Association of HLA-B35 with mucocutaneous lesions in Israeli patients with rheumatoid arthritis receiving gold treatment

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SUMMARY Seventy four Israeli patients with rheumatoid arthritis (RA) were studied for possible association between HLA antigens and adverse reactions to gold treatment (aurothioglucose). HLA-B35 was significantly increased in patients who developed gold induced mucocutaneous lesions. These results are in accord with earlier reports, despite the different genetic background of the Israeli RA population and the different type of gold compound used.

Key words: dermatitis, gold toxicity.

Numerous works have shown that genes in the HLA system are associated with susceptibility to a number of diseases, including rheumatoid arthritis (RA).¹ The frequency of DR4 was found to be increased in most RA populations studied,^{2,3} and it has been suggested that certain DR antigens, especially DR3, are related to drug toxicity.⁴ Recently it has also been observed in patients with RA treated with sodium aurothiomalate that class I antigens (B35 and Cw4) are associated with the development of nephritis and dermatitis.^{5,6} We have previously reported that HLA-DR1 and not DR4 is associated with RA in Israeli patients,⁷ as opposed to other Caucasian populations. The type of gold used by us (sodium aurothioglucose) is also different from the preparations studied previously. We report the relation between HLA and gold salt toxicity in Israeli patients.

Patients and methods

This study was carried out on 74 patients from the outpatient clinic of the department of rheumatology, Ichilov Hospital. All patients were classified as having definite or classical RA according to the American Rheumatism Association criteria. Patients were assessed clinically, and specific atten-

tion was paid to drug history, including response and adverse reactions, presence of extra-articular manifestations, and Sjögren's syndrome. Results of routine haematological and biochemical tests and the presence of rheumatoid factor (RF) and anti-nuclear factor were recorded for each patient.

Patients had been treated for up to 10 years with sodium aurothioglucose (Solganal, Schering, Berlin). Gold was given by the following regimen: test doses of 10 mg and 25 mg one week apart, 50 mg doses for 20 consecutive weeks, maintenance regimen of 50 mg/2 weeks for three months and 50 mg/3–4 weeks indefinitely. Mucocutaneous lesions consisting of a maculopapular rash or aphthous stomatitis were considered to be due to gold therapy when they appeared during treatment and disappeared after gold treatment was discontinued.

HLA TYPING

HLA-A, B, C antigens were determined by the microlymphocytotoxicity technique.⁸ HLA-DR typing was performed on T cell depleted B cell enriched lymphocytes by extended incubation cytotoxicity testing.⁹ The HLA antigen frequency was compared with that of healthy controls typed by the same laboratory.

STATISTICAL ANALYSIS

Differences between groups were compared by the χ^2 test with Yates's correction. The relative risk

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(RR) was calculated according to Woolf's equation. The p value was corrected for the number of tested antigens (p_c).

Results

Table 1 summarises the demographic and clinical data of patients with (group A) and without (group B) gold salt toxicity. There were no significant differences between the groups with respect to age, sex, disease duration, and the presence of rheumatoid factor.

Thirty four of 74 patients who received gold treatment developed side effects: 20 had mucocutaneous reactions, nine proteinuria, and five developed haematological abnormalities (leucopenia or thrombocytopenia). Gold induced mucocutaneous toxic reactions were observed after a mean (SD) of 4.6 (4.4) months. Two patients had two or more adverse reactions simultaneously.

HLA-A, B, C (class I), and DR (class II) antigen frequencies in 74 patients with and without adverse reactions to gold were compared with those of the control population (Table 2). No significant difference was found in the frequency of HLA antigens when patients with RA and no side effects (group B) were compared with healthy controls (group C). In contrast, patients with gold induced mucocutaneous lesions had an increased frequency of the HLA-B35

antigen as compared with groups B or C ($p_c < 0.05$). HLA antigen frequencies were similar in the other side effect groups and did not differ statistically from those of groups B and C.

RA patients having HLA-B35 were calculated to have an increased relative risk of 3.1 of developing gold induced mucocutaneous lesions as compared with B35 negative patients.

Discussion

The association between HLA-DR2 and DR3 and toxic reactions to gold and penicillamine in patients with RA was first suggested by Panayi and Wooley.⁷ Since then many reports with conflicting results have been published. Although some authors found no correlation between HLA-DR antigens and gold toxicity,¹⁰ other studies described significant associations with B8 and DR3.¹¹⁻¹³ Gold salt dermatitis has recently been related to class I B35 antigen, thus adding further information to the possible genetic factors associated with various adverse reactions. Similarly, our results show that patients with RA carrying the HLA antigen B35 were at a greater risk (RR=3.1) of developing mucocutaneous reactions to gold. We did not observe an increase in the frequency of B35 among patients with RA having other gold induced side effects. In contrast with other works, our patients with RA carrying the HLA antigens DR3 and B8 were not more prone to develop toxic reactions to gold. The different genetic background of the Israeli population, in whom RA is associated with DR1 and not DR4, and the use of a different gold preparation (aurothioglucose) may explain these differences. Interestingly, Israeli patients having generalised granuloma annulare have an increased frequency of HLA-B35,¹⁴ further supporting the association between this antigen and skin eruptions.

In Caucasians and in the Israeli Jewish population there is a linkage disequilibrium between B35 and DR1. The fact that we have previously observed a

Table 1 Clinical characteristics of patients with RA with (group A) and without (group B) side effects

	Group A (n=34)	Group B (n=40)
Age (mean (SD)) (years)	58 (11.2)	60 (13.4)
M/F ratio	1:3.5	1:3.3
Disease duration (mean (SD)) (years)	6.1 (3.7)	5.6 (4.2)
RF positive (%)	71	68
ANF positive (%)	23	25

Table 2 Frequency of class I and II antigens in the various groups tested

HLA antigen	Gold induced side effects (group A)			No side effects (group B) (n=40)	Healthy controls (group C) (n=300)
	Mucocutaneous (n=20)	Proteinuria (n=9)	Haematological (n=5)		
B35 (%)	60*	11	20	31.5	31.3
DR1 (%)	30	22	20	20.3	13.7
DR3 (%)	11	11	20	20.0	16.5
DR4 (%)	35	33	40	44.4	38.3
DR5 (%)	35	55	40	37.0	42.5

* $p_c < 0.05$.

association between DR1 and RA and that in this disease B35 is associated with gold induced mucocutaneous lesions may indicate that indeed genes conferring susceptibility to RA and gold induced side effects are in linkage with this B35-DR1 haplotype. The mechanisms by which the presence of an HLA antigen is associated with the pathogenesis of a given disease are still unclear, however.

In conclusion, our results further confirm a strong association between mucocutaneous lesions induced by gold treatment and HLA-B35, despite the different genetic background of our population and the use of a different gold compound (aurothioglu-cose).

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