Substitution of conventional cyclosporin with a new microemulsion formulation in renal transplant patients: results after 1 year

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Abstract
Background. A new galenic form of cyclosporin A has been developed, based on microemulsion technology. The bioavailability of the compound is relatively independent of food intake and bile flow. It was the purpose of this prospective clinical trial to study the safety of the microemulsion form of cyclosporin A.

Methods. Three hundred and two renal transplant patients, stratified according to transplant age, were switched from the conventional to the new microemulsion formulation of cyclosporin A. A 1:1 conversion ratio was used. Measurements included CsA levels, S-creatinine, liver enzymes, uric acid, and blood pressure. Measurements were performed at baseline and on days 4, 8, 15, 29 and months 3, 6 and 12 after conversion. Dose adjustments were performed to achieve trough levels of 80–120 ng/ml.

Results. Within the 12-month observation period the cyclosporin dose was reduced by 14.7% (from 204 ± 60 mg/day at baseline to 174 ± 51 mg/day after conversion, P<0.001). Acutely, i.e. by day 8, a 1:1 dose conversion resulted in a modest increase of mean drug trough levels (from 114 ng/ml at baseline to 120 ng/ml, P<0.01). This increase was accompanied by an increase in serum creatinine concentration, a decrease in calculated creatinine clearance, and an increase in uric acid values (P<0.05). Liver enzymes remained unchanged while systolic and mean arterial blood pressure decreased (P<0.05). After 1 month, drug trough levels had decreased to baseline (112 ng/ml) and remained there until month 6. They were significantly lower after 12 months (102±33 ng/ml, P<0.001). Creatinine clearance values increased to above baseline at 6 and 12 months. Within the 1-year period there occurred 24 (=8%) episodes of biopsy-proven rejection and seven episodes of cyclosporin-attributed nephrotoxicity.

Conclusions. The 1:1 conversion from conventional cyclosporin A to the microemulsion formulation is efficacious and safe, but an initial dose reduction of 10% is advised in patients with trough levels in the high-normal range.

Key words: cyclosporin as microemulsion; nephrotoxicity; rejection episodes; renal transplantation

Introduction
Cyclosporin is not an easy drug to use. The drug's pharmacokinetic profile is difficult to predict because its water insolubility results in variable gastrointestinal absorption [1–5]. A new microemulsion formulation has been developed, the bioavailability of which is independent of food intake and bile flow [6–8]. The simpler pharmacokinetics of the microemulsion formulation allow an improved prediction of whole blood concentrations, greater precision when treating rejection, and an increased margin of safety [9–11]. However, the microemulsion formulation could lead to toxic drug levels and decreased renal function if these characteristics are not considered when switching a patient from the conventional to the microemulsion formulation. On the other hand, reduction of drug dose could result in lower levels and greater chances for rejection. Our aim was to investigate the feasibility and safety of a 1:1 drug conversion in 302 patients with stable renal allografts.

Subjects and methods

The study was approved by the University's Committee on Human Subjects and informed consent was obtained. Subjects were invited to participate if they had stable serum...
creatinine values, stable drug trough levels, and had not been hospitalized for the 6 months prior to the study. At least eight regular visits to the outpatient clinic were mandatory, which included an examination by a physician and laboratory values (see below) at day 1 (baseline and conversion), and days 4, 8, 15, and 29, as well as at months 3, 6 and 12. Three hundred and two (302) patients were randomly stratified according to graft age: >5 years (n = 84, 28.1%); 3–<5 years (n = 65, 21.7%); 1–<3 years (n = 103, 34.5%); <1 year (n = 47, 15.7%). The obligatory conversion ratio between Sandimmun and Sandimmun Neoral (SN) was 1:1 at start. The drug dose was adjusted to maintain the levels within the therapeutic window of 80–120 ng/ml monoclonal trough level.

Serum creatinine, uric acid, and aspartate aminotransferase were measured by automated methods. Creatinine clearance was calculated from the formula of Cockcroft and Gault [12] and Keller [13]. Whole-blood trough levels were measured by an immunoassay (TDX, Abbott Co., Wiesbaden, Germany). Blood pressure and heart rate were measured by a trained nurse with a mercury sphygmomanometer in the patients after they had been sitting quietly for 5 min. CsA doses were routinely registered.

Quality of life before and after the switch was assessed using a numerical red to white to brown colored Welzel scale [14]. Serious adverse events were primarily classified according to the Adverse Reaction Terminology of the WHO (WHOART). Statistical analysis was performed with the SAS statistical programm. Due to logistical problems and the limited financial support it was not possible to investigate a real control group. However, the analysed 302 patients were randomly selected according to graft age from the total outpatient population of roughly 750 patients. Therefore the study design called for a critical descriptive analysis only with a comparison of baseline values to subsequent values during treatment. Thus we compared the postconversion values for all parameters with the preconversion values by means of a non-parametric 'sign' test. This approach provided a highly critical view of the changes. The large number of subjects allowed us to detect very small changes that would normally not come to clinical attention. For comparisons across the strata of the total sample we relied on t test as appropriate. Data are expressed as median and range, or mean ± SD to display the fiducial limits. A P value ≤0.05 was considered significant.

Results

The results are summarized in Table 1.

Demographic data

Three hundred and two patients were enrolled in the study. Sixty percent of patients were men; their mean age was 51 years (range 19–70 years). On average, renal transplantation had been performed 43 (range 1–170 months) prior to the study. The overall incidence of previous rejection episodes in these patients was 36%. The last rejection had occurred on average 21 months (range 0.5–110 months) before the drug change. After 3, 6 and 12 months, 272, 275 and 280 patients respectively, could be analysed. The mean duration of haemodialysis treatment was 42 months.

Antihypertensive medication

At start 88% of the study population needed concomitant antihypertensive medication including various types of calcium antagonists (n = 193, 27.5%), diuretics (n = 168, 24%), beta-blockers (161, 23%), vasodilating agents (n = 80, 11.4%) ACE inhibitors (43, 6.1%) and/or clonidine (n = 56, 8%). The number of antihypertensive drugs per patient was as follows: single drug, 67 patients (24.6%); two drugs, 114 patients (41.9%); three drugs, 89 patients (32.7%); four drugs, two patients (0.7%). There was no substantial difference after the 12-months study period (NS).

Immunosuppressive medication and dose

According to the centre's policy the immunosuppressive protocol consisted in general of a 'double drug' maintenance regimen using cyclosporin and low-dose steroids (immunosuppressive drugs at start (n = 302/100%) versus after 1 year (n = 280/100%); cyclosporin monotherapy, n = 16/5.3% versus n = 21/7.5%; cyclosporin and steroids, n = 250/82.8% versus n = 220/78.6%; cyclosporin and azathioprine, n = 5/1.7% versus n = 8/2.9%; cyclosporin, steroids, and azathioprine, n = 31/10.3% versus n = 31/11.1%. Thus only a few patients at special risk were under an additional treatment with azathioprine. Their number did not change significantly over the study period. Routinely the dose of methylprednisolone was adjusted to 4 mg/day at 6 months after transplantation. The mean dose of conventional cyclosporin at start (on average unchanged for 3.5. months prior to conversion) was 204 ± 60 mg/day (2.9 ± 1.0 mg/kg per day) with similar morning and evening doses (103 mg morning vs 101 mg evening). Half the patients were begun on the liquid formulation of microemulsion cyclosporin, while the other half was given microemulsion-containing capsules. No significant differences were found in either drug levels, renal function, or safety parameters, when the liquid and capsule microemulsion formulations were compared.

Dose reductions were mainly performed on days 8, 15, and 29. During the defined 12-months observation a substantial dose reduction in response to measured drug levels, was attained. Compared to baseline (day 1), by month 1, 50.5% of the patients were receiving less microemulsion cyclosporin, compared to the earlier amount of conventional cyclosporin. The overall reduction was 13.4% per patient at day 29 and 14.7% per patient at month 12 or about 900 mg/month per patient; 20% required no change in cyclosporin dosage, while a small number (10.4%)—usually, with very low levels at the start—required an increase in dose. The dose changes compared to baseline at months 1, 3, 6, and 12 are shown in Figure 1a. In patients with trough levels >120 ng/ml the average dose reduction reached 26.2% of the previous total dose and dose reductions were achieved in 77.8% of patients (Figure 1b). Thus the additional dose reduction related to the predefined therapeutic window of 80–120 ng/ml accounted for approximately 6% only.
Table 1. Summarized results after one year

<table>
<thead>
<tr>
<th>Day/Month</th>
<th>Units</th>
<th>M3</th>
<th>n = 272</th>
<th>M6</th>
<th>n = 275</th>
<th>M12</th>
<th>n = 280</th>
</tr>
</thead>
<tbody>
<tr>
<td>CsA dose</td>
<td>mg/day</td>
<td>175.37</td>
<td>(53.85)</td>
<td>171.9</td>
<td>(49.6)</td>
<td>174.3</td>
<td>(51.1)</td>
</tr>
<tr>
<td>CsA trough level</td>
<td>ng/ml</td>
<td>108.8</td>
<td>(30.9)</td>
<td>110.1</td>
<td>(32.6)</td>
<td>101.5</td>
<td>(32.3)</td>
</tr>
<tr>
<td>Creatinine</td>
<td>mg/dl</td>
<td>1.46</td>
<td>(0.85)</td>
<td>1.48</td>
<td>(0.8)</td>
<td>1.54</td>
<td>(0.97)</td>
</tr>
<tr>
<td>GFR</td>
<td>ml/min</td>
<td>68.5</td>
<td>(25.1)</td>
<td>67.5</td>
<td>(24.6)</td>
<td>66.4</td>
<td>(25.75)</td>
</tr>
<tr>
<td>Cockcroft/Gault</td>
<td>ml/min</td>
<td>67.2</td>
<td>(11.2-143.7)</td>
<td>68</td>
<td>(10.1-154.7)</td>
<td>64.8</td>
<td>(8.9-129.7)</td>
</tr>
<tr>
<td>ALAT</td>
<td>U/l</td>
<td>2.41</td>
<td>(1.46)</td>
<td>2.67</td>
<td>(1.53)</td>
<td>2.75</td>
<td>(1.49)</td>
</tr>
<tr>
<td>HR</td>
<td>/min</td>
<td>68</td>
<td>(40-108)</td>
<td>72</td>
<td>(40-108)</td>
<td>72</td>
<td>(44-104)</td>
</tr>
<tr>
<td>Mood</td>
<td>1=excellent</td>
<td>2.0</td>
<td>(1-8)</td>
<td>2.0</td>
<td>(1-9)</td>
<td>2.0</td>
<td>(1-9)</td>
</tr>
</tbody>
</table>

D1: baseline; day of switch to Sandimmun Neoral. 1 P<0.05, 2 P<0.01, 3 P<0.001 associated with sign test proving changes from baseline. Note: In each cell of the table entries have to be read as follows: Mean (standard deviation). Median (range) CsA, cyclosporin; GFR, glomerular filtration rate; ALAT, alanine aminotransferase; MBP, mean arterial blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

Influence of graft age

The 302 patients were randomly stratified according to graft age: >5 years (n = 84, 28.1%); 3–5 years (n = 65, 21.7%); 1–3 years (n = 103, 34.5%); <1 year (n = 47, 15.7%). A nearly linear, inverse correlation between cyclosporin dose and graft age was found at all visits. Patients transplanted for more than 5 years prior to the study required the lowest dose of the microemulsion formulation (day 1: 183±51 mg/day) compared to patients transplanted between 1 month to 1 year before study entry, who instead received the highest dose (day 1: 240±66 mg/day). Nonetheless, a similar percentage reduction in microemulsion cyclosporin dose occurred.
in all graft age groups. Thus, despite differing drug doses, graft age did not significantly influence dose reduction.

Cyclosporin trough level (Figure 2)

During the study period a slight but statistically significant increase in cyclosporin trough level was seen on day 4 (114 ng/ml baseline vs 117 ng/ml, +4.3%) and day 8 (114 ng/ml baseline vs 120 ng/ml, +5%, \( P = 0.01 \)). On day 29 and after 6 months no differences were seen compared to baseline (114 ng/ml, 110 vs 114 ng/ml, respectively (\( P = N S \)). However, at month 12 cyclosporin trough levels were significantly reduced (102 ng/ml, \( P \leq 0.001 \)) when compared to baseline (114 ng/ml).

At study entry, 148 (49%) of the patients had cyclosporin trough levels that were within the therapeutic range; 38 (13%) had levels below, and 112 (38%) above the given limits. One month after conversion to the microemulsion formulation, cyclosporin trough levels in 181 (60%) patients had reached the therapeutic range. Only 20 (7%) of those patients remained below that value. However, in 98 patients (33%), the level still exceeded the therapeutic range.

Safety parameters (Figures 2 and 3)

The effects of drug substitution on calculated creatinine clearance, the mean daily drug dose and the drug trough levels are given in Figure 2. After conversion from conventional to microemulsion cyclosporin, mean
serum creatinine concentrations increased slightly from baseline (1.52 baseline vs 1.54 mg/dl, day 8: $P \leq 0.05$, Median: 1.36 vs 1.38 mg/dl). Calculated creatinine clearance was inversely correlated with cyclosporin trough levels, with a maximal reduction by day 8 of 62.9 ± 21.5 ml/min baseline vs 61.7 ± 20.6 ml/min, $P \leq 0.05$. However, after 6 and 12 months renal function had clearly improved. Calculated creatinine clearance increased from 62.9 ± 21.5 ml/min baseline to 67.5 ± 24.6 ml/min (month 6) and 66.4 ± 25.8 ml/min (month 12), $P \leq 0.001$ respectively. Figure 3, panel A-C shows the percentage change compared to baseline at day 1 in all patients with regard to cyclosporin trough level (A), serum creatinine concentration (B) and creatinine clearance (C). Thus, roughly two-thirds of the study population developed an improvement of renal function after 1 year.

The uric acid concentrations were moderately increased at day 15 (8.15 mg/dl baseline vs 8.30 mg/dl, +1.8%, $P \leq 0.05$) and day 29 (8.49 mg/dl, +4.2%, $P \leq 0.05$). However, at month 6 they had returned to baseline values (8.20 mg/dl, NS). After 12 months, there was another moderate increase to 8.34 mg/dl, $P \leq 0.05$. Aspartate aminotransferase levels remained unchanged during the 12 months observation period.

Systolic (144 ± 19 mmHg baseline, vs 138 ± 17 mmHg, $P \leq 0.05$), diastolic (86 ± 10 mmHg baseline, vs 84 ± 10), and mean arterial blood pressure (106 ± 11 mmHg baseline vs 102 ± 10 mmHg, $P \leq 0.001$) was significantly reduced after 12 months. Heart rate slightly increased (72 ± 11 baseline, vs 74 ± 12, $P \leq 0.001$). Antihypertensive medication has not to be aggravated significantly after the switch.

A total of 751 putative ‘clinical events’ were registered in 214 patients (71.6%). Adverse events not generally associated with but possibly related to cyclosporin therapy included pruritus ($n=6$) and dizziness ($n=5$). Other adverse effects associated with cyclosporin such as the new onset of gingival hyperplasia, hirsutism, or thrombotic episodes were not reported. Also observed were 29 cardiovascular events including four episodes of supraventricular arrhythmias, five cases of congestive heart failure, nine patients developed angina pectoris, and nine developed a myocardial infarction. Nine patients developed a urinary tract infection and 24 (8% incidence) episodes of biopsy-proven rejection were documented. Seven patients had clinical and biopsy-proven signs of cyclosporin nephrotoxicity (Table 2).

The quality of life and well-being assessments showed a value of 2.41 ± 1.46 (scale range 1–9, 1 = excellent) on day 1. There was a slight overall worsening on the following days with a peak on day 15 (2.71 ± 1.49, $P \leq 0.001$). The rating on day 29 was slightly improved (2.64 ± 1.58). At study entry, 273 (91.6%) patients classified their emotional state as ‘good’, compared to 262 (87.9%) patients on day 29 ($P=NS$).

**Discussion**

Cyclosporin has provided a substantial advance in organ transplantation. For instance, recent studies show that rather than being particularly nephrotoxic in renal transplant patients, cyclosporin is the single most important parameter to assure success of the procedure [15,16]. Nevertheless, the drug is not easy to use [1–9]. Despite more sophisticated approaches [17], the vagaries of cyclosporin pharmacokinetics are well known. The advent of a new, microemulsion formulation of this drug offers new perspectives to transplant patients [6–9]. We converted 302 patients...
All Patients (Day 1-29: N=299, M3: N=272, M6: N=275, M12: N=280)

A) Changes from Baseline (Day 1) in Cyclosporine-Trough-Level

B) Changes from Baseline (Day 1) in Creatinine Measure

C) Changes from Baseline (Day 1) in Creatinine Clearance (C&G)

Fig. 3. (Panel (a)-(c)) (a) Percentage change compared to baseline of cyclosporin trough level, (b) serum creatinine concentration and (c) creatinine clearance in all patients over the study period (days 4-29, and months 3-12).

with stable renal allografts from the conventional cyclosporin preparation to the new microemulsion formulation. Ours was not a randomized controlled trial. We felt that since the parent compound was not different, such a trial was not warranted. Instead, we were interested in accruing the necessary experience so that guidelines could be formulated to more easily perform this conversion. We were concerned about increased nephrotoxicity because of the improved bioavailability of the microemulsion formulation. On
Gastrointestinal disorders, liver disease, or interference by various concomitant medication may influence CsA absorption and/or metabolism [22,23]. Such confounding variables were not identified in these patients. During the observation period, aspartate aminotransferase levels were unchanged, suggesting that the risk of enhanced hepatotoxicity is negligible. The increase in blood uric acid levels may also indicate enhanced drug exposure. However, the improvement in renal function and the decrease in systolic and mean arterial blood pressures observed at month 6 at similar trough levels compared to baseline suggests that the microemulsion form may be less toxic after dose adjustment than the conventional compound. In addition the frequency and severity of rejection episodes was not increased. The rejection frequency in our transplant population had been detailed elsewhere [24]. This observation suggests a similar immunosuppressive efficacy.

Our data show that conversion from conventional cyclosporin to the microemulsion formulation is easily accomplished, effective, and safe. The acceptance of the new formulation, as documented by the quality of life determinations and the remarkable compliance during the 1-year study period, was excellent. However, the improved bioavailability of the microemulsion formulation may lead to safety problems in some patients. With the chosen 1:1 conversion ratio, some patients exhibited an increase in cyclosporin concentrations. In patients whose trough levels are in the high therapeutic range, the microemulsion formulation should be reduced by 10% compared to the conventional cyclosporin dose. Such dose reductions will be necessary in most patients. In addition to measurements of serum creatinine, three additional cyclosporin drug levels at 1, 2, and 4 weeks should be obtained. Monitoring uric acid concentrations and aspartate aminotransferase values is reasonable. Patients whose trough levels are not within the intended therapeutic range should be followed at more frequent intervals. The old formulation and the new compound should not be mixed.

Long-term follow-up will be necessary and we have to wait also for the long-term results of ongoing double-blind multicentre trials, which so far also have considered substantial lower doses (−16%) with the microemulsion formulation [25]. However, we felt that these 1-year results of a single centre are highly encouraging by clearly demonstrating safety and feasibility of a 1:1 conversion in an unselected patient population.

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References


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Editors note
Please see also the Editorial Comment by Neumayer (pp. 19–20 in this issue).