HLA compatibility index: does it have a role in patients after heart transplantation?

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Aims. To determine the impact of HLA compatibility measured by the Compatibility Index, on survival, rate of rejections, malignancies and infections in patients after heart transplantation (HTx).
Methods. We carried out a retrospective analysis of 182 consecutive patients who underwent heart transplantation in our center from January 2001 to April 2010. According to degree of HLA-A, B and DR matching (Compatibility Index, CI) the patients were divided in two groups, Group A (n=83) with an IC 0-17 and group B (n=99) with an IC 18-26. There was no significant difference in demographic parameters between recipients and donors.
Results. We found no difference in rates of rejections or infections between Group A and Group B (AR: 22 (26.5%) vs. 34 (34.3%), *P*=0.2539; infections: 21 (25.3%) vs. 27 (27%) *P*=0.7637). The distribution of infections in terms of type (bacterial, viral, fungal, including Aspergillus) was similar in both groups. The incidence of malignant tumours was infrequent (3 (3.6%) vs. 4 (4.0%), *P*=0.8817). We found trend toward lower level of tacrolimus in Group A. Long term survival was similar in both groups.
Conclusions. Based on the results of our single-center trial, we found no impact of higher degree of HLA-A,-B, and -DR matching on survival, rejection episodes or infection. Further large studies are necessary to confirm our hypothesis that subjects with better HLA compatibility could require lower dose immunosuppression.

Key words: compatibility index, heart transplantation, acute cellular rejection, infection, tumours

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INTRODUCTION

The entire lifespan of a patient with organ transplant is characterised by efforts to maintain the fragile balance between the risk of rejection on the one hand and the risk of infection, and malignancy later on, on the other. The vigorous immunosuppressive protocols we have at our disposal reduce the occurrence of severe acute rejections (ARs) to a minimum, but instead we are facing the problem that the patients with a functioning organ, die of severe infections or malignancies later on[1-3]. Unlike the situation in kidney transplantation[4] where the allocation of organs is conducted consistently according to agreements in the HLA system, it is a common practice in heart transplant patients to allocate the organ without previous knowledge of the degree of agreement in the HLA system. Even though it cannot be expected that under these circumstances, the HLA compatibility would have reasonable impact on the allocation of the heart grafts, we hypothesised that subjects with better compatibility could require lower intensity of immunosuppression.

MATERIAL AND METHODS

Definition of Compatibility Index

We chose the cut-off point of 1 disagreement in the HLA-DR system, as shown in Fig. 1. Thus we divided the patients into a group with compatibility index (CI) 0-17 and a group with CI values 18-26.

Patient population and data collection

Using a retrospective database analysis, we identified 182 consecutive patients undergoing transplantation in our facility between 1/2001 and 4/2010. According to their CIs, the patients were arbitrarily assigned to 2 groups. Group A (83 patients) with a CI in the range 0-17 and group B (99 patients) with CI values in the range 18-26. Exclusion criteria were the following: age less than 18 years, re-transplantation and mechanical cardiac support prior to transplantation.

We monitored incidence of acute cellular rejections (AR), bacterial, viral and fungal infections, duration of hospitalization, 30-day mortality and long-term survival.

The study was approved by local Institutional Ethics Committee (Protocol No. 118/2008).

Because of the retrospective nature of the study, no consent form was obtained.

Immunosuppressive protocol

The standard immunosuppressive protocol in our institution consisted of dual- or triple-drug immunosuppression, in maintenance therapy with cyklosporine A (Ciclosporinum - Sandimmunn Neoral, Novartis, Nyon, Switzerland) or tacrolimus (Tacrolimusum - Prograf, Astellas Pharma, INC, Deerfield IL, US), mycopheno-

Table 1. Basic characteristics of recipients.

Characteristics	Statistics*	Group A (CI 0-17) N=83	Group B (CI 18-26) N=99	*P*-value**
Sex (males)	N (%)	66 (79.5 %)	86 (86.9 %)	0.1831
Age [years]	N/missing	83/0	99/0	0.8674
	Mean (SD)	51.3 (10.3)	51.5 (9.9)	
	Median (Q1-Q3)	55 (47 - 58)	54 (48 - 59)	
	Minimum - Maximum	20 - 66	20 - 66	
Body Mass Index [kg/m^2]	N/missing	83/0	99/0	0.9932
	Mean (SD)	25.85 (3.50)	25.85 (3.55)	
	Median (Q1-Q3)	26.0 (23.2 - 28.7)	26.2 (23.4 - 28.4)	
	Minimum - Maximum	17.6 - 32.2	16.1 - 35.2	
Diagnosis				0.3291
CAD	N (%)	31 (37.3 %)	47 (47.5 %)	
DCM	N (%)	46 (55.4 %)	44 (44.4 %)	
Other	N (%)	6 (7.2 %)	8 (8.1 %)	
Emergency order	N (%)	53 (63.9 %)	55 (55.6 %)	0.2562
Waiting time for transplant [days]	N/missing	83/0	99/0	0.2261
	Mean (SD)	178.1 (194.3)	148.6 (172.0)	
	Median (Q1-Q3)	98 (45 - 260)	90 (27-206)	
	Minimum - Maximum	2 - 1060	1 - 1115	
Acute rejection	N (%)	22 (26.5 %)	34 (34.3 %)	0.2539

CAD– coronary artery disease, DCM – Dilated cardiomyopathy,
*Q1 = lower quartile, Q3 = upper quartile
***P*-value of Mann-Whitney test for comparison of continuous parameters between groups or Chi-square test for comparing categorical parameters

late mofetil (Mofetilis mycophenolas - Cellcept, Roche, Basel, Switzerland) and corticosteroids (in 10% of patients). All patients received initial induction therapy of daclizumab (Daclizumab - Zenapax, Roche, Basel, Switzerland). Daclizumab was routinely administrated in the direct postoperative phase, as well as statins in the maintenance therapy[5].

Schedule of endomyocardial biopsies

Endomyocardial biopsies were carried out once a week during the first month after the transplantation, once in two weeks during the second month, and once a month later on, for a total of 10 EMBs within the first year after HTx. Histological findings were assessed according to the Banff classification.

Statistical analysis

The baseline characteristics of recipients and donors and levels of immunosuppressants 6, 12 and 18 months after heart transplantation were analyzed descriptively and compared between the groups (Group A with CI 1-17 vs. Group B with CI 18-26).

Descriptive statistics used for the presentation of data are the following: absolute and relative frequencies for categorical parameters and means, standard deviation (SD), median, lower quartile (Q1) and upper quartile (Q3), minimum and maximum for continuous parameters.

As the assumption of normality was markedly violated for most of the continuous parameters (Shapiro-Wilk' test), Mann Whitney and Chi Squared test were used. Patient survival was assessed with the Kaplan-Meier analysis. The statistical difference between the survival curves was calculated by the Gehan-Wilcoxon test. Results with *P*-value < 0.05 were considered statistically significant.

Table 2. Basic characteristics of donors.

Characteristics	Statistics*	Group A (CI 0-17) N=83	Group B (CI 18-26) N=99	*P*-value**
Sex (males)	N (%)	65 (78.3 %)	84 (84.8 %)	0.2544
Age [years]	N/missing	83/0	99/0	0.3096
	Mean (SD)	37.8 (11.7)	35.7 (13.2)	
	Median (Q1-Q3)	39 (28 - 48)	37 (22 - 47)	
	Minimum - Maximum	15 - 58	11 - 57	
Body Mass Index [kg/m^2]	N/missing	83/0	99/0	0.3834
	Mean (SD)	24.49 (2.98)	24.87 (2.81)	
	Median (Q1-Q3)	24.6 (22.5 - 26.2)	24.7 (23.1 - 26.9)	
	Minimum - Maximum	16.1 - 36.6	18.5 - 33.2	
Cause of death				
Craniotrauma	N (%)	47 (56.6 %)	55 (55.6 %)	0.6112
SAH	N (%)	28 (33.7 %)	32 (32.3 %)	
Ischemia	N (%)	7 (8.4 %)	12 (12.1 %)	
Tumor		1 (1.2 %))	-	
LV EF	N/missing	83/0	99/0	0.6311
	Mean (SD)	60.1 (5.8)	60.5 (5.1)	
	Median (Q1-Q3)	60 (55 - 65)	60 (58-65)	
	Minimum - Maximum	45 - 75	46 - 75	
CIT [min]	N/missing	83/0	98/1	0.4220
	Mean (SD)	157.93 (59.0)	164.6 (52.6)	
	Median (Q1-Q3)	166 (99 - 199)	170 (129 - 200)	
	Minimum - Maximum	63 - 278	60 - 264	

SAH – subarachnoid hemorrhage, LV EF – left ventricular ejection fraction, CIT - cold ischemia time
*Q1 = lower quartile, Q3 = upper quartile
***P*-value of Mann-Whitney test for comparison of continuous parameters between groups or Chi-square test for comparing categorical parameters

RESULTS

Clinical profile of patients

According to their CIs, the patients were arbitrarily assigned to 2 groups. Group A (83 patients) with a CI in the range 0-17 and group B (99 patients) with CI values in the range 18-26. The mean (SD) follow-up in group A was 4.9 (3.1) years, in group B 5.3 (3.4) years.

Table 1 shows the basic characteristics in both recipient groups, and Table 2 the characteristics of the graft donors. There was no significant difference in demographic parameters between recipients and donors.

Acute rejections, infections and malignant tumours

We found no difference in rates of both rejections and infections between Group A and Group B (AR: 22 (26.5%) vs. 34 (34.3%), *P*=0.2539; infections: 21 (25.3%) vs. 27 (27%), *P*=0.7637). The distribution of the infections in terms of types (bacterial, viral, fungal, including Aspergillus) was similar in the two groups. The incidence of malignant tumours was infrequent (3 (3.6%) vs. 4 (4.0%), *P*=0.8817).

Levels of immunosuppressive treatment

Comparing the levels of tacrolimus or cyclosporine A during the period of 18 months after the HTx, we only found a trend toward lower level of tacrolimus in Group A 6 months after HTx (Table 3, Fig. 2 and 3).

Patient survival

The survival analysis according to Kaplan-Meier shows that long-term survival was similar in both groups (Fig. 4).

Table 3. Comparing levels of immunosuppressives 6, 12 and 18 months after heart transplantation.

Characteristics	Statistics*	Group A (CI 0-17) N=83	Group B (CI 18-26) N=99	*P*-value**
Tacrolimus [μg/L]				
6 months after HTx	N	47	51	
	Mean (SD)	11.36 (4.65)	13.49 (5.35)	0.0585
	Median (Q1-Q3)	11.1 (8.4 - 13.5)	13.2 (8.7 - 17.4)	
	Minimum - Maximum	4.7 - 27.2	4.3 - 27.0	
12 months after HTx	N	40	45	
	Mean (SD)	11.15 (3.45)	11.26 (4.23)	0.9345
	Median (Q1-Q3)	10.9 (9.1 - 13.5)	10.9 (7.6 - 14.3)	
	Minimum - Maximum	2.5 - 19.0	2.5 - 22.3	
18 months after HTx	N	33	39	
	Mean (SD)	10.05 (2.74)	9.98 (3.27)	0.6668
	Median (Q1-Q3)	10.4 (8.6 - 11.4)	9.8 (8.3 - 11.7)	
	Minimum - Maximum	3.8 - 15.4	1.5 - 19.7	
Cyclosporine A [μg/L]				
6 months after HTx	N	49	61	
	Mean (SD)	211.35 (64.28)	224.24 (62.42)	0.4498
	Median (Q1-Q3)	208.5 (177.0 - 243.0)	213.5 (182.0 - 248.0)	
	Minimum - Maximum	59.0 - 338.0	103.0 - 409.0	
12 months after HTx	N	39	51	
	Mean (SD)	187.90 (64.87)	169.87 (50.72)	0.3491
	Median (Q1-Q3)	173.0 (140.0 - 226.0)	162.0 (135.0 - 198.0)	
	Minimum - Maximum	90.0 - 424.0	83.0 - 289.0	
18 months after HTx	N	30	48	
	Mean (SD)	161.21 (50.05)	166.86 (48.34)	0.5818
	Median (Q1-Q3)	156.0 (122.0 - 192.0)	163.5 (123.5 - 207.0)	
	Minimum - Maximum	92.0 - 319.0	81.0 - 263.0	

HTx - heart transplantation

*Q1 = lower quartile, Q3 = upper quartile

***P*-value of Mann-Whitney test for comparison of continuous parameters between groups or Chi-square test for comparing categorical parameters

DISCUSSION

We present the results of a single-center study that assessed the relationship of HLA compatibility with: acute cellular rejections, infections, malignant tumours, long-term survival and intensity of immunosuppresive treatment. We found no significant relationship between CI and either rate of acute rejections or the rate of infections. The rate of malignancy was similar in the two samples. Interestingly, we found lower level of tacrolimus early (6 months) after HTx in subjects with better HLA compatibility.

The main antigenic stimulus for graft rejections comes from the HLA system. T-cells recognize genetically determined HLA antigens and initiate an immune response to foreign antigens. This explains why knowledge of HLA system agreements has received such intense attention of transplantologists across all organs.

In the field of kidney transplants (KT), patients with higher levels of agreement in the HLA system have a better prognosis and better long-term survival[4,6]. Recent studies have even suggested that an HLA-DR system disagreement is a significant risk factor for the development of non-Hodgkin lymphoma after KT, and also an important factor contributing to the accelerated development of osteoporosis, causing femoral neck fractures and resulting in marked increase in morbidity following KT (ref.[7,8]). A slightly different situation accompanies simultaneous kidney and pancreas transplantation. The results are excellent, regardless of the level of HLA system agreement[9]. When only pancreas is transplanted, in spite of the relatively small number of eligible patients,

	group A																	group B								
CI	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26
A	0	1	2	0	1	2	0	1	2	0	1	2	0	1	2	0	1	2	0	1	2	0	1	2	0	1	2
B	0	0	0	1	1	1	2	2	2	0	0	0	1	1	1	2	2	2	0	0	0	1	1	1	2	2	2
DR	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	1	2	2	2	2	2	2	2	2	2

Fig. 1. Serological Definition of HLA-Antigens Class I and II.

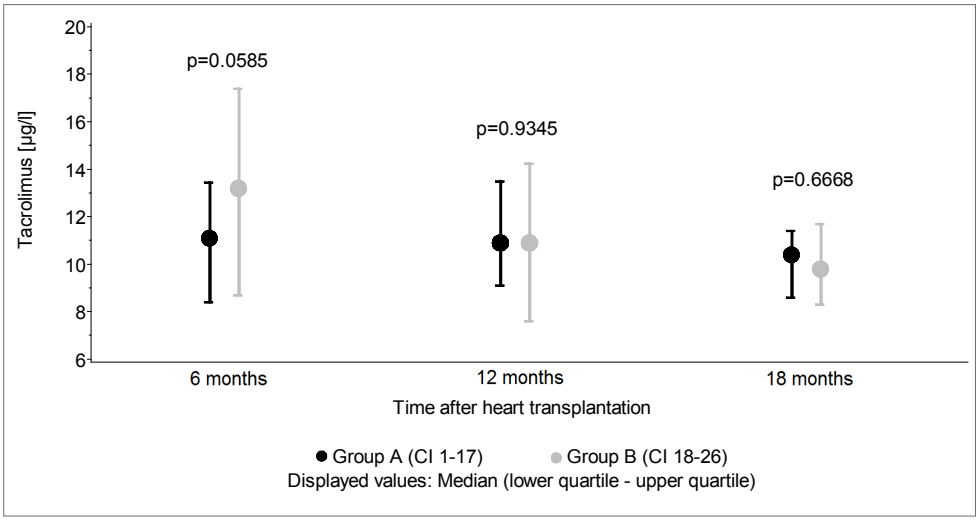

Fig. 2. Comparing levels of tacrolimus.

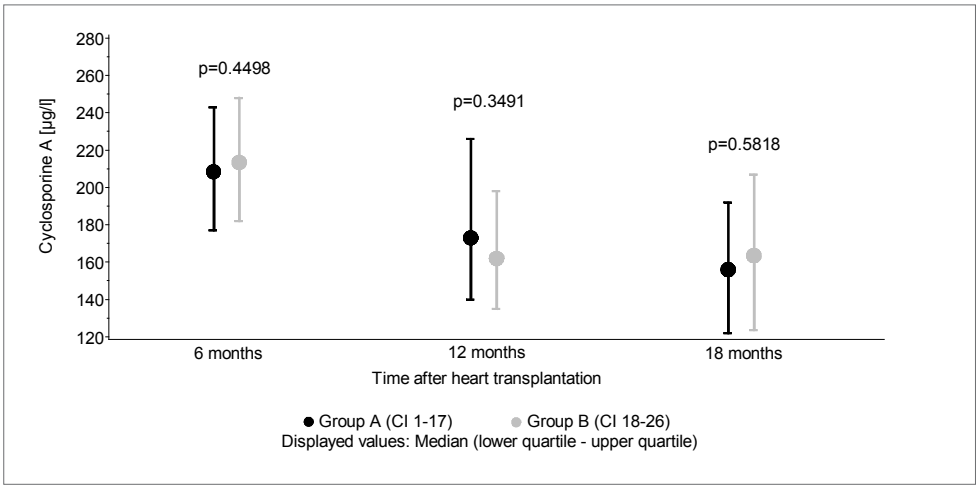

Fig. 3. Comparing levels of cyclosporine A.

acceptable results are obtained even for low levels of HLA compatibility[10].

Regarding liver transplants, no effect of HLA system compatibility was found on longer patient survival, though there have been reports of a lower rate of acute rejections in patients with higher levels of HLA compatibility[11,12]. Balan demonstrated worsened survival in a series of more than eight hundred patients after liver transplantation who had disagreements in locus A, and confirmed the well-known truth that HLA system agreement was associated with higher rate of recurrence of autoimmune liver damage and hepatitis C in the liver graft[13].

Lung transplants, on the other hand, have been shown to be associated with both better survival and lower rate of rejections in patients with good HLA system agreements[14].

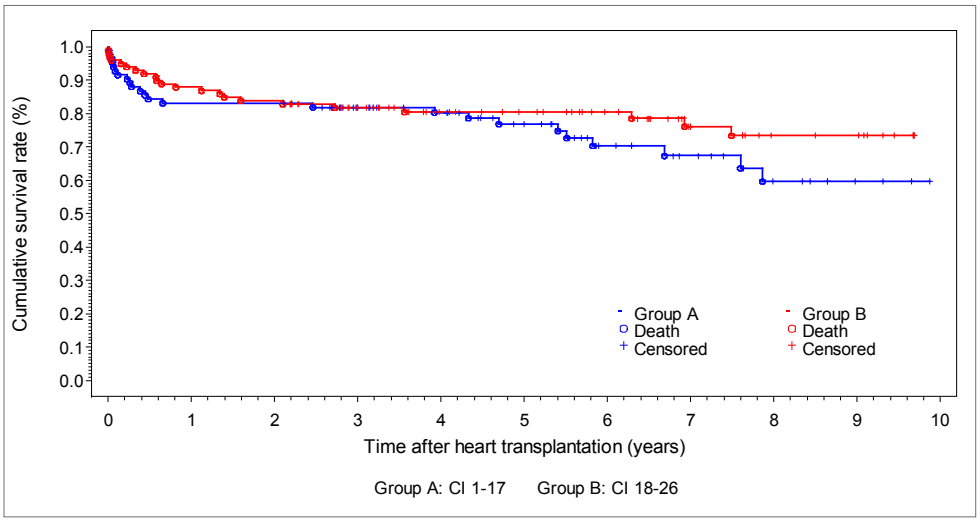

Fig. 4. Survival analysis (Kaplan-Meier).

Between 1987 and 1997 several articles were published addressing these problems as related to heart transplants[15-19]. The results, however, were controversial. While there was confirmation of the results for kidney transplants of Opelz, Yacob, Smith and Taylor, on the other hand Mascaretti and Sheldon failed to demonstrate the influence of HLA agreements on patient prognosis in terms of better survival and lower rates of complications after HTx.

Probably the most extensive analysis of the impact of HLA compatibility on the post-transplantation course for kidney, liver and heart transplants was conducted by Opelz[20]. His retrospective analysis included a total of 150,000 patients undergoing transplantations in different centres between 1987 an 1997, and the conclusions of this extensive study were clear. The study demonstrated significantly longer survival of kidney and cardiac grafts for good HLA agreement, but no influence of this agreement on the survival of liver grafts.

Event though we have not shown any "protective" effect of HLA compatibility against acute graft rejections, infections or malignancies, we demonstrated a clear trend toward lower dosage of immunosuppressive medication in subjects with higher number of agreements in the HLA system. The difference in survival between the two groups was not statistically significant.

CONCLUSION

Our single-center trial showed no significant impact of higher degree of HLA-A,-B, and -DR matching on survival, rejection episodes or infection. Further large studies are necessary to confirm our hypothesis that subjects with better HLA compatibility may require lower dose immunosuppression. In this case, based on immunological similarity and thus-reducing the dose of immunosuppressants without the risk of increased rate of AR, one might assume lower rates of infectious and possibly also oncological comorbidities in these patients.

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CONFLICT OF INTEREST STATEMENT

Author's conflict of interest disclosure: The authors stated that there are no conflicts of interest regarding the publication of this article.

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