INDOLEAMINE 2,3-DIOXYGENASE (IDO) UPREGULATION IS AN INDEPENDENT PREDICTOR OF SUSCEPTIBILITY TO INFECTIONS IN KIDNEY TRANSPLANT PATIENTS

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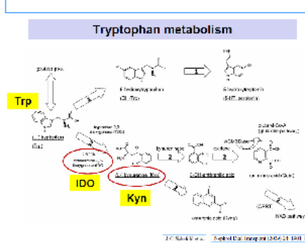
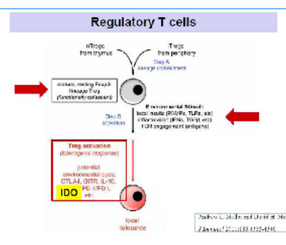
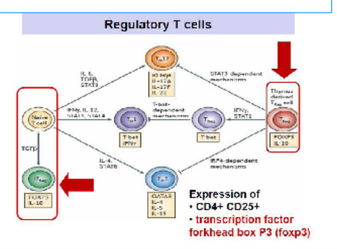
OBJECTIVES

Indoleamine 2,3 dioxygenase (IDO) is an intracellular enzyme involved in systemic immune tolerance and control of infections. IDO acts through degradation of essential amino acid Tryptophan (Trp), necessary for pathogens proliferation, suppressing the replication of bacteria and preventing viral spread. On the other hand with the attempt to terminate inflammatory response, IDO activates immunosuppressive mechanisms via Tregs facilitating further development of infection

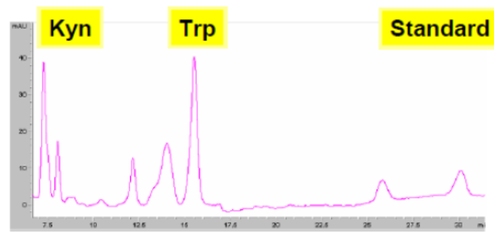






METHODS

IDO activity (Kyn/Trp)



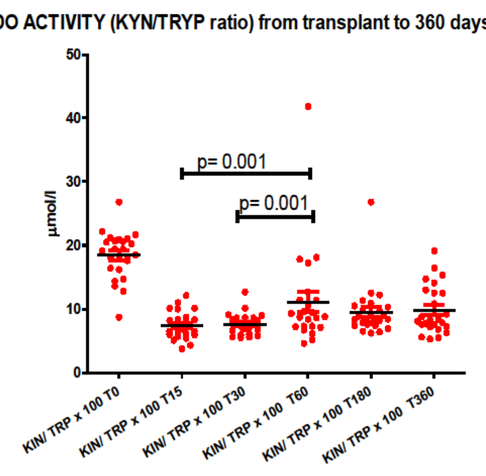
and IDO mRNA were investigated in 26 patients receiving cadaveric kidney transplant in parallel with Foxp3, IL17, Ror-C, TGFbeta, IL6 mRNAa. The percentage of Th17 and Tregs in the peripheral blood was evaluated using FACS analysis.

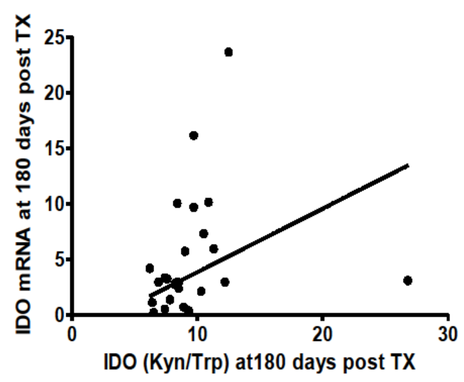
Sampling was at 0, 15, 30, 60, 180, 360 days after transplant. IDO activity was assessed in sera as Kyn/Trp ratio, simultaneously determined by isocratic RP-HPLC method withUV detection. Real time PCR (Taqman) was used to measure mRNAs normalized on Abelson housekeeping gene mRNA and expressed as fold increase.

RESULTS

IDO activity (Kyn/Trp ratio) decreases from T0 (19.1;IQR 16.3-20.8) to T30. (7.4;IQR 6.3-8.6) then increases again at T60 (8.8; IQR 7.2-11.) followed by stabilization until T360.

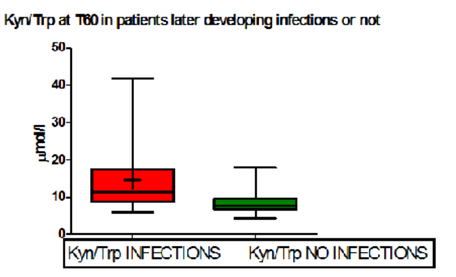
A significant correlation between IDO activity and IDO mRNA was observed at T60 (p=0.05) and T180 (p=0.02).
At T60 a significant increase of IDO activity vs T15 (p0.001) and T30 (p=0.01) and IDO mRNA expression was observed (p=0.02)



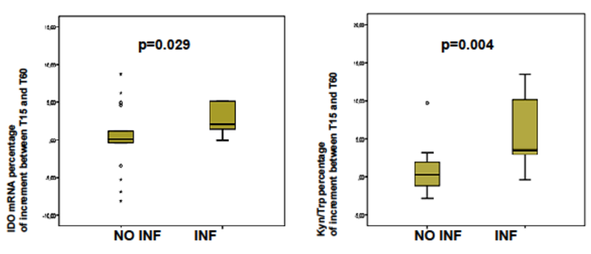


9/26 patients developed viral infections during follow-up (5 CMV after a median of 2 months, 3 BKV after 5 months, 1 HZV after 1 month).
Patients with infections (INF) had induction regimen (basiliximab and steroids) and tacrolimus through levels superimposable to those without infections (NONINF).
. At time of infection 6/9 pts were under MMF. No rejection episodes occurred before infections.
1/26 had CNI toxicity and subsequent BKV infection.

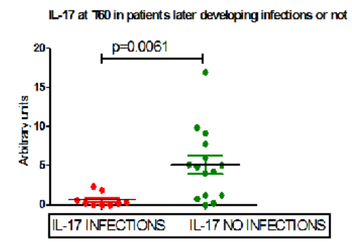
At T60 IDO activity was significantly different among INF versus NONINF (INF Kyn/Trp median 11,40;IQR 8,75-17.5, vs NONINF 7.85;QR 7-9.8 p<0.05).



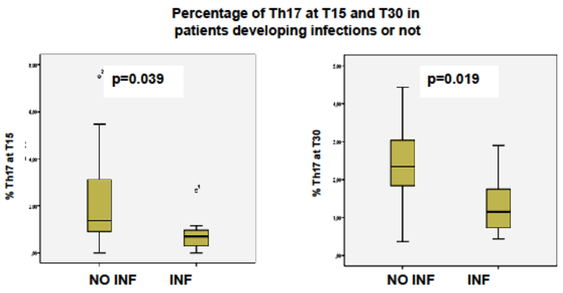
The increments of IDO mRNA and IDO activity between T15 and T60 were significantly higher in patients with INF versus NONINF (2,07±9 vs 0,07±4,43, p=0.029; 3,48±10,8 vs 0,29±3,3, p=0.004, respectively).



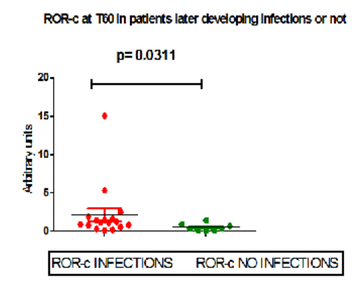
IL-17 was significantly reduced in INF (IL-17 INF 0,3;IQR 0.04-1,27 vs NONINF 4.89;IQR 1.2-7.7 p=0.006)



The percentages of peripheral Th17 were significantly lower in patients with INF versus NONINF at T15 and T30 (0.7 ± 0.67 vs 1.36 ± 2.34, p=0.039; 1.15 ± 0.74 vs 2.34 ± 1.24, p= 0.019, respectively)



Ror-C was significantly increased (Ror-C INF 1.23;IQR 0.7-1.7 vs NONINF 0.44;IQR 0.15-0.9, p=0.03).
No significant differences were found in the expression of Foxp3, TGF beta and IL6 mRNA and in the percentage of Tregs at T60 between the two groups.



CONCLUSIONS

IDO activity 60 days after transplant was significantly higher in patients who later developed viral infections, not correlated to other parameters of infection or of overimmunesuppression. Increased IDO activity and decreased IL-17 can be expression of an environment permissive to infections in transplanted patients and could represent a useful biomarker for infection prevention.

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