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Research Article

AN OVERVIEW OF HUMAN LEUKOCYTEANTIGEN (HLA) MATCHING IN RENAL TRANSPLANT PATIENTS IN DR. KARIADI HOSPITAL SEMARANG: A SINGLE CENTER REPORT

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ABSTRACT

Background: Renal transplant is one of the treatment options for patients with end-stage renal failure (ESRD) and in the renal transplant process, Human Leukocyte Antigens (HLA) plays an important role. The presence of HLA matching makes the graft survive in the recipient's body and provides a favorable outcome for renal transplant patients.
Objective: To see the effect of donor-recipient relationships on HLA matching levels in renal transplant patients in Dr. Kariadi Hospital.
Method: This study used an observational study, cross sectional design. This study was conducted in July 2018 through a review of patients' medical records from 2014 to April 2018 at Dr. Kariadi Hospital Semarang. This study involved 23 patients who underwent renal transplant and underwent examination of HLA matching. HLA matching in patients would be assessed based on locus match of HLA-A, HLA-B, HLA-C, HLA-DRB1 and the results of this study were analyzed by a descriptive method.
Results: From 23 patients, there were 17 (73.91%) renal transplant patients who had donor-recipient relationships. The number of mismatch in donor-recipients relationship was only 3 (17.65%) out of 17 patients while 14 other patients were full match.
Conclusion: The HLA matching in renal transplant patients in Dr. Kariadi Hospital Semarang were closely related to donor-recipient relationship factors.

INTRODUCTION

Kidney transplantation is still the main choice of therapy in end stage renal failure patients. When the recipient's immune system recognizes a kidney that has been transplanted as a foreign body, a graft rejection will occur. As part of the body's defense mechanism, human leukocyte antigens (HLA) is the main challenge of the graft to survive in the recipient's body. HLA matching provides an outcome advantage in kidney transplants. HLA mismatching causes more patient care, decreases graft survival, and increases mortality risk.[1,2]

Matching human leukocyte antigen (HLA) alleles between donors and recipients is crucial to reduce the risk of graft-versus-host disease (GvHD), life-threatening complications. Donor search usually starts with HLA genotyping from family members to look for HLA-identical sibling which is the optimal donor. In patients with low intra-major histocompatibility complex (MHC) recombination rates, patients and blood donors have a 25% chance of identical HLA, because they share the same two HLA haplotypes.[3] In Dr. Kariadi Hospital Semarang, many patients suffer from end stage renal disease, while the number of donors is very small. HLA is used as a screening tool in determining compatibility in donor-recipient in renal transplant. With this research, it can be seen the effect of donor-recipient relationships on HLA matching levels in renal transplant patients in Dr. Kariadi Hospital.

Human Leukocyte Antigen

During the 1950s, with the increasing application of blood transfusions, some patients who had received transfusions that were suitable for both ABO and Rh were found to have a transfusion reaction. The cause of this adverse effect is binding of antibodies to white blood cells, leukocytes, causing them to clot. Most direct antibodies react to homologous human antigen H2. These are called HLA (human leukocyte antigen).[4]
Working in Paris, Jean Dausset was the first to describe the HLA antigen, which he called MAC, the first name of the first

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three donors he found that lacked MAC antigens. In studying antigenic polymorphisms, subjects who lack antigens can be more important than those who have them. When alloantiserum anti-MAC is tested against leukocytes from the donor panel, antiserum agglutates leukocytes from one half of the donor panel, but does not affect leukocytes from the other half. This frequency indicates that each blood transfusion received by serum anti-MAC donors has been positive for MAC, thus providing primary immunization and booster with MAC antigens. Today we know the MAC by another name, HLA-A2, HLA antigen with the highest frequency in most human populations. HLA-A2 is also the most intensive HLA antigen studied.[4]

With the advent of kidney transplants in the 1960s, the main goal of HLA serologists was to assess the effects of HLA match and mismatch on transplant results. To achieve this goal, more sensitive and standardized methods are needed, as well as sharing alloantisera and characterization of all general HLA antigens. Facilitating such improvements has been a series of international workshops which began in 1964 by Bernard Amos, a student from Gorer whose work moved from mice to humans. Finally, serologists define a total of 88 antigens: 28 HLA-A, 50 HLA-B, and 10 HLA-C. These are products from HLA-A, HLA-B, and HLA-C genes, respectively. In 1968 it was shown that kidney transplants involving sibling donors fared better when siblings as donors and recipients were identical HLA compared to when they were HLA different. Subsequent analysis, of thousands of transplanted kidneys between unrelated donors and recipients, shows that graft survival correlates with the extent to which HLA matches (Figure 1). HLA-A, HLA-B, and HLA-C antigens are demonstrated as the main human transplant antigens. Human MHC on chromosome 6 is also known as HLA region or HLA complex. When this area is then useful for encoding surface antigens, transplant antigens become known as class I MHC, or HLA class I, antigens to distinguish them from their second family called MHC class II, or class II HLA, antigen. Unlike MHC class I, which is expressed by all nucleated cells, MHC class II expression is limited to relatively few cell types dedicated to the immune system. Embracing both MHC I and II classes, HLA workshops continue in the 21st century. Most recently, the 17th workshop was held at Stanford and was held in 2017 at the Asilomar Conference Grounds in Pacific Grove, California. The 18th workshop will be held in Amsterdam in 2021.[4]

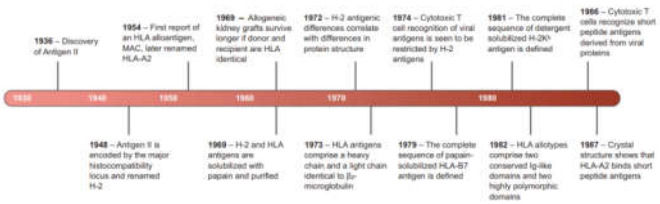

Fig 1 Timeline for the main discoveries described in this review[4]

HLA Matching

The most optimal kidney transplant results when patients and donors are in accordance with HLA. HLA incompatibility can lead to activation of alloreactive T cells and development of donor-specific antibodies (DSA), thereby significantly interfering with the survival of kidney grafts. In survival HLA-mismatched kidney transplant grafts gradually decrease with increasing numbers of incompatibilities in HLA-A, HLA-B, and HLA-DRB1. Although most studies have been devoted to studying the effects of HLA-A, HLA-B, and HLA-DRB1 mismatch on the survival of kidney grafts, several studies have shown that HLA-C and HLA-DQB1 can affect the survival of grafts as well. Because the role of HLA-A, HLA-B, and HLA-DRB1 has been widely explained, the European organ exchange organization Eurotransplant has implemented an algorithm where currently the number of HLA-A, HLA-B, and HLA-DRB1 mismatch is considered in the allocation strategy.[5] HLA matching implies that a suitable kidney graft (0–3 mismatch at HLA-A, HLA-B, and HLA-DRB1) is preferred over incompatible kidney grafts (4–6 mismatch at HLA-A, HLA-B, and HLA-DRB1). Because the number of HLA-A, HLA-B, and HLA-DRB1 mismatches is generally calculated using low-resolution HLA typing, the actual number of HLA mismatches may even be higher at high resolution levels. This allele gap between donors and recipients can contribute to a clinically relevant alloimmune response. In addition, in the current allocation strategy, mismatches at HLA-A, HLA-B, and HLA-DRB1 are considered equally important. However, the collected evidence shows that each HLA mismatch can contribute with different weights to maintain survival; some HLA mismatches seem to be more permissible / acceptable than others. Thus, a better definition of acceptable mismatch will increase the survival of graft.[5,6,7]

Immunological graft rejection can originate from T-specific cells or antibodies. T-helper cells play a role in both processes; on the one hand, CD4 + T-helper cells can provide assistance for T-cell CD8 + cytotoxics, thereby facilitating the response of CD8 + T cells directed towards the graft. However, the mechanism of CD4 + T-cells in providing assistance for CD8 + T-cells remains elusive. On the other hand, CD4 + T-helper cells play an important role in the formation of HLA-specific antibodies through activation of B cells and the transfer of IgM isotype to IgG. During this process, incompatible HLA is internalized by B-cells, processed intracellularly, and epitopes derived from HLA can then be loaded into HLA class II molecules on the B-cell surface. This T-helper cell recognizes HLA-derived epitope which promotes B cell differentiation and the transfer of IgM-to-IgG isotype. [7,10,11] Thus, production of HLA-specific IgG antibodies requires B cell activation by T-helper cells. In this process, T-helper cells and B cells recognize different epitopes from the same incompatible HLA molecule, a phenomenon called recognition.[5,6,8]

MATERIALS AND METHODS

This research was conducted through a medical record review. The study involved 23 patients who had kidney transplants at Dr. Kariadi Hospital Semarang from 2014 to April 2018. All patient medical records were carried out and data were collected in the form of age, gender, donor and recipient relationships, HLA matching. HLA matching in patients will be assessed based on locus match of HLA-A, HLA-B, HLA-C, HLA-DRB1.

RESULT

Total patients who have kidney transplants at Dr. Kariadi Hospital Semarang, from 2014 to April 2018, is 23 pairs. The characteristics of donor and kidney transplant recipients are shown in table 2.

Table 2 Characteristics of kidney transplant patients

Age	**Recipient**	**Donor**
Mean (range)	33.8 (15 - 50)	47,3 (28 - 64)
Sex	**Recipient**	**Donor**
Male (%)	17 (73.91)	13 (56.52)
Female (%)	6 (26.09)	10 (43.48)
Donor-recipient relationship		
Related (%)	17 (73.91)	
Non-related (%)	6 (26.09)	

Table 3 An overview of HLA Matching (n=23)

HLA Matching	**Pairs of patients**
Full match (%)	15 (65.22)
4 mismatch (%)	1 (4.35)
3 mismatch (%)	3 (13.04)
2 mismatch (%)	1 (4.35)
1 mismatch (%)	3 (13.04)

An overview of HLA Matching in all patients is shown in table 3, where fullmatchare found in 15 pair patients, 4 mismatchesisfound ina pair patients, 3 mismatches are found 3 patients, 2 mismatches is found in a pair patients, 1 mismatch are found in 3 pair patients.

Table 4 Donor- resipien relatedHLA Matching (n = 17)

HLA Matching	**Pairs of patients**
Full match (%)	14 (82.36)
4 mismatch (%)	0 (0)
3 mismatch (%)	0 (0)
2 mismatch (%)	1 (5.88)
1 mismatch (%)	2 (11.76)

We also calculated the rate of occurrence of mismatch in patients with the related donor-recipient relationship shown in table 4. From table 4, it can be seen that the more related relationships between donors and recipients, the more matched HLA.

DISCUSSION

This study is a preliminary study where we provide an overview of HLA matching in kidney transplant patients in Dr. Kariadi Hospital Semarang. InDr. Kariadi Hospital Semarang meanwhile HLA matching examination is limited to HLA-A, HLA-B, HLA-C, and HLA-DRB1. Where we know there is another class II MHC that can also be examined. There were 17 pairs of kidney transplant patients who had related donor-recipient relationships. This is very beneficial because the mismatch numbers themselves will decrease. In this study, the number of mismatches in related recipients was only 3 pairs of patients while the other 14 pairs were full match.

HLA typing is an important step in kidney transplantation, because the introduction of foreign HLA by recipient T lymphocytes will trigger an immune response. Lymphocyte activation initiates a cascade of mediators that direct the immune system to the allograft. HLA laboratories currently carry out serology and molecular typing methods.[10]

Class I genes (HLA-A and HLA-B) and class II (HLA-DRB1) are the most polymorphic loci throughout the HLA complex with 3830, 4647, 3382, and 2011 alleles, respectively. Polymorphism means the occurrence of several alleles, namely genes that encode various MHC antigens that are at the same locus. HLA gene polymorphisms especially in the peptide binding region are functionally important because they can cause variations in the ability and specificity of the binding of peptides. HLA genetic diversity / variation occurs at the population level. Each individual has two alleles for each HLA, one inherited from each parent.[1]

Babies inherit the HLA type from each parent, and the mother is exposed to paternal antigens expressed in developing baby cells. HLA from the father is foreign to the mother's immune system. HLA antibodies made during pregnancy do not cross the placenta and endanger the baby. Antibodies for HLA class I are more frequent than class II. The development of anti-HLA antibodies in pregnancy seems to be related to the expression of certain HLA alleles. In women, multiple pregnancies expose them to developing anti-HLA antibodies to fetal antigens of paternal origin which prevent them from becoming potential blood donors or recipients. The prevalence of HLA antibodies increases when the number of pregnancies / parity increases. The direct sensitivity of a woman to her partner and / or child makes them unsuitable as potential donors to the mother. Likewise, a study showed that female patients who received kidney allografts from their male or offspring partners experienced higher rates of rejection

CONCLUSION

This study discovered the levels of HLA matching in renal transplantation in Dr. Kariadi Hospital Semarang were closely related to donor-recipient relationship factors. It can be beneficial for next recipients to find the donor who had relationship with them. This study will help the researchers to uncover the critical areas of HLA Matching in Renal Transplant that many researchers were not able to explore.

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