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)

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. 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 and was subsequently confirmed by several other investigators throughout the world. 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.

Evidence has accumulated that HLA-DR molecules in RA not only function as susceptibility factors, but also have a role in modulating disease progression. 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. 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. 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 prosthetic dose not last forever. The failure of some arthroplasties is caused by aseptic loosening, which is often accompanied by bone destruction adjacent to the prosthetic–bone interface. There is evidence that the development of pseudosynovia at the cement–bone interface of the prosthesis seems to participate in aseptic loosening.
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. 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. 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. 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. 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 \( \chi^2 \) 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

Table 1. Distribution of susceptible alleles in relationship to TKA

<table>
<thead>
<tr>
<th></th>
<th>RA patients with TKA (n = 40)</th>
<th>RA patients without TKA (n = 40)</th>
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<tbody>
<tr>
<td>SA+/+</td>
<td>11(27.5)</td>
<td>3(7.1)*</td>
</tr>
<tr>
<td>SA+/-</td>
<td>18(45)</td>
<td>22(52.4)</td>
</tr>
<tr>
<td>SA-/-</td>
<td>11(27.5)</td>
<td>15(35.7)</td>
</tr>
</tbody>
</table>

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

* \( P = 0.04 \)