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Evaluation of HLA Matchmaker Compatibility as Predictor of Graft Survival and Presence of Anti-HLA Antibodies

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ABSTRACT

Background. HLA Matchmaker is a computer algorithm developed to evaluate donor/receptor compatibility comparing sequences of polymorphic aminoacids (eplets) present in human leukocyte antigen (HLA) molecules. The aim of this study was to evaluate the predictive value of HLA Matchmaker for patient and graft survival, graft survival free of rejection, and the presence of anti HLA antibodies.

Methods. Using this program, 62 of 173 kidney transplant patients, were retrospectively analyzed. HLA-I loci eplet mismatch value (EMM) was determined and correlated with graft survival, graft survival free of rejection, and the presence of anti HLA-I antibodies. EMM was compared with the traditional HLA antigen mismatch value (MM) in terms of the presence of anti HLA-I antibodies.

Results. Graft survival and graft survival free of rejection showed no statistical differences (*P*-value .975 and .365, respectively) while comparing patients with less or more than 10 HLA-I EMM. Patients with ≥6 HLA-B EMM had an odds ratio (OR) of 5.6 (95% confidence interval [CI], 0.47–66.45) of presenting anti HLA-I antibodies, with a sensitivity of 80% and specificity of 58.3%. For ≥2 HLA-B MM, the OR was 2.58 (95% CI, 0.46–14.5), with a sensitivity of 40% and specificity of 75%.

Conclusion. Even though in our study population compatibility by HLA Matchmaker did not correlate with graft survival or rejection-free graft survival, it showed a better sensitivity than traditional HLA antigen matching for the presence of anti HLA-I antibodies. HLA Matchmaker is a promising tool in predicting the appearance of anti-HLA antibodies.

HLA MATCHMAKER is a computer algorithm that assesses human leukocyte antigen (HLA) compatibility at a structural level by intralocus and interlocus comparisons of polymorphic aminoacid sequences of HLA molecules.[1] In its first version, each HLA antigen was seen as a chain of short, lineal sequences of polymorphic amino acids in an antibody-binding position (triplets); these triplets are considered the key elements of epitopes able to induce specific antibody production. The most recent version—Eplets HLA Matchmaker—introduces the concept of sequences of polymorphic amino acids in discontinuous positions that create on the surface of the HLA molecule conformational epitopes. The eplet version provides a broader repertoire of structural defined HLA epitopes and may provide a more accurate evaluation of the HLA compatibility.[2,3]

HLA Matchmaker is based in the following principles. First, each HLA antigen is represented by different chains of epitopes structurally defined as potential immunogenic particles capable of inducing specific antibody production. Second, patients cannot produce antibodies against epitopes present on their own HLA molecules.[2]

Initially, the program was developed to increase the chances of finding acceptable donors for hypersensitized patients.[4–6] Subsequently, Duquesnoy et al[7] demonstrated that it might also be useful in predicting the risk of graft loss according to the number of HLA-I mismatch triplets. This

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Table 1. Demographic and Baseline Characteristics

N	62
Age (yr)	40.7 ± 17
Gender	
Male	41 (66%)
Female	21 (34%)
Disease origin	
Glomerulopathies	19 (30%)
Genetic disease	9 (14%)
Diabetes mellitus	8 (13%)
Arterial hypertension	11 (18%)
Nefrouropatias	6 (10%)
HUS	3 (5%)
Unknown	6 (10%)
PRA peak (%)	11.2
Retransplant	11 (18%)
Donor source	
Deceased	44 (71%)
Living	18 (29%)
Immunosuppressive therapy	
Induction	
ATG	9 (14.5%)
BSX	22 (35.5%)
ATG+BSX	11 (18%)
Alemtuzumab	15 (24%)
No	5 (8%)
Maintenance	
ICN+Pred+AZA	10 (16%)
ICN+Pred+MMF/MyF	48 (77%)
ICN+Pred+ITORm	4 (7%)

was proved in sensitized and nonsensitized patients.[2] Haririan et al[8] also showed that this triplet compatibility could give information about renal graft outcome in African-American patients. Nevertheless, Laux et al[9] based on their own studies questioned the predictive role of triplet compatibility in graft survival. Other authors have also questioned the consistency of the epitopes in which this algorithm is based, pointing out that they might not be the unique epitopes inducing antibody formation.[10,11]

HLA Matchmaker has also been evaluated for clinical use in the selection of donors in pediatric renal desensitized receptors[12,13] and HLA allosensitized thrombocytopenic patients.[14] It has also been applied in unrelated bone marrow transplantation, lacking definitive proof of its benefit in patient survival.[2] The aim of the present study was to evaluate HLA-I eplets mismatch as predictor of graft survival, rejection-free graft survival, and the presence of anti-HLA antibodies in kidney transplant patients. Additionally, the eplet mismatch value was compared with the traditional HLA antigens mismatch, regards the presence of anti–HLA-I antibodies.

METHODS

We retrospectively analyzed 173 kidney transplants performed between January 1994 and December 2008 in Clinica Las Condes; 2 patients who lost their graft due to perioperative thrombosis were excluded. Donor and receptor HLA typification was done in the national reference center Instituto de Salud Publica. Complement dependent cytotoxicity was performed from 1994 to 2000, and low-resolution polymerase chain reaction technique (PCR-SSP) was utilized since 2000. Rejection was defined on the ground of clinical and biopsy findings according to Banff criteria. HLA Matchmaker eplet version 2.1 was obtained through its official website.[15] The 4-digit conversion program (4-digit Convert) obtained from the same website was used to assign 4-digit allele to the HLA antigen obtained with the techniques described. This program, assigns a 4-digit allele based on its frequency in different racial groups. The number of patients included in the final evaluation was significantly reduced, owing to the presence of frequent HLA antigens in our population that were not recognized by the conversion program, and because some donor/receptor pairs did not have 4 HLA-I antigens detected. Subsequently, the number of patients was reduced from 173 to 62.

Graft loss was defined as readmission to dialysis (5 patients) or patient death with functioning graft (1 patient). The number of HLA-I eplet mismatches (EMM) was defined as the sum of HLA-A and HLA-B eplet mismatches; the number of HLA-I antigen mismatches (MM) was defined as the sum of HLA-A and HLA-B antigen MM. The presence of anti HLA-I antibodies was assessed in 17 patients during the posttransplant follow-up by flow cytometry or Luminex assay.

Descriptive statistics were applied for demographics and morbidity evaluation, Cox proportional risk analysis for the risk of graft loss and survival free of rejection, and logistic regression was applied for the risk of anti–HLA-I antibody formation. For each HLA loci, patients were divided in 2 groups of EMM, according to quartiles and quintiles analysis, defining cut points at the 50th percentile for loci HLA-A 8 EMM, for loci HLA-B 6 EMM, and for loci HLA-I 10 EMM, based on a previous study.[8]

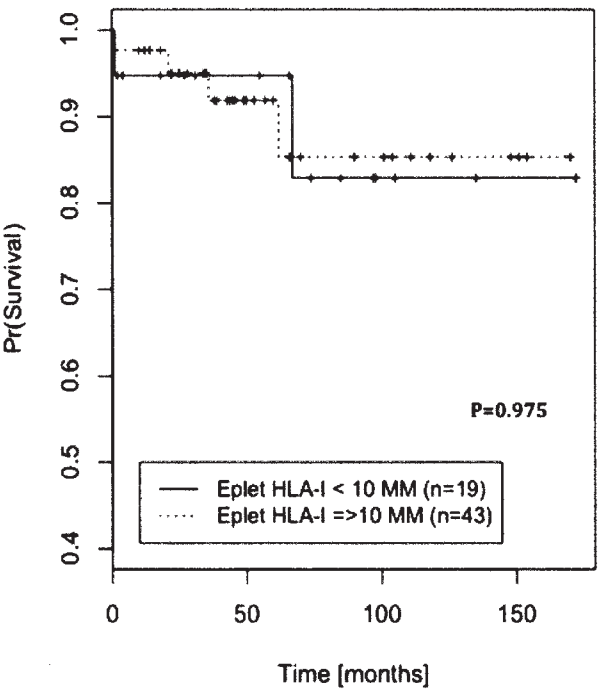

Fig 1. Graft survival for class I eplets matching using the Kaplan-Meier method.

The graft survival rate was calculated by the Kaplan–Meier method and is expressed as percentage of graft surviving. The log-rank test was used to compare survival curves; $P < .05$ was considered significant. Stata 8.0 software package was used for statistical analysis.

RESULTS

Demographics of the 62 patients included in the study is summarized in Table 1. The mean age was 40.7 years (range, 2–69). The main primary kidney diseases were glomerulopathies (30%). Eighteen percent were retransplants. Six of the 62 patients had a panel reactive antibody ≥ 15%. Seventy-one percent received a kidney from deceased donor. Immunosuppressive treatment was diverse, but results did not differ when adjusting by this variable. The mean compatibility was 3 ± 1 HLA-I MM.

Graft survival at 10 years was 84% (95% confidence interval [CI], 72–98). No differences in 10-year graft survival were detected between patients with more or less than 10 HLA-I EMM (85% vs 83%, respectively; Fig 1). Graft survival free of rejection tended to be higher in those patients with < 10 EMM (94% vs 76%), but this did not achieve statistical significance ($P = .365$; Fig 2). Anti-class I HLA antibodies were determined in 17 patients; 5 showed a positive result. Those patients with ≥12 HLA-I EMM as well as those with ≥8 HLA-A EMM had an odds ratio (OR) of 0.48 (95% CI, 0.06–3.99) for the presence of anti-HLA antibodies. For HLA-B, 4 of the 5 patients who developed anti-HLA antibodies had ≥6 EMM with an OR of 5.6 (95% CI, 0.47–66.45; Table 2).

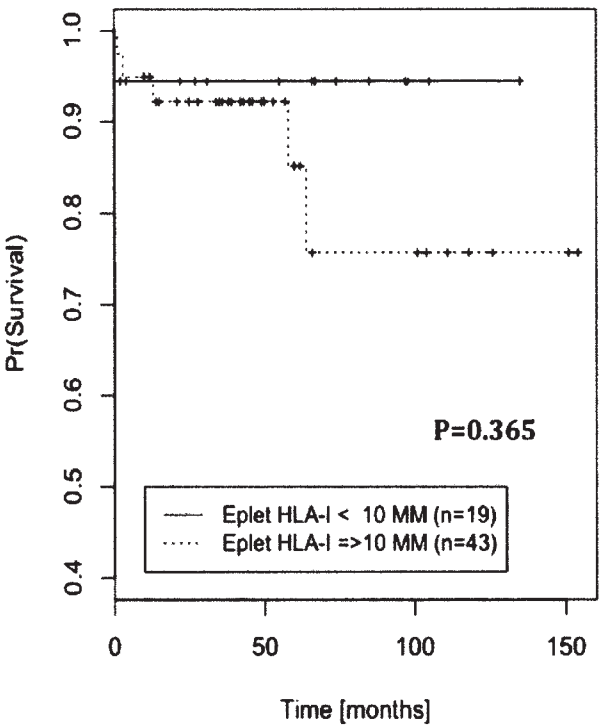

Fig 2. Rejection-free graft survival for class I eplets matching using the Kaplan-Meier method.

Table 2. Presence of Anti–HLA Antibodies During the Posttransplant Follow-up According to Loci HLA-B Eplets Mismatch

Antibodies	<6 EMM	≥6 EMM	Total
(+)	1	4	5
(−)	7	5	12
Total	8	9	17

Odds ratio, 5.6 (95% confidence interval, 0.47–66).

A comparison between EMM and traditional HLA antigen MM (HLA-A and -B) on the presence of anti–HLA-I antibodies was further performed (Table 3). No differences were found between both methods in relation to HLA-A. For HLA-B patients with ≥6 EMM, sensitivity was 80% (95% CI, 61–99) and specificity 58% (95% CI, 35–82), compared with a sensitivity of 40% (95% CI, 17–63) and specificity of 75% (95% CI, 54–95) for patients with 2 HLA-B MM.

DISCUSSION

In this group of kidney transplant patients, structural compatibility of loci HLA-I determined by the HLA Matchmaker algorithm eplet version 2.1, did not show differences in graft survival and graft survival free of rejection. Based on the theoretic principles of the algorithm, one of its possible applications could be to predict the appearance of anti-HLA antibodies. In the present study, although the number of patients was very small, there was a tendency toward higher risk of presenting anti HLA antibodies in those patients with ≥6 HLA-B EMM.

When comparing the value of HLA Matchmaker versus traditional HLA-A and -B antigen matching, on the presence of anti HLA-I antibodies, HLA Matchmaker showed a better sensitivity and a lower specificity for locus B than 2 HLA antigens MM. An important limitation of this study was the need to apply a conversion program from serologic to 4-digit allele typification. This reduced importantly the number of patients included in the study, because there was no possible conversion for some prevalent antigens in our

Table 3. Comparison Between Eplet and Serologic Compatibility for Loci HLA-A and -B as Predictors of the Presence of anti-HLA I Antibodies

	HLA A		HLA B	
	≥8E (95% CI)	2 MM (95% CI)	≥6E (95% CI)	2 MM (95% CI)
Sensitivity (%)	40 (17–63)	40 (17–63)	80 (61–99)	40 (17–63)
Specificity (%)	42 (18–65)	42 (18–65)	58 (35–82)	75 (54–95)
PPV (%)	22 (2–42)	22 (2–42)	44 (21–68)	40 (17–63)
NPV (%)	63 (39–85)	63 (39–85)	88 (72–100)	75 (54–95)

population. HLA Matchmaker is a promising tool in predicting the appearance of anti-HLA antibodies. In order to improve the predictive value of HLA Matchmaker, further development in the conversion algorithms for serologic defined HLA, suitable for other populations, would be desirable.

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