IMMUNE FUNCTION ASSAY (IMMUNKNOWTM) DROP OVER FIRST 6 MONTHS AFTER RENAL TRANSPLANT: A PREDICTOR OF OPPORTUNISTIC VIRAL INFECTIONS?

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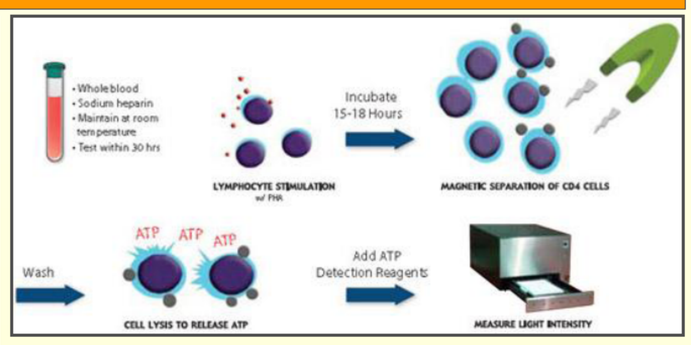
BACKGROUND and AIM

The immuknow assay (IKA) is a T-cell immune function assay which evaluates CD4+ T cell response to a non-specific mitogenic stimulus through quantification of intracellular ATP release.

In 2002 the United States Food and Drug Administration (FDA) approved it as a tool to assess cell-mediated immunoreactivity in immunocompromised patients.

While several small studies showed that IKA values are low during clinically evident infection, the role of IKA monitoring in the asymptomatic patients is still debated: two metanalysis provided conflicting results about its effectiveness as a screening tool to stratify patients according to their risk of infection or rejection.



The predictive value of single-point IKA testing is especially questioned (12), although low IKA values (<225ng/mL) were correlated with the risk of CMV and BKV reactivation.

On this basis we retrospectively analyzed trends in IKA values in a cohort of KTx patients observed over the first post-KTx six month in order to investigate correlations between low IKA values (< 225 ng/mL) and over-time trend of IKA values with the reactivation of CMV and BKV.

PATIENTS and METHODS

Study population.

Deceased-donor KTx between April 2010 and September 2012 (118 Caucasian KTRs, 55.6±11.9 years; Male 66.9%).

Patients with CMV seronegative status at time of KTx were excluded.

Induction : 91,5% Basiliximab (108/118); 8,5% rATG (10/118)

IS: TAC, MMF, st. (92.4%) or low-dose Cyclos., Everolimus, st. (7.4%)

Lab Measurements.

IKA determinations were performed at month 1, 3 and 6after surgery.

CMV and BKV PCR were analyzed at the same time (positive: viremia > 200 copies/mL)

The intracellular adenosine triphosphate activity (ATP) level was measured by a commercially available kit, (Immuknow®, Cylex Inc., USA).

IKA values were considered low when they were below 225 ng/mL, intermediate when they were between 225 ng/mL and 550 ng/mL and high when they exceeded 550 ng/mL.

Statistical Analysis.

Time dependent changes in IKA values were evaluated by means of variance analysis for repeated measures, in patients with and without positive viremia (either CMV or BKV).

Moreover we performed a ROC analysis to assess predictive value of the IKA value change between month 1 and 3 (IKA-delta) for a positive viremia at month 3; the most accurate cut-off value was the value with the highest Younden's index.

RESULTS - 1

Overtime changes of IKA values and viral reactivations

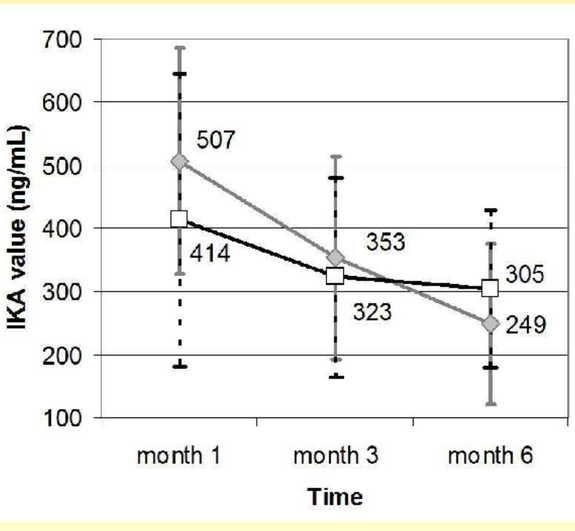
	Month 1	Month 3	Month6	Overall
IKA determinations	76	95	101	272
IKA value	422±184	330±159	300±128	-
IKA < 225 ng/mL	15,8% (n=12)	27,4% (n=26)	25,7% (n=26)	23,5% (n=64)
Positive CMV viremia	9,2% (n=7)	18,9% (n=18)	3,0% (n=3)	10,3% (n=28)
Positive BKV viremia	0	4,2% (n=4)	5,9% (n=6)	3,7% (n=10)
Any positive viremia	9,2% (n=7)	22,1% (n=21)	8,9% (n=9)	13,6% (n=37)
IKA in viremic pts.	507±232	353±158	249±125	-
IKA in NON-viremic pts.	414±179	323±160	305±127	-
Creatinine (mg/dL)	1.70±0.65	1.82±0.63	1.74±0.68	-

IKA values significantly decreased from month 1 to month 3 ($p < 0.001$) and between month 3 and 6 ($p=0.030$). There was no significant correlation between serum creatinine and IKA values at any of these time points. No CMV disease and no BKV nephropathy occurred within the observation period.

IKA values were below 225 ng/mL in 14.3% (1/7) patients with positive CMV-viremia at month 1 ($p=0.633$ vs non-viremic pts), in 27,8% (5/18) at month 3 ($p=0.687$ vs non-viremic pts) and 66.7% (2/3) at month 6 ($p=0.247$ vs non-viremic pts).

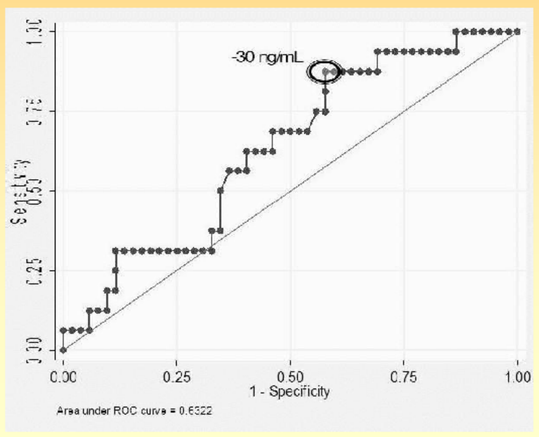
IKA values were below 225 ng/mL in 50% (2/4) patients with positive BKV-viremia at month 3 ($p=0.540$ vs non-viremic pts) and 50% (3/6) at month 6 ($p=0.363$ vs non-viremic pts).

Comparative analysis of over-time trend of IKA values revealed that IKA values significantly decreased over time significantly associated with IKA values. However patients with either CMV or BKV viremia had higher IKA values at month 1 and lower IKA values at month 6. As a consequence the mean decrease of IKA values between month 1 and 3 (IKA-delta) was -122±145 ng/mL in patients with a positive viremia at month 3 and -317± 106in patients with positive viremia at month 1 and 3; while in patients without viremia was -77±189 ng/mL ($p=0.115$).



RESULTS – 2

The ROC analysis of the IKA-delta variable for having a positive viremia (either BKV or CMV) at month 3 showed an area under the curve of 0.632 (95%CI 0.483-0.781; p = 0.067).



The most accurate cut-off value of **IKA-delta was -30 ng/mL**, having:

Sensitivity: 87.5% (95%CI: 64%-97%)
Specificity: 42.3% (95%CI: 30%-56%)
Pos. PV: 31.8% (95%CI: 20%-47%)
Neg. PV: 91.7% (95%CI: 74%-98%).

Therefore patients with a IKA drop exceeding 30 ng/mL between month 1 and 3 had a risk of 31.8% of having a positive viremia at month 3, as compared to 8.3% in patients with stable or increasing IKA values (OR= 5.13; 95%CI: 1.06-24.93; p=0.043).

CONCLUSIONS

1. IKA values frequently decline over the first six months after KTx.
2. ***Spot IKA values are not associated*** with either viral reactivation.
3. A trend of ***decreasing IKA values over time appears to be more pronounced in patients with a viral reactivation***.
   - Gralla et al showed a general pattern of reduction of IKA values between month 1 and 6 (with nearly 40% of pts with a decline > 150 ng/mL). BKV infection was associated with lower IKA values at 12 months, suggesting that a further significant decrease in immunoreactivity between 6 and 12 month increases the risk of OI.
   - This "dynamic" interpretation of IKA, if confirmed, may allow to overcome difficulty in finding an absolute threshold capable of predicting the risk for viral reactivation at a given time-point.
   - It is also possible that very low IKA values might be associated with viral reactivations because they may reflect a rapid drop from close-to-normal values and that this drop actually represents the "true" risk factor.
   - In a specular way, recent studies suggest that increase in IKA values can identify patients at risk for acute rejection.
4. Patients with a ***IKA drop (month 1-3) exceeding 30 ng/mL had a 5.1x risk of having a positive viremia*** at month 3.

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