Outcome of second line therapy in rheumatoid arthritis

D R Porter, I McInnes, J Hunter, H A Capell

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.


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 gold 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 were observed, 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 were observed. DMARD therapy was not stopped in patients entering...
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 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

<table>
<thead>
<tr>
<th></th>
<th>Died (n = 41)</th>
<th>Stopped (n = 444)</th>
<th>Still on (n = 190)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>62 (40-81)</td>
<td>57 (17-86)</td>
<td>53***</td>
</tr>
<tr>
<td>Disease duration (yr)</td>
<td>10 (1-32)</td>
<td>7 (0-66)</td>
<td>6</td>
</tr>
<tr>
<td>Pain score</td>
<td>208 (75-300)</td>
<td>208 (5-300)</td>
<td>170***</td>
</tr>
<tr>
<td>Morning stiffness (min)</td>
<td>120 (0-720)</td>
<td>120 (0-720)</td>
<td>120</td>
</tr>
<tr>
<td>Articular index</td>
<td>16 (2-31)</td>
<td>16 (0-61)</td>
<td>14</td>
</tr>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>11.8 (7-4-15-4)</td>
<td>11.6 (10-17-3)</td>
<td>11.8</td>
</tr>
<tr>
<td>Platelet count (x10^9/l)</td>
<td>446 (214-536)</td>
<td>402 (150-971)</td>
<td>419</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>68 (8-137)</td>
<td>62 (2-150)</td>
<td>59</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>48 (8-129)</td>
<td>38 (4-145)</td>
<td>50</td>
</tr>
<tr>
<td>HAQ score</td>
<td>2.3 (0-2.88)</td>
<td>2.13 (0-2-3-0)</td>
<td>2.6*</td>
</tr>
</tbody>
</table>

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.

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.
and the PCM group had a significantly higher articular index (22 vs 14 (gold); 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 vs 30 (SASP) vs 35 (PCM); K-W, p < 0.005). 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 SAPS 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 SAPS (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 SAPS, 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 al15 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 al17 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 recrudescent) 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 al14 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). This suggests that 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 patients\textsuperscript{10} for two years, and in 19–22% for five years,\textsuperscript{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,\textsuperscript{20} and 17% for five years,\textsuperscript{14} compared with 18% in this study. The major reason for the discrepancy between the literature is that the percentage of patients continuing gold therapy—the percentage of patients continuing gold over five years has been reported by Situnayake \textit{et al.}\textsuperscript{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 29–59% of patients stopped gold for this reason in the study by Situnayake. Bendix \textit{et al.}\textsuperscript{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.

We are grateful to Sister Thompson for metrology services, Prof. Sturrock for allowing us to study his patients, and Mrs. McKnight for computing expertise.

13 Capell H, Lewis D, Carey J. A three year follow up of patients allocated to placebo or oral or injectable gold therapy for rheumatoid arthritis. \textit{Ann Rheum Dis} 1986; 45: 705–11.
Outcome of second line therapy in rheumatoid arthritis.

D R Porter, I McInnes, J Hunter and H A Capell

doi: 10.1136/ard.53.12.812

Updated information and services can be found at:
http://ard.bmj.com/content/53/12/812

These include:

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/