Proteinuria in Gold-Treated Rheumatoid Arthritis

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Treatment records of 1800 patients with rheumatoid arthritis who were included in the clinical trials of auranofin in the United States were examined for data on development of proteinuria. Three percent (41) of 1283 auranofin-treated patients had an abnormal 24-hour urine protein level: 15 had mild (0.15 to 1 g/d), 17 had moderate (1 to 3.5 g/d), and 9 had heavy (> 3.5 g/d) proteinuria. Permanent renal impairment did not occur, and proteinuria did not persist beyond 12 months in most patients. Seven of eight patients who were rechallenged when the proteinuria had cleared were able to continue treatment without relapse. No clinically discernible risk factors were found. Biopsy specimens from 4 patients showed membranous glomerulonephritis, which indicates an underlying immunopathologic mechanism. In similar groups of patients, the risk of developing proteinuria with auranofin therapy is significantly less than that with parenteral gold therapy ($p < 0.05$) and similar to that with background therapy with nonsteroidal antiinflammatory drugs ($p = 0.92$). The lower incidence and relatively benign nature of proteinuria seen in this review support previous findings that auranofin is better tolerated than injectable gold.

CHRYSOTHERAPY has been used in the treatment of rheumatoid arthritis for more than 50 years. Despite its favorable effects, a major concern among clinicians has been the development of frequent and sometimes serious adverse effects. Proteinuria is a well-known complication of parenteral chrysotherapy and has a reported incidence of 5% to 25% (1-3). From 0.2% to 5% of patients eventually develop the nephrotic syndrome (4).

Auranofin ([2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranosato-*S*][triethylphosphine]gold) is a novel gold coordination complex with demonstrated antiarthritic effects upon oral administration. Its ligand structure gives it certain immunologic effects and a pharmacokinetic profile that are distinct from those of other gold compounds (5). In double-blind comparative studies with placebo or parenteral gold, the efficacy of auranofin has been shown (6-8). These trials also have indicated that use of auranofin is associated with more frequent gastrointestinal symptoms (mainly a change in bowel habit) but less systemic or mucocutaneous toxicity.

Recently, nephrotic syndrome has been described in two patients treated with auranofin (9, 10). Because of the need to evaluate critically the potential effect of this oral gold compound on the kidney, a retrospective review was made of all cases of proteinuria that occurred during the clinical trials in the United States. Our study was intended to determine the incidence and clinical characteristics of the proteinuria that developed in auranofin-treated patients and to compare these findings with those in patients treated with gold sodium thiomalate or nonsteroidal antiinflammatory drugs alone. Potential risk factors and the underlying pathophysiology of proteinuria were also studied.

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Patients and Methods

Data were derived from case reports of 1800 patients with rheumatoid arthritis who were included in the trials of auranofin in the United States. These data represent cumulative information from studies conducted at more than 60 centers from 1976 through January 1983. All patients had definite or classic rheumatoid arthritis according to the criteria of the American Rheumatism Association (10). Patients with overlapping disorders, such as systemic lupus erythematosus, polyarteritis, or juvenile rheumatoid arthritis, had been excluded from the clinical trials. Of the combined patient population, 1283 patients received auranofin, 145 received gold sodium thiomalate, and 372 received placebo. All patients were maintained on therapy with aspirin or a nonsteroidal antiinflammatory drug, or both. Some patients were treated with low-dose corticosteroids (equivalent of prednisone, 10 mg/d or less).

Each patient enrolled in the clinical trials had a complete blood count and urinalysis done 1 week before the study and again just before initiation of medication. These laboratory tests were repeated weekly, biweekly, or monthly. Most protocols required that a 24-hour urine sample be collected for determination of protein levels if proteinuria of grade 1+ or more was found on routine testing with a commercial reagent strip (Albustix; Ames Division, Miles Laboratories, Inc., Elkhart, Indiana). Quantitative urine protein levels were determined by sulfosalicyclic acid or trichloracetic acid precipitation, or both. Decisions on whether to continue therapy with the study medication and to examine further the proteinuria, including with biopsy techniques, were made by the clinical investigator after consultation with the medical monitor of the protocol.

To characterize the proteinuria that developed during auranofin therapy, we further investigated all cases in which a 24-hour urine sample showed an abnormal protein level (> 0.15 g/d). Proteinuria was classified as mild (0.15 to 1 g/d), moderate (1 to 3.5 g/d), or heavy (> 3.5 g/d). Demographic data (age, sex, and duration of rheumatoid arthritis) were evaluated by linear discriminant analysis to detect any relationship between these factors and the development of proteinuria. Certain conditions that could have increased the risk or severity of proteinuria, such as cumulative dose and blood gold levels, were also examined. Morphologic changes seen on renal biopsy specimens were reviewed for comparison with findings reported in patients treated with parenteral gold or nonsteroidal antiinflammatory agents or in patients with underlying rheumatoid disease.

Of the 1800 patients evaluated, a subset of 556 patients had participated in two comparative double-blind studies. Data from these two clinical trials were analyzed to identify any differences in the risk of developing proteinuria with auranofin, gold sodium thiomalate, or placebo therapy in patients main-

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tained on nonsteroidal antiinflammatory drug treatments. Treatment groups were similar for age, sex, and duration of rheumatoid disease (Table 1). For each group of patients, the incidence of proteinuria, defined as 1+ or greater on dipstick testing, was determined. The cumulative risk of developing proteinuria was calculated for each treatment group by a life table technique (12). The Mantel-Haenszel chi-squared statistic was calculated to compare the differences in risk among treatment groups (13).

Results

Of 1283 auranofin-treated patients who were routinely monitored for proteinuria, 41 (3%) had an elevated 24-hour quantitative urinary protein level. Nine of these patients had heavy (> 3.5 g/d), 17 had moderate (1 to 3.5 g/d), and 15 had mild (0.15 to 1 g/d) proteinuria. Nine of the forty-one patients had had positive dipstick tests for proteinuria (1+ or greater) during baseline screening or with prior nonsteroidal antiinflammatory drug therapy; however, none developed heavy proteinuria while receiving auranofin therapy. At the time of increased 24-hour urine protein excretion, pyuria and hematuria were present in 1 and 15 patients, respectively. Serum creatinine levels were elevated in 3 patients but did not exceed 3 mg/dL. Eleven patients had underlying diseases such as diabetes mellitus, hypertension, or urinary tract infection, which could have accounted for increased urinary protein excretion. Demographic variables including age, sex, and duration of disease for patients who developed proteinuria were similar to those of auranofin-treated patients who did not develop this complication (Table 2). Total daily dose and duration of therapy also were not markedly different in proteinuric and nonproteinuric patients. Neither the incidence nor severity of proteinuria could be predicted by demographic factors, blood gold levels, or time of onset. Type of concurrent therapy, including that with salicylates and nonsteroidal antiinflammatory agents, also did not differ between patients with and without proteinuria.

Treatment of proteinuria in these 41 patients consisted chiefly of discontinuing auranofin therapy. Only 3 patients received prednisone (or its equivalent) in doses ranging from 40 to 70 mg/d; immunosuppressive drugs or penicillamine were not given to any patient. Long-term follow-up information was available on 36 patients. Once the medication was stopped, proteinuria cleared in 31 patients within 1 week to 24 months. In 29 patients, proteinuria resolved within 1 year. No direct relationship was seen between degree of proteinuria and length of recovery. Proteinuria ranging from 0.23 to 1.2 g/d persisted in 5 patients from 4 months to 2 years. However, 3 of these patients had had proteinuria before initiating therapy with auranofin. Quantitative urinary protein excretion had decreased in all 5 patients. Progressive elevations in serum creatinine and blood urea nitrogen levels did not occur, nor was there evidence of permanent renal impairment.

Eight patients were rechallenged with auranofin once proteinuria resolved. Seven had no relapses upon administration of therapeutic doses. In the one patient who had a relapse, proteinuria was mild (0.9 g/d) and again cleared upon cessation of theapy. Two additional patients were maintained on auranofin therapy despite proteinuria, which eventually cleared without sequelae.

Histopathologic findings in renal biopsy specimens from four patients were consistent with membranous nephropathy. At the time of biopsy, proteinuria ranged from 1.8 to 13.7 g/d.

Of 556 patients included in the two comparative double-blind studies (6, 11), 2.5% had proteinuria on baseline screening. When these patients were removed from analysis, the incidence of 1+ proteinuria was 27% (23 of 85) in patients treated with gold sodium thiomalate, 17% (42 of 247) in those treated with auranofin, and 17% (36 of 210) for those on placebo. All patients received background therapy with nonsteroidal antiinflammatory drugs. Separate evaluation of each clinical trial produced similar results (Table 3). Life table analysis of the patients in the two comparative trials indicated that the risk of developing proteinuria was significantly greater in patients treated with gold sodium thiomalate than in those treated with auranofin ($p < 0.05$) or those on placebo ($p < 0.05$). There was no significant difference in risk between auranofin and placebo treatments (Figure 1). Therapy was withdrawn due to proteinuria in 2.4%, 1.6%, and 0.5% of patients treated with gold sodium thiomalate, auranofin, and placebo, respectively.

Table 1. Clinical Characteristics of Patients with Gold-Treated Rheumatoid Arthritis Enrolled in Two Double-Blind Comparative Trials*

	Treatment		
	Auranofin	Gold Sodium Thiomalate	Placebo
Age, *yrs*	51 ± 13	51 ± 13	50 ± 14
Sex, *n*			
Male	79	26	57
Female	168	59	153
Mean duration of disease, *yrs*	7	7	6

* Data on file at Smith Kline & French Laboratories, Philadelphia, Pennsylvania. Age is given as mean ± SD.

Table 2. Clinical Characteristics of Proteinuric and Nonproteinuric Patients Who Received Auranofin for Rheumatoid Arthritis

	Patients	
	With Proteinuria	Without Proteinuria
Patients, *n*	41	1242
Age, *yrs**	54 ± 12	52 ± 13
Sex, %		
Male	39	29
Female	61	71
Mean duration of disease, *yrs*	6.7	6.7
Average daily dose, *mg*	6	6

* Age is given as mean ± SD.

Discussion

The incidence of proteinuria detected in our review varied among patients treated with auranofin, gold sodium thiomalate, and placebo. Although the definition of

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Table 3. Incidence of Proteinuria in Patients with Gold-Treated Rheumatoid Arthritis in Two Double-Blind Comparative Trials*

Study	Treatment		
	Auranofin	Gold Sodium Thiomalate	Placebo
		%(n/n)	
Study 1	19 (15/80)	27 (23/85)	20 (10/50)
Study 2	16 (27/167)	. . .	16 (26/160)
Total	17 (42/247)	27 (23/85)	17 (36/210)

* Data on file at Smith Kline & French Laboratories, Philadelphia, Pennsylvania. Proteinuria = 1+ or greater on a commercial reagent strip.

proteinuria (1+ or greater) was conservative by most standards, it was designed to identify potential renal toxicity at its earliest stages. A significantly greater risk of developing this adverse effect was found in patients receiving gold sodium thiomalate than in the other two groups. For patients treated with auranofin, the risk was similar to that in patients receiving nonsteroidal antiinflammatory drugs as background therapy.

Results of this analysis are similar to those reported for comparative trials of auranofin and injectable gold. Of a total of 314 patients treated with auranofin and 318 administered gold sodium thiomalate, the incidence of proteinuria was 1.5 times as frequent in the parenteral gold-treated group (4.4% versus 2.8%) (14, 15). In the worldwide composite of all auranofin studies, the withdrawal rate due to proteinuria was 1.6% (50 of 3082 patients) for auranofin and 2.2% (10 of 465) for injectable gold (16). The lower dropout rate in the auranofin-treated group occurred despite some patients being on therapy for more than 4 years. In contrast, most parenteral gold-treated patients were on therapy for only 6 months or less.

Proteinuria and glomerulonephritis have also been seen in patients with rheumatoid arthritis without prior administration of gold salts (17, 18). This finding may explain why the risk of developing proteinuria with auranofin was similar to that with background therapy alone. In the Empire Rheumatism Council (1) trial of injectable gold, the incidence of proteinuria was 3% in placebo-treated patients and 4% in gold-treated patients. Causes of proteinuria in patients with rheumatoid arthritis include amyloidosis, malignancy, hypertension, and vasculitis. Patients with diabetes mellitus, urinary tract infection, congestive heart failure, or systemic lupus erythematosus are also at increased risk (19). Antiarthritic medications other than gold can induce urinary protein excretion. Proteinuria, massive at times, has been reported in patients receiving nonsteroidal antiinflammatory drugs (20), but this condition most often results from acute interstitial nephritis rather than direct glomerular damage.

With continued monthly monitoring of urinary protein excretion in patients, auranofin-induced proteinuria has been relatively benign. Approximately 75% of episodes occurred during the first 9 months; thereafter, the risk of developing this abnormality decreased progressively. In more than 80% of patients, resolution occurred within 12 months. In the present study, proteinuria that developed during auranofin therapy did not appear to sensitize the patient to relapse on rechallenge. Seven of eight patients were able to tolerate re-administration without relapse. Patients with parenteral gold-induced proteinuria have been rechallenged in a few instances with variable results (21, 22).

The underlying mechanism of gold-induced nephropathy is unknown. In rats, chronic low-dose injections of gold sodium thiomalate have produced thickening of the glomerular capillary walls and glomerular deposition of immune complexes (23). Parenteral gold has been proposed to injure renal tubular epithelial cells with subsequent release of antigen (24). Once this antigen is bound with antibody, the formed immune complex is deposited in glomerular tufts, and a localized reaction ensues. Conflicting reports have appeared, however, on verification of this hypothesis (25, 26). Gold may not be the precipitating cause of nephropathy but instead may exacerbate an underlying abnormality (17). The primary defect in glomerulonephritis has been suggested to reside with suppressor T cells that have become permissive for immune complex formation and deposition in the kidneys. In patients receiving parenteral chrysotherapy, selective in-vitro inhibition of these suppressor T cells has been shown (27).

Whether a patient develops renal disease after exposure to injectable gold may be under genetic control. Retrospective studies have shown that patients with rheuma-

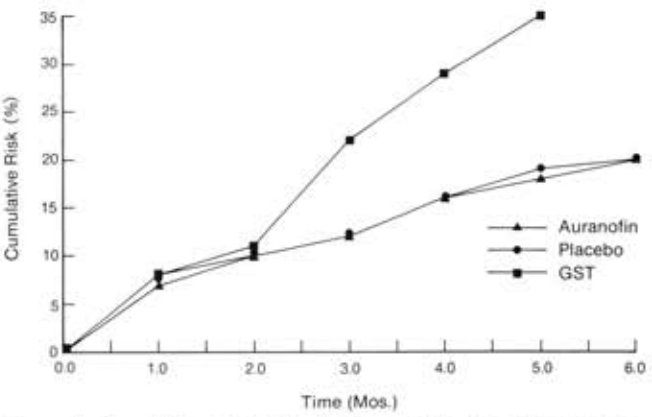

Figure 1. Cumulative risk of developing proteinuria after study entry in patients with gold-treated rheumatoid arthritis. The risk was significantly greater with gold sodium thiomalate (*GST*) than with auranofin (chi square = 6.41; $p < 0.05$, Mantel-Haenszel test) and placebo (chi square = 4.56; $p < 0.05$). There was no significant difference between auranofin and placebo (chi square = 0.010; $p = 0.92$). Proteinuria was defined as being grade 1+ or greater on dipstick urinalysis. Data on file at Smith Kline & French Laboratories, Philadelphia, Pennsylvania.

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toid arthritis who have the B-lymphocyte alloantigens HLA-DRW3 or -B8 are at increased risk of developing proteinuria with parenteral gold therapy (28, 29). The level of circulating metallothionein may also be involved in the relationship between chrysotherapy and nephrotoxicity (30).

Although why the risk of developing proteinuria is less with auranofin than with parenteral gold is not known, certain factors may be important. In laboratory animals treated with auranofin or gold sodium thiomalate, renal tissue gold concentrations were 33 times higher with the parenteral gold salt (5). Renal elimination of an orally administered dose of auranofin in humans is 15%, compared with 70% for parenterally administered gold sodium thiomalate (31). Also less gold is retained in the body 6 months after oral auranofin administration. Because gold-induced nephropathy may result from an altered immunologic response, differences in the effects of specific gold compounds on the immune system must be considered. The in-vitro and in-vivo immunopharmacologic profiles of auranofin and parenteral gold salts have been examined, and there are marked differences (32). Although many effects of auranofin and gold sodium thiomalate on humoral and cell-mediated immunity are known, more research is needed to determine what specific perturbations, if any, are responsible for the development of proteinuria and other adverse effects.

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