HLA types in patients with rheumatoid arthritis developing leucopenia after both gold and sulphasalazine treatment

HENNING BLIDDAL,¹ BIRTE EIBERG,² PEKKA HELIN,³ AND ARNE SVEJGAARD⁴

From the ¹Department of Rheumatology, Bispebjerg Hospital, Copenhagen; the ²Clinic of Rheumatology, Lyngby; the ³Department of Rheumatology, Glostrup Hospital; and the ⁴Tissue Typing Laboratory, Department of Clinical Immunology, University Hospital, Copenhagen, Denmark

SUMMARY HLA types, especially HLA-DR3, are associated with the development of toxic reactions in patients with rheumatoid arthritis after treatment with gold or D-penicillamine. In this study, after treatment with sulphasalazine, leucopenia was observed in three patients, who all had a history of leucopenia after previous gold treatment. The HLA types of these patients did not include HLA-DR3; the two patients developing mild leucopenia had HLA-DR2 and the one developing agranulocytosis had HLA-DR4.

During clinical trials of disease modifying anti-rheumatic drugs an overlap has been observed between groups of patients with toxic reactions to different drugs—for example, gold and D-penicillamine.^{1,2} A genetic predisposition to the haematotoxic reactions to these two drugs has been suggested,³ in accordance with observations of a general tendency towards association between certain HLA types and toxic reactions to anti-rheumatic drugs.⁴

We introduced sulphasalazine to more than a 100 patients with rheumatoid arthritis and observed neutropenic reactions in only three, all of whom had experienced similar previous reactions to gold.⁵

Patients and methods

PATIENTS

All three patients had classical rheumatoid arthritis at the time of treatment with sulphasalazine. Table 1 shows the principal clinical data.

HLA TYPING

HLA-A, B, and C typing and HLA-DR typing were performed as described by Jacobsen *et al.*⁶ Table 2 gives details of the three patients.

Table 2 HLA types of the three patients developing leucopenia after both gold and sulphasalazine treatment

Patient No	HLA types
1	A1,2; B27,39; Cw2; DR2,w6,w52; DQw1
2	A3,23; B7,44; Cw4; DR2,7,w53; DQw1,w2
3	A1,3; B7,17; Cw2w6; DR4,7,w52,w53; DQw2

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Correspondence to Dr Henning Bliddal, Department of Rheumatology, Bispebjerg Hospital, DK-2400 Copenhagen NV, Denmark.

Table 1 Clinical data of the three patients developing leucopenia after both gold and sulphasalazine treatment

Patient No	Sex	Age (years)	Rheumatoid arthritis onset (date)	Gold treatment (date)	Dose of gold before leucopenia (mg/day)	Sulphasalazine treatment (date)	Dose of sulphasalazine at leucopenia (mg/day)	Leucocyte counts (10 ⁹ /l)		Recovery time (days)
								Before	After	
1	F	31	1973	(1973)	1010	1985	500	6.4	1.2	14
2	F	55	1979	1979	120	1986	2000	4.3	1.2	9
3	F	51	1981	1981	500	1986	1000	5.1	0.5	21

Case reports

CASE 1

A woman born in 1942 developed rheumatoid arthritis in 1973. Within a year she went into remission after receiving 1300 mg of aurothiomalate. The rheumatoid arthritis relapsed in 1982, and for a second time remission was obtained with aurothiomalate treatment, which, however, had to be withdrawn at 1010 mg/day because of leucopenia (a reduction from 8.9 to $2.4 \times 10^9/l$). In 1985 the rheumatoid arthritis relapsed again, and this time the patient was treated for two weeks with sulphasalazine 500 mg/day. Leucocyte counts fell from 6.4 to $1.2 \times 10^9/l$, and upon withdrawal of sulphasalazine slowly normalised over 14 days. No clinical effect of the leucopenia was observed. The only other drug given during this period was aspirin, which was continued in the same dosage. Blood platelets and haemoglobin did not change during observation.

CASE 2

A woman born in 1924 developed rheumatoid arthritis in 1979, and treatment with aurothiomalate was started but had to be withdrawn after three weeks at 120 mg/day owing to leucocyte depression (a fall from 7.2 to $2.9 \times 10^9/l$). Over the following years the rheumatoid arthritis was active despite alternating treatment with azathioprine, D-penicillamine, cyclophosphamide, and prednisone.

In 1986 treatment with sulphasalazine was introduced in slowly increasing doses from 500 to 2000 mg/day. A fall in leucocytes from 4.3 to $1.2 \times 10^9/l$ was observed, which upon withdrawal of sulphasalazine normalised in nine days without clinical symptoms. Other drug treatment included prednisone and D-penicillamine, which was unaltered during this period. Blood platelets and haemoglobin were unchanged.

CASE 3

A woman born in 1930 developed rheumatoid arthritis in 1981, and treatment with aurothiomalate was started but withdrawn at 500 mg/day after a fall in leucocytes from 8.0 to $3.3 \times 10^9/l$. The rheumatoid arthritis remained active during the following years despite treatment with D-penicillamine.

In 1986 non-steroidal anti-inflammatory drugs were discontinued (upon request of the patient) and treatment with sulphasalazine was started at 1000 mg/day. After 14 days a severe bone marrow depression developed with a reduction in leucocyte counts from 5.1 to $0.5 \times 10^9/l$ (granulocytes 0, blood platelets $110 \times 10^9/l$, and haemoglobin 82 g/l). The patient was transferred to the department of infec-

tious medicine and treated symptomatically. The bone marrow recovered in 21 days and leucocyte counts normalised. The patient recovered without late sequelae.

Discussion

Sulphasalazine is generally regarded as a fairly safe disease modifying antirheumatic drug with few adverse reactions apart from gastrointestinal symptoms.^{7,8} A bone marrow depression dependent on dose does occur in a proportion of patients. More severe idiosyncrasies, such as haematotoxic reactions, may occur, however, as in our third patient. Our three patients had all experienced mild subclinical leucopenia with gold treatment, but two of these patients had subsequently received D-penicillamine without any adverse effects.

Because of persistently active rheumatoid arthritis sulphasalazine was chosen as a secondary single disease modifying antirheumatic drug for one patient (No 1) and for combined treatment with D-penicillamine in two patients (Nos 2 and 3).

The leucopenia in patients 1 and 2 was subclinical and readily reversible, indicating a toxic effect of sulphasalazine, presumably related to the sulphapyridine component of the drug.¹⁰ In contrast, the reaction in patient 3 was severe with a longstanding bone marrow depression.

A tendency towards adverse reactions has been seen in patients treated first with injectable gold and then with D-penicillamine.^{1,2} A similar observation for sulphasalazine and other preceding disease modifying antirheumatic drugs has not been previously reported. Our three patients with leucopenia were the only cases in a series of more than 100 patients treated with sulphasalazine during the same period, and the correlated previous reaction to gold cannot be explained by chance considering the very rare occurrence (<3%) of leucopenia after these two drugs. A genetic predisposition is thus suspected.

The HLA types were DR2 in the two patients with a mild neutropenia and DR4 in the patient with agranulocytosis. There is no published information about the relation between genetic markers and adverse effects to sulphasalazine, but an analogy with gold might be predicted. After gold treatment an association between HLA-DR3 and toxic reactions in general, including haematotoxic reactions, has been reported.^{3,4,11} In one study HLA-DR2 (as in two of our cases) was implicated as a marker for side effects.⁴ The occurrence of HLA-DR4 is not so informative as it is present in most patients with rheumatoid arthritis; in a study by Aaron *et al.*¹² however, this antigen was associated with severe

bone marrow reactions to gold (as in case 3) but not with milder neutropenia.

In conclusion, a shared genetic predisposition of bone marrow reactions may exist between the different disease modifying antirheumatic drugs. Thus a history of leucopenia after gold treatment indicates extreme caution during subsequent treatment with sulphasalazine. It is possible that certain HLA factors may contribute to leucopenia, but more studies are needed for clarification.

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