Auranofin: A Unique Oral Chrysotherapeutic Agent

By R. C. Blodgett, Jr., M. A. Heuer, and R. G. Pietrusko

Gold has been used for the treatment of disease in humans since the early days of civilization. Its use in rheumatoid arthritis (RA) may have had its genesis when Robert Koch evaluated gold cyanide gas for inhibiting the growth of tuberculosis bacilli. In 1927, Lande reported on the use of aurothioglucose for bacterial endocarditis and other conditions probably including rheumatic fever. He made special note of joint pain relief and suggested that a trial of gold compounds in painful arthritis might be useful. In 1929, Forestier, the "Father of Gold Therapy," referred to the work of Lande and Pick in his presentation to the Medical Society of Paris Hospitals. He surmised that if gold was useful for chronic illness such as tuberculosis, it seemed worthwhile to test its activity in RA. Over the next 50 years, numerous studies were published and a few noteworthy placebo-controlled, double-blind studies confirmed the efficacy of gold in the management of RA.

When Sutton and coworkers reported their findings on an oral gold compound with antiarthritic activity in 1972, progress was made in the history of chrysotherapy.

HISTORY OF AURANOFIN

Based upon the hypothesis that an orally absorbed gold compound administered in a low, but therapeutic dose might offer a separation of efficacy from toxicity, numerous compounds were screened and evaluated. In the intense search for such agents, 13 alkylphosphine gold coordination complexes showed antiarthritic activity when administered orally to adjuvant arthritic rats. One of the most potent compounds evaluated was auranofin. Oral administration to laboratory animals suggested that its antiarthritic potency was similar to parenteral administration of gold sodium thiomalate (GST). Since these original findings were reported over 10 years ago, more than 3,000 patients have been enrolled in worldwide studies evaluating auranofin.

CHEMISTRY

The chemical name for auranofin is 2,3,4,6-tetra-O-acetyl-L-thio-B-D-glucopyranosato-S[triethylphosphine] gold. In this coordination complex, a central atom of gold (I) is stabilized by phosphine and thiolate ligands. The unique structure of auranofin (Fig. 1) has been confirmed by crystal roentgenogram diffraction study and Mossbauer spectroscopy. Auranofin contains 29% gold by weight.

Since phosphine is not a bridging ligand, auranofin exists in a monomeric form which may contribute to its oral absorption. Previously, it was believed that GST and aurothioglucose also existed in monomeric forms. However, sophisticated synchrotron radiation evaluation has demonstrated that both these parenteral compounds must be polymeric (or oligomeric) in nature.

In contrast to injectable gold formulations, auranofin is highly lipid-soluble, possesses only a slight net charge in solution, and does not react strongly with sulfhydryl groups. These properties may facilitate the transport of auranofin across biologic membranes, making it more readily available to alter cellular processes.

When comparing auranofin to the currently available parenteral gold products, it is important to note that the activity of a gold compound is not determined solely by the presence of the metal itself. Changes in oxidation state, degree of polymerization, types of ligands, and geometric structure of the molecule can dramatically alter biologic properties ranging from pharmacokinetics to physiologic activity. The importance of the coordination complex surrounding the heavy metal has been demonstrated with another transition metal, platinum. Cis-diamine dichloroplatinum (II) is a highly active antitumor agent but the trans isomer exhibits no significant in vivo antitumor effect.
Absorption of auranofin is rapid, although incomplete. In six healthy young adult volunteers receiving a single 6 mg oral dose of auranofin, an average peak blood gold level of 0.025 mcg/ml was observed at two hours. Peak blood levels ranged from 0.014 to 0.046 mcg/ml and occurred from one to 72 hours after administration. Administration of a dilute alcohol solution containing 6 mg of radiolabeled \(^{195}\)Au-auranofin to six patients with RA produced a peak concentration of 0.066 mcg/ml within 1.2 to two hours after administration. The fraction of oral absorption of gold from auranofin was estimated to range from a minimum of 15% to a maximum of 33% in this study. Predictions based upon a complex multi-compartmental pharmacokinetic model indicated that approximately 25% of the gold contained in auranofin is absorbed.

Initial clinical trials showed that auranofin is absorbed and continued use provides relatively constant blood gold levels. Analysis of blood gold concentrations in patients receiving auranofin shows a consistent proportional relationship between the oral dose and steady-state blood gold concentrations (Fig. 2). Data were derived from patients receiving 1 to 9 mg auranofin per day for three or six months and from patients whose dosage was increased after three months. Mean serum gold concentrations increase by approximately 0.1 mcg/ml for each increment of 1 mg in the daily dose of auranofin. This dose-blood level proportionality is maintained when dosage is altered. When the daily dosage of auranofin is expressed in terms of body weight (mg/kg/day), there is a highly significant correlation with serum concentrations of gold.

Whether or not auranofin undergoes gastrointestinal alteration prior to being absorbed has not been determined. Weisman et al. have proposed the following two theories based upon their intestinal perfusion studies with radiolabeled marker: (1) auranofin is loosely and reversibly adsorbed onto the surface of small bowel mucosal cells with subsequent elution of the gold downstream into the intestinal fluid, and (2) this compound is absorbed into the enterocyte, the carrier removed, and a large portion of the elemental gold reexcreted into the lumen.

Although the effect of food on the bioavailability of auranofin has not been evaluated, in vitro analysis indicates that auranofin is stable in buffered Sustacal\textsuperscript{®} for up to three hours when the pH is in the range of 1.0 to 8.0.

Distribution

Auranofin is associated with both cellular components and plasma proteins when absorbed. In seven patients receiving auranofin for one month, an average of 41% of auranofin was associated with red blood cells. Blood gold levels were equal to or exceeded serum gold levels depending upon hematocrit. Radiolabeled \(^{195}\)Au-auranofin studies also indicated that 42% of blood gold was associated with cellular elements. Of the approximately 40% fraction of auranofin associated with erythrocytes, 37% is intracellular and the remaining 3% is bound to the cell membrane. Negligible amounts of GST bound to red blood cells or other cellular ele-
ments were found in this study. Cigarette smoking can increase the erythrocyte uptake of gold in patients treated with GST but this effect has yet to be evaluated with auranofin. Auranofin also possesses greater affinity for penetration of lymphocyte membranes as determined by carbon rod atomization analysis. Approximately 1% or less of auranofin is bound to other white blood cells and platelets. The significance of these findings is unclear but binding to cellular components may represent a biologic delivery system or serve as a reservoir of gold. The enhanced membrane penetration observed may be related to the unique monomeric nature of auranofin.

Unbound serum gold may be responsible for the cellular effects of auranofin and other gold compounds. Preliminary evaluation indicates that the ratio of free or unbound serum gold to total gold levels is greater for auranofin when compared to GST. Synovial fluid penetration occurs with auranofin. The synovial fluid/whole blood gold ratio was 1:1.7 in 18 patients receiving auranofin for 18 months.

The distribution of auranofin throughout the body is unknown. Animal data may provide some information since distribution of injectable gold compounds in humans is generally similar to that observed in laboratory animals. Tissue gold levels in the liver, kidney, spleen of rats and guinea pigs following GST administration were 35-70 times higher than observed with auranofin. Limited data in humans given GST showed that lymph nodes, adrenal glands, liver, kidneys, bone marrow, and spleen have the highest concentrations of gold. Gold has also been detected in other internal organs, including endocrine glands, muscle, and skin. The highest concentrations of auranofin in rats are found in decreasing order in the kidneys, spleen, adrenals, lungs, and liver.

In four patients whose total auranofin doses ranged from 945 to 3,600 mg, gold was detected in the skin biopsy of only one. Gold was found in all patients in concentrations ranging from 2.6 to 26.5 mcg/g tissue in similar skin biopsies performed in seven patients receiving GST in cumulative doses of 460 to 4,325 mg.

Metabolism

After auranofin is given, its fate within the body is largely unknown. Gold appears to be essential for antiarthritic activity since the non-gold containing ligands, triethylphosphine, and thio-glucopyranose are without effect in the adjuvant arthritis rat model.

Radiolabeling of gold and the phosphorus and sulfur atoms of the ligand structures provides some insight into the metabolism of auranofin. Dissociation of auranofin occurs within 20 minutes after incubation with serum from the rat or dog. Much of the parent compound, however, may not reach the systemic circulation intact if in vivo dog studies, which demonstrate extensive disruption of the coordination complex prior to absorption, can be extended to humans.

Triethylphosphine oxide is a major metabolite renal excreted in the rat. This metabolite was found in the urine in six patients with RA receiving auranofin 3 mg twice daily. It was theorized that the auranofin molecule is cleaved to form triethylphosphine oxide, acetylthiglucose, and a protein-gold complex, most likely metallothionein.

Blood Gold Levels and Elimination Half-Life

In the initial clinical trials, there was a progressive increase in blood gold levels over a period of 12 weeks in patients receiving 1 to 9 mg auranofin each day. Bandilla et al. observed steady state plasma levels at 12 weeks with no further increase in gold levels for up to 24 months with continued therapy. Other investigators have reported achievement of peak plasma levels by 10 to 16 weeks. With attainment of steady state levels, minimal variation occurs in mean blood gold levels during continuous daily administration of auranofin. The mean blood gold level at steady state approximates 0.6 to 0.7 mcg/ml in those receiving auranofin 3 mg twice a day.

In six patients with RA given 6 mg of radiolabeled Au-auranofin prior to and six months after daily auranofin, the mean plasma half-life was approximately 17 days following the first dose and 25.5 days after the second dose. The mean terminal total body content half-life was calculated to be 58 and 81 days, respectively, after the first and subsequent dose of radiolabeled auranofin.

In comparison, intramuscular GST generally provides a peak blood gold concentration of 7 mcg/ml the day of injection which gradually declines to approximately 3 mcg/ml in one week. These levels are substantially higher than
observed with auranofin. The serum half-life of GST ranges from five to six days and steady state levels are achieved in six to eight weeks.\textsuperscript{24,31-34} More of the total body burden of gold is retained than with auranofin (25%-42% vs. < 1%) although the serum half-life of GST is shorter.

The correlation of serum gold levels with efficacy or safety during auranofin therapy remains to be established. Attainment of a serum level of 0.7 mcg/ml was claimed in an open, uncontrolled study, to be associated with improvement in the clinical parameters evaluated.\textsuperscript{26} In another open trial, patients who responded had significantly lower blood gold levels at 20 and 26 weeks than patients who exhibited no response.\textsuperscript{55} Other investigators have found no convincing evidence that clinical improvement and/or toxicity are related to blood gold levels.\textsuperscript{56-59}

**Excretion**

Initial reports of gold excretion patterns on auranofin indicated that 95% of recoverable gold was eliminated via the fecal route and 5% in the urine.\textsuperscript{60} It was also estimated that after 20 weeks of auranofin, approximately 27% of gold was retained in the body.\textsuperscript{24} These preliminary results provided only a general estimation of auranofin’s elimination since methodologic problems including stool sampling design and a 10% variation in the analytical technique were evident.

With the use of a whole body radiation counting chamber, Blocka et al. found that cumulative stool elimination of auranofin gold over six months was approximately 85% and urinary excretion accounted for 15% of the dose.\textsuperscript{22} Total body retention of radiolabeled gold ranged from 0.4% to 1.3% at the end of the six month evaluation. These findings are in marked contrast to the results obtained with parenteral gold compounds. Using a similar technique, Gerber et al. found that after injection of a single 50 mg intravenous dose of GST, 25%-42% of the administered dose remained in the body at six months.\textsuperscript{51} Approximately 70% of GST is eliminated in the urine and 30% is excreted in the feces.\textsuperscript{45,51,61}

Biliary excretion and enterohepatic recirculation of gold have not been observed with auranofin.\textsuperscript{21,31} Since biliary excretion is negligible, the nature of auranofin’s “central-enteric” excretory pathway must be further investigated.\textsuperscript{38}

Table 1 summarizes the comparative pharmacokinetic properties of auranofin and GST.

### Table 1. Comparative Pharmacokinetics of Auranofin and Gold Sodium Thiomalate

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Auranofin</th>
<th>GST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral absorption</td>
<td>≥25%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Distribution in blood</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Associated with cellular components (mainly erythrocytes)</td>
<td>≥40%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Bound to serum proteins</td>
<td>≥60%</td>
<td>≈99%</td>
</tr>
<tr>
<td>Steady-state blood gold concentration</td>
<td>0.6–0.7 mcg/ml</td>
<td>3–7 mcg/ml</td>
</tr>
<tr>
<td>(6 mg po/day)</td>
<td></td>
<td>(50 mg IM/week)</td>
</tr>
<tr>
<td>Plasma elimination half-life</td>
<td>17–25 days</td>
<td>5–6 days</td>
</tr>
<tr>
<td>Route of elimination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fecal</td>
<td>85%</td>
<td>30%</td>
</tr>
<tr>
<td>Renal</td>
<td>15%</td>
<td>70%</td>
</tr>
<tr>
<td>Total body retention of a single dose after six months</td>
<td>&lt;1%</td>
<td>25%-42%</td>
</tr>
</tbody>
</table>

**PHARMACOLOGY**

Auranofin possesses antiinflammatory and antiarthritic properties although its exact mechanism of action in patients with RA is unknown. It can affect acute and chronic inflammatory processes as well as cellular and immunopathologic events involved in the perpetuation of inflammation and tissue damage (Table 2).\textsuperscript{62} Since it does not possess a general immunosuppressive action, auranofin has been referred to as an immunoregulator.\textsuperscript{63}

**Animal Models of Inflammation**

Analysis of in vivo models of inflammation in laboratory animals suggests that auranofin in doses used is equal to or more effective than GST. Kaolin and carrageenan-induced rat paw edema was significantly reduced with auranofin.\textsuperscript{62,64} Only modest inhibition of edema occurred with GST and appeared to be partially
Table 2. Antiinflammatory and Immunologic Profile of Auranofin

<table>
<thead>
<tr>
<th>Profile</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animal model of inflammation</td>
<td></td>
</tr>
<tr>
<td>Rat paw edema</td>
<td>↓</td>
</tr>
<tr>
<td>UV light erythema</td>
<td>↓</td>
</tr>
<tr>
<td>Adjuvant arthritis (rat)</td>
<td>↓</td>
</tr>
<tr>
<td>Inflammatory cell function</td>
<td>↓</td>
</tr>
<tr>
<td>Chemotaxis</td>
<td>↓</td>
</tr>
<tr>
<td>Phagocytosis</td>
<td>↓</td>
</tr>
<tr>
<td>Superoxide radical generation</td>
<td>↓</td>
</tr>
<tr>
<td>Lysosomal enzyme release</td>
<td>↓</td>
</tr>
<tr>
<td>Cell-mediated immunity</td>
<td></td>
</tr>
<tr>
<td>Oxazolone-induced delayed hypersensitivity</td>
<td>↑</td>
</tr>
<tr>
<td>Lymphocyte transformation</td>
<td>↑, ↓, or ↔</td>
</tr>
<tr>
<td>Delayed hypersensitivity skin tests</td>
<td>↑, ↓, or ↔</td>
</tr>
<tr>
<td>Humoral immunity</td>
<td></td>
</tr>
<tr>
<td>Antibody-dependent cellular cytotoxicity</td>
<td>↓</td>
</tr>
<tr>
<td>Antibody-dependent complement lysis</td>
<td>↓</td>
</tr>
<tr>
<td>Circulating immunoglobulins</td>
<td>↓</td>
</tr>
</tbody>
</table>

NOTE: (↑) denotes enhanced effect, (↓) denotes suppressed effect; and (↔) denotes no effect.

adrenal dependent since its effects were more pronounced in nonadrenalectomized rats. Equivalent antierhythmic effects were observed with auranofin and GST in guinea pigs exposed to ultraviolet light; however, extremely large doses (100 mg/kg) of GST were necessary.64 The effect of auranofin was observed to be equal or superior to GST in the adjuvant arthritic rat model which is used in screening for antiarthritic compounds.11,65,66

Inflammatory Cell Function

It has been postulated that some of the effects of auranofin are mediated through alteration of the cellular membrane which would ultimately affect important intracellular functions. Permutations in plasma membrane function were induced by auranofin by blocking prostaglandin E1-stimulated production of cyclic AMP.67 Auranofin, but not GST, inhibited incorporation of (H)thymidine and (14C)amino acids into human lymphocytes.68 Lymphocyte transformation to concanavalin A decreased progressively in 29 patients given auranofin for six months.69 These effects were thought to be due to interference with lymphocyte membrane transport activity since no effect was observed on protein synthesizing mechanisms at the intracellular level. Antiproliferative effects were observed in RAJI lymphoma, HeLa carcinoma, and Epstein-Barr virus–transformed cells.17,70 Membrane transport inhibition was not observed in these studies however. It was hypothesized that the effects of auranofin on DNA, RNA, and protein synthesis may have been due to formation of a bond with sulfhydryl groups of proteins associated with the mitotic process.

Chemotaxis of human monocytes, and to a lesser extent neutrophils, is significantly impaired by auranofin.71 When monocytes of healthy donors were exposed to auranofin or gold keratinate, chemotaxis was inhibited to a greater extent by auranofin.72 Inhibition of chemotaxis in normal individuals or patients with RA however, was only slightly more pronounced with auranofin when compared to GST.73

Phagocytic activity of macrophages is increased in patients with RA but this process can be suppressed to that of healthy individuals with the use of injectable gold salts.74,75 Similar results were observed with auranofin when evaluated for its effects on phagocytosis of IgG opsonized sheep RBCs, Candida albicans, and uptake of nitroblue tetrazolium dye.72,73,76,77

Superoxide radicals (O2⋅-) are products of the respiratory burst of activated phagocytic cells and are considered to be mediators of inflammation. Auranofin has a suppressive effect on O2 generation which may be biphasic and dose-dependent.77,79 GST had minimal suppressive effects in these studies.

Lysosomal enzyme activity is considered to play a key role in the inflammatory cascade of RA.80 Evaluation of lysosomal enzyme release (LER) by β-glucuronidase and lysozyme markers in rat leukocytes showed a dose-related inhibition with auranofin.76 “In vivo” animal studies were similar.81 When inhibition of LER was evaluated in healthy volunteers and patients with RA, auranofin had a more pronounced effect than GST with all methodologies employed.82–84 In two separate studies, it was also noted that a 43%–68% reduction in LER was correlated with clinical improvement in rheumatoid patients treated with auranofin.78,84

Although these initial reports with auranofin are encouraging, alterations of “in vitro” tests of cellular function cannot be considered indicative of clinical response.
Humoral Immunity

Humoral immunity can be affected by auranofin as evidenced by its inhibitory effect on antibody to human IgE-induced release of histamine and SRS-A from fragmented primate lung and suppression of “7S” hemagglutinating antibody response to sheep red blood cells.11,12,8 Auranofin is also capable of reducing levels of the antibodies involved in antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent complement lysis (ADCL).6,8 GST had no effect on ADCC but immune sera from GST-treated rats enhanced ADCL in these studies. Pokeweed mitogen-induced generation of immunoglobulin-secreting cells was suppressed by auranofin in concentrations one tenth those of GST required to produce a comparable level of inhibition.8 In vivo assessment of immunoglobulins and rheumatoid factors in RA showed a significant reduction in circulating levels by GST and a similar but less marked effect with auranofin.9 Similar effects on circulating immunoglobulins were observed at six months in 50 patients switched from GST to auranofin when compared to 49 control patients continued on GST therapy.10

Cell-Mediated Immunity

RA has been described as a disease of “altered” T lymphocyte/macrophage immunoregulation.11 “In vitro” and “in vivo” studies indicate that auranofin can stimulate or suppress cellular immunity. Research is currently being conducted to determine its specific effect on T cell function.9 Both auranofin and GST enhanced the delayed hypersensitivity response to oxazolone in mice; however, only auranofin stimulated this response in immunosuppressed animals.9 The response of sensitized mice to sheep RBCs was equally stimulated by auranofin or GST.

In vitro evaluation of cell-mediated immunity with Epstein-Barr virus and phytohemagglutinin (PHA) stimulation of (3H) thymidine uptake by lymphocytes was conducted in patients with RA on auranofin or GST.17,18 Auranofin-treated subjects recorded prompt and sharp decreases in PHA-induced lymphoproliferative response. A high degree of suppression of (3H) thymidine incorporation with Epstein-Barr virus was also observed. In contrast, patients given GST recorded a slower onset and less suppression of the lymphoproliferative mitogen response with PHA and no inhibition of Epstein-Barr virus-induced lymphocyte stimulation.

Variable effects have been observed with auranofin on hypersensitivity skin tests. A suppressed skin test response to dinitrochlorobenzene (DNCB) was observed in 11 of 14 patients receiving auranofin versus a normal response in 22 of 24 patients receiving GST.9 Normal responses were observed with both gold compounds when patients were skin tested with purified protein derivative (PPD), trichophyton, and mumps. In another study, patients treated for six months with auranofin had a 33% increased skin test response to PPD and a 119% increased response to streptokinase/streptodornase (SK/SD).9

Based on analysis of their data, Lorber et al. stated that the therapeutic action of auranofin appears to be cell-mediated rather than humoral when compared to GST.9

Platelet Aggregation

Auranofin inhibits platelet aggregation induced by ADP, epinephrine, and collagen.97 It appears to inhibit both the platelet release reaction and platelet aggregation.

Plasma Copper and Zinc Levels

A significant decrease in serum copper levels was present in a study of five patients who responded to auranofin.98 Ceruloplasmin concentrations were unaffected and a significant inverse relationship was also noted between serum copper levels and plasma zinc concentrations. Patients with RA who showed a pretreatment plasma copper to ceruloplasmin ratio of greater than seven were more likely to respond to chrysotherapy than patients with a value of less than seven.99

Animal Pathology/Toxicology

Acute and Subacute Toxicity

The 50% lethal dose for oral auranofin is 310 mg/kg in mice and 265 mg/kg in rats.100 Administration of auranofin in doses up to 360 times the human adult dose in rats for three months resulted in dose-related salivation, tensity and struggling during dosing, and soft stools.101 Food consumption was not affected but the main toxic effect after three months was decreased body weight. In dogs receiving up to 180 times the
human adult dose, the principal toxic sign was loss of body weight. Dose-related emesis, diarrhea, weight loss, and decreased food consumption occurred secondary to gastrointestinal irritation. Anemia also was observed.

Chronic Toxicity

Dogs receiving six to 60 times the human adult dose of auranofin for 12 months developed emesis, diarrhea, a subclinical hemolytic anemia, hypoproteinemia, and hyperplasia of the thyroid gland. In rats receiving up to 230 times the human adult dose for one year, auranofin-related lesions included renal tubular cell karyomegaly and cytomegaly, renal cortical adenomas, gastric lesions, and ileoceccolic ulcers. Renal tubular cell karyomegaly and cortical adenomas were also found in rats receiving GST over a similar one-year period. This heavy metal nephropathy is reported to be rodent-specific.

Teratology

Auranofin induced fetal edema in the rat and chiefly abdominal malformations, that is, gastrochisis and umbilical hernia, in rabbits in reproductive studies. It had a negative effect on litter size, fetal weight, and resorption in rabbits at doses 20 to 80 times the average adult human dose. These effects were not observed in rats similarly tested.

CLINICAL TRIALS

Over 3,000 patients with RA have received auranofin in the world-wide clinical trials, with some patients on therapy for over four years. Auranofin has been compared with parenteral gold salts, penicillamine, levamisole, and hydroxychloroquine. Auranofin was added to a regimen of salicylates and/or a nonsteroidal antiinflammatory drug (NSAID) in the majority of studies.

Open Studies

Initial open trials were designed to evaluate whether the effects of auranofin in laboratory experimentation could be extended to patients with RA. Most of these studies lasted from three to six months and were limited to small groups. Laboratory parameters of disease activity were carefully scrutinized. Finkelstein et al. treated eight patients with auranofin for three months in the first clinical trial, and found improvement in objective and subjective clinical signs as well as resolution of biochemical and immunologic parameters. Similar results were observed by others. Clinical benefits included increased grip strength and a reduction in the number of tender and swollen joints, joint size, and duration of morning stiffness. Clinical improvement was paralleled by resolution of abnormal immunoglobulin levels and rheumatoid factor titers. The majority of adverse effects involved the gastrointestinal tract and were generally mild and self-limited. Data derived from approximately 100 patients showed that auranofin was absorbed orally, exhibited a therapeutic effect, and was well-tolerated.

After initial observations that showed auranofin to be relatively safe and well tolerated, dosage range evaluations were carried out in open trials. The initial dose of auranofin was 1 or 3 mg twice a day for one month. The dose was generally decreased after this period of time, and the investigator was able to adjust the dose based on clinical judgment after three or six months. A general migration in dose toward 6 mg per day followed. Although the variability in dosing and open nature of the study precluded statistical analysis, it was the subjective opinion of the investigators that auranofin was of benefit to most patients and it possessed an adequate safety profile. Two patients were withdrawn for side effects and three patients were dropped due to lack of efficacy of the 87 patients treated with auranofin during these trials.

Weisman et al. found that a clinical response occurred in 66%–75% of the patients followed for periods up to one year in a follow-up report of 104 patients included in seven of these original studies. The number of patients dropped from the studies due to toxicity averaged 8%. Radiologic evidence for inhibition of disease progression was observed in three of 15 patients on auranofin for more than four years. According to the investigators, auranofin's therapeutic effect was comparable to that of injectable gold for most patients but without the serious toxic complications.

Preliminary reports of world-wide open studies evaluating auranofin's effectiveness show a 50%–75% clinical improvement rate in 276 patients treated for up to 12 months.
dose of auranofin ranged from 4 to 8 mg daily. Bandilla et al. reported their experience in patients given auranofin for at least one year.\textsuperscript{59} Seventy percent of the 91 patients improved clinically. Subjective parameters such as morning stiffness and overall pain showed improvement as early as the twelfth week. Articular and activity indices and erythrocyte sedimentation rate (ESR) showed significant changes only after nine months. Patients who responded well in the first year of therapy continued to show improvement over the following years.\textsuperscript{121} Ten patients were withdrawn for lack of efficacy and 17 patients were discontinued due to untoward effects during the first year of the study. Diarrhea caused discontinuation in 7\%, mucocutaneous reactions in 3\%, and leukopenia in 1\%.

Eight of 10 patients who received auranofin 3 mg twice a day completed a two year open study.\textsuperscript{122} A satisfactory therapeutic response was seen in 50\% of patients at six months and 75\% at 12 and 24 months.

Double-Blind Controlled Studies

Two controlled, double-blind studies were conducted to determine the ideal daily dose of auranofin. Calin et al. reported in a multicenter study that 137 patients with RA were randomly assigned to receive either 1 or 9 mg of auranofin daily.\textsuperscript{28} The code could be broken at three months if therapeutic benefit seemed inadequate. Those on low dose were entitled to have the dosage increased to 3 mg and then to 6 or 9 mg. Individuals who could not tolerate the dosage due to side-effects had the dosage decreased, still blinded, to 33\% of the original dose. Significantly more patients on 1 mg/day, 57\% (32 of 56) at three months, dropped out due to lack of efficacy than those receiving 9 mg/day, 33\% (20 of 60). A reduction in dosage was necessary in two patients on the 1-mg dose versus 13 patients receiving the higher 9-mg dose. Diarrhea was the most frequent adverse effect and appeared to be dose-dependent. The relative lack of efficacy of the 1-mg dose and the higher prevalence of diarrhea associated with 9 mg/day indicated that a dosage between these two extremes would be more suitable for the majority of patients.

A similarly designed study was carried out by Bernhard et al. comparing 2 and 6 mg daily doses of auranofin in 273 patients.\textsuperscript{123,124} More positive measures of improvement were noted at three months with the 6 mg dose. However by the six-month evaluation, global efficacy ratings for both the 2 and 6 mg dosage regimens were equivalent. Although the incidence of diarrhea was slightly higher for the 6 mg dose (34\% vs. 22\%), dropout rates due to complications were similar. Thus, a quicker response seemed apparent with the 6 mg dose at the expense of slightly more frequent, but not more severe adverse reactions.

Weiss conducted a follow-up evaluation of patients who were enrolled in the above dosage range studies, some for up to 24 months.\textsuperscript{125} A dose of 6 mg per day seemed to be the most desirable regimen. Patients receiving 6 mg daily had a significant decrease in morning stiffness, fatigue, and pain as well as a reduction in ESR, IgA, IgM, IgG, and latex agglutination titer. Of the 418 patients treated, 11\% were withdrawn due to lack of efficacy and 9.8\% had adverse reactions requiring drug withdrawal. Diarrhea occurred in 35\% and in combination with other symptoms in 53\%. The incidence of dermatitis was 35\% and mucous membrane lesions developed in 10.3\%. Other side-effects included proteinuria (three patients), thrombocytopenia (three patients), abnormal liver function tests (two patients), and fever (one patient).

Katz et al. reported on a placebo-controlled, double-blind study, involving 289 patients at 18 centers throughout the United States.\textsuperscript{126} This study was designed to compare the efficacy of auranofin 3 mg twice a day to placebo when added to a regimen of aspirin or a single NSAID. It was divided into two 26-week segments; the first segment being double blind and the second portion open label with a provision to change the dose. Data on 84 auranofin and 60 placebo group patients were analyzed for efficacy at three and six months. When compared to placebo, there was a statistically significant improvement in the number of tender and swollen joints and grip strength. There were no statistically significant differences between auranofin and placebo when morning stiffness or time to onset of fatigue were evaluated. After six months, 50 (65\%) of 77 patients on auranofin compared to 25 (43\%) of 58 patients on placebo showed marked or moderate improvement.
Significant decreases in ESR, IgM, and IgA levels were found. Mean IgG levels were significantly decreased at three months but not at six months. Dropouts due to insufficient therapeutic effect represented 30% of all patients on placebo and only 5% on auranofin. Seven auranofin patients and one placebo patient were removed from the study due to adverse reactions. Dropouts associated with auranofin were due to diarrhea (two patients), skin rash (two patients), proteinuria (one patient), thrombocytopenia (one patient), and dysgeusia (one patient). The placebo patient was withdrawn due to proteinuria. This study indicated that auranofin provides a significant additional therapeutic benefit when added to a regimen of aspirin or NSAID.

Comparative Clinical Trials

Several large double-blind studies have been conducted to compare the efficacy and safety of auranofin with GST. Schattenkirchner et al. found a marked and similar improvement in the clinical and laboratory parameters of RA for both auranofin and GST-treated groups in a double-blind multicenter trial involving 121 patients. Eighty-nine patients had been on therapy longer than six months and 68 patients for longer than one year. The number of adverse effects was similar in both treatment groups; however, withdrawals were more frequent with GST. Gastrointestinal intolerance was more frequent with auranofin and mucocutaneous reactions were twice as common with GST.

A multicenter, placebo-controlled comparative study has been completed by the Cooperative Systematic Studies of Rheumatic Diseases group in the United States. Of 209 patients initially enrolled in the study, 161 patients completed at least 20 weeks of therapy with auranofin 3 mg twice a day, weekly GST injections, or placebo. Both auranofin and GST were effective and superior to placebo in improvement of painful and/or swollen joints, physician assessment of disease activity, and decrease in ESR. However, patients on GST showed a more rapid recovery from anemia and a reduction in thrombocytosis when compared to auranofin-treated subjects. Withdrawals for adverse effects with GST were four to five times more frequent. Thrombocytopenia (two patients), proteinuria (two patients), elevated liver enzymes (three patients), nitritoid reaction (three patients), and gold pneumonitis (one patient) were observed only in the GST group. Other GST-related problems that resulted in discontinuation of therapy included skin rash (eight patients), stomatitis (four patients), leukopenia (one patient), and diarrhea (one patient). Withdrawals in auranofin treatment included one patient each for rash, diarrhea, stomatitis, eosinophilia, and leukopenia.

Sixty-three of 90 initially randomized patients have been followed for at least six months by Lewis et al. in a placebo-controlled comparative study of auranofin and GST. Although improvement was seen slightly earlier in the GST group, reductions in ESR and C-reactive protein were similar for both active treatment groups at six months. Auranofin and GST both provided favorable clinical and laboratory improvement. Side effects requiring withdrawal prior to six months occurred in three patients receiving auranofin (leukopenia, diarrhea, and hematuria) and in five patients on GST (rash in three patients, nitritoid reaction, and proteinuria). Eleven placebo patients dropped out due to lack of benefit.

A total of 175 patients have been enrolled in several smaller controlled comparative trials. Preliminary evidence suggests that the efficacy of auranofin approaches that of parenteral gold salts among the patients evaluated at six months to one year. Patient withdrawals due to adverse on-therapy conditions were generally less frequent with auranofin.

Many open trials comparing auranofin with injectable gold have been conducted or are currently in progress. Menard et al. examined the effects of auranofin and GST in 112 patients in a prospective, open study. Ninety-two patients completed three months and 65 patients continued therapy for six months. No significant differences were found between the two gold compounds in terms of objective and subjective indices of disease activity. In both groups, 50% had improved after three months and 70% responded to therapy after six months. Of the 57 patients admitted into the auranofin group, seven patients were withdrawn for lack of effect and four patients for development of side effects, mainly gastrointestinal. Two patients were withdrawn for lack of effectiveness and eight patients...
developed side effects that required discontinuation of the 55 patients treated with GST.

In another randomized, open study comparing auranofin and GST in 60 patients, Smith et al. reported that after two years of therapy, 56% of patients receiving auranofin were in remission versus 82% of those on GST. In a review of the demographic data, however, auranofin patients as a group had more active disease at the start of the study and there was more severe structural damage according to radiographic analysis. None of the patients receiving auranofin had to be withdrawn from the study compared with eight patients in the GST group.

Thirty-eight patients were randomly allocated to treatment with either auranofin or GST in an open comparison conducted by Prouse et al. Noticeable response commenced within six to 12 weeks as evidenced by a greater than 25% increase in grip strength and more than a 25% reduction in joint count, morning stiffness, and pain score. Auranofin and GST appeared equally effective at 12 and 24 months and no major treatment problems occurred in either group.

Equivalent therapeutic effects were observed with auranofin and parenteral gold compounds in other open comparable trials. Side effects were notably milder and less common in those receiving auranofin.

Early results of an open study comparing auranofin with GST and penicillamine in 42 patients suggest that auranofin is well-tolerated. None of the auranofin patients were withdrawn due to adverse effects at nine months, whereas five patients on GST and one patient on penicillamine were discontinued.

Significant improvement in disease activity assessed by the usual clinical and laboratory parameters was observed for both auranofin and penicillamine in a single-blind study of 40 patients. There were no significant differences between the two drugs for any of the parameters monitored. One auranofin-treated patient was dropped due to diarrhea and another for erosive gastritis. Five penicillamine patients were removed—four for dermatitis and one for proteinuria (3.6 g/24 hr). Franchimont et al. reported that auranofin was as effective as penicillamine and better tolerated in a similar study of 46 patients.

Huskisson and Scott compared auranofin, penicillamine, and levamisole in an open parallel study involving 36 patients. Clinical measurements at six months showed no statistically significant differences among the treatment groups. Four patients receiving auranofin were withdrawn due to lack of efficacy and seven patients on levamisole were removed for the same reason. Three penicillamine patients were dropped due to nephrotic syndrome, severe proteinuria, and lack of effect.

SAFETY

Gastrointestinal and mucocutaneous reactions were the major adverse effects reported in more than 3,000 patients who received auranofin. Most side-effects were mild, of short duration, and usually resolved with continuation of therapy or a reduction in dose. Although proteinuria occurred in most studies, it was usually mild and transient with therapy being discontinued in 1.6% of the patients. Hematologic changes necessitated withdrawal in less than 1% and included thrombocytopenia (0.5%), anemia (0.1%), leukopenia (0.1%), and eosinophilia (0.1%). Elevation in liver enzymes resulted in discontinuation of auranofin in 0.4%. No abnormal trends were observed in other laboratory parameters. Due to study design and anticipated general clinical practice, most patients were receiving concurrent salicylate or NSAID therapy and some were also on corticosteroids.

Direct comparative studies with GST show that auranofin causes fewer and less severe adverse reactions (Fig. 3). Withdrawal rates for parenteral gold salts have ranged from approximately 15%-30% during the first six months of therapy. When injectable gold is continued for five years or longer, Lockie et al. have reported a dropout rate of 59% due to major toxicity. Luukkainen also observed a dropout rate of 49% for toxic effects in 293 patients treated with parenteral gold for up to six years.

Gastrointestinal

Changes in stool pattern are evident in up to 40% of patients with diarrhea being the most
AURANOFIN IN RA

Fig. 3. Side effects of auranofin and gold sodium thiomalate (GST) including 243 patients treated with auranofin and 244 patients administered GST. (Data compiled from references 129, 133, 139, 141, 142, 144, and 149).

frequently encountered on-therapy condition.12

The reported effects of auranofin ranged from
increased frequency and loose stools to frank
diarrhea. Over 50% of all episodes of diarrhea
occurred during the first three months of therapy
and slightly less than 3% of patients have been
withdrawn from therapy due to this problem.

In the blinded dosage range studies, it was
apparent that diarrhea was more prevalent at the
higher daily doses of auranofin and responded, in
most instances, to a reduction in dosage.28,123 The
comparative trials with GST indicated that gas-
trointestinal reactions, primarily diarrhea, occur
twice as often with auranofin.

Gastrointestinal tract complaints other than
diarrhea occurred in 17% of all study patients
resulting in discontinuation of auranofin in
0.9%.12 Katz et al. reported that upper gastroin-
testinal symptoms such as nausea, vomiting, and
bloating were similar to placebo.126

Mucocutaneous Reactions

Approximately 30% of patients on auranofin
developed a reaction related to the skin which
included rash, pruritus, and rarely alopecia.21

Most rashes were mild in nature and discontinu-
ation of therapy was necessary in only 4%.

Side-effects involving the mouth (stomatitis) or
eye (primarily conjunctivitis) were both reported
in approximately 10% and necessitated with-
drawal of therapy in 1% and 0.3%, respectively.

The incidence, severity, and need to discon-
tinue therapy resulting from mucocutaneous
reactions were less with auranofin in comparison
to GST.20,28,140,141

Six cases of herpes zoster developed during
auranofin therapy in clinical trials in the United
States.21 Although patients with herpes zoster do
not have an increased prevalence of occult can-
cers or increased risk of developing subsequent
carcinomas as originally believed, nonetheless
these cases have been observed closely because of
the reported immunoregulatory activity of aura-
nofin.155 All episodes cleared spontaneously
despite continued therapy in five out of six
patients. The incidence of herpes zoster in aura-
nofin-treated patients (0.8%) was slightly higher
than in patients with RA not receiving gold
therapy (0.4%), but is less frequent than in
patients given parenteral gold compounds
(3.1%).21,156,157 Vasomotor (nitritoid) reactions
have not been reported with auranofin.

Renal

As with parenteral gold preparations and peni-
cillamine, proteinuria and rarely glomeruloneph-
ritis have been observed during auranofin ther-
apy.158,159 Proteinuria was generally not a major
problem. It occurred at various times during
treatment and resulted in drug discontinuation in
1.6%.12
Development of proteinuria can also occur with NSAID therapy and as a consequence of RA.\textsuperscript{160,161} The incidence of proteinuria was higher in the placebo group in the study by Katz et al.\textsuperscript{126}

The incidence of proteinuria in the published comparative trials was 2.2\% (eight of 364) for auranofin and 4.6\% (13 of 281) with parenteral gold.\textsuperscript{50,128,140-149,162} The dropout rate for proteinuria was four times as high with injectable chrysotherapy (2.1\% vs. 0.5\%).

Other abnormalities in renal function such as elevation in blood urea nitrogen, serum creatinine, and uric acid have also been reported and were associated with 0.1\% of withdrawals.\textsuperscript{21}

**Hepatic**

Mild and transient abnormalities in serum transaminases and alkaline phosphatase have been reported during therapy with auranofin. Three (0.4\%) of 823 patients were removed from clinical trials due to elevations in liver enzymes.\textsuperscript{21} This low incidence is noteworthy since almost all patients were receiving aspirin or NSAID which have known hepatotoxic potential.\textsuperscript{163,164} Although intrahepatic cholestasis has been previously described with GST, it has not been reported with auranofin.\textsuperscript{165}

**Hematologic**

A mean reduction in hemoglobin of 0.5 g/dl which gradually recovered to pretreatment levels was noted in the first three months of therapy with auranofin. Three (0.4\%) of 823 patients were removed from clinical trials due to elevations in liver enzymes.\textsuperscript{21} Mild anemia occurred in a few instances which resulted in discontinuation of auranofin in four patients.

Intermittent elevations and depressions of the WBC count were observed in patients with RA on auranofin. However, only 11 patients (0.4\%) were removed because of leukopenia.\textsuperscript{12} The WBC returned to normal levels after discontinuation. Several cases from the European experience had evidence of peripheral destruction of neutrophils. Eosinophilia has resulted in the discontinuation of therapy in one patient.

Six cases of thrombocytopenia (platelet count <100,000/mm\textsuperscript{3}) possibly related to auranofin have been evaluated.\textsuperscript{166} Once thrombocytopenia was detected, discontinuing auranofin resulted in a return to a normal platelet count within one to eight weeks. Morbidity was minimal. There were no prodromal symptoms or practical laboratory tests which could predict an impending drop in platelet count. This reaction did not appear to be related to total dose or duration of therapy. The incidence of auranofin associated thrombocytopenia (0.5\%) appears to be less than that associated with injectable gold salts (1\%–3\%) or penicillamine (8\%).\textsuperscript{167-169}

**Miscellaneous**

Deposition of minute particles resembling gold within the cornea have been identified during ophthalmologic examination in two patients.\textsuperscript{12} This phenomenon was not associated with ocular symptoms and required no modification in therapy. Up to 40\% of patients who have received a cumulative dose of parenteral gold exceeding 1,500 mg developed corneal chrysiasis.\textsuperscript{170}

Auranofin does not appear to have significant adverse effects upon the central nervous system (CNS).\textsuperscript{12,126} Only 2\% noted symptoms possibly related to the CNS among 418 patients treated with auranofin for up to 24 months.\textsuperscript{125} Nine reports were single episodes of headache or dizziness and no patients were excluded from further study due to these effects.

**RADIOGRAPHIC CHANGES**

The disease-modifying effect of auranofin was assessed in 143 patients by evaluating the rate of progression of erosive changes over 12 and 24 months.\textsuperscript{171,172} Pre- and posttherapy hand roentgenograms were independently graded by two readers blinded for sequence and source of film. Two different methods of analysis were employed. When compared to films from a prior placebo-treated group of patients, auranofin slowed the progression of erosive disease.

Three of 15 patients treated with auranofin after four years were judged as having sustained radiographic improvement when evaluated by a radiologist blinded to patient identity and film sequence.\textsuperscript{111} The effects of auranofin on retarding joint-space erosion were considered similar to those that have been reported to occur with conventional parenteral gold therapy. A radiographic comparison of 83 patients receiving auranofin and 74 patients on parenteral gold for 12 months showed that both medications could retard the progression of joint erosion and mean joint grade.\textsuperscript{173} Of the patients receiving intra-
muscular gold injections, 72% showed no progression in joint erosion compared to 58% of the auranofin-treated patients.

DRUG INTERACTIONS

Information concerning potential drug interactions with auranofin is limited. Salicylates, NSAIDs, and corticosteroids have been administered concurrently without apparent hazard in the clinical studies involving auranofin. Thus far, there do not appear to be any therapeutic problems caused by coadministration of auranofin with a variety of other agents.

DOSAGE

The dose of auranofin most commonly employed during the clinical trials was 6 mg given once daily or in two divided doses. Side effects including dose-related alterations in bowel habit did not appear to differ in patients receiving either dosage regimen. Since patient compliance could be enhanced with a once a day dosage schedule during chronic auranofin therapy, a major study is now underway to compare the safety and efficacy of 6 mg administered once daily in the morning or evening versus 3 mg twice a day. To date, 449 patients have been entered and the preliminary data suggest that the number of untoward events and withdrawal rates are similar in both groups. All parameters of efficacy improved and no differences in response could be detected in either group.

Intermittent therapy with auranofin (3 mg once daily every other week) proved to be less effective than continuous therapy with 6 mg daily.

It may be anticipated that patients currently receiving injectable gold salts would be converted to auranofin because of its relative safety and ease of oral administration. In a placebo-controlled, double-blind study, 99 patients were randomly assigned to receive either continued GST therapy or auranofin therapy for six months. All of the patients were receiving GST prior to study entry and were clinically controlled. When compared to the GST control group, there was no evidence of clinical deterioration in the auranofin switchover subjects during the six month study. Laboratory parameters of underlying disease activity were similar in both treatment groups. Two of the patients switched to auranofin and three of the patients maintained on GST failed to complete the study because their disease could not be controlled. No new or unusual patterns of toxicity developed during the overlap period when GST and auranofin were administered simultaneously. In a smaller switchover study involving 38 patients, clinical indices of efficacy were comparable for auranofin and GST at the completion of the trial. However, in terms of improvement in laboratory parameters of disease activity, there was a more marked trend in favor of GST.

SUMMARY

Auranofin is a chemically unique gold coordination complex with demonstrated antiarthritic properties on oral administration. Its pharmacokinetic and immunologic profiles are distinct from injectable gold compounds.

When auranofin is added to a regimen of salicylates and/or a nonsteroidal antiinflammatory drug for the treatment of RA, significant additional therapeutic benefit is observed. Published studies indicate that auranofin given 6 mg per day approaches the efficacy of parenteral gold salts in the treatment of rheumatoid disease. Noticeable improvement in clinical and laboratory parameters of disease activity has been observed by the third month of auranofin therapy. Further benefit occurs in some patients during the remainder of the first year of treatment.

In the more than 3,000 patients treated with auranofin, the most frequently reported side effects were gastrointestinal (mainly diarrhea) and mucocutaneous. Most side effects were mild in nature and the withdrawal rate due to all adverse reactions averaged 11%.

Auranofin differs from injectable gold by producing more gastrointestinal but fewer mucocutaneous reactions. The severity of these reactions is less with auranofin and causes fewer withdrawals from therapy.

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