Auranofin Versus Placebo in the Treatment of Rheumatoid Arthritis*

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In a six-month, multicenter, double-blind study involving 340 patients, auranofin, 3 mg twice daily, was compared with placebo in the treatment of adult-onset rheumatoid arthritis. All patients were continued on a therapeutic regimen of salicylates and/or a newer nonsteroidal anti-inflammatory drug. Patients in both treatment groups who completed six months of therapy with coded medications showed significant improvement in the clinical features of rheumatoid arthritis (that is, number of tender and swollen joints, severity of pain, grip strength and duration of morning stiffness); however, the mean improvement was greater in the auranofin-treated group. Fifty-two percent of the auranofin-treated patients compared with 24 percent of the placebo-treated patients ($p < 0.05$) were judged by their physician to have shown marked or moderate improvement. Only in the auranofin-treated patients was there significant improvement from baseline in the laboratory parameters of disease activity: erythrocyte sedimentation rate, IgA, IgG, and IgM. After at least three months of therapy, 30 percent (46 of 152) of the placebo-treated patients but only 9 percent (13 of 152) of the auranofin-treated patients ($p < 0.05$) withdrew from coded medication due to insufficient therapeutic effect. Study medication was discontinued by 5 percent (eight of 152) of the auranofin-treated patients and 3 percent (four of 152) of the placebo-treated patients because of adverse therapy events ($p = 0.24$). This study demonstrates the efficacy of auranofin when added to salicylates and/or nonsteroidal anti-inflammatory drugs in the treatment of rheumatoid arthritis.

Auranofin is a chemically-distinct gold compound with demonstrated antiarthritic effects following oral administration. In early clinical trials, auranofin improved clinical and laboratory parameters of rheumatoid arthritis disease activity and was well-tolerated [1–3]. In a prior report on 289 patients, Katz et al [4] found that auranofin was significantly more effective than placebo when added to a nonsteroidal anti-inflammatory drug for the treatment of rheumatoid arthritis. The purpose of this communication is to provide final analysis of 340 patients with rheumatoid arthritis who were enrolled in the aforementioned double-blind comparative trial.

MATERIAL AND METHODS

Patients entering this six-month, prospective, controlled study had active adult-onset, definite or classic rheumatoid arthritis, fulfilling the American Rheumatism Association criteria [5]. All patients received stable doses of nonsteroidal anti-inflammatory drugs for at least one month prior to entry. Systemic corticosteroids were allowed if the daily dose did not exceed 7.5 mg prednisone for women and 10 mg for men.

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* A complete list of the participants of the Multicenter Auranofin Trials Study appears at the end of this article.

TABLE I Patient Characteristics on Admission

Characteristic	Auranofin	Placebo
Male (n)	56	45
Female (n)	114	125
Median age (year)	53	53.5
Number receiving corticosteroids	25	33
Median disease duration (year)	4.3	4.0
Functional class (n)		
I	12	16
II	136	121
III	21	31
IV	1	0
NS	0	2
Anatomic stage (n)		
I	35	31
II	89	102
III	40	34
IV	1	0
NS	5	3

NS = not stated.

Patients were randomly assigned to the coded medication, either auranofin (3 mg twice a day) or placebo (twice a day), which was added to the baseline nonsteroidal anti-inflammatory drugs. The demographics of the 340 patients in the trial are shown in **Table I.** Eighteen patients in each group violated the protocol and were excluded. Three- and six-month efficacy data were analyzed. Measures of efficacy used in this trial included global response, number of tender and swollen joints, grip strength, duration of morning stiffness, pain severity, and onset-of-fatigue time. Westergren erythrocyte sedimentation rate and serum IgG, IgM, and IgA levels were determined at three-month intervals.

If a patient had not responded sufficiently after at least three months of therapy, the investigator had the option of breaking the code. Placebo-treated patients whose code was broken could enter another clinical trial and receive auranofin; auranofin-treated patients could remain on open auranofin for the duration of the study or withdraw from the study and be treated with conventional therapy. Patients whose drug code was broken due to insufficient therapeutic effect were considered drug failures.

Patients experiencing adverse events during therapy could, if their physician advised, continue the study drug, reduce the dose to 3 mg daily, or temporarily or permanently discontinue the study medication depending on the nature and severity of the problem. In the event of an adverse event during therapy, the investigator could break the double-blind code. Patients whose double-blind codes were broken, or who stopped the study medication for more than two weeks during the first 16 weeks of the study or three weeks thereafter because of an adverse event during therapy, were considered drug failures as they were unable to tolerate it long enough to realize therapeutic effect.

Because of study design, comparison of proportion of therapeutic failures in both treatment groups or, conversely, the proportion of patients who were able to complete six months of medication, provided a measure of overall efficacy of auranofin. Exclusion criteria were stated in the protocol prior to study initiation.

STATISTICAL METHODS

Each parameter of efficacy was analyzed at three and six months. Only patients receiving coded medication and meeting all protocol requirements were included in the analysis. Quantitative data were analyzed using a covariance model that accounted for the baseline value, duration of disease, age, use of corticosteroids, investigator, and study drug. Prior to pooling the data, the drug investigator interaction (as demonstrated by results from one investigator that differ vastly from those of the other participants in the multicenter study, indicating an unusual patient population or a similar nondrug effect) was tested for significance ($p < 0.05$). If a significant interaction was detected, the data for that parameter were not pooled for analysis. Improvement from baseline was also analyzed within each treatment group by means of the paired t test. Qualitative data, such as global

TABLE II Physician-Determined Global Efficacy

	Three Months				Six Months			
	Auranofin + NSAID		Placebo + NSAID		Auranofin + NSAID		Placebo + NSAID	
Assessment	Number	Percent	Number	Percent	Number	Percent	Number	Percent
Marked or moderate improvement	56	43	42	29	68	52*	32	24
Minimal improvement	48	37	58	40	26	20	24	18
No improvement	23	17	29	20	5	4	14	11
Worse	4	3	15	11	2	2	5	4
Therapeutic failure†	—	—	—	—	29	22	57	43
Totals	131	100	144	100	130	100	132	100

NSAID = nonsteroidal anti-inflammatory drug.
* $p < 0.05$, auranofin versus placebo.
† Patients who withdrew for insufficient therapeutic effect or adverse reaction.

efficacy and drug-related withdrawals, were analyzed using the Mantel-Haenszel X^2 statistic. As all patients received active medication (nonsteroidal anti-inflammatory drugs), statistical analyses were based upon two-tailed tests with alpha = 0.05.

RESULTS

Three hundred and forty patients entered this study, with 170 patients randomly assigned to each treatment group. One hundred and sixteen patients (68 percent) receiving auranofin and 90 patients (54 percent) receiving the placebo completed six months of coded study medication according to the protocol stipulations. Eighteen patients on each regimen did not meet the protocol requirements and were excluded from all analyses. Of the eligible patients, 30 percent (46 of 152) of the patients receiving placebo withdrew for insufficient therapeutic effect compared with 8 percent (13 of 152) of those receiving auranofin ($p < 0.05$). Eight auranofin-treated and four placebo-treated patients discontinued study medication due to adverse events during therapy ($p = 0.24$). An additional eight auranofin-treated and seven placebo-treated patients temporarily discontinued taking the coded drug longer than permitted and were ineligibile for efficacy comparisons. There was no significant difference between groups for exclusions because of adverse events during therapy ($p = 0.32$). Seven auranofin-treated and five placebo-treated patients withdrew from protocol for nondrug-related reasons.

Physician assessment of global response at three and six months is shown in **Table II.** Significantly ($p < 0.05$) more patients receiving auranofin plus nonsteroidal anti-inflammatory drugs than those receiving placebo plus nonsteroidal anti-inflammatory drugs exhibited marked or moderate improvement at six months. Data from patients who improved minimally at three months were reanalyzed at six months. In 56 percent (27 of 48) of the auranofin-treated but only in 17 percent (10 of 58) of the placebo-treated group was marked or moderate improvement attained ($p < 0.05$) (**Table III**). Auranofin-treated patients who remained on protocol for six months showed significant ($p < 0.05$) reductions in

TABLE III Global Efficacy at Six Months for Patients with Minimal Improvement at Three Months

Assessment	Auranofin + NSAID (n)	Auranofin + NSAID Percent	Placebo + NSAID (n)	Placebo + NSAID Percent
Marked or moderate improvement	27*	56*	10	17
Minimal	13	27	15	26
None	0	—	7	12
Worse	0	—	2	4
Therapeutic failure†	8	17	24	41
Totals	48	100	58	100

NSAID = nonsteroidal anti-inflammatory drug.
* $p < 0.05$, auranofin versus placebo.
† As defined in Table II.

TABLE IV Clinical Results

	Prestudy	3 Months	Prestudy	6 Months
Number of tender joints				
Auranofin	23.4 (130)*	15.3†‡	22.4 (106)	11.3†§
Placebo	22.4 (140)	17.3‡	21.2 (78)	13.4§
Number of swollen joints				
Auranofin	22.0 (130)	16.2‡	21.2 (106)	11.6†‡
Placebo	20.6 (140)	16.90†‡	19.7 (78)	13.3‡
Grip strength				
Auranofin	137.4 (128)	152.7‡	133.6 (106)	163.5‡
Placebo	136.6 (143)	144.7‡	145.9 (77)	162.3‡
Duration of morning stiffness				
Auranofin	2.62 (122)	1.64‡	2.51 (96)	1.65‡
Placebo	2.37 (135)	1.87‡	2.39 (73)	1.32‡
Pain severity				
Auranofin	5.59 (130)	3.94†‡	5.50 (106)	2.79‡
Placebo	5.34 (143)	4.54‡	5.09 (78)	3.17‡
Fatigue onset time (nearest ½ hour)				
Auranofin	6.68 (91)	6.97	6.61 (71)	7.32
Placebo	5.34 (143)	6.55	5.77 (53)	7.01‡

* Figures in parentheses indicate the number of patients.
† Significant difference between auranofin and placebo ($p < 0.05$).
‡ Significant ($p < 0.05$) improvement from baseline.
§ Significant drug by physician interaction detected.

TABLE V Laboratory Results

	Prestudy	3 Months	Prestudy	6 Months
Erythrocyte sedimentation rate				
Auranofin	44.0 (113)*	37.2†	42.2 (96)	31.2†
Placebo	39.0 (127)	35.7†	35.8 (69)	33.4
IgA				
Auranofin	231.9 (105)	219.2†	230.3 (83)	208.0†‡
Placebo	224.4 (126)	234.2	211.2 (63)	215.6
IgG				
Auranofin	1117.1 (105)	1031.8†	1144.7 (83)	972.2†
Placebo	1042.1 (125)	1044.7	1047.1 (62)	994.4
IgM				
Auranofin	133.7 (105)	106.4‡	116.9 (83)	100.9†‡
Placebo	127.4 (124)	126.6	112.6 (62)	114.7

* Figures in parentheses indicate the number of patients.
† Significant ($p < 0.05$) improvement from baseline.
‡ Significant difference between auranofin and placebo ($p < 0.05$).
Significant drug by physician interaction detected.

number of tender joints and pain severity at three months when contrasted to those receiving placebo. The swollen joint count at three and six months was significantly reduced ($p < 0.05$) (**Table IV**). At six months, only the auranofin-treated group showed a significant ($p < 0.05$) reduction from baseline in erythrocyte sedimentation rate and serum IgG level. Compared with placebo, auranofin lowered serum IgM and IgA levels significantly ($p < 0.05$) (**Table V**).

Approximately 30 percent of auranofin-treated and 13 percent of placebo-treated patients experienced one or more episodes of loose stools or diarrhea. These symptoms usually were mild in nature and of short duration, causing less than 2 percent of auranofin-treated patients to withdraw from protocol. The frequency of untoward effects related to skin, mucous membranes, and upper gastrointestinal tract was similar in both treatment groups. Five percent (18 of 152) of auranofin-treated and 3 percent (four of 152) of placebo-treated patients withdrew because of adverse events during therapy (**Table VI**).

TABLE VI Adverse Reactions Causing Withdrawal from Protocol

Adverse Reaction	Auranofin + NSAID (152)*	Placebo + NSAID (152)*
Diarrhea	2	0
Upper gastrointestinal complaints	0	1
Rash	3	0
Stomatitis	0	1
Proteinuria	2	1
Thrombocytopenia	1	0
Leukopenia	0	1
Totals	8	4

NSAID = nonsteroidal anti-inflammatory drugs.
* Number of patients.

COMMENTS

This multicenter trial supports previous work [4] that shows that auranofin is of benefit in managing patients with rheumatoid arthritis. When added to baseline anti-inflammatory medication, auranofin-treated patients experienced greater clinical and laboratory improvement than those treated with placebo. Of importance is the finding that only 8.5 percent of auranofin-treated patients withdrew from study for insufficient therapeutic effect, compared with 30 percent of placebo-treated patients. This factor had a profound effect on the efficacy measures: exclusion of withdrawn patients from the six-month evaluation skews the results in favor of the placebo-treated group, making that regimen appear more efficacious. If patients withdrawn for insufficient therapeutic effect or adverse events during therapy are included in the analysis, all clinical and laboratory parameters of disease activity show a statistical difference ($p < 0.05$) in favor of auranofin.

Roentgenograms of patients in this study were described recently [6]. Films from patients treated with auranofin with nonsteroidal anti-inflammatory drugs for 12 months (six months double-blind, six months open label) or with placebo plus nonsteroidal anti-inflammatory drugs for six months followed by auranofin plus nonsteroidal anti-inflammatory drugs for six months were compared. Patients who received auranofin for the full 12 months showed less advancement of erosive disease than those who received placebo for six months followed by auranofin for six months.

With the exception of lower gastrointestinal effects, adverse reactions were similar in both groups. If such safety is substantiated in the postmarketing period, auranofin could offer patients with rheumatoid arthritis the benefits of disease-modifying antirheumatic therapy with less risk of serious toxicity than is associated with other drugs in this category.

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