Medical Journal of the
Islamic Republic of Iran

Volume 9
Number 3
Fall 1374
November 1995

ADVERSE REACTIONS OF GOLD SODIUM THIOMALATE IN RHEUMATOID ARTHRITIS PATIENTS IN SOUTHERN IRAN

A. RAJAEE

From the Department of Medicine, Rheumatology Unit, Hafez Hospital, Shiraz University of Medical Sciences, Shiraz, Islamic Republic of Iran.

ABSTRACT

To confirm the side-effects of gold sodium thiomalate (GSTM), we carried out a retrospective study examining 102 consecutive patients with rheumatoid arthritis attending the Rheumatology Unit of Hafez Hospital, Shiraz, Iran, in whom GSTM was initiated between 1983-1989. Only patients with classical or definite RA (ARA criteria) were included in this study. Patients were categorized as having developed toxicity to gold if rash, stomatitis, leukopenia (<4000/mm^3), thrombocytopenia (<100,000/mm^3), anemia (Hb<10gm/dL), microscopic hematuria (more than 5 RBC in each HPF) and proteinuria (1+or more) appeared during chrysotherapy. Sixty-six (64.7%) patients developed adverse reactions. More significant side-effects were pruritus (57.8%), eosinophilia (23.5%), microscopic hematuria (20.5%), and low Hb (20.5%). Inadequate primary response and relapses on therapy accounted for termination in 15.6% of patients, nephrotic syndrome in 0.9%, hepatitis in 1.9%, colitis in 2.9%, persistent pruritus in 1.9%, extensive lichenoid rash in 3.9%, persistent stomal ulcer in 0.9% and persistent hematuria in 1.9% of patients. Lichenoid rash was more significant and more extensive in our series compared to others.

Key Words: Gold therapy; eosinophilia; gold sodium thiomalate; rheumatoid arthritis; adverse reactions

MJIRI, Vol. 9, No. 3, 189-192, 1995.

INTRODUCTION

Gold compounds have been advocated for the treatment of numerous diseases of humans, animals and plants since the eighth century. A combination of gold and mercury was called an elixir of life by Paracelsus in the early sixteenth century.[1] A mixture of gold salts alone was recommended for the treatment of lupus vulgaris in 1913 and pulmonary tuberculosis in 1924.[2]

The beneficial effects of aurothioglucose (Solganal) in patients with bacterial endocarditis, rheumatic fever and other poorly-defined disorders, based on the hypothesis that gold had nonspecific antiseptic effects, were reported by Lande et al. in 1927.[3] Believing that tuberculosis and rheumatoid arthritis had one etiology, Forester applied gold thiopropanol sodium sulfonate (allochrysine) for the treatment of rheumatoid arthritis.[4] This led to the use of gold therapy in the treatment of RA in late 1920.[3,5,8,9]

In addition to rheumatoid arthritis, gold treatment is advocated for selected cases of juvenile rheumatoid arthritis (JRA), psoriatic arthritis affecting peripheral joints, and pemphigus and other serious bullous skin disorders.[10]

The present study was undertaken (a) to confirm and to investigate the side-effects of GSTM in rheumatoid arthritis patients in southern Iran, (b) to compare these side-effects with other reports and (c) to see if there is

any difference between type of side-effects in our group compared to others.

MATERIALS AND METHODS

GSTM was started for 102 patients with classical and definite rheumatoid arthritis, functional class II-IV as defined by the American Rheumatism Association, who were admitted to the Rheumatology Unit of Shiraz University of Medical Sciences, located in Hafez Hospital. All were unresponsive to non-steroidal anti-inflammatory drugs (NSAIDs). Most patients were taking aspirin or other NSAIDs including ibuprofen, indomethacin, and diclofenac Na. These drugs were allowed throughout the study. Seventeen patients received steroid medication, none in excess of 5 mg prednisolone per day. None of the patients were receiving chloroquine or cytotoxic drugs.

All patients had an initial laboratory evaluation including total and differential WBC counts, Hb, platelet count, ESR, CRP, rheumatoid factor titers, urinalysis and stool for OB. HLA-DR antigen studies were not available in this institution during the study. Radiological examinations of the chest and affected joints were obtained from all patients. Gold salt was injected intramuscularly according to the following schedules: patients were initially given 10 mg of gold sodium thiomalate, with 20 mg the second day, followed by 50 mg on the third day and then 50 mg at weekly intervals to a total of 1 gm. At the end of 20 weekly injections, if the response was clinically acceptable, the same dose of gold was given at biweekly intervals to 2 grams and then 4 week intervals to 3 grams.

A complete blood count, differential count, Hb, platelet count and urinalysis was performed before each injection of gold throughout the study and if there was significant abnormal data the physician withheld the drug. The patients were examined by the physician or specially-trained medical personnel for stomatitis, skin rash, itching or diarrhea before each injection and medication was withheld when toxic reactions were seen.

Table I. Demographic and epidemiologic data in RA patients treated with GSTM*

No. of patients	102
Mean age (yr)	33.1
Range (yr)	18-57
Mean duration of disease (yr)	1.5
Range (yr)	0.5-3
Male/female ratio	19/83
No. of seropositive patients	79

* Gold sodium thiomalate

RESULTS

Of the 102 patients studied, 83 were female and 19 male (mean age: 33.1; range: 18-57 years). Mean duration of disease was 1.5 years (range 6-63 months). Seventy-nine patients were seropositive and twenty-three seronegative (Table I).

Table II shows the toxic reactions that occurred in our group. From a total of 64.7% toxic reactions, 83% developed before receiving 1 gm of GSTM, the majority (68.6%) occurring within the first 4-6 months. The most common side-effects were pruritus (57.8% of patients), eosinophilia (23.5%), microscopic hematuria (20.5%) and low Hb (less than 10 gm/dL) (20.5%). Eosinophilia occurred as an isolated event in 13 patients. The range of eosinophilia was between 420-510/mm^3. Cutaneous

Table II. Adverse reactions of GSTM* in 102 rheumatoid arthritis patients

Adverse Reactions	No.	%
Mucocutaneous		
Pruritus	59	57.8
Erythematous rash	11	10.7
Scaling rash	8	7.8
lichenoid rash	6	5.8
Stomatitis	8	7.8
Alopecia	1	0.9
Bone Marrow		
Low Hb	21	20.5
Leukopenia	2	1.9
Eosinophilia	24	23.5
Thrombocytopenia	3	2.9
Kidney		
Hematuria	21	20.5
Proteinuria	8	7.8
Nephrotic syndrome	1	0.9
Liver		
Hepatitis	2	1.9
Intestine		
Colitis	3	2.9

* Gold sodium thiomalate

skin rash occurred in 10.7% of patients as erythematous, 7.8% as scaling and 5.8% as lichenoid plaques. In 3.9% of patients the lichenoid rash was extensive. Transient proteinuria occurred in 7.8% of patients, leukopenia in 1.9%, and thrombocytopenia in 2.9% with the platelet count falling to 75000-85000/ mm^3. Gold hepatitis occurred in 1.9% of patients, intestinal colitis in 2.9%, nephrotic syndrome in 0.9%, stomatitis in 7.8% and alopecia in 0.9%.

Temporary interruption of therapy occurred in 78.4% of patients and termination of treatment in 26.4%. The major reasons for stopping GSTM were colitis, hepatitis, persistent pruritus, persistent hematuria, nephrotic syndrome and persistent stomal ulcer. Inadequate primary response and relapses on therapy accounted for termination in 15.6% of patients. 11.7% of our patients were eventually lost to follow-up.

DISCUSSION

The place of gold therapy in rheumatoid arthritis is well established.[4,6] For more than 50 years, gold has occupied a central position in the treatment of chronic polyarthritis. Gold therapy is indicated in patients with rheumatoid arthritis with active and progressive disease unresponsive to adequate treatment including rest, physical therapy and NSAIDs.[7] The most common adverse reactions of gold salts are dermatitis, pruritus, stomatitis, proteinuria, hematuria, eosinophilia, myalgia, alopecia and vaginitis, in addition to some rare complications.[11,12,25,26]

Of our patients, 64.7% developed adverse reactions compared to the results of Ward et al. and Williams et al. who reported 27% and 41%, respectively.[5,11]

In general, skin reactions occur in about 20-30% of patients. Pruritus usually heralds most skin manifestations due to gold therapy. In our series 57.8% of cases developed pruritus compared to previous studies which report approximately 85%.[12] Erythematous skin rash (10.7%), scaling rash (7.8%) and lichenoid rash (5.8%) were other skin manifestations in our patients. Compared to previous reports the lichenoid rash was higher in our group.[12] GSTM therapy was terminated in two cases with persistent pruritus and in 4 cases with extensive lichenoid skin rash. Alopecia occurred in 0.9% of the patients.

Of all the side-effects the most insidious and dangerous is blood dyscrasia, which appears suddenly and unexpectedly in some cases. In this study, leukopenia occurred in 1.9% compared to previous reports of 0.5%.[13,14] Thrombocytopenia is a life-threatening complication of gold salt therapy. The mechanism of its development is unclear, but it may be due to direct marrow suppression or to specific anti-platelet antibody production.[15] In our study, gold-induced thrombocytopenia occurred in 2.9% of cases, compared to the 1.3% reported in other series.[16,17] Hemoglobin levels dropped between 1-3 grams in 20.5% of patients but rose to near normal values by decreasing the dose of GSTM or following remission of the patients' disease. In previous reports, low hemoglobin levels occurred in 42%.[13,14]

Eosinophilia has been a recognized complication of gold therapy for many years, although its incidence and significance have not been fully defined in previous studies. A total incidence of 21-47% in other studies demonstrated that eosinophilia may be the most common side-effect encountered in gold therapy.[18,19] In our series, eosinophilia was the second most common side-effect, occurring in 23.5% of patients. Eosinophilia returned to normal spontaneously without temporary interruption of gold treatment.

Proteinuria occurred in 7.8% of our patients which was transient and subsided with the temporary interruption of GSTM. Proteinuria was not seen early in the course of treatment and was detected only in patients who had received between 1-2 grams of GSTM. The prevalence of proteinuria is 3-26% in other series.[20,21] Hematuria occurred in 20.5% of patients, compared to previous reports of 10%.[20,21] Hematuria was transient and subsided after temporary interruption of GSTM, except in two cases where GSTM treatment was terminated because of persistent hematuria. Nephrotic syndrome is one of the frequent and serious renal abnormalities associated with gold therapy and was encountered in 0.2%-2.6% of patients in previous reports.[22] In our study, only one patient developed nephrotic syndrome (0.9%). Nevertheless, we are not sure whether it was related to gold therapy or D-penicillamine that had been taken previously. Stomatitis occurred in 7.8% of cases but resolved spontaneously within a few weeks of cessation of chrysotherapy, except in one patient with generalized lichenoid rash who had a stomal ulcer for six months. Stomatitis occurred in 60-80% of patients in one study, while isolated stomal ulcer was seen in 8.3% in another.[5] Hepatitis and colitis are two of the rare but more severe manifestations of gold toxicity.[23,24,27] In our series 1.9% developed hepatitis and 2.9% colitis. GSTM treatment was terminated in these patients. Except in rheumatoid arthritis patients with lichenoid rash, colitis and other persistent GSTM adverse reactions, low-dose gold therapy was restarted after adverse reactions subsided without any significant GSTM toxicity during regular follow-up. Only one patient with previous transient pruritus developed a lichenoid rash causing GSTM

therapy to be terminated in this patient. In our Iranian group of patients, in comparison to other reports, lichenoid rash was more significant and more extensive.

ACKNOWLEDGEMENT

I am grateful to Dr. S. Merat for computer assistance and to Mrs. A. Zakerinia and Miss F. Faramarzy for typing this manuscript.

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