DISEASE-MODIFYING DRUGS
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INJECTABLE GOLD COMPOUNDS: AN OVERVIEW
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SUMMARY
Injectable gold compounds have enjoyed widespread, but occasionally controversial, use in rheumatoid arthritis since the early 1920s. This overview examines the data from controlled trials and longer-term observational studies. We conclude that gold is equivalent to other widely used second-line agents in terms of efficacy. Toxicity profiles are similar, apart from methotrexate. It is most efficacious and toxic in the first 2 yr of treatment. There appears to be a dose–response relationship for both efficacy and toxicity. Gold is one of the few agents that decreases the rate of progression of erosions (RR 0.38, 95% CI 0.23–0.64). Gold compounds, therefore, have a definite place in the rheumatologist’s armamentarium, but further research is required to determine optimal monitoring regimes as well as the role of maintenance therapy and combination therapy.

KEY WORDS: Gold compounds, Injectable, Efficacy, Toxicity.

INJECTABLE gold compounds have been used for the treatment of chronic arthritis since the early 1920s. Forestier [1] was one of a substantial number of early investigators who published virtually simultaneously on the therapeutic benefits of gold. He studied gold complexed with thiopropanolsulphonate (Allochrysine) in 550 subjects. He concluded that it was beneficial for rheumatoid arthritis (RA; early or late), Still’s disease, metastatic arthritis (probably Reiter’s syndrome), some forms of tuberculosis arthritis and ankylosing spondylitis. He also stated, without being specific, that monitoring for toxicity should be done at frequent intervals. The use of gold compounds remains controversial to this day with much disagreement in the literature, but some of Forestier’s conclusions have stood the test of time even though injectable gold complexes have been subject to more rigorous and detailed scientific scrutiny than perhaps any other therapeutic agent in rheumatology. In this review, we would like to discuss the controlled trial evidence relating to gold efficacy and toxicity, including the data from meta-analyses and longer-term observational studies.

CHEMISTRY
Several gold compounds are available worldwide with differences between countries. These include sodium aurothiomalate (myocrisin), aurothioglucose (Gold-50, Solganol), gold thiopropanolsulphonate (Allochrysine), gold thiosulphate (Sanochrysin) and gold 4-amino-2-mercaptobenzoic acid (Krysolgan). All are polymeric water-soluble complexes, in contrast to auranofin which is a monomeric lipid-soluble compound. These properties, plus their high molecular weight, mean that the gold complexes are poorly absorbed and of consequent low efficacy when administered orally. Most data relating to pharmacokinetics are available for aurothiomalate. After i.m. injection, aurothiomalate is rapidly absorbed with maximal plasma levels at 2 h. Plasma levels do correlate with dose and body weight (see [2] for a more detailed discussion). Gold is slowly eliminated from the body, especially in the terminal elimination phase, and gold has been found in tissues up to 23 yr after the last dose of aurothiomalate [3].

EFFECTIVENESS
There have been a number of placebo-controlled randomized trials of gold dating back to 1940 [4—12]. All have shown that gold is clearly superior to placebo in RA, but not in psoriatic arthritis [13], although this last trial had a relatively small sample size. However, there are some limitations with these studies. Firstly, they are all short term. The longest follow-up was 30 months in the Empire Research Council (ERC) trial [6, 7] but, even in this trial, gold was only administered for the initial 5 months and after 18 months subjects could choose whether or not they would have gold treatment. Thus, we have to rely on observational studies for demonstration of long-term efficacy or lack thereof. Secondly, none of the trials analysed the results by intention-to-treat analysis. In general, this will only be a significant problem if there were substantial dropouts, which only applies to the Co-operating Clinics trial [8]. Lastly, clinical trials generally analyse changes in groups of subjects assigned to the intervention. While this is appropriate statistically, it may make more sense to look at changes in individuals because of the not uncommon opinion among clinicians that patients can often be split into responders and non-responders.

Forestier reported that 60% of his patients benefited greatly from treatment [1]. Results since then have been somewhat more modest. Fraser [5] reported a great

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improvement in 42% of subjects compared to 8% of those given placebo, but otherwise the clinical trials do not report remission rates. A retrospective life table analysis found that 38% were in remission at 6 months, but that this was sustained past 12 months in only 19% [14]. Longer-term observational studies have shown that this trend continues with ~10% in remission at 6 yr [15]. Other long-term studies have looked at discontinuation rates which include both loss of efficacy and toxicity. Up to 50% of patients had discontinued gold by 25 months in one study [16] and by 2 yr in another [17]. This compares to 60 months for methotrexate [16].

However, others have shown that the difference in discontinuation rates between methotrexate and gold is only evident in the first 6 months of treatment, and is similar after this time [18]. Nevertheless, it is this marked decline in efficacy with gold over time that has prompted some to question its overall usefulness [19]. However, a meta-analysis has shown that the magnitude of the short-term effect with gold is similar to that of salazopyrin, methotrexate and penicillamine [20] and, with the exception of methotrexate, long-term dropout rates are similar, suggesting that any conclusions about gold therapy may well apply to all slow-acting agents.

A re-analysis of clinical trials reported outcomes in individuals and found that a definition of improvement that includes a ≥20% improvement in at least four outcome variables occurs in only 4% of those given placebo. In contrast, 37% of those given gold improved by this degree, similar to penicillamine and methotrexate [21]. An overview of some of the placebo-controlled trials found that, after adjusting for placebo, gold improved active joint count by 30%, grip strength by 14%, functional capacity by 14%, haemoglobin by 5% and ESR by 20%, all of which were statistically significant [22]. Gold therapy has also been reported to improve survival in RA [23], but this may be due to the Hawthorn effect where patients who are more closely monitored tend to do better in the long term.

DOES GOLD PREVENT EROSIONS OCCURRING OR PROGRESSING?

In 1983, Iannuzzi et al. [24] concluded that gold probably does prevent the progression of erosions, but did not quantify the size of the benefit. There are five studies that examine this issue; four are randomized trials and one is a comparative study [25]. When the results are tabulated as relative risk estimates (Table II), we can see that three of the five are individually significant (despite relatively small sample sizes), one is suggestive and the other shows no effect, but has very wide confidence limits. The original studies did not state that any of these results were significant, presumably because they used χ² testing rather than analysis of 2 × 2 tables. When all the individual trials are pooled, there was a 62% reduction in the relative risk of progression or an 18% reduction in the absolute risk of progression, both of which are highly significant. Clearly then, gold substantially decreases the risk of progression of joint damage, but around 25% of subjects progress despite gold treatment and it appears to have no consistent effect in terms of reversal of pre-existing joint damage.

MAINTENANCE THERAPY

There is a paucity of studies that examine the role of maintenance therapy with gold. One study found no advantage of fortnightly over monthly maintenance injections in terms of efficacy, but the fortnightly group had more toxicity [26]. Another randomized subjects to maintenance therapy of 100 mg fortnightly with aurothioglucose or placebo and found no differences between subjects at 12 months [27]. Examination of the raw data in this trial, however, suggests both a trend to better efficacy and a lower relapse rate in the maintenance group. There have been no randomized studies of gold withdrawal in those in remission on established treatment. These limitations indicate the need for further research in this area.

IS THERE EVIDENCE FOR A DOSE RESPONSE?

Table II summarizes the studies pertaining to this question. Some overall conclusions can be drawn from these studies. Firstly, there is suggestive evidence for a dose response in terms of efficacy. If we assume that all studies are samples from the same population of subjects with RA, then in weekly doses: 10 mg < 25 mg = 50 mg = 1 mg/kg = 100 mg < 150 mg ≤ 200 mg. There is no direct comparison for 200 mg vs 150 mg, but 200 mg definitely has less relapses than 50 mg [27], while 200 mg appeared superior to 100 mg in an earlier study [4]. In most cases, these differences are statistically significant. The exceptions would appear to be due to type II error as the magnitude of the differences appears quite large [4, 28, 29]. However, this improvement in efficacy is balanced by a similar increase in toxicity, with increasing doses being associated with increased toxicity in the same order. Response to gold does not appear to be predicted by blood levels as, with one exception, studies have found no association (see [2]).

### Table I

Overview of the effect of gold on radiological progression

<table>
<thead>
<tr>
<th>First author</th>
<th>Treatment arm</th>
<th>Control arm</th>
<th>RR of progression (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zalman [4]</td>
<td>3/16</td>
<td>2/12</td>
<td>1.15 (0.17–7.82)</td>
</tr>
<tr>
<td>ERC [6, 7]</td>
<td>10/73</td>
<td>22/80</td>
<td>0.44 (0.20–0.95)</td>
</tr>
<tr>
<td>CC [8]</td>
<td>3/20</td>
<td>9/19</td>
<td>0.23 (0.06–0.87)</td>
</tr>
<tr>
<td>Sigler [9]</td>
<td>4/13</td>
<td>10/14</td>
<td>0.21 (0.05–0.92)</td>
</tr>
<tr>
<td>Luukainen [25]</td>
<td>18/32</td>
<td>14/18</td>
<td>0.40 (0.12–1.32)</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td>0.38 (0.23–0.64)</td>
</tr>
</tbody>
</table>

*The denominator here is the number of subjects rather than the number of joints, as in the original manuscript, to adjust for excessive weighting that would have resulted from pooling.
TABLE II
Overview of controlled trials of varying dosages of gold

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Weekly dose (mg)</th>
<th>Number</th>
<th>Duration (months)</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ellman [4]</td>
<td>1940</td>
<td>200 ± 100 ± 0</td>
<td>90</td>
<td>9</td>
<td>Dose response for efficacy and toxicity</td>
</tr>
<tr>
<td>Cats [27]</td>
<td>1976</td>
<td>200 ± 50</td>
<td>196</td>
<td>5</td>
<td>Decreased relapse rate with higher dose</td>
</tr>
<tr>
<td>Rothermich [46]</td>
<td>1976</td>
<td>1/kg ± 50</td>
<td>97</td>
<td>5</td>
<td>Increased toxicity with higher dose</td>
</tr>
<tr>
<td>Furst [29]</td>
<td>1977</td>
<td>150 ± 50</td>
<td>47</td>
<td>10</td>
<td>No difference in efficacy or toxicity</td>
</tr>
<tr>
<td>Sharp [54]</td>
<td>1977</td>
<td>50 ± 25</td>
<td>75</td>
<td>24</td>
<td>Less toxicity with aurothioglucose</td>
</tr>
<tr>
<td>McKenzie [28]</td>
<td>1981</td>
<td>50 ± 10</td>
<td>60</td>
<td>12</td>
<td>Improved efficacy (NS)</td>
</tr>
<tr>
<td>Griffin [55]</td>
<td>1983</td>
<td>50 ± 10</td>
<td>41</td>
<td>12</td>
<td>Increased toxicity</td>
</tr>
</tbody>
</table>

CAN WE IMPROVE OR PREDICT RESPONSE?

Corticosteroid induction
Corticosteroid induction at the time of commencing gold appears useful in terms of both long-term efficacy and toxicity, particularly pulsed i.v. methylprednisolone [30] and, to a lesser extent, i.m. corticosteroid [31], while pulsed oral prednisolone does not appear as effective [32].

Combination therapy
There is evidence to support improved efficacy with a suggestion of increased toxicity for some combinations of slow-acting agents, particularly hydroxychloroquine at the time of commencing gold [33], but not in those with a suboptimal response [34], salazopyrin [35] and possibly cyclosporin [36].

Other
Response may also be predicted by HLA antigen status, notably A3 positive and DR4 negative [37], but this finding was not replicated by other investigators [38]. Skin toxicity occurring during treatment may also be predictive of long-term remission with all of the reported cases in one series going into remission for up to 68 months [39].

USE IN OTHER CONDITIONS
Gold therapy has also been reported to be useful in kala-azar [40], discoid lupus [41], juvenile chronic arthritis [42], palindromic rheumatism [43], bullous skin conditions [44], asthma [45] and possibly psoriatic arthritis [13].

TOXICITY
Table III lists the complications that have been reported with gold therapy. Of these, only cutaneous reactions were more common in the treatment group as compared to the control group in clinical trials, with gold subjects being 4.9 times as likely to develop them [22]. This may reflect the short period of observation in clinical trials, the rarity of individual side-effects or coincidental occurrence of these events in patients with RA. Withdrawals due to side-effects occur in 11% of cases (after adjusting for placebo) during clinical trials [22]. However, drop-outs rise over time so that of the 80% who have stopped gold at 5 yr, just under half (35% of the total) are due to toxicity although, as we have noted above, most of these occur in the first 12 months [14]. Aurothioglucose appears less toxic than aurothiomalate in equivalent doses [46].

MANAGEMENT OF TOXICITY
In general, most adverse reactions to gold resolve spontaneously, although they may take some considerable time.

Mucocutaneous
Eosinophilia and itch may be an early sign that mucocutaneous reactions are imminent. Skin reactions usually settle with cessation of gold and may require topical or systemic corticosteroid preparations. Occasionally, gold can be restarted in very low doses [47] or can be changed to aurothioglucose in a lower dose with success in up to 60% of cases [48].

Haematological
Minor changes in platelets or white cells can be observed, but abrupt changes or clinically significant changes require cessation. Spontaneous improvement is usual, but again corticosteroids may be required. Aplastic anaemia may be life threatening, but the prognosis is improving, particularly with bone marrow transplantation which may lead to marked improvement in RA as well.

| TABLE III
Reported toxic effects due to gold compounds |
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td><strong>Mucocutaneous</strong></td>
</tr>
<tr>
<td>Chrysiasis, dermatitis, stomatitis, alopecia</td>
</tr>
<tr>
<td><strong>Renal</strong></td>
</tr>
<tr>
<td>Proteinuria, glomerulonephritis</td>
</tr>
<tr>
<td><strong>Post-injection reactions</strong></td>
</tr>
<tr>
<td>Nitritoid, arthralgia, local pain</td>
</tr>
<tr>
<td><strong>Haematological</strong></td>
</tr>
<tr>
<td>Eosinophilia, cytopenia</td>
</tr>
<tr>
<td><strong>Immunological</strong></td>
</tr>
<tr>
<td>IgE antibodies to gold</td>
</tr>
<tr>
<td><strong>Hepatitis</strong></td>
</tr>
<tr>
<td><strong>Colitis</strong></td>
</tr>
<tr>
<td><strong>Lung abnormalities</strong></td>
</tr>
<tr>
<td>Pneumonitis, bronchiolitis obliterans</td>
</tr>
<tr>
<td><strong>Neurological</strong></td>
</tr>
<tr>
<td>Neuropathy, encephalopathy, myokymia</td>
</tr>
</tbody>
</table>
Other

Other reactions usually require cessation or suspension of gold. Specific management is not clear for nephropathy, gold lung or colitis, but is along general lines for these conditions.

OPTIMAL MONITORING REGIME

Much of current monitoring practice for gold has evolved out of the knowledge of toxicity rather than demonstration of effectiveness. Liang and Fries [49] recommended a weekly self-administered questionnaire, monthly full blood count, weekly urinalysis and monthly physician review. This may or may not be the optimal strategy and there is a strong need for a controlled trial of different monitoring regimes given the difficulties of adhering to strict protocols [50] and expense involved with current regimes.

SAFETY IN PREGNANCY AND LACTATION

Gold is teratogenic in animals, but whether this is so in humans is controversial (see [51]). Certainly, gold can be found in fetal issue, breast milk and the tissues of breastfeeding infants. Isolated case reports of deformity have been reported, but these may reflect coincidence rather than a causal effect. In the only series reported, no teratogenicity was observed [52]. Given the uncertainty, it would appear optimal to suspend gold as soon as pregnancy occurs and restart it with caution in the puerperium, depending on need. Alternatively, it may be feasible to prevent the postpartum flare of arthritis by restarting gold in the second trimester after major organogenesis has occurred. Reports on the effect of lactation on infant health are conflicting as to whether significant absorption occurs in the child [51]. These may reflect variation in the time of breastfeeding in comparison to gold administration and weight-adjusted doses may be higher than the mother's [53]. Some caution is required in recommending breastfeeding to those on gold, although it must be stated that no adverse reactions in the children of these mothers have been reported at this stage.

CONCLUSIONS

(1) Gold complexes are often effective treatment of RA, particularly in the first 1–2 yr, in terms of clinical, functional and radiological criteria.
(2) Gold is equivalent to methotrexate, sulphasalazine and D-penicillamine in terms of its short-term efficacy.
(3) Toxicity is a substantial problem with aurothiomalate, but appears less so with aurothioglucose.
(4) There is suggestive evidence in the literature for a dose–response relationship for both efficacy and toxicity.
(5) Induction therapy with parenteral corticosteroids improves the efficacy and toxicity profiles for gold.
(6) More research is required to determine optimal monitoring regimes as well as the role of maintenance therapy and combination therapy.

REFERENCES


