THE VALIDATION OF TACROLIMUS DOSE PREDICTION ALGORITHM IN TUNISIAN KIDNEY TRANSPLANT POPULATION

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BACKGROUND

Optimal immunosuppression with tacrolimus (Tac) after kidney transplantation is a delicate balance between preventing rejection and avoiding adverse effects. Its narrow therapeutic margin and high interindividual variability require personnalisation of doses.

Aims: We aimed to validate a previously established linear regression algorithm at Sahloul university Hospital (UH) population to predict stable Tac dose, on La Rabta UH population.

PATIENTS ET METHODS

Study population

- ✓ Our retrospective study included kidney transplant recipients from:
  - * Sahloul University Hospital, Sousse (N=223)
  - * La Rabta University Hospital, Tunis (N=76).
- ✓ The validity of linear regression algorithm previously established at Sahloul population was tested on La Rabta population.
- ✓ We collected data on adverse effects and rejection.

Methods

- ✓ **PCR-RFLP** : Genotyping was performed for seven polymorphisms in the CYP3A5 (rs776746), CYP3A4 (rs2740574 and rs35599367), ABCB1 (rs1128503,rs2032582 and rs1045642), and POR (rs1057868)
- ✓ **SPSS26:** statistical analysis .

RESULTS AND DISCUSSION

Table 1: Characteristics of both studied population

Characteristics		La Rabta UH (N=76)	Sahloul UH (N=223)
Sex ratio (male/female)		2,04	1,90
Age (years) mean ± SD		37,18 ± 10,16	32,9 ± 13,2
BMI (kg/m²) mean ± SD		24,43 ± 4,61	23,1 ± 5,8
Hypertension n (%)		47 (79,66)	134 (60)
Diabetes n (%)		5 (8,47)	17 (7,6)
Induction Treatment	ATG n (%)	72 (94,74)	130 (58,2)
	Basiliximab n (%)	4 (5,26)	93 (41,7)
Maintenance Treatment	Tacrolimus n(%)	76 (100)	223 (100)
Type of donors	LRD n (%)	61 (80,26)	210 (94,1)
	ULD n (%)	9 (11,84)	-
	CD n (%)	6 (7,89)	13 (5,8)
Donor age (years) mean ± SD		44,16 ± 11,02	37,7 ± 15,36
HLA compatibility	≤ 3 n (%)	53 (69,74)	141 (63,2)
	>3 n (%)	23 (30,26)	82 (36,8)
Discharge creatinine level (µmol/L) median [min-max]		132,6 [61,88-689,5]	135 [33 – 1196]
Serum albumin (g/L) median [min-max]		40 [21 – 50]	35 [17 – 49]
Type of rejection	Acute rejection n (%)	17 (22,37)	51 (27,8)
	Chronic rejection n (%)	10 (13,15)	23 (12,5)

SD: Standard Deviation; **BMI** : Body Mass Index; **ATG:** Antithymocyte Globuline; **LRD**: Living Related Donor ; **ULR :** Unrelated Living Donor between couple; **CD :** Cadaveric Donor

The two populations are comparable for the majority of characteristics except for hypertension, diabetes, induction treatments, and types of donor. Despite these differences, the algorithm remains applicable.

Table 2: Allelic frequencies of studied polymorphisms in both populations

Polymorphisms	La Rabta University Hospital		Sahloul University Hospital	
	Allelic frequencies	p	Allelic frequencies	p
CYP3A5*3 (A6986G)	A (*1): 0,21 G (*3): 0,79	0.069	A (*1): 0,20 G (*3): 0,80	0.420
CYP3A4*1b (– 392 A>G)	A (*1): 0,17 G (*1B):0,83	0,529	A (*1): 0,20 G (*1B): 0,80	0,570
CYP3A4 *22 (15389 C>T)	C (*1) : 0,97 T (*22): 0,03	0,766	C (*1) : 0,07 T (*22) : 0,93	0,290
ABCB1 (1236 C > T)	C : 0,63 T : 0,37	0,876	C : 0,61 T : 0,39	0,339
ABCB1 (2677 G>A)	G : 0,94 A : 0,06	0,069	G : 0,67 A : 0,33	0,730
ABCB1 (3435 C > T)	C : 0,6 T : 0,4	0,553	C : 0,74 T : 0,26	0,240
POR*28 C>T	C : 0,62 T : 0,38	0,090	C : 0,66 T : 0,34	0,110

p: Hardy Weinberg equilibrium

- ✓ All polymorphisms are conform to Hardy-Weinberg equilibrium.
- ✓ The allelic frequencies are comparable between the two populations.
- ✓ The pre-establisehd linear regression-based algorithm for predicting the initial tacrolimus dose in our laboratory takes into account age, sex, BMI, CYP3A5*3 genotype and CYP3A4*1B genotype
- ✓ Applying the pre-establisehd to the La Rabta population, we found that the dose predicted by the linear regression algorithm (DPA) closely matched the achieved clinical steady-state (ACS) (0.0793±0.0388 vs 0.0795±0.0347, respectively; p=0.904). However, when comparing the initial dose (ID) originally prescribed by clinicians (ID=0.0846±0.025) and the ACS (0.0795±0.0347), we observed a significant difference (p=0.002) (Table 3).
- ✓ Reaching the steady-state dose takes from 10 days to 8 months, a period associated with a high risk of adverse effects and rejection, hence the importance of using a dose prediction algorithm.

Table 3: Comparison of doses and time to reach clinical steady state

	mean ± SD	P	Time to reach clinical steady state
ACS	0.0795±0.0347	-	75 [18-240] days
DLRA	0.0793±0.0388	0.904	-
ID	0.0846±0.025	0.002	-

Conclusion

Our initially developed algorithm underwent validation in a distinct tunisian region and it is now poised for refinement using machine learning in order to develop a high-performing application tailored to our population. The application of artificial intelligence could significantly enhance the lifespan of kidney transplant patients