EXTENDED REPORT

Long term efficacy and safety of cyclosporin versus parenteral gold in early rheumatoid arthritis: a three year study of radiographic progression, renal function, and arterial hypertension


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Objective: To compare the three year safety and efficacy of cyclosporin and parenteral gold in the treatment of early, active, severe rheumatoid arthritis (RA), and to study the reversibility of cyclosporin associated renal dysfunction in patients who discontinued cyclosporin treatment.

Methods: The patients continued to receive cyclosporin or parenteral gold in an 18 month open extension to an 18 month randomised, parallel group study. The main efficacy variable was blinded evaluation of radiographic progression of joint damage. Safety variables included serum creatinine, calculated creatinine clearance, and blood pressure.

Results: Radiographic progression during follow up was similar in both groups. About 60% of the patients in the intention to treat groups (n=272) and about half of the patients in the completer groups (n=114) had definite radiographic progression in joint damage (increases > 6 in the Larsen-Dale score), and about one in three also had substantial progression (>18 increase in Larsen-Dale score). Both systolic and diastolic blood pressure were significantly increased in the cyclosporin group compared with the gold group, and 12/139 (9%) versus 3/139 (2%) (p=0.03) had notably raised blood pressure. The mean serum creatinine increased by 28% at the treatment end point in the cyclosporin group as compared with 7% in the gold group. The mean calculated creatinine clearance was reduced by 16% and increased by 1% in the cyclosporin and gold groups, respectively, at the end of the study. At the final follow up visit after discontinuation of cyclosporin (at least three months after treatment was stopped) the mean serum creatinine was increased by 15% and creatinine clearance reduced by 16%. Sustained increases in serum creatinine at this post-treatment end point were mostly seen in patients with a raised serum creatinine during treatment at least 50%.

Conclusion: Three year changes in radiographic damage during cyclosporin and parenteral gold were similar in patients with early, active RA. Abnormal renal function and raised blood pressure were often seen in the cyclosporin treated patients.

Rheumatoid arthritis (RA) is a chronic, debilitating condition, characterised by progressive erosion of the articular surfaces of joints. Joint damage is cumulative, with rapid destruction in the early stages. As a result, early intervention is advocated to slow radiographic destruction, and disease modifying antirheumatic drugs (DMARDs), including parenteral gold, decrease the rate of progression of structural joint damage.

Several studies over the past decade have shown that cyclosporin is effective in the treatment of active, severe RA refractory to other treatments, has possible benefits over other antirheumatic drugs, and is effective in combination with methotrexate. The efficacy of cyclosporin in early, severe RA has recently been evaluated in an open, randomised, 18 month multicentre study with a blinded radiographic end point. The radiographic data showed that cyclosporin treatment did not differ from parenteral gold in retarding progression of joint damage over an 18 month treatment period. The results of an 18 month extension to that original study are reported here.

The primary objective of this extension was to compare the safety of three years of treatment with cyclosporin or parenteral gold in adults with early, active, severe RA. The secondary objective was to compare progression of radiographic damage and changes in functional ability. We also wanted to determine the reversibility of cyclosporin associated renal dysfunction in patients who discontinued cyclosporin treatment prematurely.

PATIENTS AND METHODS

Patients and design
This study is an extension of the SIMERA trial which has been reported previously. Briefly, patients aged between 18 and 65 years, with a diagnosis of early, active, and severe RA were eligible for inclusion in the original study. Patients were excluded if they had previously received cyclosporin or parenteral gold treatment; had impaired kidney or liver function, hypertension, a history of malignancy, uncontrolled infection, leucopenia or thrombocytopenia, hereditary angioedema, epilepsy, gastrointestinal ulcer or malabsorption syndrome; or were hypersensitive to, or otherwise intolerant of, gold compounds. In the original trial, 375 patients with early, active, and severe RA were randomly split in equal numbers to receive cyclosporin or parenteral gold. The patients were stratified according to their continuing treatment with non-steroidal anti-inflammatory drugs; RA, rheumatoid arthritis.

Abbreviations: DMARDs, disease modifying antirheumatic drugs; HAQ, Health Assessment Questionnaire; ITT, intention to treat; NSAIDs, non-steroidal anti-inflammatory drugs; RA, rheumatoid arthritis
corticosteroids. The duration of the main study was 18 months and the patients were evaluated for markers of RA progression, including x-ray assessment of joint damage and disability index, and for the incidence of adverse events.

All patients who were treated in the main study were eligible for the extension, whether or not they were receiving the original study drug. The participating patients continued to receive cyclosporin, parenteral gold (sodium aurothiomolate), or other DMARDs (if the original trial drug had been discontinued) for a further 18 months.

Cyclosporin (Sandimmun, soft gelatin capsules containing 25 mg or 100 mg of the drug) was taken as two doses a day (morning and evening). The rules for cyclosporin dosing remained the same as in the original study; that is, the dose could be adjusted to optimise efficacy and tolerability, with a maximal dose of 5 mg/kg/day. It was obligatory to reduce the cyclosporin dose by 25% if serum creatinine increased >50% above the pretreatment baseline level, while the dose could not be increased if the serum creatinine was >30% above the pretreatment baseline value.

Parenteral gold was given in commercially available formulations according to local practice. Usually gold was continued with monthly 50 mg injections subsequent to an initial cumulative dose of 1000 mg obtained after weekly 50 mg injections. Patients who discontinued cyclosporin or gold could receive other DMARDs. However, treatment with DMARD combinations was not permitted. Any drugs known to alter cyclosporin pharmacokinetics were permitted only if no alternative was available. Low dose corticosteroids (<10 mg prednisolone/day) and non-steroidal anti-inflammatory drugs (NSAIDs) were allowed.

Both the original study and this extension were conducted in accordance with the standards of Good Clinical Practice, US Federal Regulations and the Declaration of Helsinki. Written informed consent was obtained from all eligible patients who agreed to participate in the study.

Assessments
For patients receiving cyclosporin, blood pressure and serum creatinine concentrations were monitored, and dose adjustments made if necessary, at two month intervals during study treatment. Patients who discontinued cyclosporin and who did not have any clinical abnormality at the time of discontinuation were monitored at six month intervals thereafter. Patients who discontinued cyclosporin and had a clinical abnormality were monitored at two month intervals until for six months or until the abnormality had resolved. All patients receiving gold were followed up at six month intervals.

Structural joint damage was determined from radiographs of the hands, wrists, and feet. In the original study, radiographs were taken at the beginning (month 0), after 10 months, and at the end (month 18). During the extension phase, x-ray examinations were made at the end of follow up (month 36), and also in patients withdrawing from treatment. The radiological progression between months 0 and 36 was based on a re-evaluation of the baseline x-ray findings together with the month 18 and month 36 x-ray findings. At this re-evaluation all radiographs from each patient were assessed at the same time by a "blinded" radiologist who read the radiographs in a random order. For each patient, 32 joints were evaluated to yield an overall joint damage score (Larsen-Dale score), wrist joint weight 5, other joints weight 1, total score range 0–200). In addition to the Larsen-Dale score the number of eroded joints (score range 0–32) and total number of erosions were also determined.

Physical disability was determined using Health Assessment Questionnaire (HAQ) scores (range 0–3), determined at six month intervals from month 0 to month 36. Patients' subjective assessment of disease activity was based on the disease activity at the end of follow up and was reported using a five point verbal rating scale.

Adverse events were recorded during treatment and after discontinuation of the study drug to month 36. Treatment safety was evaluated at two month intervals in the cyclosporin group and at six month intervals in the gold group in all patients who had received at least one dose of the study drug. All adverse events were characterised according to their severity and likely relation to the study drug. Renal function was assessed by comparing the serum creatinine concentration and calculated creatinine clearance at the start of the study with that at the end of the extension. A notable rise in blood pressure was defined as follows: systolic blood pressure of at least 180 mm Hg with an increase of at least 40 mm Hg or systolic blood pressure of more than 200 mm Hg; diastolic blood pressure at least 105 mm Hg with an increase of at least 30 mm Hg or diastolic blood pressure more than 115 mm Hg.

The reversibility of the cyclosporin induced renal dysfunction was studied in all patients who provided serum creatinine values before cyclosporin treatment, during cyclosporin treatment, and at least three months after discontinuation of cyclosporin. Thus, the groups studied for the reversibility of renal function and for safety and efficacy were not identical because the former also included patients who did not participate in the extension.

Statistical analyses
The main efficacy variables were the radiographic score for joint damage and the HAQ score. Safety variables included serum creatinine concentration and blood pressure.

For efficacy end points, analyses were made on an intention to treat (ITT) and completer basis, without applying the last observation carried forward method. The “ITT group” comprised all patients who had received at least one dose of cyclosporin or gold in the original study (n=360) and who provided efficacy data on at least one clinic visit during the extension. The “completer group” comprised all patients who had received the study drug for at least 15 of the 18 months’ duration of the original study and for at least 15 of the 18 months' duration of the extension study. The “safety group” included all patients who had received at least one dose of cyclosporin or gold and who had provided safety data at least once during the extension. The “reversibility of the cyclosporin induced renal dysfunction group” included patients who provided serum creatinine values before and during cyclosporin treatment and at least three months after the discontinuation of cyclosporin.

Continuous data were summarised using means, standard deviations (SD), medians and ranges. Categorical data were summarised using frequency tables. Patient characteristics were compared using Student's t test (continuous data) or Fisher's exact test (categorical data). All statistical tests were two sided with a 5% significance level. Treatment differences in efficacy variables were evaluated by two way analysis of variance for baseline values and two way analysis of covariance for changes from baseline values, with treatment group, country, and their interaction as factors in the statistical model.

RESULTS
Patients
Two hundred and seventy eight patients from the original study (159 from each group) entered the extension and were included in the safety analysis. Six patients (three in each group) provided no efficacy data during the extension and were therefore excluded from the ITT group (that is, the ITT group comprised 136 in each group) (table 1). Of these, 81 in the cyclosporin group and 76 in the gold group started the extension with their original drug, and there were 61 and 53 patients, in the cyclosporin and gold groups, respectively. The “reversibility of the cyclosporin induced renal dysfunction” group comprised 91 patients.
The demographic characteristics at baseline between the two treatment groups were not significantly different. Demographic characteristics were also similar in the cohorts of the original and the extension study (table 1).

**Treatment**
The mean cyclosporin dose was 3.0 mg/kg/day at the start of the extension (month 18), 2.8 mg/kg/day by month 24, and 2.7 mg/kg/day by month 36. NSAIDs were given to 83% of the patients of each of the two randomised treatment groups and systemic corticosteroids to 58% of patients randomly allocated to receive cyclosporin and to 50% of the gold group. After stopping the study drug methotrexate was used by 43 (32%) in the cyclosporin group and 44 (32%) in the gold group.

**Efficacy**
Table 2 shows the changes in the Larsen-Dale score, number of eroded joints, and number of erosions between the original study baseline, month 18, and month 36. No significant difference in the extent of radiographic progression assessed by any of these methods was detected between patients in the cyclosporin and gold groups, either in the ITT (table 2) or completer groups (data not shown).

The Larsen-Dale score increased numerically by more than six in a similar proportion (62%) in both groups. A substantial increase in joint damage (that is, an increase in Larsen-Dale score of more than 18) by month 36 was seen in 46/121 (38%) in the cyclosporin group and 44 (32%) in the gold group. Stoping the study drug methotrexate was used by 43 (32%) in the cyclosporin group and 44 (32%) in the gold group.

The ability of patients to carry out routine daily activities improved between the original study baseline and month 36 in both treatment groups (data not shown). Patients in the cyclosporin group (ITT) showed a slightly greater improvement than patients receiving gold (mean (SD) change in HAQ score by month 36: cyclosporin –0.54 (0.61) from a baseline value of 1.13 (0.54); gold –0.45 (0.70) from a baseline value of 1.08 (0.62); p=0.04). Two way analysis of covariance of changes in HAQ score from baseline gave a difference in adjusted means (cyclosporin–gold) of –0.17 (95% confidence interval –0.33 to –0.01).

No significant difference between treatment groups was seen in patients’ assessments of changes in disease activity. Fifty five per cent of cyclosporin patients in the extension study (ITT group) considered their disease to be “much better” at month 36 than at baseline, compared with 49% of patients receiving gold.

**Long term renal function**
The mean serum creatinine increased by 28% at the treatment end point (when treatment was stopped or at the end of the study) in the cyclosporin group as compared with 7% in the gold group. In the completer group serum creatinine increased at month 36 by 23% and 5% in the cyclosporin and gold groups, respectively. In the safety group the mean calculated creatinine clearance was reduced by 16% in the cyclosporin group and by 1% in the gold group at month 36 as compared with the pretreatment baseline values.

The reversibility of cyclosporin induced renal dysfunction was studied in 91 patients who had sufficient data for analysis, including a serum creatinine value at least three months from baseline comparisons.

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**Table 1**  Patient characteristics (mean (SD) for continuous variables, number (%) for counts)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cyclosporin (n=177)</th>
<th>Gold (n=183)</th>
<th>Cyclosporin (n=136)</th>
<th>Gold (n=136)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex</td>
<td>121 (68)</td>
<td>128 (70)</td>
<td>93 (68)</td>
<td>96 (71)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>48.2 (11.4)</td>
<td>48.7 (10.8)</td>
<td>47.9 (11.1)</td>
<td>49.2 (10.5)</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>0.94 (0.80)</td>
<td>0.92 (0.86)</td>
<td>0.90 (0.78)</td>
<td>1.03 (0.85)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>70.8 (13.5)</td>
<td>70.1 (13.1)</td>
<td>71.0 (13.0)</td>
<td>70.1 (13.3)</td>
</tr>
<tr>
<td>Previous DMARD</td>
<td>74 (42)</td>
<td>81 (44)</td>
<td>57 (42)</td>
<td>61 (45)</td>
</tr>
<tr>
<td>Previous corticosteroids</td>
<td>62 (35)</td>
<td>82 (45)</td>
<td>48 (35)</td>
<td>60 (44)</td>
</tr>
<tr>
<td>Number of swollen joints</td>
<td>8.6 (3.5)</td>
<td>8.6 (3.7)</td>
<td>8.6 (3.5)</td>
<td>9.2 (3.7)</td>
</tr>
<tr>
<td>ESR (mm/1st h)</td>
<td>48.1 (25.5)</td>
<td>42.0 (24.1)</td>
<td>46.6 (24.6)</td>
<td>42.7 (24.5)</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>34.8 (39.0)</td>
<td>31.6 (35.0)</td>
<td>33.3 (35.7)</td>
<td>30.3 (32.8)</td>
</tr>
</tbody>
</table>

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**Table 2**  Radiographic progression of joint damage in the intention to treat population (n=272, mean (SD) and median (IQR))

<table>
<thead>
<tr>
<th>Score</th>
<th>Cyclosporin (n=121)*</th>
<th>Gold (n=121)*</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Increase from baseline by month 18</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Larsen-Dale score</td>
<td>1.48 (1.88) 8 (0.24)</td>
<td>1.40 (1.89) 6 (0.22)</td>
<td>0.81</td>
</tr>
<tr>
<td>Number of eroded joints</td>
<td>1.00 (13.1) 6 (0.17)</td>
<td>1.03 (13.1) 6 (0.14)</td>
<td>0.42</td>
</tr>
<tr>
<td>Increase from baseline by month 36</td>
<td>15.5 (17.3) 12 (0.25)</td>
<td>13.9 (17.2) 10 (1.20)</td>
<td>0.52</td>
</tr>
<tr>
<td>Number of erosions</td>
<td>4.0 (5.1) 2 (0.7)</td>
<td>4.0 (5.2) 2 (0.7)</td>
<td>0.60</td>
</tr>
<tr>
<td>Increase from baseline by month 18</td>
<td>2.6 (3.3) 2 (0.4)</td>
<td>2.8 (4.2) 1 (0.4)</td>
<td>0.68</td>
</tr>
<tr>
<td>Increase from baseline by month 36</td>
<td>3.7 (4.3) 3 (0.6)</td>
<td>3.8 (5.4) 2 (0.5)</td>
<td>0.61</td>
</tr>
<tr>
<td><strong>Increase from baseline by month 36</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improvement from baseline by month 18</td>
<td>7.5 (13.2) 2 (0.10)</td>
<td>7.5 (13.6) 2 (0.9)</td>
<td>0.67</td>
</tr>
<tr>
<td>Improvement from baseline by month 36</td>
<td>5.8 (9.4) 3 (0.8)</td>
<td>5.3 (8.5) 2 (0.6)</td>
<td>0.25</td>
</tr>
<tr>
<td>Improvement from baseline by month 36</td>
<td>10.0 (13.3) 6 (1.15)</td>
<td>8.4 (11.7) 4 (1.12)</td>
<td>0.30</td>
</tr>
</tbody>
</table>

IQR, interquartile range
*Thirty patients failed to provide complete x ray findings between baseline and month 36; †p value from two way analysis of covariance for baseline comparisons and from two way analysis of covariance for change from baseline comparisons.
Serious adverse events and withdrawals

Serious adverse events during exposure to the study drug in the extension study (that is, before or on the last day of the study drug) were seen in 17 patients (12/84 (21%) patients who were receiving cyclosporin compared with none in the gold group. A drug to treat hypertension was used by 18/84 (21%) patients who were receiving cyclosporin at the beginning of the extension as compared with 9/76 (12%) patients in the gold group.

Table 3  Percentage serum creatinine increase from baseline at the last post-treatment observation in subgroups with different levels of maximum creatinine increases during cyclosporin treatment

<table>
<thead>
<tr>
<th>Maximum % increase in serum creatinine during treatment</th>
<th>n</th>
<th>Mean (range) baseline serum creatinine (µmol/l)</th>
<th>% Increase in serum creatinine at last post-treatment end point</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30</td>
<td>35</td>
<td>75 (51 – 101)</td>
<td>7.7 (14.5)</td>
</tr>
<tr>
<td>30–50</td>
<td>18</td>
<td>72 (54 – 98)</td>
<td>7.3 (15.0)</td>
</tr>
<tr>
<td>≥50</td>
<td>31</td>
<td>70 (51 – 97)</td>
<td>25.3 (17.5)</td>
</tr>
</tbody>
</table>

The number of patients reporting adverse events was 56 in the cyclosporin group and 36 in the gold group. Of these events, 34 and eight, respectively were considered related to the study drug, and 10 versus 0 patients reported events that were classified as severe. The pattern of adverse events was as expected, with dominance of hypertension, rise in creatinine, and gastrointestinal discomfort in the cyclosporin group; cutaneous reactions in the gold group. The proportion of patients who received the study drug and who withdrew during the extension study as a result of adverse events was 10/84 (12%) in the cyclosporin group and 4/76 (5%) in the gold group. Of these, three patients withdrew from cyclosporin treatment owing to raised creatinine and three stopped gold treatment because of rash.

DISCUSSION

This 18 month, open extension study showed that joint damage progressed at similar rates in patients with early, active, severe RA who received three years of treatment with cyclosporin or parenteral gold. About one third of the patients in both groups had insignificant or no progression of joint damage; these patients can perhaps be regarded as treatment successes, although radiographically stable disease has been seen in about 10% of patients with early RA even without DMARD treatment. In the extension study as a result of adverse events was 10/84 (12%) in the cyclosporin group and 4/76 (5%) in the gold group. On the other hand, major proportions of the patients (about 50–60%) progressed above limits close to values found as the measurement error with the Larsen-Dale method in other studies, and about one third also had substantial progression defined as an increase in the Larsen-Dale score of 18 or more. When interpreting these findings, it should be noted that patients included in this study had active disease with markers known as predictors of progressive joint damage (rheumatoid factor, early erosive disease, or raised acute phase reactants). However, the results also indicate that at least one third of the patients needed more effective treatment. The present results may therefore be of interest when the role of DMARDs and the new expensive and effective tumour necrosis factor blocking agents is discussed.

Despite progression of joint damage, the ability to carry out everyday activities, shown by a decrease in the HAQ score, improved in both treatment groups. This finding supports the observation that physical functioning is not determined by structural changes alone, at least during the early phase of RA. A similar lack of association between structural damage and function has also been seen previously in early RA. The functional improvement reflects the improved joint function reported in earlier studies of treatment with gold and cyclosporin. In our study the improvement in the disability score over the 36 months of treatment was slightly greater for patients receiving cyclosporin than for those receiving gold (ITT group). However, a somewhat higher proportion of cyclosporin treated patients was also taking corticosteroids and the level of statistical significance was borderline.

A major concern about the long term use of cyclosporin in RA is the agent’s potential nephrotoxicity. This study...
confirms that an increase in serum creatinine as well as blood pressure is often seen in cyclosporin treated patients, both when considering this treatment arm separately and in comparison with gold injections. Furthermore, the average serum creatinine concentration remained raised in the cyclosporin group, even after discontinuation of treatment (table 3).

Renal biopsies of patients with RA have suggested that structural nephropathy induced by cyclosporin is rare and that it does not progress when treatment is stopped. However, no systematic prospective biopsy data are available in patients with RA. One such study of 30 patients with psoriasis, biopsied annually for eight years, reported progressive arterional hyalisation and interstitial fibrosis. The long term data of renal function during and after cyclosporin treatment of RA are sparse. Assan et al reported a long term follow up of patients with type I diabetes who had been treated with high doses of cyclosporin (initial doses 7.5–10 mg/kg/day). A fraction of the patients had structural changes in the renal biopsy specimens taken after about 13 months’ treatment. Their results showed an improvement in renal function after discontinuation of cyclosporin irrespective of the renal biopsy findings. Van den Borne et al followed up 83 patients with RA originally receiving cyclosporin treatment. When cyclosporin was stopped, increases in serum creatinine were partially irreversible in patients who had creatinine increases >30% compared with baseline. It should, however, be kept in mind, that creatinine is a relatively insensitive marker of renal function, not least in patients with RA. The present results are in line with these above results: renal function improved when cyclosporin was stopped, although a full recovery was generally not seen. The decrease of renal function as compared with pretreatment baseline was, however, rarely of major clinical significance. The highest post-treatment increase compared with baseline was 64% (table 3).

Long term studies usually face methodological concerns that may influence interpretation of the results. The present extension was planned after the start of the original 18 month study, which required a new informed consent and therefore also had an impact on the number of patients lost for the complete 36 month follow up. However, the patient characteristics of the extension study group did not differ from those of the original group (table 1), but we cannot exclude the possibility that the results were, to some extent, influenced by some unknown selection bias. Another methodological limitation is related to the treatment regimens used in this study. No universal agreement exist about the optimal regimen of gold related to the treatment regimens used in this study. No uniform protocol was being used for the patients treated with cyclosporin deviated slightly from the present universally accepted recommendations for the use of cyclosporin in RA. The approved recommendations restrict the allowed rise in serum creatinine concentration to 30% above the pretreatment value, whereas the SIMERA protocol as well as the study by van den Borne et al tolerated an increase up to 50%. Even higher increases were seen in the present study (table 3).

The observed “reversibility of the cyclosporin induced renal dysfunction group” is somewhat biased because data on reversibility were available only from patients who stopped the cyclosporin treatment, and did not incorporate those patients who were “treatment successes” and continued to receive treatment with cyclosporin. Thus the data are not fully representative of the renal effects of cyclosporin in current routine practice, but they are valuable in evaluating suggested dose strategies. Analysis of the reversibility of the renal function (table 3) showed that the rise in serum creatinine during prescription is a reliable surrogate marker for reversibility of renal function when cyclosporin is stopped. It also confirmed the reversibility of renal function below the baseline-creatinine +30% is relatively safe for long term renal function during cyclosporin treatment.

In conclusion, the results from this extension study show that the efficacy of cyclosporin is similar to that of parenteral gold in the treatment of early active and severe RA. However, definite progression in joint damage was seen in about half of the patients completing the study drug over three years. This result should be taken into account when selecting gold or cyclosporin in early and active RA. The comparative safety data for renal function and blood pressure favour gold rather than cyclosporin. This study emphasizes that rigorous monitoring of blood pressure and serum creatinine levels and strict adherence to recommended dose adjustments according to the creatinine level are mandatory in cyclosporin treated patients to reduce the risk of long term, and possibly permanent, damage of the renal function in some patients.

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