EFFECT OF INTRAMUSCULAR GOLD THERAPY ON THE COURSE OF RHEUMATOID ARTHRITIS

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Abstract — Gold preparations are one of the oldest disease modifying drugs in the treatment of rheumatoid arthritis. There are different reports about the effects and complications of these compounds. These opposite reports may be due to the difference in genetic and ethnic background of patients. This study was designed to evaluate our results in gold therapy and compare them with those of western countries. We evaluated the results of gold therapy in 75 rheumatoid arthritis patients. Gold had good effects in 2/3 of patients and adverse effects was found in 1/4. The effect of gold was appeared after 6 months on clinical parameters and after 3 months on laboratory data. The beneficial effect of gold was lost after 24 months of treatment.
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INTRODUCTION

Rheumatoid Arthritis (RA) is a chronic inflammatory disease (1). Clinical manifestations include polyarthritis specially with hand involvement, joint deformity, and rarely extra-articular feature in a prolonged and severe disease (2). The pathogenesis is unknown. Basically it may be due to a special genetic background and some defects in the neuroendocrine axis, producing abnormal immune responses that cause joint's cartilage destruction (3). The treatment of RA is based on its pathogenesis. The new trend in the treatment is an aggressive approach by the early use of disease modifying antirheumatic drugs (DMARDs) with low dose of steroids. Gold is the first DMARDs used for RA since the early 20th century. There are many different opinions about gold therapy:

* Gold therapy reduces the progression rate of RA (5).
* Gold has no place in recent rheumatology (6).
* Gold therapy lowers the mortality rate of RA (7).
* Gold efficacy is only for short time (8).

The role of gold in the treatment of RA is through the regulation of humoral and cellular immunity (9-17). It repair the scavenger systems (18-21) and control the changes in cell mediators or enzymes (22-38). They increase the expression of major histocompatibility complex (MHC) class II (39). There are many reports about their efficacy (40-45) or adverse effects (46-56). The discrepancy in different reports may be due to the duration of the study. The aim of this study was to demonstrate the result of gold therapy for the treatment of RA.

MATERIALS AND METHODS

Patients who received gold were classified by the 1987 RA criteria of the American College of Rheumatology (57) and selected for this study. Every patient received 10 mg gold as a test dose at the beginning of the treatment. Then if patients had no adverse reaction received 50 mg every week until a total dose of one gram. According to patient's response, the injection interval increased to two weeks and then to one month until a total dose of two grams.

Our protocol had 3 parts: The first part included the sex, the age at the onset of RA, the age at the institution of gold therapy, the actual age, the duration of gold therapy and the total amount of gold. The second part was for the quantitation of the disease activity. This data was checked every 3 months for the first year and then every 6 months until 5 years of treatment. It included, duration of the morning stiffness, number of swollen joints, number of tender joints, the global physician's assessment, the patient's global assessment, and the amount of steroid or NSAID used. It also included paraclinical data such as ESR, CRP, RF, and hemoglobin. The last part of the protocol was the evaluation of the adverse effects of gold therapy. The results were expressed in terms of the mean± S.D. of the mean. The data were analysed by student's t-test for the test of significance.

RESULTS

Of a total 128 patients who were admitted, 53 RA pateints were excluded because they received the gold in combination therapy with another DMARD, or they left from follow-up. The analysis was done on 75 patients. The 83% of patients were female and 17% were male. The sex and Age distribution of patients are shown in Table 1.

The evaluation of morning stiffness during gold therapy is shown in Table 2. As shown in this table the duration of the morning stiffness have irregular fluctuation.

Table 1. Sex and age distribution of patients

	Mean	S.D.
Age of patients on gold	43 years	14.5
Age at disease onset	33 years	13.2
Interval from initial gold therapy	6 years	4.7
Duration of treatment	20 months	11.9
Total amount of gold (mean)	188 mg	992.8

Table 2. Morning stiffness during gold therapy

Months	Mean (minutes)	S.D.	P Value
Before treatment	144.38	189.68	-
3	86.49	204.93	0.16
6	70.14	164.37	0.07
9	32.52	50.98	0.002
12	96.76	182.62	0.28
18	23.95	39.64	0.009
24	30	38.34	0.02
30	61.11	76.88	0.22
36	85	114.11	0.48

The decrease in the number of painful joint has been shown in Table 3 and the decrease in the number of swollen joints has ben shown in Table 4.

Table 3. Changes in number of painful joints.

Months	Mean (minutes)	S.D.	P Value
Before treatment	12.22	8.9	-
3	8.75	10.56	0.11
6	6.06	7.85	0.002
9	4.39	5.76	0.0002
12	6.17	7.81	0.007
18	8.56	7.95	0.13
24	3.88	3.72	0.01
30	3.25	2.22	0.05
36	7	9.9	0.42

Table 4. Changes in number of swollen joints.

Months	Mean (minutes)	S.D.	P Value
Before treatment	12.4	10.6	-
3	10.2	11.8	0.3
6	6.7	8.6	0.001
9	6.3	7.5	0.0007
12	7.1	7.6	0.006
18	6.8	7.3	0.01
24	7.6	8.6	0.07
30	5.6	6.1	0.1
36	3.6	7.5	0.02

The change in the daily antiinflammatory drug is shown in Table 5. The NSAID dosage was calculated as the number of 25 mg indomethacin capsules, or its equivalent.

Table 5. Changes in indomethacin daily dosage (in number of 25 mg capsules)

Months	Mean	S.D.	P Value
Before treatment	4.1	1.58	-
3	3.7	1.7	0.22
6	3.4	2.2	0.04
9	2.9	1.7	0.0004
12	3.1	1.6	0.002
18	2.9	1.9	0.003
24	3.0	2.2	0.02
30	3.7	1.5	0.5
36	3.4	1.5	0.3

As shown in Table 6 the amount of prednisolone required to control of the inflammation decreased gradually. It became statistically significant after 6 and the sparing effect lasted up to 18-24 months.

Table 6. Changes in prednisolone dosage (mg)

Months	Mean	S.D.	P Value
Before treatment	7.7	2.7	-
3	7.2	2.9	0.2
6	6.3	2.1	0.002
9	6.0	2.3	0.0008
12	6.1	2.5	0.003
18	6.3	2.6	0.03
24	7.1	3.6	0.4
30	8.1	3.3	0.8
36	7.5	1.8	0.8

The effect of gold therapy on paraclinical data is shown in Table 7. The increase of the mean hemoglobin reached a significant level after 9 months of treatment and lasted up to 12-18 months.

Table 7. Variation of hemoglobin (g/dl)

Months	Mean	S.D.	P Value
Before treatment	12.1	1.5	-
3	12.4	1.5	0.3
6	12.6	1.3	0.08
9	12.9	1.6	0.02
12	12.7	1.4	0.04
18	12.5	1.4	0.3
24	12.5	1.3	0.4
30	13	1.5	0.1
36	13.5	1.3	0.04

The decrease of ESR (Table 8) reached to significant amount after 3 months and lasted 42-48 months. The highest ESR was observed at the beginning of gold therapy.

Table 8. Alteration in erythrocyte sedimentation rate at the first hour (mm)

Months	Mean	S.D.	P Value
Before treatment	56.1	30.2	-
3	33.1	21.6	0.000003
6	30.1	22.1	0.000001
9	34.1	27.4	0.0001
12	28.5	23.1	0.000002
18	26.6	21.1	0.00003
24	31.3	26.1	0.002
30	18.1	15.1	0.0002
36	10.43	9.1	0.0002

The decrease in the percentage of patients with a positive CRP (Table 9) became statistically significant after 6 months of gold therapy. The good result was maintained up to 24-30 months (no patient had CRP^+ after 24 months.

Table 9. Changes in CRP

Months	Total measured	CRP^+ in %	P Value
Before treatment	31	87	-
3	14	71	0.4
6	13	46	0.01
9	12	42	0.008
12	9	33	0.004
18	8	25	0.002
24	2	0	0
30	3	67	0.9
36	5	40	0.06

The reduction in the percentage of patients with a positive RF is shown in Table 10, started after 3 months of gold therapy. It reached a statistically significant value only after 18 - 24 months of treatment.

Table 10. Changes in Rheumatoid Factor

Months	Total measured	RF^+	P Value
Before treatment	50	72	-
3	22	68	0.96
6	19	74	0.66
9	16	56	0.38
12	12	42	0.1
18	6	17	0.02
24	2	0	0.17
30	6	33	0.15
36	5	80	0.36

Figures 1 and 2 show the physician's global assessment and patient's global assessment. 27% of our patients showed side effects to gold therapy. Cutaneous side effect were seen usually after 6 months of gold therpay. Skin manifestation (45%) subsided entirely after the drug withdrawl. Hematuria was detected in 60% of patients. It was labile and disappeared despite the gold therapy. Proteinuria was seen in five patients, but only one had a nephrotic syndrome. Gold therapy was discontinued in patients with proteinuria, resulting in a return to normal of the uninalysis. The mean interval of the established renal complications since the beginning of gold therapy was 8.4 months.

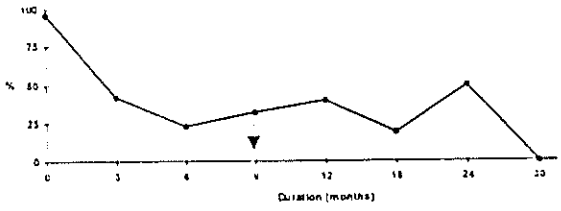

Fig. 1. Physcian assessent as "percentage of active disease"

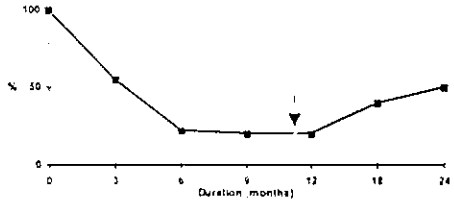

Fig. 2. Patient's assessment for the severity of the disease

Other side effects were rare. One case of purpura observed after 18 months of the treatment, in spite of normal platelet count. It disappeared after 3 months, while the patient continued the gold therapy. One case of transaminase and alkaline phsophatase elevation, observed without clinical symptoms, after 9 months of treatment. It also disappeared 9 months later, despite gold therapy.

DISCUSSION

Iran has different ethnic groups including Caucasians, Turks, and Semites. It is interesting to compare the effect of gold therapy in Iran with Western countries and with Asian countries. As there was no similar report in Asia, we compared our results only with Western reports. Table 11 shows patients' characteristics in Iran and compares them with Sweden (40), Finland (58), Birmingham (59), and USA (60). The mean age of patients on gold therapy was 43.1 years in our study, while for other studies it was in the 6th decade of life. There was a delay for prescription of gold therapy in all of studies, as well as in Iran. It may be a consequence

Table 11: Comparison the result from Iran with other reports:

	Iran	Sweden (1983)	Sweden (1985)	Finland (1991)	Birmingham (1984)	Epstein (1991)
Women %	82.6	-	-	74.9	-	75
Mean age at RA onset (yrs)	32.5	-	-	36.7	-	-
Mean age at Gold onset (yrs)	37.9	-	-	39.5	-	-
Mean age of patients (yrs)	43.1	53	54	-	-	55
Interval till start of Gold (yrs)	5.5	6.4	7.3	2.7	-	10.2
Mean treatment duration (months)	20.2	20	26	-	-	-
Mean doese of Gold (mg)	188	1084	1343	-	-	-

Table 12: Comparison of side effects of gold therapy in Iran and Birmingham

	Iran	Bendix (1983)	Bendix (1985)
Cutaneous side effect	23%	41%	25%
Renal side effect	17%	19%	6%
No response	14%	14%	25%
Remission	17%	2%	3%
Pregnancy	6%	-	-
Lack of compliance	17%	-	-
Lack of follow-up	8%	-	-

of the pyramid strategy for the others, while in Iran it was mainly due to the first choice of DMARD which was rarely the gold. The difference in the duration of gold therapy in our study and the others was not statistically significant. Table 12 compares side effects of gold therapy in Iran with two studies from Birmingham (58-61).

In our study, we had two groups of patients: (1) patients received gold for 6 to 12 months, and (2) patients received gold for 24 to 30 months. The number of painful and swollen joints and the duration of morning stiffness decreased continuously until 18 to 24 months of treatment. Then all of them strated to rise again. This shows that the effect of gold therapy is not sustained during the time. This is also in favor of the Fries Saw tooth strategy (62). The fluctuation of the clinical response shows that gold therapy has no effect before 6 months of treatment. The double blind study of the Empire Rheumatism Concil (42) showed that the initial effect of gold therapy started 3 months after its initiation, and remained effective 12 months after its discontinuation. The reduction in the antiinflammatory drug, dosage became statistically significant after 6 months of gold therapy, which correspond to the beginning of gold's therapeutic effect. In our study, 33% of patients withdrew gold because of its inefficacy. The withdrawal took place after a mean treatment time of 19 months. In conclusion, our study demonstrates the same result for gold therapy as the reports from Western countries. The efficacy of gold starts only after 6 months of treatment. The first clinical clue for its efficacy is the relief of swollen joints. The earliest sign of gold efficacy is the decrease of ESR, which appears after 3 months of treatment. The good therapeutic response will not last forever, it is therefore better to change it with another DMARD as advised by Fries in his Saw Tooth strategy.

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