ADDING LOW-DOSE CYCLOSPORIN A TO PARENTERAL GOLD THERAPY IN RHEUMATOID ARTHRITIS: A DOUBLE-BLIND PLACEBO-CONTROLLED STUDY

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SUMMARY
A double-blind, randomized comparison between parenteral gold therapy (PGT) and cyclosporin A (CyA) vs PGT and placebo during 6 months was performed in 40 RA patients experiencing a decreasing effect of ongoing PGT. Patients' overall assessment of health was the only efficacy variable significantly better in the CyA- and PGT-treated vs the placebo- and PGT-treated group. Higher blood pressure and more signs of renal impairment were found during the 6 months treatment in the former compared with the latter group. Six months after the end of the combination therapy, a higher potassium value in the CyA-treated group was the only difference. In conclusion, no effects additional to those expected with single-drug therapy or additional risks of side-effects of either drug were found when combining low-dose CyA with ongoing PGT in RA patients with long disease duration.

KEY WORDS: Drug therapy, Combination, Gold sodium thiomalate, Cyclosporin A, Arthritis, Rheumatoid.

RHEUMATOID arthritis (RA) is a severe disease with an increased mortality [1, 2] and a high risk of functional disability [3, 4]. The conventional pharmacological treatment with single disease-modifying anti-rheumatic drugs (DMARDs) in sequence often fails to induce remission or prevent disease progression [3, 5, 6] and entails a considerable risk of discontinuation due to side-effects [7–11]. Combining DMARDs could be expected to overcome this loss of efficacy and at the same time minimize side-effects by the use of lower doses of two drugs, but available data have been rather disappointing and have not allowed combination therapy to be recommended for routine use [12–17].

This concept of combining drugs has remained attractive, however [13, 14, 18–20]. Some previous reports on combinations of parenteral gold treatment (PGT) and other DMARDs have suggested an increased efficacy [21–28], but others have failed to find an additive effect [29–31]. Bensen et al. [32] recently reported on the efficacy of combined therapy with cyclosporin A (CyA) and PGT. The different side-effect profiles of CyA and PGT, and possibly different modes of action [33, 34], suggest these drugs to be a logical combination.

A decreasing efficacy of PGT was a practical problem in 1991, when it was still the most frequently prescribed DMARD in our department. The patients of this study were therefore invited to participate in this double-blind, randomized study adding CyA or placebo to their ongoing PGT.

PATIENTS AND METHODS

Patients
Between September 1991 and November 1992, 40 out-patients at the Department of Rheumatology, Sahlgrenska University Hospital, Gothenburg, were included in the study (Table I). The inclusion criteria were age between 18 and 70 yr with disease onset after age 16, fulfilment of the 1987 revised ARA criteria of RA [35] and functional class I–III [36]. The patients had an insufficient response to >6 months PGT (> 1000 mg), defined as unremitting disease, morning stiffness > 15 min and fulfilment of not more than two of the other five ARA remission criteria [37]. Finally, they were to have taken an NSAID in a stable dose for >2 weeks before entry and to have given their informed consent. No eligible patient refused to enter the study.

The exclusion criteria were previous treatment with cytotoxic or immunosuppressive drugs, ongoing prednisolone therapy >10 mg/day, intra-articular corticosteroids <2 weeks before baseline, concomitant medication with known nephrotoxic drugs other than gold or drugs with known interaction with CyA. Patients with impaired renal function, tested by s-creatinine (>100 μmol/l in any of three tests), chrome-EDTA clearance (below the lower normal limit), proteinuria (>0.2 g/24 h), and hyperkalaemia, hyperuricaemia and/or hypomagnesaemia, and those with impaired liver function tests, s-bilirubin (>21 μmol/l) and more than twice the upper limit of the normal range of s-ASAT (<0.7), s-ALAT (<0.7) and s-ALP (<5.0 kkat/l) were excluded. Patients with leucopenia (<3000/mm^3), thrombocytopenia (<150 000/mm^3) and hypertension (diastolic >90 mmHg or systolic >160 mmHg) or a history of previous or ongoing antihypertensive treatment were also excluded. Finally, a history or presence of other
diseases, pregnancy, lactation, alcohol or drug abuse excluded patients. One patient was excluded due to hypertension and another due to an abnormal chrome-EDTA clearance.

Outcome measures

The blinded examiner recorded the duration of morning stiffness (minutes), Ritchie Articular Index [38], number of tender and swollen joints, the patient's assessment of pain on motion and at rest, ARA remission criteria, grip strength, ESR, haemoglobin and CRP.

Other DMARDs previous to gold (%)

<table>
<thead>
<tr>
<th>DMARDs previous to gold (%)</th>
<th>Cyclosporin A</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimalarials</td>
<td>68</td>
<td>67</td>
</tr>
<tr>
<td>Auranofin</td>
<td>21</td>
<td>24</td>
</tr>
<tr>
<td>D-penicillamine</td>
<td>26</td>
<td>24</td>
</tr>
<tr>
<td>Sulphasalazine</td>
<td>11</td>
<td>10</td>
</tr>
</tbody>
</table>

Mean dose of gold (mg) (range) (mg)

<table>
<thead>
<tr>
<th>Dose and range</th>
<th>Cyclosporin A</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>2546 (1070–5590)</td>
<td>2635 (1060–6420)</td>
<td>2</td>
</tr>
</tbody>
</table>

Evaluation of drug safety and tolerability

The unblinded clinician made a general physical examination and recorded subjective adverse events. He asked the patients to assess the tolerability of the test drug and recorded his own assessment on the scale very good, good, moderate, poor and very poor (graded 1–5). All patients were followed for 6 months after they stopped taking the test drug.

Laboratory tests comprised leucocyte and platelet counts, serum potassium, magnesium, creatinine, uric acid, total bilirubin, alkaline phosphatases, amino-transferases and urine tests with dipsticks (glucose, protein, erythrocytes), antinuclear antibodies (ANA), anti nuclear antibodies (ANA) and chrome-EDTA clearance.

Months 0, 1, 2, 3, 4, 5, 6, 8, 10 and 12. Clinical examination, laboratory tests and recording of adverse events.

Months 0 and 6. ANA.

Months –0.5, 6 and 12. Chrome-EDTA clearance.

Month 6. The unblinded clinician's and patients' assessments of tolerability of the test drug.

Treatments

The PGT was continued unchanged with individualized dosages of sodium aurothiomalate (Myocrisin®), generally 20–40 mg by i.m. injection given every 2 or 3 weeks and occasionally weekly. CyA (Sandimmun®) in a starting dose of 2.5 mg/kg/day or placebo in identical capsules were added at study entry (see the following section on study design). NSAIDs were given as stable doses as possible and intra-articular corticoids were given as required, but not during the 2 weeks preceding the blinded examiner's examinations. Systemic corticoids (<10 mg prednisolone/day) were allowed.

The remaining capsules of CyA and placebo, and the empty blisters, were brought back by the patients and were counted at the monthly visits. New capsules were then requisitioned from the pharmacy.

To further test the patients' compliance, blood samples were taken 2–20 h after the last intake of the test drug at months 1, 3 and 5, and frozen at −20°C for later analysis of CyA concentrations by a specific monoclonal RIA method (Cyclotrac SR®, Incstar Corporation, Still Water, MN, USA).

All concomitant medication for diseases other than RA was also registered.
Morning stiffness was chosen as the primary variable since a significant \( P < 0.01 \) effect was found in a previous placebo-controlled trial of CyA in RA \[44\]. Based on this study, it was calculated that 40 patients would give a power of 76\% at the 0.05 level, two-tailed test. The patients were sequentially allocated to the two treatments by a computer program based on nine pre-selected variables: age, sex, duration of RA, morning stiffness, ESR, pain at rest, number of ARA remission criteria fulfilled, rheumatoid factor titre \( \geq 1/80 \) \[45\] and the amount of previous gold.

Each month, the patients met the unblinded clinician at the same time of the day for clinical examination, laboratory tests and adjustment of therapy due to adverse events.

At months 2, 4 and 6, the patients first visited the blinded examiner, who compared her recordings with data at study entry. Based on these findings, she made an overall assessment of health, which was passed over as a written report, together with the patient's own overall assessment of health, to the unblinded clinician. When the patient was improved according to one or both of these assessments, the dosage was unchanged. When there was no improvement or the patient was worse, the test drug dose was increased to 3.75 or 5 mg/kg/day, provided no subjective adverse reactions, diastolic blood pressure > 95 mmHg or abnormal laboratory tests were registered. The test drug was reduced by 25\% at one or two regular monthly visits when s-creatinine was > 150\% of baseline or 130–150\% on two occasions, s-potassium > 5.1, s-bilirubin > 200\% of baseline or liver enzymes > 3 times the upper limit of the normal range. If the tests were not normalized, the test drug was withdrawn. In the case of hypertension, treatment with a Ca antagonist or beta-blocker was initiated before reducing the dose or withdrawing the test drug.

The study was performed in accordance with the Helsinki declaration and was approved by the Medical Products Agency and the local ethical committee.

**Statistical methods**

To evaluate the most powerful statistical procedure for comparison between the two groups regarding efficacy without affecting the significance level, the correlation coefficients between the values at month 0 and months 2, 4 and 6 were calculated. When the coefficients were > 0.5, differences between the respective time periods were compared between the groups. With coefficients < 0.5, the mean values at each time were compared between the two groups. This was found for three of the efficacy variables: number of swollen joints, pain on motion and number of fulfilled ARA remission criteria. For all other efficacy variables, comparisons were made using the differences between the time periods.

Fisher's permutation test \[46, 47\], which includes Fisher's exact test as a special case, was used for comparison between treatment groups. Fisher's test for paired comparisons \[46\] was applied to analyse the change from baseline of laboratory variables, body mass index, blood pressure and radial pulse. Two-tailed tests were used and a significance level of 0.05 was chosen. Pitman's test \[46\] was used to test the correlation between the patient's overall assessment and the baseline variables.

Tests for trend in contingency tables \[48\] were used for comparison between treatment groups regarding the change of dose at months 2 and 4, and the imaginary change at month 6 provided the study had continued.

**RESULTS**

**Patients**

Nineteen patients were randomized to treatment with PGT and CyA, and 21 to PGT and placebo treatment. At the start of the study, no statistically significant difference except for HAQ Dressing was found between the two groups (Tables I and IV). Thirty-six patients completed the 6 months combination therapy. Three patients treated with CyA withdrew from the trial after 1.5, 3 and 5.5 months due to a feeling of general discomfort with a wish to withdraw, relapse of disease necessitating a high dose of prednisolone, and a period of vomiting and diarrhoea prohibiting the intake of the capsules, respectively. One patient treated with placebo developed a dermatitis from PGT after 12 months treatment and withdrew from the study after 1.5 months.

**Treatment**

Patients' compliance, tested by counting the remaining capsules of 1 month's prescription, was satisfactory in all patients. CyA was found in all blood samples at the end of months 1, 3 and 5, except in one patient at month 1.

The mean dose of PGT during 6 months therapy was 358 mg (range 160–560) in the CyA-treated group and 364 mg (range 90–800) in the placebo group. The mean final dose of CyA was 2.89 ± 0.69 mg/kg/day (range 1.70–3.75) with a peak at month 3.
Overall health, score*  
AIMS score (0-10)§  
HAQ, total score (0-3)J  
ARA remission criteria fulfilled (number)  
Overall tolerability, score}  
Overall efficacy, score{  
Plasma viscosity (Pa.s)  
CRP 0/g/ml)  
Grip strength (Newton)  
Pain on motion (mm)  
Pain at rest (mm)  
Tender joints (number)  
Swollen joints (number)  
Ritchie index  
Morning stiffness (min)  
ESR (mm/h)  
CRP (µg/ml)  
Haemoglobin (g/l)  
Plasma viscosity (Pa.s)  
ARA remission criteria fulfilled (number)  
HAQ, total score (0-3)§  
AIMS score (0-10)§  

Based on the blinded examiner’s and the patients' assessments, a larger (not significant) proportion of patients with a need to increase the dose of the test drug due to inefficacy was found in the placebo (12/20) than in the CyA-treated group (4/17) at month 4 (Table II). Provided the study had continued, the same assessments at month 6 indicated that 14/20 in the placebo group and 5/16 in the CyA-treated group would have needed a higher dose (P < 0.05). The difference was mainly due to an increase of the test drug dose in the placebo group because of inefficacy.

No significant differences regarding 6 months cumulative doses of intra-articular Depo-Medrone®, Lederspan® or oral prednisolone were observed between the CyA-treated group and the placebo group.

of 2.97 ± 0.83 mg/kg/day (range 1.25–3.75). The corresponding doses for the placebo group were 3.75 ± 0.99 and 2.95 ± 0.63 mg/kg/day, respectively. The test drug doses were significantly higher in the CyA-treated group at month 5 (P < 0.05) and at month 6 (P < 0.01), based on the prescriptions at months 4 and 5, respectively. The 95% confidence interval for the difference between groups at month 6 was −1.45 to −0.27. Tests for trend in contingency tables showed significant differences between the CyA and the placebo groups regarding change of dose of the test drug at month 4 (P < 0.01) and the imaginary change at month 6 (P < 0.05) provided the study had continued (Table II).

**TABLE III**  
Mean values (± s.d.) of assessments at month 6

<table>
<thead>
<tr>
<th></th>
<th>Cyclosporin A</th>
<th>Placebo</th>
<th>Significance of difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall health, score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients' assessments</td>
<td>2.3 ± 1.1</td>
<td>3.0 ± 0.9</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>Examiner's assessments (blinded)</td>
<td>2.6 ± 1.0</td>
<td>3.0 ± 0.9</td>
<td>n.s.</td>
</tr>
<tr>
<td>Overall efficacy, score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients' assessments</td>
<td>3.1 ± 1.6</td>
<td>4.6 ± 1.0</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td>Clinician's assessments (unblinded)</td>
<td>3.6 ± 1.6</td>
<td>4.6 ± 1.0</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>Overall tolerability, score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients' assessments</td>
<td>1.5 ± 1.1</td>
<td>1.1 ± 0.2</td>
<td>n.s.</td>
</tr>
<tr>
<td>Clinician's assessments (unblinded)</td>
<td>1.7 ± 0.9</td>
<td>1.0 ± 0.0</td>
<td>P &lt; 0.001</td>
</tr>
</tbody>
</table>

*Score: 1: much better; 2: better; 3: no change; 4: worse; 5: much worse.  
JScore: 0 - good health; 3 = bad health.  

**TABLE IV**  
Efficacy variables at month 0 and change at month 6 (mean ± s.d.)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Change at month 6</th>
<th>Significance of difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cyclosporin A</td>
<td>Placebo</td>
<td>Cyclosporin A</td>
</tr>
<tr>
<td>Morning stiffness (min)</td>
<td>123 ± 137</td>
<td>134 ± 112</td>
<td>−25 ± 106</td>
</tr>
<tr>
<td>Ritchie index</td>
<td>20 ± 9</td>
<td>19 ± 10</td>
<td>−1 ± 8</td>
</tr>
<tr>
<td>Tender joints (number)</td>
<td>14 ± 6</td>
<td>13 ± 5</td>
<td>−2 ± 4</td>
</tr>
<tr>
<td>Swollen joints (number)</td>
<td>11 ± 3</td>
<td>10 ± 3</td>
<td>−0.5 ± 3</td>
</tr>
<tr>
<td>Pain at rest (mm)</td>
<td>32 ± 26</td>
<td>37 ± 28</td>
<td>0.4 ± 31</td>
</tr>
<tr>
<td>Pain on motion (mm)</td>
<td>54 ± 20</td>
<td>47 ± 24</td>
<td>−11 ± 30</td>
</tr>
<tr>
<td>Grip strength (Newton)</td>
<td>56 ± 39</td>
<td>66 ± 67</td>
<td>−2 ± 24</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>40 ± 23</td>
<td>40 ± 26</td>
<td>10 ± 18</td>
</tr>
<tr>
<td>CRP (µg/ml)</td>
<td>41 ± 23</td>
<td>27 ± 21</td>
<td>−6 ± 29</td>
</tr>
<tr>
<td>Haemoglobin (g/l)</td>
<td>116 ± 11</td>
<td>119 ± 15</td>
<td>−2 ± 12</td>
</tr>
<tr>
<td>Plasma viscosity (Pa.s)</td>
<td>2 ± 0.1</td>
<td>2 ± 0.2</td>
<td>−0.1 ± 0.1</td>
</tr>
<tr>
<td>ARA remission criteria fulfilled (number)</td>
<td>0.4 ± 0.6</td>
<td>0.4 ± 0.5</td>
<td>0.2 ± 0.5</td>
</tr>
<tr>
<td>HAQ, total score (0–3)</td>
<td>1.4 ± 0.7</td>
<td>1.5 ± 0.6</td>
<td>−0.1 ± 0.4</td>
</tr>
<tr>
<td>AIMS score (0–10)§</td>
<td>1.6 ± 2.3</td>
<td>2.4 ± 2.5</td>
<td>0.7 ± 1.0**</td>
</tr>
</tbody>
</table>

†Significance was calculated on the differences of means between groups.  
§Score: 0 = good health; 3 = bad health.  
$\$Score: 0 = good health; 10 = bad health. Differences within groups: *P < 0.05; **P < 0.01.
Efficacy
The patients' overall assessment of health at month 6 was better (P < 0.05) in the group treated with CyA than in the placebo group (Table III). ESR was higher (P < 0.05) at months 4 and 6 in the CyA-treated than in the placebo group. No other significant differences were found between the two groups regarding the altogether 35 efficacy variables (Table IV).

No significant correlations were found between the patients' overall assessment at month 6 and 47 baseline variables. A better effect of the test drug at month 6 in the CyA- than in the placebo-treated group was noted by both the unblinded clinician (P < 0.05) and the patients (P < 0.01) (Table III).

Tolerability
No serious side-effect was noticed during the 6 months therapy among the 76 adverse events reported by 32 patients, 17 of whom were treated with CyA and 15 with placebo. More (P < 0.01) CyA-treated patients were found with one or more 'other' events, which included hyperkalaemia, hypomagnesaemia, hyperuricaemia, palpable lymph nodes, goitre, gynaecomastia, vitamin B12 deficiency, weight loss, lumbago and drug intoxication (Table V).

Four adverse events in each group required symptomatic treatment. With unchanged treatment, dose reduction or interruptions, the adverse events disappeared or were tolerated. Eight of the 19 patients on CyA had the dosage reduced because of side-effects, in one patient twice. Dose reduction was significantly (P < 0.05) more frequent in the CyA than in the placebo group (1/21).

During the 6 months treatment period, significantly higher systolic and diastolic blood pressure, leucocyte counts and values of potassium, creatinine and uric acid were found in the CyA- than in the placebo-treated group (Table VI). Subsequent analyses of changes from baseline within each group showed significant increases of the same variables in the CyA-treated group. In the placebo-treated group, a significant decrease of creatinine and an increase of uric acid were found (Table VI). No significant differences between the groups were found regarding body mass index, radial pulse, platelets, magnesium, total bilirubin, alkaline phosphatases and aminotransferases, chrome-EDTA clearance or ANA.

The overall tolerability of the test drug, assessed by the unblinded clinician, was better (P < 0.001) in the placebo than in the CyA-treated group. No significant difference was found between the two groups regarding the patients' assessment of overall tolerability (Table III).

At month 12, the higher (P < 0.01) number of 'other' adverse events, as well as the higher (P < 0.05) value of potassium in the CyA- than in the placebo-treated group, persisted. Five adverse events remained in five patients treated with CyA; oedema necessitating diuretics, slight dyspepsia, rhinitis, slight goitre and a persistent weight reduction. In two patients treated with placebo, an increase of aminotransferases and a decrease of chrome-EDTA clearance, respectively, were still present, but no significant differences between the two groups were found.

DISCUSSION
Patients' overall assessment of health was the only efficacy variable significantly better in the CyA- and PGT-treated vs the placebo- and PGT-treated group. Higher blood pressure and more signs of renal impairment were found during the 6 months treatment period.
in the former compared with the latter group. Six months after the end of the combination therapy, a higher potassium value in the CyA-treated group remained.

The mean test drug dose was higher in the placebo group than in the CyA-treated group at months 5 and 6. The test dose was increased more frequently in the placebo than in the CyA-treated group at month 4 and would also have been at month 6, provided the study had continued.

**Efficacy**

Outcome measures for clinical trials in RA are based on general recommendations [49, 50]. Effect on morning stiffness was previously reported in two studies [44, 51] but, like us, Tugwell et al. [52] found no significantly reduced morning stiffness in a CyA-treated group compared with a placebo group. The variability of morning stiffness within and between patients makes it difficult to use as an outcome measure [49, 53]. An ESR reduction has generally not been found in CyA-treated RA patients [34, 44, 51, 52] and the change in the CyA-treated group of this study was thus not interpreted as a sign of unfavourable response to this drug.

In this study, two active treatments were compared, which reduces the intergroup outcome differences. The sample sizes required to obtain a significant outcome were calculated for the different variables based on the present results. For the Ritchie index, 104 patients would have been required and ~400 would have been needed to obtain significant results in half of the most favourable outcome variables with a power of 80% at the 0.05 level. However, we think that the present approach to testing new therapies is informative, since enough experience is gathered without exposing an unnecessary number of patients.

Considering sample size and characteristics, doses and statistical methods (t-test for paired comparisons), a comparison of the same outcome variables between our results and the three published placebo-controlled studies of CyA in RA [44, 51, 52] suggested that the results were rather similar.

The lower doses of CyA at month 6 in our patients compared with those of the other studies could depend on less strict assessment of inefficacy and stricter indications for dose reductions due to adverse events. The different trends in adjustment of doses between the CyA- and the placebo-treated groups at month 4 mainly depended on differences in efficacy of the test drug. The assessments for dose change at months 4 and 6 thus suggested a therapeutic effect in the CyA vs the placebo group, which was further supported by the patients' and the clinician's assessments. However, the efficacy of adding low-dose CyA to ongoing PGT was not very impressive.

A new definition of improvement in RA was recently presented [54]. It requires 20% improvements in defined outcome variables. According to this definition, 0/21 patients in the placebo group and 3/19 patients in the CyA-treated group were improved. The numbers are too few to perform reliable significance testing, but could be of interest for future comparisons with other studies of combination therapy in RA.

**Adverse events**

Increased blood pressure in CyA-treated patients is a common and predictable side-effect related to a reduction in glomerular filtration and an increased s-creatinine [34, 55]. The renal tubular effects of CyA, causing impaired secretion of uric acid and reduced fractional excretion of, for example, potassium [34], occur independently of a reduced glomerular rate.

The renal side-effect of PGT is mainly proteinuria due to a membranous glomerulonephritis [33] occurring during the first year of treatment [11]. Considering that the mean duration of treatment with PGT in our patients was ~4 yr and the type of renal adverse events, it is unlikely that they were due to PGT. The study design, exposing patients first to PGT before adding CyA/placebo, reduced drop-outs because of time-dependent side-effects [11] and is clinically more justifiable than starting the two drugs at the same time.

In the controlled studies [44, 51, 52, 56] comparing low-dose CyA with placebo, significant renal impairment was also found as well as hypertension [51, 52]. Hypertension has also been reported in studies comparing CyA with other DMARDs in RA patients [57-59]. Other well-described side-effects of CyA—hypermotichosis, tremor, gingival hyperplasia, dyspepsia and paraesthesiae—also reported in RA patients [52, 59], were not observed in our patients, probably due to our lower doses.

The only side-effect attributable to PGT was dermatitis in a patient in the placebo group. This was within the hazard function for discontinuation due to mucocutaneous side-effects [11].

We thus did not find an increased risk of side-effects when combining CyA and PGT, and the side-effects in the CyA-treated group could be explained by this drug.

**Combinations of PGT or CyA with other DMARDs**

Although combination therapy is becoming an increasingly popular option in patients with insufficient response to single DMARDs, there is a lack of systematic studies evaluating this approach. We have found 12 reports on studies combining PGT with another DMARD [21-32], but only four of them are controlled and double blind. A study of PGT and antimalarials (AM) vs PGT and placebo only found CRP, one of 13 efficacy variables, to reach statistical significance [27]. No improved outcome was found when adding AM to ongoing PGT in another study [31]. Bucillamine or placebo was added to ongoing PGT in a 3 month study by Yasuda et al. [28]. Three efficacy variables out of nine improved in a PGT + bucillamine-treated group. No overall improvement of efficacy was found in a group taking PGT and D-penicillamine (DPA) vs PGT + placebo or DPA + placebo [29].

We have found one placebo-controlled study of CyA in combination with another DMARD. Tugwell et al.
[60] reported significant improvements in patients treated with methotrexate (MTX) and CYA vs MTX and placebo. In the open and uncontrolled study by Bensen et al. [32], demonstrating efficacy when adding CYA to ongoing PGT or MTX, previous therapy or disease duration were not mentioned. The mean dose of CYA was 250 mg/day, which was higher than in our study.

Pending new approaches to the treatment of RA, it is essential to continue the systematic exploration of various ways of using existing drugs, single or combined, more efficiently and also to share the experience of trials with only modest results with the rheumatology community.

CONCLUSIONS
Consistent with previous studies combining PGT with other DMARDs, the additive effect of combining PGT with CYA had a small impact on clinical outcome. No increased risk of side-effects of either drug was observed. Comparisons with studies on single therapy with CYA suggested that the observed outcome of adding CYA to PGT could be expected from low-dose CYA therapy. We did not find it justifiable to continue PGT with decreasing efficacy by adding low-dose CYA in RA patients with long disease duration.

ACKNOWLEDGEMENTS
The skilful assistance of Birgitha Archenholtz, OT as the blinded examiner is greatly appreciated. Statistical advisers were Anders Odén and Helena Johansson. Financial support was obtained from Gothenburg University, Göteborgs läkaresällskap and Sandoz, Sweden.

REFERENCES


