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HLA DRB1*01 and DRB1*04 phenotyping does not predict the need for joint surgery in rheumatoid arthritis. A retrospective quantitative evaluation of 300 French patients

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ABSTRACT

Objective. *To determine if the presence of HLA-DR disease-associated epitopes predicts the need for total joint arthroplasty or joint fusion in rheumatoid arthritis (RA).*

Methods. *Tertiary-referral, monocenter study. Three hundred RA patients (1987 ACR criteria) were retrospectively evaluated; outcome measure was recourse to total joint arthroplasty, joint fusion or bone resection. HLA-DR1 and DR4 were considered as the disease-associated epitopes (subtypes were not available for analysis). Analysis was performed using the lifetable method (Kaplan-Meyer technique).*

Results. *Of the 300 patients included, 78% were women, mean age: 56 ± 14 years, mean RA follow-up: 12 ± 9 years. Phenotyping: 73% of patients carried one (52%) or two (21%) disease-associated epitopes. Surgery was performed on 24% of the patients during follow-up. The most frequent surgery was total hip arthroplasty (13% of patients). According to lifetable analysis, 13% of patients had surgery (total joint arthroplasty or joint fusion) after 10 years of follow-up, 34% after 20 years. There was no statistically significant difference in recourse to surgery according to absence or presence (single or double-dose) of disease-associated epitopes. Similar results were observed if the event was the second surgical procedure on a given patient.*

Conclusion. *This study failed to demonstrate a relation between HLA phenotyping and the severity of RA defined by the requirement for surgery.*

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease which often leads to joint destruction. The ability to predict future destructive disease is an important goal, especially since there is a narrow therapeutic window between the stages of persistent synovitis and irreversible cartilage loss (1). Several predictors of outcome are recognized, which although useful in epidemiological studies are of limited value in clinical practice. HLA-DRB1 alleles associated with RAshare a sequence homology within the third hypervariable region (2). These alleles include HLA-DRB1*0401, *0404, *0405, *0408, *1402, *1001, *0101, and *0102 (3). HLA-DR disease-associated epitopes (DAE) have been reported to be predictive of severity in RA (4, 5). Joint surgery recourse is a well defined and easily quantified outcome for RA severity evaluation, and one which may be evaluated retrospectively.

In this study, we analyzed retrospectively in 300 RA patients the relationship between HLA-DR phenotyping and recourse to joint surgery.

Materials and methods

Patients

Outpatients fulfilling the 1987 ACR criteria for RA (6) followed in our tertiary-referral clinic (Cochin Hospital, Paris, France) were studied retrospectively. Patient selection was performed in December 2001. Patients were selected through a computer survey of patient files: visit between January 1998 and December 2001, key-words “rheumatoid arthritis” and “HLA typing”. Clinical records were reviewed: date of disease onset, date of last information (last visit or last telephone contact), rheumatoid factor status (positivity at any time during follow-up by nephelometry, positive titers ≥ 20 IU/ml), number of disease-modifying drugs (DMARDs) prescribed, history of joint surgery and dates (arthroplasties including hip, knee, shoulder or metacarpophalangeal arthroplasties, arthrodeses [joint fusions] including wrist, ankle or mediotarsal arthrodeses, bone resections including metatarsophalangeal bone resections). Synovectomies were not noted. Arthroplasties and arthrodeses were considered as reflecting structural severity of RA.

HLA-DR genotyping

After extraction of genomic DNAfrom peripheral blood cells, HLA-DR phenotyping was performed using polymerase chain reaction (PCR-SSO, Biotest Elpha, Buc, France). HLA-DRB1*01 and DRB1*04 were considered as the DAE (2). Subtypes were not available for analysis. Patients were grouped according to the number of DAE: no DAE, one DAE (DRB1*01 or

DRB1*04) or two DAE ("double-dose": DRB1*01/01, *01/04 or *04/04).

Statistical analysis

Statistical analysis was performed using PCSM software. Qualitative variables were compared by Chi-squared tests with Yates' correction and Fisher's exact test when appropriate. Duration of disease before surgery was analyzed through Kaplan-Meyer's life-table technique, with comparisons by Log-Rank tests. The significance level was set at 0.05.

Results

Patients and HLA-DRB1 alleles.

A total of 335 patient files were selected through our computer search. Twenty-two patients did not satisfy ACR criteria for RA; and for 13 patients surgery status was not available. Thus 300 Caucasian unrelated outpatients were included: they are described in Table I. There were 66 men, 234 women; mean age at last visit was 56.2 ± 14 years. Mean follow-up (mean disease duration at last visit) was 11.9 ± 9 years. A total of 71% had positive rheumatoid factor; patients had been prescribed a mean of 3.7 DMARDs (mainly methotrexate, hydroxychloroquine and gold salts).

DAE were present in a single or double dose in 218 patients (72.6%). Forty-one patients were DRB1*01 (13.6%), 116 were DRB1*04 (38.7%), 30 were DRB1*04/*04 (10%), 2 were DRB1 *01/*01 (0.7%), 29 were DRB1*04/*01 (9.7%). The only significant difference between the groups according to number of DAE was rheumatoid factor positivity (52.8%, 73% and 81.8% respectively with no, one or two DAE).

Surgery

Recourse to surgery is shown in Table II. During follow-up 72 patients (24%) had surgery: 13% arthroplasty, 11% arthrodesis, and 19% bone resection. The most frequent surgery was hip arthroplasty (39 patients, 13%). There was no statistical difference in cumulated recourse to surgery during follow-up according to number of DAE. There was also no difference in recourse to surgery according to the DRB1* phenotype: for any type of surgery, cumulated recourse to surgery concerned 12 DRB1*01 patients (29.3%), 26 DRB1*04 patients (22.4%), one DRB1*01/*01 patient, 7 DRB1*01/*04 patients (24.1%), and 9 DRB1*04/*04 patients (30%); differences were not significant. According to the type of surgery, results are similar (data not shown).

Lifetable analysis

Figure 1 represents duration of disease before first surgical procedure (arthrodesis or arthroplasty), for the 300 patients. After 10 years of follow-up, 13.1% of patients had undergone surgery (33.7% after 20 years). There was no significant difference in duration of disease before first surgical procedure, according to absence or presence (single or double dose) of DAE. Analyses according to specific genotypes, or with the event defined as any joint surgery including bone resection, gave similar results.

If the event was not recourse to the first surgery but recourse to the second surgery there were also no differences

Table I. Patient characteristics according to the number of disease-associated epitopes (DAE). DRB1*01 and *04 were considered as the DAE.

	All patients	No DAE	One DAE	Two DAE	p
Number of patients	300	82	157	61	
Women: no. (%)	234 (78)	62 (75.6)	128 (81.5)	44 (72.1)	NS
Age (years): mean ± SD [Range]	56.2 ± 14.0 [18-82]	56.2 ± 13.4 [24-82]	56.3 ± 13.7 [18-82]	55.7 ± 15.5 [25-86]	NS
Disease duration (yrs.): mean ± SD [Range]	11.9 ± 9.2 [0.2-45.6]	12.1 ± 9.8 [0.3-45.6]	12.0 ± 9.2 [0.2-43.3]	11.6 ± 8.3 [0.5-36.5]	NS
Rheumatoid factor positivity: %	71.6	52.8	73.0	81.8	0.02
Number of DMARDs: mean ± SD	3.7 ± 1.8	3.6 ± 1.8	3.7 ± 1.8	3.9 ± 1.7	NS

no.: number, SD: standard deviation

Table II. Number of surgical procedures performed over a mean follow-up period of 11.9 years in 300 RApatients, according to the number of disease-associated epitopes (DAE).

	All patients N = 300	No DAE N = 82	One DAE N = 157	Two DAE N = 61	p
Surgery: no. (%)	72 (24)	17 (21)	38 (24)	17 (28)	NS
Arthroplasty: no. (%)	39 (13)	9 (11)	21 (13)	9 (15)	NS
Arthrodesis: no. (%)	34 (11)	6 (7)	18 (11)	10 (16)	NS
Arthroplasty or arthrodesis: no. (%)	57 (19)	12 (15)	30 (19)	15 (25)	NS
Bone resection: no. (%)	21 (7)	5 (6)	12 (8)	4 (7)	NS

according to number of DAE (results not shown: after 10 years: 8%, 15% and 17% recourse to second surgery respectively for no, one or two DAE; difference not significant).

Discussion

This retrospective study did not evidence a relationship between presence or absence of the disease-associated epitopes (defined by DRB1*01 and *04) and joint surgery. This relationship was not evidenced for presence or absence of DAE, or for specific subtypes. Few authors report such a relationship. Weyand (3) analyzed over 15 years recourse to reconstructive surgery in 102 RA patients and concluded that double dose DAE patients were at risk of surgery (61% had surgery versus 25% with one DAE). Crilly (7) in a retrospective case-control study found more double dose DAE in the surgery group (32% versus 9%), but no difference in single dose DAE distribution. For Toda (8) total knee arthroplasty was not influenced by HLA typing; however, duration of disease before surgery was shorter in the group with two DAE. Finally, Eberhardt (9) found that one DAE was a risk factor for surgery in 99 patients followed up for 5 years.

The discrepancy between our study and the literature cannot be explained by recruitment differences: this population is representative of tertiary care RApatients: severe, rheumatoid-factor positive patients, necessitating multiple DMARDs; there are more women than is usual in RA cohorts which reflects our outpatient population. However it should be noted that we did not collect all known prognostic factors (for instance, anti-cyclic citrullinated peptide antibodies or steroid intake). Furthermore the previous studies about the relation between DAE and joint surgery were not conducted in a French population; there are potential influences on RA genetic factors related to different populations. Distribution of shared epitopes in this population is similar to published reports, although lower than in Weyand's classic study (3): 96% of his patients had the disease-associated epitope. The number of surgical procedures is slightly lower than usually reported in the literature (33 to 35% after 15 years) (10,11) since we reported only certain surgical procedures, reflecting structural severity of RA.

The main limitation of our study is that we did not analyze genetic subtypes (*0401, *0404, *0408). This was not possible because most HLAtyping was performed between 1990 and 1998, when genetic subtyping was not commonly performed in our center. Results would perhaps also be different in another, less severe, population, such as community-based RApatients.

We conclude that HLA-DR phenotyping without the subtypes did not have prognostic significance in predicting joint surgery in our French tertiary care cohort.

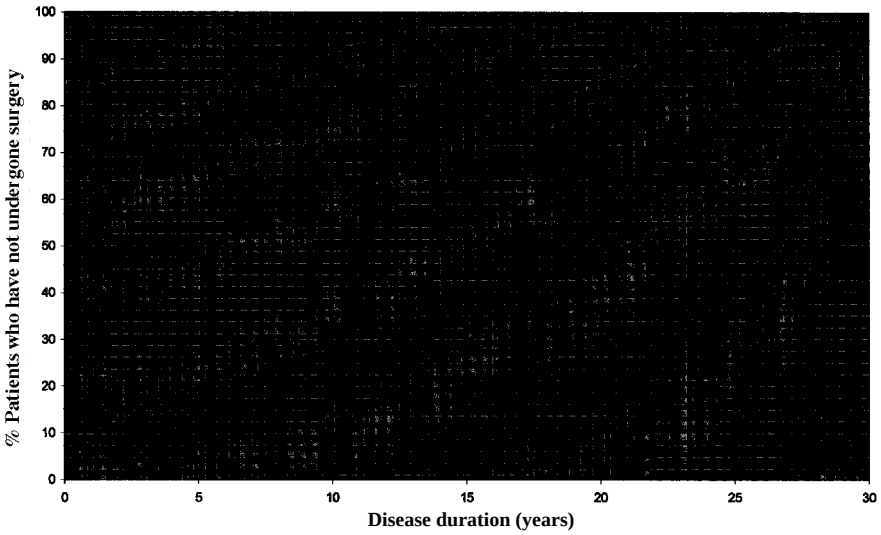

Fig. 1. Percentage of patients who have not undergone a first joint surgery (arthroplasty or arthrodesis) over time for 300 RApatients: lifetable analysis.

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