Economic evaluation of the personalisation of immunosuppressive therapy in kidney transplantation by means of an in vitro diagnostic test (Immunobiogram®) in Spain

CARLOS JIMÉNEZ MARTÍN[1], JOSÉ MARÍA PORTOLÉS[2], MARTA CRESPO[3]. CARLOS RUBIO-TERRÉS[4], DARÍO RUBIO-RODRÍGUEZ[4], TERESA DÍEZ[5], ISABEL PORTERO SÁNCHEZ[5]

[1]La Paz University Hospital, Madrid, Spain. [2]Puerta de Hierro University Hospital, Majadahonda (Madrid), Spain. [3]Hospital del Mar Barcelona, Spain. [4]Health Value, Madrid, Spain. [5]Biohope, Madrid, Spain.

Abstract

Objective: Immunobiogram (IMBG) is an in vitro diagnostic immune function bioassay that evaluates the pharmacodynamic immune response profile of each patient to individual immunosuppressants (IMS) in renal transplant. The objective was to estimate the potential economic and health impact of the use of IMBG for the Spanish National Health System (NHS).

Methods: The evolution of a cohort of patients with kidney transplantation at least 1 year after transplantation (time horizon of 5 years) was simulated using a second-order Monte Carlo simulation for two scenarios: renal failure in patients with high immunological risk (HR), and adverse events (AE) in stable patients (non-HR). The transition probabilities were obtained from a clinical study with IMBG and a systematic review. The cost associated with graft failure (dialysis, re-transplantation), IMS and AE management were obtained from Spanish sources.

Results: IMS adjustment, according to the IMBG could contribute to a risk reduction of graft failure with a saving per HR patient of €20,263 (95% CI €17,520-23,678) (100% saving probability). The expected reduction in the AE rate would generate savings per non-HR patient of €1,409 (95% CI €41-3,316) (97.8% saving probability). Compared with the option of not using IMBG, 0.5256 (95% CI 0.3388, 0.7452) years of life and 0.0219 (95% CI 0.0115; 0.0356) quality-adjusted life years (QALY) would be gained in each patient evaluated with IMBG.

Conclusions: IMBG could contribute to a risk reduction of graft failure and AEs related with IMS, with gain in years of life and QALY, as well as with considerable savings for the NHS.

Key words: diagnosis; Immunobiogram; kidney transplantation; personalized medicine; rejection.

INTRODUCTION

Kidney transplantation is the treatment of choice for patients with end-stage renal disease, because it improves short- and long-term survival compared to dialysis[1]. A study in Ireland observed a 47% reduction in mortality over 5 years in kidney transplantation patients compared to dialysis waiting list patients[2].

Rejection and infection are the most important complications after solid organ transplantation[3]. To reduce the risk of rejection (graft failure), kidney transplantation patients require long-term treatment with immunosuppressive therapy (IMS)[4].

Currently, IMS regimens are based on the recommendations from the international clinical practice guidelines[4-6]. The treatment is fundamentally performed based on the patient's immunological risk profile, the plasma levels of some IMS and the tolerance to the treatment. However, biomarkers of the pharmacodynamic response to individual IMS that could help nephrologists establish personalized treatments for each patient are not yet available. Individualization of IMS therapy is a necessity, and various models and programmes are being developed to that end[7,8].

Costs associated with renal graft rejection are very high. The cost in Spain updated to 2019 of haemodialysis and peritoneal dialysis is estimated at €46,000 and €35,659, respectively[9]. The estimated cost of the re-transplantation would amount to €45,384[10].

Autor para correspondencia

Darío Rubio Rodríguez. Health Value.
Health Economics & Research of Outcomes Consulting.

C/ Virgen de Aránzazu, 21. 5º B.
28034 - Madrid.

Telephone number: +34 917293503.

Email: drubiorodriguez@healthvalue.org.

Immunobiogram® (IMBG) is an immunological function bioassay, based on the antibiogram concept, performed using an in vitro culture of peripheral blood mononuclear cells (PBMCs)[11]. This in vitro diagnostic bioassay, which combines a biotechnology test and a data interpretation program, will help physicians select the most appropriate IMS and IMS doses for each kidney transplant patient. The IMBG allows to know in vitro the sensitivity profile of each patient to the different IMS drugs used in kidney transplantation to avoid graft rejection. The test is performed on a blood sample of the patient. In the IMBG the isolated immune cells are activated and exposed to different immunosuppressive drugs to measure the ability of each IMS to inhibit the activation and proliferation of immune cells in each patient. Using a fluorescence-emitting reagent, the inhibition along a concentration gradient of IMS can be quantified, and a dose-response inhibition curve of each IMS can be described for each patient. This results in a profile of greater or lesser sensitivity to the different drugs used, which is different in each individual. It is a system of low technical complexity, which could be used as a routine method in hospitals.

The BH-Pilot 2015 is a proof-of-concept (PoC) study in kidney transplant patients, which analysed IMBG results in 70 kidney transplant patients at least 1 year after transplantation (maintenance period of immunosuppression). These patients were classified into three categories based on an immune risk assessment: (i) HR patients (with a history of rejection, positive HLA antibodies or impaired renal function, or combinations of the above criteria); (ii) controlled patients (who maintain good graft function with conventional maintenance immunosuppression); and (iii) low immune risk patients (with no immune risk criteria and stable immunosuppressive therapy, with low levels of IMS for years) (non-HR)[11]. According to the results of this study, performed in Spain, 55% of patients with HR would be resistant to at least one of the IMS they were being treated and 78% of stable, non-HR patients would be sensitive to all IMS (66% when taking together non-HR and controlled patients), allowing for a dose adjustment that would lead to a hypothetical reduction in the incidence of rejection or the rate of adverse events (AE) respectively. This study revealed an association between the sensitivity of individual patients to the IMS regimen and their immunological risk of transplant rejection. According to this study, incorporation of the IMBG assay into clinical settings could facilitate personalized optimization and monitoring of IMS therapy[12].

The study objective was to estimate the economic and health impact for the Spanish National Health System (NHS) of the use of Immunobiogram in patients with kidney transplants, at least one year after the transplant, and in treatment with IMS.

METHODS

Patient population

We simulated the evolution of a cohort of 1,000 hypothetical patients, at least one year after kidney transplantation and on maintenance treatment with IMS.

Time horizon

The simulation was conducted for a period of 5 years. This was considered to be the time needed to capture all the modelled effects (graft failure, dialysis, re-transplantation, adverse events) according to the opinion of clinical experts.

Perspective of the study

In the base case, the study was conducted from the perspective of the NHS, so only direct health costs were considered. A sensitivity analysis was carried out, from the societal perspective, including the work costs linked to graft rejection.

Type of model and methodology

A cost and effects analyses were performed. A probabilistic model was made for the indicated patient cohort, using a second-order Monte Carlo simulation. The methodology used in this model has been previously described[13-16]. The model probabilities were adjusted to beta distributions and the costs to gamma distributions[17-19].

Structure of the model

Two scenarios were considered: (i) graft failure in high immunological risk (HR) patients (Figure 1) and (ii) the occurrence of AE in stable (non-HR) patients with possible adjustment of IMS doses (Figure 2). In the first scenario (Figure 1), at least one year after kidney transplantation, the patient with HR may or may not be resistant to IMS depending on the result obtained with the IMBG test. If resistance is detected, the dose or IMS selection may or may not be adjusted according to the result of the diagnostic test, and the graft may or may not fail. If this occurs, dialysis and/or re-transplantation would be required. The patient may die at any time during the simulation with or without rejection. In the second scenario (Figure 2), the non-HR patient may or may not be sensitive to IMS; if sensitive, there is the possibility of adjusting the IMS doses, so that in patients with adjustment the occurrence of AE would be reduced, and they could die during the simulation.

FIGURE 1

ESTIMATED IMPACT OF IMMUNOBIOGRAM® ON RENAL GRAFT FAILURE IN PATIENTS AT HIGH RISK OF REJECTION. (IMS: IMMUNOSUPPRESSIVE THERAPY)

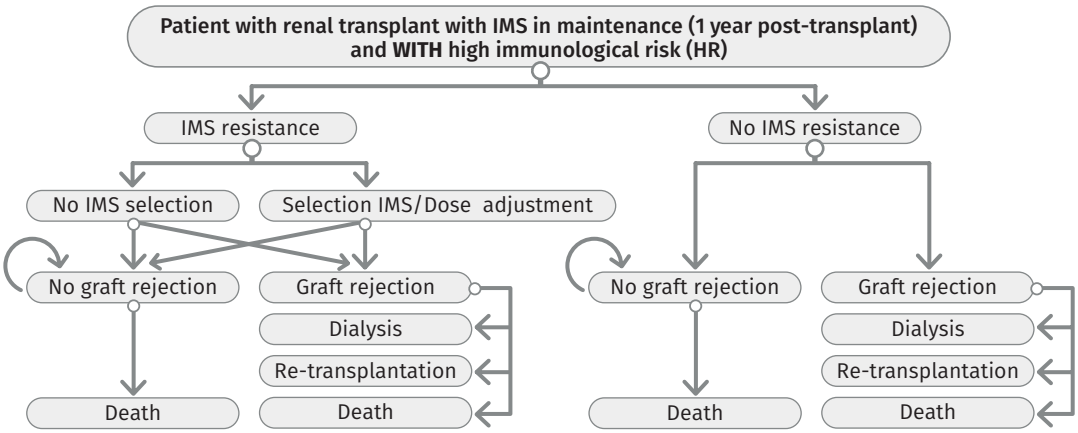
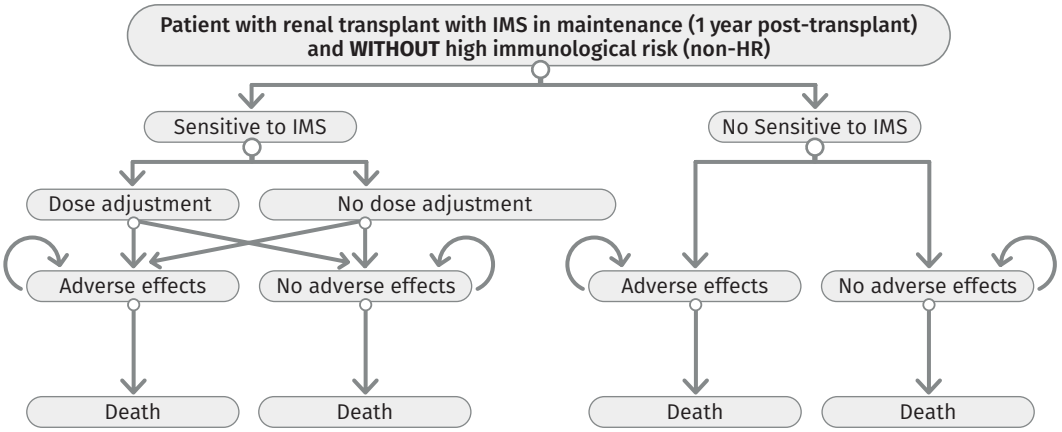


FIGURE 2

ESTIMATED IMPACT OF IMMUNOBIOGRAM® ON THE ADVERSE EVENTS OF IMS THERAPY ON PATIENTS WITHOUT HIGH RISK OF REJECTION. (IMS: IMMUNOSUPPRESSIVE THERAPY)



Premises of the model: probabilities

All assumptions in the model were validated by a panel of Spanish clinical experts with experience in transplant patient management (co-authors: CJM, JMP, MC). The percentage of patients with a resistance or sensitivity profile to IMS in the IMBG, of HR and non-HR patients, the probabilities of reducing the risk of graft failure, selecting the most effective IMS or adjusting the doses and reducing the rate of AE as a result of adjusting the dose in IMS-sensitive patients, were obtained from the clinical study with Immunobiogram mentioned above (BH-Pilot)[21] and from a systematic review of the literature and the tacrolimus data sheet[10,20-26] (Table 1).

Premises of the model: costs

For a 5-year time horizon, it was estimated that one test would be performed annually on patients with HR and only one test in total on non-HR patients. The costs associated with graft failure (dialysis, re-transplantation), IMS therapy and management of IMS-related AEs were obtained from Spanish sources[9,13,27-38] (Table 2). All costs were adjusted for expected 5-year mortality. We estimated the costs of the following AEs (the most frequent and of greatest clinical relevance): malignant neoplasms, cytomegalovirus infection, post-transplant diabetes, post-transplant hyperlipidaemia, anaemia, high blood pressure, cardiovascular events (peripheral cardiac, cerebrovascular and vascular events)[26,39] (Table 2). Indirect costs, due to lost working hours, were estimated from a previously published study[40] (Table 2). All costs (expressed in euros, €) were updated to 2019.

Premises of the model: utilities

Years of life and QALYs gained were calculated from published data[41-43] (Table 3).

Sensitivity analyses

A probabilistic model was made, using a second-order Monte Carlo simulation. In addition, a deterministic sensitivity analysis was carried out from the social perspective. Using a conservative approach, an analysis was not performed for time horizons greater than 5 years, due to the lack of reliable longer-term data.

TABLE 1

PROBABILITIES USED IN THE ECONOMIC MODEL

Item	Value	Sources
Proportion of population HR/non-HR	35%/65%	*23*
IMS-resistant HR patients	**55%**	*21*
IMS selection and IMS dose adjustment, according to the Immunobiogram result in HR	90%	*Expert panel*
Risk of graft failure in HR (5 years)	19.1%	*20*
Prevention of failure if IMS is selected	50%	*Expert panel*
Risk of graft failure in HR if IMS dose selection/adjustment (5 years)	10.5%	*Calculated**
Dialysis patients if the graft is not functional	100%	*Expert panel*
Patients with renal re-transplantation	17%	*10*
Survival 5 years after the renal transplantation	88.9%	*25*
IMS sensitivity in non-HR/controlled patients	**66%**	*21*
Probability of dose adjustment in IMS-sensitive patients	30%	*Expert panel*
AE risk reduction by adjusting the IMS dose	30%	*Expert panel*
Probability of malignant neoplasms (5 years)	41.4% (24.8-68.1%)	*24*
Cytomegalovirus infection	32.0%	*26*
Post-transplant diabetes	24.0%	*26*
Post-transplant hyperlipidaemia	17.3%	*26*
Anaemia	23.6%	*26*
Arterial hypertension	27.2%	*26*
Cardiovascular events	21.8%	*22*

*Calculation: 19.1% x (1-0,45). **AE**: adverse events; **HR**: high immunological risk; **non-HR**: non-high immunological risk; **IMS**: immunosuppressive therapy.

TABLE 2

USE OF RESOURCES AND UNIT COSTS

Item	Value	Sources
Use of resources		
Immunobiogram test number in non-HR (5 years)	1	*Biohope*
Immunobiogram test number in HR (5 years)	5	*Biohope*
Consultation with the nephrologist for Immunobiogram	0	*Expert panel*
Haemodialysis / Peritoneal dialysis if graft failure	83%/17%	*34*
IMS usage rates Tacrolimus Everolimus Cyclosporine A Sirolimus Mycophenolate mofetil Azathioprine	 84.3% 1.4% 4.5% 3.3% 69.6% 1.3%	*36*
Costs		
Immunobiogram (1 test)	€1,000	*Biohope*
Haemodialysis (per year)	€46,211	*9*
Peritoneal dialysis (per year)	€35,659.83	*9*
Renal re-transplantation	€45,384.05	*9*
Average cost of IMS (5 years)*	€10,481.13 (€5,122.95-16,107.85)	*28,32 Calculated**
Average cost of malignant neoplasms (5 years) **	€6,897 (€3,117-14,013)	*27,29,31,38,39 Calculated***
Other AE (adjusted for frequency) (5 years) Cytomegalovirus infection Post-transplant diabetes Post-transplant hyperlipidaemia Anaemia Arterial hypertension Cardiovascular events***	 €1,995.04 (€1,596.04-2,394.05) €490.02 (€392.02-661.62) €206.83 (€165.47-278.46) €97.24 (€82.68-111.79) €425.75 (€340.60-842.32) €2,313 (€1,851-2,776)	 *28* *30,33* *35* *14* *37* *38*
Indirect costs (due to loss of working hours) in kidney transplant patients	€5,688.48 (€4,622.24-6,753.60)	*40*
Indirect costs (due to loss of working hours) in patients with kidney dialysis	€7,332.64 (€6,414.24-8,249.92)	

*Calculation according to the use rates and public prices; Average body weight (from 15 years of age): 70.5 kg[32].
**Calculation according to the average cost (Groups related by diagnosis or unit costs) of the most frequent malignancies after kidney transplantation[26,39]: melanoma, basal cell carcinoma, squamous cell carcinoma, renal cell cancer, bladder cancer, breast cancer, colorectal cancer, uterine cancer, prostate cancer, leukaemia, lung cancer, lymphoma and myeloma.
***Average cost of cardiac, cerebrovascular and peripheral vascular events, according to their frequency in Mattos et al.[22]
Abbreviations: **AE**: adverse events; **HR**: high immunological risk; **non-HR**: non-high immunological risk; **IMS**: immunosuppressive therapy.

TABLE 3

LIFE EXPECTANCY AND UTILITIES CONSIDERED IN THE MODEL

Item	Value	Sources
Life expectancy (years)		
General population	83.4	*41*
Kidney dialysis patient	62.4	*42*
Kidney transplant patient	68.4	*42*
Utilities		
Functioning graft	0.712 ± 0.272	*43*
Haemodialysis	0.443 ± 0.317	*43*
Peritoneal dialysis	0.569 ± 0.329	*43*
Loss of utilities due to graft failure	0.248 ± 0.047	*43*

TABLE 4

COSTS IMPACT RESULTS, PER PATIENT.

A) NHS perspective

GRAFT FAILURE				IMS DOSE ADJUSTMENTS & ADVERSE EVENTS				TOTAL			
Item	WITH IMBG	W/o IMBG	Difference	Item	WITH IMBG	W/o IMBG	Difference	Item	WITH IMBG	W/o IMBG	Difference
Mean	20,105 €	40,368 €	**-20,263 €**	Mean	21,501 €	22,911 €	**-1,409 €**	Mean	21,012 €	29,021 €	**-8,008 €**
SD	7,459 €	8,844 €	-	SD	5,513 €	6,293 €	-	SD	6,194 €	7,186 €	-
LL 95%CI	8,003 €	25,523 €	-17,520 €	LL 95%CI	12,574 €	12,615 €	-41 €	LL 95%CI	10,974 €	17,133 €	-6,159 €
UL 95%CI	38,307 €	61,986 €	-23,678 €	UL 95%CI	33,408 €	36,723 €	-3,316 €	UL 95%CI	35,122 €	45,565 €	-10,443 €
Saving probability:			100.0%	Saving probability:			97.8%	Saving probability:			100.0%

B) Societal perspective

GRAFT FAILURE				IMS DOSE ADJUSTMENTS & ADVERSE EVENTS				TOTAL			
Item	WITH IMBG	W/o IMBG	Difference	Item	WITH IMBG	W/o IMBG	Difference	Item	WITH IMBG	W/o IMBG	Difference
Mean	20,879 €	41,777 €	**-20,897 €**	Mean	21,501 €	22,911 €	**-1,409 €**	Mean	21,284 €	29,514 €	**-8,230 €**
SD	7,585 €	9,072 €	-	SD	5,513 €	6,293 €	-	SD	6,238 €	7,266 €	-
LL 95%CI	8,557 €	26,530 €	-17,973 €	LL 95%CI	12,574 €	12,615 €	-41 €	LL 95%CI	11,168 €	17,485 €	-6,317 €
UL 95%CI	39,349 €	63,878 €	-24,529 €	UL 95%CI	33,408 €	36,723 €	-3,316 €	UL 95%CI	35,487 €	46,227 €	-10,740 €
Saving probability:			100.0%	Saving probability:			97.8%	Saving probability:			100.0%

NHS: National Health System of Spain; **SD**: standard deviation; **IMBG**: Immunobiogram; **IMS**: immunosuppressive therapy; **LL**: lower limit; **US**: upper limit; **95% CI**: 95% confidence interval.

RESULTS

Cost analysis

Base case (NHS perspective)

It is estimated that the use of IMBG would lead, within 5 years, to a reduction in the risk of renal graft failure in patients with HR from 19.1% to 10.5% (Table 1). At the same time, in non-HR patients, adjusting the dose of IMS in treatment-sensitive patients would result in a reduction in the frequency of AE (Table 1).

Reducing the risk of renal graft failure would generate savings in the patient with HR of €20,263 (95% CI €17,520-23,678) and a probability of savings with IMBG of 100% (savings would occur in the 1,000 patients of the hypothetical cohort analysed) (Table 4a).

The expected reduction with Immunobiogram in the AE rate would generate savings in non-HR patients of €1,409 (95% CI €41-3,316) with a probability of savings of 97.8% (Table 4a).

Considering both subject populations with kidney transplants (HR and non-HR), with Immunobiogram the savings per patient would amount to €8,008 (95% CI €6,159-10,443) with a probability of savings of 100% (Table 4a).

Sensitivity analysis (Societal perspective)

Indirect costs per patient, associated with graft loss were €634.03 (95% CI €452.60, 850.50) (Table 5). From the societal perspective, the savings per patient would be €8,230 (95% CI €6,317-10,740) (Table 4b).

Health outcomes analysis

Compared with the option of not using IMBG, 0.5256 (95% CI 0.3388, 0.7452) years of life would be gained in each patient evaluated with IMBG. Likewise, in each patient evaluated with IMBG, 0.0219 (95% CI 0.0115; 0.0356) QALYs would be gained (Table 6).

TABLE 5

INDIRECT COSTS PER PATIENT DERIVED FROM GRAFT REJECTION.

Item	WITH IMBG	W/o IMBG	Difference
Mean	774.89 €	1,408.92 €	-634.03 €
SD	125.87 €	228.75 €	-
LL 95%CI	554.76 €	1,007.36 €	-452.60 €
UL 95%CI	1,041.56 €	1,892.07 €	-850.50 €
		Saving probability:	100%

SD: standard deviation; **IMBG**: Immunobiogram; **LL**: lower limit; **US**: upper limit; **95% CI**: 95% confidence interval.

TABLE 6

LIFE YEARS AND QALYS GAINED WITH IMBG, PER PATIENT.

Item	Life years			QALYs		
	Life years lost WITHOUT IMBG	Life years lost WITH IMBG	Life years gained WITH IMBG	QALYs lost WITHOUT IMBG	QALYs lost WITH IMBG	QALYs gained WITH IMBG
Mean	1.1680	0.6424	0.5256	0.0488	0.0268	0.0219
SD	0.2321	0.1277	-	0.0138	0.0076	-
LL 95%CI	0.7542	0.4154	0.3388	0.0255	0.0141	0.0115
UL 95%CI	1.6578	0.9126	0.7452	0.0792	0.0436	0.0356

SD: standard deviation; **IMBG**: Immunobiogram; **LL**: lower limit; **QALYs**: quality-adjusted life years; **US**: upper limit; **95% CI**: 95% confidence interval.

DISCUSSION

According to the present economic model, the personalization of IMS therapy through the IMBG in vitro diagnostic test, at least one year after the kidney transplantation, could generate gain in years of life (0.5256) and QALYs (0.0219) in each patient evaluated with IMBG, and savings per patient of €8,008 over a 5-year time horizon. These savings would be obtained by reducing the risk of graft failure and the AEs associated with IMS; both factors would also determine the gain in life years and in QALYs. In the specific case of patients with HR of graft loss, the savings per patient would amount to €20,263. No other study similar to ours has been identified in renal transplantation. A systematic review on biomarkers in metastatic colorectal cancer has been published[44]. According to this study, the average savings per patient who underwent genotyping amounted to $272.34[44,45].This figure serves to determine the relevance of the savings obtained in our model.

In assessing these results, we must first consider that it is a theoretical model, which is, by definition, a simplified simulation of reality. In this respect, as is usual in models, probabilities, costs and utilities had to be assumed from different sources. However, the main limitation of the study is that only preliminary results on the clinical performance of the IMBG are available[11], therefore, the results of this analysis should be considered preliminary, pending the final results of the TRANSBIO study[46].

Regarding the strengths of the model, the estimation of the use of resources was made by a panel of Spanish clinical experts and the unit costs were obtained from Spanish sources, which justifies the applicability of the results to the Spanish healthcare environment. On the other hand, to attempt to minimise the limitations of the model, Monte Carlo simulations were carried out, obtaining probabilities of savings of 100%, or close to 100%, which denotes the stability of the model for the assumptions taken.

CONCLUSIONS

According to the economic model, the use of the immunobiogram, at least one year after the kidney transplantation, could facilitate the adjustment of the IMS treatment according to the patient's immune response profile, and would reduce the risk of graft failure and adverse events associated with IMS, leading to gain in years of life and QALYs, as well as with considerable savings for the Spanish NHS.

The preliminary results of this model should be confirmed when the final results of the TRANSBIO study are available. ■

Conflicts of interest:

Carlos Rubio Terrés is Director of Health Value, a company that has received fees in connection with this study. Dario Rubio Rodriguez is a Senior Consultant at Health Value. Teresa Díez and Isabel Portero are employees of Biohope, the company that sponsored the study. Carlos Jimenez, Jose Maria Portoles and Marta Crespo are members of the Biohope Clinical Experts Advisory Committee.

Contribution of the authors:

C Rubio-Terrés and D Rubio-Rodríguez carried out the economic model. All authors contributed significantly to the development of the model. C Rubio-Terrés and D Rubio-Rodríguez wrote the first draft. All authors interpreted the data and commented on the first draft. All the authors approved the final version of the manuscript.

Disclosure Statement:

The preliminary results of this study, were presented as a poster (reference: PUK-7) at the ISPOR Europe 2019 congress, Copenhagen, Denmark, 2-6 November 2019. The poster abstract was published in Value in Health. 2019; 22 (Suppl 3): S194.

The preliminary results of this study, were also presented as a poster at the American Congress of Transplantation 2020, the abstract having been published with the following reference: Rubio C, Jiménez C, Crespo M, Portolés J, Rubio D, Diez T, Portero I. Evaluation of the Economic Impact of a New IVD Immunoassay (Immunobiogram) for Immunosuppressive Treatment Adjustment in Kidney Transplant Recipients in Spain [abstract]. Am J Transplant. 2020; 20 (suppl 3). Available at URL: https://atcmeetingabstracts.com/abstract/evaluation-of-the-economic-impact-of-a-new-ivd-immunoassay-immunobiogram-for-immunosuppressive-treatment-adjustment-in-kidney-transplant-recipients-in-spain/ (access: March 30, 2021).

REFERENCIAS

1. Kälble T, Lucan M, Nicita G, Sells R, Burgos Revilla FJ, Wiesel M; European Association of Urology. EAU guidelines on prostate cancer. Eur Urol. 2005; 47: 156-66.
2. Kaballo MA, Canney M, O'Kelly P, Williams Y, O'Seaghdha CM, Conlon PJ. A comparative analysis of survival of patients on dialysis and after kidney transplantation. Clin Kidney J. 2018; 11: 389-93.
3. Cippà PE, Schiesser M, Ekberg H, van Gelder T, Mueller NJ, Cao CA, Fehr T, Bernasconi C. Risk Stratification for Rejection and Infection after Kidney Transplantation. Clin J Am Soc Nephrol. 2015; 10: 2213-20.
4. NICE. Immunosuppressive therapy for kidney transplant in adults. Technology appraisal guidance. Published: 11 de octubre de 2017. Available at URL: nice.org.uk/guidance/ta481 (access: 21/06/2019).
5. Rodríguez Faba O, Boissier R, Budde K, Figueiredo A, Taylor CF, Hevia V, Lledó García E, Regele H, Zakri RH, Olsburgh J, Breda A. European Association of Urology Guidelines on Renal Transplantation: Update 2018. Eur Urol Focus. 2018; 4: 208-15.
6. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. Am J Transplant 2009; 9 (Suppl 3): S1–S157.
7. Langman LJ, Jannetto PJ. Individualizing Immunosuppressive Therapy for Transplant Patients. Clin Chem. 2016; 62: 1302-3.
8. Peeters LEJ, Andrews LM, Hesselink DA, de Winter BCM, van Gelder T. Personalized immunosuppression in elderly renal transplant recipients. Pharmacol Res. 2018; 130: 303-7.
9. Márquez-Peláez S, Caro-Martínez A, Adam-Blanco D, Olry-de-Labry-Lima A, Navarro-Caballero JA, García-Mochón L, et al. Eficiencia de la diálisis peritoneal frente a hemodiálisis para el tratamiento de la insuficiencia renal. Sevilla: Agencia de Evaluación de Tecnologías Sanitarias de Andalucía, 2013.
10. Arce J, Rosales A, Caffaratti J, Montlleó M, Guirado L, Díaz JM, Villavicencio H. Retrasplante renal: factores de riesgo y resultados. Actas Urológicas Españolas 2011; 35: 44-50.
11. Di Scala, J. Portolés, C. Jiménez, D. Janeiro, E. González , B. Sánchez Sobrino , M. López Oliva, J. Richter , A. Ortega, J. Pascual , I. Portero. IMMUNOBIOGRAM a new immunological tool to personalize immunosuppressive therapy in kidney transplant recipients. WS.A 2.04.02. 5th European Congress of Immunology 2018, 2-5th September 2018, Amsterdam.
12. Portoles JM, Jimenez C, Janeiro D, Lopez-Oliva MO, Ortega-Carrion A, Blanquez D, et al. The Immunobiogram, a Novel In Vitro Assay to Evaluate Treatment Resistance in Patients Receiving Immunosuppressive Therapy. Front Immunol. 2021; 11: 618202. doi: 10.3389/fimmu.2020.618202.
13. Mayoralas S, Huerta A, Parrondo J, Rubio-Terrés C, Rubio-Rodríguez D. Monte-Carlo simulation to estimate the health care cost avoided with fluticasone furoate/vilanterol due to exacerbation rate reduction in Spanish COPD patients. Value in Health 2014; 17: A603.
14. Isla D, De Castro J, Juan O, Grau S, Orofino J, Gordo R, Rubio-Terrés C, Rubio-Rodríguez D. Costs of adverse events associated with erlotinib or afatinib in first-line treatment of advanced EGFR-positive non-small cell lung cancer. ClinicoEconomics and Outcomes Res. 2017; 9: 31-38.
15. Anguita P, González C, Cañete M, Rubio-Rodríguez D, Rubio-Terrés C. Coste de los efectos adversos asociados a enzalutamida o apalutamida en el tratamiento del cáncer de próstata resistente a la castración no metastásico en España. Rev Esp Econ Salud. 2019; 14: 794-805.
16. Manito N, Rubio-Rodríguez D, González J, Díez C, Enjuanes C, Segovia-Cubero J, Delgado JF, Campo C, Rubio-Terrés C, Comín-Colet J. Análisis económico del tratamiento ambulatorio intermitente con levosimendán de la insuficiencia cardiaca en España. Rev Esp Cardiol. 2019. DOI: 10.1016/j.recesp.2019.06.019.
17. Briggs A, Claxton K, Sculpher M. Decision Modelling for Health Economic Evaluation. Oxford, UK: Oxford University Press; 2006.
18. Gray AM, Clarke PM, Wolstenholme JL, Wordsworth S. Applied methods of cost-effectiveness analysis in health care. Oxford: Oxford University Press, 2011.
19. Rubio-Terrés C, Rubio-Rodríguez D. Probabilistic Analysis: Sensitivity Analysis or Main Result? (Editorial). Pharmacoeconomics: open access. 2016; 1: 2. http://dx.doi.org/10.4172/pe.1000e102.
20. ERA-EDTA Registry: ERA-EDTA Registry Annual Report 2016. Amsterdam UMC, location AMC, Department of Medical Informatics, Amsterdam, the Netherlands, 2018. Available at URL: https://www.era-edta-reg.org/files/annualreports/pdf/ AnnRep2016.pdf (access: 18/97/2019).

21. Di Scala M. Immunobiogram: a new immunological tool to personalize immunosuppresive therapy in kidney transplant recipients. BST18 – Basic Science in Transplantation Meeting 2018. PP07. Available at URL: https://www.esot.org/events-education/events/11394/ posters/2765 (access: 21/06/2019).
22. de Mattos AM, Prather J, Olyaei AJ, Shibagaki Y, Keith DS, Mori M, et al. Cardiovascular events following renal transplantation: role of traditional and transplant-specific risk factors. Kidney Int. 2006; 70: 757-64.
23. Foucher Y, Daguin P, Akl A, Kessler M, Ladrière M, Legendre C, et al. A clinical scoring system highly predictive of long-term kidney graft survival. Kidney Int. 2010; 78: 1288-94.
24. Jürgensen JS, Ikenberg R, Greiner RA, Hösel V. Cost-effectiveness of modern mTOR inhibitor based immunosuppression compared to the standard of care after renal transplantation in Germany. Eur J Health Econ. 2015; 16: 377-90.
25. Morales JM, Marcén R, del Castillo D, Andres A, Gonzalez-Molina M, Oppenheimer F, et al. Risk factors for graft loss and mortality after renal transplantation according to recipient age: a prospective multicentre study. Nephrol Dial Transplant. 2012;27 (Suppl 4): iv39-46.
26. Prograf® (tacrolimus) capsules. Food and Drugs Administration. Available at URL: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/050709s031lbl.pdf (access: 09/11/2018).
27. Arrospide A, Soto-Gordoa M, Acaiturri T, López-Vivanco G, Abecia LC, Mar J. [Cost of breast cancer treatment by clinical stage in the Basque Country, Spain]. Rev Esp Salud Publica. 2015; 89: 93-7.
28. Consejo General de Colegios Oficiales de Farmacéuticos. Bot Plus 2.0. Available at URL: https://botplusweb.portalfarma.com/botplus.aspx (access: 05/11/2018).
29. Hart WM, Nazir J, Baskin-Bey E. An incidence model of the cost of advanced prostate cancer in Spain. J Med Econ. 2014; 17: 125-31.
30. Hidalgo A, Oliva J, Rubio M, Zozaya N, Villoro R, García S. Estudios de coste de la diabetes tipo 2: una revisión de la literatura. Madrid: Agencia de Evaluación de Tecnologías Sanitarias - Instituto de Salud Carlos III, February de 2015.
31. Mar J, Errasti J, Soto-Gordoa M, Mar-Barrutia G, Martinez-Llorente JM, Domínguez S, García-Albás JJ, Arrospide A. The cost of colorectal cancer according to the TNM stage. Cir Esp. 2017; 95: 89-96.
32. Ministry of Health and Consumer Affairs. Encuesta Nacional de Salud 2001. Talla y peso medio, según grupo de edad y sexo. Available at URL: http://www.mscbs.gob.es/estadEstudios/estadisticas/inforRecopilaciones/atlas/atlasDatos.htm (access: 05/11/2018).
33. Nuño-Solinís R, Alonso-Morán E, Arteagoitis JM, Ezkurra P, Orueta JF, Gaztambide S. Costes sanitarios de la población con diabetes mellitus tipo 2 en el País Vasco (España). Endocrinolo Nutric. 2016; 63: 543-50.
34. ONT. Organización Nacional de Trasplantes. Informe de Diálisis y Trasplante 2014. XLV Congreso Nacional de la Sociedad Española de Nefrología. Valencia, 3-6 octubre, 2015. Available at URL: http://www.ont.es/infesp/Registros/ REGISTRO%20RENAL%20ONT-SEN-REER%202015.pdf (access: 05/11/2018).
35. Ramírez de Arellano A, Coca A, de la Figuera M, Rubio-Terrés C, Rubio-Rodríguez D, Gracia A, Boldeanu A, Puig-Gilbert J, Salas E. Economic evaluation of Cardio inCode®, a clinical-genetic function for coronary heart disease risk assessment. Appl Health Econ Health Policy. 2013; 11: 531-42.
36. Registro de enfermos renales de Cataluña. Informe estadístico 2016. Barcelona: Servicio Catalán de Salud / Organización Catalana de Transplantes (OCATT), 2016.
37. Sicras-Mainar A, Navarro-Artieda R. [Cost of arterial hypertension according to levels of morbidity in primary care setting]. Med Clin (Barc). 2009; 133: 290-5.
38. Tarifas para facturación de servicios sanitarios y docentes de Osakidetza para el año 2018. Servicio Vasco de Salud, Enero de 2018.
39. Chapman JR, Webster AC, Wong G. Cancer in the transplant recipient. Cold Spring Harb Perspect Med. 2013; 3: a015677.
40. Julián-Mauro JC, Cuervo J, Rebollo P, Callejo D. Situación laboral y costes indirectos en pacientes con insuficiencia renal: diferencias entre distintas modalidades de tratamiento renal sustitutivo. Nefrologia. 2013; 33: 333-41.

41. Instituto Nacional de Estadística. Esperanza de vida en buena salud al nacer por sexo, esperanza de vida y periodo. Available at URL: https://www.ine.es/jaxi/Datos.htm?path=/t00/ICV/Graficos/dim3/&file=312G2.px#!tabs-tabla (access: 30/03/2021).
42. Kramer A, Pippias M, Noordzij M, Stel VS, Andrusev AM, Aparicio-Madre MI. The European Renal Association - European Dialysis and Transplant Association (ERA-EDTA) Registry Annual Report 2016: a summary. Clin Kidney J. 2019 Feb 26;12(5):702-720.
43. Lee AJ, Morgan CL, Conway P, Currie CJ. Characterisation and comparison of health-related quality of life for patients with renal failure. Curr Med Res Opin. 2005; 21: 1777-83.
44. Seo MK, Cairns J. Do cancer biomarkers make targeted therapies cost-effective? A systematic review in metastatic colorectal cancer. PLoS One. 2018; 13: e0204496.
45. Gold HTHMJ, Blinder V, Schackman B. R. Cost effectiveness of pharmacogenetic testing for uridine diphosphate glucuronosyltransferase 1A1 before irinotecan administration for metastatic colorectal cancer. Cancer. 2009; 115: 3858-67. doi: 10.1002/cncr.24428.
46. Evaluation of Immunobiogram® as a Tool in Adjustment of Immunosuppressant Therapy for Renal Transplant (TRANSBIO). NIH US National Library of Medicine. ClinicalTrials.gov identifier: NCT03562845. Available at URL: https://clinicaltrials.gov/ct2/show/record/NCT03562845?view=record (access: 03/02/2022).