# Immunobiogram, a New In Vitro Diagnosis (IVD) Immunoassay to Test the Sensitivity Profile of Kidney Transplant Recipients to Immunosuppressive Drugs: Further Results From BH-pilot Study

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## INTRODUCTION

Patients with Kidney Transplantation (KT) have a persistent risk of graft rejection. To limit this risk they require long term treatment with immunosuppressive drugs (IMSs). IMSs regimens are currently established based on guidelines and empirically.

Immunobiogram (IMBG) is an IVD Immunoassay developed by Biohope (BH) to measure the PBMCs sensitivity profile of each patient to a panel of IMSs in KT recipients, with the goal to help clinicians to adequate IMSs treatment.

## OBJECTIVES

- To develop a semiautomatic model for the data interpretation of IMBG results that allow to evaluate IMBG dose/response curves to IMSs and to qualify patients´ sensitivity /resistance profile to each IMS tested.

- To perform a segmentation analysis of patients based on the in vitro response integrating biologic and clinical data.

## METHODS

IMBG is based on PBMCs 3D culture in semi-solid matrix submitted to immune stimulation. IMBG reveals the capacity of an IMS gradient to inhibit the activation of immune cells, which can be translated into a dose/response curve. 7 IMSs are tested (*Di Scala M et al 2018*)

BH-pilot study included 70 KT patients. The 60 patients classified as **high-risk (HR), standard (SP) or low immunological risk patients (LR)** based on renal function and immunological criteria and with a valid IMBG using restrictive criteria were included in the analysis.
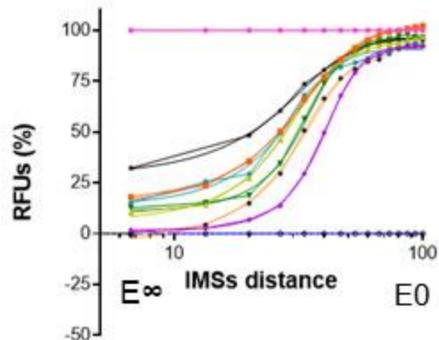


**Key curve parameters** (KPI): ID50, AUC (Area under the curve), slope and response at maximal (E∞) or minimal (E0) IMS concentration points.

For each patient and IMS all KPIs were analyzed to generate a score and compared against the average of the study population and based on this comparison the level of patient sensitivity was determined (mathematical score). An expert-based independent evaluation of all IMSs responses per patient was also performed.
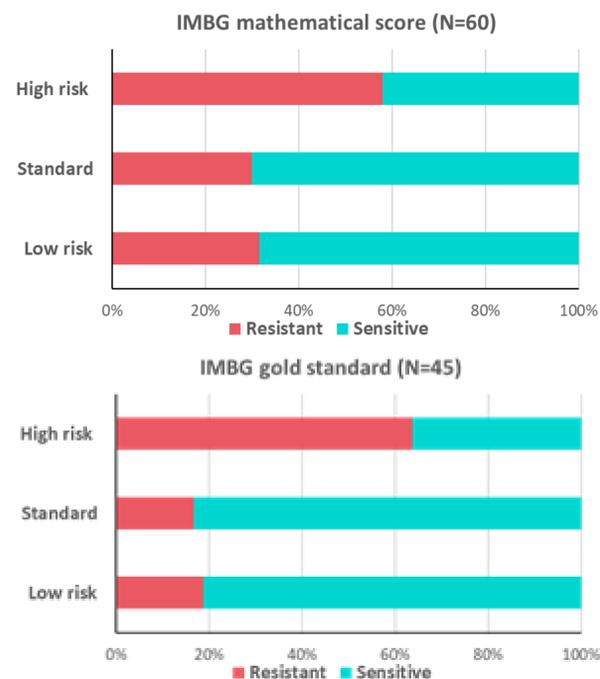
## RESULTS

### Demographic, immunological and clinical patient characteristics

|  | Low Risk N=21 | Standard N=20 | High risk N=19 |
|---|---|---|---|
| **Recipient characteristics** | | | |
| Age (mean, CI 95%) | 63 (56.4-69.6) | 57.2 (52.1-62.3) | 48.1 (40.4-55.8) |
| Gender (male) (% patients) | 52% | 65% | 63% |
| Time since last KT(months,mean CI 95%) | 21,50 (18.1-24.9) | 6,35 (4.65-8.06) | 4,95 (3.58-6.33) |
| Previous transplantation (%) | 0% | 10% | 58% |
| Previous acute rejection episodes (%) | 0% | 0% | 68% |
| PreTransplant No. HLA mismatches (mean) | 3.3 | 4.05 | 4.37 |
| PreTransplant HLA mismatches ≥ 3 (%) | 67% | 80% | 95% |
| PostTransplant dnDSA (%) | 0% | 0% | 89% |
| Elective Biopsy (%) | 0% | 5% | 74% |
| Abnormal Biopsy | | 5% | 68% |
| Biopsy with graft rejection findings (%) | | 0% | 68% |
| **Donor characteristics** | | | |
| Donor age (mean, CI 95%) | 37.5 (28.7-46.4) | 51 (45.4-56.5) | 44.9 (39.3-50.6) |
| Donor type- Deceased (%) | 90% | 85% | 89% |
| **Kidney Function** | | | |
| Blood Cr level ≥ 1,5 mg/dl (%) | 4% | 25% | 68% |
| Proteinuria ≥ 500 mg/day (%) | 42% | 15% | 42% |
| eGFR (ml/min/1.73 m$^2$) ≤ 50 (%) | 9,50% | 35% | 63% |

| Immunosuppressive treatment | | | |
|---|---|---|---|
| Mean number of IMS (mean CI 9%) | 1.86 (1.69-2.02) | 2.70 (2.48-2.52) | 3 (2.80-3.16) |
| Treatment with MMF | 2% | 80% | 90% |
| Treatment with tacrolimus | 9% | 80% | 95% |
| Treatment with ciclosporin | 24% | 5% | 5% |
| Treatment with an mTOR inhibitor | 62% | 25% | 5% |
| Treatment with corticosteroids | 62% | 75% | 100% |
| Treatment with azathioprine | 24% | 0% | 0% |

With the mathematical score, 58% of HR patients showed a low sensitivity profile in IMBG (resistance at least at one of the IMS that the patient was taking). 71% of LR showed a high sensitivity profile in IMBG (sensitivity to all IMSs that the patient was taking) (NS).

In a "gold standard" set of patients (in which both mathematical and expert evaluation delivered equal results (full agreement), 63% of HR had an IMBG resistant profile and 83% of LR had a sensitive profile (N=45, Chi-squared = 6.4375 p = 0.040)



IMBG mathematical score (N=60)



IMBG gold standard (N=45)

Segmentation analysis used the IMBG curves as a basis for patient classification. Key KPIs were **Initial Response** (E∞) and **Global Response** (AUC).

Results of the segmentation analysis were shown in distribution maps, where IMBG results per IMS was segmented into 4 quadrants, taking the median and the quartiles Q1/Q3 to divide them:
- **R**: Resistant (with a bad IR and GR)
- **S**: Sensitive (with a good IR and GR)
- **Sp**: (Sprinter) (with a good IR and a bad GR)
- **M**: (Maintenance) (with bad IR and good GR)
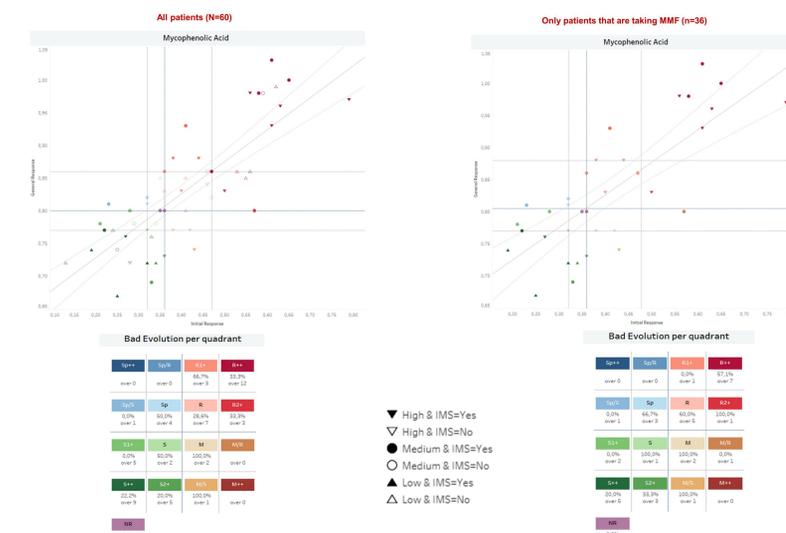


## CONCLUSIONS

IMBG outcomes can be automatically read to qualify patients´ sensitivity /resistance profile to each IMS tested. IMBG, taken together with other variables, may help physicians to adequate the immunosuppressive therapy of each individual patient with KT

## REFERENCES

1. Hirano T. et al. Cellular pharmacodynamics of immunosuppressive drugs for individualized medicine. International Immunopharmacol 2007; 7: 3-22

2. Di Scala M et al. Immunobiogram, a new tool to personalize immunosuppressive therapy in kidney transplant recipients. Basic Science Transplantation BST18,Rotterdam.