Parenteral Gold Preparations. Efficacy and Safety of Therapy After Switching from Aurothioglucose to Aurothiomalate

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ABSTRACT. ***Objective.*** For reasons of insufficient quality of the raw material, aurothioglucose was withdrawn from the Dutch market at the end of 2001. Aurothiomalate became available as an alternative preparation. We followed a cohort of patients during the first year after switching from aurothioglucose to aurothiomalate to study efficacy and tolerability.

Methods. Patients were observed at baseline and at 3 and 12 months after switching. At each visit, data on adverse drug reactions (ADR), withdrawal, and disease activity were collected.

Results. In total 120 patients were included [age 63 (SD 15) yrs, 68% female, 93% with rheumatoid arthritis, duration of disease 15 (SD 9) years, 82% IgM rheumatoid factor-positive, with 9 (SD 9, range 0.1–45) yrs of previous aurothioglucose therapy]. Nineteen patients (16%) reported an ADR taking aurothiomalate not previously experienced with aurothioglucose, the most frequently reported being pruritus, dermatitis/stomatitis, and chrysiasis/hyperpigmentation. Twenty-nine patients (24%) withdrew from aurothiomalate within 12 months of followup for reasons of inefficacy (14%), ADR (7%), or disease in state of remission (3%). Kaplan-Meier estimates show aurothiomalate survival rates of 78.5% after 12 months. No statistically significant differences between the disease activity indicators during followup visits compared with the baseline visit were detected for the patients continuing aurothiomalate.

Conclusion. Within the first 12 months after switching from aurothioglucose, 24% of patients withdrew from aurothiomalate. Sixteen percent of patients reported novel ADR. For the population continuing to take aurothiomalate no clinically relevant changes in disease activity were recorded after switching. (J Rheumatol 2005;32:1026–30)

Key Indexing Terms:
AUROTHIOMALATE AUROTHIOGLUCOSE WITHDRAWAL
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Since 1943 in The Netherlands aurothioglucose (ATG; Auromyose®) was the only parenteral gold preparation available. For reasons of insufficient quality of the raw material, ATG was withdrawn from the Dutch market at the end of 2001. This resulted in an estimated 1000 to 1500 patients in The Netherlands switching from ATG to another treatment option.

Although intramuscular gold currently is not the first option for rheumatologists in treating patients with rheumatoid arthritis (RA), these preparations remain a part of the treatment paradigm[1]. Studies show efficacy of intramuscular gold to be similar with methotrexate in different settings[2-4]. Rheumatologists requested continuing availability of a parenteral gold salt for prescription purposes. The Dutch Medicines Evaluation Board, after an accelerated procedure, licensed aurothiomalate (ATM; Tauredon®) as an alternative gold preparation as requested.

Both ATG and ATM have been studied in over 50 randomized, controlled trials each. Comparable efficacy of ATG and ATM was shown in a 2-year followup study in 125 patients[5]. Studies of the switch from ATM to ATG show the latter is tolerated well after the switch[6] or prevents postinjection reactions related to ATM injections[7]. Although it has never been formally studied, some publications suggest that switching from ATG to ATM may introduce clinical prob-

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lems. Differences in toxicity have been observed in studies comparing ATM and ATG[5].

To investigate suggestions of negative tolerability of the aqueous ATM preparation, we monitored patients switching from the oily ATG preparation Auromyose® to the aqueous ATM preparation Tauredon® in a national case series study in The Netherlands.

MATERIALS AND METHODS

At the time of withdrawal of ATG (August 2001) rheumatologists in The Netherlands were asked to take part in the study; participating rheumatologists included their patients consecutively. Patients with 12-month followup, withdrawal, or death were eligible for inclusion in the study.

Followup. Baseline data consisted of patient, disease, and treatment characteristics. Followup visits took place at 3 and 12 months. Adverse drug reactions (ADR) on therapy were recorded on a standard form listing 34 different ADR known to be related to gold therapy. Novel ADR were defined as ADR not previously reported at the baseline visit with respect to the ATG treatment. In case of withdrawal from ATM, the time until withdrawal and the reason for withdrawal were recorded. Efficacy of therapy was recorded as changes in erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), a visual analog scale (VAS) score of patients' and rheumatologists' estimation of disease activity, and a categorical (better, equal, worse) estimation of change in disease activity compared to the previous visit by patient and rheumatologist.

ATM dosing. The ATG dose was converted to the ATM dose on a 1:1 milligram basis, since ATG and ATM contain a comparable fraction of elementary gold, 50.3% and 50.5%, respectively. Rheumatologists were allowed to adjust the ATM dose as needed, adapting frequency of administration or dose per administration.

Statistical analysis. SPSS 12.0.1 for Windows was used for data collection, data validation, data selection, and statistical analysis. Student t test was used for comparing mean values of disease activity indicators between visits. Kaplan-Meier estimates were used to calculate the cumulative probability of withdrawal from ATM. The relation between baseline variables and withdrawal from ATM was studied by logistic regression analysis. A p value of 0.05 is considered significant.

RESULTS

Population. Since most hospitals did not run out of stock of ATG immediately, it took until October 2002 for the last patients to be included. One hundred twenty patients were included by 30 rheumatologists in 18 hospitals. Mean age of the patients was 63 (SD 15) years, 68% were female, and patients used ATG for 9 (SD 9, range 0.1–45) years before switching to ATM. The indication for gold therapy was rheumatoid arthritis (RA) in 93% of patients, with a mean duration of disease of 15 (SD 9) years. Eighty-two percent of patients with RA were positive for IgM rheumatoid factor (RF). Table 1 shows the treatment characteristics of the population. Two patients died, 3 and 4 months, respectively, after switching to ATM, for reasons not related to gold treatment (brain tumor, cardiac arrest).

Adverse drug reactions. Nineteen patients (16%) reported one or more novel ADR during followup (Table 2). The patient group reporting a novel ADR during ATM treatment did not differ significantly from the patient group not reporting a new ADR with respect to age, sex, IgM RF status, erosive disease, presence of rheumatoid nodules, duration of RA, weekly ATM dose, cumulative ATG dose, or number of previous disease modifying antirheumatic drugs (DMARD). However, patients reporting a new ADR had a longer median duration of previous ATG therapy compared to patients not reporting a new ADR, 117 and 66 months, respectively ($p = 0.048$).

Withdrawal. Twenty-nine (24%) patients withdrew from

Table 1. Treatment characteristics at baseline. Data are mean (SD) unless stated otherwise.

Treatment characteristics	
Parenteral gold prescribed as first DMARD, %	21
No. of DMARDs prior to parenteral gold, range	1.8 (1.5), 0–7
Concomitant corticosteroid use, %	12
Concomitant other DMARD use, %	18
Methotrexate	9
Sulfasalazine	3
Hydroxychloroquine	3
Other	3
Indications for gold therapy, %	
RA	93
JIA	3
PsA	3
Other	1
Parenteral gold characteristics	
Duration of ATG treatment, mo	109 (109)
Median	75
Range	1–542
Weekly dose of ATG, mg; %	
< 10	27
≥ 10– < 25	30
≥ 25	53
Cumulative ATG dose, mg	9045 (11,929)
Median	5300
Range	100–75,000

PsA: psoriatic arthritis, ATG: aurothioglucose, DMARD: disease modifying antirheumatic drug, JIA: juvenile idiopathic arthritis, RA: rheumatoid arthritis.

Table 2. Novel adverse drug reactions (ADR) reported in relation to ATM therapy during 12 month followup.

ADR	Reported by n (%)	Withdrawn, n
Pruritus	8 (7)	5
Dermatitis/stomatitis	6 (5)	3
Chrysiasis/pigmentation	5 (4)	0
Proteinuria	4 (3)	0
Urticaria	2 (2)	0
Headache	2 (2)	0
Vasomotor reactions	2 (2)	1
Arthralgia/myalgia	2 (2)	0
Palpitations	1 (1)	0
Mild enterocolitis/upper abdominal complaints	1 (1)	1
Pain in upper arms	1 (1)	1

ATM, after a mean of 5.9 (SD 3.0) months. Reasons for ATM withdrawal were inefficacy (59%), ADR (28%), a combination of inefficacy and ADR (3%), and RA in remission (10%). Table 2 shows the number of patients withdrawing from ATM due to a specific ADR, with some patients reporting more than one ADR. Kaplan-Meier estimates for the probability of ATM survival are shown in Figure 1.

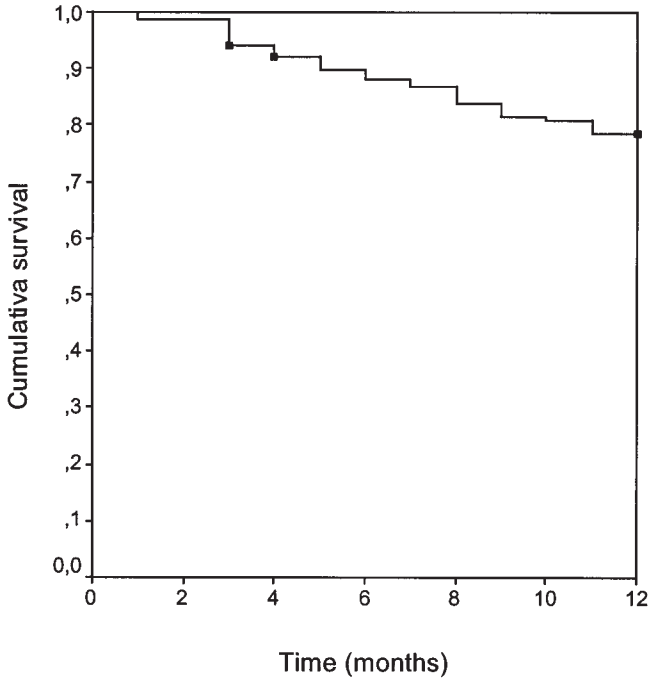

Figure 1. Kaplan-Meier estimate of aurothiomalate withdrawal (■: censored observation).

Determinants for ATM withdrawal. For the patients withdrawing from ATM, with the exception of withdrawal due to disease in remission, a number of variables possibly associated with withdrawal were studied. Of the variables studied, age, sex, body mass index, duration of rheumatic disease, presence of rheumatoid nodules, erosive disease, IgM RF status, and cumulative ATG dose were found not to be associated with withdrawal. However, duration of ATG therapy > 72 months [relative risk (RR) 3.0, 95% confidence interval (CI) 1.3–6.7] or pretreatment with one or 2 DMARD (RR 3.3, 95% CI 1.4–7.6) was found to be predictive for lower withdrawal rates compared with patients taking ATG therapy for ≤ 72 months and pretreatment with > 2 DMARD, respectively.

Disease activity. Completeness of data on disease activity at each visit was above 80% at every visit for ESR (range 83% to 100%), VAS score as rated by patient (range 80% to 89%), and VAS as rated by the rheumatologist (range 81% to 94%). CRP data were recorded in 60% to 73% of the baseline and followup visits. Disease activity variables (Figure 2) did not differ significantly between baseline and the followup visit after 3 and 12 months, respectively. Patients' and rheumatologists' ratings of disease activity compared with the baseline visit are shown in Table 3. Patients' ratings tend to worsen during followup; rheumatologists' ratings showed no tendency for better or worse rating.

DISCUSSION

Our study showed that 24% of patients switching from ATG to ATM during a 12-month period withdrew from ATM, mainly for reasons of inefficacy or ADR. After switching, 16% of patients reported novel ADR. For the population

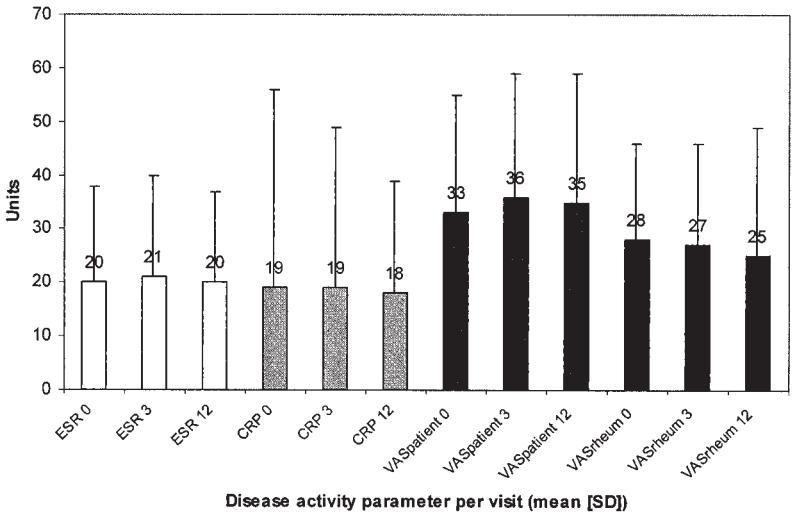

Figure 2. Disease activity indicators for patients continuing aurothiomalate treatment (values are mean ± standard deviation). CRP: C-reactive protein, mg/l; ESR: erythrocyte sedimentation rate, mm/h; VAS patient/VAS rheum: visual analog scale score as recorded by patient/rheumatologist, respectively (mm, on 100 mm scale). Accompanying numbers indicate followup duration in months.

Table 3. Patients' and rheumatologists' ratings of disease activity compared to baseline visit.

	Visit After 3 Months	Visit After 12 Months
Patients' rating, %		
Better	17	7
Equal	46	62
Worse	37*	32*
Rheumatologists' rating, %		
Better	13	12
Equal	71	73
Worse	16*	15*

* Percentages including patients withdrawn from treatment for inefficacy of therapy.

continuing ATM, no clinically relevant changes in disease activity were recorded.

A head-to-head comparison of ATG and ATM on efficacy[8] found no significant differences between the 2 gold salts. Our data are in accord with that study.

There was a considerable difference between rheumatologists and patients in the rating of disease activity during followup visits compared with the baseline visit. An explanation for these differences may be that both groups estimate disease activity from different viewpoints and references. Whether the structured followup during the study may have influenced these ratings is not known. In the reporting of ADR, it has to be recognized that the structured followup may have led to the tendency to attribute ADR to ATM. All reported novel ADR are known to be potentially related to parenteral gold therapy from previous studies.

The novel ADR most frequently reported for ATM therapy in our study were pruritis and dermatitis/stomatitis. This finding is in accord with the results from other studies, with skin eruptions and stomatitis having a 2.8-fold and 3.2-fold higher incidence, respectively, in the ATM group compared to the ATG group[5,8]. It must be noted that these results are derived from studies conducted in the 1970s, when requirements for study design, followup, and publication were different compared to today.

Can we explain the higher incidence of stomatitis/dermatitis and pruritis for ATM in comparison to ATG? First, if the gold is involved in these sequelae, then the difference in the pharmacokinetic profiles of the 2 preparations may play a role. The absorption of ATM from aqueous solutions is known to be very rapid, with gold peak serum concentrations between 10 minutes and 2 hours[8,9]. Applying the oily vehicle of ATG results in delayed gold peak serum concentrations — these peak levels may not be reached for as long as 6 to 8 hours after injection. Although several authors conclude that serum gold levels and clinical efficacy or ADR are not associated[10,11], the high concentration directly after injection of the aqueous solution may explain the negative tolerability profile of the aqueous preparations.

Second, thiomalate may play a role in the ADR, although the work of Rudge, *et al*[12] does not support this. They found no correlation between plasma levels or urinary excretion of free thiomalate between patients with and those without ADR during ATM therapy.

Third, Ernestam, *et al*[13] showed *in vitro* production of interleukin 10 (IL-10) in peripheral blood mononuclear cells to be related with a lack of skin reactions *in vivo*. Whether ATM and ATG have differential effects on IL-10 production and whether they may be an explanation for the differences in the incidence of skin reactions remains to be elucidated.

How can we interpret the survival rate of ATM after switching from ATG? ATG was withdrawn from the market suddenly and without prior warning to rheumatologists and pharmacists, leaving no opportunity to conduct a comparative, blinded trial for switching from ATG to ATM. Therefore, a comparison of the withdrawal rate, in our study 24% in 12 months, with data from populations in other studies is needed. Comparing data from other trials with our data 2 options remain. (1) If after switching, ATM is considered as *de novo* gold therapy, withdrawal data from followup of *de novo* gold populations are relevant. Results from these studies show that withdrawal from gold therapy within 12 months varies between 30% and 47%[2,14,15] in patients with RA. (2) ATM therapy, after switching from ATG, can be considered a continuation of gold therapy already under way. Specific information on withdrawal rates from gold therapy after longterm followup is not available (the mean duration of ATG therapy in our study was 75 months). However, some data can be derived from longterm followup studies in RA. Pincus, *et al*[16] reported a withdrawal rate of 24% between 24 months and 60 months of therapy. Assuming an equal percentage of the population withdrawing each year, this withdrawal rate leads to an estimated 8% of patients withdrawing each year. Galindo-Rodriguez, *et al*[17] reported a withdrawal rate of 13% between 3 and 6 years of gold therapy, estimating an annual withdrawal rate of 4% to 5%.

Thus, on the basis of withdrawal rates, ATM therapy after switching from ATG in our study cannot be considered a *de novo* start of gold therapy, since the incidence of withdrawal is lower compared with control populations, nor can it be considered a continuation of gold therapy since the incidence of withdrawal is higher compared with longterm followup populations.

At the time of withdrawal of ATG from the market, rheumatologists and their patients had to reconsider treatment options. Possible options were switching from ATG to ATM, withholding treatment, or introduction of a non-gold-containing DMARD. Considering the efficacy of newly available options such as leflunomide and tumor necrosis factor-α-blocking therapies, it is remarkable that only 24% of patients withdrew from ATM therapy in our study, despite the occurrence of novel ADR in some patients. A certain degree of satisfaction with current gold therapy may have played an important role in deciding to continue parenteral gold therapy.

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