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[Intervention Review]

Injectable gold for rheumatoid arthritis

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ABSTRACT

Background

Gold compounds have been used in several conditions affecting man since the 18th century (tuberculosis, lupus vulgaris, bacterial endocarditis, etc.) however, in the past decade the use of injectable gold for rheumatoid arthritis has markedly declined, and its clinical usefulness has been doubted.

Objectives

To estimate the short-term benefit and risk of side-effects of injectable gold for rheumatoid arthritis.

Search methods

We searched the Cochrane Musculoskeletal Group trials register, and MEDLINE, up to July 1997, using the search strategy developed by the Cochrane Collaboration (Dickersin 1994). The search was complemented with bibliography searching of the reference list of the trials retrieved from the electronic search. Key experts in the area were contacted for further published and unpublished articles.

Selection criteria

Randomized clinical trials (RCT) comparing injectable gold against placebo in patients with rheumatoid arthritis were included.

Data collection and analysis

Methodological quality of the RCTs was assessed by two reviewers (MS, BS) ($\kappa=1.0$). Rheumatoid arthritis outcome measures were extracted by two reviewers from the publications for the 6 month endpoint. Sufficient data was obtained to conduct a pooled analysis of the number of swollen joints, physician global assessment, patient global assessment and erythrocyte sedimentation rate (ESR). Results were analyzed as standardized weighted mean differences for swollen joints and global assessments and weighted mean differences for ESR. Toxicity was evaluated with pooled odds ratios for withdrawals. Heterogeneity was estimated using a chi-square test. Fixed effects models were used throughout.

Main results

Four trials and 415 patients were included. A statistically significant benefit was observed for injectable gold when compared to placebo. The standardized weighted difference (effect size) between gold and placebo for the number of swollen joints was -0.5, translating into a percentage change of 30% in favour of gold adjusted for placebo. Statistically significant differences were also observed for ESR and

patient and physician assessments. Twenty two percent of the treated patients withdrew from toxicity compared to 4% of controls (OR=3.9 - 95%CI: 2.1 - 7.2).

Authors' conclusions

Although its use can be limited by the incidence of serious toxicity, injectable gold has an important clinically and statistically significant benefit in the short term treatment of patients with rheumatoid arthritis.

PLAIN LANGUAGE SUMMARY**Injectable gold for treating rheumatoid arthritis**

Injectable gold has been used to treat several conditions since the 18th century. This review included four trials and 415 patients. Patients receiving gold injections had 30% fewer swollen joints compared to patients receiving placebo. Improvements were also found for blood work and patient and physician assessments in those patients receiving gold injections. 22% percent of the treated patients withdrew from toxicity compared to 4% of patients taking placebo.

Although its use can be limited by the incidence of serious harms, injectable gold has an important clinically and statistically significant benefit in the short term treatment of patients with rheumatoid arthritis.

BACKGROUND

Gold compounds have been used in several conditions affecting man since the 18th century (tuberculosis, lupus vulgaris, bacterial endocarditis, etc.). [Laude 1927](#) was the first to use aurothioglucose (Solganal) in rheumatoid arthritis (RA), and [Forestier 1935](#) used gold thiopropanol sodium sulfanate (Allochrysine) in more than 550 cases of RA with beneficial results. Since then, different gold compounds have been developed and clinical trials have confirmed the beneficial results reported by Forestier. However, the estimate of the magnitude of the clinical benefit found with injectable gold salts in RA varies considerably across studies. Furthermore, in the past decade the use of injectable gold for rheumatoid arthritis has markedly declined, and its clinical usefulness has been doubted ([Epstein 1991](#)).

OBJECTIVES

To conduct a systematic review of the literature using qualitative and quantitative methods on the short-term efficacy and toxicity of injectable gold in RA.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized clinical trials (RCTs) published in English, with a minimum duration of the study of 20 weeks.

Types of participants

Patients with a diagnosis of rheumatoid arthritis (as stated in the publication)

Types of interventions

Intervention group: injectable gold (sodium aurothiomalate) for at least 20 weeks

Control group: placebo

Types of outcome measures

All the outcome measures in OMERACT ([OMERACT 1993](#)) were included for potential analysis, although only some were consistently measured. OMERACT measures for efficacy include:

- Number of tender joints per patient
- Number of swollen joints per patient
- Acute phase reactants
- Pain
- Functional status
- Physician global assessment
- Patient global assessment
- Radiological damage

Toxicity was evaluated using withdrawals and dropouts (total and organ-specific)

Search methods for identification of studies

A comprehensive MEDLINE search was performed using the strategy developed by the Baltimore Cochrane Centre from 1966 to July 1997. In addition, reference lists of all the trials selected through the electronic search were manually searched. References

in textbooks were also hand searched. The Cochrane Controlled Trials Register (CCTR) was also searched.

Four RCTs complied with the selection criteria after completing the literature searches

Data collection and analysis

Data extracted from the publications included study characteristics and outcome measures of efficacy and toxicity.

Efficacy

The results on efficacy were analyzed for the 6 month endpoints. Although some trials had longer duration this endpoint was chosen because it was reported in all the RCT.

Only 3 trials could be evaluated for efficacy by meta-analysis ([ERC 1960](#), [Sigler 1974](#), [Ward 1983](#)). The additional trial only reported data as medians with no measure of dispersion ([CCC 1973](#)). The only efficacy measures adequately reported for pooling were: number of swollen joints (2 RCTs); physician global assessment; patient global assessment (2 RCTs); ESR (2 RCTs).

For number of swollen joints, one of the trials did not include a standard deviation ([Sigler 1974](#)). This was estimated using the coefficient of variation from the other trials ($CV=SD/mean$; in this case 0.8). The same method was used to estimate the standard deviation for global assessments for the [ERC 1960](#) trial ($CV=0.3$).

End-of-trial results were pooled as standardized weighted means for the number of swollen joints, and the global assessments. This was necessary because of the variation in the outcome measures included in each study (e.g. different number of swollen joints). Trial results were entered in RevMan (the Cochrane Collaboration software) using the same direction to enable the pooling of results where the lowest value was improvement the highest value was worsening. Negative values in standardized weighted means indicate a benefit of injectable gold over placebo. ESR results were pooled using a weighted mean difference.

Toxicity

Toxicity results were generally reported as overall results at the end of the trial, and were therefore pooled for different trial follow-ups.

Toxicity was analysed using a pooled odds ratio for total withdrawals, and dropouts and withdrawals for specific reasons.

The heterogeneity of RCTs for each pooled analysis was estimated using a chi-squared test.

Fixed effects models were used throughout.

RESULTS

Description of studies

Four randomized controlled trials ([ERC 1960](#), [CCC 1973](#), [Sigler 1974](#), [Ward 1983](#)) met the criteria for inclusion. The patients in these trials were similar as assessed by patient's age, inclusion criteria, duration of disease and activity at entry. Although there was no statistically significant difference in baseline joint count in the 3 studies that reported this data, patients in the [Ward 1983](#) study had a longer mean duration of disease and more joints involved on average. The [CCC 1973](#) paper did not include baseline joint

counts. The drug regimens all used sodium aurothiomalate at similar doses for 20-22 weeks, tapered thereafter for studies with longer duration of follow up. Sample sizes varied from 32 to 199. Three trials reported the side effects in sufficient detail to allow clinical and statistical assessment. The studies of [Sigler 1974](#) and [Ward 1983](#) reported on all patients who entered their studies; the [ERC 1960](#) enrolled 199 and analyzed 185. The [CCC 1973](#) enrolled 68 and analyzed 33.

Tests of homogeneity did not show any one study to be statistically different from the others.

Risk of bias in included studies

The methodological quality of the studies was assessed independently by two of the reviewers (MS, BS) using a quality scale validated and published by [Jadad 1996](#). This scale includes an assessment of randomization, double-blinding procedures and description of withdrawals. The possible range of scores is 0 (worst) to 5 (best). Two studies had a score of 4, and the other two a score of 5. The kappa for agreement between observers on the quality scores was 1.0 (perfect agreement).

Effects of interventions

In the pooled analysis of clinical benefits all the efficacy measures considered for the study reached levels of statistical significance of <0.05 . There was a reduction in the number of swollen joints corresponding to an effect size of 0.5. Statistically significant differences favouring gold were also observed for global assessments. These differences were of approximately the same magnitude: 0.6 for the physician assessment and 0.4 for the patient assessment. A statistically significant difference of 13 mm was observed for ESR.

The data available on side effects allowed pooled analysis of the following: total withdrawals and dropouts, toxicity withdrawals, dermatitis and stomatitis, proteinuria and hematological side effects. The other side effects were present in too low a frequency for meaningful pooling. Thirty percent of the patients receiving gold discontinued therapy compared to 15% of patients on placebo [OR=2.2 - (95%CI: 1.4 - 3.6)]. Twenty two percent of the treated patients withdrew from toxicity compared to 4% of controls (OR=3.9 - 95%CI: 2.1 - 7.2). A statistically significant difference was observed for withdrawals from mucocutaneous toxicity (OR: 4.2). Although proteinuria was noted in the different studies to be present from 2.4 to 4.2% of patients receiving gold, it was also present in 2.3 to 4.7% of control patients. Thus, in the pooled analysis albuminuria was estimated to be more frequent by 0.7% in gold treated patients, an OR of 1.4 which is not statistically significant. Three percent of the patients receiving gold withdrew because of hematological effects, compared to none in the placebo group (therefore, the OR could not be estimated).

Withdrawals from lack of efficacy were significantly higher in the placebo group: 7% vs. 2% (OR:0.28 - 95%CI: 0.10 - 0.75)

Sensitivity analysis was carried out using the extremes of the range of the variance of the individual studies. No substantive change in the effect size or level of statistical significance was seen.

DISCUSSION

The purpose of this systematic review was to evaluate the efficacy and toxicity of injectable gold for the treatment of patients with RA. It raises a number of methodologic issues, but combines a qualitative approach with a quantitative meta-analytic technique which we believe provides a useful method for synthesizing the evidence for clinicians to use for clinical decision making.

The studies pooled all directly addressed the objective and used similar criteria for RA, the disease of interest. Study selection bias was minimized by selecting only randomized trials. Although some of the major outcome measures in the trials were sufficiently homogeneous to allow pooling, there was some lack of standardization of the outcome measurements and even complete omission of some in some studies. These studies were all published before the establishment of the OMERACT and the American College of Rheumatology (ACR) core set of measures for RA ([OMERACT 1993](#), [Felson 1993](#)); the most recent trial in this review was published in 1983. Many of the measures evaluated are considered nowadays of doubtful value (grip strength, ring size). The statistical methods used were those recommended for this type of data. There was, however, some inconsistency in the methods of presenting the data in the published reports of these studies. For example, one study [[CCC 1973](#) 1973] only reported medians and could not be pooled with the others in the analysis for efficacy. Some assumptions had to be made as well in relation to the standard deviations in some of the measures since these were not reported.

The primary objective of our study was to resolve uncertainties in relation to the efficacy of injectable gold for the treatment of patients with RA. Major differences in the range of the estimates of benefit in the endpoints had been reported in individual RCTs ([ERC 1960](#), [CCC 1973](#), [Sigler 1974](#), [Ward 1983](#)). Mean improvement in joint counts ranged in these studies from a minimum of 2.6 joints to a maximum of 12.0 joints, which could only be partially attributed to differences in scoring methods. Other measures such as grip strength also showed varying results. The pooled estimate of clinical benefit from injectable gold in the present meta-analysis provides an estimate of benefit that makes appropriate adjustments for the different sample sizes and degree of precision across the studies. It also takes into account the use of different scoring techniques by standardizing the weighted differences (e.g. different number of possible swollen joints measured in each study). All variables included in our analysis are included in the OMERACT core set of outcome measures for RA. The 4 variables for which there was sufficient data for pooling (number of swollen joints, ESR, physician global assessment and patient global assessment) all showed a statistically significant benefit when compared to placebo. Standardized measures showed a difference of approximately 0.5; an effect size of 0.3 or greater is considered to be clinically significant when assessing disease activity in patients with rheumatoid arthritis ([Kazis 1989](#)). A significant difference was also observed in withdrawals from lack of efficacy. Patients receiving placebo were 3.5 times more likely to withdraw from inefficacy than those receiving gold.

Toxicity was increased in the gold group. Most withdrawals from toxicity were due to skin reactions. The incidence of proteinuria appeared to be low, and was similar in gold treated patients and controls. Close to 3 % of the patients receiving gold had to

discontinue therapy because of hematological toxicity including leucopenia and thrombocytopenia. The relatively low prevalence of renal and hematological side effects limits the usefulness of clinical trials to evaluate these serious toxicities, given the limited sample sizes in these studies. Cohort studies may be more appropriate to evaluate the incidence of these disorders.

Treatment of rheumatoid patients with injectable gold has markedly decreased in the past decade, and its efficacy has been doubted (Epstein 1991). Despite these trends, the short term efficacy of gold was evident in this systematic review. Limitations to its potential use would appear to be mostly related to toxicity.

AUTHORS' CONCLUSIONS

Implications for practice

The studies involved patients representative of those currently considered for gold therapy in the practices of the authors and their colleagues; thus we consider the results to be relevant to clinical decisions about this therapy. Although its use can be limited by the incidence of serious toxicity, injectable gold has an important clinically and statistically significant benefit in the short term treatment of patients with rheumatoid arthritis.

Implications for research

Since there are additional specific issues particularly relevant to slow acting antirheumatic drugs, it might be useful to consider establishing supplementary guidelines or criteria for the standardization of reporting for clinical trials of antirheumatic drugs, following the guidelines from CONSORT (Bedd 1996); this would avoid the need to obtain additional data and analyses from the original investigators (which is often hard to obtain after the study is published). Specific issues for RA include:

(1) Standardization of timing: there is considerable variation in the duration of trials of many of the slow acting anti-rheumatic drugs which makes it difficult to compare them; thus the timing of assessments should be at regular intervals, preferably standardized, so that studies of longer duration can be compared with shorter ones using data at the same points in time. The clinical heterogeneity in the follow-up duration of the studies included in this review only allowed us to pool results for the first 6 months of treatment.

(2) Comparability of groups: the description of the demographic and clinical characteristics of the patients is important, to allow for meaningful pooling of results and generalizability

(3) Details of the inclusion and exclusion criteria are also needed for deciding on the generalizability of the results. For example, there are frequently age restrictions because of the regulatory agencies concerns about toxicity in the elderly, yet this age group poses major therapeutic challenges and good quality data are needed for informed decisions.

(4) Different drug studies use different outcomes and different methods of measuring them, making it difficult or impossible to compare or combine the results. These issues will hopefully be resolved by applying the criteria established by OMERACT and the ACR in relation to the evaluation of patients with RA in clinical trials.

(5) Some studies publish only the end-of-treatment results while others publish the difference between beginning and end of treatment; some publish their statistics as medians while others publish just means. For valid meta-analysis (or simple comparisons by clinicians reading the articles) manuscripts should provide standardized data on each endpoint, perhaps a minimum of the following: means and medians of each one at baseline and at end of treatment, plus their variance.

(6) Although the reporting of means or medians is the traditional method of reporting the magnitude of benefit, clinical significance can be usefully complemented by reporting the proportion of patients achieving a predetermined degree of improvement, e.g., the Ward 1983 et al study reported on the proportion of patients achieving a 50% reduction in joint count. This provides useful information to the clinician on the probability of a major improvement. Several sets of criteria are available (Paulus, ACR and Euler) (Felson 1995). This information on the proportion of patients achieving a specified level of improvement can be combined across studies. The proportion of patients improving or developing adverse reactions, rather than means, is also needed for developing decision analysis algorithms, another important application of a pooled estimate.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

CCC 1973

Methods	Randomized allocation Double blind allocation and assessment Sample size at entry gold:36; placebo:32
Participants	Patients with active RA (definite or classical) Mean age not specified Duration of disease not specified No previous treatment with gold or antimalarials

CCC 1973 (Continued)

Interventions	Aurothiomalate - First 3 weeks 10, 15, 25 mg IM weekly, thereafter 50 mg weekly for 17 weeks; dose decreased progressively to 50 mg every 4 weeks until the end of the trial
Outcomes	Outcomes reported at baseline and month 6 Efficacy measures - number of active joints, grip strength, morning stiffness, ESR, 50 foot walk
Notes	Patients included in the analysis: 61% in the gold group 66% in the control group Quality score:5 This RCT only included for toxicity, results on efficacy reported as medians. Statistically significant differences in efficacy were only observed for ESR

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

ERC 1960

Methods	Randomized allocation Double blind allocation and assessment Sample size at entry: gold:99; placebo:100
Participants	Patients with active RA (definite or classical) Mean age - 48.7 yrs Duration of disease - 66% 1 to 3 yrs; 34% 3 to 5 yrs No previous treatment with gold
Interventions	Aurothiomalate - 50 mg IM weekly Treatment duration - 20wks
Outcomes	Outcomes reported at baseline and months 1, 3, 6, 12 and 18 Efficacy measures - Physician's estimate of functional capacity; subjective estimate of fitness by patient, number of joints involved, grip strength, ESR, radiological damage
Notes	Patients included in the analysis: 91% in the gold group 95% in the control group Quality score: 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Sigler 1974

Methods	Randomized allocation Double blind allocation and assessment Sample size at entry: gold 13; placebo 14
Participants	Patients with active RA (definite or classical) Mean age - 45 yrs Mean duration of disease - gold 28 months; placebo 35 months No previous treatment with gold
Interventions	Aurothiomalate - First 3 weeks 10, 15, 25 mg IM weekly, thereafter 50 mg weekly for 18 weeks; dose decreased progressively to 50 mg every 4 weeks until the end of the trial
Outcomes	Outcomes reported at baseline and months 6, 12 and 24 Efficacy measures - number of swollen joints, grip strength, ring size, walking time, ESR, radiological damage
Notes	Patients included in the analysis: 100% in the gold group 100% in the control group Quality score: 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Ward 1983

Methods	Randomized allocation Double blind allocation and assessment Sample size at entry: gold 75; placebo 46
Participants	Patients with active RA (definite or classical) Mean age - 49 yrs Mean duration of disease - gold 76 months; placebo 64 months No previous treatment with second line drugs
Interventions	Aurothiomalate - First 3 weeks 10, 15, 25 mg IM weekly, thereafter 50 mg weekly for 19 weeks Treatment duration - 22wks
Outcomes	Outcomes reported at baseline and week 22 (5.5 months) Efficacy measures - Number of tender joints and score, number of swollen joints and score, grip strength, morning stiffness, functional class, physician and patient global assessment
Notes	Patients included in the analysis: 100% in the gold group 100% in the control group Quality score: 5

Risk of bias

Injectable gold for rheumatoid arthritis (Review)

Ward 1983 (Continued)

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

DATA AND ANALYSES
Comparison 1. Injectable gold vs. placebo - Efficacy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of swollen joints	3	309	Mean Difference (IV, Fixed, 95% CI)	-4.58 [-6.50, -2.65]
2 Physician global assessment	2	281	Mean Difference (IV, Fixed, 95% CI)	-0.34 [-0.48, -0.20]
3 Patient global assessment	2	282	Mean Difference (IV, Fixed, 95% CI)	-0.48 [-0.77, -0.19]
4 ESR	2	257	Mean Difference (IV, Fixed, 95% CI)	-13.16 [-18.14, -8.18]

Analysis 1.1. Comparison 1 Injectable gold vs. placebo - Efficacy, Outcome 1 Number of swollen joints.

Study or subgroup	Treatment		Control		Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)			
CCC 1973	13	7.8 (6.4)	14	11.9 (9.5)		10.06%	-4.1[-10.17,1.97]
ERC 1960	90	7.8 (6.4)	95	12.6 (9.3)		70.69%	-4.8[-7.09,-2.51]
Ward 1983	54	14 (13)	43	18 (9)		19.25%	-4[-8.39,0.39]
Total ***	157		152			100%	-4.58[-6.5,-2.65]
Heterogeneity: Tau ² =0; Chi ² =0.13, df=2(P=0.94); I ² =0%							
Test for overall effect: Z=4.66(P<0.0001)							

Analysis 1.2. Comparison 1 Injectable gold vs. placebo - Efficacy, Outcome 2 Physician global assessment.

Study or subgroup	Treatment		Control		Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)			
ERC 1960	90	1.7 (0.5)	95	2 (0.6)		76.41%	-0.3[-0.46,-0.14]
Ward 1983	53	2.3 (0.6)	43	2.8 (0.8)		23.59%	-0.47[-0.76,-0.18]
Total ***	143		138			100%	-0.34[-0.48,-0.2]
Heterogeneity: Tau ² =0; Chi ² =1.02, df=1(P=0.31); I ² =2.02%							
Test for overall effect: Z=4.76(P<0.0001)							

Analysis 1.3. Comparison 1 Injectable gold vs. placebo - Efficacy, Outcome 3 Patient global assessment.

Analysis 1.4. Comparison 1 Injectable gold vs. placebo - Efficacy, Outcome 4 ESR.

Comparison 2. Injectable gold vs. placebo - Toxicity

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Withdrawals and dropouts	4	415	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.22 [1.38, 3.56]
2 Withdrawals from inefficacy	4	415	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.28 [0.10, 0.75]
3 Withdrawals from toxicity	4	394	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.90 [2.12, 7.17]
4 Withdrawals from skin and mucosal toxicity	4	415	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.17 [2.10, 8.27]
5 Withdrawals from renal toxicity	4	415	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.53 [0.09, 3.16]
6 Withdrawals from hemaetological toxicity	4	415	Peto Odds Ratio (Peto, Fixed, 95% CI)	6.05 [1.18, 31.04]

Analysis 2.1. Comparison 2 Injectable gold vs. placebo - Toxicity, Outcome 1 Withdrawals and dropouts.

Analysis 2.2. Comparison 2 Injectable gold vs. placebo - Toxicity, Outcome 2 Withdrawals from inefficacy.

Analysis 2.3. Comparison 2 Injectable gold vs. placebo - Toxicity, Outcome 3 Withdrawals from toxicity.

Analysis 2.4. Comparison 2 Injectable gold vs. placebo - Toxicity, Outcome 4 Withdrawals from skin and mucosal toxicity.

Analysis 2.5. Comparison 2 Injectable gold vs. placebo - Toxicity, Outcome 5 Withdrawals from renal toxicity.

Analysis 2.6. Comparison 2 Injectable gold vs. placebo - Toxicity, Outcome 6 Withdrawals from hemaetological toxicity.

WHAT'S NEW

Date	Event	Description
22 September 2008	Amended	Converted to new review format. C045-R

DECLARATIONS OF INTEREST

None known

INDEX TERMS**Medical Subject Headings (MeSH)**

Antirheumatic Agents [administration & dosage] [*therapeutic use]; Arthritis, Rheumatoid [*drug therapy]; Injections; Organogold Compounds; Risk

MeSH check words

Humans