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Outcome of attempts to treat rheumatoid arthritis with gold, penicillamine, sulphasalazine, or dapsone

K. A. GRINDULIS AND B. McCONKEY

From the Division of Rheumatology, Department of Medicine, Dudley Road Hospital, Birmingham B18 7QH

SUMMARY The outcome of attempts to continue treatment indefinitely with either gold, penicillamine, sulphasalazine, or dapsone was studied in 240 patients with rheumatoid arthritis (RA). The usual reason for discontinuing treatment was the occurrence of an adverse effect. This led to 53% of patients stopping gold, 33% sulphasalazine, 32% penicillamine, and 17% dapsone. The next most frequent reason was that the drug was ineffective, leading to discontinuation in 37% of patients having dapsone, 24% sulphasalazine, 19% pencillamine, and 16% gold. Other reasons for stopping treatment were infrequent. The high discontinuation rate of these drugs over 2 years in part accounts for the conflict of opinion on whether they can alter the course of RA; their efficacy must to a large extent be governed by their acceptibility.

In rheumatoid arthritis (RA) the effects of 'remission-inducing drugs' (RIDs) have often been studied over periods of 6 to 12 months. In this time some drugs, notably gold[1] and penicillamine,[2] influence the disease favourably. Less is known about the effects of more prolonged treatment. Gold and penicillamine, for example, have seldom been studied for periods exceeding 18 months and rarely compared with each other or with sulphasalazine (SAS)[3] or dapsone.[4] We describe a comparison between these 4 drugs with emphasis on how long treatment could be continued.

Patients and methods

We studied 240 outpatients, 179 women and 61 men, with classical or definite RA (ARA criteria). They comprised all those treated by us with gold, penicillamine, SAS, or dapsone for the first time between January 1973 and December 1978. Seventy-four patients started gold, 43 penicillamine, 121 SAS, and 98 dapsone. Approximately half the patients received more than one of these drugs during the study period. All patients could have completed 2 years' continuous therapy with one of the 4 drugs at the time of analysis as it was our intention to continue each indefinitely so long as clinical and laboratory results were satisfactory.

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Correspondence to Dr B. McConkey, Dudley Road Hospital, Birmingham B18 7QH.

Gold, penicillamine, SAS, and dapsone were not given in a particular order. Patients took nonsteroid anti-inflammatory drugs in addition to these RIDs. Adrenal corticosteroids (usually prednisolone 2·5–7·5 mg daily) were not commenced at the same time as a RID, except in one patient taking penicillamine, and the dose seldom changed.

Breaks in treatment of less than 2 weeks were ignored; resumption of treatment after a longer interval was considered a second course and excluded from this study.

Gold was given as intramuscular 'Myocrisin' (sodium aurothiomalate) 50 mg weekly for 20 weeks, then 50 mg fortnightly; penicillamine dose was 125 mg daily for variable periods, increasing by 125 mg increments to a maximum of 750 mg daily; SAS dose was 0·5 g daily, increasing by 0·5 g increments at weekly intervals to a maintenance dose of 2 g daily; dapsone dose was 50 mg daily for 1 week, then 100 mg daily.

Treatment duration was calculated to the nearest month.

Results

The groups of patients matched in sex distribution, age, duration of RA, and the proportion seropositive (Table 1). However, the mean ESR and serum C-reactive protein (CRP) were higher in patients treated with gold or penicillamine than those taking SAS or dapsone (Table 1). Patients receiving penicil-

Table 1 *Pretreatment patient details*

	No. of patients	*Sex*		*Mean age, yr (range)*	*Mean duration RA, yr (range)*	*Seropositive (RW>1/16) %*	*Mean serum CRP mg/l (range)*	*Mean ESR mm/h (range)*	*Concomitant corticosteroids %*
		M	*F (%)*						
Gold	74	23	51 (69)	54·3 (13–75)	5·8 (0·5–24)	70	65·4 (4–350)	62·4 (8–160)	15
Penicillamine	43	10	33 (77)	54·3 (22–76)	8·3 (0·5–36)	74	63·1 (0–340)	62·8 (9–140)	44
Sulphasalazine	121	29	92 (76)	52·0 (17–77)	7·2 (0·5–41)	64	44·7 (0–260)	51·8 (3–142)	15
Dapsone	98	24	24 (76)	54·0 (22–76)	7·5 (1–31)	69	48·4 (0–230)	53·1 (6–180)	29

lamine or dapsone were taking corticosteroids more often than those having gold or SAS.

Approximately half the patients who had started penicillamine, SAS, or dapsone, and three-quarters of those who started gold, discontinued treatment within the first year (Table 2). After 2 years there were few patients left in any treatment group.

The reasons for treatment termination were different for each of the four drugs.

GOLD

The commonest reason for discontinuing gold (Table 3) was toxicity in 39 patients (53%). Rash was the most frequent adverse reaction and, like most other unwanted effects, usually occurred within the first 12 months. Eight patients had proteinuria and 3 thrombocytopenia. A full account of the adverse reactions with this and the other 3 drugs is shown in Table 4.

Twelve patients (16%) discontinued gold because they had not improved and 2 patients because their disease relapsed following initial improvement.

Table 2 *Percentage of patients stopping treatment with gold, penicillamine, sulphasalazine, or dapsone*

	% Patients stopping treatment (months)			
	6	*12*	*18*	*24*
Gold (n=74)	50	76	81	86
Penicillamine (n=43)	36	48	62	69
Sulphasalazine (n=121)	42	53	68	73
Dapsone (n=98)	41	54	78	83

PENICILLAMINE

Adverse effects in 14 patients (32%) were the commonest reason for discontinuing penicillamine. Gastrointestinal upset, including loss of taste and dysgeusia, was the usual reason. Two patients (4%) developed the nephrotic syndrome and one thrombocytopenia. Rashes were rare.

Eight patients (19%) discontinued penicillamine within 2 years because they were no better and 3 patients (7%) because of a relapse of their disease.

SULPHASALAZINE

The commonest reason for discontinuing treatment was an adverse effect in 40 (33%) patients. The most frequent problems were nausea, malaise, dyspepsia, and dizziness, usually occurring in the first 2 months of treatment; only 2 patients discontinued SAS for these reasons after 6 months. Five patients had a rash, and one patient had neutropenia but recovered within 6 weeks.

Inadequate benefit in 29 patients (24%) was the next most frequent reason for discontinuation. Fourteen patients (11%) stopped treatment because their

Table 3 *Reasons for discontinuing gold, penicillamine, sulphasalazine, and dapsone within 2 years*

	% Discontinuing because of:				
	Adverse effects	*Dubious or no benefit*	*Disease relapse*	*Disease improved*	*Miscellaneous*
Gold (n=74)	53	16	3	0	14
Penicillamine (n=43)	32	19	7	0	11
Sulphasalazine (n=121)	33	24	11	0	5
Dapsone (n=98)	17	37	11	12	6

Table 4 *Details of adverse reactions*

Gold (74 patients)			*Penicillamine (43 patients)*		
Rash		20	Gastrointestinal upset (incl. taste abnormalities)		7
Proteinuria (incl. 1 nephrotic syndrome)		8	Proteinuria		2
Thrombocytopaenia		3	Rash		1
Other:			Thrombocytopaenia		1
Alopecia	2		Other:		
Eosinophilia	1		Malaise/nausea	2	
Dyspepsia	1		Vitiligo	1	
Colitis	1				3
Sore throat	1				
Dry skin	1				
Severe pain at injection site	1				
		8			
Total		39 (63%)	Total		14 (32%)
Sulphasalazine (121 patients)			*Dapsone (98 patients)*		
Nausea/malaise± dyspepsia		27	Rash		3
Rash		5	Gastrointestinal upset		2
Neutropaenia		1	Anaemia		1
Other:			Pallor		1
Dizzy/light-headed	2		?Anaemia related, e.g.		
Depression	2		Light-headedness		
Headache	1		Malaise		
Folate-deficiency anaemia	1		Blurred vision		6
*Psychosis	1		Other:		
		7	Depression	1	
			Insomnia	1	
			*Vaginitis	1	
			*Leg ulcer	1	
					4
Total		40 (33%)	Total		17 (17%)

*Doubtfully related to drug.

RA relapsed, each after remissions lasting at least 8 months.

DAPSONE

The most frequent reason for stopping dapsone, in 36 patients (37%), was that it had proved ineffective. Seventeen patients (17%) stopped the drug because of adverse reactions. No side effect was predominant, and only one patient stopped the drug because of anaemia. Marked pallor, despite modest (<2 g/dl) falls in haemoglobin, was a contributory factor in 6 patients.

Discussion

The criteria for treatment with each drug were the same.[5] Thus we expected the groups of patients to be comparable, and they matched in many respects. However, the mean ESR and serum CRP before treatment suggest we had inadvertently selected patients with more active disease for treatment with gold or penicillamine. We cannot say how much these initial differences might have influenced the results. More active disease might be more resistant to treatment but, conversely, may have a greater capacity for improvement.

When all treatments are considered together the results are discouraging. Despite our intention to continue each drug indefinitely so long as clinical and laboratory evidence suggested it was beneficial, only about half the patients were still receiving their drug at a year and a fifth at 2 years.

The principal problems were adverse effects in a third of patients taking penicillamine or SAS and in half of those taking gold. Dapsone differed from the other 3 drugs in that adverse effects were less important, and failure to derive benefit was the main reason for discontinuing treatment. With so few patients able to continue treatment for periods exceeding a year it is not surprising that difficulty has been encountered in proving these drugs have a disease modifying effect.

Could the performances of these drugs be improved? We doubt from our more recent experience[6] whether the performance of penicillamine could have

been bettered; a disturbing feature of this drug was the occurrence of potentially life-threatening adverse effects. It is also hard to see how the outcome of treatment with dapsone could be improved except perhaps in combination with other drugs. Its superiority over placebo has, however, been established,[7] and in view of its relative safety it is worth retaining as a therapeutic possibility despite the small proportion of patients likely to benefit.

Many of the patients who discontinued gold did so because of minor rashes or slight proteinuria; with hindsight, and in view of the recent study by Newton *et al.*,[8] a bolder policy to continue treatment might have been better. However, as with penicillamine, dangerous adverse effects did occur, and how much the results could have been improved is uncertain.

In contrast to gold and penicillamine adverse effects of SAS, though frequent, were seldom dangerous; to date we have had only one such, neutropenia, with subsequent full recovery. Patients with RA appear to tolerate SAS less well than patients with ulcerative colitis; we interpret their symptoms as a central effect of the drug or its sulphapyridine moiety. Such symptoms often occurred in the first month of treatment, and it is possible that a different dose regimen would reduce the problem.

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