Association between gold induced skin rash and remission in patients with rheumatoid arthritis

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SUMMARY The coincidence of skin eruption and remission induced by gold has not previously been reported. In 50 out of 247 patients with rheumatoid arthritis treated with gold salts (Solganal) between 1977 and 1987 treatment was stopped owing to adverse reactions. Skin rashes were present in 31 patients, 10 had nephropathy, and nine patients had aphthous stomatitis. All 31 patients who developed skin eruption entered a concomitant clinical and laboratory remission. The remission satisfied the American Rheumatism Association preliminary criteria and was accompanied by a significant decrease of mean erythrocyte sedimentation rate from 43 (SD 13) to 25 (11) mm/h. Disease was exacerbated in 23 patients after three to 60 months. Eight patients are in remission at present, five to 68 months after gold treatment was discontinued. In contrast, no remission was noticed among the 19 patients with nephropathy or stomatitis.

Gold injections in rheumatoid arthritis are associated with a relatively high rate of side effects. It is our experience that some patients show a considerable therapeutic response to gold at the very moment of skin eruption. Colleagues with whom we shared this observation have had similar experiences. Publications on this topic are few as most reports describe therapeutic or side effects of gold without analysing their mutual interrelationships.

The report of the Empire Rheumatism Council¹ is the only study we could find that examined the relation between the toxic effects of gold and improvement. This work, however, found a better overall outcome in patients without toxicity, without analysing the various side effects separately.

We report a striking and previously undescribed association between skin eruption and remission induced by gold.

Patients and methods

Between 1977 and 1987 247 patients with definite or classical rheumatoid arthritis were treated with sodium aurothioglucose (Solganal). Their medical and laboratory records were reviewed retrospectively. All 51 patients in whom gold treatment was discontinued

owing to side effects were asked to participate in the prospective phase of the study. All but one who was lost to follow up, are still being followed up in our outpatient clinic. Drug history (other than gold), a detailed questionnaire about sicca symptoms, routine haematology and blood biochemistry (rheumatoid factor (latex), and antinuclear factor determinations (on HEp₂ cells) were performed in all patients.

Side effects were classified into cutaneous (maculopapular, urticarial, or desquamating rash), mucosal (aphthae or stomatitis), renal (proteinuria of more than 500 mg/24 h), and haematological (leucopenia $<3 \times 10^9$ white blood cells/l, thrombocytopenia $<100 \times 10^9$ /l). Eosinophilia was considered as an absolute count $>0.5 \times 10^9$ /l. Toxicity was attributed to gold if it appeared during the course of treatment was clinically characteristic, and disappeared after treatment was stopped. Clinical remission was defined according to the preliminary criteria of the American Rheumatism Association² and included duration of morning stiffness, joint pain, tenderness and swelling, and erythrocyte sedimentation rate below 30 mm/h for women or 20 mm/h for men.

Student's *t* test was used for statistical analysis.

Results

Patients were divided into three groups according to the type of gold toxicity: group A—31 patients with

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Table 1 Clinical characteristics of the patients with rheumatoid arthritis with side effects due to gold

	Group A* (n=31)	Group B* (n=10)	Group C* (n=9)
Age (years)†	59 (11)	63 (13)	61 (13)
M/F ratio	1/4.6	1/4	1/3.5
Disease duration (years)†	7.9 (7.6)	9.2 (8.1)	9.3 (6.1)
No (%)			
RF‡ positive	21 (68)	8 (80)	7 (78)
No (%) with sicca symptoms	6 (19)	3 (30)	2 (22)

*Group A=patients with skin rashes; group B=patients with gold induced proteinuria; group C=patients with aphthous stomatitis without skin eruption.

†Values are mean (SD).

‡RF=rheumatoid factor.

Table 2 Clinical outcome and erythrocyte sedimentation rates at the time of discontinuation of gold owing to side effects

	Group A§ (n=31)	Group B§ (n=10)	Group C§ (n=9)
Cumulative dose of gold (mg)	406 (180)	811 (193)*	315 (204)
Number of remissions	31	None	None
Duration of remission (range, months)	3-68	None	None
ESR‡ before toxic reaction	43 (13)	48 (14)	38 (12)
ESR after toxic reaction	25 (11)*	45 (16)	35 (17)

*p<0.05.

†Values are mean (SD).

‡ESR=erythrocyte sedimentation rate.

§For explanation of groups see Table 1.

skin rashes, four of them with concomitant stomatitis; group B—10 patients with gold induced proteinuria; group C—nine patients with aphthous stomatitis without skin eruption. Table 1 summarises the characteristics of the patients. There were no significant differences among the groups with respect to age, sex, disease duration, the presence of rheumatoid factor, and sicca symptoms.

Table 2 reports the clinical outcome and laboratory results at the time of the discontinuation of gold. All 31 patients who developed gold induced skin rash (group A) entered a concomitant clinical remission accompanied by a significant fall of erythrocyte sedimentation rate. The duration of remission varied greatly among the patients. Exacerbation occurred after an average of 12 months (range 3-60 months). Eight patients are in remission at present, five to

68 months after skin rash occurred. In contrast, none of the patients who suffered from proteinuria (n=10), stomatitis (n=9), or thrombocytopenia (n=2, data not shown) had a clinical remission or a significant fall of erythrocyte sedimentation rate. Skin and mucosal lesions occurred earlier than gold induced nephropathy (p<0.05). Eosinophilia (range 0.6-2.1×10⁹/l) preceding gold toxicity was noticed in four patients with skin eruption, but in none of the 19 patients of groups B and C.

Treatment of the skin rash required prednisone (dose range 10-20 mg/day) in four patients for a period of one to four weeks. Five patients received a single injection of corticotrophin. One patient who was receiving prednisone 10 mg/day before the start of gold treatment continued with the same regimen at the time of skin eruption and during the following remission.

During the remission eight patients did not require any drugs, 10 patients used analgesics sporadically, while only 13/31 patients required non-steroidal anti-inflammatory drugs.

A history of allergy to drugs other than gold was present in five of the 31 patients of group A, in none of the patients who developed gold nephrotoxicity, and in one patient with stomatitis.

Discussion

When designing the present study we expected to discover a few patients in whom rash and response to gold coincided. On collecting the data we were surprised by the complete overlap between the two phenomena. All 31 patients who stopped gold thioglucose because of skin rash presented concomitant remissions of their disease, lasting five to 68 months and accompanied by a fall of erythrocyte sedimentation rate. In contrast, none of the patients with other gold induced side effects presented a similar response.

Although gold is the classical second line drug in rheumatoid arthritis, many facets of its activity remain obscure. The efficacy of gold was reported by the Empire Rheumatism Council in 1961,³ and by subsequent studies.⁴⁻⁷ Gold induced toxicity, most commonly mucocutaneous, has also been extensively reported.^{3,6,8} No means of predicting the beneficial outcome of gold treatment exists, though HLA-DR2 has generally been found to be associated with a better prognosis.⁹ Side effects have been associated with histocompatibility markers; renal and bone marrow toxicity were found to be related to HLA-B8 and DR3.¹⁰⁻¹² A association between mucocutaneous side effects and HLA-B35 has been reported by our group.^{13,14}

The correlation between toxicity and benefit of gold has not been previously described. The only work designed for the study of this aspect is the 1961 Empire Rheumatism Council subcommittee report 'The relation of toxic reactions in gold therapy to improvement in rheumatoid arthritis'.¹ In their report 31 patients who had toxic reactions were compared with 46 patients without toxicity. Temporary remissions were not reported in this group, and the 31 toxic cases were considered as a whole without analysing the different side effects. Not surprisingly, these patients, devoid of gold (or of any other second line drug), fared worse at 30 months. The authors conclude their report as follows: 'This trial does not confirm the idea previously held by some clinicians that good therapeutic results are usually to be expected where gold salts have produced toxic effects'.

Further understanding of the immunological and clinical events occurring during chrysotherapy may explain the coincidence of skin rash and remission induced by gold and find the golden mean between the two.

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