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Research article

# Rheumatoid arthritis, gold therapy, contact allergy and blood cytokines

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## Abstract

**Objective:** To study the clinical and biochemical effects of a low starting dose for gold therapy in rheumatoid arthritis patients with a contact allergy to gold.

**Methods:** Serum cytokines were assayed before and 24 h after the first injection of gold sodium thiomalate (GSTM).

**Results:** Contact allergy to gold was found in 4 of 19 patients. Compared to gold-negative patients (starting dose: 10 mg GSTM), there was a larger increase in serum TNFalpha ($p < 0.05$), sTNF-R1 (NS), and IL-1 ra ($p < 0.05$) in gold-allergic patients.

**Conclusions:** Cytokines are released in blood by GSTM in RA patients with gold allergy. To minimize the risk of acute adverse reactions the starting dose of GSTM should be lowered to 5 mg. Alternatively, patients should be patch-tested before gold therapy; in test-positive cases, 5 mg is recommended as the first dose.

## Introduction

Contact allergy to gold, as diagnosed by patch testing with gold sodium thiosulfate (GSTS), is very common among patients with eczematous disease [1–3]. These patients are allergic also to other monovalent gold salts such as gold sodium thiomalate (GSTM)[4].

We have previously shown that contact allergy to gold is frequent also in rheumatoid arthritis (RA) patients[5]. Furthermore, it has been shown that subjects with a contact allergy to gold experience acute reactions, cutaneous as well as general, if they are exposed parenterally to their contact allergen[6]. The reactions are accompanied by a release of plasma cytokines and acute phase reactants during the first 24 h after the gold injection[7].

Gold therapy in RA with GSTM is usually started with a "test dose" of 10 mg to avoid hypersensitivity reactions. In the present study a starting dose of 5 mg was given to patients with a gold allergy while test negative patients obtained the higher standard dose; clinical reactions were registered as well as changes in body temperature and plasma cytokines.

## Material and methods

### *Patients, testing, treatment*

The study was performed in 19 patients with RA, 4 males and 15 females, aged 30–75 years, mean age 63.5 years. They all had RA according to the classification criteria of ACR[8] with a median duration of 23 ms (range 4 ms to 20 ys). The patients were selected because of a planned treatment with parenteral gold and informed consent was obtained. Only one of the patients had previously obtained parenteral gold therapy which, however, had soon been withdrawn because of lacking effect. At the time of the study, all patients were on non-steroidal anti-inflammatory drugs; in addition, 2 were treated with sulfasalazine, 2 with chloroquine, 1 with methotrexate, and 10 with corticosteroids (dosage 3.75–15 mg prednisolone/day, mean 9.1 mg/day). The study was approved by the Ethics committee of the Lund University Medical Faculty.

Before gold treatment, the patients were patch tested with GSTS 0.5, 2.0 and 5.0 w/w %, GSTM 36.0 w/w % (Myocrisin$^R$, Rhone Poulenc Rorer), and auranofin 47 w/w % (Ridaura$^R$, SmithKline Beecham), all mixed in petrolatum[6]. Patches were applied on the back for 48 h using Finn Chambers$^R$ on Scanpor$^R$. Since patch test reactions to gold salts often are delayed and the early reactions longlasting[9] the tests were read one week after application using criteria for positive patch tests from the International Contact Dermatitis Research Group [10].

Immediately before the first gold treatment, a venous blood sample was withdrawn, centrifuged and freeze-stored. Also, the body temperature was measured. The patients were then given an intramuscular injection of GSTM. If the outcome of patch tests was positive for a gold salt the patients obtained a dose of 5 mg; if negative, the dose was 10 mg. The patients were observed for cutaneous or other reactions during the following 24 h. At this point, another blood sample was taken. The body temperature was registered 10 and 24 h after the injection.

### *Laboratory studies*

Enzyme-linked immunosorbent assay of neutrophil gelatinase associated lipocalin (NGAL) and soluble tumour necrosis factor receptor type 1 (sTNF-R1) was performed as earlier described[11,12]. Tumour necrosis factor-alpha (TNF-α) and interleukin-1 receptor antagonist (IL-1 ra) were measured with ELISA kits (Quantikine™ from R&D Systems, Minneapolis, USA).

### *Statistics*

Change of plasma cytokines was calculated using the Wilcoxon rank sum test.

**Table 1: Positive test reactions in four RA patients one week after application of patch tests.**

| Test substance | F 51 | F 70 | M 71 | F 57 |
|---|---|---|---|---|
| GSTS 0.5 % | - | - | (+) | - |
| GSTS 2.0 % | ++ | ++ | + | (+) |
| GSTS 5.0 % | ++ | ++ | +(+) | +(+) |
| GSTM | ++ | + | + | - |
| Auranofin | - | - | - | - |

## Results

### *Clinical reactions*

The results of patch testing are given in Table 1. A contact allergy to GSTS was observed in 4 of the 19 patients. Three of the GSTS-positive patients were allergic also to GSTM but no positive test reactions could be demonstrated to auranofin.

With one exception among the 19 patients, there were no side effects suspected to be caused by GSTM during the first 24 h after the i.m. injection. Thus, one patient (F 51, Table 1) with a seronegative RA but patch test positive to GSTS felt ill 10 h after the 5 mg GSTM injection with malaise, vomiting and tachycardia, and a discrete macular rash was observed over the abdomen. There was no temperature rise and she was well again at 24 h.

### *Laboratory results*

The body temperature did not change during the first 24 h after the GSTM injection. The mean temperature among the 19 patients was 37°.1 C immediately before the treatment as well as 10 and 24 h thereafter. Nor was there a change of body temperature in the 4 patients with a gold allergy.

The blood cytokine assays, the results of which are presented in Table 2, showed a statistically significant increase of TNF-alpha and IL-1 ra in the gold-positive patients after the GSTM injection. No such increase was seen in the gold-negative patients who, however, had high baseline values.

## Discussion

Contact allergy to gold is common, not only among patients with eczematous disease[1], but also in certain reference groups. Thus, Goldermann et al found 6.0 % positive to GSTS among healthy controls[13], Gruvberger et al 10.3 % among plastic plant employees[14], Fleming et al 4.8 % among volunteers in the staff of a dental hospital[15], and Isaksson et al 12.5 % among other plastic plant employees[16], none of which had any occupation-

**Table 2: Blood cytokines in RA patients allergic and not allergic to gold: mean baseline values and mean percentual change after GSTM injection.**

| | TNF-alpha | | sTNF-R1 | | IL-1 ra | | NGAL | |
|---|---|---|---|---|---|---|---|---|
| | Base | Increase | Base | Increase | Base | Increase | Base | Increase |
| Gold neg(n = 15) | 6.3 | 5 | 4.8 | -6 | 625 | 0.3 | 200 | 12 |
| Gold pos (n = 4) | 3.5 | 60* | 1.6 | 8 | 326 | 82* | 185 | 10 |

Baseline values are given in pg/ml plasma (TNF-alpha, IL-1 ra), ug/l serum (sTNF R1), and ug/l plasma (NGAL). * = $p < 0.05$ compared to gold negative patients.

al contact with metallic gold. Test concentrations in these studies were never higher than 0.5 % which in some cases may be too low.

Thus, in our case report[17] and prospective study[5] we found 9 RA patients with contact allergy to gold; 6 of the 9 were patch test negative to GSTS 0.5 % and had been considered negative if an extended skin testing had not been performed. This may explain the negative test results among RA patients observed by Fleming et al[18]. A contributing factor may have been concomitantly given immunosuppressant drugs. Another factor may be the lower frequency of gold dental fillings in the Scottish than in the Swedish population[19]. A positive correlation between contact allergy to gold and the presence of dental gold has been suggested [20–22] and recently ascertained[23].

After gold therapy, only few RA patients have a contact allergy to gold[5,13,24]. Before such treatment, however, gold allergy is fairly frequent[5]. It was therefore not surprising in the present study to find 4 out of 19 patients patch test positive to GSTS (Table 1). As mentioned above, no one was positive to 0.5 %, only to higher concentrations. It is possible that the disease proper may imply a partial immunosuppression[25].

Longterm cutaneous side effects are very common during treatment with gold preparations. Mucocutaneous side effects were the reason for withdrawing treatment with gold in 20 % of cases in RA[26]. In the present study, two of the four gold-positive patients were continued on a series of GSTM treatment without cutaneous side effects. One of them (F 57, Table 1) had to stop treatment because of albuminuria. The other (F 70) obtained a total of 2840 mg GSTM during 2 years and her disease went into remission. The remaining two test-positive patients did not receive further GSTM courses, one (F 51) because of the acute adverse effects, the other (M 71) because of nephrosclerosis. Among the 15 test-negative patients all were given courses of GSTM injections which, however, had to be discontinued in 8 cases because of adverse effects such as albuminuria, haematuria, thrombocytopenia etc but no skin complaints.

An allergic pathogenesis of "gold dermatitis", the frequent longterm side effect of chrysotherapy, has been suggested but was not supported by an early histopathological study[27]. Nor has this hypothesis been corroborated by positive allergological tests, e.g. patch tests[13,26]. An immunohistochemical and electron microscopic study[28] as well as an in vitro lymphocyte proliferation study[24], however, speak in favour of some type of allergic mechanism behind "gold dermatitis". In this latter report it was also noted that 1/13 RA patients with "gold dermatosis" was patch test positive to gold salts. She was the only one to endure an acute, cutaneous and generalized reaction to the first GSTM dose of 10 mg, i.e. the type of response described from our group[29].

On the basis of the present small material, it is impossible to evaluate the importance of a contact allergy to gold for the risk of traditional cutaneous ("gold dermatitis") or generalized side effects. However, the acute reactions discussed in the present paper may be avoided if the patients before treatment are properly skin tested and/or the starting dose chosen with care.

Several cytokines are instrumental in the pathogenesis of the allergic contact dermatitis, in the primarily elicited eczematous reaction as well as in the endogenous flare up after systemic provocation[30]. TNFalpha, sTNF-R1, and IL-1 ra are released in blood when GSTM is given by intramuscular injection to a subject with contact allergy to GSTS[7]. The release has been shown to be specific and activated only by the proper contact allergen[31]. This specificity was confirmed in the present work: gold allergen, when given to gold-positive patients, released the cytokines, not when given to gold-negative patients (Table 2). Obviously, GSTM is not a cytokine releaser by pharmacological or toxicological properties which seems to hold true also for rheumatic patients.

The baseline values of all cytokines were numerically higher in the gold-negative patients than in the gold-positive ones (Table 2). There was, however, no statistical difference for any cytokine, nor any other difference (age, gender) between the two groups under study. The absence of a cytokine release among gold-negative patients could possibly be explained by an earlier release which thus had been missed by our single blood sampling at 24 h. True, we have earlier shown that the release of cytokines after systemic provocation with the contact allergen is obvious already after 6 h[7]. It was, however, not less after 24 h and the assay can therefore not be considered false-negative. With regard to release of sTNF-R1 there was a numerical but statistically not significant increase when comparing gold-positive and gold-negative patients (Table 2) which might be explained by the small patient material.

TNF-alpha and other cytokines seem to play a pathogenetic role also in the joint inflammation of RA[32], providing a rationale for the increasing use of anti-TNF-alpha drugs in this disease. Not surprisingly, in the present study blood baseline values of TNF-alpha, sTNF-R1 and IL-1 ra were fairly high (Table 2). After the systemic gold treatment the cytokines were released to a high degree in patients with a contact allergy to gold but not in those negative at patch testing. The difference was statistically significant for TNF-alpha and IL-1 ra, not for sTNF-R1.

A pathogenetic role played by neutrophilic leukocytes in the arthritic process has earlier been suggested[33]. However, no release of the leukocytic protein NGAL was provoked by GSTM (Table 2) which is in accordance with recent results[34].

The cytokine release was thus demonstrated also in patients given the very low starting dose of 5 mg GSTM. In other words: the biochemical reaction is evident in the absence of clinical side effects. Interestingly, patients with eczematous disease and gold allergy in many cases experience acute influenza-like symptoms with fever as well as muscle and joint aches when given even a small GSTM injection[6]. The absence of such side-effects in the present study might be due to the antipyretic drugs taken by the patients.

In the present study, RA patients with a contact allergy to gold were given a starting dose of GSTM reduced to 5 mg while the gold-negative patients obtained the regular starting dose of 10 mg. Only one of the 19 patients had an acute reaction with malaise and a rash and she was one of the 4 gold-positive patients. In our previous work[5] two gold-positive RA patients were given 5 mg GSTM without problems. Thus, we have given 6 such patients a test dose of 5 mg GSTM without acute side-effects in 5 of them. We conclude that 10 mg GSTM is without risk in a gold-negative patient while 5 mg may be a recommended starting dose for a gold-positive patient, thereby avoiding acute allergic reactions in most cases.

## Competing interests

None declared.

## Acknowledgements

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