Longitudinal analysis of immune cell phenotypes in the circulation of kidney transplant recipients and clinical correlations – a prospective study.

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Introduction

- Immune cellular responses are implicated in all clinical aspects of kidney transplantation.
- There are little data regarding the additional clinical value of regular monitoring of immune cells phenotypes expression in the circulation of kidney transplant recipients (KTRs).

❑**The aim of our prospective study, was a longitudinal follow-up analysis of immune cell subtypes, including monocytes subpopulations, natural killer (NK) cells and regulatory T cells (Tregs) in the circulation of KTRs and potential clinical correlations.**

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Immunosuppression and monocyte subsets

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In KTx, steroid intake was associated with higher total, classical and pro-inflammatory monocyte counts, but fewer non-classical monocytes.

Monocyte (subset) counts according to intake of classes of immunosuppressants

	Total monocytes		Classical monocytes		Intermediate monocytes		Non-classical monocytes	
Steroid								
N ($n = 44$)	565 ± 214	**P < 0.001**	461 ± 181	**P < 0.001**	28 ± 16	**P = 0.009**	76 ± 41	**P = 0.004**
Y ($n = 108$)	733 ± 230		637 ± 202		37 ± 22		58 ± 29	
CNI								
N ($n = 37$)	714 ± 210	P = 0.345	612 ± 185	P = 0.351	38 ± 19	P = 0.205	64 ± 30	P = 0.953
Y ($n = 115$)	675 ± 246		578 ± 219		33 ± 22		63 ± 35	
MMF/MPA								
N ($n = 48$)	703 ± 227	P = 0.501	614 ± 210	P = 0.276	33 ± 17	P = 0.535	56 ± 27	P = 0.080
Y ($n = 104$)	675 ± 243		574 ± 212		35 ± 23		67 ± 36	
mTORI								
N ($n = 125$)	678 ± 245	P = 0.622	584 ± 219	P = 0.719	34 ± 22	P = 0.360	63 ± 34	P = 0.514
Y ($n = 27$)	705 ± 200		600 ± 174		38 ± 16		67 ± 30	

CNI: calcineurin inhibitor; MMF: mycophenolate mofetil; MPA: mycophenolic acid; mTORI: mammalian target of rapamycin inhibitor; N: no; Y: yes. P-values below 0.05 are given in bold letters.

Circulating NK-Cell Subsets in Renal Allograft Recipients With Anti-HLA Donor-Specific Antibodies

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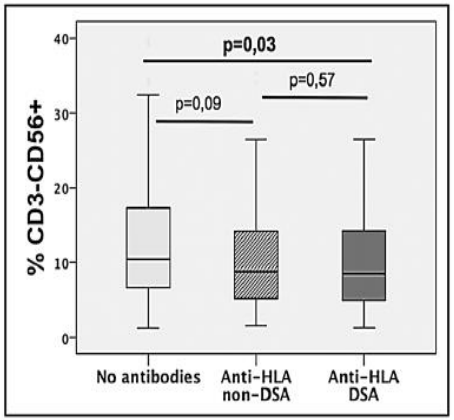

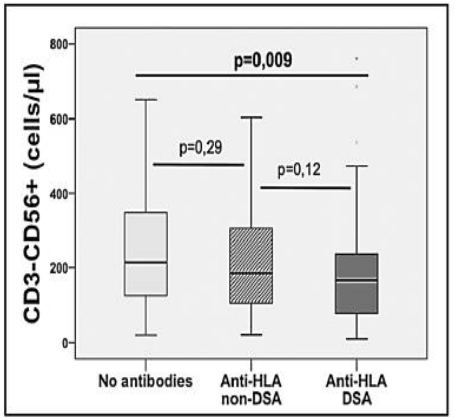

DSA and HLA non-DSA patients displayed lower proportions of NK-cells compared with patients without detectable anti-HLA antibodies.

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Long-term CD4 lymphopenia is associated with accelerated decline of kidney allograft function

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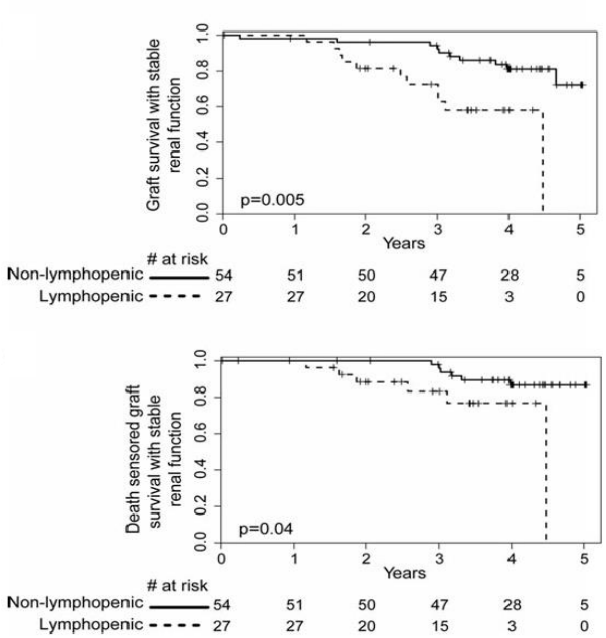

Long-term CD4 lymphopenia significantly associated with a hastened decline in graft function [HR = 3.89 P = 0.005] even after censoring for death [HR = 3.52, P = 0.04].

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Kidney allograft rejection is associated with an imbalance of B cells, regulatory T cells and differentiated CD28-CD8+ T cells: analysis of a cohort of 1095 graft biopsies

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- Compared to normal/subnormal biopsies, rejection of all types was marginally associated with a decrease in the percentage of circulating B cells and significantly associated with an increase in the ratio of CD28-CD8+ T cells to Tregs (p=0.01).

Methods

- 48 stable KTRs were initially enrolled.
- All patients were under triple immunosuppressive regimen, including corticosteroids, mycophenolate mofetil or mycophenolate acid and calcineurin inhibitors (CNIs) (43% on cyclosporine and 57% on tacrolimus).
- Exclusion criteria included history of acute rejection, cardiovascular disease (CVD), malignancy, autoimmunity and active or chronic infections.
- Clinical and laboratory parameters were recorded at baseline (T0).
- Patients were then prospectively followed and clinical and laboratory parameters were recorded at 12 months (T1).
- Patients who developed acute rejection, new-onset CVD, malignancy or who were hospitalized during the follow-up period were excluded.

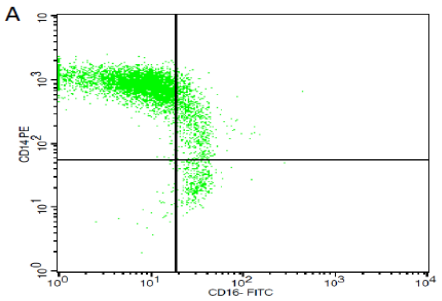
Methods

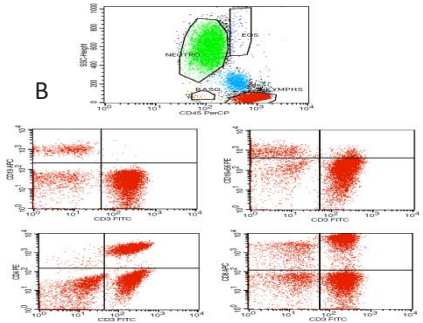
- **The peripheral blood immune cell subsets were measured by flow cytometry at baseline (T0) and after 12 months (T1):**

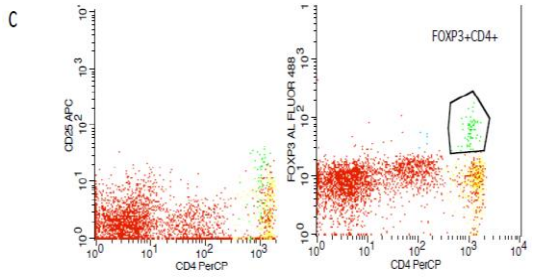
✓ *CD14++CD16-, CD14++CD16+ and CD14+CD16++ absolute values and percentages out of total monocytes*

✓ *NK cells (CD3+CD16+56+) absolute values and percentages out of total lymphocytes*

✓ *CD3-CD19+ B lymphocytes, CD3+ CD4+ T cells, CD3+CD8+ T cells and Tregs (CD4+CD25+ FoxP3+) absolute values and percentages out of total lymphocytes*







Results

- 40 KTRs (mean age 58 +/-9.28 years, 67% males) were included in the study analysis.
- Mean eGFR (CKD-EPI) declined from 58 +/-17 at T0 to 53 +/-18ml/min/1.73 m2 ($p< 0.01$).
- No significant changes in spot urine protein to creatinine ratio (UPCR) nor in inflammatory markers (CRP, ESR) were observed between T0 and T1.
- Overall, there was a decrease in mean monocytes counts ((648±241/µL versus 537 ±194/µL, $p=0.01$) and mean lymphocytes counts (2115 ±127/µL versus 1925±724/µL, $p=0.49$ respectively).
- The mean counts of the classical CD14++CD16- monocytes subtype increased at T1 (533±224/µL) compared to T0 (451±185/µL) ($p=0.04$), whereas the rest immune cell subsets did not show any significant change.
- CNI blood levels displayed no significant changes during the follow-up period compared with baseline.

A greater increase in the difference (Δ) of the pro-inflammatory CD14++CD16+ monocytes count from T1 to T0 (ΔCD14++CD16+ monocytes = CD14++CD16+ monocytes at T1-CD14++CD16+ monocytes at T0) was associated with a greater eGFR decline (ΔeGFR = eGFR T1 – eGFR T0) ($\rho = -0.339$, $p=0.046$).

Conclusion

- The results of our study suggest that greater increases in levels of pro-inflammatory CD14++CD16+monocytes are associated with increased yearly graft function loss.
- Future research studies with longer follow-up are required to specify the role of immune subpopulations as potential prognostic biomarkers in KTRs.

Acknowledgments: None

References

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