

Long term treatment of rheumatoid arthritis with sulphasalazine, gold, or penicillamine: a comparison using life-table methods

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SUMMARY Life-table analysis was applied to the records of 317 patients with rheumatoid arthritis (RA) treated with sulphasalazine (SAS), 201 treated with sodium aurothiomalate (gold), and 163 with penicillamine. They comprised all those treated in our department with these drugs between January 1973 and July 1984. Risks of treatment termination for all reasons were similar for each drug at five years (gold 92%, penicillamine 83%, SAS 81%). The risk of treatment termination due to inefficacy was less for gold (29.5%) than for penicillamine (38.1%) or sulphasalazine (41.2%). Adverse effects, however, led to withdrawal of gold in 57%, penicillamine in 41.2%, and SAS in 37%; the most effective drugs appeared most toxic. Serious adverse effects were much more common in association with gold (17.4%) and penicillamine (12.3%) than with SAS (1.6%). Sulphasalazine appears as well tolerated over long periods in RA as gold or penicillamine and is associated with fewer serious adverse effects; of these drugs, it might therefore be considered the agent of first choice.

Many patients with rheumatoid arthritis (RA) need second line drugs but few continue to take them for the long periods necessary to make a significant impact on the disease.¹ The two drugs most often studied in this respect have been gold and penicillamine. Sulphasalazine (SAS) has also been found to have the properties associated with second line drugs.²⁻⁴ There have been two studies of long term treatment with SAS, one a comparison with gold, penicillamine and dapsone over two years⁵ and the other a comparison with gold over three and a half years.⁶ Both studies suggested that SAS shares with gold and penicillamine the problems of premature treatment withdrawal, though possibly to a lesser degree and for different reasons.

In this study we examined the incidence, timing, and reasons for treatment termination in patients with RA treated with gold, penicillamine, or SAS for up to five years.

Patients and methods

We reviewed the records of all patients who had received SAS, penicillamine, or gold in the unit for the first time between January 1973 and July 1984. Three hundred and seventeen patients (244 women, 73 men) had received SAS, 163 (130 women, 33 men) penicillamine, and 201 (140 women, 61 men) gold. Each patient had definite or classical RA (American Rheumatism Association criteria), and the criteria for initiating treatment with a disease modifying drug were the same throughout.⁷ Clinical details are shown in Table 1. χ^2 Analysis with Yates's correction was applied to test for differences in sex, rheumatoid factor positivity, concurrent corticosteroid therapy, and the proportion of patients receiving prior treatment with other disease modifying therapy. Ranked analysis of variance was used to compare age, duration of disease at onset of therapy, initial serum C reactive protein, and erythrocyte sedimentation rate (ESR) since these data were not normally distributed.

Sulphasalazine, enteric coated, was started at a dose of 0.5 g daily, increasing by 0.5 g weekly to a maintenance of 2 g daily in most patients, though higher doses (2.5-3.0 g) were used in some. Initially,

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Table 1 Clinical details and pretreatment laboratory data

Treatment group	No	Sex (%F)	Age (years)	Disease duration (years)	Concurrent corticosteroid therapy (%)	Serum† C-reactive protein (mg/l)	ESR (mm/h)	RF >1/40† (%)
SAS	317	77	53 (45-62.5)‡	5 (2-10)	21.5*	37 (19-71)	45 (30-68)	74.8
Penicillamine	163	79.8	55 (47-64)	7 (3-12)	28.8	38 (18-66.5)	51 (32-71.5)	81.5*
Gold	201	69.7*	54 (44-61)	4 (1-8)**	29.4	52 (28-104)**	51 (32.5-70.5)	72.6

*Significant $p < 0.05$ (χ^2 test); ** $p < 0.01$ (ranked analysis of variance).

†Serum C reactive protein (CRP) by radial immunodiffusion; rheumatoid factor (RF) by RA latex method.

‡Values are median (interquartile range).

the penicillamine dose was 125 mg daily, increasing by 125 mg increments at two to three month intervals to a maximum of 750 mg daily; maintenance was usually between 375 and 500 mg daily. Sodium aurothiomalate was given at a dose of 50 mg weekly for 20 weeks and then 50 mg on alternate weeks for approximately one year; thereafter 50 mg monthly. All patients were also treated with a non-steroidal anti-inflammatory drug (NSAID) and in some cases (Table 1) with corticosteroids, usually prednisolone 7.5 mg or less daily.

Treatment details were recorded on a card system independent of case notes, thus facilitating information retrieval. For all patients previous disease modifying therapy was noted, and those who were not receiving either gold, penicillamine, or sulphasalazine for the first time were excluded. When treatment was terminated a note was made of the date and reason by the attending doctor. Clinical assessment was at six to 12 week intervals and by 'clinical score'; each patient was given an arbitrary pretreatment score of 100 and at each subsequent visit the score was adjusted by plus or minus 2 or 4 depending on the response to the question 'do you feel better, worse, or the same compared with your last visit?' This method appears to reflect other clinical assessments, including articular index, visual analogue pain scale, and grip strength.⁸

We used the ESR and serum C reactive protein level as laboratory tests of treatment efficacy. Urine was tested for blood and protein before each gold injection, weekly in patients receiving penicillamine and at each clinic visit in those receiving SAS. Treatment was discontinued if proteinuria was 2 g or more in 24 hours or associated with oedema plus hypoalbuminaemia. Full blood counts, including platelets, were done every six weeks in patients receiving gold or penicillamine and at clinic visits in those receiving SAS. A confirmed platelet count of $100 \times 10^9/l$ or less was regarded as thrombocytopenia.

Standard methods of life-table analysis⁹ were applied to the three groups. Instead of death, treatment termination was taken as the end point. For those patients who died for unrelated reasons while receiving treatment or were lost to follow up the observation time was censored; they were not included in the population at risk from then on. Once generated, the total termination incidence curves were partitioned by the reasons for treatment termination.

Each instance of treatment termination was assigned one main reason: (a) Treatment failure: patients either had no benefit at any time or their disease relapsed during therapy. (b) Adverse effects: major categories were cutaneous reactions,

Table 2 Number and proportion (%) of patients receiving therapy with sulphasalazine, gold, or penicillamine as the first to fifth disease modifying drug

	1st drug n (%)	2nd drug n (%)	3rd drug n (%)	4th drug n (%)	5th drug n (%)	Total
Sulphasalazine	189 (59.6)	85 (26.8)	32 (10.1)	9 (2.8)	2 (0.6)	317
Gold	114 (56.7)	65 (32.3)	19 (9.5)	1 (0.5)	2 (1.0)	201
Penicillamine*	48 (29.4)	49 (30.1)	49 (30.1)	13 (8)	4 (2.5)	163

*The penicillamine group was significantly different from the two remaining groups ($p < 0.01$, χ^2 test).

loss or alteration of taste, 'central' (nausea, vomiting, dizziness, malaise), gastrointestinal (abdominal pain, diarrhoea), renal (haematuria, proteinuria > 2 g/day, nephrotic syndrome), and haematological (neutropenia, thrombocytopenia, anaemia, hypogammaglobulinaemia). Other adverse effects were classified as 'miscellaneous'. (c) Improvement: patients were judged to have improved sufficiently to warrant withdrawal of therapy.

Results

The clinical details of the three groups were similar (Table 1). There was a small but significant difference between the proportion of men treated with gold and penicillamine ($p < 0.05$), and the penicillamine group contained significantly more seroposi-

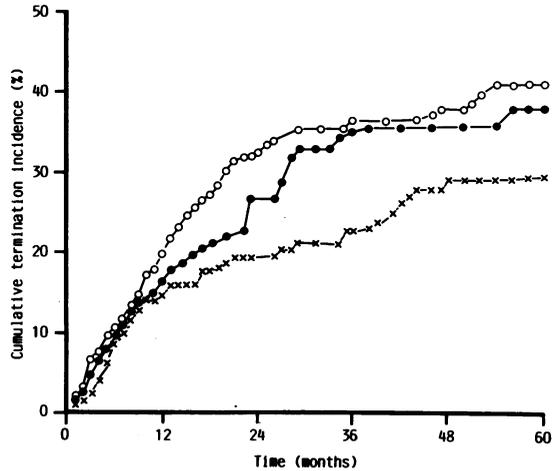


Fig. 2 Treatment termination due to inefficacy (gold, penicillamine, and sulphasalazine) over five years (x gold, ● penicillamine, ○ sulphasalazine).

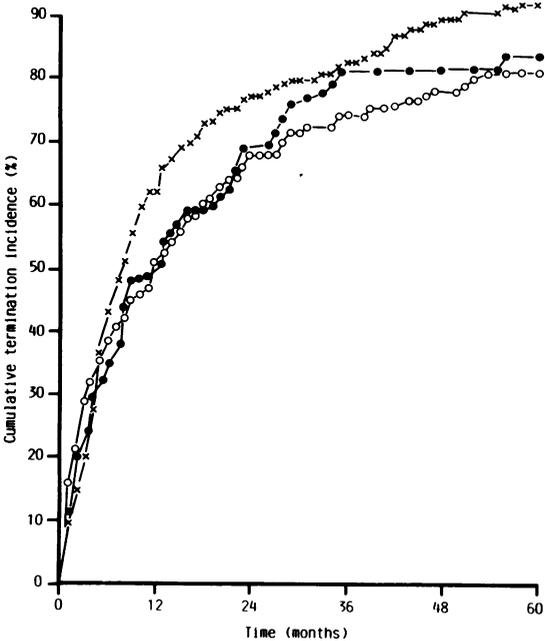


Fig. 1 Total treatment termination for three drugs (gold, penicillamine, and sulphasalazine) over five years (x gold, ● penicillamine, ○ sulphasalazine).

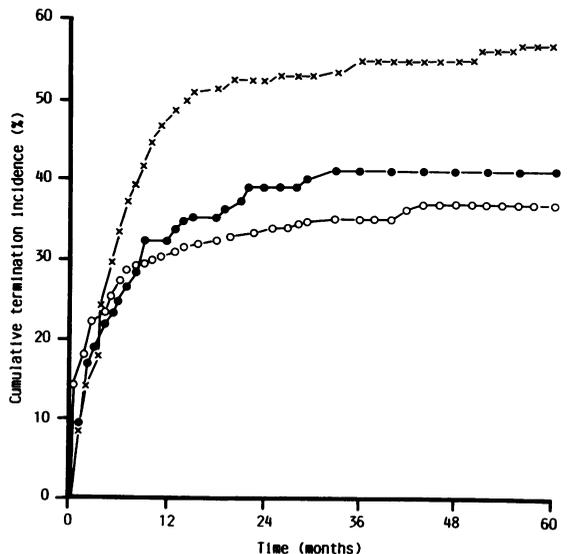


Fig. 3 Treatment termination incidence due to all adverse effects (gold, penicillamine, and sulphasalazine) over five years (x gold, ● penicillamine, ○ sulphasalazine).

tive patients than those receiving gold ($p < 0.05$). Patients treated with gold had had RA for a shorter time than those treated with penicillamine ($p < 0.01$) and sulphasalazine ($p < 0.01$). Fewer patients treated with SAS were receiving concurrent corticosteroid therapy ($p < 0.05$). Ranked analysis of variance showed no significant differences between the three groups for ESR, though serum CRP in the gold group was significantly higher than in the two other groups ($p < 0.01$). The frequency of previous disease modifying therapy with either gold, sulphasalazine, penicillamine, dapsone, levamisole, or chloroquine was assessed for each group (Table 2). With SAS and gold similar proportions of patients had received this therapy as the first to fifth disease modifying drug. Patients treated with penicillamine had more frequently received previous disease modifying therapy before inclusion in the study ($p < 0.01$).

Fig. 1 shows the incidence of treatment termination for all reasons for the three drugs. By six months 39% patients taking SAS, 36% penicillamine, and 43% gold had stopped treatment. At two years the proportions were 68% with SAS, 69% penicillamine, and 77% gold. The curves become flatter thereafter and between two and five years only a further 13% patients stopped SAS, 14% penicillamine, and 15% gold. Thus by five years 81% patients had stopped SAS, 83% penicillamine, and 92% gold. The median time of treatment termination (when 50% of those who were to stop treatment within five years had done so) was six to seven months for SAS and gold and seven to eight months for penicillamine.

Fig. 2 shows termination incidence curves for treatment failure. By two years 33% patients had stopped SAS, 27% penicillamine, and 20% gold. Between two and five years, withdrawals due to treatment failure increased more slowly and there was no change in the relative order of the drugs.

Small but roughly equal proportions of patients (gold 5%, penicillamine 4%, SAS 3%) stopped treatment with each drug within five years because of improvement.

Fig. 3 shows treatment termination due to adverse effects. Relatively few adverse reactions led to withdrawal of treatment later than 24 months; by five years 37% of patients had stopped SAS, 41.2% penicillamine, and 57% gold. In patients taking SAS the curve for treatment termination was steepest during the first six months (Fig. 3) largely because of 'central' side effects (nausea, dizziness, headache, and vomiting); the median time for their development was within one month (Fig. 4). Gastrointestinal side effects accounted for a smaller proportion and their median time of occurrence was later,

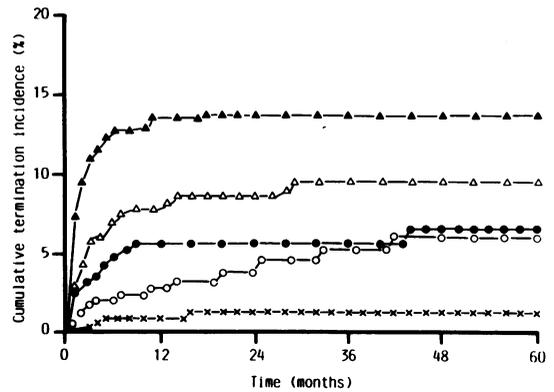


Fig. 4 Treatment termination incidence due to type of adverse effect for sulphasalazine (▲ central, ● cutaneous, △ gastrointestinal, ○ miscellaneous, × haematological).

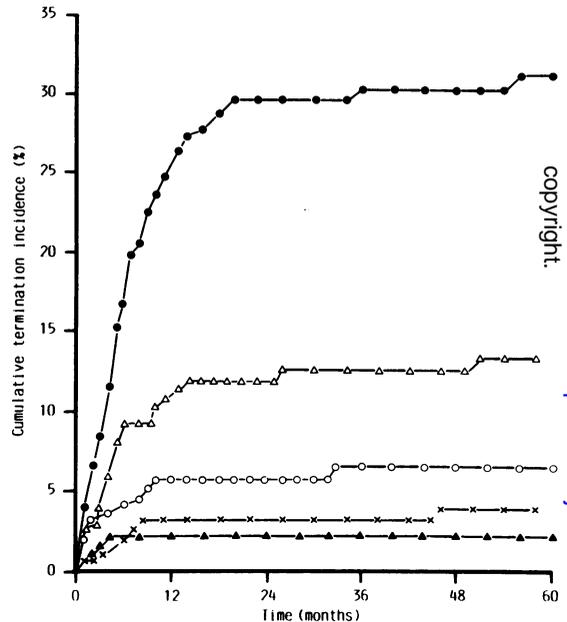


Fig. 5 Treatment termination incidence due to type of adverse effect for gold (▲ central, ● cutaneous, △ renal, ○ miscellaneous, × haematological).

between two and three months. Haematological adverse effects led to withdrawal of 1.4% patients. With gold (Fig. 5) the most frequent adverse effects leading to withdrawal were cutaneous reactions and affected 31.2% patients by five years. Renal side effects of gold (proteinuria or haematuria, or both) led to withdrawal in 13.5% patients and haematological side effects in 3.9%. With penicillamine (Fig. 6) renal adverse effects led to withdrawal of 10.5%

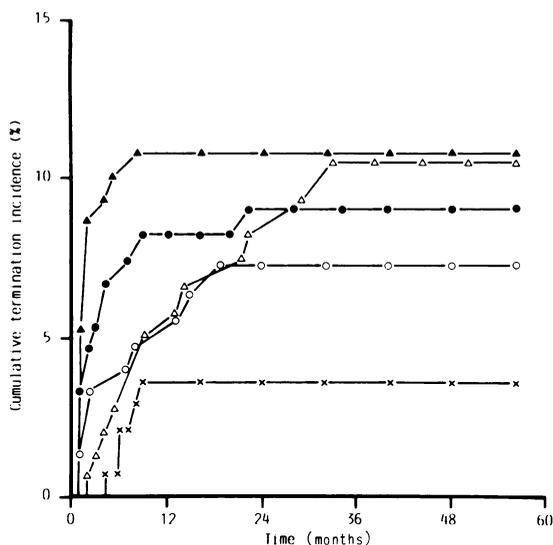


Fig. 6 Treatment termination incidence due to type of adverse effect for penicillamine (▲ taste loss, ● cutaneous, △ renal, ○ miscellaneous, × haematological).

patients, taste loss 10.8%, and cutaneous reactions 9%. Haematological adverse effects caused 3.6% to stop penicillamine.

To categorise an adverse effect as 'serious' is arbitrary, but we considered that haematological, renal, pulmonary, and generalised cutaneous reactions represented unreasonable additional risks to the patient and they are summarised in Table 3. With SAS five serious adverse reactions (four haematological, one cutaneous) were encountered during treatment of 317 patients. One patient developed neutropenia (total white cell count $2.4 \times 10^9/l$ with less than 11% polymorphs), but recovery occurred within eight days of stopping treatment. Three patients had severe anaemia. In two it was megaloblastic and haemoglobin fell to 7.7 g/dl (77 g/l) and 6.9 g/dl (69 g/l) respectively. In the first patient serum folate was $<1.0 \mu g/l$ (normal

range 3–20) and vitamin B₁₂ normal; in the second serum vitamin B₁₂ was 87 ng/l (normal range 150–1000) and folate normal. Investigations did not provide evidence of malabsorption or pernicious anaemia, and the anaemia was attributed to SAS in each case. The third case of anaemia (Hb 5.3 g/dl (53 g/l)) was normocytic, hypochromic with normal serum iron, vitamin B₁₂, and folate and responded to transfusion; this may have been a sideroblastic anaemia. One severe generalised skin eruption occurred with SAS.

More adverse reactions were classified as serious with gold and penicillamine than with SAS (Table 3). Predominant were proteinuria and haematuria, and four patients receiving gold and three receiving penicillamine developed a nephrotic syndrome. Five cases of thrombocytopenia were encountered during gold treatment and five during penicillamine therapy. One patient receiving gold developed hypogammaglobulinaemia, four had exfoliative dermatitis, one interstitial pneumonitis, and one an anaphylactic reaction to injection of the first dose.

Discussion

Several factors influenced our choice of particular disease modifying therapy. During the early part of the study gold was usually our drug of first choice. Later, we more often chose SAS since we had evidence that this drug had a more favourable safety profile. These factors explain in part the finding that patients treated with penicillamine had more frequently received previous therapy with other disease modifying drugs, and it is possible that this might have had an unfavourable effect on treatment outcome. A substantial number of patients in each group, however, had already had some other disease modifying drug (Table 2). The differences between groups with respect to sex, disease duration, and seropositivity seem to us unlikely to have influenced drug tolerance. Although more patients treated with gold and penicillamine were receiving therapy with corticosteroids than those treated with sulphasala-

Table 3 Serious adverse effects during sulphasalazine, penicillamine, and gold therapy

Drug	Haematological	Cutaneous	Renal	Miscellaneous	Total
Sulphasalazine (n=317)	Severe anaemia (3) Neutropenia (1)	Generalised cutaneous eruption (1)	—	—	5
Penicillamine (n=163)	Thrombocytopenia (5)	—	Proteinuria + haematuria (12) Nephrotic syndrome (3)	—	20
Gold (n=201)	Thrombocytopenia (5) Hypogamma- globulinaemia (1)	Exfoliative dermatitis (4)	Proteinuria + haematuria (19) Nephrotic syndrome (4)	Interstitial pneumonitis (1) Anaphylaxis (1)	35

zine, steroid doses were small and were not changed. The effect of low dose corticosteroids on treatment outcome is unknown, though in one study steroids did not influence the rate of gold withdrawal.¹⁰

Comparisons of drugs also depend on uniform methods of assessing their efficacy. We used one subjective and two objective criteria: the 'clinical score', ESR, and serum C reactive protein. These three assessments together compare favourably with other 'process' measurements of rheumatoid activity.⁸

Life-table analysis as a method of displaying data has been explored by Richter *et al*,¹¹ and we felt it to be the most appropriate means of depicting the reasons for treatment termination with each drug since it displays graphically both the time and cumulative importance of each. It also enabled us to include greater numbers in the analyses since we were not restricted to the inclusion of patients who could have completed a certain length of treatment, a device necessary in an 'intention to treat' analysis.

Treatment termination rates with each drug were similar and comparable with those of most other studies,¹ which report approximately 50% treatment withdrawal by 12 months due mainly to adverse reactions. In the only previous analysis of gold using life-table methods Richter *et al* found that 50% of 93 patients had stopped treatment by 5 years.¹¹ This result is much better than that achieved in other studies and our own (92% withdrawal at five years), but Richter *et al* included only patients who had already received 1 g of gold (20 weeks' treatment) at the time of entry.

The three drugs were infrequently stopped because they were effective and miscellaneous reasons accounted for no more than 6–7% of terminations with each by five years. There were thus two main reasons for withdrawal: treatment was ineffective or intolerable adverse effects occurred. Over five years 29.5% of patients discontinued gold owing to inefficacy of the drug compared with 38% of those receiving penicillamine and 41% receiving SAS. Thus gold appears superior to the other drugs. The data on adverse effects, however, place them in the converse order; unwanted reactions were more common with gold than with SAS or penicillamine (gold 57%; penicillamine 41%; SAS 37%). Severe adverse effects were far more common with gold and penicillamine than with SAS; only patients receiving gold or penicillamine developed proteinuria or thrombocytopenia, though thrombocytopenia is known to be an occasional hazard of SAS therapy; exfoliative dermatitis also occurred only during treatment with gold, though a severe generalised skin eruption was encountered in one patient

receiving SAS. Haematological adverse effects did occur with SAS; there was one case of neutropenia and three of severe anaemia. In one patient the anaemia may have been due to folate deficiency. SAS is known to stress folate metabolism.^{12 13} In a prospective study, however, SAS did not appear to cause folate deficiency in rheumatoid patients. The causes of anaemia in the other two patients are uncertain and their relation to SAS in doubt.

For both gold and penicillamine the frequency and type of adverse reactions are in accord with general experience.^{10 15–21} Our finding of 10.8% termination of penicillamine for dysgeusia is higher than found in most previous reports, though the incidence of this complication is up to 33%.²¹ Our patients were told that taste alteration or loss was likely to be temporary but many would not tolerate the symptom.

No previous studies have considered the treatment of RA with SAS for periods up to five years. In the only other long term study 49% patients stopped taking SAS by two years⁶; our figure for the same period was 68%. We cannot satisfactorily explain the difference, but in both studies withdrawal was due mainly to nausea, dizziness, and dyspepsia. It is uncertain whether these are central effects of central sulphapyridine or local gastric intolerance, or both. Gastrointestinal side effects of SAS appear to be more common in RA than in inflammatory bowel disease²² perhaps because of the additive effects of NSAIDs in RA and because of difficulty in distinguishing some drug and disease effects in inflammatory bowel disease.

We have investigated whether our performance with these three drugs has improved by comparison with our previously published figures relating to 1973–78. For penicillamine our policy has changed little since 1978 and the present figures have altered little (48% termination after one year and 69% after two years). Figures for gold have improved slightly over the same period from 76% to 64% at one year and from 86% to 78% at two years, reflecting our improved experience with the drug. For sulphasalazine we have treated 196 patients since the 1977 analysis; the one year figures have improved from 53% to 49.4% and those at two years from 73% to 65.8%. The lack of major improvement in drug tolerance may be explained by the fact that we rapidly learnt that gradual increments in dose were necessary for optimum compliance.

Could these results be improved? Before comparisons with other studies are made it must be realised that treatment termination rates are often better under formal trial protocols²⁰ because there appears to be a higher threshold for treatment withdrawal than in routine clinical practice. Im-

improvements with gold might be made with flexible dose schemes²³ and by adopting low dose regimens to reintroduce therapy after cutaneous reactions.²⁴ Penicillamine is less toxic at low doses¹⁹ but may also be less potent. With SAS a dose higher than our usual 2 g daily might be better but probably at the cost of increased side effects.²⁵ Lower doses remain to be tested and might, if effective, be associated with less adverse effects. It has been suggested that antiemetics might help nausea during SAS therapy,²⁵ but our experience has not been encouraging. The assessment of acetylator phenotype may help to reduce toxicity by permitting lower doses in slow acetylators, and desensitisation after SAS induced rashes is simple and effective.²⁶ It is, however, unlikely that any of these measures will allow major improvements in the performance of these drugs.

The data show that there is little difference between SAS, gold, and penicillamine when judged either by the frequency of treatment termination due to adverse effects or by inefficacy within five years. Since sulphasalazine was least often associated with serious adverse effects it is now our first choice when initiating disease modifying therapy for RA.

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