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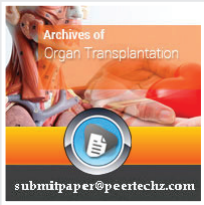

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Case Report

Safe immunosuppression. New tool for personalized immunosuppressant treatment in renal transplantation. A case report

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Abstract

Background: The adjustment of immunosuppressive therapy after kidney transplantation (KT) to avoid graft rejection remains an important challenge for clinicians. It is difficult to achieve a good balance between under-immunosuppression (with an increased risk of graft rejection) and over-immunosuppression (with an increased risk of side effects) by only relying on the available information about immunosuppressive drugs (IMS).

Immunobiogram® (IMBG) is a novel in vitro diagnostic test that provides clinicians with information about the patient's sensitivity to individual IMS.

Objective: To present a case report of a patient with renal transplant in the maintenance phase who presented several complications probably related to the immunosuppression during the follow-up, where the use of IMBG as complementary information helped clinicians to guide the therapeutical decision.

Methods: IMBG is a first-in-class in vitro immunoassay that involves the culture of the patient peripheral blood mononuclear cells (PBMCs) in a semi-solid 3D matrix, then submitted to immune stimulation. It reveals the capacity of an IMS over a gradient to inhibit the activation of immune cells. The read-out allows the building of a dose-response curve per IMS tested, which is mathematically analyzed by a software using the key curve parameters and finally to be translated into a sensitivity map to IMS.

Findings: We present a case report of a 72-year-old patient with a cadaveric donor kidney transplant receiving standard immunosuppressive treatment with mycophenolate, tacrolimus, and corticosteroids. The patient presented several episodes of infections during the follow-up (SARS-CoV2, Cytomegalovirus, spondylodisquitis by *Staphylococcus aureus*, and emphysematous cystitis) which were managed with different treatment adjustments such as de-escalation of mycophenolate and switching to mTOR. The information provided by the IMBG showed a lack of sensitivity to mTOR which allowed to confirm the final adjustment to a treatment with tacrolimus and corticosteroids, remaining the patient stable since then.

Discussion: Despite various adjustments to the immunosuppressive therapy during the follow-up, the patient continued experiencing adverse effects that could be related to an over-immunosuppression state. The IMBG provided pharmacodynamic information that complemented the clinical and pharmacokinetic data available, facilitating the individualization of the treatment.

Conclusion: The case highlights the potential of the IMBG as a complementary clinical tool for personalized treatment of kidney transplant patient management.

Introduction

One of the main challenges that clinicians face during kidney transplantation (KT) follow-up is to accurately balance the risk of graft rejection while minimizing the incidence of side effects related to immunosuppressive therapy, such as opportunistic infections or cancer [1].

The immunosuppressive treatment in KT patients is based on a combination of immunosuppressive drugs (IMS) with different mechanisms of action. In clinical practice, treatment is adjusted empirically by clinicians following clinical guidelines, based on the patient's rejection-risk profile and time since transplant and taking into account the incidence of adverse events related to immunosuppression [2].

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When clinicians have to tailor immunosuppression during the patients´ post-transplant management, they have information about IMS plasma levels but not about the individual patient response to the different drugs available for the treatment. Therefore, there is an unmet need for pharmacodynamic biomarkers to help guide treatment choices and dosages [3].

IMBG is a novel in vitro diagnostic (IVD) that provides clinicians with valuable, complementary information about the patient's response to individual immunosuppressive drugs.

Here we present a case of a 72-year-old male patient with End Stage Renal Disease (ESRD), who received a renal transplant and presented several complications related to the immunosuppression regime during the follow-up. The IMBG test was carried out to complement the clinical and pharmacokinetic information of the patient.

Case description

A 72-year-old male patient with ESRD secondary to chronic tubulointerstitial nephropathy received in September 2017 a kidney cadaveric transplant 5/6 ABDRDQ HLA mismatch. He received basiliximab induction and maintenance immunosuppression with tacrolimus, mycophenolate mofetil (MMF), and prednisone. The patient continued in the same immunosuppressive regimen until July 2022 when he presented a SARS-CoV2 infection. At this point, an impairment in kidney function was observed, and an acute rejection was suspected, so intravenous methylprednisolone bolus was administered. Some days later, Cytomegalovirus (CMV) replication was detected and MMF was withdrawn until the infection was controlled. He was discharged from the hospital with an immunosuppressive regimen of tacrolimus (serum levels 5.4 ng/ml), MMF 500 mg every 12 hours, and prednisone 5 mg per day.

In October 2022 the patient was admitted to the hospital due to a CMV infection-related digestive hemorrhage. During admission, a solid soft tissue tumor of lipomatous lineage was also detected located in the extension compartment of the elbow and proximal forearm. It was decided to modify his IMS regimen making a switch from MMF to mTOR (everolimus), but nevertheless maintaining a triple-drug scheme. At discharge, tacrolimus and everolimus serum levels were 6.9 ng/ml and 4.1 ng/ml and he was maintained with prednisone 5 mg per day.

The patient presented further complications in December 2022, namely a spondylodiscitis L4-L5 secondary to *Staphylococcus aureus* and an emphysematous cystitis.

Regarding kidney function, the patient presented plasma creatinine levels of 2.6 mg/dl, creatinine clearance at 23 ml/min, and proteinuria of 1.5 g per day, which increased to almost nephrotic range following initiation of everolimus treatment.

Based on both, the observed multiple infectious and neoformations development, we suspected an over-immunosuppressive status. To evaluate IMS sensitivity to the prescribed drugs an IMBG was performed and everolimus was withdrawn.

IMBG is a novel in vitro diagnostic (IVD) tool developed and manufactured by the company Biohope Scientific Solutions for Human Health SL, based in Spain. It provides clinicians with pharmacodynamic information on the in vitro sensitivity to individual IMS in renal transplant patients during the maintenance phase [4].

The IMBG test is performed on isolated peripheral mononucleare cells (PBMC) from a simple, standard blood venous sample. It allows a semi-quantitative determination of the metabolic activity of mononuclear peripheral blood cells in response to authorized immunosuppressive drugs. The product consists of a fluorescence assay on lymphocytes from peripheral blood samples and a software that analyses, processes, and interprets the results, giving information on drug sensitivity [4].

IMBG is based on a 3D-cell culture assay where PBMCs are embedded in a semi-solid matrix and loaded in the longitudinal channels of a plate. At the end of each channel, there is a disk preloaded with a predetermined and constant concentration of each immunosuppressant tested. The IMBG assay is designed to simultaneously test the following IMS: mycophenolic acid, tacrolimus, methylprednisolone, sirolimus, and everolimus. The immunosuppressant diffuses along the channel and inhibits the activation/proliferation of T lymphocytes according to the level of sensitivity of each patient to the immunosuppressant. Using a fluorometer validated for diagnosis and a vital probe, the metabolic and proliferative activity of the PBMCs of the patients exposed to the battery of drugs is analysed in relation to two controls: a positive activation control (stimulated PBMCs not exposed to IMS) and a blank control. The fluorescence signal is measured at 15 points (raw data) along the channel for each immunosuppressant. The data is processed and interpreted by a specific software that calculates the parameters that describe the dose/response curves on the panel of IMS tested for each patient and qualifies their sensitivity profile to each IMS [4].

The IMS doses used in vitro in the IMBG are not comparable to physiological doses. The IMBG collects pharmacodynamic information on the patient's response to each IMS in vitro, and this response has been found to be associated with clinical outcomes [5]. It does not provide information on the effect of the dose taken by the patient. What has been observed is that the pharmacodynamic effect of the IMS on immune cells changes along the in vitro concentration gradient.

A z-score for each IMS is calculated based on the mean and standard deviations of the dose-response curve parameters obtained for each drug when compared to a reference population of renal transplant patients in the maintenance phase. The reference population included a wide range of patients over 18 years old. The results are plotted in a z-score box indicating the patient´s relative sensitivity to each IMS by means of standard deviations (SD) in relation to the reference population [6].

These results offer a clear map of the level of sensitivity of the patient's immune cells to the five IMS tested. A z-score value of 0 indicates no deviation from the average response observed in a representative sample of renal transplant

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recipients. Values below or above 0 indicate how the patient deviates from the normal distribution of the population mean. Therefore, a positive z-score value indicates higher sensitivity of the patient's immune cells to the drug compared to the population mean. While a negative z-score value indicates lower sensitivity to the drug compared to the population mean [6].

The IMBG results for this patient are shown in the Table 1.

For this case report the results obtained indicated a very close to average sensitivity to the drugs mycophenolate, tacrolimus, and steroids, and a clear well below average sensitivity for everolimus (z-score = -1.6 SD).

The IMBG readout indicated that, on the one hand, the use of everolimus (z-score negative -1.6) was likely, not efficacious and could potentially be the source of the observed adverse events and, on the other hand, that the main contribution to protection against rejection was from tacrolimus and prednisone. Therefore, a dual IMS regime based on tacrolimus and prednisone could be a better choice for this patient.

Currently, the patient is maintained under tacrolimus and prednisone. He has not presented new opportunistic infections, his kidney function is stable, and proteinuria has decreased.

Discussion

Immunosuppressive drugs are widely used to prevent rejection in organ transplant recipients. However, the clinical efficacy of immunosuppressants varies considerably between individuals.

In this case, despite various adjustments to the immunosuppressive therapy during the follow-up, the patient continued experiencing adverse effects that could be related to an over-immunosuppression state. The IMBG pattern of this patient showed a low sensitivity to everolimus. We hypothesize that the mTOR inhibitor drug may be adding adverse events, while not contributing as much as tacrolimus or prednisone to prevent rejection. Thus, it was conceivable to give a try to a dual immunosuppressive regimen based on tacrolimus and prednisone.

Previous studies have described the use of PBMC functional assays to evaluate the individual pharmacodynamics in renal transplant patients receiving immunosuppressive therapy, but they do not allow to test simultaneously the patient's sensitivity to a battery of immunosuppressants and they are not available for use in clinical practice [7,8].

Some molecular biomarkers can estimate the probability of graft rejection (e.g. donor-derived cell-free DNA, RNA in blood and urine, gene expression assays). Others can assess the patient's global immunosuppression status (e.g. ELISPOT, Immuknow). However, there is a lack of biomarkers that predict the pharmacodynamic response to specific drugs in routine clinical practice [9].

IMBG is intended to fulfill the unmet clinical need for effective diagnostic tools that can help clinicians tailor immunosuppression therapy to the sensitivity profile of the individual patient. Therefore, IMBG can provide clinicians with valuable information on a given patient's likely response to a range of immunosuppressants, based on which they can evaluate dose adjustments of the patient's current immunosuppressant regimen or alternative treatment options.

Table 1: Immunobiogram report. Map of the sensitivity determined to individual IMS.

IMMUNOBIOGRAM

CURRENTLY PRESCRIBED IMMUNOSUPPRESSANTS

Mycophenolate	Tacrolimus	Steroids	Sirolimus	Everolimus
NO	**YES**	**YES**	NO	**YES**

RESULTS

SENSITIVITY TO INDIVIDUAL IMMUNOSUPPRESSANTS

Z-SCORE	Mycophenolate	Tacrolimus	Steroids	Sirolimus	Everolimus
3					
2					
1					
0	0,2		0,6	0,1	
-1		-0,7			
-2					-1,6
-3					

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Conclusions

Improvement of patient outcomes in renal transplantation depends on the development of new tools and strategies to help physicians personalize immunosuppressive therapy with the goal of preventing graft rejection, decreasing adverse events related to immunosuppression, and extending patient survival.

The Immunobiogram test can provide clinicians with key, relevant information about the patient´s response to individual immunosuppressive drugs.

The case presented highlights the potential of the Immunobiogram as a complementary clinical tool for personalized treatment of kidney transplant patients' management.

References

1. Hariharan S, Israni AK, Danovitch G. Long-Term Survival after Kidney Transplantation. N Engl J Med. 2021 Aug 19;385(8):729-743. doi: 10.1056/NEJMra2014530. PMID: 34407344.

2. Baker RJ, Mark PB, Patel RK, Stevens KK, Palmer N. Renal association clinical practice guideline in post-operative care in the kidney transplant recipient. BMC Nephrol. 2017 Jun 2;18(1):174. doi: 10.1186/s12882-017-0553-2. PMID: 28571571; PMCID: PMC5455080.

3. Neuberger JM, Bechstein WO, Kuypers DR, Burra P, Citterio F, De Geest S, Duvoux C, Jardine AG, Kamar N, Krämer BK, Metselaar HJ, Nevens F, Pirenne J, Rodríguez-Perálvarez ML, Samuel D, Schneeberger S, Serón D, Trunečka P, Tisone G, van Gelder T. Practical Recommendations for Long-term Management of Modifiable Risks in Kidney and Liver Transplant Recipients: A Guidance Report and Clinical Checklist by the Consensus on Managing Modifiable Risk in Transplantation (COMMIT) Group. Transplantation. 2017 Apr;101(4S Suppl 2):S1-S56. doi: 10.1097/TP.0000000000001651. PMID: 28328734.

4. Portoles JM, Jimenez C, Janeiro D, Lopez-Oliva MO, Ortega-Carrion A, Blanquez D, Arribas L, Gomez C, Diez T, Pascual J, Portero I. The Immunobiogram, a Novel In Vitro Assay to Evaluate Treatment Resistance in Patients Receiving Immunosuppressive Therapy. Front Immunol. 2021 Jan 25;11:618202. doi: 10.3389/fimmu.2020.618202. PMID: 33569062; PMCID: PMC7868528.

5. Pascual J, Jiménez C, Krajewska M, Seron D, Kotton CN, Portolés J, Witzke O, Sorensen SS, Andrés A, Crespo M, Paz-Artal E, Díez T, Ortega A, Portero I. The Immunobiogram, a novel in vitro diagnostic test to measure the pharmacodynamic response to immunosuppressive therapy in kidney transplant patients. Transpl Immunol. 2022 Dec;75:101711. doi: 10.1016/j.trim.2022.101711. Epub 2022 Sep 9. PMID: 36096417.

6. Pascual J, Crespo M, Portoles J, Jimenez C, Ortega-Carrion A, Diez T, Portero I. The IMBG Test for Evaluating the Pharmacodynamic Response to Immunosuppressive Therapy in Kidney Transplant Patients: Current Evidence and Future Applications. Int J Mol Sci. 2023 Mar 8;24(6):5201. doi: 10.3390/ijms24065201. PMID: 36982276; PMCID: PMC10049381.

7. Hirano T. Cellular pharmacodynamics of immunosuppressive drugs for individualized medicine. Int Immunopharmacol. 2007 Jan;7(1):3-22. doi: 10.1016/j.intimp.2006.09.020. Epub 2006 Oct 23. PMID: 17161812.

8. Kurata Y, Kato M, Kuzuya T, Miwa Y, Iwasaki K, Haneda M, Amioka K, Watarai Y, Uchida K, Nakao A, Kobayashi T. Pretransplant pharmacodynamic analysis of immunosuppressive agents using CFSE-based T-cell proliferation assay. Clin Pharmacol Ther. 2009 Sep;86(3):285-9. doi: 10.1038/clpt.2009.61. Epub 2009 Apr 29. PMID: 19404248.

9. Danger R, Sawitzki B, Brouard S. Immune monitoring in renal transplantation: The search for biomarkers. Eur J Immunol. 2016 Dec;46(12):2695-2704. doi: 10.1002/eji.201545963. PMID: 27861809.

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