Tolerance after solid organ transplantation (SOT)

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A kidney transplant for LIFE with a deceased-donor kidney

The long story of Angela D. born in 1946

- Deceased kidney transplantation on July 25th 1970 (Cambridge UK, Sir Roy Calne)
  - HLA A and B fully matched
- For more than 53 years her serum creatinine has remained stable:
  - Currently at 90 μmol/L, eGFR at 54 mL/min; microalbuminuria at 17 mg/L
- Immunosuppression relies on Prednison 5 mg/d and Azathioprin 100 mg/d
- She has experienced three times (1993, 2018, and 2023) transient nephritic syndrome that resolved spontaneously (IgA nephropathy?)
- She has no anti-HLA alloantibodies
- She has experienced a few skin cancers (Bowen disease; basal cell carcinoma; squamous cell carcinoma) treated by surgery
- Current comedications include irbesartan, rosuvastatin and vitamin D.

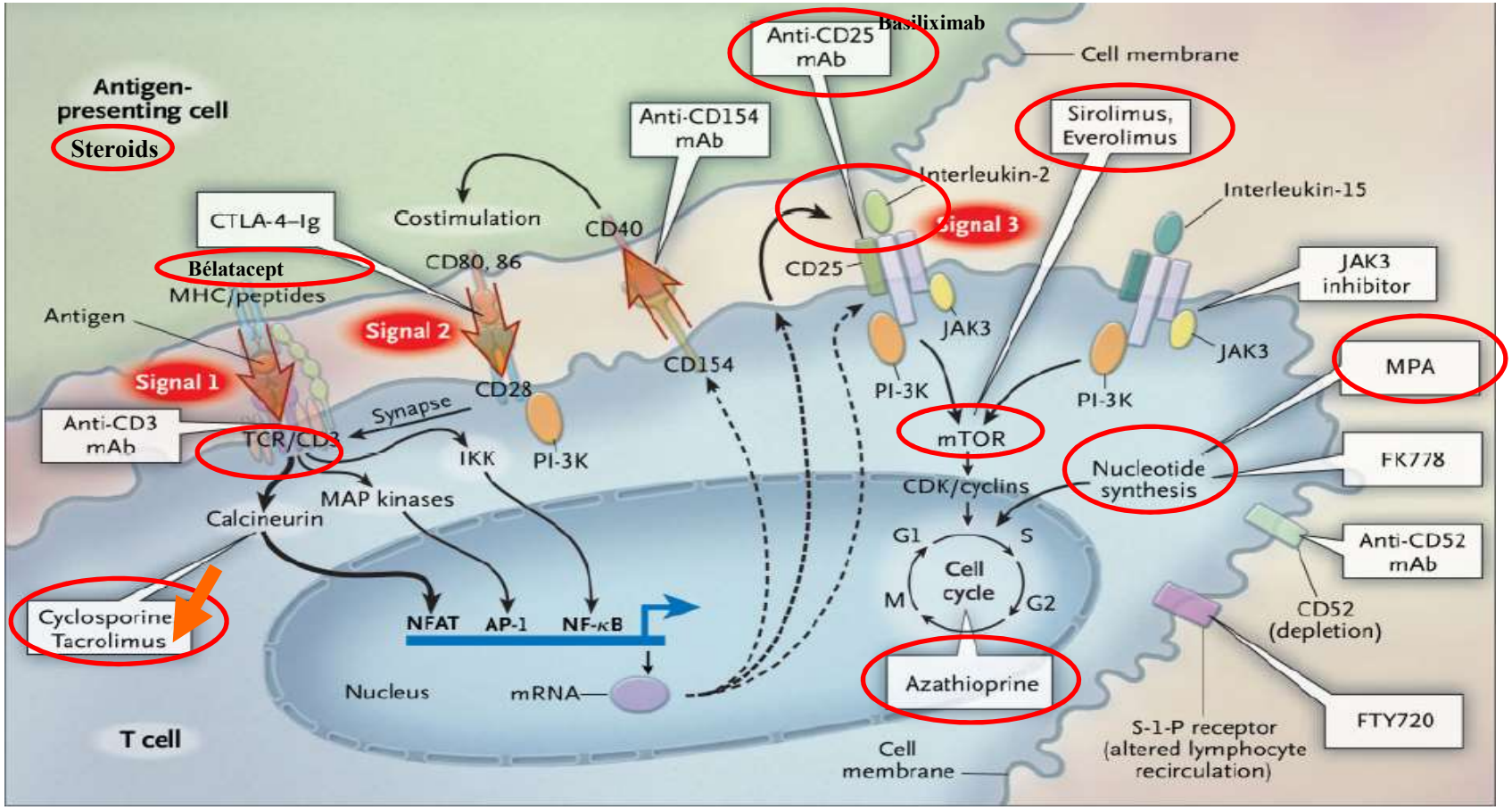
Near Cahors (France) where she leaves

Long term succes for a kidney transplant

- There is NO tolerance, i.e. life-long immunosuppression is mandatory: is it true?
- Immunosuppressive drugs have narrow therapeutic windows
  - Therefore combining various immunosuppressive drugs make sense
- Cornerstone drugs:
  - Calcineurin inhibitors, i.e. tacrolimus OR ciclosporine A
  - Mycophenolic acid (Cellcept/Myfortic) OR Azathioprine
    - These can be replaced by mTOR-inhibitors, e.g. Everolimus OR Sirolimus
  - Corticoids are optional beyond 3 months post-transplantation

Tacrolimus-based therapy remains the cornerstone of immunosuppression after solid organ transplantation

Mechanisms of action of immunosuppressants

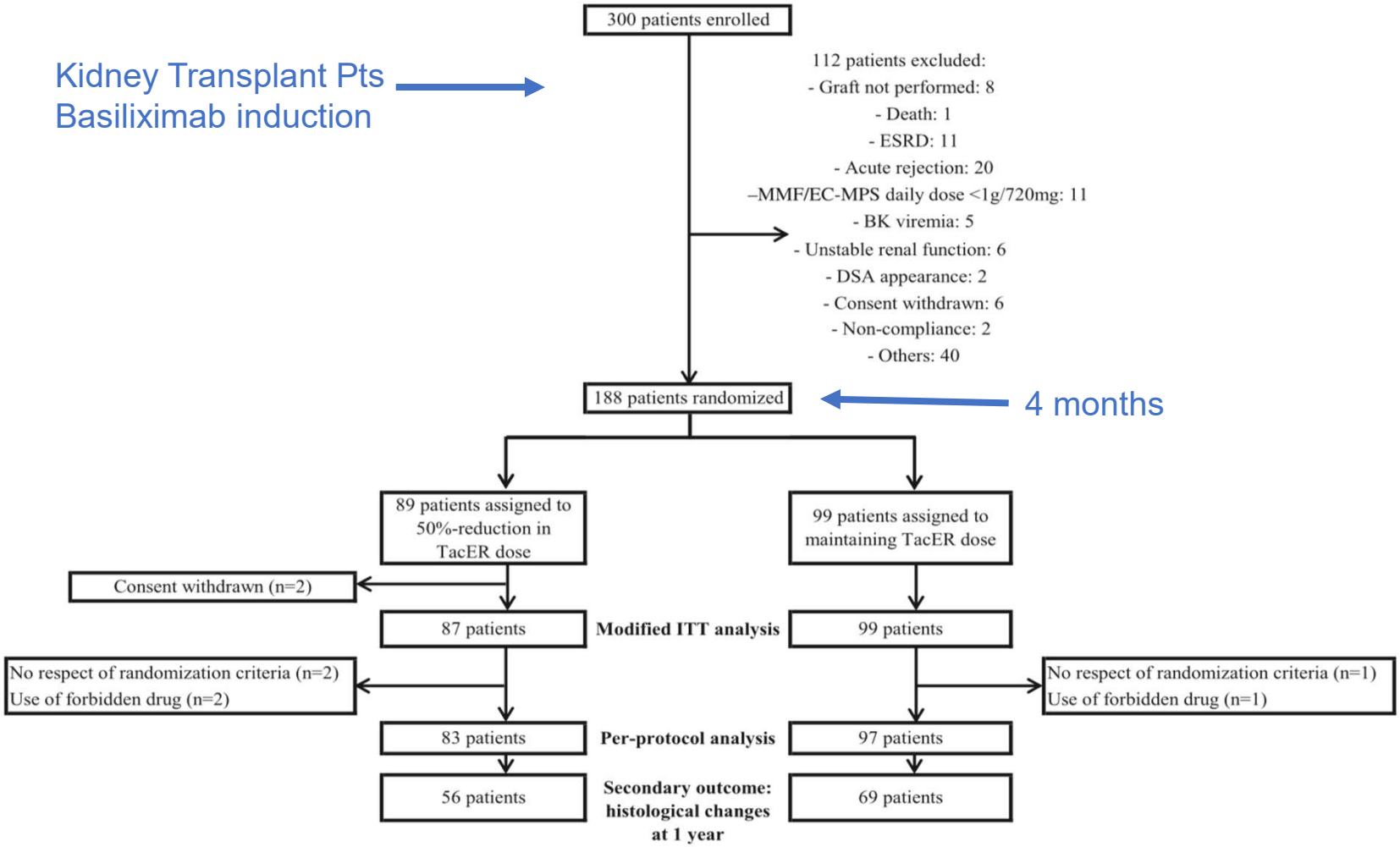


Is it possible to extremely minimize immunosuppression?

The risk of CNI minimization

Multicenter RCT conducted in France

Kidney Transplant Pts
Basiliximab induction



Gatault P. et al. Am J Transplant 2017; 17: 1370

Reduction of Extended-Release Tacrolimus Dose in Low-Immunological-Risk Kidney Transplant Recipients Increases Risk of Rejection and Appearance of Donor-Specific Antibodies : A randomized Study

- 4 months posttransplant 186 stable steroid-free KTx patients were randomized (1:1) : Group A (n=87) had a 50% reduction in TacER dose with a targeted TacER trough level (C0) >3 µg/L; group B (n=99) had no change in TacER dose (TacER C0 7-12 µg/L).

- The primary outcome was estimated GFR at 1 year. KTx biopsy at 1-year.

- TacER C0 was lower in group A than in group B at 6 mo (4.1 ± 2.7 vs. 6.7 ± 3.9 µg/L, $p < 0.0001$) and 12 mo (5.6 ± 2.0 vs. 7.4 ± 2.1 µg/L, $p < 0.0001$).

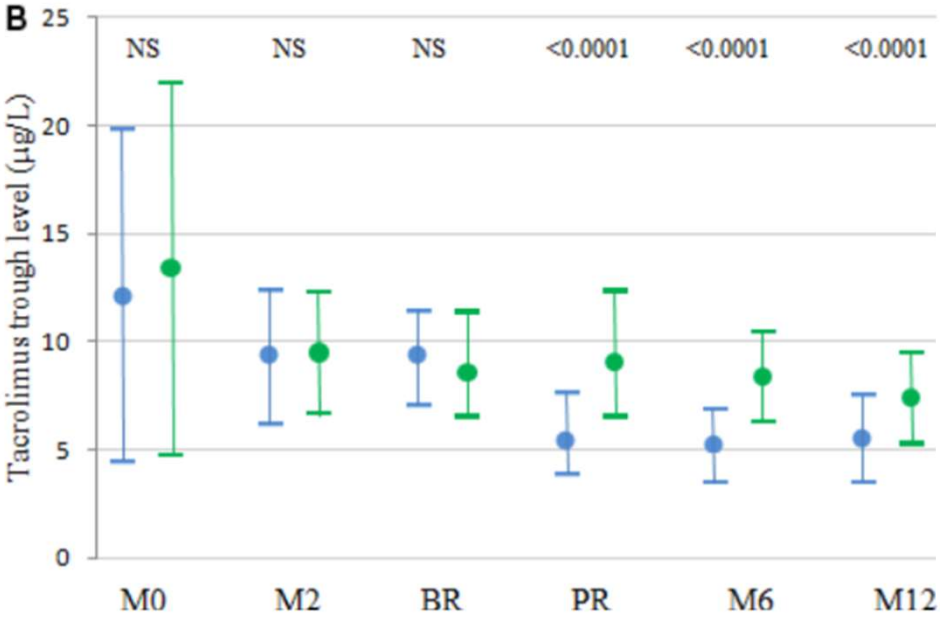
- **Estimated GFR was similar in both groups at 12 mo** (group A, 56.0 ± 17.5 mL/min per 1.73 m²; group B, 56.0 ± 22.1 mL/min per 1.73 m²).

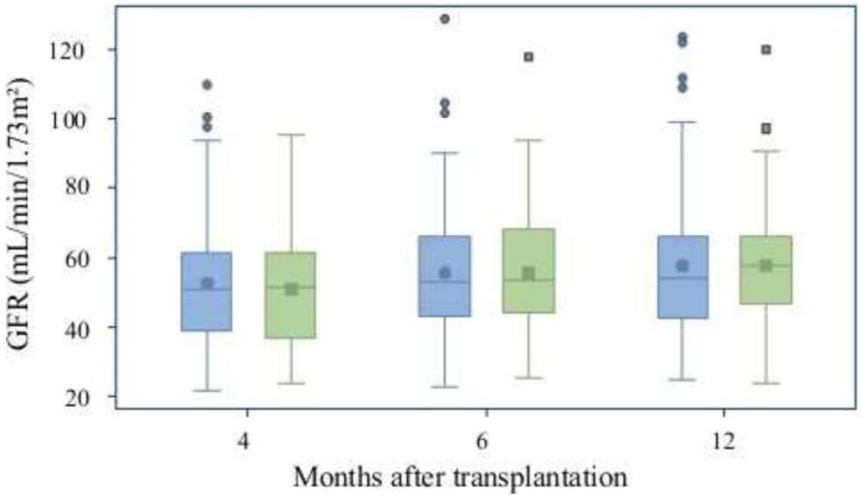
- More rejection episodes occurred in group A (tacrolimus minimization) than group B (11 vs. 3; $p = 0.016$).

- At 1-year, subclinical inflammation occurred more frequently in group A than group B (inflammation score [i] >0: 21.4% vs. 8.8%, $p = 0.047$; tubulitis score [t] >0: 19.6% vs. 8.7%, $p = 0.076$; i + t: 1.14 ± 1.21 vs. 0.72 ± 1.01, $p = 0.038$). Anti-HLA donor-specific antibodies appeared only in group A (6 vs. 0 patients, $p = 0.008$).

Gatault Ph, et al. Am J Transplant. 2017;17(5):1370-1379

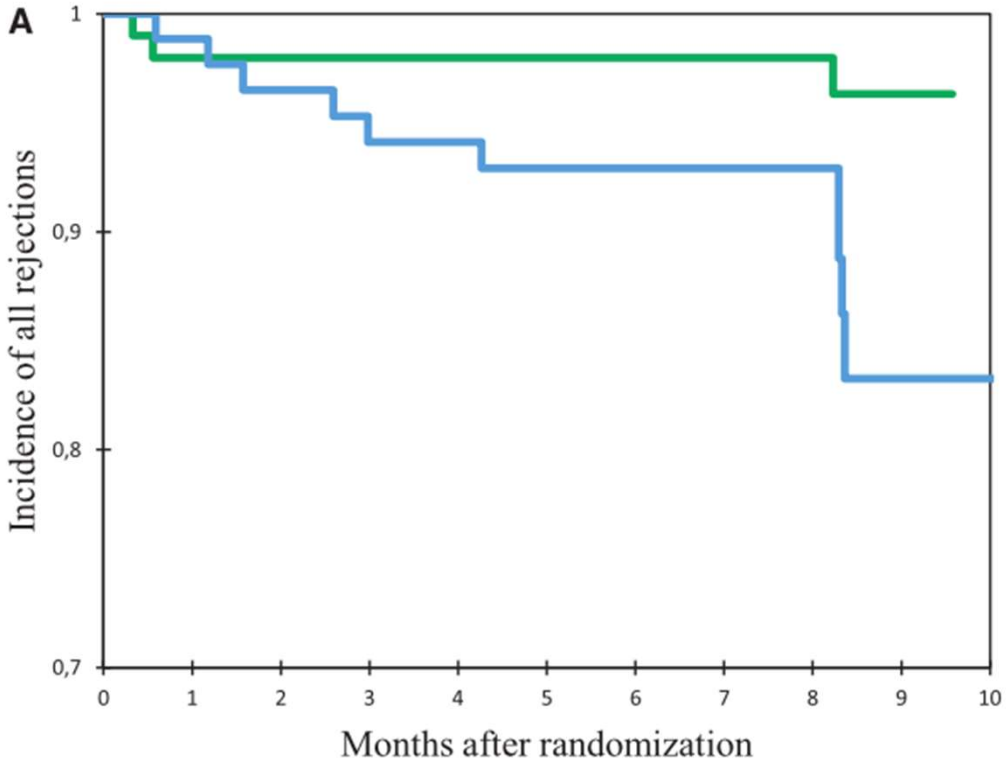
The risk of CNI minimization





Gatault P. et al. Am J Transplant 2017; 17: 1370

The risk of CNI minimization



High tac No patient developed *de novo* DSA

Low tac 6 /87 patients developed *de novo* DSA

Gatault P. et al. Am J Transplant 2017; 17: 1370

Reduction of Extended-Release Tacrolimus Dose in Low-Immunological-Risk Kidney Transplant Recipients Increases Risk of Rejection and Appearance of Donor-Specific Antibodies : A randomized Study (cont'd)

Rejection episodes occurring after randomization

Rejection	Group A, low TacER (n = 87)	Group B, standard TacER (n = 99)
Number of rejections (%)	10 (11)	3 (3)
Subclinical	3	0
Type		
Borderline	2	3
Stage I	5	0
Stage II	2	0
ABMR	1	0

ABMR, antibody-mediated rejection; TacER, extended-release tacrolimus.

Gatault Ph, et al. Am J Transplant. 2017;17(5):1370-1379

RCTs to STOP immunosuppression after kidney transplantation

Adverse Outcomes of Tacrolimus Withdrawal in Immune-Quiescent Kidney Transplant Recipients (1)

- *The Clinical Trials in Organ Transplantation-09 (CTOT-09)Trial was a randomized, prospective study of non sensitized primary recipients of living donor kidney transplants.*

- *Subjects received rabbit antithymocyte globulin, tacrolimus, mycophenolate mofetil, and prednisone.*

- *Six months post-transplantation, subjects without de novo donor-specific antibodies (DSAs), AR, or inflammation at protocol biopsy were randomized to wean off or remain on tacrolimus. The intended primary end point was the change in interstitial fibrosis/tubular atrophy score between implantation and 24-month protocol biopsies*.

Hricik DE et al. AJT, 2015

Adverse Outcomes of Tacrolimus Withdrawal in Immune-Quiescent Kidney Transplant Recipients (2)

- **The study was terminated prematurely** because of unacceptable rates of AR (4 of 14) and/or *de novo* DSAs (5 of 14) in the tacrolimus withdrawal arm.
- Positive urinary CXCL9 predated clinical detection of AR by a median of 15 days. Analyses showed that >16 HLA-DQ epitope mismatches and pretransplant, peripheral blood, donor-reactive IFN-γ ELISPOT assay results correlated with development of DSAs and/or AR on tacrolimus withdrawal.
- **CNI withdrawal must be strongly discouraged** in kidney transplant recipients who are receiving standard-of-care immunosuppression, including those who are deemed to be immunologically quiescent on the basis of current clinical and laboratory criteria.

Hricik DE et al. AJT, 2015

Failure of Calcineurin Inhibitor (Tacrolimus) Weaning Randomized Trial in Long-Term Stable Kidney Transplant Recipients (1)

- *Prospective, randomized, multicenter, double-blind placebo-controlled clinical study to analyze the benefit-risk ratio of tacrolimus weaning on highly selected patients (≥4 years of transplantation, normal histology, stable graft function, no anti-HLA immunization).*

- *The primary endpoint was improvement of renal function.*

- Fifty-two patients were scheduled in each treatment arm, placebo compared to the CNI maintenance arm. Only 10 patients were eligible and randomized.

Dugast et al. AJT, 2016

Failure of Calcineurin Inhibitor (Tacrolimus) Weaning Randomized Trial in Long-Term Stable Kidney Transplant Recipients (2)

- Five patients were assigned to the placebo arm and five were assigned to the tacrolimus maintenance arm. In the tacrolimus maintenance arm, all patients maintained stable graft function and no immunological events occurred.

- **Contrastingly**, in the tacrolimus withdrawal arm, all five patients had to reintroduce a full dose of tacrolimus since three of them presented an acute rejection episode (one humoral, one mixed, and one borderline) and two displayed anti-HLA antibodies without histological lesion (one donor-specific antibodies [DSA] and one non-DSA).

- Clearly, **tacrolimus withdrawal must be avoided** even in long-term highly selective stable kidney recipients. Dugast et al. AJT, 2016

Long-term observations from the tacrolimus weaning randomized clinical trial depicts the challenging aspects for determination of low-immunological risk patients

- *The long-term outcomes of patients included in this clinical trial, i.e. 10 years after randomization!*
- All patients are alive with a functional allograft.
- They all receive tacrolimus therapy except one with recurrent cutaneous neoplasia issues.
- Long-term eGFR is comparable between patients of the two randomized groups (46.4 ml/min vs 42.8 ml/min).
- All *de novo* DSAs that occurred during the study period became non-detectable in the long run and all acute rejection episodes were reversed.
- The retrospective assessment of HLA DQ single molecule epitope mismatching determined that a majority of patients who developed *de novo* DSA after tacrolimus withdrawal would have been considered at high immunological risk (and therefore NOT minimized!).
- ***Minimization of immunosuppression remains a challenging objective, mainly because of the issues to properly select very low immunological risk patients.***

Masset et al. Front Immunol 2022

TOLERANCE

- The induction and maintenance of **robust immune tolerance** has been the holy grail of immunology for decades.

- In the absence of **robust unresponsiveness** of the immune system to self antigens (immune tolerance), uncontrolled reactivity can lead to disorders like food allergies and autoimmune diseases.

- In the setting of **organ transplantation** *Tolerance is defined as a functioning allograft in the ABSENCE of any immunosuppression*

- The term “unresponsiveness” that has been associated with immune tolerance refers to a lack of pathogenic immunity characterized by immune-cell inactivation or deletion or to the diversion of pathogenic immunity to protective immunity through the engagement of regulatory cells, deviation in cell differentiation, or development of immune barriers.

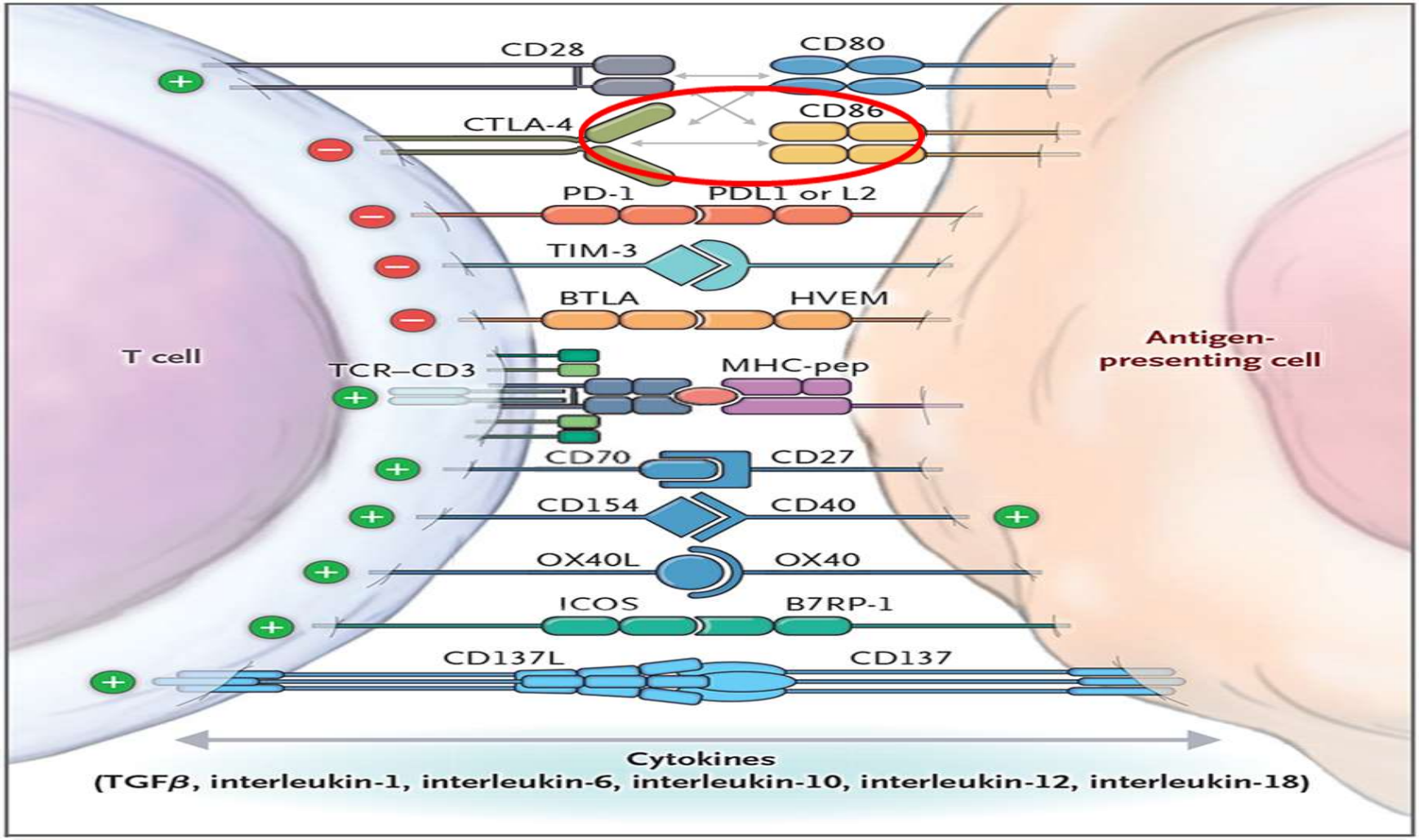
- Thus, implicit in current approaches to the development of tolerogenic drugs is the assumption that successful therapies would treat and prevent allergic and autoimmune diseases, as well as lead to immunosuppression-free organ and stem cell–derived tissue transplantation and protein-replacement approaches in congenital diseases such as hemophilia

- **Mechanisms associated with tolerance** :

  - Thymus and central tolerance

  - Peripheral tolerance
    - Blocking CD28/CD80-CD-86 pathways by CLTA4-Ig = Belatacept (animal models)
    - Checkpoints, including CTLA-4 and programmed death 1 (PD-1), shut down immune activation when engaged by their ligands, which leads to active tolerance induction
    - Tregs, a subset of CD4+ T cells expressing a master transcriptional repressor, forkhead box P3 (FOXP3).
    - Tregs are generated in the immune periphery, under conditions in which naive CD4+ T cells encounter antigen in the context of suppressive factors such as TGF-β, interleukin-10, bacterially derived metabolic products, or altered stimulatory pathways.

Blocking CD28/CD80-CD-86 pathways by CLTA4-Ig



- **Inducing tolerance** :

  - Resetting the immune system
    - autologous hematopoietic stem-cell transplantation (HST)
    - massive immune-cell depletion (alemtuzumab, ant-CD52 MoAb)

  - Targeting pathogenic T cells
    - anti-CD3 monoclonal antibody
    - a soluble form of the CD2 costimulatory receptor LFA-3 (alefacept)
    - inhibitors of the costimulatory pathway, e.g., abatacept; belatacept
    - induction of antigen-specific tolerance with the use of autoantigen therapeutic drugs

  - Targeting regulatory pathways
    - increase or enhance Treg numbers and activity in patients

Clinical operational tolerance

The Natural History of Clinical Operational Tolerance After Kidney Transplantation Through Twenty-Seven Cases (1)

- *European cohort of 27 kidney transplant recipients displaying operational tolerance (OT), compared to two cohorts of matched kidney transplant recipients under immunosuppression and patients who stopped immunosuppressive drugs and presented with rejection.*
- A lower proportion of operationally tolerant patients received induction therapy, a difference likely due to the higher proportion (18.5%) of HLA matched recipients in the tolerant cohort.
- These OT patients were also significantly older at the time of transplantation ($p = 0.0211$) and immunosuppression withdrawal ($p = 0.0002$) than recipients who rejected their graft after weaning.
- Finally, these patients were at lower risk of infectious disease.

Brouard S, et al. AJT 2012; 12: 3296–3307

The Natural History of Clinical Operational Tolerance After Kidney Transplantation Through Twenty-Seven Cases (2)

- Among the 27 patients defined as operationally tolerant at the time of inclusion, 19 still display stable graft function (mean 9±4 years after transplantation) whereas 30% presented slow deterioration of graft function. Six of these patients tested positive for pre-graft anti-HLA antibodies.

* Biopsy histology studies revealed an active immunologically driven mechanism for half of them, associated with DSA in the absence of C4d. This study
suggests that operational tolerance can persist as a robust phenomenon, although eventual graft loss does occur in some patients.

Brouard S, et al. AJT 2012; 12: 3296–3307

The Natural History of Clinical Operational Tolerance After Kidney Transplantation Through Twenty-Seven Cases (3)

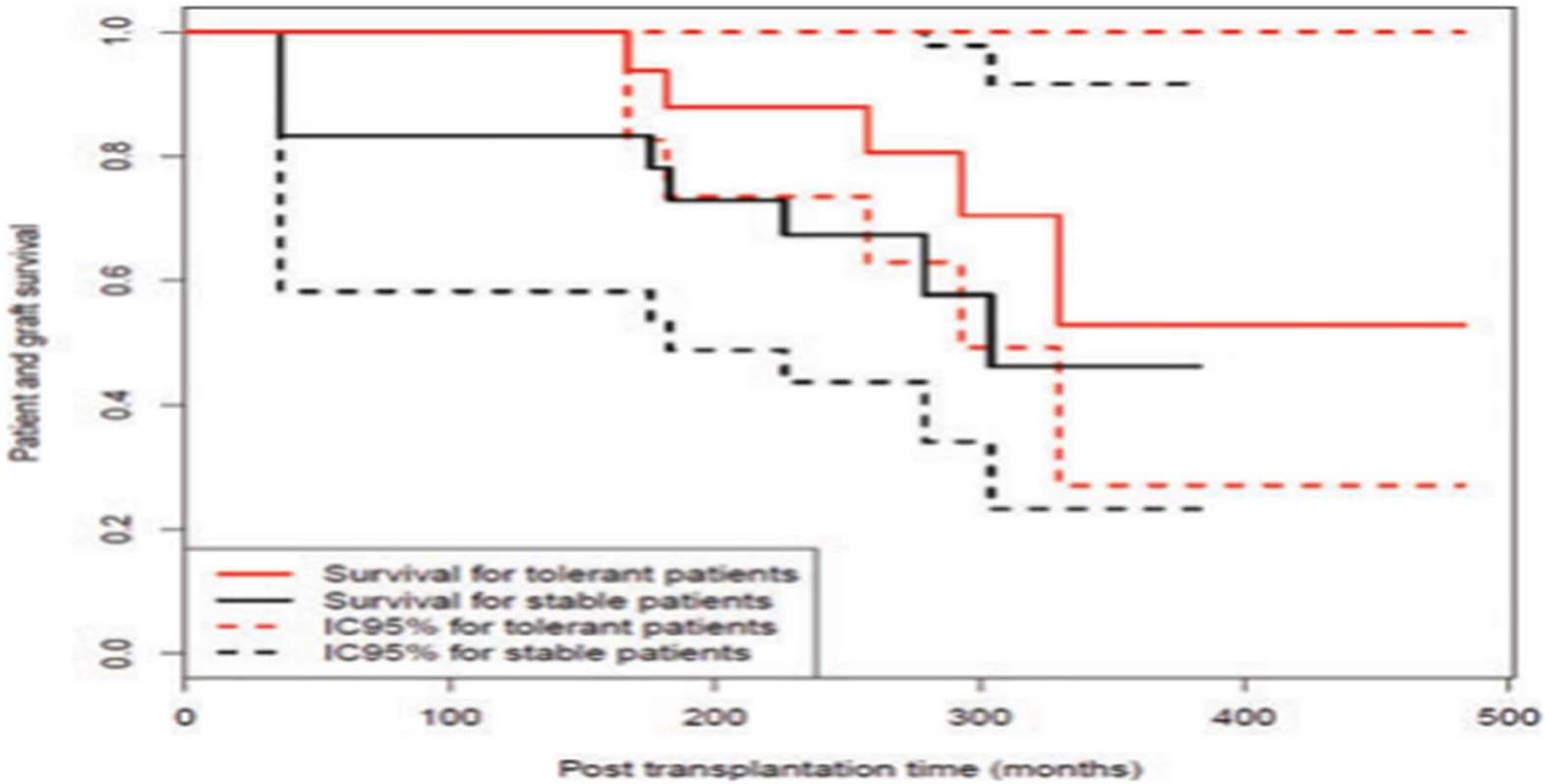
Diagnostic classification assay from operationally tolerant patients

27 Operationally tolerant patients		
13 patients	**6 patients**	**8 patients**
• Functional graft • Without HLA Abs	• Functional graft • With HLA Abs (± DSA)	• Graft failure • With or without HLA Abs (± DSA)
Operational tolerance	Operational tolerance (Lack of a destructive immune response toward the graft Partial operational tolerance)	Lose of operational tolerance

Brouard S, et al. AJT 2012; 12: 3296–3307

The Natural History of Clinical Operational Tolerance After Kidney Transplantation Through Twenty-Seven Cases (4)

Graft and recipient survival probability according to time posttransplant and status of operational tolerance or stable under immunosuppression.



Masset et al. Front Immunol 2022

The DESCARTES-Nantes survey of kidney transplant recipients displaying clinical operational tolerance and almost tolerant patients (1)

- *Kidney recipients maintaining a prolonged allograft survival in the absence of immunosuppressive drugs and without evidence of rejection are supposed to be exceptional.*

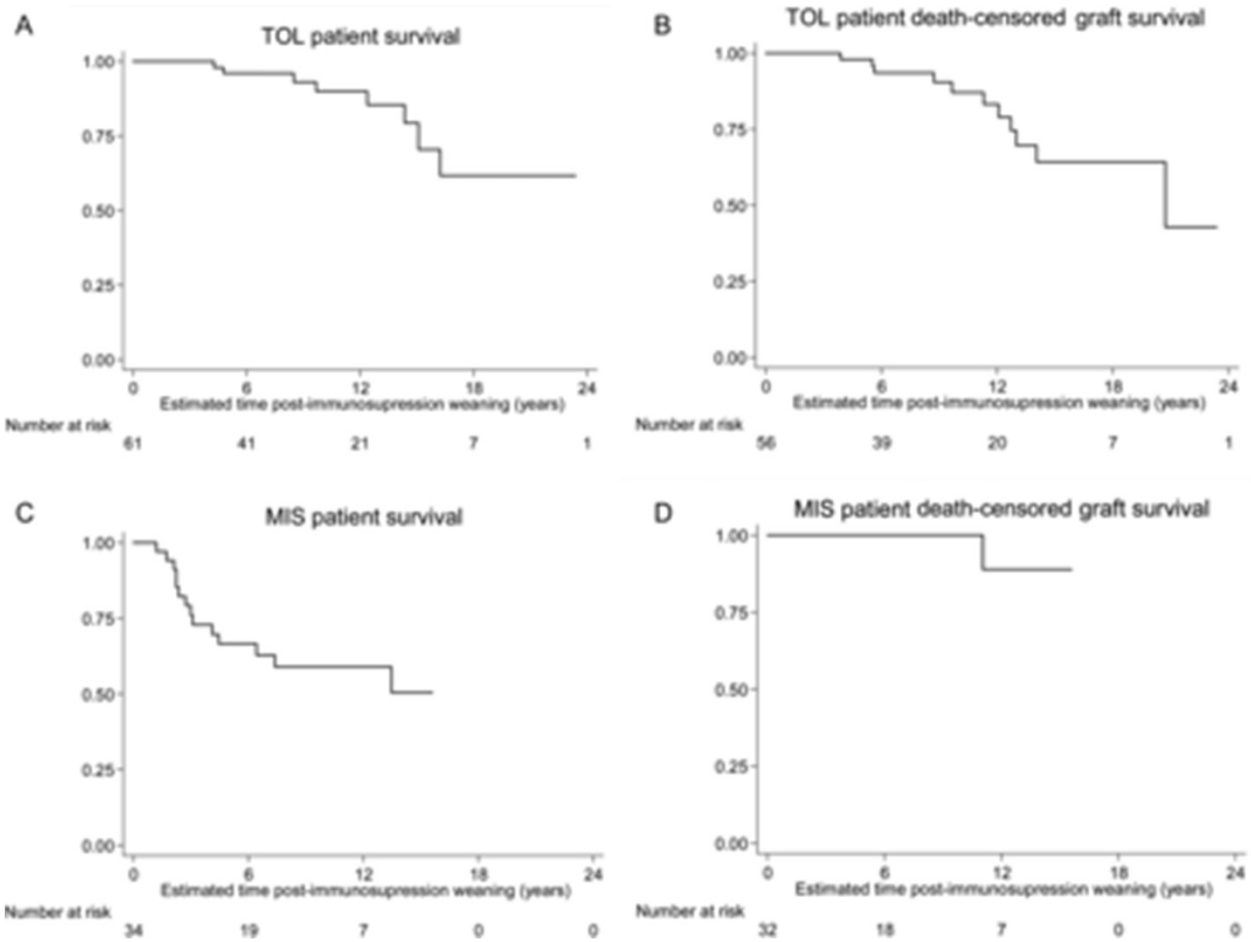
* European-wide survey to identify 'operationally tolerant' patients (TOL; defined as having a serum creatinine <1.7 mg/dL and proteinuria <1 g/day or g/g creatinine despite at least 1 year without any immunosuppressive drug) and 'almost tolerant' patients (minimally immunosuppressed patients (MIS) receiving low-dose steroids).

- 61 TOL and 34 MIS patients. Of the 61 TOL patients, 26 were previously described by the Nantes group and 35 new patients. Most of them were noncompliant patients.
- At data collection, 31/35 patients were alive and 22/31 still operationally tolerant. For the remaining 9/31, 2 were restarted on immunosuppressive drugs and 7 had rising creatinine of whom 3 resumed dialysis. **Operational tolerance might be transient**
- Considering all patients, 10-year death-censored graft survival post-immunosuppression weaning reached 85% in TOL patients and 100% in MIS patients.
- *With 218 913 kidney recipients surveyed, cumulative incidences of operational tolerance and almost tolerance were estimated at 3 and 1.5 per 10 000 kidney recipients, respectively.*

Massart A, et al. NDT 2016; 31:1002-1013

The DESCARTES-Nantes survey of kidney transplant recipients displaying clinical operational tolerance and almost tolerant patients (2)

(A) TOL patient survival. (B) TOL patient death-censored graft survival. (C) MIS patient survival. (D) MIS patient death-censored graft survival. TOL and MIS patients who returned on higher immunosuppressive drug levels before reaching death or graft loss were excluded from death-censored graft survival analysis (patients T11, 28, 32, 48 and 60; M7 and 8).



Massart A, et al. NDT 2016; 31:1002-1013

Identification of a B cell signature associated with renal transplant tolerance in humans

- *Largest cohort to of tolerant renal transplant recipients, as defined by stable graft function and receiving no immunosuppression for more than 1 year.*

- Comparison of their gene expression profiles and peripheral blood lymphocyte subsets with those of subjects with stable graft function who are receiving immunosuppressive drugs as well as healthy controls.
- In addition to being associated with clinical and phenotypic parameters, **renal allograft tolerance was strongly associated with a B cell signature** using several assays.
- Tolerant subjects showed increased expression of multiple B cell differentiation genes, and a set of just 3 of these genes distinguished tolerant from nontolerant recipients in a unique test set of samples.
- This B cell signature was associated with upregulation of CD20 mRNA in urine sediment cells and elevated numbers of peripheral blood naïve and transitional B cells in tolerant participants compared with those receiving immunosuppression.

- These results point to a critical role for B cells in regulating alloimmunity.

Newell KA, et al. JCI 2010;120(6):1836-1847

Total lymphoid irradiation and bone marrow infusion from HLA-matched donor

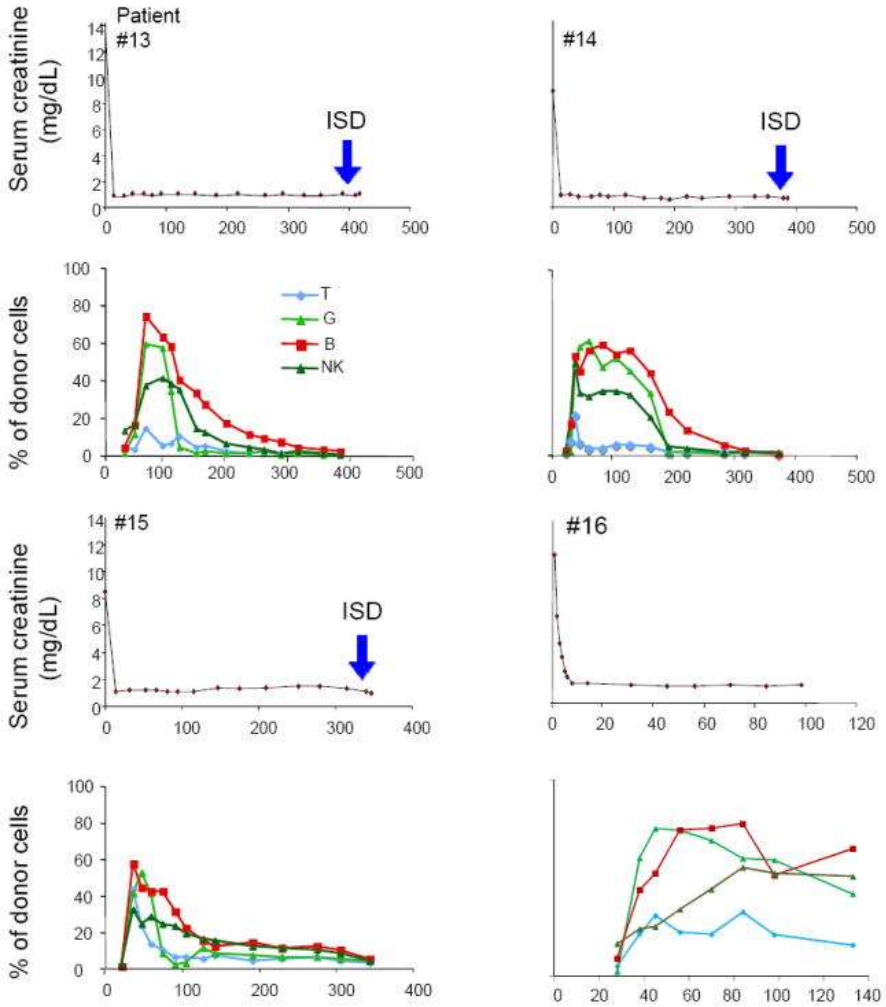
Tolerance and Withdrawal of Immunosuppressive Drugs in Patients Given Kidney and Hematopoietic Cell Transplants (1)

* 16 patients conditioned with total lymphoid irradiation and ATGs were given kidney transplants and an injection of CD34+ hematopoietic progenitor cells and T cells from *HLA-matched donors* in a tolerance induction protocol.

- 15 patients developed multilineage chimerism without graft versus host disease (GVHD), and 8 with chimerism for at least 6 months were withdrawn from anti-rejection medications for 1 to 3 years (mean- 28 months) without subsequent rejection episodes.
- 4 patients were not withdrawn due to return of underlying disease or rejection episodes.
- Blood cells from all patients showed early high ratios of CD4+CD25+ regulatory T cells and NKT cells versus conventional naïve CD4+ T cells, and **those off drugs showed specific unresponsiveness to donor alloantigens.**
- Conclusion: total lymphoid irradiation and ATG promoted the development of persistent chimerism and tolerance in a cohort of patients given kidney transplants and hematopoietic donor cell infusions. All 16 patients had excellent graft function at the last observation point with or without maintenance drugs.

Scandling JD, et al. AJT 2012;12(5):1133-1145

Tolerance and Withdrawal of Immunosuppressive Drugs in Patients Given Kidney and Hematopoietic Cell Transplants (2)



Days after kidney transplantation

Serum creatinine concentrations, immunosuppressive drug withdrawal and chimerism among lymphocytes and granulocytes (G) in 4 patients followed for less than 18 months.

Scandling JD, et al. AJT 2012;12(5):1133-1145

Chimerism, Graft Survival, and Withdrawal of Immunosuppressive Drugs in HLA Matched After Living Donor Kidney and Hematopoietic Cell Transplantation

- *22 HLA matched patients were given combined living donor kidney and enriched CD34(+) hematopoietic cell transplants and enrolled in tolerance protocols using posttransplant conditioning with total lymphoid irradiation and anti-thymocyte globulin*.

- Persistent chimerism for at least 6 months was associated with successful complete withdrawal of immunosuppressive drugs in 16 of 22 matched patients without rejection episodes or kidney disease recurrence with up to 5 years follow up thereafter.

- None of the 22 patients had kidney graft loss or graft versus host disease with up to 14 years of observation.

Scandling JD, et al. AJT 2015;15(3):695-704

Mixed chimerism and acceptance of kidney transplants after immunosuppressive drug withdrawal (1)

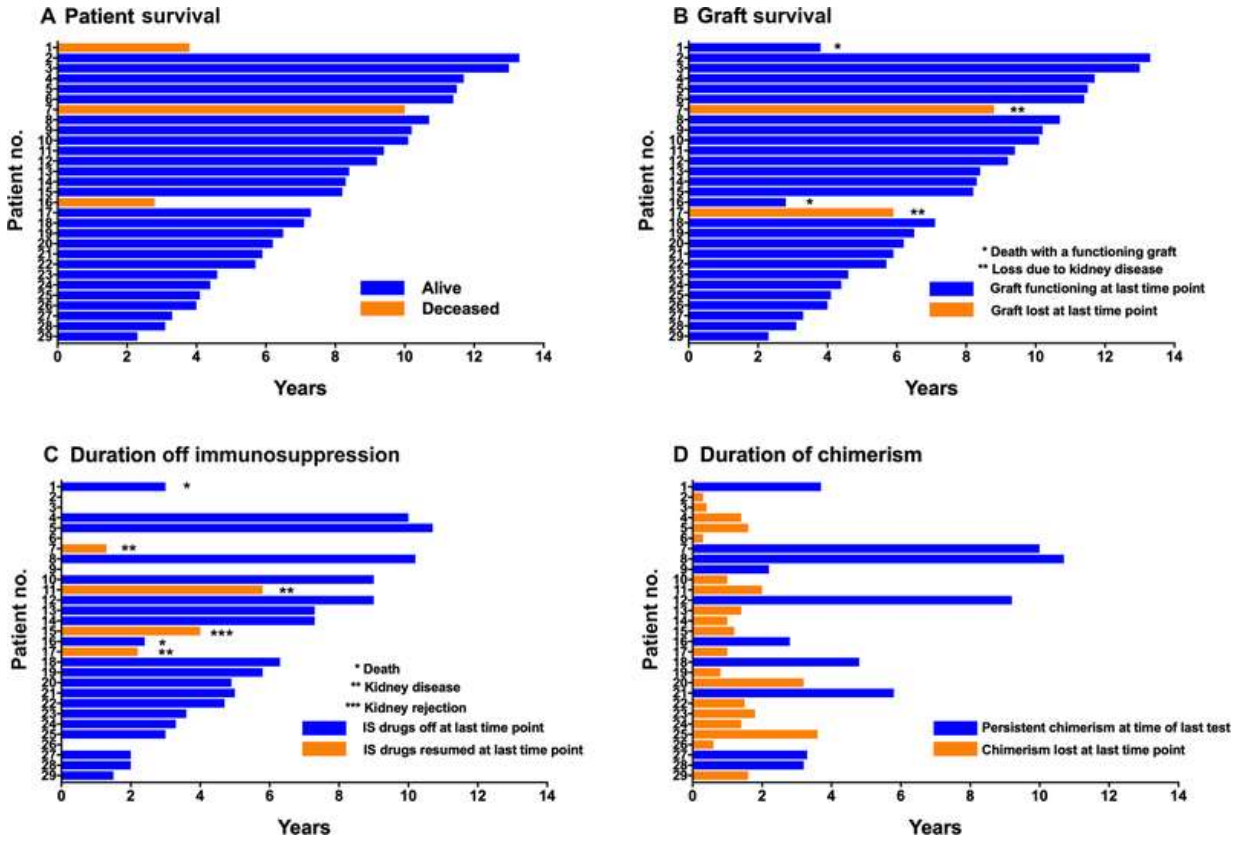
** To determine whether persistent mixed chimerism and tolerance can be established in patients undergoing living donor kidney transplantation following infusion to allograft recipients with donor T cells and hematopoietic progenitors after posttransplant lymphoid irradiation.*

- In 24 of 29 fully human leukocyte antigen (HLA)-matched patients who had persistent mixed chimerism for at least 6 months, complete IS drug withdrawal was achieved without subsequent evidence of rejection for at least 2 years.
- In 10 of 22 HLA haplotype-matched patients with persistent mixed chimerism for at least 12 months, reduction of IS drugs to tacrolimus monotherapy was achieved.
- Withdrawal of tacrolimus during the second year resulted in loss of detectable chimerism and subsequent rejection episodes, unless tacrolimus therapy was reinstituted.
- No evidence of rejection was observed in all surveillance graft biopsies obtained from mixed chimeric patients withdrawn from IS drugs, and none developed graft-versus-host disease.

Busque S, et al. Sci Transl Med 2020;12(528):eaax8863

Mixed chimerism and acceptance of kidney transplants after immunosuppressive drug withdrawal (2)

Patient survival, graft survival, duration of complete withdrawal of IS drugs, and duration of chimerism in HLA-matched patients.

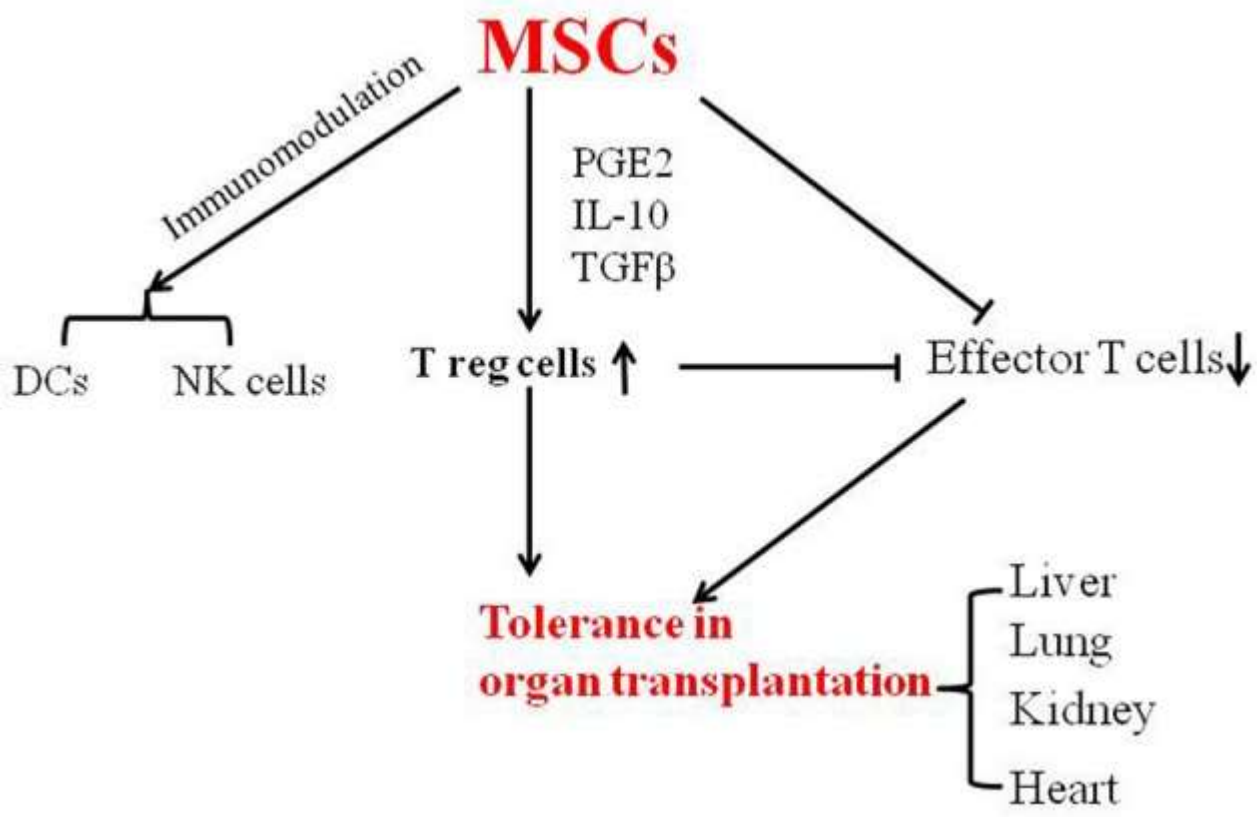


(A) Patient survival. (B) Graft survival. (C) Duration off IS drugs. Patients without bars did not meet criteria to achieve IS drug withdrawal. (D) Duration of chimerism up to the last time point tested.

Busque S, et al. Sci Transl Med 2020;12(528):eaax8863

Mesenchymal stem cells for inducing tolerance in organ transplantation

MSCs induce tolerance in organ transplantation.



Guo K, et al. Front Cell Dev Biol 2014;2:1-4

Induction Therapy With Autologous Mesenchymal Stem Cells (MSCs) in Living-Related Kidney TransplantsA Randomized Controlled Trial FREE (1)

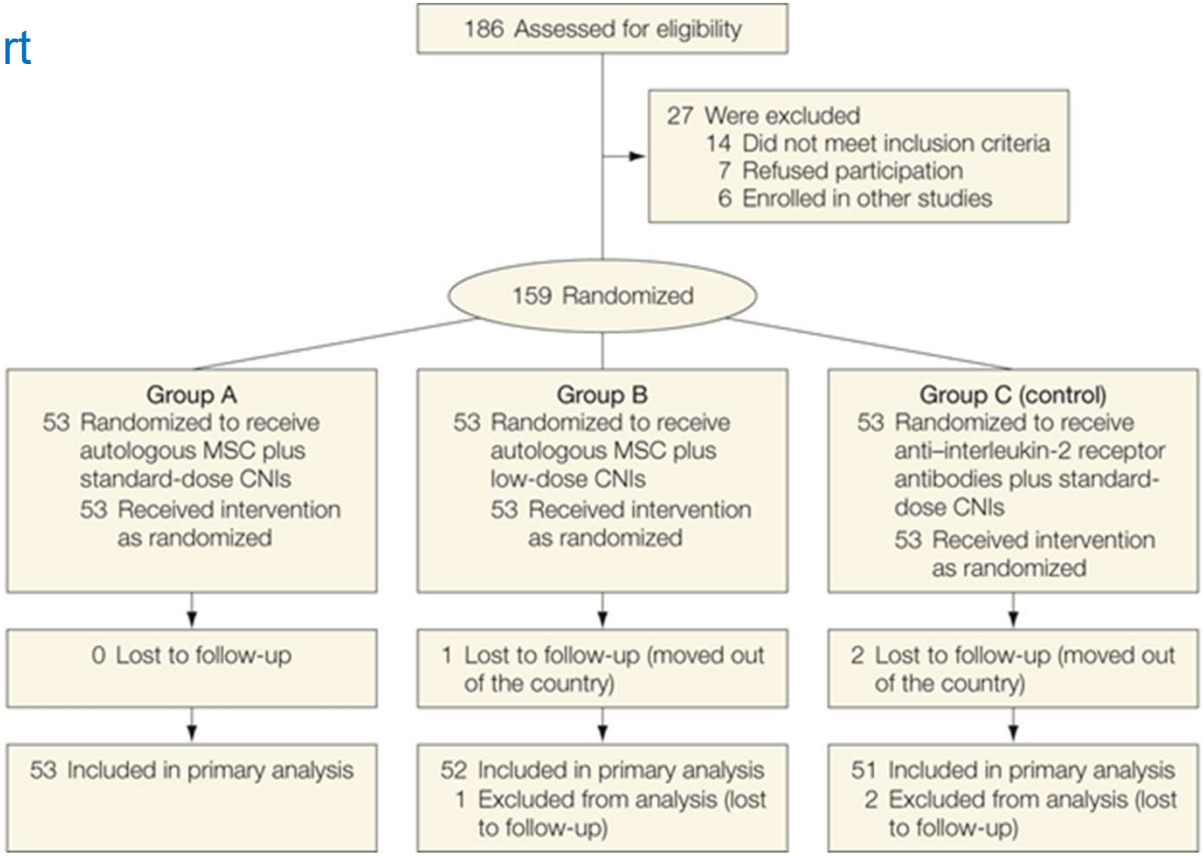
To assess autologous MSCs as replacement of antibody induction (basiliximab) for patients with end-stage renal disease who undergo ABO-compatible, cross-match-negative kidney transplants from a living-related donor.

- 159 patients were enrolled in a single-site, prospective, open-label, randomized study from February 2008-May 2009.
- Patients were inoculated with marrow-derived autologous MSC (1-2 x 10(6)/kg) at kidney reperfusion and two weeks later. Fifty-three patients received standard-dose and 52 patients received low-dose CNIs (80% of standard); 51 patients in the control group received anti-IL-2 receptor antibody (basiliximab) plus standard-dose CNIs.
- The primary measure was 1-year incidence of acute rejection and renal function (eGFR).
- Patient and graft survival at 13 to 30 months was similar in all groups.
- After 6 months, there were significantly less acute rejection episodes in the MSCs group (less than 8%) vs. 21% in the controls.
- None of the patients in either autologous MSC group had glucocorticoid-resistant rejection vs. (7.8%) in the controls.
- **Renal function recovered faster among MSC groups showing increased eGFR levels during the first month after surgery than the control group. Finally, eGFR at 1-year was significantly better in MSCs groups.**

Tan J, et al. JAMA 2012.307(11):1169-1177

Induction Therapy With Autologous Mesenchymal Stem Cells in Living-Related Kidney Transplants.A Randomized Controlled Trial FREE (2)

Study Flowchart

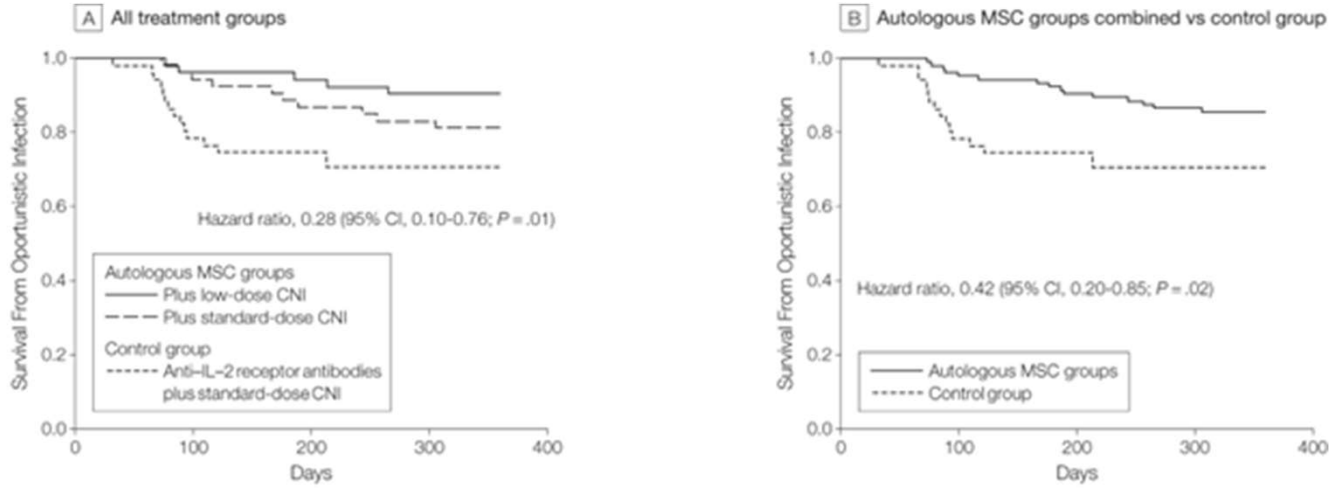


CNI indicates calcineurin inhibitors; MSC, mesenchymal stem cells.

Tan J, et al. JAMA 2012.307(11):1169-1177

Induction Therapy With Autologous Mesenchymal Stem Cells in Living-Related Kidney TransplantsA Randomized Controlled Trial FREE (3)

First Occurrence of Opportunistic Infection



No. at risk				
Autologous MSC groups				
Low-dose CNI	52	50	49	47
Standard-dose CNI	53	50	46	44
Control group	51	40	38	36

No. at risk				
Autologous MSC groups	105	100	95	91
Control group	51	40	38	36

Kaplan-Meier estimates of survival curves were evaluated to verify proportional hazards assumption, as well as potential stratification by other factors such as sex and calcineurin inhibitor (CNI) types, which would allow shape of hazard to depend on level of these other factors but still assume proportionality among groups. Cox models were fit to model and compare risk of opportunistic infection among the groups. Patients with no observed opportunistic infection were considered to have censored data at the study end point. A, shows that the initial results indicate comparable risk between groups treated with autologous mesenchymal stem cells (MSCs) but significantly decreased risk of opportunistic infection in the MSC group receiving low-dose CNI compared with the control group. B, Because the autologous MSC treated groups were comparable, an overall comparison of autologous MSC-treated groups vs control was performed. Results of this comparison suggest autologous MSC-treated groups have significantly decreased risk of opportunistic infection compared with the control group.

Tan J, et al. JAMA 2012.307(11):1169-1177

Low-dose tacrolimus combined with donor-derived mesenchymal stem cells after renal transplantation: a prospective, nonrandomized study (1)

- *Single-center pilot study with the aim to investigate the use of low-dose tacrolimus in combination with mesenchymal stem cells (MSCs) vs. standard of care*

- Donor-derived, bone marrow MSCs combined with a sparing dose of tacrolimus (0.04-0.05 mg/kg/day) were administered to 16 *de novo* living-related kidney transplant recipients
- 16 other patients received a standard dose of tacrolimus (0.07-0.08 mg/kg/day).
- ALL patients had induction with methylprednisone pulses plus Cyclophosphamide for 3 days
- MMF + prednisone for all

- The safety of MSC infusion, acute rejection, graft function, graft survival, and patient survival were evaluated over ≥24 months following kidney transplantation.

- All patients survived and had stable renal function at the 24 month follow-up.

Pan GH, et al. Oncotarget 2016;7(11):12089-12101

Low-dose tacrolimus combined with donor-derived mesenchymal stem cells after renal transplantation: a prospective, nonrandomized study (2)

Comparison of the adverse effects between the control (n = 16) and experimental (n = 16) groups

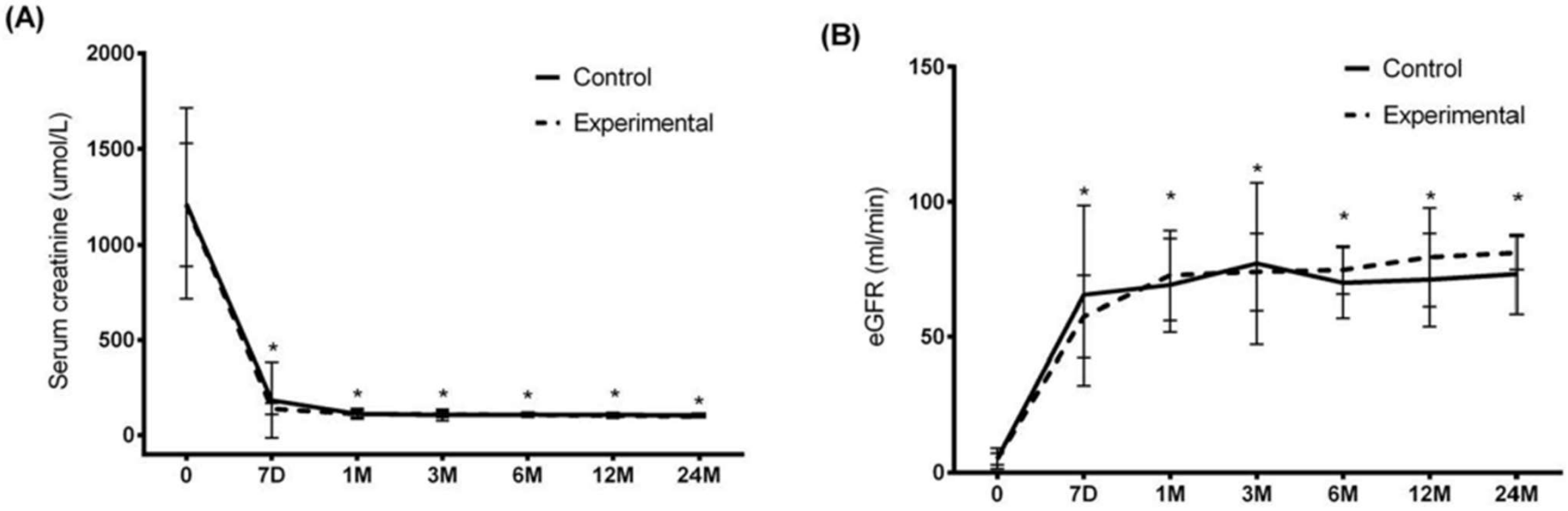
	Control (n = 16)	Experimental (n = 16)	P-value
Acute rejection	3 (18.8)	0 (0.0)	0.226
Diabetes	0 (0.0)	1 (6.3)	1.000
Hyperlipidemia	3 (18.8)	1 (6.3)	0.600
Anemia	0 (0.0)	2 (12.5)	0.484
Lung infection	7 (43.8)	3 (18.8)	0.252
Liver dysfunction	1 (6.3)	1 (6.3)	1.000
Incomplete intestinal obstruction	0 (0.0)	1 (6.3)	1.000
Fever	1 (6.3)	0 (0.0)	1.000
Perirenal hematoma	1 (6.3)	0 (0.0)	1.000

Data were presented as count and percentage and tested using Chi-square test.

Pan GH, et al. Oncotarget 2016;7(11):12089-12101

Low-dose tacrolimus combined with donor-derived mesenchymal stem cells after renal transplantation: a prospective, nonrandomized study (3)

Serum creatinine and eGFR throughout the study period



A. Serum creatinine and B. eGFR were measured in the experimental and control groups. Data were presented as mean (standard deviation). Linear mixed model revealed a significant time effect ($P < 0.001$). Asterisk indicates significantly different from baseline, $P < 0.003$

Pan GH, et al. Oncotarget 2016;7(11):12089-12101

Allogeneic mesenchymal stem cells as induction therapy are safe and feasible in renal allografts: pilot results of a multicenter randomized controlled trial (1)

** 42 renal allograft recipients were recruited and divided into trial and control groups. The trial group (21 cases) received 2 × 106/kg human umbilical-cord-derived MSCs (UC-MSCs) via the peripheral vein before renal transplantation, and 5 × 106 cells via the renal artery during the surgical procedure.*

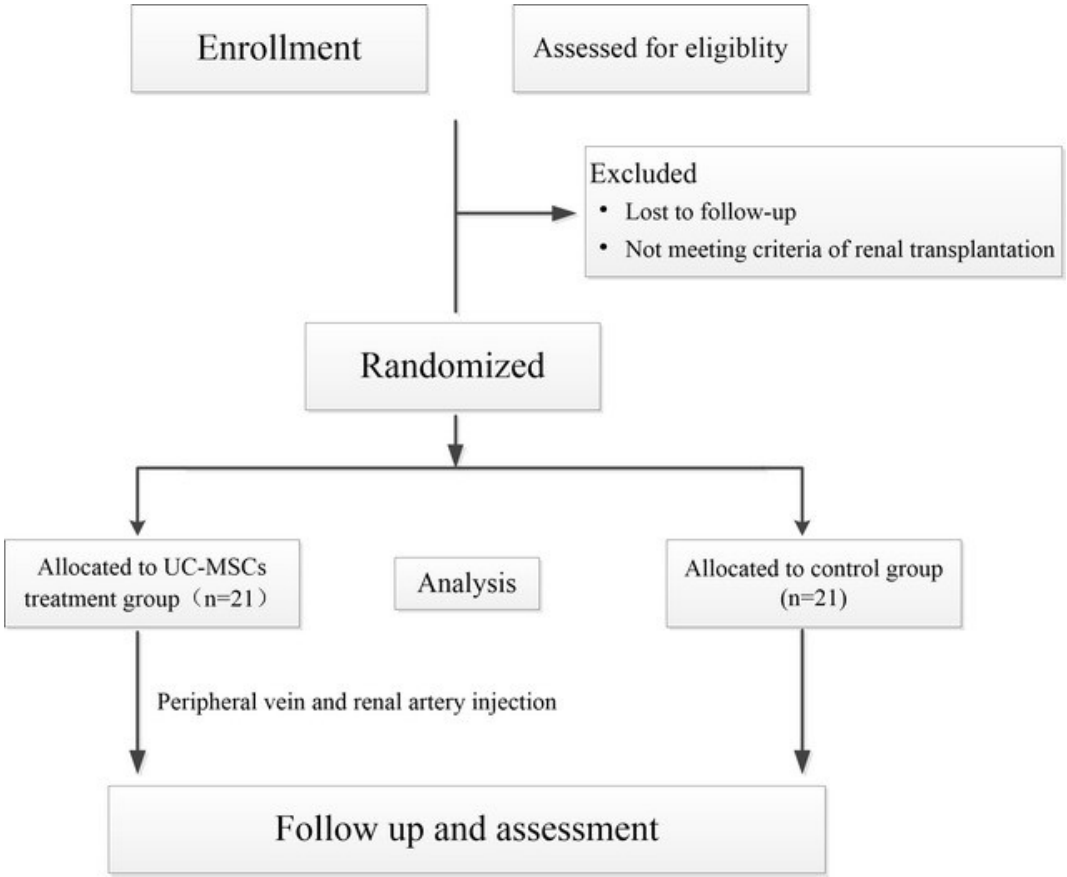
- *All recipients received standard induction therapy (ATG) along with CNI, MMF and steroids.*

- Treatment with UC-MSCs achieved comparable graft and recipient survivals with non-MSC treatment (P = 0.97 and 0.15, respectively).
- No increase in postoperative complications, including DGF and acute rejection, were observed (incidence of DGF: 9.5% in the MSC group versus 33.3% in the non-MSC group, P = 0.13; Incidence of acute rejection: 14.3% versus 4.8%, P = 0.61).
- Equal postoperative estimated glomerular filtration rates were found between the two groups (P = 0.88).
- All patients tolerated the MSCs infusion without adverse clinical effects.
- Additionally, a multiprobe fluorescence in situ hybridization assay revealed that UC-MSCs administered via the renal artery were absent from the recipient's biopsy sample.

Sun Q, et al. J Trans Med. 2018.16(1):52

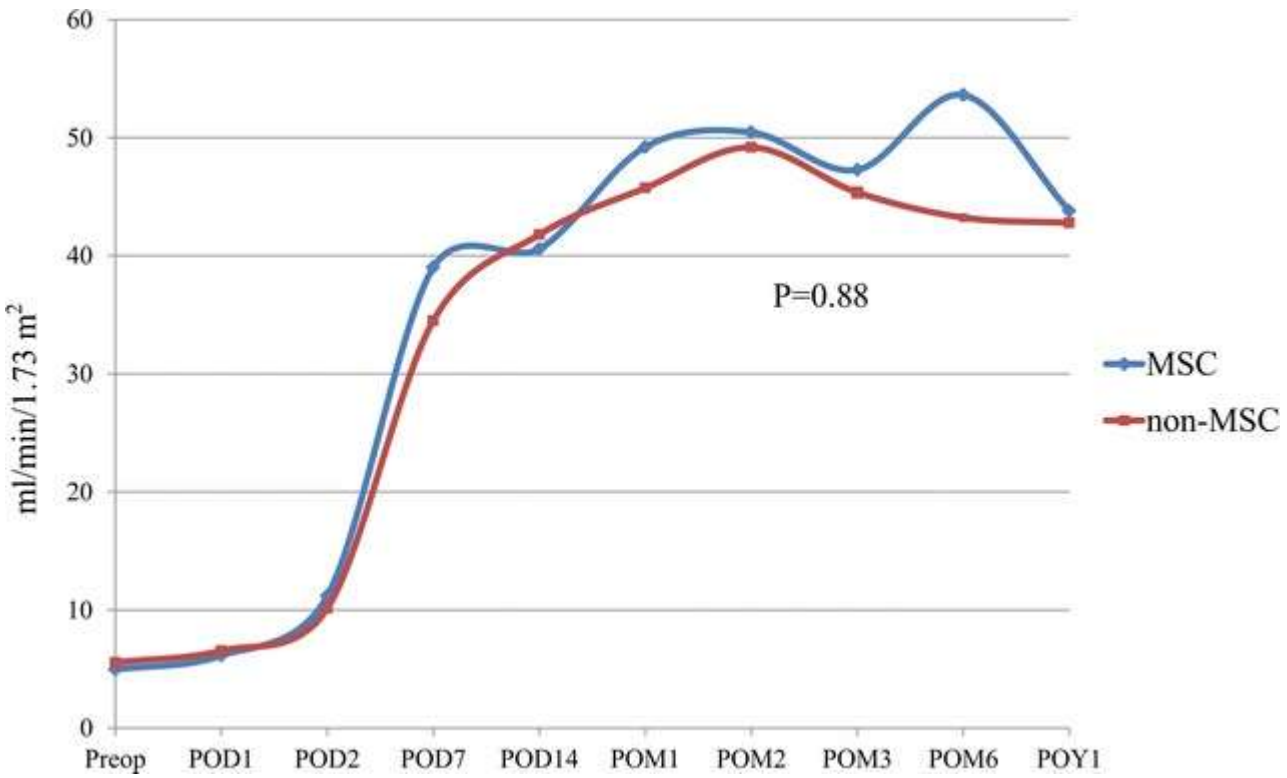
Allogeneic mesenchymal stem cells as induction therapy are safe and feasible in renal allografts: pilot results of a multicenter randomized controlled trial (2)

Study design and protocol for UC-MSCs administration in renal transplantation to prevent DGF and acute rejection



Sun Q, et al. J Trans Med. 2018.16(1):52

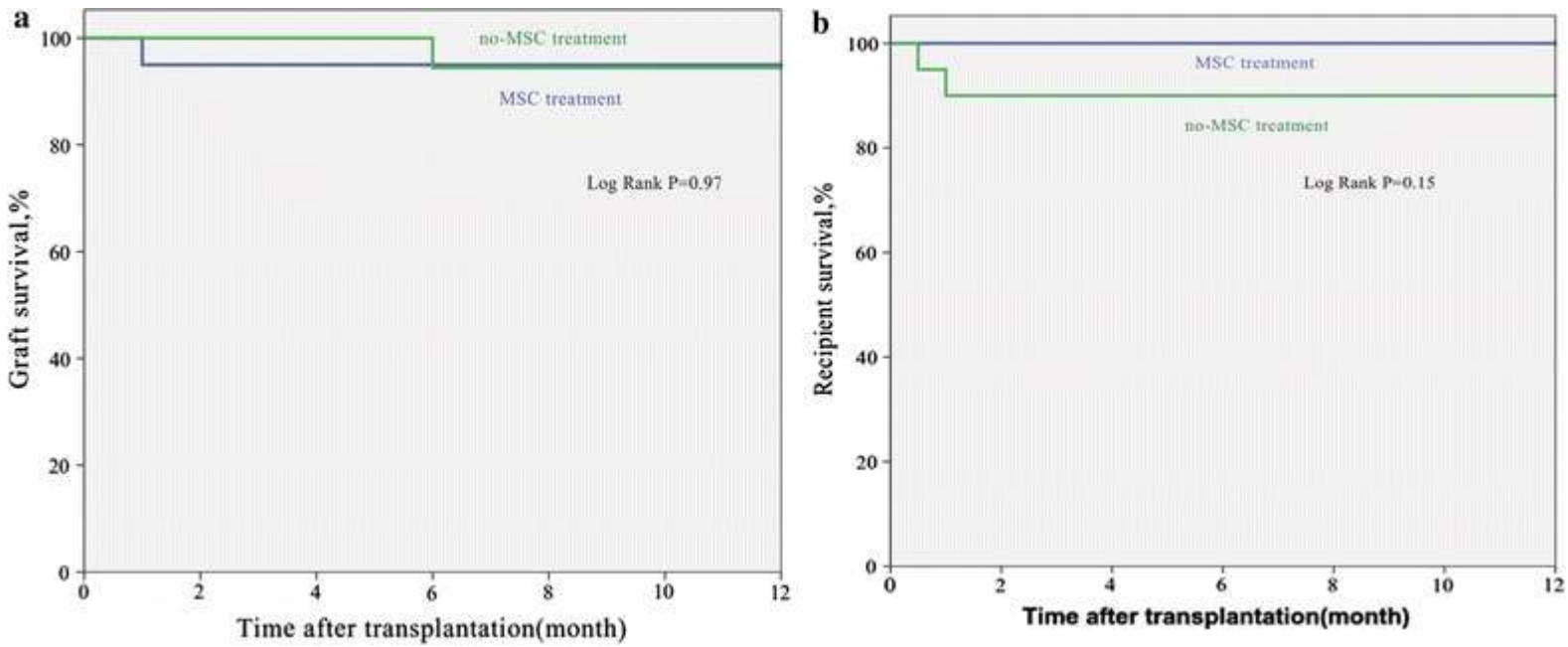
Allogeneic mesenchymal stem cells as induction therapy are safe and feasible in renal allografts: pilot results of a multicenter randomized controlled trial (3)



The eGFR curves at different time points during the follow-up period in UC-MSCs and non-MSC groups. No significant difference in eGFR changes postoperatively between the two groups was found (P = 0.88)

Sun Q, et al. J Trans Med. 2018.16(1):52

Allogeneic mesenchymal stem cells as induction therapy are safe and feasible in renal allografts: pilot results of a multicenter randomized controlled trial (4)



3 Kaplan–Meier survival estimates after renal transplantation in recipients of kidneys with or without UC-MSCs. a Graft survival in the MSC group was comparable to that in the non-MSC group (P = 0.97). b A similar analysis revealed no signifcant diference in recipient survival between the two groups (P = 0.15)

Sun Q, et al. J Trans Med. 2018.16(1):52

Polyclonal Regulatory T cell Therapy for Control of Inflammation in Kidney Transplants (1)

Chandran S, et al. AJT 2017 ; 17(1):2945-2954

A Phase I Clinical Trial with Ex Vivo Expanded Recipient Regulatory T cells in Living Donor Kidney Transplants

Mathew JM, et al. Sci Reports 2018.8/7428

CONCLUSION

TOLERANCE is NOT for the near future

Tacrolimus-based immunosuppression is the BEST one

Do NOT minimize too much tacrolimus exposure !

Thank you for your attention