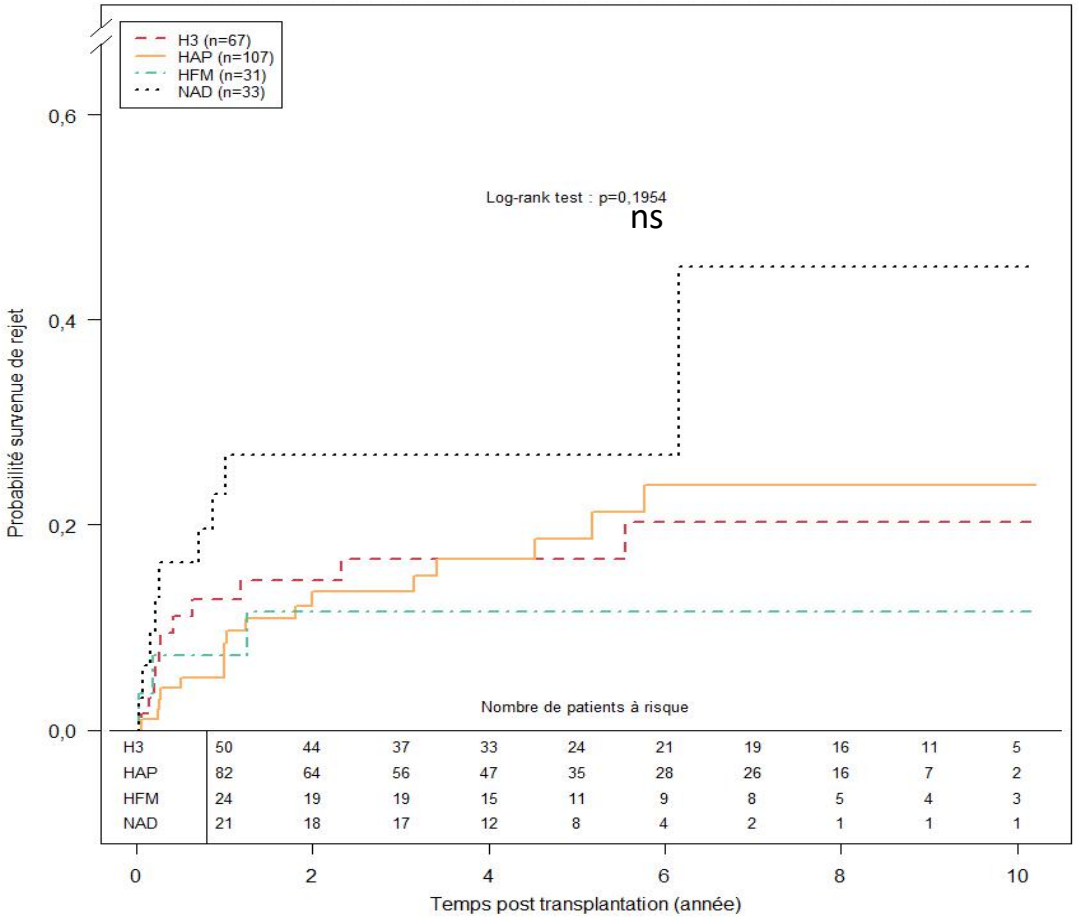


➥ **At the center level, allograft survival for patients transplanted with NAD is acceptable**

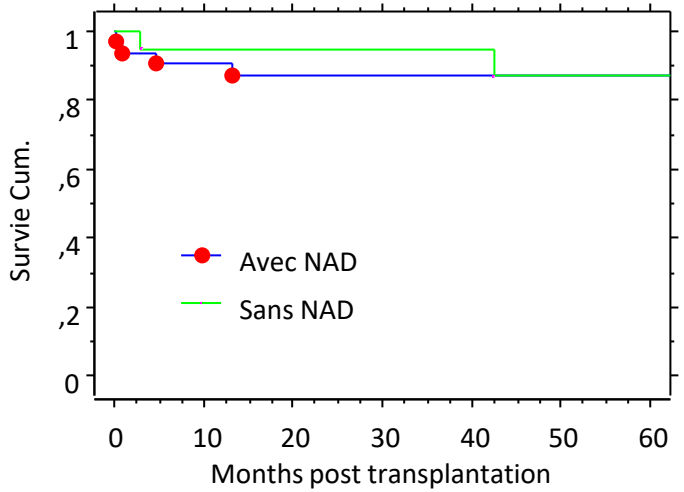
Data on file CHU Nantes 2024

NAD transplantation: risk of rejection and infections

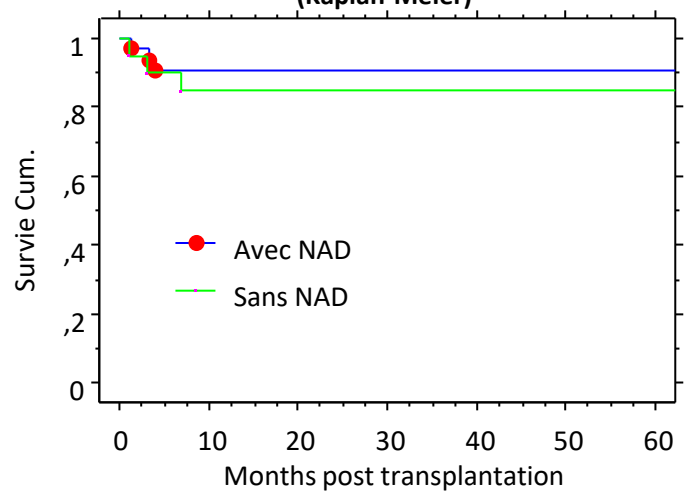
Probability of rejection depending on allocation protocol (n=238)



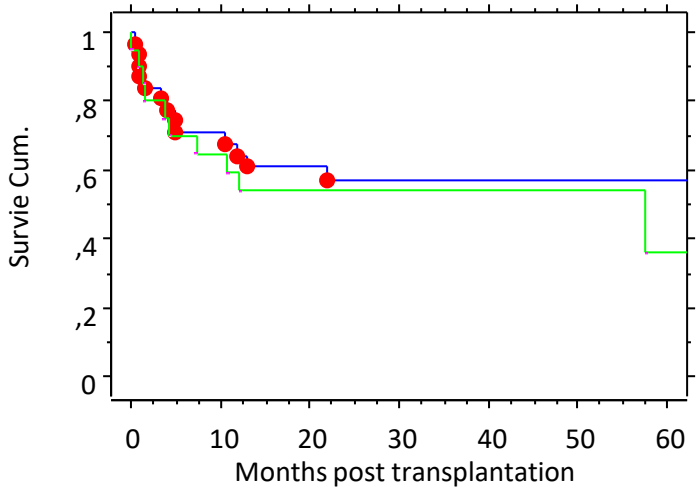
Cytomegalovirus infection (Kaplan-Meier)



BK virus infection (Kaplan-Meier)



Severe bacterial infections (Kaplan Meier)



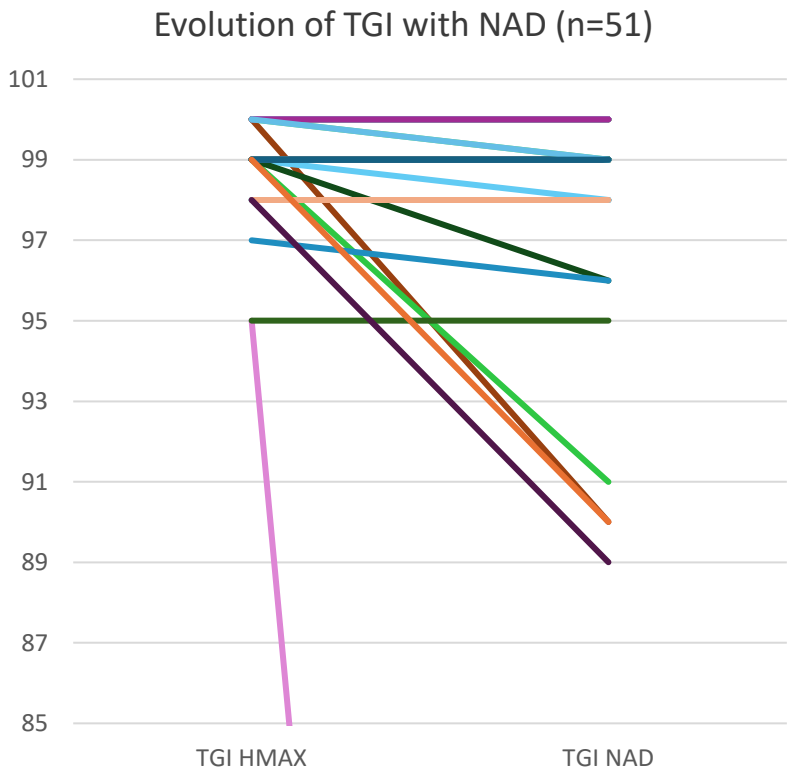
➥ **Possibly a trend towards a higher risk of rejection?**

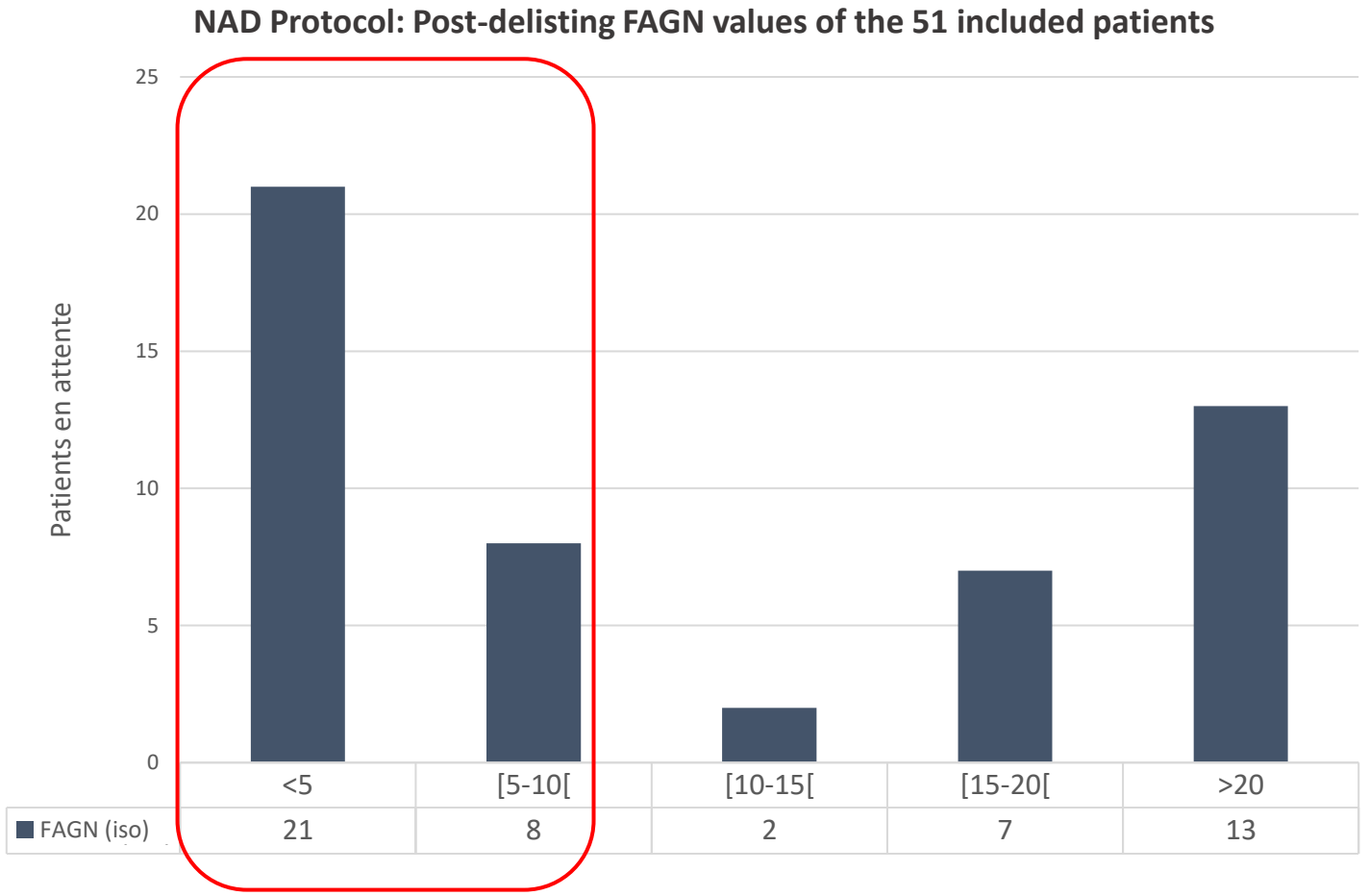
➥ **No increase in infectious morbidity**

Data on file CHU Nantes

How many patients take advantage of NAD?

- Currently :
  51 patients included in NAD
  - with 17 in temporary contraindication
- Waiting for **10,4 years [1,6 – 23,6]**

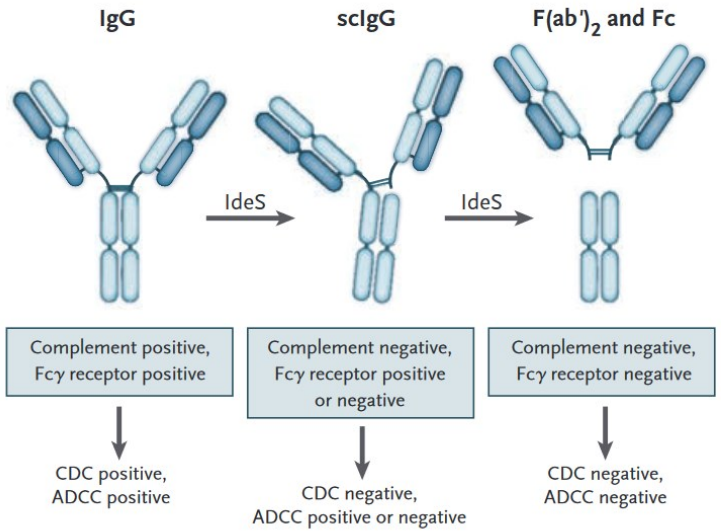




- **More than 50% of patients in NAD did not have a clinically relevant increase in FAGN**

FAGN: facilité d'accès à la greffe à l'échelon national. Data on file CHU Nantes

Imlifidase for desensitization in kidney transplantation



➥ By rapid cleaving DSA, imlifidase allows transplantation across **positive CDC**

18-75 yo, highly sensitized cPRA >95%

2 DSA > 3000 MFI
ATGAM

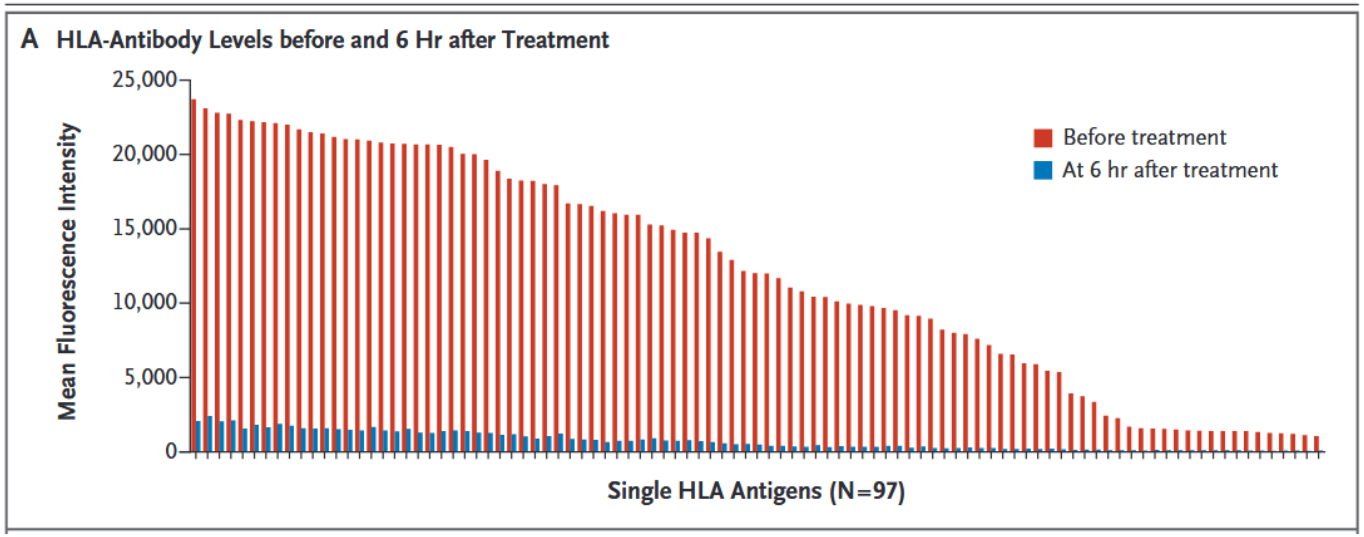
DSA + positive XM
Alemtuzumab, RTX, IVIg

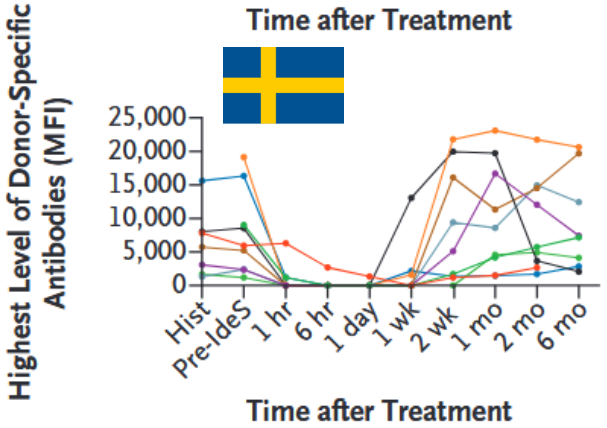
Table 1. Characteristics of the Patients and Donors.*

Characteristic	Total (N=25)	Sweden (N=11)	United States (N=14)	P Value
Recipient				
Age — yr	46.2±14	52.4±12.3	41.4±13.9	0.05
Male sex — no. (%)	11 (44)	4 (36)	7 (50)	0.69
At least 1 previous kidney transplant received — no. (%)	14 (56)	5 (45)	9 (64)	0.27
Donor				
Deceased — no. (%)	23 (92)	9 (82)	14 (100)	0.18
Cold ischemia time — hr	15.8±7.5	10.6±6.8	19.9±5.2	<0.001
Delayed graft function — no./total no. (%)	10/24 (42)	0/11	10/13 (77)	<0.001
Immunologic variables				
Anti-HLA donor-specific antibody positive — no. (%)	22 (88)	9 (82)	13 (93)	0.18
No. of anti-HLA donor-specific antibodies	2.3±1.8	2.2±1.6	2.4±1.9	0.79
Mean fluorescence intensity				
Class I	5660±2364	4192±2372	6375±1996	0.04
Class II	8199±5639	10,464±7051	6500±3571	0.06
Negative anti-HLA donor-specific antibodies at 1 to 6 hr after treatment — no. (%)	25 (100)	11 (100)	14 (100)	>0.99
Positive cross-match at transplantation — no. (%)†	20 (80)	7 (64)	13 (93)	0.13
Estimated GFR at 1 to 6 mo after transplantation — ml/min/1.73 m^2	58±30	49±13	70±36	0.14
Follow-up — mo	4.7±1.9	5.7±0.9	4.0±2.4	0.03
Graft loss — no. (%)	1 (4)	0	1 (7)	>0.99

Jordan et al, NEJM 2017

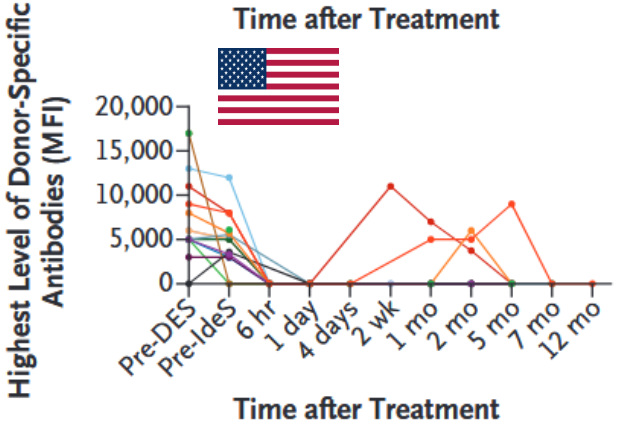
Imlifidase for desensitization in kidney transplantation





No allograft lost

3 ABMR concurrent of DSA rebound

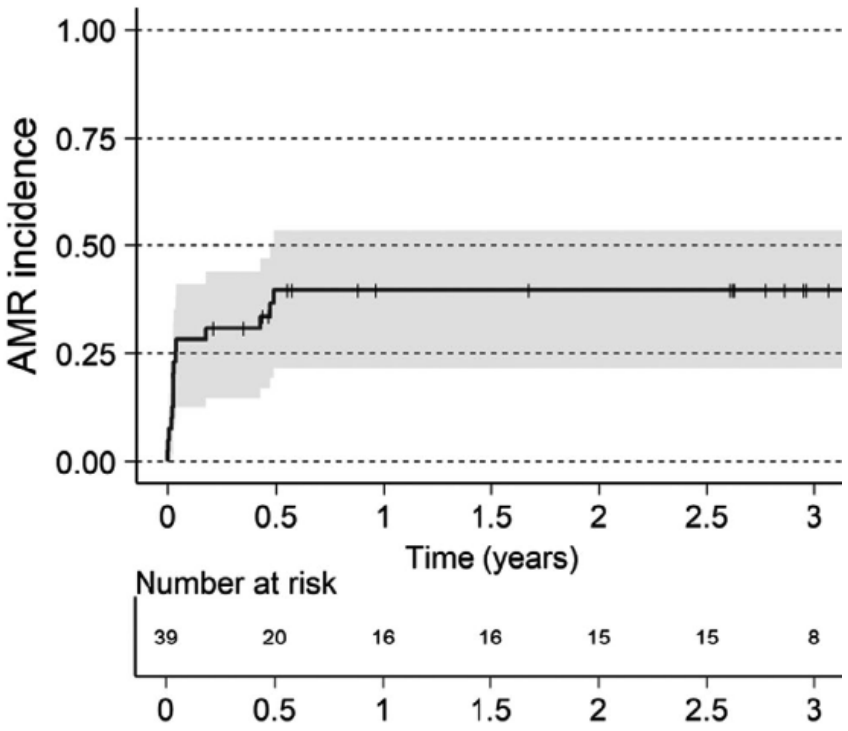


1 immediate allograft lost due to non-HLA antibodies

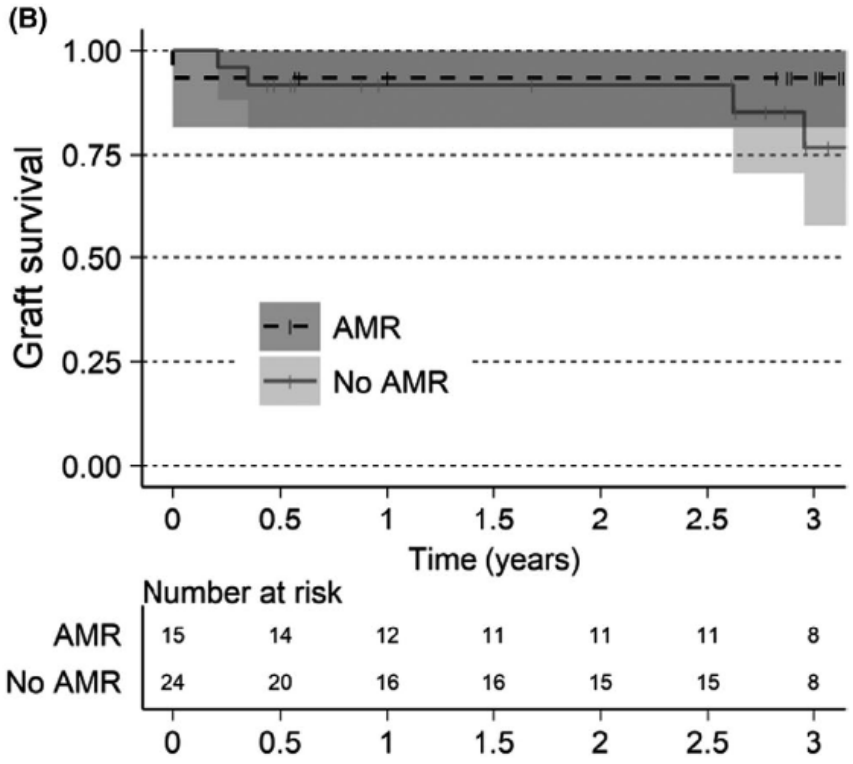
2 ABMR concurrent of DSA rebound

Jordan et al, NEJM 2017

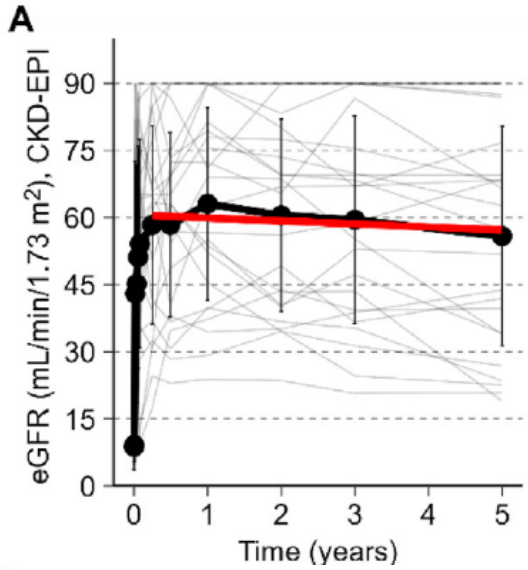
Mid/Long-term results of Imlifidase

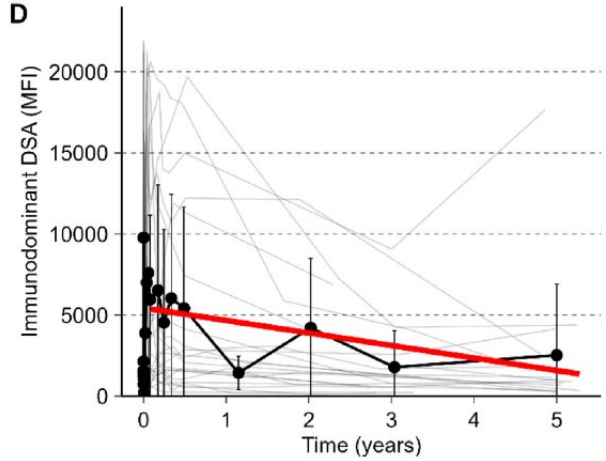


➥ The rate of AMR at 3 years was 38%



➥ Which did not seem to impact mid-term allograft survival/function (82% at 5-years)





AMR: Antibody-Mediated Rejection. Adapted from Jordan et al, NEJM 2017 and Kjellman et al, AJT 2021, Jordan et al, AJT 2025

French guidelines for use of imlifidase in desensitization

Requirements for selecting a patient

Patients eligible for this treatment

- cPRA ≥ 98% (on the last serum)
- Age ≤ 65 years
- Time on the waiting list ≥ 3 years
- Number of previous kidney transplantation from: 0 to 2 (multidisciplinary consensus required beyond 2 grafts)
- Kidney graft biopsy with a low risk of complication
- Patient information

Transplant unit profile

Access to plasmapheresis 7 days a week

Delisting of HLA antibodies

Allow only HLA antibodies with MFI not exceeding 5000 after 1:10 dilution

Organ offer

Donor profile: Avoid

elderly donors
donation after cardiac death
long ischemia time
acute kidney injury

DSA

MFI of immunodominant DSA A, B, DRB1, DQB1 > 6000 except for Cw and DP

Pre-imlifidase virtual positive crossmatch on recent serum

(No cell crossmatch)

Imlifidase 0.25 mg/kg

4 to 6 hours after imlifidase infusion

Cell crossmatches

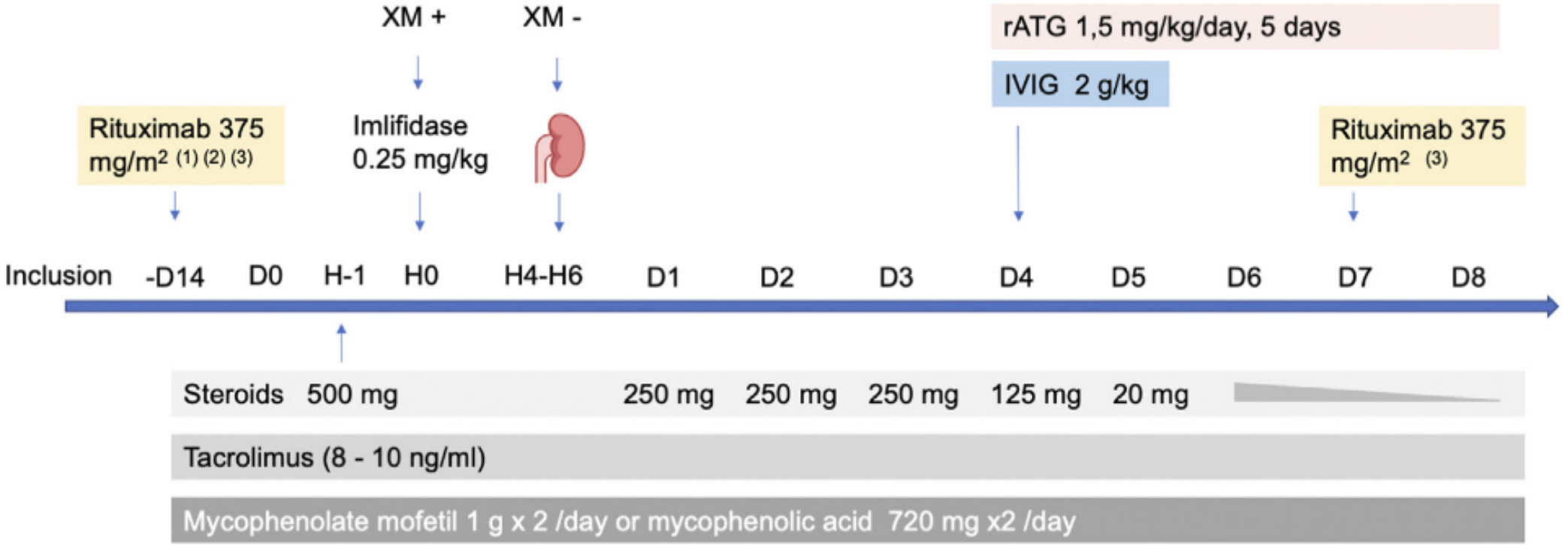
- Prospective post-imlifidase negative complement-dependent cytotoxicity crossmatch
- Prospective (or retrospective) flow cytometry crossmatch on recent, and day 0 pre- and post-imlifidase sera

Transplantation

Timeline

cPRA, calculated panel reactive antibody. Couzi et al, Transplant Int 2023

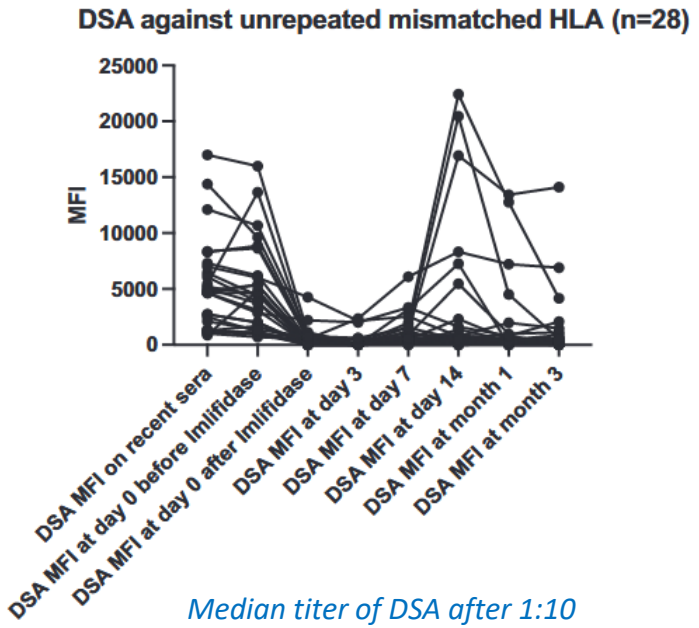
Immunosuppressive protocol

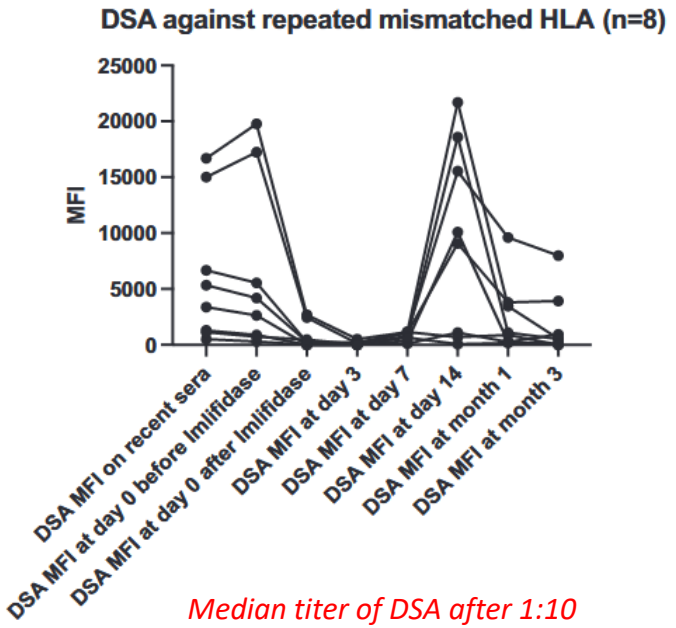


(1) A pre-transplant injection of Rituximab can be proposed at least two weeks before transplantation (-D14)
(2) A pre-transplant injection requires a crossmatch with an anti-rituximab antibody
(3) This is an off-label use of Rituximab

cPRA, calculated panel reactive antibody. Couzi et al, Transplant Int 2023

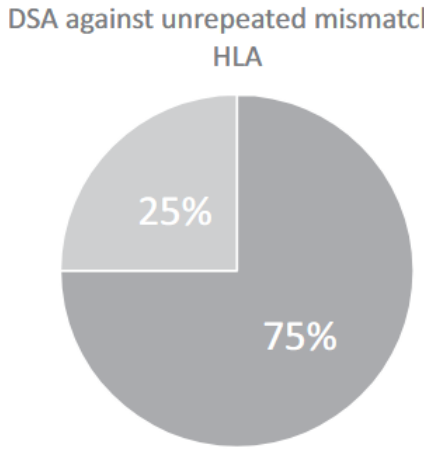
The first French patients (n = 9)

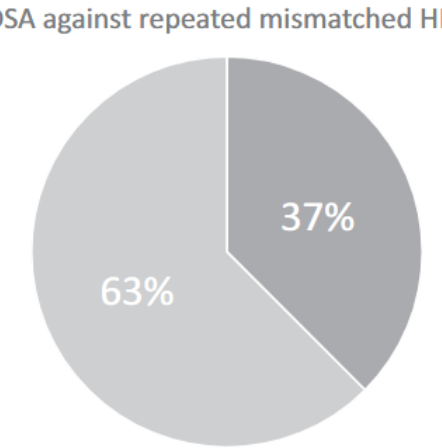




Median titer of DSA after 1:10 dilution (MFI) : ***897***

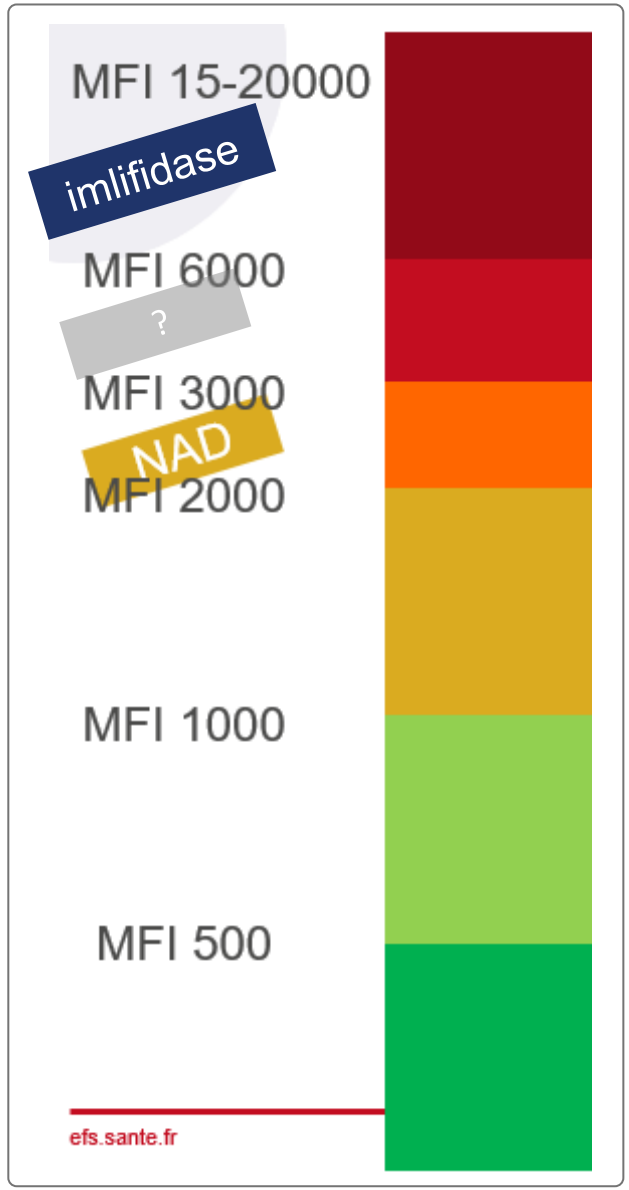
Median titer of DSA after 1:10 dilution (MFI) : ***4858***





Kamar et al, KI Reports 2024

What about patients without possible delisting?



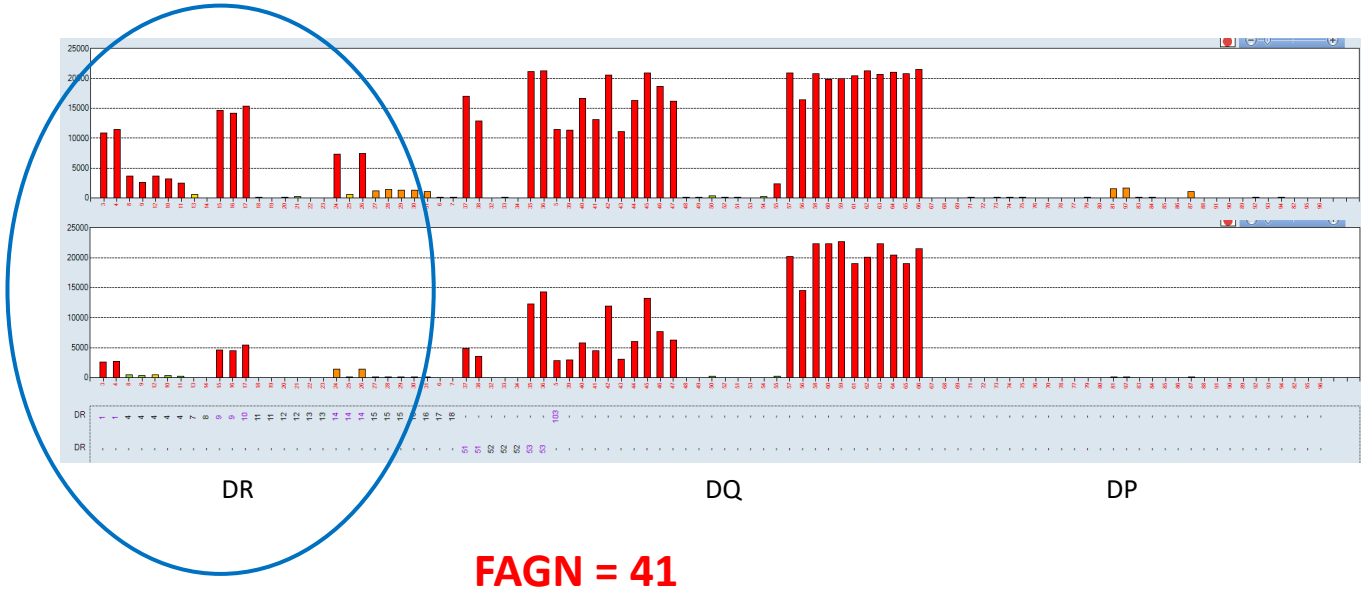
Example : 43yo F, waiting for 3rd Kidney since 2003, highly sensitized

FAGN = 0 (TGI : 100%)

- **NAD:** RETRAIT CRISTAL Ac antiHLA selon NAD : A25 A29 A43 A68 B13 B27 B37 B38 B39 B41 B47 B48 849 B850 B53 857 B58 B59 B61 B64 B65 B72 B77 DR8 DB11 DB12 (LAN

FAGN = 6

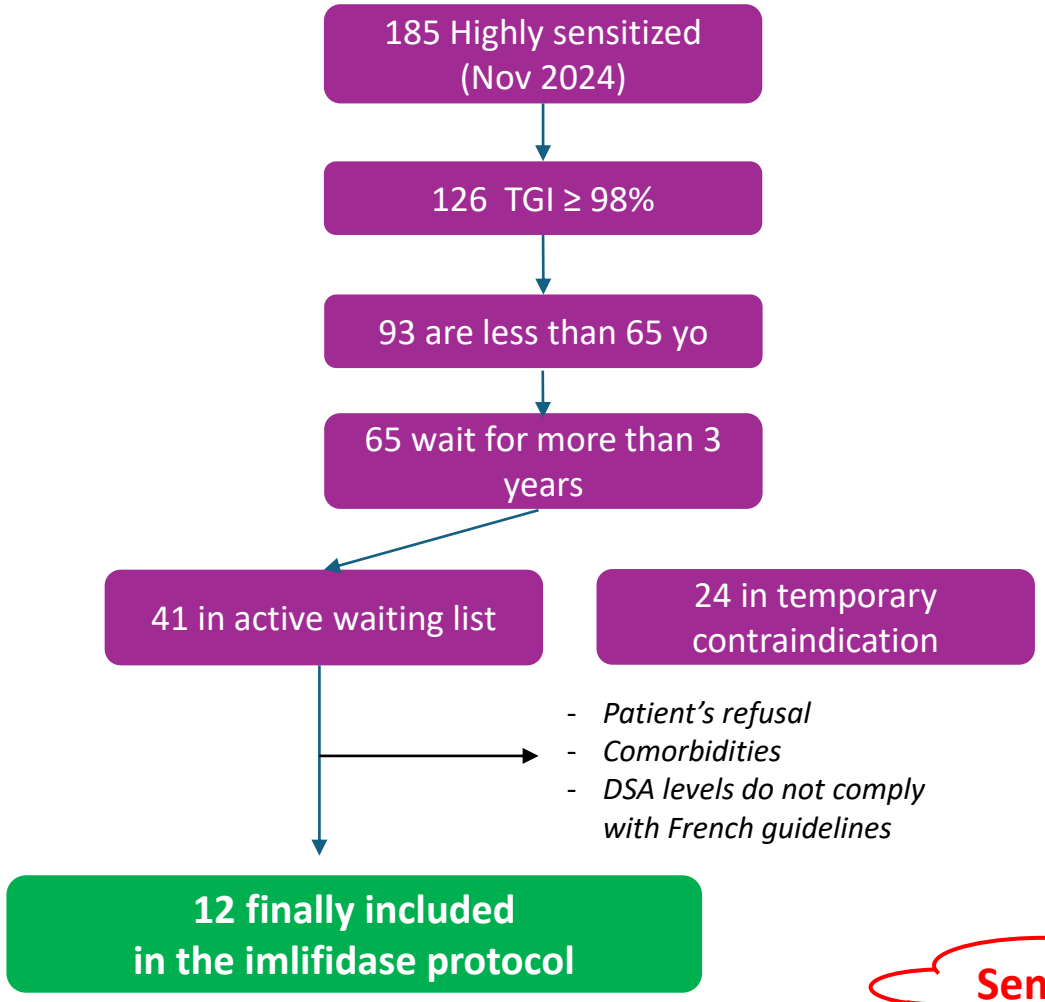
- **Sera dilution (imlifidase protocol)**



FAGN = 41

Data on file CHU & EFS Nantes

How many patients are eligible for imlifidase in our center according to French guidelines?



TGI pre-imlifidase	TGI post-dilution
100%	93%
100%	71%
99%	96%
99%	83%
99%	89%
99%	88%
99%	87%
99%	95%
99%	96%
100%	99%
99%	98%
99%	98%

Semi-annual update

Data on file CHU Nantes

5 patients transplanted in Nantes

High DSA MFI

(Very) Long Cold Ischemia Time and sometimes ECD allografts

Veinous anastomosis on inferior cava vein → biopsy…

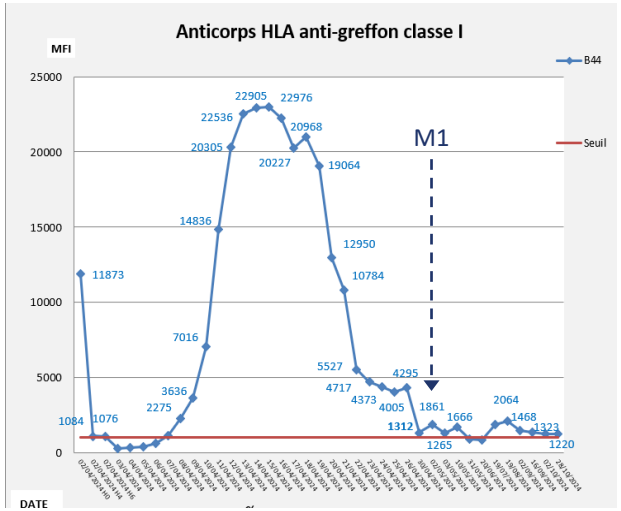
One patient with prophylactic eculizumab for aHUS

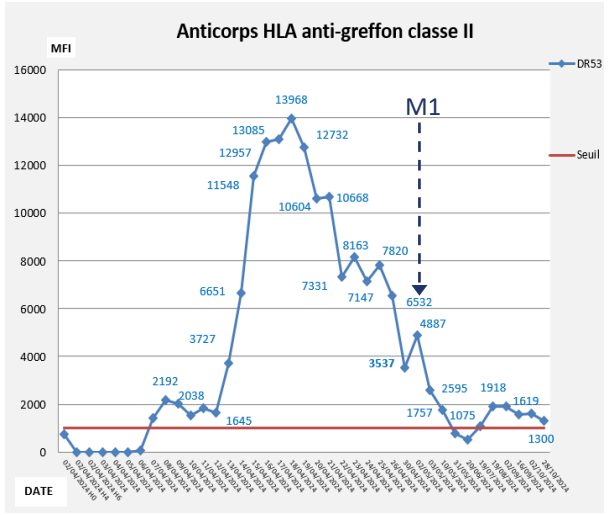
Many post-operative and infectious complications (2 ICU hospitalizations)

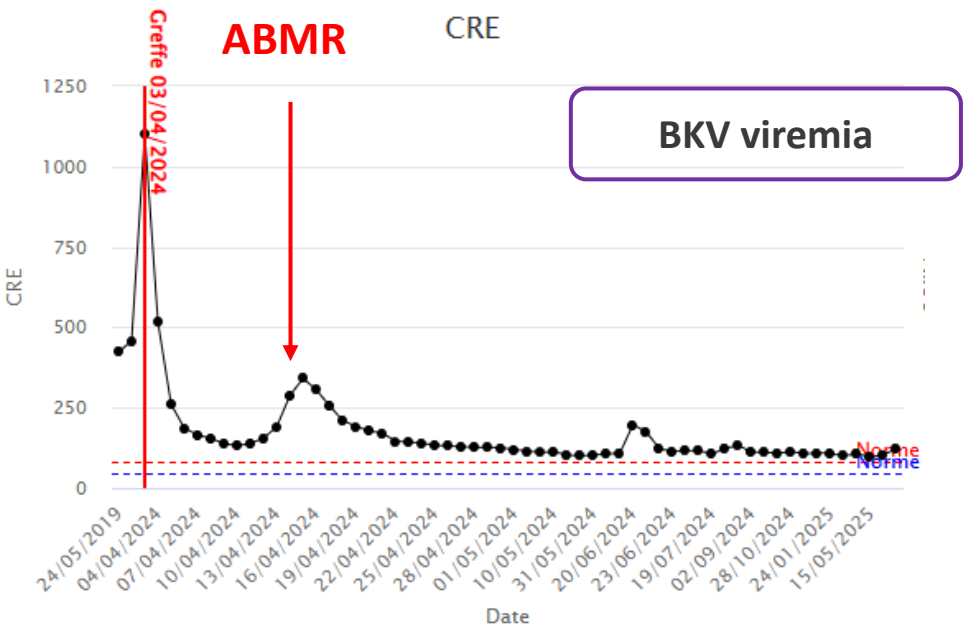
	P1	P2	P3	P4	P5
Recipient gender	M	F	F	F	F
Recipient age	47	40	53	43	57
Recipient BMI	30	23.8	17.3	20.5	27.5
Transplant rank	2	1	3	2	2
TGI pre-Imlifidase	100	100	99	99	99
TGI post-dilution	93	71	96	83	87
Class I DSA last serum	B44	B8, B39	A32, Cw2	Cw12	A32, B53, Cw7
Max MFI of immunodominant DSA	13744	8674	1417	6131	8500
Cumulated MFI	13744	14206	1971	6131	22765
Class II DSA last serum	DR53, DQ6	DR16, DQ5	DR103, DR16, DR51	DR10, DR52	DR14, DQ5
Max MFI of immunodominant DSA	1018	4201	10270	8924	3445
Cumulated MFI	2018	4863	19673	12752	6714
Class I DSA Day 0	B44	B8, B39	Cw5	Cw2	A32, B53, Cw7
Max MFI of immunodominant DSA	11873	6097	1105	7373	8500
Cumulated MFI	11873	10084	1105	7373	22765
Class II DSA Day 0	DR53	DQ5	DR103, DR51,DR16	DR10,DR52	DR14, DQ5
Max MFI of immunodominant DSA	760	5068	12191	10774	3445
Cumulated MFI	760	5068	20104	15604	6714
LCT Crossmatch	Neg	Neg	Pos	Neg	Pos
CMF Crossmatch	Pos	Pos	Pos	Pos	Pos
Repeat Mismatch	No	NA	Yes	Neg	Neg
Cold Ischemia Time (hours)	14h25	17h32	26h	21h33	17h
Donor Age (years)	51	51	62	47	73
Donor creatininemia (µmol/l)	103	74	71	70	107
Vascular anastomosis	Iliac	Iliac	Cava	Iliac	Iliac
Imlifidase Protocol	Yes	Yes	Yes	Yes	Yes
Systematic associated drugs					
D0 Rituximab	No	No	No	No	No
Eculizumab	No	No	Yes (aHUS)	No	No
Other	No	No	No	No	No
Post-operative complications	Venous thrombosis (catheter)	None	Hematoma Venous thrombosis	Urinoma, Hematoma x2 (Hemorrhagic shock),	Pulmonary edema due to graft stenosis, Urinoma
Infectious complications	Digestive bacteriemia, BKV	None	UTI x2 (Septic shock), CMV	UTI x 3	BKV, CMV
Duration of hospitalization (days)	32	28	40	35	19
Rehospitalization during the first 3 months	Yes	No	Yes	Yes	Yes

aHUS: atypical hemolytic uremic syndrome. Data on file CHU Nantes.

Patient 1







Eculizumab for ABMR (weekly then maintenance until Month 3)
10 PLEX from DSA rebound continued until Month 3

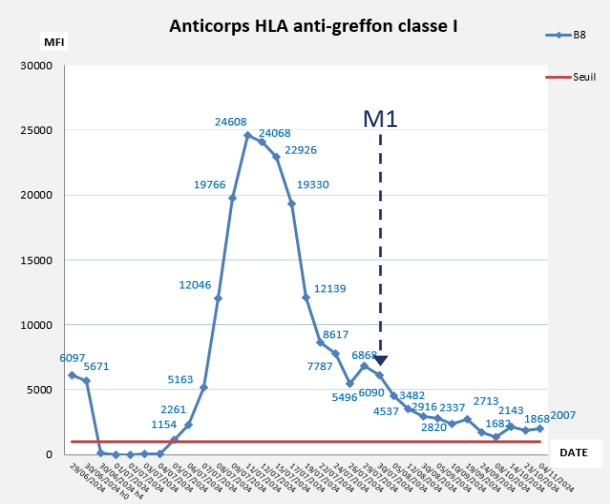
M18 post-transplant

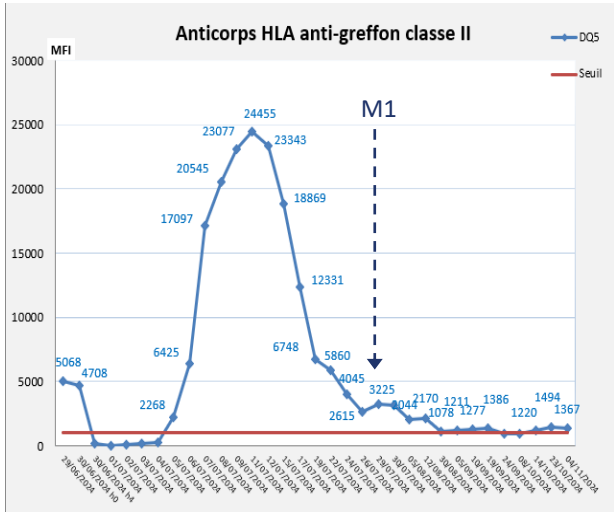
- SCr = 123µmol/l (eGFR = 60ml/min) Pu = 0.04g/g
- DSA neg

P1	Time	g	i	t	v	cpt	cg	ci	ct	cv	C4d	Conclusion
	Day 6 (Rebound)	0	0	0	0	0	0	0	0	0	+	Possible ABMR
	Day 13 (Allograft dysfunction)	1	1	0	1	0	0	0	0	0	+++	ABMR
	Day 30 (control post ABMR)	0	0	1	0	1	0	0	0	1	+++	ABMR
	Day 90 (protocolar)	1	1	2	0	0	0	0	0	0	+	ABMR+BL
	M12 (protocolar)	1	0	0	0	0	0	0	0	2	neg	pAMR

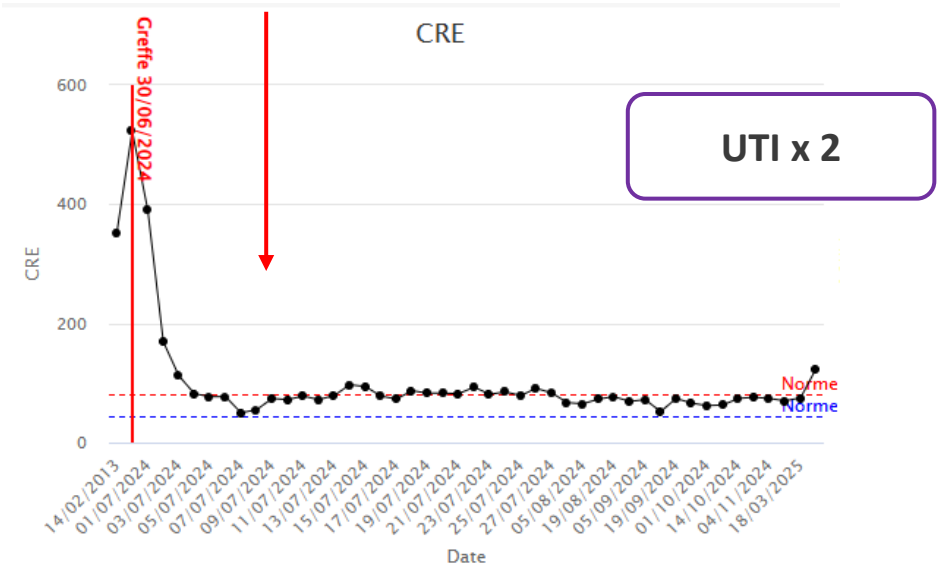
Data on file CHU Nantes

Patient 2





ABMR



Eculizumab for ABMR (weekly then maintenance until Month 3)
10 PLEX from DSA rebound continued until Month 3

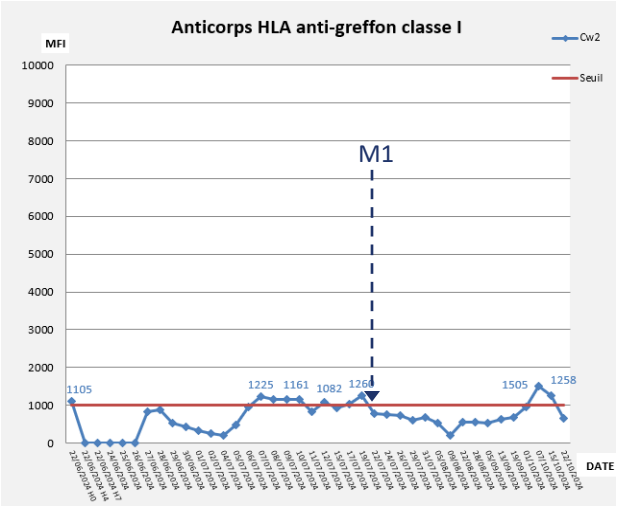
M18 post-transplant

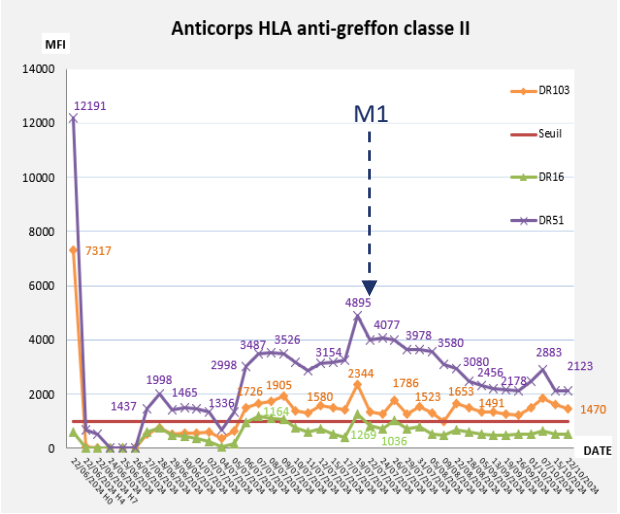
- SCr = 84 µmol/l (eGFR = 77ml/min) Pu = 0.15g/g
- DSA Pos (MFI 1200)

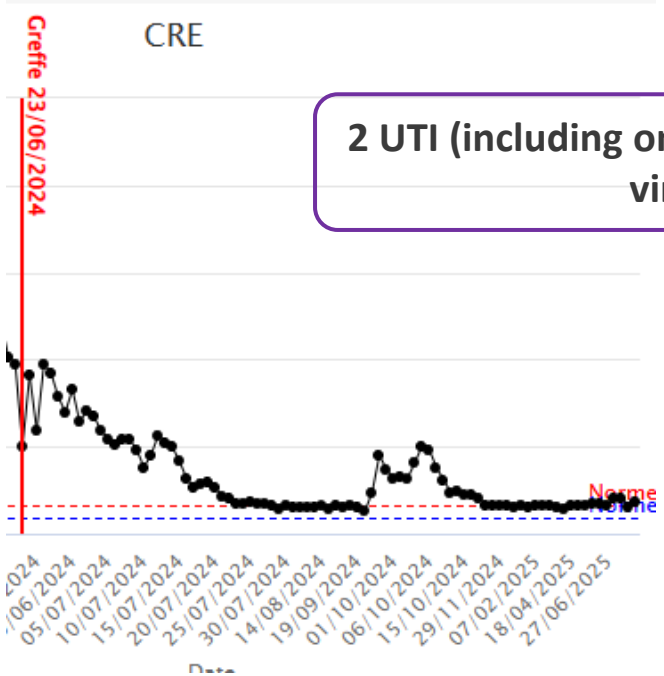
P2	Time	g	i	t	v	cpt	cg	ci	ct	cv	C4d	Conclusion
	Day 9 (Rebound)	1	0	0	0	0	0	0	1	0	+++	ABMR
	Day 90 (Protocolar)	0	0	0	0	0	0	0	1	1	0	Normal
	M12 (Protocolar)	0	0	0	0	0	0	0	1	1	0	Normal

Data on file CHU Nantes

Patient 3







2 UTI (including one septic shock), CMV viremia

Eculizumab de novo (prophylaxis for aHUS recurrence)
10 PLEX from DSA "rising" continued until Month 3

M12 post-transplant

- SCr = 94 µmol/l (eGFR = 60ml/min) Pu < 0.05g/g
- DSA Neg

P3	Time	dd-cfDNA	Conclusion
	Month 4	1.29%	Possible subclinical ABMR (but cofounding factor = UTI) ?
	Month 5	0.4%	No ABMR

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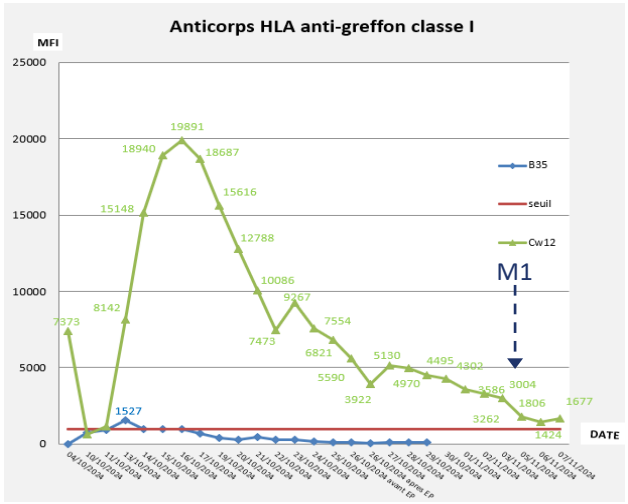
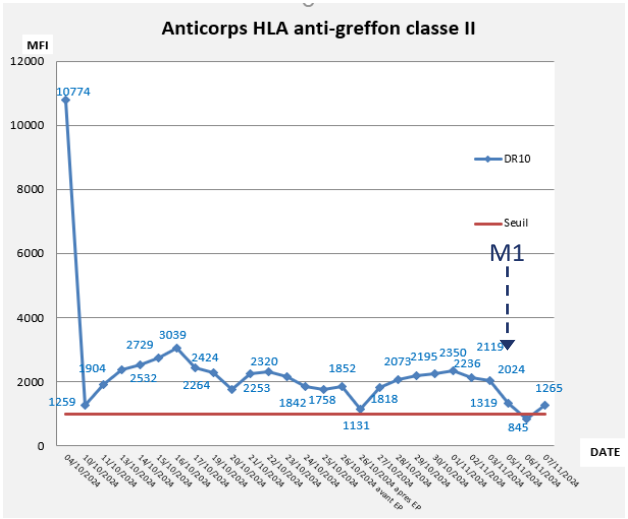
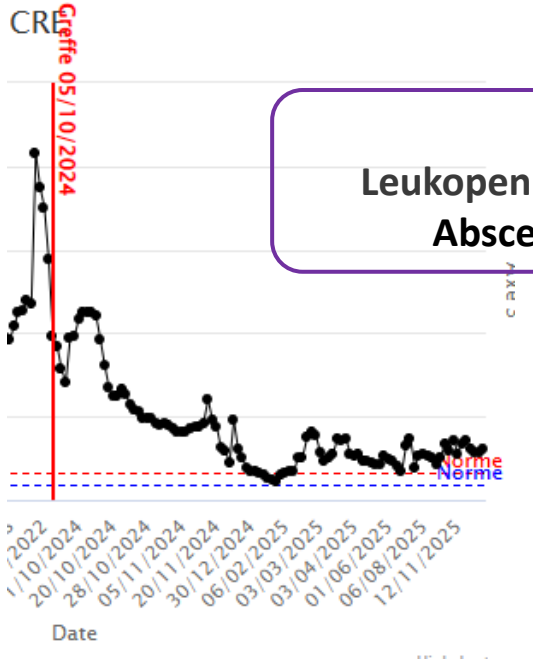
Patient 4







UTI x7
Leukopenia : decrease MMF
Absceding erysipela

Eculizumab for ABMR (weekly then maintenance until Month 3)
10 PLEX from DSA rebound continued until Month
Tocilizumab from Month 3

M15 post-transplant

- SCr = 152 µmol/l (eGFR = 35ml/min) Pu = 0.26g/g
- DSA MFI 2000

P4	Time	g	i	t	v	cpt	cg	ci	ct	cv	C4d	Conclusion
	Day 30 (Rebound)	1	0	0	0	3	0	0	0	0	0	ABMR
	Day 90 (Protocolar)	3	0	0	0	3	0	0	0	0	0	ABMR
	M5 (Control post AMR)	3	1	0	0	2	1	1	0	0	0	ABMR
	M12 (Protocolar)	0	0	0	0	1	0	2	2	X	0	pABMR

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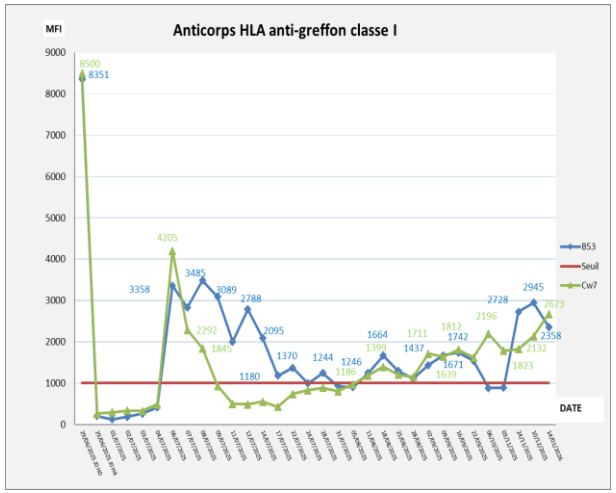
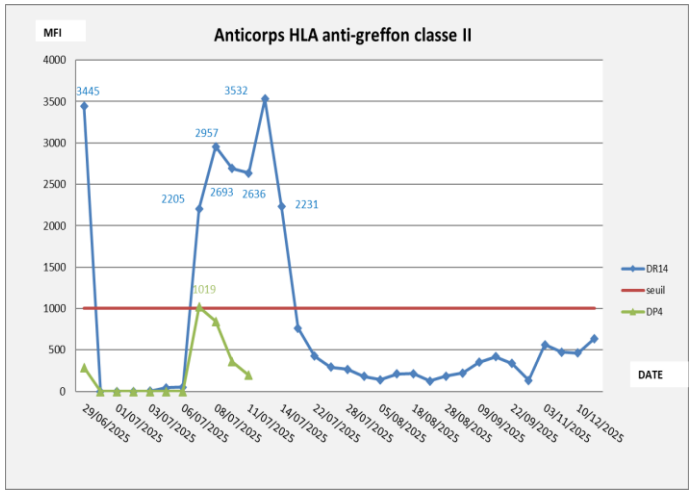
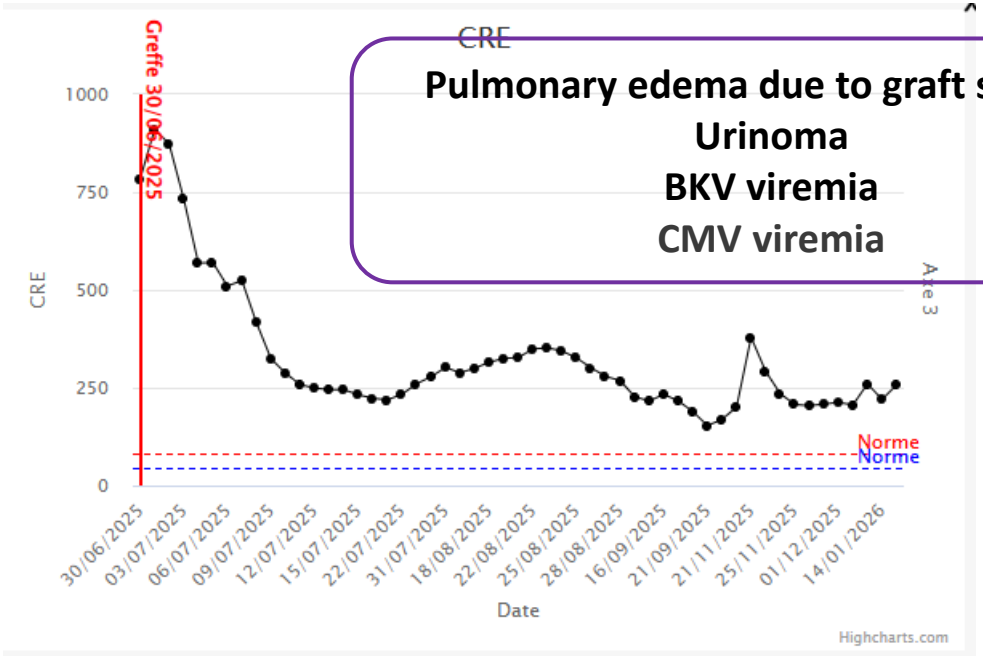
Patient 5







Pulmonary edema due to graft stenosis
Urinoma
BKV viremia
CMV viremia

10 PLEX from DSA "rising" continued until Month 3
Histological AMR not treated because concurrent UTI

M6 post-transplant

- SCr = 257 µmol/l (eGFR = 17ml/min) Pu = 0.18g/g
- DSA MFI 2000

P5	Time	g	i	t	v	cpt	cg	ci	ct	cv	C4d	Conclusion
	Day 7 (Rebound)	0	0	0	0	0	0	0	1	1	0	No Rejection
	M2 (Proteinuria)	1	0	0	0	3	0	2	2	1	0	AMR
	M3 (Control)	0	0	0	0	0	0	1	1	2	0	No Rejection

Data on file CHU Nantes

French cohort – update Dec 2024

N = 30 patients

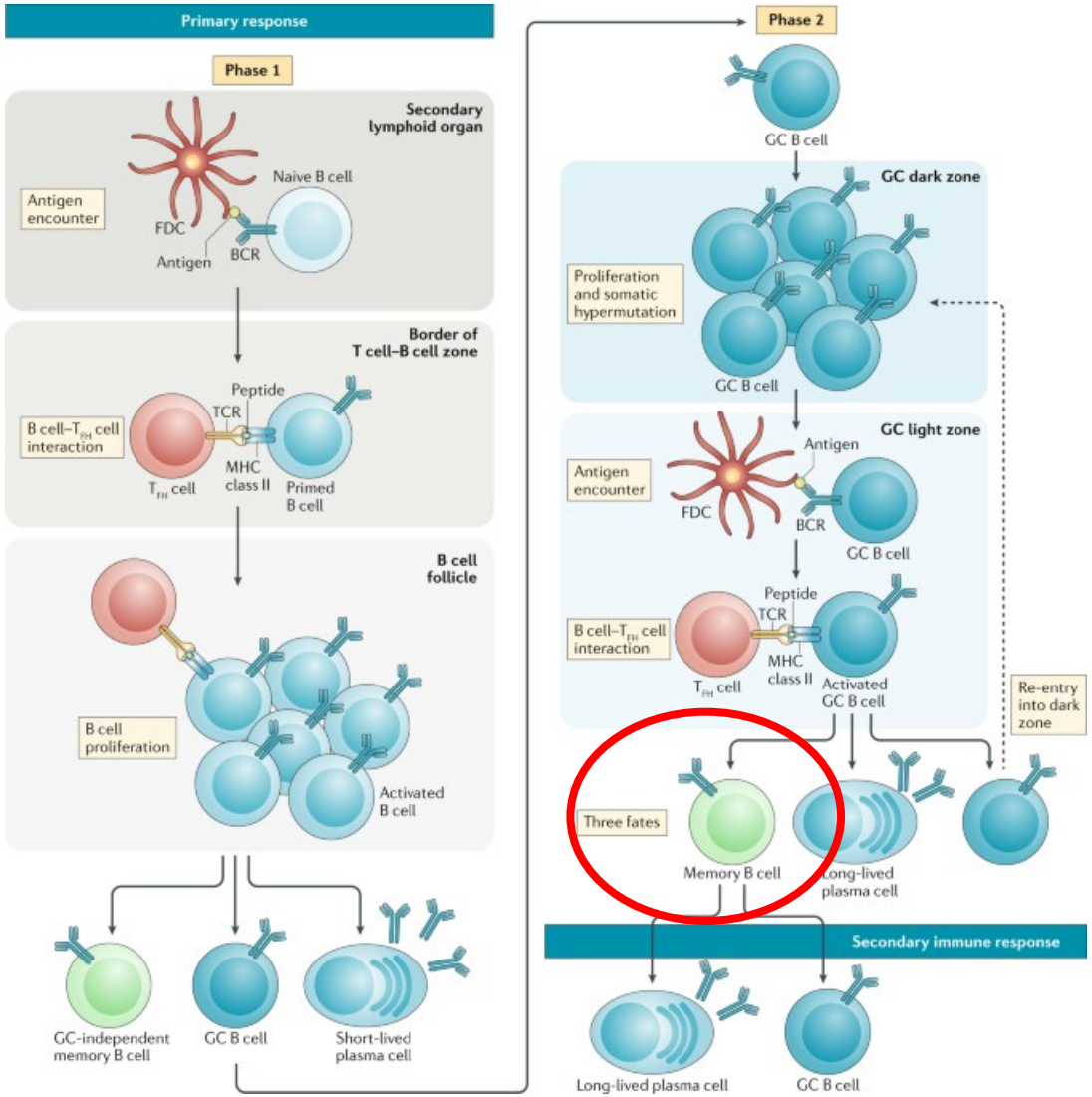
Presentation of Lionel Couzi, SFT 2024

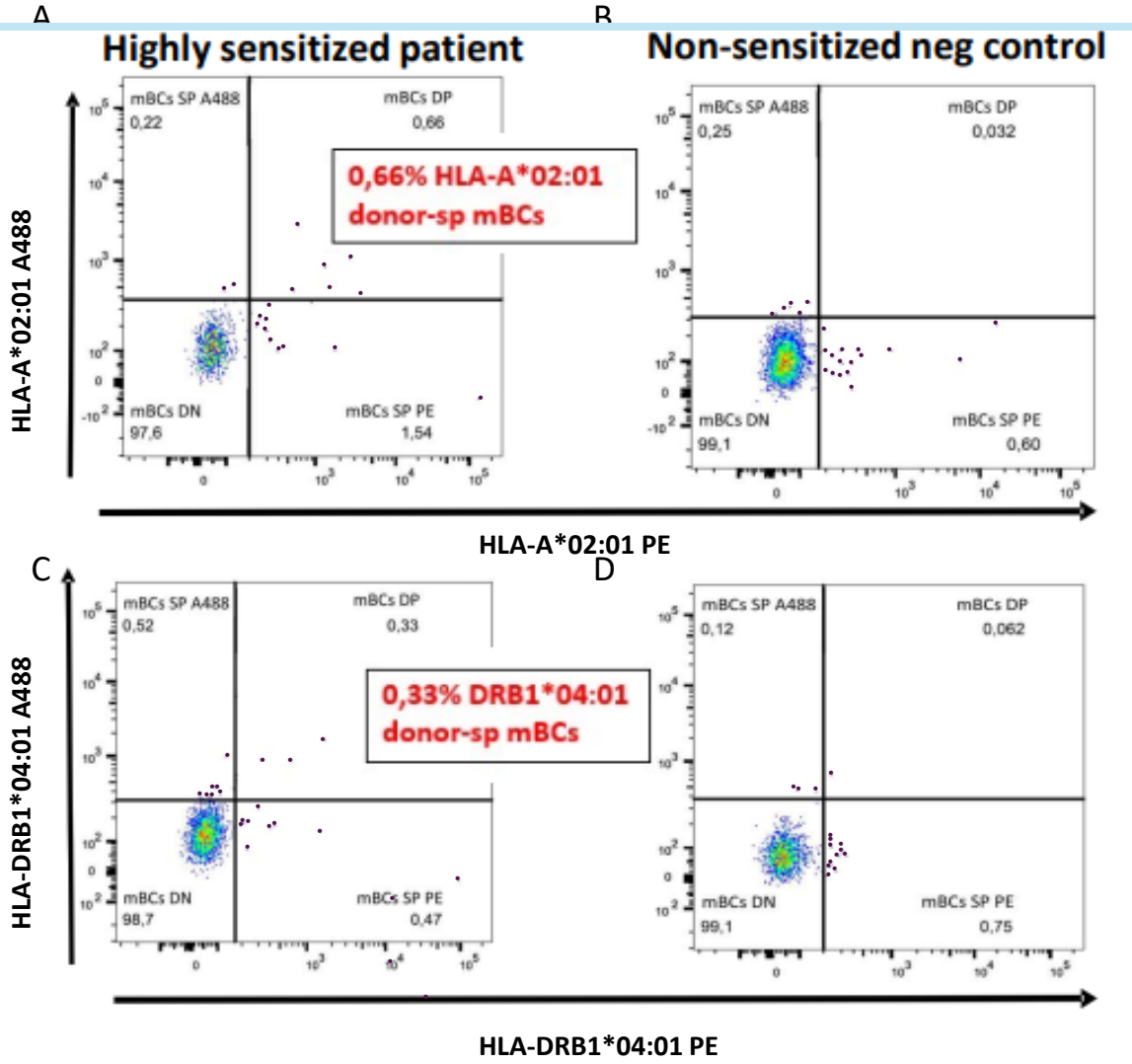
French cohort – update Dec 2024

N = 30 patients

Presentation of Lionel Couzi, SFT 2024

Memory B cells

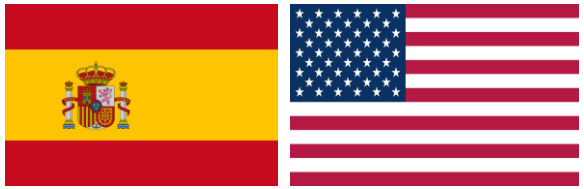




Akkaya et al, Nature Rev Immunol, 2020

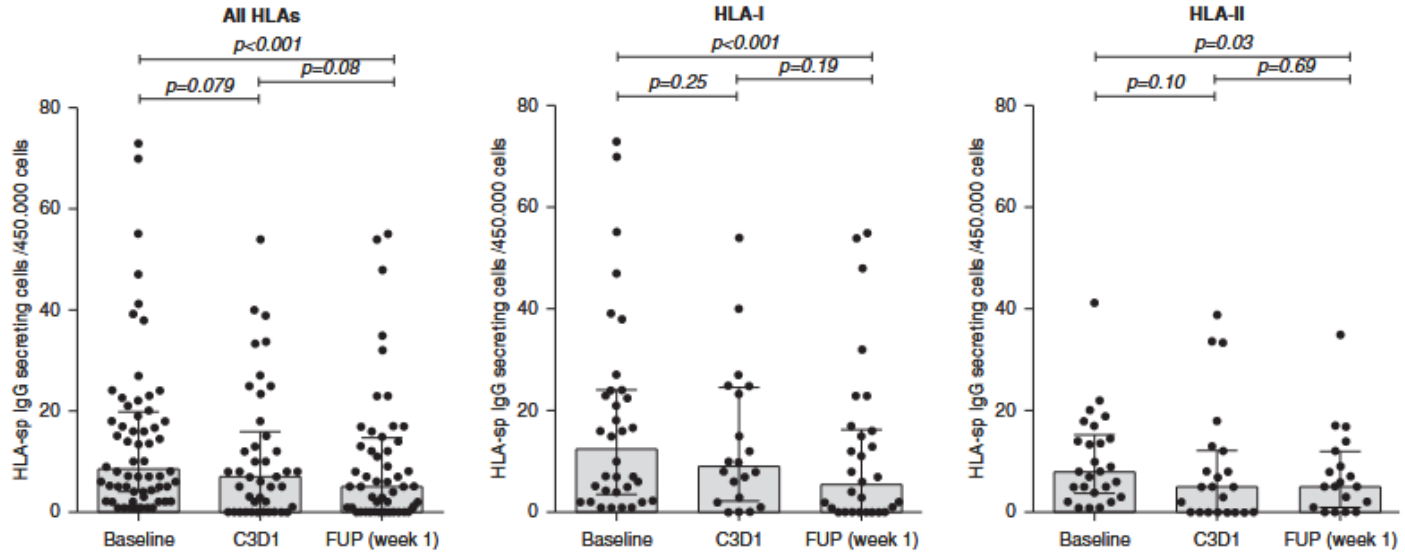
Kervella et al, Current Opin Transplant, 2024

Isatuximab (anti CD38) for desensitization



N = 23 highly sensitized patients

Phase I/II : Safety of Isatuximab (anti CD38) + effect on pre-transplant desensitization



Only 39% of patients had reached target cPRA

(i.e., decrease in the cPRA level that would result in at least doubling the theoretical likelihood of finding a compatible donor)

82% of patients had a decrease of at least one DSA < 3000

After 8 weeks of treatment, we observed a significant decreased in specific secreting memory B cells which correlates with decrease in antibody production

Vincenti et al, JASN 2024

Memory B cells and DSA rebund after Imlifidase

N = 22 highly sensitized patients that received Imlifidase

→ Early DSA rebound was correlated with subsequent AMR

→ Increased plasmacells and switched-mBcs in patients with rapid DSA rebound and ABMR

	ABMR (n=12)	No ABMR (n=10)	p-value
BASELINE CARACTERISTICS			
Sex (male); n (%)	5 (42 %)	6 (60 %)	0.392
Age (mean + SD)	50 ± 11.1	50.43 ± 11.04	0.592
Time on dialysis (years)	12.3 ± 7.6	11.15 ± 6.8	**0.003**
Time on the waiting list (years)	7.58 ± 3.78	7.3 ± 3.17	0.888
Number of prior KT			0.266
0	1 (8.3 %)	1 (10 %)	
1	4 (33.3 %)	7 (70 %)	
2	5 (41.2 %)	2 (20 %)	
3	2 (16.6 %)	0 (0 %)	
Past pregnancy	4 (33.3 %)	3 (30 %)	0.457
Past Blood transfusion	10 (83.3%)	8 (80%)	0.279
Last cPRA (Mean + SD)	99 ± 2.03	99.37 ± 1.4	0.906
CDC cross-match (Positive)	1 (8.3%)	0 (0%)	0.350
FC cross-match (Positive)	12 (100 %)	10 (100 %)	0.906
Number of DSA (mean + SD)	4.19 ± 1.91	4.28 ± 1.95	0.130
Class I	2.29 ± 0.96	2.29 ± 0.96	0.709
Class II	1.91 ± 1.7	2 ± 1.7	0.122
Sum of DSA MF; median (IQR)	10425 (6949-25047)	15343 (7061-19400)	0.760
iDSA MFI; median (IQR)	8360 (4799-11935)	5651 (3370-7940)	0.177
iDSA HLA class			0.392
Class I	5 (41.6%)	6 (60%)	
Class II	7 (58.39%)	4 (40%)	
POST-KT IMMUNOLOGICAL DATA			
Time of highest iDSA MFI (days, mean + SD)	15.75 ± 3.03	13.6 ± 5.08	0.4510
Highest iDSA MFI; median (IQR)	15617 (1607-20240)	1438 (785-2436)	**0.0137**
Sum of DSA MFI; median (IQR)	28059 (3381-44938	3609 (1791-11856)	**0.0423**

Table. Demographical and immunological characteristics of KT patients presenting or not ABMR.ABMR Antibody-mediated rejection, CDC complement-dependent cytotoxicity, cPRA calculated panel-reactive antibodies, DSA donor-specific antibody, FC flow cytometry, IQR interquartile range, KT kidney transplantation, iDSA immunodominant DSA, SD standard deviation.

Kervella et al, ATC 2025

Conclusions

- **Non-Active Desensitization** is the **first option to be considered** before active desensitization for highly sensitized patients
- Desensitization with imlifidase is a **promising strategy** but restricted **to some highly sensitized patients only**
- Occurrence of **DSA rebound seems associated with early ABMR**
- Early and active treatment of AMR seems to provide satisfactory allograft survival and function (mid-term)
- The risk of **infectious complications** associated to desensitization and high immunological risk transplantation **requires careful selection and close monitoring** of imlifidase treated patients
- **Need to better identify patients that will present a DSA rebound**… mBCs ?

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