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HLA-DRB1 haplotype did not affect the medium-term results of total knee arthroplasty in patients with rheumatoid arthritis

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Abstract This study investigated whether the HLA-DRB1 "susceptible allele" (SA) genotype is predictive for total knee arthroplasty (TKA) failure in patients with rheumatoid arthritis (RA). The results of 49 TKAs (30 RA patients) with an average follow-up of 7.9 years (range 5–15 years) were analyzed using a 12-item questionnaire and the Knee Society system. HLA-DRB1 alleles were used to estimate the severity of RA and divide the patients into three categories depending upon the gene dose of SA (SA+/+, SA+/−, and SA−/−). For all three categories, the 12-item questionnaire had significantly improved postoperatively, but without significant difference. We divided the 12 items of the questionnaire into two groups: knee-relevant parameters and general parameters. Patients in all three groups improved similarly in knee-relevant parameters. In contrast, those homozygous for SA (SA+/+) benefited less in general parameters. The average radiolucency score was 1.87 mm, with no difference being detected among the three groups. The HLA-DRB1 genotype did not affect the survival of the knee implants. Overall, patients without the RA-associated HLA gene benefited most from TKA as they improved not only in knee function, but also in parameters of general functional status.

Key words Disease severity · Human leukocyte antigen (HLA) · Rheumatoid arthritis (RA) · Susceptible allele (SA) · Total knee arthroplasty (TKA)

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Introduction

Rheumatoid arthritis (RA) is an autoimmune disease that primarily targets the diarthrodial joints and results in progressive function loss and eventually disability. Although outcomes vary widely, more than 40% of patients have developed a disability after 10 years.[1] RA is a multigene disease with a complex inheritance pattern. Of all disease-risk genes, polymorphic HLA alleles are the best studied. An association between RA and HLA-Dw4 was first reported by Stastny in 1976[2] and was subsequently confirmed by several other investigators throughout the world.[3–5] DNA sequence analysis of RA-susceptible alleles in HLA-DRB1 has indicated that disease susceptibility can be mapped to a sequence motif in the third hypervariable region of the HLA-DRβ chain. This sequence stretch has been named the shared epitope, and is characterized by the amino acid motif QRRAA in HLA-DRB1*0101, *0102, *0404, *0405, *0408, *0410, and *1402, the QKRAA motif in HLA-DRB1*0401, and the RRRAA motif in HLA-DRB1*1001.[6]

Evidence has accumulated that HLA-DR molecules in RA not only function as susceptibility factors, but also have a role in modulating disease progression.[4] Extraarticular spreading of RA, known to increase the risk of morbidity and mortality, has been associated with a double dose of RA-associated HLA genes.[7] Furthermore, the destruction of knee joints progresses more rapidly in RA patients who are positive for the shared epitope, and they need total knee arthroplasty (TKA) earlier in the disease course.[8] Allelic combinations of HLA-DR genes can thus be utilized as surrogate markers to estimate disease severity. Arthroplasty surgery is one of the most successful surgical procedures for severe destruction of the knee joint. However, the prosthesis dose not last forever. The failure of some arthroplasties is caused by aseptic loosening, which is often accompanied by bone destruction adjacent to the prosthesis–bone interface.[9] There is evidence that the development of pseudosynovia at the cement–bone interface of the prosthesis seems to participate in aseptic loosening.[10] Immuno-

histochemical analysis of periprosthetic tissue revealed that $CD4^+$ T cells were preferentially encountered in aggregates that accumulated around small capillaries.[11]

Several features of RA would affect the short- and long-term outcome of TKA in RA patients. RA patients are regularly treated with corticosteroids and immunosuppressants that potentially increase the risk of arthroplasty failure. Conversely, the systemic nature of RA decreases the activity level of affected patients, which could improve the necessity for knee replacements. It remains unclear how disease severity influences the long-term result of joint arthroplasty. We have an interest in the influence of the HLA-genotype, which is believed to be associated with disease severity, on the long-term outcome of TKA in RA patients. This study was designed to examine the medium-term outcome of TKA in RA patients, with particular interest in the possible effect of a shared epitope on HLA-DRB1 alleles.

Materials and methods

Between 1982 and 1993, 143 TKAs were performed on 91 consecutive patients with RA in Kansai Medical University Hospital. All patients (80 women and 11 men) fulfilled the American College of Rheumatology 1987 criteria for the diagnosis of RA.[12] Among these were 40 patients who were genotyped for HLA-DRB1 alleles. Two patients died of causes unrelated to the index arthroplasty. None of the patients who died had had a revision. Three living patients declined a radiographic follow-up evaluation, and five patients were lost to postoperative follow-up before 5 years. Thus, 49 knees in 30 patients, including 27 females and 3 males, were available for postoperative evaluation. The average age of these 30 patients was 68.2 years (range 35–78). The follow-up ranged between a minimum of 5 years and a maximum of 15 years (mean 7.9 years).

Forty cases were available for the comparison analysis of gene frequencies, and another 40 rheumatoid patients without TKA were selected from the rheumatoid patient database.

Patients were managed with Kinematic Condylar Total Knee Replacement (Howmedica, Rutherford, NJ, USA) before July 1990, and subsequently with Kinemax Total Knee Systems (Howmedica). The femoral and tibial components were cemented in place with Simplex bone cement (Howmedica) by finger-packing. All the operative procedures were performed by one of two senior orthopedic surgeons.

The postoperative roentgenograms included standard anterior–posterior (AP) and lateral views. The X-rays were rated with the roentgenographic knee evaluation system endorsed by the Knee Society.[13] All the radiographs were examined by a single observer. The measurements of radiographs were carried out twice for each patient and generally varied by 1 degree, but rarely by more than 2 degrees.

Each patient was clinically evaluated with a 12-item questionnaire developed to analyze knee function. This questionnaire was modified from the Stanford Health Assessment Questionnaire by J. Dawson.[14] Each item is scored from 1 to 5, and the scores are combined to produce a single score with a range from 12 (least difficulties) to 60 (most difficulties). Sixty-two patients whose preoperative and postoperative radiographs were available were sent a return envelope and asked to complete the questionnaire before the operation and at the follow-up evaluation. Of these 62 patients, seven had moved their residence, four were dead, and ten did not respond. Of the remaining 41 patients who were available for analysis, 29 were genotyped for HLA-DRB1 alleles.

After obtaining the study subjects' informed consent, peripheral blood was drawn. A commercial HLA-DRB1 typing kit (Innogenetics, Zwijnaarde, Belgium) was used to determine the HLA-DRB1 genotype.

HLA-DRB1*0101, *0102, *0401, *0404, *0405, *0410, *1402, and *1001 were regarded as susceptible alleles for RA on the basis of previous reports.[4,15] The patients were divided into three groups according to their possession of susceptible alleles. The SA+/+ group consisted of patients with two susceptible alleles in both of the HLA-DRB1 genes. The SA+/− group consisted of patients with one susceptible allele and one nonsusceptible allele. The SA−/− group consisted of patients with two nonsusceptible alleles.

Statistical analysis

Either the χ^2 test or the Wilcoxon signed rank test was used, as appropriate. Probability values were established using the specific statistical software StatView (Abacus Concepts, Berkeley, CA, USA). A comparison was considered significant when $P < 0.05$.

Results

Inheritance of two RA susceptible genes increases the risk of destructive knee disease

To assess whether HLA-DRB1 alleles had an influence on the degree of destructive knee disease in RA, we compared HLA-DRB1 genotypes in patients with and without TKA (Table 1). Two-patient cohorts were matched for disease

Table 1. Distribution of susceptible alleles in relationship to TKA

	RA patients with TKA ($n = 40$)	RA patients without TKA ($n = 40$)
SA+/+	11(27.5)	3(7.1)*
SA+/−	18(45)	22(52.4)
SA−/−	11(27.5)	15(35.7)

Values are the number (%) of patients
RA, rheumatoid arthritis; TKA, total knee arthroplasty; SA, susceptible allele
* $P = 0.04$

Table 2. Characteristics of RA patients with TKA

	Total	SA +/+	SA +/−	SA −/−
Number of patients	30	8	12	10
Sex (male/female)	3/27	0/8	0/12	3/7
Number of operated joints	49	14	20	15
Age at the time of the operation (mean ± SD) (years)	54.9 ± 9.6	51.3 ± 5.5*	58.4 ± 8.8	53.7 ± 12.5
Disease duration at the time of the operation (mean ± SD) (years)	14.0 ± 8.1	16.4 ± 8.0	11.3 ± 4.4	15.5 ± 11.0
Duration of follow-up (mean ± SD) (years)	7.9 ± 2.6	8.5 ± 2.6	7.2 ± 2.3	8.5 ± 2.9

RA, rheumatoid arthritis; TKA, total knee arthroplasty; SA, susceptible allele
* $P = 0.03$

Table 3. Alignment of endoprosthesis[a]

Angle	SA −/− ($n = 14$)	SA +/− ($n = 20$)	SA +/+ ($n = 15$)	P value[b]
AP femoral angle (α)	95.7 ± 2.1	96.4 ± 3.0	97.0 ± 3.6	0.47
AP tibial angle (β)	89.0 ± 3.1	88.7 ± 3.2	87.6 ± 4.2	0.52
Lateral femoral angle (γ)	8.4 ± 7.4	3.5 ± 4.5	4.3 ± 6.1	0.06
Lateral tibial angle (δ)	94.3 ± 3.6	91.7 ± 5.2	82.3 ± 33.3	0.19
Femorotibial angle (FTA)	175.3 ± 3.3	174.9 ± 2.6	175.4 ± 5.2	0.93

[a] Values shown are mean ± SD
[b] Significance level calculated using one-way factorial ANOVA
One knee was found to be in a varus position. On the lateral-view radiograph, one femoral component in each group was placed in slight extension
SA, susceptible allele

duration. Among the 40 patients with TKA, only 27.5% lacked HLA-DRB1 genes conferring RA risk. However, the majority of patients with less destructive knee disease typed negative for RA-susceptible genes, and only a small proportion of the patients expressed two RA-risk alleles. In summary, RA patients with RA-risk alleles on both haplotypes are much more likely to progress to advanced destructive involvement of the knee joints necessitating TKA.

Distribution of RA severity categories among patients with TKA

An allelic combination of RA-susceptible genes can be used as a surrogate marker to estimate disease severity. To estimate the medium-term outcome of TKA in RA patients, and to investigate the possible influence of the severity of the underlying polyarthropathy, 30 patients with TKA who were available for follow-up for a minimum of 5.5 years were divided into three categories according to whether or not they possessed susceptible alleles (Table 2). Most of the patients carrying two RA-susceptible genes had bilateral TKAs (75%). In contrast, only half of the patients who lacked RA-related genes had unilateral TKA (50%). Double-dose RA patients were significantly younger (51.3 years) than single-dose patients (58.4 years) when they required knee replacements ($P = 0.03$).

Radiographic results

The alignment of each endoprosthesis was analyzed using anteroposterior (AP) and lateral radiograph views (Table 3). Overall, each component was seated in an appropriate position and there were no significant differences among the three groups. In five knees the α-angle was greater than 100°, and there was no femoral component with an angle less than 90°.

A radiolucent line was noted at the bone–cement interface in 53.3% of the arthroplasties in the SA−/− group, 57.9% in the SA+/− group, and 53.8% in the SA+/+ group. The lines were 3 mm or more thick in 13.3%, 15.7%, and 15.4%, respectively. All the radiolucent lines were incomplete, and were seen under either the medial or the lateral tibial plateau. The radiolucent score was found by summing the thickness (mm) of the radiolucent line in each zone (Table 4).

Medium-term outcome of TKA measured by the 12-item knee questionnaire

Table 5 gives the mean scores for each question on the knee questionnaire before surgery and at final follow-up. In all three groups, the postoperative summed scores had decreased significantly, but no significant differences were found among the three groups ($P = 0.434$). Subsequently,

Table 4. Assessment of radiolucency in knee arthroplasty[a]

Area	SA −/− (n = 14)	SA +/− (n = 20)	SA +/+ (n = 15)	P value[b]
Femur (lateral)	0.8 ± 1.1	0.6 ± 1.0	0.4 ± 0.8	0.53
Tibia (AP)	1.1 ± 1.5	0.9 ± 1.0	0.7 ± 1.1	0.62
Tibia (lateral)	0.3 ± 0.6	0.4 ± 0.8	0.2 ± 0.2	0.73
Total	2.3 ± 2.8	1.9 ± 2.5	1.3 ± 1.8	0.58

[a] Values shown are mean ± SD
[b] Significance level calculated using one-way factorial ANOVA
SA, susceptible allele

the 12 items were divided into two groups according to their relevance to knee function. There were five knee-relevant parameters, and the rest were labeled general parameters. In terms of knee-relevant parameters, significant improvements were observed in three items in the SA+/+ and SA+/− groups, and in four items in the SA−/− group. The numbers of general parameters which showed significant improvement were three in the SA+/+ group, four in the SA+/− group, and 6 in the SA−/− group. There was a negative correlation between the general parameters and the dose of susceptible alleles. Trouble with transport was not significantly improved in any of the groups, although usual levels of pain had significantly decreased in all groups ($P < 0.0001$).

Discussion

There have been increasing concerns that the longevity of TKA will be limited by loosening, and that the appearance of radiolucent lines at the bone–cement interface may be a prodrome to clinical loosening.[16] The meaning of a radiolucent line is controversial; radiolucent lines can and do develop in some knees and not in others, and the factors responsible for this seem to be related to as yet undefined factors at the bone–cement interface. The cause of loosening is not clear, but may be due in part to secondary host reactions against the implant-derived, foreign material. Recently, a layer of connective tissue, called synovial-like membrane, developing at the implant–bone interface has received attention.[17] Histomorphological analyses have demonstrated that the periprosthetic inflammatory tissue contains various types of cell, including macrophages, fibroblasts, T cells, and multinucleated giant cells.[18,19] Interestingly, the existence of T lymphocytes on this membrane suggests that an antigen recognition event may be involved in the course of aseptic loosening of the endoprosthesis. Therefore, we speculated that the radiolucent zone might be an indication of RA synovitis. If the synovial-like membrane at the implant–bone interface and the inflamed synovial membrane in RA did share similar mechanisms, patients with more severe RA might have more pronounced radiolucent zones. However, patients in the severe disease category had a tendency to have less radiolucency, although there was no statistical difference (2.3 mm in SA−/−, 1.9 mm in SA+/−, and 1.3 mm in SA+/+).

We had forecast that patients in the SA+/+ group might gain less benefit from TKA because the bone quality of patients in this category is generally poor. Our results suggest that the activity of the patient, more than the disease severity, may determine aseptic loosening. Patients with multiple joint involvement may have some advantage when it comes to the long-term outcome of joint arthroplasty; expectations of functional improvement are often limited, and overall the patient may place less stress on the prosthetic joint and the bone–cement interface than the more active patient with limited joint involvement.

Most of the radiographs were satisfactory with regard to femorotibial alignment and the position of the individual components. These results were consistent in each group and it seemed that the severity of the RA process did not influence the radiographic results of TKA.

To assess the clinical outcome of TKA, the questionnaire developed by Dawson was used in this study.[14] Because it consists of only 12 items, it imposed very little burden on the patients and resulted in a consistently higher completion rate when compared with other widely used health-status questionnaires. Every patient who replied had completed every question. This questionnaire was developed to be used specifically to evaluate the outcome of TKA. However, this system is still susceptible to other influences, such as pain and disability arising from other weight-bearing joints and other symptomatic conditions. Therefore, the 12 items were divided into two groups: parameters directly related to knee function, and those reflecting the general level of function. The knee-relevant parameters consisted of five items, all dependent simply on knee functions. In contrast, the remaining seven items were unified as general parameters because they were probably influenced by other determining factors.

The scores before and after surgery were not different among the three groups, and improved to the same extent in each category. The numbers of knee-relevant parameters which had improved after surgery were three in the SA+/+ and SA+/− categories, and four in the SA−/− patient subset. The general parameters were obviously influenced by disease severity; only three out of seven parameters had improved after surgery in the SA+/+ group. In contrast, six parameters had improved in patients with less severe RA. From these findings, it can be concluded that the severity of RA exerts the most influence on the general parameters.

We examined the medium-term clinical and radiological outcomes of cemented TKA in 30 patients with rheumatoid arthritis, and found that both were excellent. The severity of the disease, as estimated by the expression of disease-risk genes, did not affect the survival of the knee implants. Patients without RA-associated HLA alleles, who were assumed to have a mild form of the disease, overall benefited most from TKA. In these patients, not only was knee function improved, but the parameters of general functional status were also higher after surgery. On the other hand, patients with susceptible alleles in both HLA-DRB1 genes benefited less in the general parameters. Multiple joint involvement is very common in patients with severe RA, so the status of adjacent joints may contribute to

Table 5. Clinical assessment using a 12-item questionnaire

Question	SA +/+ group			SA +/− group			SA −/− group		
	Preop	Final	*P*	Preop	Final	*P*	Preop	Final	*P*
Knee-relevant parameters									
1. Usual levels of knee pain	4.71 (0.76)	1.57 (0.79)	0.018	4.58 (0.67)	2.33 (1.07)	0.0033	4.45 (0.69)	2.00 (1.26)	0.0051
2. Pain in standing up from sitting	4.29 (1.11)	1.43 (0.53)	0.018	3.42 (1.44)	1.92 (1.16)	0.0077	3.55 (0.93)	2.00 (1.00)	0.011
3. Difficulty with kneeling	4.29 (0.49)	4.00 (1.73)	0.69	4.08 (1.16)	3.83 (1.59)	0.61	4.45 (0.69)	3.45 (1.51)	0.043
4. Sense of knee instability	3.57 (1.40)	1.29 (0.49)	0.028	3.33 (1.50)	2.08 (1.24)	0.012	3.09 (1.58)	1.91 (1.14)	0.14
5. Trouble with walking down stairs	4.57 (0.53)	3.86 (1.35)	0.25	3.83 (1.19)	3.50 (1.57)	0.45	4.09 (1.04)	2.64 (1.36)	0.0077
Subtotal	21.43 (3.55)	12.14 (2.12)	0.018	19.25 (4.62)	13.25 (5.19)	0.0068	19.64 (3.88)	12.00 (4.78)	0.0076
No. of parameters improved	3 of 5			3 of 5			4 of 5		
General parameters									
1. Trouble with washing and drying	4.14 (1.07)	3.14 (1.86)	0.31	4.25 (0.87)	2.75 (1.71)	0.018	4.00 (1.10)	2.73 (1.56)	0.044
2. Trouble with transport	4.43 (0.79)	4.29 (0.95)	0.69	4.08 (1.16)	3.67 (1.44)	0.29	4.09 (1.04)	3.55 (1.37)	0.14
3. Walking time before severe pain	3.86 (1.35)	3.14 (1.35)	0.40	3.75 (1.22)	3.00 (1.21)	0.075	3.64 (1.50)	2.00 (1.55)	0.015
4. Limping when walking	4.71 (0.49)	2.14 (1.46)	0.028	3.67 (1.56)	2.33 (1.56)	0.028	4.64 (0.67)	2.27 (1.35)	0.0051
5. Pain in bed at night	4.14 (1.46)	1.71 (0.95)	0.028	3.83 (1.64)	1.92 (0.90)	0.018	4.18 (0.87)	2.09 (1.22)	0.0077
6. Work interference due to pain	4.57 (0.53)	1.57 (0.79)	0.018	3.92 (1.31)	2.42 (1.31)	0.0077	3.64 (1.21)	1.91 (0.94)	0.0077
7. Doing household shopping alone	4.43 (0.79)	3.71 (1.38)	0.29	3.92 (1.31)	3.33 (1.61)	0.11	3.91 (1.30)	1.91 (0.54)	0.0051
Subtotal	30.29 (4.82)	16.00 (3.56)	0.028	27.42 (8.35)	19.42 (7.75)	0.0051	28.09 (6.30)	16.46 (6.44)	0.0033
No. of parameters improved	3 of 7			4 of 7			6 of 7		
Total	51.71 (8.42)	31.86 (6.36)	0.028	46.67 (12.68)	33.32 (12.32)	0.0037	47.73 (9.92)	28.45 (11.07)	0.0044
No. of parameters improved	6 of 12			7 of 12			10 of 12		

Values shown are mean ± SD
SA, susceptible allele

the discrepancy in general function after TKA. Patients in this category may require a combination of interventions to treat their disability, including measures targeted at the systematic component of RA.

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