Analysis of Immunobiogram pharmacodynamic dose-response curves to immunosuppressants in kidney transplant recipients: further results from TransBio Study

TTS2020 VIRTUAL

Abstract ID #604

Julio Pascual[1], Carlos Jiménez[2], Magdalena Krajewska[3], Daniel Seron [4], Camille Kotton [5], Jose María Portolés[6], Oliver Witzke[7], Soren Sorensen[8], Amado Andrés [9], Teresa Diez [10], Álvaro Ortega [10], Isabel Portero [10].

[1]Nephrology Department and Kidney Transplantation, H del Mar, Barcelona, Spain; [2]Nephrology Department, H La Paz, Madrid, Spain; [3]Department of Nephrology and Transplantation Medicine, Wroclaw Medical University, Poland; [4]Nephrology Department, H Vall d'Hebron, Barcelona, Spain; [5]Transplant Infectious Diseases Division, Massachusetts General Hospital, Boston , MA, United States; [6]Nephrology Department, H Puerta de Hierro, Madrid, Spain; [7]Department of Infectious Diseases, University Hospital Essen, University Duisburg-Essen, Essen, Germany; [8]Nephrology Department, Rigshospitalet, Copenhagen , Denmark; [9]Nephrology Department, H 12 de Octubre, Madrid, Spain; [10]Biohope Scientific Solutions for Human Health, Madrid, Spain

INTRODUCTION

Immunobiogram (IMBG) is a novel pharmacodynamic immune function assay developed by Biohope to measure **in vitro** the sensitivity profile of patient's lymphocytes when exposed to a panel of immunosuppressive drugs (IMS).

TRANSBIO is an international, multicenter study to evaluate IMBG in patients with a maintenance immunosuppressive treatment at least one year after Kidney Transplantation (KT); main study results have been presented elsewhere (1).

The sensitivity profile to each IMS tested is obtained from its dose/response curve and measured with Key Curve Parameters (KCP).

In this analysis, the dose-response curves obtained in the subsamples of patients treated with Mycophenolate (MPA) or with Tacrolimus (TAC) were analyzed to identify the KCP capable to predict clinical outcomes.

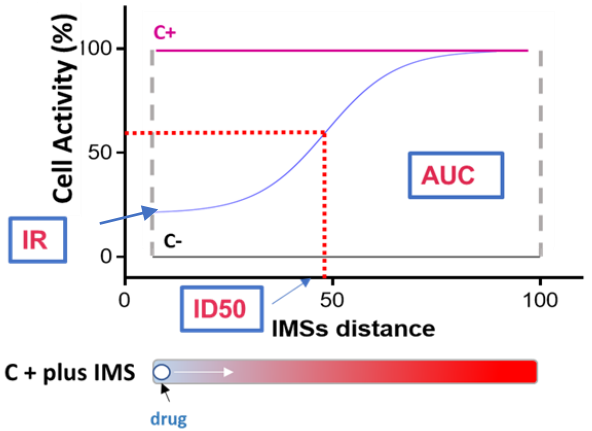
METHODS

IMBG test builds on the in-vitro measurement of the metabolic activity of immunologically activated PBMCs, in response to individual immunosuppressive drugs. It reveals the capacity of an IMS over a dose gradient to inhibit the activation & proliferation of lymphocytes through dose-response curves, mathematically analyzed by a software.

In TRANSBIO study IMBG results were compared between patients with a Bad-Clinical-Evolution (BCE) (with a progressive deterioration in renal function AND objective signs of immunological rejection in biopsy and/ or dnDSA strength) and a Good-Clinical-Evolution (GCE) (patients with no previous rejection episodes AND no dnDSA AND a stable renal function and IMS treatment for the last 12 months)

European Union Horizon 2020 Programme for Research and Innovation - SME instrument Phase 2 - Grant agreement Nº 733248.

IMBG Dose-response curve for each IMS



IMBG Key Curve Parameters (KCP)

- Initial Response (IR): Immunosuppresion at the higher IMS dosage
- Final Response (FR): Immunosuppresion at the lowest IMS dosage
- Area Under the Curve (AUC): Global Immunosuppresion
- ID50: IMS dosage at Half-Maximum inhibitory Response
- Slope

RESULTS

103 patients were included in the study, 53 with GCE and 50 with BCE. Baseline patients´ characteristics and treatment are described in Table 1 and 2.

In the subsample of patients taking MPA (n=85), 2-sample t test showed significant differences between mean values of IR, FR and AUC in patients with BCE vs GCE ($p<0.05$). For patients treated with TAC (n=85), there was a significant difference in ID50 mean values between patients with BCE vs GCE ($p<0.05$).

Table 1. Demographic, immunological and clinical patient characteristics	Good Clinical Evolution (N=53)	Bad Clinical Evolution (N=50)	p GCE vs BCE
Recipient age, mean (SD)	52.02 (11.09)	47.54 (12.03)	p > 0.05
Recipient gender, (% male)	29 (54.7 %)	30 (60 %)	p > 0.05
Recipient age in last KT, mean (SD)	43.53(12.06)	41.10 (13.84)	p > 0.05
Time since last KT in years, mean (SD)	8.42 (6.34)	6.40 (5.62)	p > 0.05
Previous transplantation (% patients)	4 (7.3%)	12 (24%)	**p < 0.05**
Previous acute rejection episodes (%)	0%	28 (56%)	NA
PreTransplant HLA mismatches, mean (SD)	3.59 (1.51)	4.10 (1.39)	p > 0.05
Post Transplant dnDSA (%)	0%	30 (60%)	NA
Elective Biopsy (% patients)	0%	40 (78%)	NA
Donor age > 60 years old (%)	4 (8.3%)	6 (12,5%)	p > 0.05
Donor age, mean (SD)	44.3 (13.9)	43,9 (15.87)	p > 0.05
Donor type (% living donors)	10 (18.9%)	7 (14%)	p > 0.05
Blood Creatinine level mg/dl, mean (SD)	1,23	2, 09	NA
Proteinuria > 300 mg/day	12 (22.6 %)	29 (58 %)	NA
eGFR (ml/min/1.73 m2) mean (SD)	61,7 (16.4)	38,25 (15.4)	NA

Table 2. Immunosuppressive treatment	Good Clinical Evolution (N=53)	Bad Clinical Evolution (N=50)	p GCE vs BCE
Induction therapy with timoglobulin) (%)	6 (13%)	23(46%)	**p < 0.001**
Treatment with Mycophenolate (%)	45 (85%)	40(80%)	p > 0.05
Treatment with Tacrolimus (%)	44 (83%)	41(82%)	p > 0.05
Treatment with Cyclosporine (%)	5 (9%)	9(18%)	p > 0.05
Treatment with Everolimus (%)	4 (7%)	6(12%)	p > 0.05
Treatment with Sirolimus (%)	2 (4%)	2(4%)	p > 0.05
Treatment with Steroids (%)	43 (81%)	48(96%)	**p < 0.05**
Treatment with Azathioprine (%)	2 (4%)	1(2%)	p > 0.05
Treatment with 2 IMS (%)	14 (26.4 %)	3 (6 %)	**p < 0.01**
Treatment with 3 IMS (%)	39 (73.6 %)	47 (94 %)	**P < 0.01**

In the logistic regression analysis, IR, FR and AUC for patients treated with MPA and ID50 for the ones treated with TAC were significantly associated with a worse prognosis ($p<0,05$).

When adjusted for simultaneous corticosteroids intake as confounding factor, IR and AUC for MPA and ID50 for TAC remained significantly associated with prognosis (Table 3)

Table 3: OR for key curve parameters by IMS (BCE vs GCE) adjusted by steroids treatment

	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B) Lower	Upper
IR_MPA	4,224	1,946	4,711	1	0,03	68,3	1,506	3097,38
IMS_STE	-1,866	0,849	4,823	1	0,028	0,155	0,029	0,818
Constant	0,868	0,997	0,758	1	0,384	2,382		
AUC_MPA	5,023	2,319	4,691	1	0,03	151,922	1,612	14315,937
IMS_STE	-1,638	0,823	3,957	1	0,047	0,194	0,039	0,976
Constant	-2,484	2,147	1,338	1	0,247	0,083		
FR_MPA	4,175	2,345	3,17	1	0,075	65,039	0,657	6442,87
IMS_STE	-1,525	0,819	3,471	1	0,062	0,218	0,044	1,083
Constant	-2,868	2,746	1,09	1	0,296	0,057		
ID50_TAC	-1,172	0,498	5,549	1	0,018	0,31	0,117	0,821
IMS_STE	-2,392	1,123	4,535	1	0,033	0,091	0,01	0,827
Constant	9,052	3,176	8,125	1	0,004	8533,85		

DISCUSSION

The Key Curve Parameters (KCP) obtained from IMBG dose-response curves for MPA and TAC are significantly associated with the clinical outcomes, which probably is capturing the effect of medication over causality.

There is a different profile in the KCPs most informative for MPA and TAC, what can be linked to a diverse impact of these drugs over lymphocytes proliferation (MPA) or activation (TAC) (2)

Pharmacodynamic models should always be adjusted for corticosteroids intake.

CONCLUSIONS

In kidney transplanted patients, the dose-response curves of the inhibitory effect of immunosuppressive drugs over patients´ lymphocytes proliferation and activation obtained in vitro with IMBG are significantly associated with the clinical outcome.

Different curve parameters are better descriptors of this association depending on the immunosuppressive drug, what could be linked with their mechanism of action.

[1] Pascual J et al. Analytical robustness and clinical consistency evaluation of a new in vitro diagnostic biotechnological immunoassay to help decision-making in adjustment of immunosuppressant therapy for kidney transplantation: TRANSBIO STUDY. *Transplant International* 2019; 32(Suppl. 2): 279–319
[2] Fallahi-Sichani M et al. Metrics other than potency reveal systematic variation in responses to cancer drugs. *Nat Chem Biol.* 2013 Nov; 9(11): 708–714.