Ridaura®
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Gold Therapy in Rheumatoid Arthritis

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Gold Therapy for RA
Summary

- In 1927, K Lande reported the use of aurothioglucose by injection in patients with a variety of rheumatic diseases
- J Forestier first reported the use in rheumatoid arthritis (RA)
- Gold compounds have been used to treat rheumatoid arthritis (RA) since 1929.
- Gold was developed as a treatment for tuberculosis (TB)
- In early 1920's many thought that TB and RA were related
- This was proven to be incorrect, but gold did show beneficial effects on RA
- Subsequent randomized trials confirmed the effectiveness of gold in RA
- Gold has also been used in psoriatic and juvenile idiopathic arthritis
- Since the 1980's the use of gold has declined due to new products such as methotrexate and newer biologics & non-biologic DMARDs showing greater benefits and less side effects

1. Gold Therapy in the Treatment of Rheumatoid Arthritis. Paul Davis. Can Fam Physician 1988; 34:445-452
2. Gold Therapy for Rheumatoid Arthritis – Is It Still Used. Carol Eustice VeryWell January 2017

Jacques Forestier MD

Jacques Forestier (1890-1978), French physician. Forestier qualified as a doctor in Paris, where he worked with rheumatology patients. He pioneered the use of gold salts as a remedy for rheumatoid arthritis, still considered to be an effective treatment for the condition.

In Memoriam, Dr Jacques Forestier July 27, 1890 – March 15, 1978
Arthritis & Rheumatism Vol. 21 Issue 8, 23 November 2005

Gold - Early Studies

- Numerous uncontrolled studies were performed in the 1930s & 1940s
- First double-blind controlled study undertaken by Fraser in 1945
- By 1960 that gold therapy was more widely regarded as an appropriate and effective treatment for rheumatoid disease as reported in the controlled study of the Empire Rheumatism Council
- In all studies the problem of toxicity remained paramount
- In the US, the 1973 report of the Cooperating Clinics generally supported the conclusions of previous studies
- In 1984, the development of an oral formulation, Auranofin added a new dimension to gold therapy.

Gold Therapy in the Treatment of Rheumatoid Arthritis. Paul Davis. Can Fam Physician 1988; 34:445-452

Pharmacology (1)

- Therapeutic gold compounds
  - Gold sodium thiomalate (GST) – contains 50% gold in a water based solution – administered by intramuscular (IM) injection every 1-4 weeks
  - Gold sodium thioglucose (in a sesame oil solution) also IM injection was withdrawn in 2006
  - Auranofin, gold triethylphosphine compound taken orally on a daily basis

Use of gold compounds in rheumatic disease. Alice Klinkhoff, MD
UpToDate: November 22, 2017

Pharmacology (2)

- Mechanism of Action (MOA)
  - There are several *possible* mechanisms by which gold may affect the immune response and disease process in RA
  - However, the exact MOA of gold in RA remains uncertain despite extensive experience and an excess of data
- Possible:
  - The ability of gold compounds to dissociate antigenic peptides from major histocompatibility antigen class II antigen presenting molecules, demonstrated in vitro for human leukocyte antigen (HLA)-DRB1, may be relevant, given the significant association between HLA-DR genotype and RA
  - Experimental evidence also suggests that GST acts to block prostaglandin E2 production and a number of proinflammatory genes
  - Nanogold showed antiangiogenic and anti-inflammatory properties in a collagen-induced arthritis model in rats
  - In another study, GST increased the expression of mitogen-activated protein kinase (MAPK)-1, a possible arthritis suppressor gene
  - In patients treated with gold, decreased serum concentrations of immunoglobulins, rheumatoid factor, and circulating immune complexes can be seen.

Use of gold compounds in rheumatic diseases. Alice Klinkhoff MD. UpToDate November 22, 2017

Gold - Pharmacokinetics

The pharmacokinetics of oral gold (auranofin) in some respects resemble, and in other respects differ from, those of existing parenteral gold compounds such as gold sodium thiomalate (GST).

- This may in part relate to physicochemical differences as GST is a water-soluble polymeric compound in vitro whereas auranofin is lipid-soluble and characteristically monomeric.
- Furthermore, intramuscularly administered gold is greater than 95% bioavailable, whereas only 20 to 30% of an orally administered dose of auranofin is absorbed.

Clinical pharmacokinetics of oral and injectable gold compounds.
Blocke KL, et al. Clin Pharmacokinet. 1986 Mar-Apr;11(2):133-43

IM Gold - Pharmacokinetics

- Gold sodium thiomalate (GST) - standard IM 50mg dose
  - Rapidly absorbed with 95% bioavailable
  - Peak plasma concentrations (cMax) in 2-6 hours
  - Decline in levels
    - Initial rapid decline t ½ of 9.7 hours
    - Slow decline t ½ of 5-6 days
  - Serum gold levels rise with each weekly injection
  - Plateau (3-5 mg/l) reached in 5-8 weeks
  - 40% of GST eliminated
    - 70% in urine, 30% in feces
    - Remainder retained in kidneys, adrenals and reticuloendothelial system for up to 25 years!

Use of gold compounds in rheumatic diseases. Alice Klinkhoff MD. UpToDate November 22, 2017

Oral Gold - Pharmacokinetics

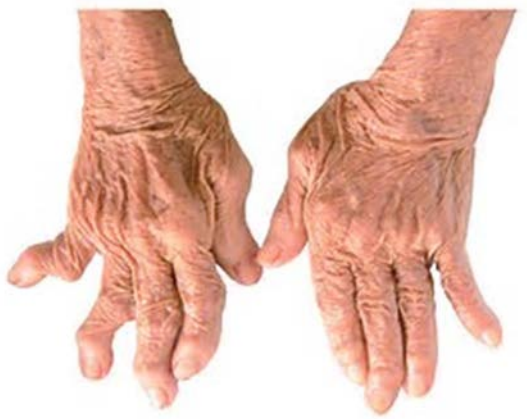
- Auranofin 6mg taken orally on a daily basis
  - Enters circulation via gastrointestinal mucosa
  - Approximately 25% is absorbed
  - Peak plasma concentrations (cMax) at 2 hours in new patients and 1.2 hours in patients taking auranofin for >6 months
  - Terminal plasma half-life of auranofin is 26 days (21-35), terminal body half-life is 80 days (40-128)
  - Of a single dose: 85% excreted in feces, 15% in urine
  - Retained to a much lesser degree than GST
    - 300mg elemental gold retained following 20 x 50mg injections of GST
    - 75mg elemental gold retained following 20 weeks of auranofin 6mg daily
    - Comparable studies in humans are not available for auranofin but animal studies have shown comparatively less affinity for the liver, kidney and spleen
- There are no known pharmacologic drug interactions between therapeutic gold and any non-biologic or biologic DMARDs

Use of gold compounds in rheumatic diseases. Alice Klinkhoff MD. UpToDate November 22, 2017
Riduara PI Revised October 2017 PI 09306 1017

Use of Gold in RA

- Gold can be used to control synovitis and prevent damage in patients with active rheumatoid arthritis (RA)
- Gold can be administered either as monotherapy or in combination with other disease-modifying antirheumatic drugs (DMARDs), including both nonbiologic and biologic DMARDs

Etanercept in combination with sulfasalazine, hydroxychloroquine, or gold in the treatment of rheumatoid arthritis. J Rheumatol. 2006;33(2):213. Epub 2005 Dec 15



Approved Indications for Ridaura®:

RIDAURA (auranofin) is indicated in the management of adults with active classical or definite rheumatoid arthritis (ARA criteria) who have had an insufficient therapeutic response to, or are intolerant of, an adequate trial of full doses of one or more nonsteroidal anti-inflammatory drugs. RIDAURA should be added to a comprehensive baseline program, including nondrug therapies.

Riduara PI Revised October 2017 PI 09306 1017

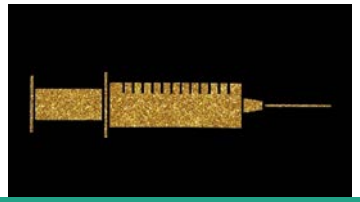
Current Use of Gold in RA

- Gold is used most often in certain types of patients since biologic agents for RA have become available.
- In a series of 71 patients referred for gold therapy for RA between 2007 and 2009, the more common reasons for referral included:
  - Suboptimal response to methotrexate (MTX) and other DMARDs
  - Limited DMARD options, most often because of liver disease
  - History of previous benefit with gold
  - Inappropriate for biologics
  - Planned pregnancy
- The oral gold preparation auranofin, is less often used because it is less effective than parenteral gold (GST), has diarrhea as a common side effect, and requires close monitoring because of the potential for serious side effects.

Characterization of patients with arthritis referred for gold therapy in the era of biologics.
Cheung JM, J Rheumatol. 2012 Apr;39(4):716-9. Epub 2012 Feb 15

Dosing of Parenteral Gold

- Test doses of GST are given initially, 10 & 25mg one week apart
- Followed usually by weekly dosing (typically 50mg) until the desired clinical response is achieved
- Then the frequency of injections is tapered, usually to every 2-4 weeks, for maintenance therapy
- However, the most effective and least toxic dose and schedule for the administration of intramuscular (IM) gold therapy has not been established experimentally
- In patients who worsen while on monthly-maintenance gold, resumption of weekly injections often results in improvement in control of disease activity
- This typical approach has evolved based largely upon case series, several clinical trials, and clinical experience



Use of gold compounds in rheumatic diseases. Alice Klinkhoff MD. UpToDate November 22, 2017

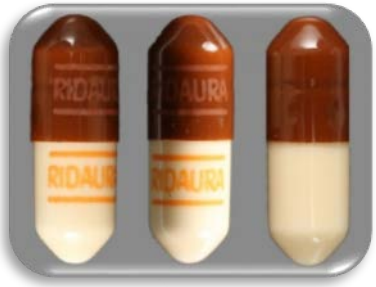
Dosing/Monitoring of Oral Gold

Dosing oral gold

- The usual dose of auranofin is 6 mg orally daily (taken as a single dose or 3 mg twice daily)

Monitoring oral gold — Suggested approach to monitoring for adverse events in patients receiving oral gold therapy:

- Patients should be questioned for symptoms such as pruritus, rash, stomatitis, or metallic taste
- Patients should have:
  - baseline CBC with differential, platelet count,
  - serum creatinine, liver function tests, and urinalysis.
  - A CBC and differential, platelet count, and urinalysis should be performed at least monthly during use of auranofin
  - Abnormalities should be addressed in the same fashion as with parenteral gold.



Use of gold compounds in rheumatic diseases. Alice Klinkhoff MD. UpToDate November 22, 2017

Efficacy of Oral Gold

- Orally administered gold (auranofin), is less effective for the treatment of RA than the parenterally administered form of gold GST, although it has fewer side effects.
- Oral gold also appears less effective than other traditional DMARDs, including MTX and sulfasalazine.
- Some trials have also compared oral gold with other DMARDs.
- Several randomized trials that have compared auranofin with placebo and/or GST illustrate the relative efficacy of auranofin

Use of gold compounds in rheumatic diseases. Alice Klinkhoff MD. UpToDate November 22, 2017

Clinical Trials (1)

In a 20-week trial involving 193 patients, a significantly greater proportion of patients receiving GST or auranofin experienced a decrease of at least 50 percent in the number of swollen joints compared with patients receiving placebo (37 and 28 versus 12 percent). The frequency of discontinuation for lack of benefit was lower with GST than auranofin, and less in patients on either gold compound compared with placebo (1 versus 19 versus 60 percent, respectively).

Comparison of auranofin, gold sodium thiomalate, and placebo in the treatment of rheumatoid arthritis. A controlled clinical trial. Ward JR, et al. Arthritis Rheum. 1983;26(11):1303

In a three-year randomized trial involving 90 patients, those assigned to receive either GST or auranofin showed clinical improvement by articular index, grip strength, and morning stiffness in both gold treatment groups compared with those receiving placebo. Discontinuation for inefficacy was most common in patients receiving placebo and more common with auranofin than with GST.

A three year follow up of patients allocated to placebo, or oral or injectable gold therapy for rheumatoid arthritis. Capell HA, et al. Ann Rheum Dis. 1986;45(9):705

Clinical Trials (2)

A 24-month open-label randomized trial found decreased benefit from gold therapy in patients treated with oral gold after achieving remission on parenteral gold therapy. Switching to oral gold was compared with continuing maintenance parenteral gold in patients with RA in remission on parenteral gold therapy. Half of 46 patients randomized to oral gold resumed parenteral therapy due to loss of control or new side effects. Radiographic progression and clinical deterioration was greater in those randomized to oral gold, and new adverse reactions occurred in 16 of 24 who switched from parenteral to oral gold.

Randomized trial of switching rheumatoid arthritis patients in remission with injectable gold to auranofin.
Prete PE, et al. Clin Rheumatol. 1994;13(1):60

Determinants of Efficacy

- The variable response to gold has led to attempts to identify predictors of efficacy and toxicity.
- Immunogenetic data suggest that human leukocyte antigen (HLA) phenotypes may affect response to gold.
- One study found that the presence of HLA-DR3 was associated with greater likelihood of benefit from gold therapy*.
- DR3 has also been associated with increased risk of side effects from gold, including rash and proteinuria.
- However, in clinical practice it is not usual to perform HLA typing before treating patients with gold.

*The influence of HLA phenotypes on the response to parenteral gold in rheumatoid arthritis. Speerstra F, et al. Tissue Antigens. 1986;28(1):1

Summary - Oral vs. IM Gold

- Both forms of gold therapy have a place in RA
- Comparative studies suggest IM gold may be slightly more beneficial than oral gold in inducing disease remission
- A larger number of patients receiving injections are able to complete therapy
- Drop-out rates due to lack of therapeutic effect are greater with oral gold
- In patients who continue on oral gold the quality of remission is similar to that obtained with injectable gold
- Injectable gold has a higher incidence of more serious side effects such as nephrotoxicity, thrombocytopenia and aplastic anemia
- Lower potential therapeutic benefit with oral gold offers an increased safety margin

Use of gold compounds in rheumatic diseases. Alice Klinkhoff MD. UpToDate November 22, 2017

Reassessing the Efficacy of Gold Therapy for Rheumatoid Arthritis

- Because of its purity, gold is an inert element when used in the human body. This biocompatibility has made it extremely useful in many areas of dentistry and medicine. Its anti-inflammatory and antimicrobial actions have since been widely recognized.
- The mechanisms whereby gold compounds exert anti-inflammatory effects are not fully understood, but mounting evidence indicates that gold is stored in lysosomes in which it inhibits the processing of antigenic agents and the release of inflammatory cytokines.
- Even though the use of gold products to treat rheumatoid arthritis has declined since the development of newer anti-inflammatory agents and biologic disease-modifying antirheumatic drugs (DMARDs), its efficacy still appeals to many.
- In a systematic review of auranofin for the treatment of rheumatoid arthritis, this gold compound was found to be more efficacious than placebo in relieving tender joints, pain, and reducing erythrocyte sedimentation rate.
- The reassessment of an old therapy is not new in medicine, and the future of gold therapy looks bright. Increasing bacterial resistance to antibiotics has added energy to medical science's ever-expanding search for antibacterial and antiviral therapies. In addition, the use of gold therapy as an anticancer agent appears promising, as does its more common use as a DMARD.

Reassessing the Efficacy of Gold Therapy for Rheumatoid Arthritis. Sego S, Clinical Pain Advisor Aug 17, 2016

Guidelines

- Gold therapy (IM and oral) has not been included in the American College of Rheumatology Recommendations for the use of Nonbiologic and biologic DMARDs in Rheumatoid Arthritis sine prior to 2008

American College of Rheumatology 2008 Recommendations for the Use of Nonbiologic and Biologic Disease-Modifying Antirheumatic Drugs in Rheumatoid Arthritis. Saag, K et al. Arthritis & Rheumatism Vol. 59. No. 6 June 15 2008. pp 762-784

- In 2012 the ACR updated their guidelines from 2008 stating: "Cyclosporine, azathioprine, and gold were included in the literature search, but due to the lack of new data and/or infrequent use, they were not included in scenarios and the recommendations."

2012 Update of the 2008 American College of Rheumatology Recommendations for the Use of Nonbiologic and Biologic Disease-Modifying Antirheumatic Drugs in Rheumatoid Arthritis. Singh, J et al. Arthritis & Rheumatism Vol. 64. No. 5 May 2012. pp 625-639

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PRESCRIBING INFORMATION | Rx Only

RIDAURA® (auranofin) contains gold and, like other gold-containing drugs, can cause gold toxicity, signs of which include: fall in hemoglobin, leukopenia below 4,000 WBC/cu mm, granulocytes below 1,500/cu mm, decrease in platelets below 150,000/cu mm, proteinuria, hematuria, pruritus, rash, stomatitis or persistent diarrhea. Therefore, the results of recommended laboratory work (See PRECAUTIONS) should be reviewed before writing each RIDAURA prescription. Like other gold preparations, RIDAURA is only indicated for use in selected patients with active rheumatoid arthritis. Physicians planning to use RIDAURA should be experienced with chrysotherapy and should thoroughly familiarize themselves with the toxicity and benefits of RIDAURA.

In addition, the following precautions should be routinely employed:

1. The possibility of adverse reactions should be explained to patients before starting therapy.
2. Patients should be advised to report promptly any symptoms suggesting toxicity. (See PRECAUTIONS—Information for Patients.)

INDICATIONS AND USAGE

RIDAURA (auranofin) is indicated in the management of adults with active classical or definite rheumatoid arthritis (ARA criteria) who have had an insufficient therapeutic response to, or are intolerant of, an adequate trial of full doses of one or more nonsteroidal anti-inflammatory drugs. RIDAURA should be added to a comprehensive baseline program, including nondrug therapies.

Unlike anti-inflammatory drugs, RIDAURA does not produce an immediate response. Therapeutic effects may be seen after three to four months of treatment, although improvement has not been seen in some patients before six months.

When cartilage and bone damage has already occurred, gold cannot reverse structural damage to joints caused by previous disease. The greatest potential benefit occurs in patients with active synovitis, particularly in its early stage.

In controlled clinical trials comparing RIDAURA with injectable gold, RIDAURA was associated with fewer dropouts due to adverse reactions, while injectable gold was associated with fewer dropouts for inadequate or poor therapeutic effect. Physicians should consider these findings when deciding on the use of RIDAURA in patients who are candidates for chrysotherapy.

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CONTRAINDICATIONS

RIDAURA (auranofin) is contraindicated in patients with a history of any of the following gold-induced disorders: anaphylactic reactions, necrotizing enterocolitis, pulmonary fibrosis, exfoliative dermatitis, bone marrow aplasia or other severe hematologic disorders.

ADVERSE REACTIONS

The adverse reactions incidences listed below are based on observations of 1) 4,784 RIDAURA-treated patients in clinical trials (2,474 U.S., 2,310 foreign), of whom 2,729 were treated more than one year and 573 for more than three years; and 2) postmarketing experience. The highest incidence is during the first six months of treatment; however, reactions can occur after many months of therapy. With rare exceptions, all patients were on concomitant nonsteroidal anti-inflammatory therapy; some of them were also taking low dosages of corticosteroids.

Reactions occurring in more than 1% of RIDAURA-treated patients

Gastrointestinal: loose stools or diarrhea (47%); abdominal pain (14%); nausea with or without vomiting (10%); constipation; anorexia*; flatulence*; dyspepsia*; dysgeusia.

Dermatological: rash (24%); pruritus (17%); hair loss; urticaria.

Mucous Membrane: stomatitis (13%); conjunctivitis*; glossitis.

Hematological: anemia; leukopenia; thrombocytopenia; eosinophilia.

Renal: proteinuria*; hematuria.

Hepatic: elevated liver enzymes.

**Reactions marked with an asterisk occurred in 3-9% of the patients. The other reactions listed occurred in 1-3%.*

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Reactions occurring in less than 1% of RIDAURA-treated patients

Gastrointestinal: dysphagia; gastrointestinal bleeding†; melena†; positive stool for occult blood†; ulcerative enterocolitis.

Dermatological: angioedema.

Mucous Membrane: gingivitis†.

Hematological: aplastic anemia; neutropenia†; agranulocytosis; pure red cell aplasia; pancytopenia.

Hepatic: jaundice.

Respiratory: interstitial pneumonitis.

Neurological: peripheral neuropathy.

Ocular: gold deposits in the lens or cornea unassociated clinically with eye disorders or visual impairment.

†Reactions marked with a dagger occurred in 0.1-1% of the patients. The other reactions listed occurred in less than 0.1%.

Reactions reported with injectable gold preparations, but not with RIDAURA (auranofin) (based on clinical trials and on postmarketing experience)

Cutaneous Reactions: generalized exfoliative dermatitis

Incidence of Adverse Reactions for Specific Categories—18 Comparative Trials

	RIDAURA (445 patients)	Injectable Gold (445 patients)
Proteinuria	0.9%	5.4%
Rash	26%	39%
Diarrhea	42.5%	13%
Stomatitis	13%	18%
Anemia	3.1%	2.7%
Leukopenia	1.3%	2.2%
Thrombocytopenia	0.9%	2.2%
Elevated liver function tests	1.9%	1.7%
Pulmonary	0.2%	0.2%

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