Outcome of second line therapy in rheumatoid arthritis

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Abstract

Objectives—To study the functional outcome in patients with rheumatoid arthritis (RA) who tolerate second line drug therapy for five years.

Methods—We enrolled into prospective controlled trials, 190 patients with rheumatoid arthritis who tolerated 'disease modifying' antirheumatic drug therapy for five years. Demographic data were recorded. Disease activity was measured every six months for two years and annually thereafter, using clinical and laboratory variables. Patient function was measured using the modified Health Assessment Questionnaire. The change in each variable was analysed using paired Wilcoxon tests.

Results—Patient function improved significantly compared with baseline. The improvement was maximal after one to two years, and thereafter function started to decline slowly. After five years of treatment the patients' function was still significantly better than before treatment had started. There were highly significant improvements in all variables measured to assess disease activity, which remained well controlled throughout the five year period.

Conclusion—Good control of disease activity and improved function can be achieved long term in approximately 30% of RA patients treated with injectable gold, sulphasalazine or penicillamine.

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Remarkably little is known about the impact of drug therapy on the long term functional outcome of patients with rheumatoid arthritis (RA). In the short and medium term, disease modifying antirheumatic drugs (DMARDs) have been shown to reduce the disease activity of RA,¹⁻³ but the crucial question—whether long term DMARD therapy has a beneficial effect on long term functional outcome—remains unanswered. Many patients do have declining function,⁴ despite therapy, but it is unknown if their disease may have progressed faster without the use of DMARDs. This is an extremely difficult problem to study;⁵ long term placebo controlled trials are not acceptable because (a) notwithstanding any effect on disease progression, the use of DMARD therapy does lead to amelioration of symptoms in most patients; (b) long term

controlled studies are blighted by the poor side effect profile of the available DMARDs, such that a minority of patients continue on any drug for as long as five years;⁶ (c) the 'natural history' of patient function in the absence of drug therapy is not known. Function is likely to decline in the long term for reasons unrelated to the rheumatoid disease process, including ageing and comorbidity.

Sulphasalazine (SASP), penicillamine (PCM), and intramuscular gold sodium thiomalate (gold) are used in the treatment of rheumatoid arthritis. Their efficacy in controlling disease activity has been established in double blind, placebo controlled trials.¹⁻³ There is some evidence that gold¹ and SASP⁷ also slow radiological progression, but very little is known about functional outcome in patients treated with these drugs for long periods. This report is an observational study of 675 patients originally enrolled in prospective, controlled studies from a single unit. Two issues regarding long term efficacy are addressed: first, in what percentage of patients is disease activity controlled in the long term (over five years), as well as in the short term? Second, in those patients with good 'control' of disease activity over five years, is there evidence of continuing functional decline?

Patients and methods

We enrolled 675 patients with RA in prospective controlled trials.⁸⁻¹³ They were treated with SASP (n = 222), PCM (n = 158), or gold (n = 295) and followed up for five years. Forty one patients (6%) died, 444 patients (66%) stopped treatment and 190 patients (28%) continued on treatment for five years. In all trials, the indication for DMARD therapy was active synovitis not adequately controlled with NSAID therapy alone. Oral corticosteroid therapy was not permitted, but intra-articular steroid injections were allowed. Intramuscular gold was given first as a 10 mg test dose, then 50 mg weekly until a response was obtained, when the frequency of injections was decreased. In most instances, maintenance injections were given every four weeks. The dose of PCM was started at 125 mg daily and increased each month until a response was seen, side effects supervened, or the maximum permitted dose of 1000 mg/day was reached. Enteric coated SASP was started at 0.5 g daily with weekly increments of 0.5 g until the target dose of 40 mg/kg per day in divided doses was reached or side effects supervened. DMARD therapy was not stopped in patients entering

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‘remission’. A single nurse metrologist assessed 645/675 patients and the remaining 30 were assessed by one of two other metrologists, in the same unit.

Information was collected at six monthly intervals for two years, and annually thereafter. It included:

- (1) Demographic data—age and disease duration.
- (2) Disease activity—duration of morning stiffness, Ritchie articular index, visual analogue pain score, erythrocyte sedimentation rate (ESR), and C reactive protein concentration (CRP).
- (3) Functional outcome—a modified Health Assessment Questionnaire (HAQ) was completed by the patient. The use of an appliance to complete a task led to a score of 2 (equivalent to ‘much difficulty’) being assigned to that activity.

ESR, pain score, and morning stiffness were recorded in all 190 patients continuing therapy for five years, but the articular index (n = 141), CRP (n = 89) and HAQ score (n = 134) were not recorded in all the trials.

The improvement for each variable was analysed within groups using paired Wilcoxon testing. For each patient, the mean improvement (‘area under the curve’) in each variable over the five year period was calculated.¹⁴ Subgroup analysis compared the improvement achieved with SASP, PCM, and gold. The patients who stopped therapy, and those who died, were compared with those who continued treatment for five years, for data obtained at the outset of treatment. Between groups comparisons were by Kruskal-Wallis (K-W) analysis.

Results

Table 1 shows the demographic details, initial function, and initial disease activity of patients who died, stopped therapy, or continued on treatment for five years. Patients destined to continue on treatment for five years were younger (K-W, p < 0.001), with a trend towards having milder disease, although this

Figure 1 Changes in measures of disease activity over five years of therapy. n = Number of patients for whom the measure was available. ESR = Erythrocyte sedimentation rate; CRP = C reactive protein.

only reached significance with pain score (K-W, p < 0.001) and HAQ score (K-W, p < 0.02).

There were highly significant improvements in all measures of disease activity in the patients continuing treatment (paired Wilcoxon, all variables p < 0.001). The improvement was maximal at one year, and disease activity was controlled throughout the five year period (fig 1). HAQ score decreased significantly between years 0 and 1 (p < 0.0001); between year 1 and year 5, the score increased significantly (p < 0.001), but at five years it was still significantly lower than before treatment started (p < 0.0001) (fig 2).

Subgroup analysis showed there were no significant differences in age, sex, or disease duration between the patients treated with SASP, PCM, or gold. At the start of treatment the groups were well matched for pain score, morning stiffness and ESR, but the gold group had a significantly lower HAQ score (2.0 v 2.25 (PCM) v 2.33 (SASP); K-W, p < 0.05),

Figure 2 Changes in Health Assessment Questionnaire (HAQ) score over five years of therapy. The score was significantly lower (p < 0.0001) at all time points compared with year 0, but significantly greater (p < 0.001) at year 5 than at year 1.

Table 1 Demographic, clinical and laboratory data at the start of the trials in patients who subsequently died, stopped therapy or continued on therapy for five years

	Died (n = 41)	Stopped (n = 444)	Still on (n = 190)
Age (yr)	62 (40–81)	57 (17–86)	53*** (19–80)
Disease duration (yr)	10 (1–32)	7 (0–66)	6 (1–36)
Pain score	208 (75–300)	208 (5–300)	170*** (20–300)
Morning stiffness (min)	120 (0–720)	120 (0–720)	120 (0–720)
Articular index	16 (2–31)	16 (0–61)	14 (0–61)
Haemoglobin (g/dl)	11.8 (7.4–15.4)	11.6 (10–17.3)	11.8 (7.8–17.3)
Platelet count (×10 ⁹ /l)	446 (214–536)	402 (150–971)	419 (156–985)
ESR (mm/h)	68 (8–137)	62 (2–150)	59 (2–150)
CRP (mg/l)	45 (6–129)	38 (4–145)	50 (6–256)
HAQ score	2.32 (0.4–2.88)	2.13 (0.2–3.0)	2.0* (0–3.0)

Values are median (range). ESR = Erythrocyte sedimentation rate; CRP = C reactive protein; HAQ = Health Assessment Questionnaire. n = Number of patients. Significant difference (Kruskal-Wallis) compared with Died or Stopped: *p < 0.05; ***p < 0.001.

Table 2 Reasons for stopping therapy

	Gold (n = 295)	PCM (n = 158)	SASP (n = 222)
Side effect (%)	45	42	33
Loss of effect (%)	6	9	16
Lack of effect (%)	3	9	12
Death (%)	7	5	6
Moved away (%)	0.3	1	1
Intercurrent illness (%)	2	8	3
Poor compliance (%)	3	4	3
Still on after 5 yr (%)	34	22	26
	100	100	100

Gold = Gold sodium thiomalate; PCM = penicillamine; SASP = sulphasalazine.

and the PCM group had a significantly higher articular index (22 *v* 14 (gold) *v* 19 (SASP); K-W, $p < 0.001$). At one year there were no significant differences between the groups, but after five years the gold group had a lower ESR (18 *v* 30 (SASP) *v* 35 (PCM); K-W, $p < 0.05$). Area under the curve analysis showed that with gold therapy there was a greater mean improvement in ESR (K-W, $p < 0.03$) and morning stiffness (K-W, $p < 0.01$), and with PCM there was a greater improvement in articular index (K-W, $p < 0.01$). There were no significant differences between the groups in mean improvement in pain score or HAQ score. Overall, 20.4% of patients stopped their therapy because of inefficacy, with more patients stopping SASP for this reason than PCM or gold. After five years of treatment, more patients remained on treatment with gold (34%), than with PCM (22%), or SASP (26%), but the difference was not statistically significant (life table analysis). There were a similar number of deaths in each group, and none of the deaths could be attributed to drug toxicity (table 2).

Discussion

There is substantial evidence from short term controlled clinical trials that SASP, PCM, or gold therapy results in improvement in a range of clinical and laboratory measures of disease activity. What is disputed is whether the use of DMARDs influences disease progression over a five to 10 year period. Capell *et al*¹⁵ found that patients maintained on DMARD therapy for the majority of the time have a better outcome over 10 years than those receiving short periods of treatment, and there is some evidence that long term gold therapy is associated with reduced mortality.¹⁶ Epstein *et al*¹⁷ attempted to study the effect of gold therapy on RA over five years, as measured by the HAQ score. They compared a group of patients treated with gold for a variable length of time, with patients who were not treated with gold, but may have been treated with other DMARDs. In both groups, they found that the HAQ score did not change significantly over five years.

The patients analysed are a highly selected subgroup of patients, comprised of the 28% of patients who not only tolerated DMARD therapy for five years, but also 'responded' well to treatment. Our results suggest that we achieved good control of disease activity in

these patients (fig 1). However, because it is our policy to consider changing DMARD therapy in patients with persistent (or recrudescing) disease activity (in an attempt to achieve better control of their RA), it is possible that those patients continuing to receive therapy may simply represent a group who tolerate therapy, and enter natural remission—that is, the improvements seen may not be the result of their DMARD therapy. This seems unlikely, for two reasons: first, patients who have their DMARD therapy withdrawn almost invariably relapse; second, we have previously demonstrated that only a very small minority of our patients treated with placebo show a substantial improvement in disease activity over six months.¹⁸ It probably is true that the functional outcome of these patients represents the best we can achieve with these drugs, and this emphasises the need for a multidisciplinary approach to the treatment of RA, involving drug therapy, physiotherapy, occupational therapy, and surgery. This study does not address the outcome of treatment in patients who did not tolerate their assigned therapy, or who had their therapy changed because of inefficacy. It does seem likely that patients who have their DMARD therapy changed because of poor control of disease activity are likely to have a worse outcome, but it is possible that patients who develop side effects from one DMARD may fare no worse, if the subsequently tolerate a different DMARD long term. Data from a group of 123 patients followed up for 10 years lend support to this supposition.¹⁵

The work of Hassell *et al*¹⁴ suggests that sustained control of disease activity results in a significant impact on functional outcome, and our results would support this. Although the improvement in function is likely to be partly attributable to DMARD therapy, the effects of other therapies, including joint replacement surgery, should not be forgotten. The HAQ score improved over the first year of DMARD therapy, and the HAQ score after five years of treatment was still significantly better than before DMARD therapy was started. There was a significant slow decline in function during years one to five suggesting that, despite good control of disease activity, disease progression was still occurring. However, it is important to remember that other factors may influence the HAQ score in the long term, such as ageing and comorbidity (for example, cerebrovascular disease).

Functional ability is not a perfect measure of disease outcome, because it is likely to be affected by disease activity in addition to disease outcome. Thus showing that the HAQ score decreases in the long term does not necessarily imply that the rate of disease progression has been reduced. There is very little evidence available about the natural history of RA in the long term, as measured by patient function, and it is impossible to be certain whether the slow decline in function seen between years one and five represents a decrease in the 'natural' rate of disease progression.

The comparisons of gold, PCM and SASP show a strikingly similar response over the first year of therapy, and very similar results over the five year period. Over five years, area under the curve analysis showed that ESR and morning stiffness improved more in the gold group, suggesting that gold therapy may be more effective in suppressing disease activity in the long term. However, multiple statistical analyses were performed, and the potential dangers of subgroup analyses are well recognised. The greater improvement in articular index with PCM might be because this group started with a higher articular index (22 v 14 (gold) v 19 (SASP); K-W, $p < 0.001$). There is some evidence that better control of the ESR over several years is correlated with reduced radiological progression,^{14 15} and this suggests that if the lower ESR in the gold group is a true effect, it could be of clinical significance. In contrast, there were no differences between the groups in functional outcome after five years, suggesting that any superiority of gold over PCM and SASP is marginal, and of limited clinical significance.

The percentage of patients tolerating DMARD therapy in this study compares favourably with previous studies. Previous studies have found that SASP is continued in 27% of patients¹⁹ for two years, and in 19–22% for five years,²⁰ compared with 26% of patients continuing SASP therapy for five years in this study. Similar results have been found with PCM, 31% of patients continuing therapy for two years,²⁰ and 17% for five years,⁶ compared with 22% in this study. The most striking difference from the literature is our result with gold therapy—the percentage of patients continuing gold over five years has been reported by Situnayake *et al*⁶ to be as low as 8%, compared with 34% of our patients. One of the reasons for this discrepancy is that very few patients stopped gold therapy because of inefficacy in our study, but 29.5% of patients stopped gold for this reason in the study by Situnayake. Bendix *et al*²¹ found that 31% of patients continued gold for more than four years. This study demonstrates that it is possible to maintain a larger number of patients on long term gold therapy, with demonstrable sustained benefit, than was previously thought possible.

Conclusion

This study has provided evidence for the long term efficacy of DMARD therapy. Good control of disease activity and improved function were achieved for five years in approximately 30% of patients with active RA. The improvement in functional abilities suggests a possible effect on disease outcome, in addition to disease process. Toxicity remains a major problem, such that a minority of

patients tolerate gold, SASP, or PCM for five years, but more patients can be maintained on long term DMARD therapy than has previously been reported. In the absence of curative therapy for severe RA, the significant amelioration of disease achieved with the judicious use of DMARDs is worthy of emphasis.

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