HLA-Matched Donor-Recipient Combinations and Kidney Transplant Probabilities in a Specific Colombian Population

Compatibilidad HLA donante-receptor y probabilidades de trasplante renal en una población colombiana

Compatibilidade HLA doador-receptor e probabilidades de transplante renal em uma população colombiana

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Abstract

Introduction: In Colombia, despite the fact that kidney transplants are the most common type of transplant surgery, a great number of transplanted patients do not achieve the desired Human Leucocyte Antigen (HLA) compatibility. HLA compatibility plays an important role in graft survival; patients with matched-HLA have a lower chance of graft-versus-host disease and graft rejection. *Objective*: To determine the probability of finding an HLA-matched donor-recipient pairs according to HLA–A, –B and –DRB1 frequencies in a specific Colombian population. *Materials and methods*: The study included a total of 484 unrelated individuals (61 donors and 423 recipients) from the HLA registry. HLA alleles were determined by polymerase chain reaction sequence with specific indicators. *Results*: HLA–A*02, –A*24, –B*35 and –DRB1*04 alleles showed the highest minimum allele frequency (>10 %). In addition, HLA–A*24–B*35–DRB1*04 was the most frequent extended haplotype in both donors and recipients (7.38 % and 6.76 %, respectively). Our experimental evidence showed that the maximum chance of finding at least one HLA allele-matched kidney is 20.3 % for a patient with the most frequent extended haplotype, whereas for patients with rare or non-common haplotypes this probability is rather unlikely. *Discussion*: In terms of probability, the chance of finding an HLA matched kidney donor/recipients in our region is low. This is due, at least in part, to the higher number of alleles and a the lower donation rate. Therefore, to define the HLA profile of a population is important for establishing transplantation programs and alternative strategies in the kidney donation and allocation processes.

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Keywords: Human Leukocyte Antigen, Kidney, Probability, Matching, Transplantation.

Resumen

Introducción: en Colombia, el trasplante renal es el más común, sin embargo, un gran número de personas trasplantadas no tiene la compatibilidad HLA deseada. Esta compatibilidad es importante en la supervivencia del trasplante; pacientes con HLA-compatible tienen un menor chance de rechazo o desarrollo de la enfermedad injerto frente a hospedero. *Objetivo*: determinar la probabilidad de encontrar compatibilidad HLA receptor-donante acorde con las frecuencias en población colombiana de *HLA–A*, *–B* y *–DRB1*. *Materiales y métodos*: el estudio incluyó 484 individuos no relacionados (61 donantes y 423 receptores) con registro de HLA. Los alelos HLA fueron determinados por reacción en cadena de la polimerasa con iniciadores específicos. *Resultados*: los alelos HLA–A*02, –A*24, –B*35 y –DRB1*04 tuvieron la frecuencia alélica mínima más alta (>10 %). El alelo extendido HLA–A*24–B*35–DRB1*04 fue el más frecuente, en donantes y receptores (7,38 % y 6,76 %, respectivamente). Nuestro análisis mostró que el máximo chance de encontrar un riñón con un alelo HLA compatible es de 20,3 % para un paciente con el haplotipo extendido más frecuente, mientras para pacientes con haplotipos raros o no comunes esta probabilidad es mínima. *Conclusión*: en términos de probabilidad, el chance de encontrar en nuestra región, un riñón con compatibilidad HLA entre donante/receptor es baja. Por lo menos, en parte, es debido al alto número de alelos y a la baja tasa de donación. Por lo tanto, determinar el perfil de HLA de una población es importante para establecer programas de trasplante y estrategias alternativas en donación de riñones y procesos de asignación.

Palabras clave: antígenos leucocitario humano, riñón, probabilidad, compatibilidad, trasplante.

Resumo

Introdução: Na Colômbia, o transplante renal é o mais comum, no entanto, um grande número de pessoas transplantadas não tem a compatibilidade HLA desejada. Esta compatibilidade é importante na supervivência do transplante; pacientes com HLA-compatível têm uma menor chance de rejeição ou desenvolvimento da enfermidade enxerto versus hospedeiro. *Objetivo*: determinar a probabilidade de encontrar compatibilidade HLA receptor-doador conforme às frequências em população colombiana de HLA–A, –B e –DRB1. *Materiais e métodos*: O estudo incluiu 484 indivíduos não relacionados (61 doadores e 423 receptores) com registro de HLA. Os alelos HLA–A*02, –A*24, –B*35 e –DRB1*04 tiveram a frequência alélica mínima mais alta (>10 %). *Resultados*: O alelo estendido HLA–A*24–B*35–DRB1*04 foi o mais frequente, em doadores e receptores (7,38 % e 6,76 %, respectivamente). Nossa análise mostrou que a máxima chance de encontrar um rim com um alelo HLA compatível é de 20,3 % para um paciente com o haplótipo estendido mais frequente, enquanto para pacientes com haplótipos raros ou não comuns esta probabilidade é mínima. *Conclusões*: em termos de probabilidade, a chance de encontrar em nossa região, um rim com compatibilidade HLA entre doador/receptor é baixa. Pelo menos em parte, é devido ao alto número de alelos e à baixa taxa de doação. Pelo tanto, determinar o perfil de HLA de uma população é importante para estabelecer programas de transplante e estratégias alternativas em doação de rins e processos de atribuição.

Palavras-chave: antígenos leucocitário humano, rim, probabilidade, compatibilidade, transplante.

Introduction

Kidney transplantation provides to patients with chronic renal disease the hope of regaining a more normal life. However, the waiting time for a kidney transplant since a patient with end-stage kidney disease is placed on the kidney waiting-list is often long and unlikely (1). The application of this medical procedure depends on a wide number of factors. Those related to ensure the immunological compatibility include blood group compatibility; negative T and B cell complement-dependent cytotoxicity crossmatch test using donor lymphocytes as target cells; negative screening test to detect recipient reactive antibodies against HLA antigens; and compatibility between the donor and recipient HLA genes.

In transplants, the human leukocyte antigen (HLA) system not only has the ability to recognise the difference between self and non-self, but also play an important role in the graft survival (2). This system is the most polymorphic genetic system known in the human genome, which maps to a region of approximately 3600 kb of DNA in the short arm of chromosome 6 at position 6p21.3 (3, 4). HLA genes are divided into class I (*HLA–A*, *–C*, and *–B*) or class II (*HLA–DR*, *–DQ*, and *–DP*) genes depending on the structure and function (5). The *HLA–A*, *–B* and *–DRB1* are the most highly polymorphic genes in the HLA. Nonetheless, amongst all sequenced alleles of the HLA only between 27 and 30 % of them are recognised as common variants, whereas the rest are rare variants because they have been found once (6). HLA matching test has an important clinical impact on kidney transplantation; mainly in the selection of suitable recipients for a donor as well as in the graft outcome. It is known that patients with HLA-matched have a lower chance of graft-versus-host disease and graft rejection (7, 8). In addition, there is evidence that shows that HLA mismatches correlate with graft survival; where antigen mismatches in the class I molecules have a minor impact in the graft survival that those in the class II molecules. So, when selecting the best recipient for a donor, becomes more important class II over class I HLA antigens (9).

Several studies have been performed in order to determine the HLA polymorphisms in different populations and ethnic groups; showing a wide variability across them (10, 11). Determining which HLA alleles and haplotypes are present in well-defined populations (and their frequencies) has practical applications, including calculating the probability of finding a suitable HLA-matched donor for a recipient. Thus, patients with common HLA alleles on conserved haplotypes are more likely to find matched unrelated donors than those with rare genotypes (12). This, added to the fact that the proba-bility to identify a suitable HLA matched kidney donor/recipients increases when both recipient and donor are from the same racial and ethnic background (13). In this way, the aim of this study was to investigate the probability of finding an HLA matching donor for the next recipient in the kidney waiting-list base on the HLA frequencies in a Colombian population.

Materials and methods

Dataset

The study included a total of 484 unrelated individuals (61 effective donors and 423 recipients in the waiting-list between 2003 and 2010) from the Department of Santander, Colombia. This was a descriptive retrospective study based on data obtained from the HLA registry. All individuals belong to the transplant program of the Donation and Transplantation Network in Colombia (regional No. 4). The HLA genotypes were collected as part of a routine

diagnostic procedure for determining the HLA compatibility between donors and recipients. This procedure involved no more than minimal risk to the subjects according to the Declaration of Helsinki and the Article 11 of the Resolution 008430 of 1993 of the Ministry of Health from Colombia. The confidentiality, privacy, and security of genetic test information in electronic health records was preserved at all times during the data gathering and analysis.

HLA typing

Genomic DNA was isolated from 7 ml of EDTA-treated blood sample using the standard salting-out technique (14). HLA–A, –B and –DRB1 loci were typed at low to intermediate resolution by polymerase chain reaction with a sequence specific primer (SSP) typing method using the *Biotest ABDR SSPtray* kit (Bio-Rad Laboratories, Inc.; Germany) according to the manufacturer's protocols. The PCR products were analysed by electrophoresis on agarose gel (2 %) run in *TBE* buffer containing ethidium bromide. Each DNA band was recognised according to its size using the molecular weight size marker *SSP-SizeMarker* (One Lambda, Inc.; USA). DNA-based HLA typing results were defined using the *Bio-Rad SSP typing 1.0* software. The assignment of alleles was performed according to the World Health Organization HLA nomenclature[5] and the HLA Dictionary (15).

Statistical analysis

HLA–A, –B and –DRB1 allelic frequencies were obtained by direct counting. Haplotype frequencies were estimated using the expectation-maximization (EM) algorithm implemented in Arlequin software v. 3.5 (16). As input parameters were chosen 500 starting points and 1000 interactions; a ε-value = 10^{-7} was defined as threshold for stopping the EM algorithm. Hardy-Weinberg equilibrium (HWE) was estimated using the Markov-chain algorithm implemented in Arlequin software v. 3.5 (16). As input parameters were selected 10^6 steps in Markov chain and 10^5 dememorization steps. A p-value < 0.05 was considered such evidence of deviation from Hardy–Weinberg equilibrium.

The probability of finding an HLA-matched donor for the recipients in the waiting list was estimated according to following equation (17, 18).

$$P_{(k)} = q \times \sum_{i=1}^{n} \left\{ p\mathrm{R}_i \times 1 - p\mathrm{D}_i)^k \right\} \quad (1)$$

where the probability of finding at least an HLA-matched donor for the next q recipient in need of a transplant in a sample of donors from a donors population is given by $[1-(1-p\mathrm{D}_i)^k]$; $p\mathrm{R}_i$ represents the probability that a recipient has a haplotype i, $p\mathrm{D}_i$ represents the probability that a random donor match the haplotype i, $(1-p\mathrm{D}_i)$ represents the probability that a donor from a donors population not match any recipient in the waiting list, and $(1-p\mathrm{D}_i)^k$ represents the probability that none of k random donors match a given recipient in the waiting list.

The above mentioned equation for estimating $P_{(k)}$ can be derivate with respect to k donors in order to estimate the number of additional donors required to increase by 1 % the expectative of finding a donor with complete or partial HLA match for a q recipient in the waiting list. This is presented in the following equations,

$$P'_{(k)} = -q \times \sum_{i=1}^{n} p\mathrm{R}_i \times \left(1 - p\mathrm{D}_i\right)^k \times In\left(1 - p\mathrm{D}_i\right) \quad (2)$$

$$q_{(k)} = \frac{-P'_{(k)}}{\sum_{i=1}^{n} p\mathrm{R}_i \times \left(1 - p\mathrm{D}_i\right)^k \times \mathrm{In}\left(1 - p\mathrm{D}_i\right)} \quad (3)$$

where $P'_{(k)}$ represents the change between the final expectative and the initial probability of finding at least an HLA-matched donor for the haplotype i.

In order to estimate $P_{(k)}$ and $P'_{(k)}$ were established the following three genogroups according to the *i* constructed haplotypes for a particular HLA–A –B –DRB1: genogroup 1 is defined when $i = 1$ and this is given by the sum of the frequencies of each HLA–A, –B and –DRB1 alleles; genogroup 2 is defined when $i = 2$ and this is given by the sum of the frequencies of the HLA–A–B, HLA–B–DRB1 and HLA–A–DRB1 haplotypes; and genogroup 3 is defined when $i = 3$ and this is given by the frequency of the extended haplotype HLA–A–B–DRB1. These genogroups can also be grouped into three scenarios for increasing the probability of finding at least one HLA-matched donor for a haplotype *i* of a recipient: scenario X is composed by the genogroups 1, 2 and 3; scenario Y is composed by the sum of double genogroups: 1 + 2, 2 + 3 and 1 + 3; and scenario Z is the full sum of all genogroups: 1 + 2 + 3.

Results

Allele frequencies

The allelic frequencies of the loci *HLA–A*, *–B* and *–DRB1* are listed in table 1. In the donors' group was identified 15 alleles for the locus *HLA–A*, 25 alleles for the locus *HLA–B* and 14 for the locus *HLA–DRB1* and in the recipients' group was identified 20, 34, and 15 different alleles for the locus *HLA–A*, *–B* and *–DRB1*, respectively. HLA–A*02, HLA–A*24, HLA–B*35 and HLA–DRB1*04 were the most frequent HLA alleles in both donor and recipient groups with a minimum allele frequency (MAF) of above 10 %, whereas HLA–A*28, HLA–B*41, HLA–B*56 and HLA–B*63 showed allelic frequencies of <1 % in both groups (table 1). All alleles found in the donors group were also found in the recipients group although with small differences in their frequencies. Only 15 HLA alleles (5 of *HLA–A*, 9 of *HLA–B* and 1 of *HLA–DRB1*) were found exclusively in the recipients group and showed a very low allelic frequency (~0.1–1.2 %). The genotype frequencies for the locus *HLA–B* for both groups were distributed in accordance with Hardy-Weinberg equilibrium (HWE) when the expected and observed genotype frequencies were compared (donor: $p = 0.210$; recipient: $p = 0.071$). However, the HWE was only verified for the locus *HLA–A* in the donors' group ($p = 0.103$) and for the locus (table 2) *HLA–DRB1* in the recipients' group ($p = 0.342$).

Haplotype frequencies

A total of 1117 haplotypes were estimated by combining the allelic variants from the loci *HLA–A*, *–B* and *–DRB1*: 256 in donors and 861 in recipients; 153 of which had a frequency of more than 1 % (table 2 and 3). The extended haplotype HLA–A*24–B*35–DRB1*04 was the most frequent between donors (7.38 %) and recipients (6.76 %). The second most common haplotype in donors was HLA–A*02–B*51–DRB1*04, whereas in recipients was HLA–A*29–B*44–DRB1*07 (table 3). Regarding the haplotypes made up of the HLA loci component *HLA–A*, *–B* and *–DRB1* the most commons were HLA–A*24–B*35, HLA–B*35–DRB1*04, and HLA–A*24–DRB1*04 in both groups, followed by the haplotypes HLA–A*02–B*51, HLA–B*51–DRB1*04 and HLA–A*02–DRB1*13 in the donors' group and HLA–A*24–B*61, HLA–B*44–DRB1*07 and HLA–A*02–DRB1*04 in the recipients' group (table 2).

Matching probabilities

The probability of finding a complete or partial HLA-matched donor/recipient pair was estimated based on a model of the three most common haplotypes found in the regional No. 4: HLA–A*24–B*35–DRB1*04 (the most frequent in both donor and recipient groups); HLA–A*29–B*44–DRB1*07 (the second most frequent in recipients but not in donors; with a difference

Table 1. HLA-A, -B and -DRB1 allele frequencies

Donors								Recipients							
HLA-A		HLA-B				HLA-DRB1		HLA-A		HLA-B				HLA-DRB1	
Allele	(%)	Allele	(%)	Allele	(%)	Allele	(%)	Allele	(%)	Allele	(%)	Allele	(%)	Allele	(%)
A*02	17.21	B*35	18.85	B*63	0.82	DRB1*04	21.31	A*02	22.81	B*35	19.03	B*64	1.18	DRB1*04	24.59
A*24	15.57	B*51	10.66	B*48	0.82	DRB1*07	13.11	A*24	20.09	B*44	8.87	B*42	1.06	DRB1*08	8.51
A*01	12.30	B*44	8.20	B*41	0.82	DRB1*13	9.84	A*03	6.26	B*07	6.86	B*52	0.83	DRB1*07	8.51
A*29	7.38	B*07	7.38	B*50	0.82	DRB1*11	8.20	A*29	6.15	B*61	6.50	B*13	0.83	DRB1*01	8.16
A*68	6.56	B*61	5.74	B*56	0.82	DRB1*01	7.38	A*68	6.03	B*51	6.38	B*41	0.83	DRB1*11	6.97
A*03	5.74	B*65	5.74			DRB1*15	7.38	A*01	5.08	B*39	4.96	B*63	0.71	DRB1*15	6.86
A*31	4.92	B*18	4.10			DRB1*17	5.74	A*11	4.49	B*65	4.61	B*56	0.71	DRB1*13	6.62
A*33	4.92	B*08	3.28			DRB1*08	4.10	A*30	3.78	B*18	3.66	B*53	0.59	DRB1*17	6.26
A*11	4.10	B*57	3.28			DRB1*12	2.46	A*31	3.78	B*08	3.55	B*15	0.59	DRB1*14	6.03
A*30	3.28	B*55	3.28			DRB1*14	2.46	A*33	2.60	B*38	3.07	B*37	0.47	DRB1*16	4.37
A*26	3.28	B*60	2.46			DRB1*10	1.64	A*32	2.25	B*48	2.36	B*72	0.12	DRB1*18	2.36
A*23	1.64	B*38	2.46			DRB1*16	1.64	A*26	2.01	B*45	2.25	B*81	0.12	DRB1*10	1.30
A*25	1.64	B*62	2.46			DRB1*09	0.82	A*23	1.54	B*62	2.13	B*54	0.12	DRB1*09	1.06
A*32	1.64	B*49	2.46			DRB1*18	0.82	A*74	0.95	B*50	1.89	B*67	0.12	DRB1*12	0.59
A*28	0.82	B*13	2.46					A*36	0.83	B*60	1.65			DRB1*103	0.12
		B*58	1.64					A*25	0.59	B*49	1.54				
		B*39	1.64					A*66	0.47	B*57	1.42				
		B*27	1.64					A*28	0.47	B*27	1.30				
		B*42	1.64					A*69	0.12	B*58	1.30				
		B*64	0.82					A*34	0.12	B*55	1.18				

Table 2. HLA-A, -B and -DRB1 haplotype frequencies

Donors									Recipients								
HLA-A, -B			HLA-B, -DRB1			HLA-A, -DRB1			HLA-A, -B			HLA-B, -DRB1			HLA-A, -DRB1		
Haplotype		(%)	Haplotype		(%)	Haplotype		(%)	Haplotype		(%)	Haplotype		(%)	Haplotype		(%)
A*24	B*35	9.84	B*35	DRB1*04	8.70	A*24	DRB1*04	9.00	A*24	B*35	9.77	B*35	DRB1*04	9.43	A*24	DRB1*04	9.43
A*02	B*51	5.74	B*51	DRB1*04	5.74	A*02	DRB1*13	6.50	A*24	B*61	3.77	B*44	DRB1*07	3.56	A*02	DRB1*04	4.62
A*03	B*07	3.28	B*35	DRB1*11	3.69	A*01	DRB1*11	4.10	A*02	B*51	3.41	B*07	DRB1*15	3.18	A*02	DRB1*13	3.70
A*02	B*35	2.46	B*07	DRB1*15	3.28	A*29	DRB1*07	3.88	A*29	B*44	3.40	B*61	DRB1*04	2.53	A*24	DRB1*16	2.53
A*11	B*35	2.46	B*44	DRB1*07	3.28	A*02	DRB1*17	3.28	A*03	B*07	2.92	B*35	DRB1*08	2.41	A*29	DRB1*07	2.48
A*24	B*61	2.46	B*51	DRB1*07	3.28	A*01	DRB1*04	3.09	A*02	B*44	2.82	B*65	DRB1*01	2.32	A*24	DRB1*14	2.45
A*29	B*51	2.46	B*08	DRB1*17	2.46	A*01	DRB1*01	2.46	A*02	B*35	2.20	B*51	DRB1*04	2.16	A*02	DRB1*11	2.44
A*01	B*57	1.64	B*13	DRB1*07	2.46	A*03	DRB1*01	2.46	A*02	B*39	1.96	B*35	DRB1*16	2.12	A*24	DRB1*08	2.21
A*01	B*58	1.64	B*60	DRB1*13	2.46	A*03	DRB1*15	2.46	A*11	B*35	1.62	B*39	DRB1*04	2.09	A*03	DRB1*15	2.03
A*01	B*61	1.64	B*65	DRB1*13	2.46	A*30	DRB1*17	2.46	A*02	B*50	1.47	B*08	DRB1*17	1.91	A*31	DRB1*04	2.00
A*02	B*08	1.64	B*61	DRB1*04	1.86	A*31	DRB1*04	2.46	A*02	B*61	1.43	B*44	DRB1*04	1.69	A*68	DRB1*08	1.86
A*02	B*38	1.64	B*07	DRB1*10	1.64	A*33	DRB1*08	2.46	A*33	B*65	1.39	B*39	DRB1*08	1.44	A*02	DRB1*17	1.83
A*02	B*60	1.64	B*18	DRB1*17	1.64	A*24	DRB1*13	2.36	A*24	B*39	1.32	B*35	DRB1*11	1.35	A*02	DRB1*01	1.82
A*02	B*62	1.64	B*35	DRB1*15	1.64	A*24	DRB1*07	1.76	A*01	B*08	1.29	B*61	DRB1*08	1.34	A*02	DRB1*08	1.80
A*03	B*35	1.64	B*44	DRB1*15	1.64	A*11	DRB1*11	1.64	A*02	B*18	1.09	B*07	DRB1*04	1.27	A*01	DRB1*04	1.48
A*11	B*65	1.64	B*55	DRB1*14	1.64	A*24	DRB1*15	1.64	A*26	B*38	1.06	B*44	DRB1*15	1.12	A*29	DRB1*11	1.37
A*24	B*08	1.64	B*58	DRB1*01	1.64	A*31	DRB1*12	1.64	A*68	B*35	1.05	B*07	DRB1*01	1.11	A*02	DRB1*14	1.36
A*30	B*18	1.64	B*35	DRB1*13	1.23	A*68	DRB1*04	1.64	A*31	B*35	1.05	B*35	DRB1*14	1.02	A*03	DRB1*04	1.35
A*31	B*07	1.64	B*51	DRB1*11	1.23	A*02	DRB1*04	1.56							A*33	DRB1*01	1.24
A*31	B*35	1.64	B*35	DRB1*01	1.04	A*02	DRB1*07	1.15							A*02	DRB1*07	1.24
A*33	B*65	1.64													A*01	DRB1*07	1.12
A*68	B*44	1.64													A*30	DRB1*17	1.08

Table 3. HLA-A, -B and -DRB1 extended haplotypes frequencies

Donors				Recipients			
HLA-A, -B, -DRB1				HLA-A, -B, -DRB1			
Extended haplotype			(%)	Extended haplotype			(%)
A*24	B*35	DRB1*04	7.38	A*24	B*35	DRB1*04	6.76
A*02	B*51	DRB1*04	3.69	A*29	B*44	DRB1*07	2.33
A*02	B*08	DRB1*17	2.46	A*24	B*35	DRB1*16	2.14
A*24	B*61	DRB1*04	2.46	A*02	B*51	DRB1*04	1.96
A*01	B*35	DRB1*11	1.64	A*24	B*61	DRB1*04	1.90
A*01	B*58	DRB1*01	1.64	A*02	B*35	DRB1*04	1.69
A*01	B*61	DRB1*04	1.64	A*03	B*07	DRB1*15	1.60
A*02	B*35	DRB1*15	1.64	A*24	B*61	DRB1*08	1.34
A*02	B*44	DRB1*04	1.64	A*02	B*44	DRB1*13	1.06
A*02	B*60	DRB1*13	1.64	A*03	B*07	DRB1*04	1.05
A*03	B*07	DRB1*10	1.64	A*02	B*18	DRB1*11	1.05
A*11	B*35	DRB1*11	1.64				
A*11	B*65	DRB1*13	1.64				
A*24	B*35	DRB1*07	1.64				
A*26	B*07	DRB1*15	1.64				
A*29	B*44	DRB1*07	1.64				
A*30	B*18	DRB1*17	1.64				
A*68	B*35	DRB1*04	1.64				
A*01	B*57	DRB1*04	1.23				
A*02	B*51	DRB1*13	1.23				

in frequency of 0.62 %), and HLA–A*02–B*51–DRB1*04 (the second most frequent in donor but not in recipient; with a difference in frequency of 1.73 %) (table 3). In this scenario, we can realistically model the current imbalance between supply and demand of kidneys for transplantation based on HLA-matched.

Our results showed that a recipient with HLA–A*24–B*35–DRB1*04 will have 6.8 % as the maximum chance of finding a fully HLA-matched donor among 86 donors from our donor population. However, the same chance could be achieved by 21 donors if one HLA-mismatch is allowed or by 9 donors if two HLA-mismatches are allowed (figure 1A). Nevertheless, this chance can also be doubled by 60 donors assuming a HLA-fully-matched haplotype plus genogroups with one or two mismatches and by 15 donors assuming only genogroups with one and two mismatches (figure 1A). Assuming all of possible genogroups and combination of genogroups, the recipient with HLA–A*24–B*35–DRB1*04 had a probability of 20.3 % as the maximum chance of finding at least an HLA-matched donor among 71 donors from our donors' population (figures 1A and 1B). This maximum chance was of 7.0 % among 248 donors for a recipient with HLA–A*29–B*44–DRB1*07, whereas for a recipient with HLA–A*02–B*51–DRB1*04 was of 5.9 % among 112 donors (figure 1B).

On the other hand, the probability of allocating an organ from a donor with at least a genogroup of a particular HLA increases linearly

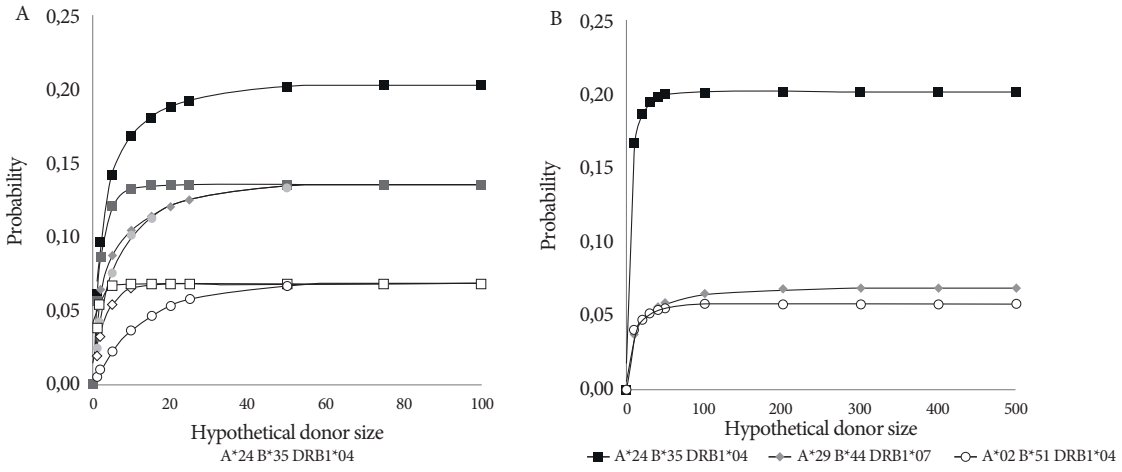

Figure 1. A relation between the hypothetical size of an organ donor population and the probability of finding a fully or partially HLA-matched unrelated donor for the next potential recipient waiting for a kidney transplant. The figure [A] shows that the probability of finding an HLA-matched donor/recipient pair for a patient with the HLA–A*24–B*35–DRB1*04 (the most frequently found in both donor and recipient groups) increases according to the number of HLA-mismatches allowed: one-haplotype-matched pairs (white circles), two-allele-matched pairs (white diamonds) and one-allele-matched pairs (white squares). We have named these three groups Genogroup 3, 2 and 1, respectively, and they form a scenario that we have named Scenario X. Other scenarios were formed in order to increase the probability of finding at least one HLA-matched donor/recipient pair for this haplotype: Scenario Y formed by the sum of double genogroups: 1 + 2 (grey circles), 1 + 3 (grey diamonds) and 2 + 3 (grey squares); and Scenario Z is the full sum of all genogroups: 1 + 2 + 3 (black squares). In this last scenario, it is represent the maximum chance of finding at least an HLA-matched donor. The figure [B] shows the Scenario Z for patients with HLA–A*24–B*35–DRB1*04, HLA–A*29–B*44–DRB1*07 (the most frequent in both donor and recipient groups) or HLA–A*02–B*51–DRB1*04 (the second most frequent in donor but not in recipient).

according to the number of available recipients that matching at least a genogroup of this particular HLA (figure 2). Thus, a donor with at least a genogroup of the HLA–A*24–B*35–DRB1*04 will have a probability of 100 % as the maximum chance of allocating an organ if the waiting list has at least 16 recipients with at least a genogroup for this HLA or by 6 recipients if there is at least 12 donors (figure 2A). This probability can also be achieved when the donor has at least a genogroup of the HLA–A*29–B*44–DRB1*07 or HLA–A*02–B*51–DRB1*04 as long as in the waiting list there is at least 24 recipients with any of these two haplotypes (figure 2B).

In order to estimate the number of additional donors required to increase by 1 % the chance of finding at least an HLA-matched for a recipient or group of recipients with a particular HLA, we derive the equation 1 with respect to number of donors (Equations 2 and 3). The number of additional donors increases exponentially according to the number of available recipients with the particular HLA (figure 3). Thus, for increasing the prior probability in each recipient with HLA–A*24–B*35–DRB1*04 from 20.3 % to 21.3 % as the maximum chance of finding at least one HLA-matched donor is required 89 more donors for 50 recipients or 4082 more donors for 100 recipients in a waiting list with that haplotype (figure 3). Increasing by 1 % the prior probability in the case of recipients with HLA–A*29–B*44–DRB1*07 or

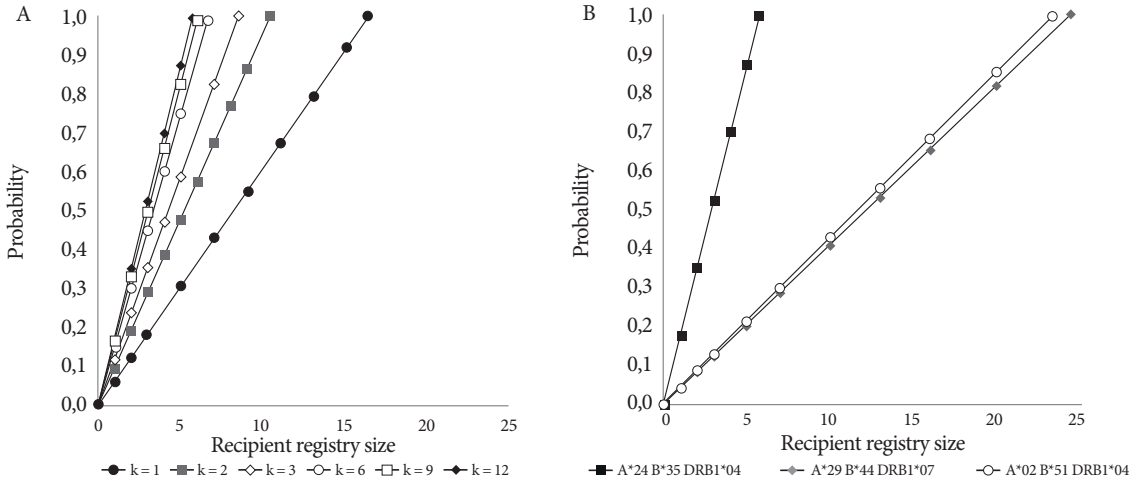

Figure 2. A relation between the hypothetical size of a recipient registry and the probability of allocating a fully or partially HLA-matched unrelated kidney for the next potential recipient waiting for transplantation. The figure [A] shows that the probability of allocating an organ with respect to the number of donors (k) for the extended haplotype HLA–A*24–B*35–DRB1*04 (the most frequently found in both donor and recipient groups) increases linearly according to the number of available recipients that matching at least a genogroup of this particular HLA. The figure [B] shows the probability of organ allocation with respect to a maximum of 12 donors (k = 12) for patients with HLA–A*24–B*35–DRB1*04, HLA–A*29–B*44–DRB1*07 (the most frequent in both donor and recipient groups) or HLA–A*02–B*51–DRB1*04 (the second most frequent in donor but not in recipient) where recipients and donors match at least a genogroup of these haplotypes.

HLA–A*02–B*51–DRB1*04 will require 133 or 583 more donors for a waiting list with 100 recipients on it, respectively (figure 3).

Discussion

Colombia had a kidney donation rate of 18.5 per million population (pmp) for the year 2009; ranking 6th among the 21 countries that conform the Latin American Network/Council of Donation and Transplant (19). A total of 674 kidney transplant procedures were performed in 2013 (12.1 % less than in the year 2012) representing 73.18 % of all organ transplants performed during that year. Nevertheless, to December 31, 2013, there were around 1600 people waiting for a kidney transplant, which is almost 24 % more than the last year (20).

The Donation and Transplantation Network in Colombia is divided into six regionals. The regional No. 4 is formed by the departments of Santander, Norte de Santander, Arauca and Cesar. At the end of the year 2013 were reported 55 procedures of transplant surgery; ranking 4th among the six regionals not only because reported about 6 % of transplants, but also because reported a family refusal rate of 25 % (20). In this context, of the 674 kidney transplant procedures performed during the year 2013 in Colombia only 32 were carried out by the regional No. 4; a very low rate compared to national average (20). In addition of the difficulty of finding an organ with this regional overview there are also other issues that need to be addressed in order to improve the transplant outcome, such is the case of the HLA compatibility.

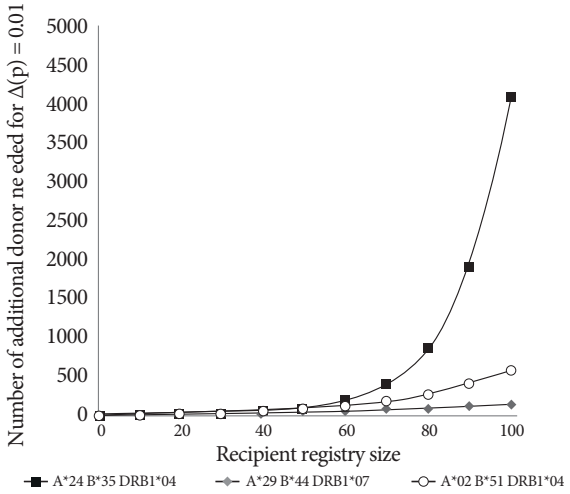

Figure 3. A relation between the hypothetical size of a recipient registry and the number of additional donors required to increase by 1% the expectative of finding a fully or partially HLA-matched unrelated donor for the next potential recipient or group of recipients waiting for a kidney transplant. The figure shows that the number of additional donors increases exponentially according to the number of available recipients with a particular HLA. In the figure is represented this increment of expectative for patients with HLA–A*24–B*35–DRB1*04 (the most frequently found in both donor and recipient groups), HLA–A*29–B*44–DRB1*07 (the most frequent in both donor and recipient groups) or HLA–A*02–B*51–DRB1*04 (the second most frequent in donor but not in recipient).

The HLA compatibility is an important criterion at the time of allocating an organ because it influences the graft survival (7, 21). In this context, and taking into account that HLA allele frequencies vary significantly among populations (10,11), we determined the probability of finding unrelated HLA-matched donor-pairs for kidney transplantation in the scenario of the regional No. 4.

Our statistical analyses showed that the extended haplotype HLA–A*24–B*35–DRB1*04 was the most frequent among donor and recipient (table 3) and that the haplotypes HLA–A*24–B*35, HLA–B*35–DRB1*04 and HLA–A*24–DRB1*04 as well as the alleles HLA–A*24, HLA–B*35 and HLA–DRB1*04 were also highly frequent in the two groups (table 1 and 2). These results are in agreement with previous reports in Colombian (22-24) and other Latin American populations (10) where these alleles and haplotypes are the most frequently found.

It is well known that patients with more common HLA alleles are more likely to find an unrelated HLA-matched donor than patients with less common HLA alleles (12) and this probability depends on the frequency of those alleles in a particular population (17,18). Our results showed, for instance, that for a patient with the most common HLA alleles and their haplotypes the maximum chance of finding at least an HLA-matched donor will be 20.3 % if there are a minimum of 71 random donors from our population (figure 1A). This probability dropped considerably by about 75 % for patients with less common alleles/haplotypes assuming more than 100 random donors (figure 1B). According to the donation rate in the regional No. 4 were only 19

effective donors during the year 2013 [20], whereby the probability of finding an HLA-matched donor-recipient pair will decrease by about 2 % more in the case of the three most frequent haplotypes (figure 1). Therefore, the probability of finding an HLA-matched donor/recipient pair for patients with rare alleles will be very low.

The differences in the frequency of HLA alleles and their haplotypes observed between donors and recipients had an important impact on the probability to finding HLA-matched donor/recipient pairs due to the disbalance between supply and demand of organs for donation. Thus, for instance, in the case of a patient with HLA–A*29–B*44–DRB1*07 for which there is more demand than supply (table 3), the maximum chance of allocating a kidney according to this HLA was 0.86 % if at least one HLA allele in the donor is part of this extended haplotype in the recipient, whereas in the case of a patient with HLA–A*02–B*51–DRB1*04 for which there is more supply than demand (table 3), the maximum chance of allocating a kidney according to the HLA was 1.3 % if at least one HLA allele in the donor is part of this extended haplotype (figure 2B). Nevertheless, increasing the number of donors, the probability of allocating an organ also increases (linearly) according to the number of available recipients in the waiting list that matching at least an allele for a particular HLA (figure 2). The results of these analyses suggest that for patients with uncommon HLA alleles and/or haplotypes and also have differences in the frequencies between donors and recipients, the probability of allocating a kidney base on HLA will be little unlikely (12).

On the other hand, we calculated an additional expectation of finding an unrelated HLA-matched donor for each recipient in the waiting list. This new probability depends on the number of patients waiting for a kidney transplant and on the HLA frequency differences between donors and recipients (figure 3). For example, in order to increase by 1 % the chance of finding at least an HLA-matched donor for each recipient with the extended haplotype HLA–A*24–B*35–DRB1*04, and who have a prior probability of 18.4 %, will be needed to add three more donors as long as on the waiting list there are 10 recipients with this haplotype. And fewer additional donors will be required for recipients with less common HLA alleles and/or haplotypes (figure 3). Therefore, increasing the number of donors, the expectation of finding an unrelated HLA-matched donor for each recipient in the waiting list also increases even for those patients with rare alleles and/or haplotypes (figure 2). In fact, if the donation rate in this regional is increased by about 10 pmp, which is approximately the national average donation rate reported between 2010 and 2013 (20), then the probability of finding an HLA-matched donor for each recipient will increase by about 90 % of the prior maximum estimated chance.

In conclusion, the probability of finding HLA-matched donor/recipients pairs for kidney transplantation in the regional 4 seems to be unlikely. This is, at least in part, because there is a great diversity of alleles and a poor donation rate. In addition, and even though the HLA compatibility is not the only criterion considered for kidney transplantation, this criterion is important to estimate the graft survival. Therefore, we believe that our results are useful to define alternative strategies in the kidney donation and allocation processes; for example, giving priority to those patients with less common haplotypes when there is an HLA-matched.

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Disclaimer

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