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A three year follow up of patients allocated to placebo, or oral or injectable gold therapy for rheumatoid arthritis

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SUMMARY Ninety patients randomly allocated to receive auranofin, matching placebo, or sodium aurothiomalate have been followed up for three years. Inefficacy led to cessation of treatment in 14 patients receiving auranofin, 27 receiving placebo, and one receiving sodium aurothiomalate. Twenty seven of the patients receiving placebo were reallocated within the study and 16 continued therapy at three years. This group showed similar statistically significant improvement in clinical and laboratory parameters at one, two, and three years to those on an active drug from the outset. Patients who discontinued auranofin because of inefficacy were offered sodium aurothiomalate therapy—eight patients in this group completed three years of treatment on sodium aurothiomalate and showed significant improvement in some but not all parameters. A hand radiograph erosion score showed a deterioration in 80% of patients remaining on auranofin, 75% of those on sodium aurothiomalate, and 80% of the original placebo group who continued an active drug for three years. Although more patients discontinued auranofin over the study period because of inefficacy, no difference could be shown between the degree of improvement in the subgroup who remained on auranofin and those receiving sodium aurothiomalate. No disadvantage in outcome could be shown for patients originally assigned to placebo.

Key words: auranofin, sodium aurothiomalate.

It has been suggested that auranofin is less toxic than sodium aurothiomalate,[1] but controlled data about efficacy are needed to evaluate the role of this oral gold preparation in the management of rheumatoid arthritis. In addition, since long term therapy with a second line agent is necessary to demonstrate sustained benefit it is vital to continue with studies over several years, even when a drug has been shown to be effective in the short term.[2] Of equal importance is prolonged meticulous monitoring to detect possible late toxicity.

The use of a placebo group in any study poses ethical problems and there is a need for careful follow up of patients originally assigned to placebo to ensure that no adverse outcome is apparent. This study was begun in 1980 and six month and one year results have previously been published.[3 4] This report deals with a minimum of three years of follow up of patients receiving either sodium aurothiomalate or auranofin, or alternatively a minimum of three years after patients changed from placebo to one of these two active drugs. Data are also available on patients who discontinued auranofin and were reassigned to sodium aurothiomalate.

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Patients and methods

Ninety patients with definite or classical rheumatoid arthritis[5] were enrolled in the study. No patient was receiving corticosteroids or had received these drugs for three months before the study, and similarly none had received another second line agent in the three months before the study. All continued non-steroidal anti-inflamatory drugs, as necessary, throughout. All had active disease which required the addition of second line therapy because of failure to respond sufficiently to non-steroidal anti-inflammatory drugs alone.

TREATMENT ALLOCATION

Patients were randomly allocated to receive auranofin, matching placebo, or injectable sodium aurothiomalate (30 in each group). The sodium aurothiomalate treatment regimen consisted of a 10 mg test dose and 50 mg weekly until response, at which time the injections were spaced out to fortnightly, three weekly, and ultimately four weekly. Thirty patients received auranofin in a dose of 3 mg twice daily, and 30 received auranofin placebo which was identical in appearance to auranofin and given in a similar dose of one tablet twice daily. When patients discontinued the initial therapy they were offered a further allocation within the study if it was thought safe and appropriate. Patients were encouraged to continue therapy for 24 weeks unless side effects supervened. Thereafter, if they felt they had failed to derive benefit from their medication an alternative was offered. Of the 30 patients initally allocated to placebo, all had discontinued therapy by 36 weeks because of lack of effect; 27 were randomly reallocated to receive either sodium aurothiomalate or auranofin. Ten of these 27 patients went on to receive sodium aurothiomalate, and 17 auranofin. Formal analysis in this study is restricted to the patients who either received sodium aurothiomalate or auranofin first, or immediately after placebo. It was considered of interest to transfer patients who failed on auranofin to sodium aurothiomalate, but these patients cannot be included in the total treatment group since they represent a poor prognostic group and would bias the study: they are therefore analysed separately.

The standard clinical and laboratory measurements of efficacy were performed, and *x* rays of hands were analysed by modification of the Sharp method[6] at the start of the study and one and three years later.

Statistical analysis was by non-parametric tests.[7]

Results

Retrospective analysis of the initial Mallya and Mace index[8] in the 90 patients shows that none had mild disease, i.e., grade 1, 14 were in grade 2, 70 in grade 3, and six in grade 4.

At three years 17 (57%) of the 30 patients originally allocated to sodium aurothiomalate remained on treatment compared with seven (23%) allocated to auranofin. All the placebo patients had discontinued therapy before one year (the figures for sodium aurothiomalate and auranofin at that stage were: 22 of 30 (73%) remained on sodium aurothiomalate, 17 of 30 (57%) remained on auranofin.) A summary of the reasons for discontinuation of therapy in the three treatment groups by original allocation is shown in Table 1. Overall, adverse reactions were the most common reason for discontinuation of sodium aurothiomalate (nine patients), whereas inefficacy was the most common reason for discontinuation of auranofin (14 patients).

Of the 10 patients who received sodium aurothiomalate after placebo, four were still on therapy at three years. Of the 17 patients who received auranofin after placebo, nine remained on treatment at three years. Efficacy has been assessed on both the 17 of 30 and 21 (i.e., 17+4) of 40 (i.e., 30+10) patients receiving sodium aurothiomalate, and the seven of 30 and 16 (i.e. 7+9) of 47 (i.e., 30+17) auranofin patients. The median and range of clinical and laboratory parameters and the p values of the Wilcoxon matched pairs signed ranks test comparing initial values with those at one, two, and three years for sodium aurothiomalate and auranofin are shown in Appendices 1 and 2. In the sodium aurothiomalate groups all the parameters except grip strength changed significantly and remained improved over the three years; in the auranofin

Table 1 *Outcome over three years by original treatment allocation*

	Placebo		*Sodium aurothiomalate*		*Auranofin*	
	n	%	*n*	%	*n*	%
Adverse event	2	7	9	30	5	17
Inefficacy	27	90	1	3	14	47
Intercurrent illness	1	3	1	3	3	10
Non-compliance	0	0	2*	7	1**	3
Total who discontinued therapy	30	100	13	43	23	77
Total on original therapy	0	0	17	57	7	23

*Remission; **moved.

group all the parameters except grip strength and haemoglobin improved and all except the erythrocyte sedimentation rate (ESR) remained significantly better at three years. In addition, the group originally assigned to placebo, who then went on to either sodium aurothiomalate or auranofin and who reached three years of therapy (n=16), are shown in Appendix 3. This group also improved significantly over the three year period. Of the 14 patients who stopped auranofin because of inefficacy and went on to sodium aurothiomalate, five were still on sodium aurothiomalate and responding at three years. In addition, a further five patients received sodium aurothiomalate after both placebo and auranofin had failed; three of these five were still receiving sodium aurothiomalate therapy at the end of three years. Thus a total of eight of the patients who were considered to have a poor prognosis in that they had failed to respond to auranofin were still receiving sodium aurothiomalate treatment at three years; response in this group is shown in Appendix 4. Although many parameters improved significantly, the response was not as good as that seen in the original sodium aurothiomalate group or in those who received sodium aurothiomalate after placebo.

In addition, one patient who received sodium aurothiomalate for more than a year and had responded well but developed a rash was changed to auranofin; the rash did not recur and she continued therapy for three years, with good response.

Table 2 *Adverse effects leading to withdrawal of therapy: three year follow up*

	Sodium aurothiomalate (n)	*Auranofin (n)*
Rash	6	1
Nitritoid reaction	1	—
Cholestatic jaundice	1	—
Diarrhoea	—	2
Leucopenia	—	1
Proteinuria	1	—
Haematuria	—	1
Total	9	5

Original allocation 30 in each group.

Table 3 *Treatment outcome at three years in the original three groups*

	Placebo	*Sodium auro-thiomalate*	*Auranofin*
Still receiving auranofin	9	1	7
Still receiving sodium aurothiomalate	7	17	5
Alternative second line drug	10	8	13
No further second line drug	2	1	2
Not attending the Centre for Rheumatic Diseases	0	1	1
Died	2	2	2
Total	30	30	30

Thus 6/90 died during the three year follow up; 82/84 surviving patients still attend the Centre for Rheumatic Diseases; and 77/82 are still on second line therapy.

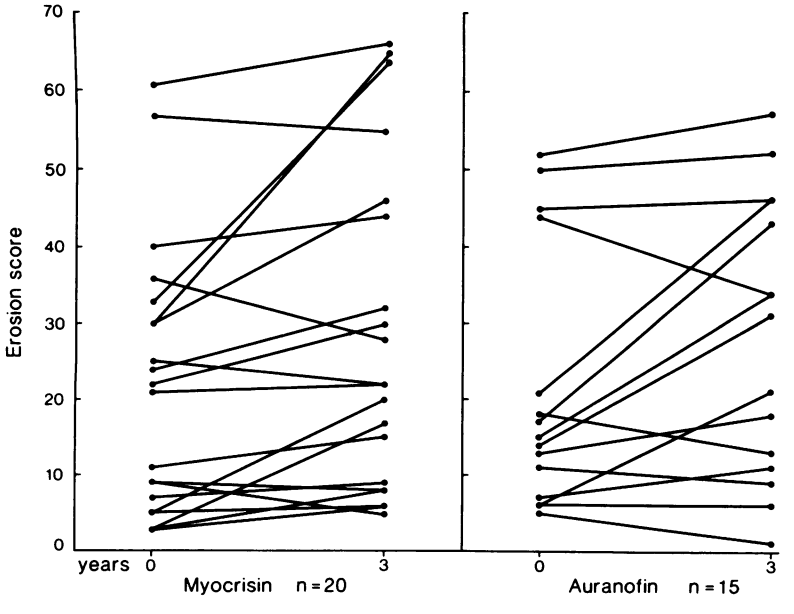

Fig. 1 *Changes in erosion score on hand x ray (modified Sharp method) in sodium aurothiomalate (Myocrisin) and auranofin groups.*

Table 4 *Changes in clinical and laboratory parameters in two patients who showed marked radiological progression, and one patient who showed little change over three years of sodium aurothiomalate therapy*

	Patient 1				*Patient 2*				*Patient 3*			
	0	*1 year*	*2 years*	*3 years*	*0*	*1 year*	*2 years*	*3 years*	*0*	*1 year*	*2 years*	*3 years*
Pain (mm)*	40	37	18	20	60	0	0	0	ND	0	1	1
Grip (mmHg)	64	79	76	86	107	116	118	118	67	71	71	75
Hb (g/dl)†	11·0	12·3	12·4	12·4	11·4	12·8	13·2	13·8	11·4	11·1	10·5	12·8
ESR (mm/1st h)	65	18	16	15	38	11	4	6	91	86	59	33
Platelets$\times 10^{-9}$/l	651	507	457	537	599	292	286	276	497	372	446	296
CRP (mg/l)‡	40	37	—	—	41	10	—	—	13	10	—	—
Erosion score	30	46	—	68	30	37	—	46	57	63	—	55

*Visual analogue—10 cm scale.
†SI conversion: g/dl×10=g/l.
‡CRP=C reactive protein.

TOXICITY

A summary of adverse events leading to withdrawal of therapy in the two treatment groups is shown in Table 2. One auranofin patient developed a sudden dramatic fall in white cell count after five weeks of therapy; he remained in remission throughout the three year period of follow up despite receiving no further second line drug, and required only minimal doses of non-steroidal anti-inflammatory drugs intermittently. All patients who developed diarrhoea on auranofin recovered completely on stopping therapy. No sustained toxicity was demonstrated with either drug.

The total treatment outcome over the three years by original treatment allocation is shown in Table 3. Six patients died during the three year follow up, two in each group. The causes appeared unrelated to therapy, though one patient originally allocated to sodium aurothiomalate was withdrawn from the study at 12 weeks because of cervical cord disease and the need for surgery, and active rheumatoid arthritis and vasculitis were largely responsible for his death. Of the 84 surviving patients, 82 still attend this centre; of the two who do not attend, one has moved and could not continue auranofin because supplies were not available at the time in the new area; the other (receiving sodium aurothiomalate) had gone into remission and had not felt it necessary to continue to attend a specialist clinic. The other sodium aurothiomalate patient who had received no further second line therapy but was still attending this centre had also gone into remission initially and had wished to stop therapy in order to try and fall pregnant; she has not, however, succeeded in doing so and is now being assessed for penicillamine therapy. Of the 82 patients still attending this centre, 77 are either on their original second line therapy or have had an alternative second line drug during the three year follow up period.

At the end of three years, of the 30 patients originally allocated to placebo, nine were still receiving auranofin, seven receiving sodium aurothiomalate, 10 had received alternative second line drugs, and two had died, one of whom had in the interim received a second line agent. Thus out of the 30, a total of 29 went on to receive a second line drug and their outcome was similar to those who received sodium aurothiomalate or auranofin in the first instance.

RADIOLOGY

Films at 0 and 3 years were available in 20 patients receiving sodium aurothiomalate and 15 receiving auranofin. The erosion scores on hand *x* ray for these patients are shown in Fig. 1. Deterioration was seen in 15 patients in the sodium aurothiomalate group, with four showing improvement and one no change. The median and range for the scores at 0 and 3 years were 22 (3–61) and 25 (5–69) respectively. In the auranofin patients 12 deteriorated, one improved, and two showed no change. The median and range at 0 and 3 years were 15 (5–52) and 31 (1–57) respectively. Both groups showed significant deterioration (Wilcoxon), and reduction of the ESR to less than 30 mm/1st h did not protect against progression of *x* ray change. Overall, only five patients in each group showed marked deterioration. No correlation with any clinical variable could be shown. Details of the clinical and laboratory scores versus erosions for two patients who deteriorated most markedly, and one who improved, while receiving sodium aurothiomalate are shown in Table 4.

Discussion

It is reassuring to note that the patients who were allocated to placebo within the study fared no worse than those who received an active drug from the

outset. It is true that the placebo group experienced a period of some months without beneficial effect, but this also occurred in 14 patients who received auranofin in the first instance. Thus if patients are meticulously followed up and all those who have received placebo are offered an active second line drug it would seem ethical to include such a group as necessary. It is of interest that this placebo group was clearly capable of showing a response to an active drug but that spontaneous improvement in placebo patients or indeed in the other patients who discontinued the active agents because of inefficacy or toxicity was not seen.

Overall, sodium aurothiomalate appears to be a more effective agent in the treatment of rheumatoid arthritis than auranofin, and the proportion of patients discontinuing the drug because of inefficacy is much higher with auranofin. The group of patients who found auranofin ineffective but then showed a response to sodium aurothiomalate lends further weight to the impression that auranofin is not such a powerful second line agent as injectable gold, but the numbers in this study are insufficient to test this hypothesis statistically. Nevertheless, a subgroup of patients treated with auranofin achieved a response very similar to that of a group treated with sodium aurothiomalate, and the toxicity was somewhat lower. Unfortunately, auranofin is not free of haematological side effects and this means that monitoring needs to be continuous with either drug. Thus the original hopes of a much safer form of gold have not been realised.

Radiological deterioration was seen in most patients over three years. Unfortunately, insufficient one year films were available to allow comment on possible slowing of progression after the first year of therapy (allowing for the expected deterioration in the initial months of treatment). This is a fault which cannot be rectified at this stage but is highly relevant to future study design. Other workers who have maintained more patients on placebo over one year have suggested that auranofin produces a slowing in radiological progression in rheumatoid arthritis.[9]

It is worthy of note that patients with severe rheumatoid arthritis such as those involved in this study continue to need active therapy over many years. When treating a disease such as rheumatoid arthritis it would appear that only those patients who die or emigrate are lost to the rheumatologist's load. The extent to which auranofin will lighten that load is unclear: this study suggests that beneficial effects will be demonstrable in a proportion of patients with rheumatoid arthritis but that careful monitoring remains mandatory.

Apendix 1

Table *Median (range) and p values (Wilcoxon) for patients receiving sodium aurothiomalate or auranofin first over one, two, and three years*

	Sodium aurothiomalate first (n=17)				*Auranofin first (n=7)*			
	0	*1 year*	*2 years*	*3 years*	*0*	*1 year*	*2 years*	*3 years*
Articular index	10 (6–40)	5 (0–37)	4·5 (0–25)	5·5 (0–21)	14 (11–17)	5 (0–12)	4·1 (0–12)	7·5 (3–10)
p		0·016	0·003	0·012		0·028	0·028	0·028
Grip (mmHg)	108 (55–358)	115 (58–300)	100 (65–300)	102 (57–300)	99 (60–253)	128 (60–300)	103 (55–300)	99 (47–240)
p		0·313	0·569	0·642		0·043	0·142	0·917
Morning stiffness (h)	1·16 (0–4·00)	0·46 (0–2·4)	0·48 (0–2·4)	0·38 (0–1·5)	1·83 (0·6–2·5)	0·50 (0–1·5)	0·4 (0–1·0)	0·5 (0–1·0)
p		0·041	0·013	0·011		0·028	0·028	0·028
Hb (g/dl)*	11·3 (9·2–15·4)	12·6 (9·7–15·4)	12·4 (9·7–15·7)	12·6 (9·0–15·7)	12·6 (10·4–15·3)	12·2 (10·4–15·4)	12·5 (10·6–15·5)	12·6 (10·8–15·2)
p		0·028	0·052	0·009		0·866	0·398	0·345
ESR (mm/1st h)	55 (4–102)	23 (1–86)	16 (1–68)	15 (1–46)	50 (8–81)	19 (2–52)	16 (3–59)	17 (1–58)
p		0·0001	0·001	0·0001		0·018	0·063	0·052
Platelets$\times 10^{-9}$/l	402 (282–651)	345 (196–507)	318 (206–470)	326 (222–641)	487 (181–653)	303 (170–521)	302 (198–429)	365 (172–505)
p		0·004	0·001	0·001		0·018	0·028	0·063

*SI conversion: g/dl×10=g/l.

Appendix 2

Table *Median (range) and p values (Wilcoxon) matched pairs signed rank test for patients receiving sodium aurothiomalate or auranofin first or after placebo*

	Sodium aurothiomalate first and after placebo (n=21)				*Auranofin first and after placebo (n=16)*			
	0	*1 year*	*2 years*	*3 years*	*0*	*1 year*	*2 years*	*3 years*
Articular index	10·5 (6–42)	9·8 (0–37)	8·5 (0–26)	8 (0–23)	17·2 (0–55)	7 (0–35)	8 (0–36)	9·7 (3–23)
p		0·011	0·002	0·009		0·001	0·001	0·002
Grip (mmHg)	108 (55–358)	117 (57–300)	118 (65–300)	106 (54–300)	93 (48–253)	105 (60–300)	94 (54–300)	98 (47–240)
p		0·263	0·305	0·421		0·162	0·211	0·307
Morning stiffness (h)	1·13 (0–24)	0·60 (0–24)	0·5 (0–24)	0·437 (0–1·5)	1·66 (1·0–24)	0·96 (0–24)	0·54 (0–4)	0·75 (0–2)
p		0·10	0·002	0·004		0·028	0·005	0·002
Hb (g/dl)*	11·3 (9·2–15·9)	12·8 (9·7–15·9)	12·4 (9·7–17)	12·7 (90–166)	12·8 (10·4–15·3)	13·0 (10·4–15·4)	12·7 (10·6–15·7)	12·9 (108–163)
p		0·005	0·011	0·002		0·875	0·205	0·096
ESR (mm/1st h)	55 (3–107)	18 (1–86)	16 (1–68)	15 (1–46)	45·5 (4–90)	24·5 (2–58)	17·5 (3–105)	24·5 (1–84)
p		0·000	0·000	0·000		0·002	0·036	0·014
Platelets$\times 10^{-9}$/l	402 (235–651)	345 (181–507)	318 (206–470)	326 (206–641)	383 (181–653)	303 (170–521)	316 (182–471)	365 (172–505)
p		0·003	0·001	0·001		0·030	0·019	0·109

*SI conversion: g/dl×10=g/l.

Appendix 3

Table *Group originally assigned to placebo (n=16) who then went on to receive either sodium aurothiomalate or auranofin and reached three years of therapy*

	0	*1 year*	*2 years*	*3 years*
Articular index	32 (0–55)	10·2 (0–35)	12·0 (0–36)	14·5 (4–23)
p		0·002	0·003	0·005
Grip (mmHg)	79 (48–160)	105 (57–158)	106 (54–155)	119 (54–171)
p		0·363	0·149	0·030
Morning stiffness (h)	3·93 (0·75–24)	1·04 (0–24)	0·92 (0–4)	0·75 (0–2·0)
p		0·028	0·005	0·004
Hb (g/dl)*	12·7 (9·1–15·9)	13·3 (10·6–15·9)	12·9 (11·0–17·0)	13·0 (10·9–16·7)
p		0·060	0·025	0·008
ESR (mm/1st h)	46 (3–127)	24 (7–58)	17·2 (1–105)	24·5 (1–84)
p		0·005	0·018	0·006
Platelets$\times 10^{-9}$/l	360 (235–618)	290 (181–466)	316 (182–471)	356 (208–415)
p		0·191	0·118	0·173

*SI conversion: g/dl×10=g/l.

Appendix 4

Table *Sodium aurothiomalate after auranofin (n=8)*

	0	*1 year*	*2 years*	*3 years*
Articular index	15·5 (6–45)	6 (0–16)	6·5 (0–17)	8·5 (2–11)
p		0·142	0·116	0·068
Grip (mmHg)	79·5 (61–136)	104 (70–135)	106 (96–126)	125 (99–130)
p		0·046	0·046	0·080
Morning stiffness (h)	1·25 (0·50–24)	0·60 (0–3)	0·25 (0–1)	0·5 (0–1)
p		0·173	0·028	0·068
Hb (g/dl)*	10·1 (9·1–13·4)	12·2 (10·1–14·3)	13·5 (10·1–14·2)	12·9 (10·4–14)
p		0·028	0·043	0·018
ESR (mm/1st h)	80·5 (28–127)	35 (7–82)	23 (7–85)	25·5 (5–81)
p		0·018	0·018	0·012
Platelets$\times 10^{-9}$/l	373 (294–523)	312 (211–355)	278 (235–395)	265 (239–392)
p		0·063	0·063	0·063

*SI conversion: g/dl×10=g/l.

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