

Orthopedics • This Week

Gold Injections for Anti-Inflammation?

By Robin Young

From 1935 to the mid-1980s gold in an injectable form was treatment of choice for severe joint pain. Then new anti-inflammatory compounds in the 1980s combined with a dispute between the FDA and Schering Plough in 1998 over production of medical grade gold virtually eliminated gold as an anti-inflammatory treatment in the United States.

In the roughly 50 years that injectable gold was used to treat arthritic patients, scientists were able to document that gold has anti-inflammatory activity, inhibits inflammatory enzymes and affects mitochondrial activity. Specifically, drugs that are gold based inhibit expression of NF kappaB, tumor necrosis factor (TNF) and other cytokines.

A new company, ArthroGen, GmbH of Heidelberg, Germany, has developed a novel approach to using gold as an anti-inflammatory.

Founded in 2000 by Professor Ulrich Schneider M.D., ArthroGen has introduced the first new gold based product in decades called GOLDIC (which refers to gold-induced cytokines). This month ArthroGen announced completion of an 8 patient pilot study which came after an even more ambitious 34 patient knee study.

In the most recent study eight patients suffering from lumbar spine disc herniation pain received a series of four



Source: Wikimedia Commons and Andrew Magill as modified by RRY Publications LLC

gold injections in the region of their affected nerve roots. The injections were given at 3 to 7 day intervals. After one month, according to Dr. Schneider and ArthroGen, patients reported significant pain relief (visual analog scale and global assessment). Again, according to the company, by the fourth injection of GOLDIC some of the patients were virtually symptom free.

ArthroGen describes GOLDIC as a platform technology where the patient's own blood is mixed with gold particles and when injected may trigger increased production of certain cytokines

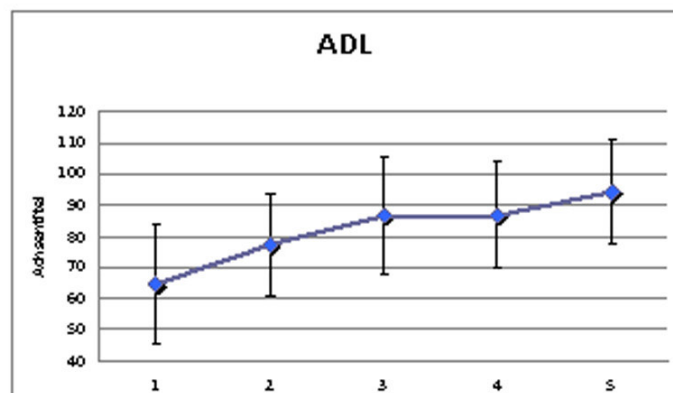
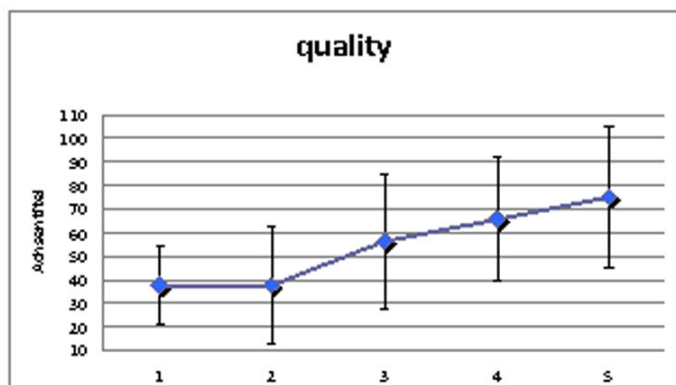
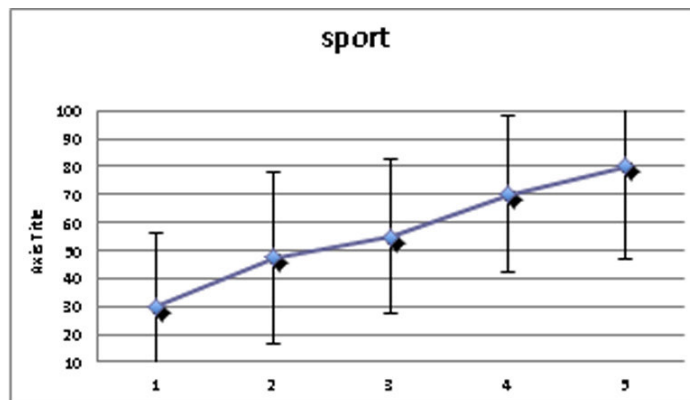
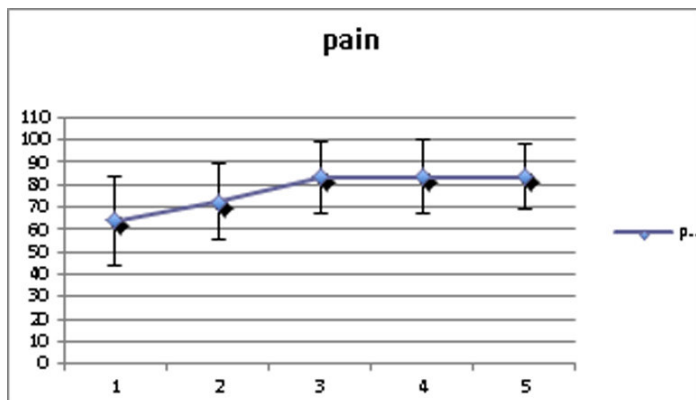
and important proteins like gelsolin. The company is targeting GOLDIC for orthopedic and trauma surgery.

In the firm's first human clinical study of its novel gold injection system, 34 patients with knee osteoarthritis (Kellgren stage 3-4) received four intra-articular injections with GOLDIC. The clinical result was measured by the Knee injury and Osteoarthritis Outcome Score (KOOS) and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) at 1, 3, 6, and 12 months post-treatment.

Patients consistently showed significant improvement as the following charts illustrate.

(1935). "Rheumatoid arthritis and its treatment with gold salts—results of six years experience." *J Lab Clin Med* 20: 827–40.)

with gold salts over a period of five years. At the time, this was the largest series of cases reported. The two investigators reported clinical improvement



Source: Arthrogen, GmbH

The analysis of the KOOS data showed not only a reduction of symptoms, but also a significant increase of sports activity three months after the GOLDIC treatment.

A Short History of Injectable Gold

In 1935, Paris-based Jacques Forestier, M.D., published six years of his clinical experience treating 550 patients with gold injections for rheumatoid arthritis, tuberculosis arthritis and ankylosing spondylitis. He reported that a particular form of gold was an effective treatment for these diseases of the musculoskeletal system. (Forestier J.

In his landmark retrospective patient survey, Forestier reported that 70% to 80% of his arthritic patients treated with gold salts (more about the specific chemical composition of these "salts" later) responded well to the therapy. In 1936, nine years after he first introduced gold therapy to his European colleagues for arthritis treatment, he expanded his previous review and reported that in chronic progressive rheumatoid polyarthritis patients, the advance of the disease was arrested by gold therapy in 85% of his cases.

In 1937, Hartfall and Garland reviewed 900 cases of chronic arthritis treated

in approximately 80% of the cases of rheumatoid arthritis and clinical improvement in approximately 50% of the cases of osteoarthritis. Hartfall and Garland also reported that the benefits of gold salts for osteoarthritis patients were not comparable nor as positive as those for patients with rheumatoid arthritis.

Then in 1961, the British Empire Rheumatism Council sponsored a carefully constructed prospective, double blind, controlled study of the efficacy and toxicity of gold salt treatment for RA. The study, which was published in the *Annals of Rheumatoid Diseases*, showed

that patients subjectively experienced improved disease activity, better grip strength, reduced numbers of use of analgesic tablets, lower inflammatory markers and hemoglobin. (a PDF of the study is available at this website: <http://ard.bmj.com/content/19/2/95.full.pdf>)

From the study:

“On comparing the gold-treated and control groups, it is apparent that by all criteria, except radiological progression, the gold-treated group showed a definite and greater degree of improvement than the control group from the third month onwards, and this was maintained until the eighteenth month, that is, over one year after completion of the course of injections, although slightly reduced in degree after the twelfth month. A later assessment will be made after a further one year’s follow-up, but to date the advantage clearly lies with the gold-treated group. Although part or all of this improvement may disappear within the next few years, one cannot ignore any form of therapy which gives temporary amelioration of symptoms in a progressive and painful disease, unless the hazards of therapy outweigh the advantages: such hardly seems to have been the case in this trial, though skin reactions were troublesome in a significant number of gold-treated patients and albuminuria was noted on four occasions. Steroid therapy and dimer-caprol (B.A.L.), not available to the earlier workers with gold salts, can effectively reduce the severity of such side-effects and lessen the dangers of this form of therapy.”

So, How Does Gold Work?

To start with, the term gold salts is a misnomer. It refers to a mixture of mineral gold (Au) and sodium chloride

(NaCl) from the 19th century. In the 20th century gold salts referred to gold thioglucose or gold thiomalate—neither of which was an actual salt.

Gold compounds, which can be ingested any number of ways, accumulate slowly in the body and, over time, reduce inflammation. Oral ingestion of gold is the least therapeutic method of introducing gold to the body. Today, gold, if ever used therapeutically is used to treat children with juvenile idiopathic arthritis who are unresponsive to non-steroidal anti-inflammatory drugs like methotrexate.

Gold is an expensive treatment.

Is a 2nd Generation Gold Better Than Steroids or Small Molecules?

Arthrogen is not the only company working on a second or even third generation gold anti-inflammatory injection. Six years ago then Harvard post-doc researcher Brian DeDecker, who was searching for a new drug to treat autoimmune diseases, stumbled upon the biochemical phenomenon that explains gold’s mechanism of action in the human body.

He published his eureka moment in the February 2006 issue of *Nature Chemical Biology*.

Dr. DeDecker wrote “Biochemical experiments indicate the metal-bound major histocompatibility complex (MHC) protein adopts a ‘peptide-empty’ conformation that resembles the transition state of peptide loading. Furthermore, these metal inhibitors block the ability of antigen-presenting cells to activate T-cells. This previously unknown allosteric mechanism may help resolve how gold drugs affect the progress of rheumatoid arthritis and may

provide a basis for developing a new class of anti-autoimmune drugs.”

Specifically, Dr. DeDecker was tackling one of the key shortcomings of the small molecule approach to blocking the autoimmune response. To block it, any compound must disrupt certain specific MHC-peptide interactions. MHCs bind peptide antigens in endosomes and present them on the cell surface where they are recognized by CD4 T cells. But small molecule compounds (which are what most drugs are) have very hard time disrupting the tightly bound peptides and they tend to dissociate slowly from MHC proteins.

Autoimmune diseases, like rheumatoid arthritis, result when the body’s immune system becomes over-active and can attack the body itself. There are approximately 80 separate autoimmune diseases which affect an estimated 25 million people annually in the U.S., of which the most common disease is RA.

Available for Licensing

Dr. DeDecker, who is now with the University of Colorado, has continued to work on gold-based therapeutic compounds and is letting the world know that he has created gold compounds with higher affinity and specificity for treating RA. Since gold compounds work by displacing the autoimmune peptide from the MHC molecule, they address the root cause of autoimmune disease by disrupting immune cell recognition of self-peptides.

In effect, DeDecker has invented a form of antibody or aptamer which will interact with MHC-gold complexes to more efficiently (than either small molecule compounds or classic gold salts) prevent self-peptides from being recognized by the immune system.

He believes his second-generation gold drugs will be more effective, more specific and less expensive than the classic gold salts, with fewer side effects for autoimmune diseases like RA. He also hopes to fine-tune these metal complexes into MHC class II allele specific molecules that could open up new platforms for the treatment of other au-

toimmune diseases including juvenile diabetes, multiple sclerosis, and lupus.

GOLDIC and Other Gold Compounds

There is no question but that Arthro-Gen's novel approach to gold injections is extremely intriguing. Furthermore,

Dr. DeDecker has looked at gold with fresh clinical eyes and he also has come up with some very interesting and valuable insights. Just taking a stab in the dark here, but further research seems to be indicated. ♦

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