Observations in clinical and experimental ocular autoimmunity

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Chapter 15

Long Term Follow-up of Patients with Endogenous Uveitis Treated with Combination Cyclosporine and Ketoconazole

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Abstract

**Purpose:** Combined treatment with cyclosporine and ketoconazole in autoimmune diseases has received little attention. This report outlines the long term outcome of a cohort of patients that were placed on combination therapy for endogenous uveitis. **Method:** Six patients who were initially treated with only cyclosporine (CSA) were followed long term on a combination of cyclosporine and ketoconazole (KCZ). Data was analyzed for visual acuity, number of flare-ups and signs of systemic toxicity. **Results:** Patients were on CSA for a mean of 13 months and CSA/KCZ for a mean of 33 months. While patients had a number of flare-ups prior to combination therapy, only 2 flare-ups in 2 patients were noted during combined therapy P = 0.055. Three patients showed signs of renal toxicity on CSA, 2 continued to show signs of toxicity on CSA/KCZ. One patient stabilized and maintained normal renal parameters. Elevation of systolic and diastolic pressure was present in 3 of 6 patients with CSA. While the systolic pressure remained the same with CSA/KCZ, diastolic pressure was within normal parameters in all patients (P = 0.03). No toxicity related to ketoconazole alone was observed. **Conclusion:** Combination of cyclosporine and ketoconazole is safe and effective in the treatment of endogenous uveitis. It appears to be more effective in preventing recurrences than cyclosporine alone, and does not lead to an increased risk of renal toxicity over cyclosporine alone. It also represents a significant cost saving over cyclosporine monotherapy.

Introduction

Cyclosporine A (CSA) was introduced for the treatment of endogenous uveitis in late 1983, and has been used successfully by a number of groups. In one report, over 50% of patients with endogenous uveitis unresponsive to steroids alone were controlled on CSA or a combination of CSA and steroids. Cyclosporine is non cytotoxic. It inhibits the activation of CD4+ lymphocytes by preventing the synthesis and secretion of IL-2 and its receptor. This inhibition is dose dependent.

Toxicity related to cyclosporine is also dose dependent. When the dose of oral CSA is kept below 5 mg/kg/day and large swings in serum creatinine levels are avoided, the incidence of irreversible changes in renal function are quite low. However, CSA blood levels tend to vary considerably between individuals due largely to variations in the rate of absorption from the gastrointestinal tract, and the rate of CSA metabolism through cytochrome P-450 microsomal enzymes. Thus, medications that affect cytochrome P450 can have a dramatic effect on blood CSA levels. Phenytoin, a potent inducer of hepatic cytochrome P450, can cause a significant drop in serum CSA levels within 2 hours of its administration. Other agents such as phenobarbital, rifampin, isoniazid have similar effects. Drugs that inhibit the hepatic microsomal enzyme P-450 will increase CSA plasma levels. This inhibition results in increased blood concentration of CSA, necessitating a reduction in the oral dose to maintain serum levels within the therapeutic range. Drugs like cimetidine, erythromycin, oral contraceptives, androgens, and methylprednisolone are all reported to cause elevations in serum CSA levels. Some calcium channel blockers, especially verapamil have also been observed to increase CSA plasma concentration.

An imidazol e derivative, ketoconazole has a broad antifungal spectrum of activity, and is known
to inhibit cytochrome P-450. A number of studies have shown that it can be combined successfully with cyclosporine to prevent graft rejection. Ketoconazole has no known direct renal effect which is a major concern of cyclosporine therapy, and it does not alter the systemic blood pressure. Its main toxicity is hepatocellular, in a dose dependent manner, whereas cyclosporine is not commonly reported to severely alter hepatic function. Thus the association of the two drugs is not contraindicated at least in terms of additive toxicities. The addition of a cytochrome inhibitor such as ketoconazole can drastically reduce cyclosporine requirements, which represents a significant cost saving over the duration of treatment. On this basis, we have tried the combination of both agents, i.e., CSA and ketoconazole in the treatment of endogenous uveitis. Initial results were extremely encouraging. However, we also wanted to determine the long-term outcome of combined therapy. In this study, we report on these initial patients treated with cyclosporine and ketoconazole, now followed for up to five years on combination therapy.

**Patient Selection and Method**

This study reports on the long term follow-up of patients that were entered in a double masked randomized study comparing cyclosporine/ketoconazole to cyclosporine/placebo. The study had been approved by the Institutional Review Board of the National Eye Institute. All study participants gave informed consent prior to enrollment. Patients with endogenous uveitis of non infectious origin, treated at the NIH with cyclosporine A were considered eligible for entry provided that the uveitis had been stable on medication for at least 1 month. In the initial phase of the study, 10 patients were randomized. Four patients received ketoconazole (200 mg/day) and 6 patients were given a placebo. These patients were carefully followed for signs of renal toxicity or recurrence of uveitis for a period of 3 months. As previously reported in the Journal, patients on ketoconazole were able to reduce their dose of cyclosporine by over 70% without any recurrence of uveitis. Four of 6 patients receiving the placebo had a recurrence. Recurrence was defined as a decrease in visual acuity of 2 or more lines as measured on the Early Treatment of Diabetic Retinopathy Study eye chart (ETDRS), or a two step increase in vitreal haze.

After completing the double masked portion of the study, all patients were given the option of entering an open arm, designed to evaluate the long term effect of the combination of cyclosporine A and ketoconazole. Six patients (3 males and 3 females) entered this arm of the study. Three patients had Behçet’s disease, two intermediate uveitis and one patient had Sarcoidosis. The diseases were confirmed according to established criteria as previously described. Patients were treated for as long as was clinically indicated or until they showed signs of persistent renal or hepatic toxicity. Renal toxicity was defined as any increase in serum creatinine concentration by 30% or more, a decrease in the 24-hour creatinine clearance by more than 30%. Hepatic toxicity was defined as a doubling of the hepatic enzymes. Patients were also given the option of switching to an alternate form of therapy if such therapy became available. Cessation of combined therapy for any reason was considered the end point of the protocol. At the time of data analysis, 2 patients were still being treated on protocol. Two patients were taken off the study because of depressed creatinine clearances, 3 months after starting therapy. Both of these patients had shown signs of renal toxicity while on cyclosporine monotherapy. One patient was taken off all medication, and one patient elected to enter a different therapeutic protocol. At each clinic visit, best corrected visual acuity was measured on ETDRS eye charts. Patients had a complete
**Table 1: Baseline Characteristics of Patients at Initiation of Cyclosporine or Cyclosporine/Ketoconazole (Mean ± S.E.M.) n = 6**

<table>
<thead>
<tr>
<th></th>
<th>Cyclosporine</th>
<th>Cyclosporine + Ketoconazole</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>35.7 ± 11.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cyclosporine Dose (mg/kg/day)</strong></td>
<td>6.8 ± 0.9 (Range: 4 - 10)</td>
<td>1.4 ± 0.2 (Range 0.8 - 2)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Prednisone dose (mg/day)</strong></td>
<td>19.2 ± 0.2 (Range 15 to 40)</td>
<td>14.2 ± 2.7 (Range 5 - 25)</td>
<td>0.111</td>
</tr>
<tr>
<td><strong>Visual Acuity (letters)</strong></td>
<td>56 ± 8</td>
<td>56 ± 7</td>
<td>0.932</td>
</tr>
<tr>
<td><strong>Serum Creatinine (mg/dL)</strong></td>
<td>0.92 ± 0.08</td>
<td>1.18 ± 0.08</td>
<td>0.043</td>
</tr>
<tr>
<td><strong>Creatinine Clearance (mL/min)</strong></td>
<td>105.3 ± 7.2</td>
<td>90.2 ± 7.8</td>
<td>0.008</td>
</tr>
<tr>
<td><strong>Systolic Blood Pressure (mm Hg)</strong></td>
<td>122 ± 4</td>
<td>127 ± 6</td>
<td>0.415</td>
</tr>
<tr>
<td><strong>Diastolic Blood Pressure (mm Hg)</strong></td>
<td>77 ± 5</td>
<td>84 ± 5</td>
<td>0.206</td>
</tr>
</tbody>
</table>

* Mean ± standard error of the mean.

...eye exam including funduscopy. Blood was taken to measure hepatic and renal functions. Every 3 to 6 months, a 24 hour creatinine clearance was obtained. Prior to final discharge, all measurements were repeated.

Il patients had been treated at the NIH with cyclosporine for a variable period of time prior to being placed on cyclosporine and ketoconazole. For the purposes of this analysis, this initial treatment period was compared to the treatment with the drug combination. Visual acuity, recorded as the number of letters read on an ETDRS chart, serum creatinine levels, creatinine clearance values, and systolic and diastolic blood pressure measurements were compared at baseline for both periods using a two-tailed paired Student's t-test. Similarly, changes in values between baseline and the end of treatment were compared with the same statistical test. The null hypothesis was rejected at a significance level of P < 0.05.

**Results**

For the group as a whole, the mean age was 35.7 years when first treated with cyclosporine. Baseline characteristics such as visual acuity, prednisone dose, systolic and diastolic blood pressures were similar for both study periods (table 1). Renal function was somewhat poorer when the patients were started on combination therapy. Serum creatinine was higher and creatinine clearance lower at the time than when the patients were first treated with cyclosporine. Both differences were statistically significant p < 0.05. The cyclosporine dose was also significantly different in both periods, being 80% lower (p=0.002) after starting ketoconazole. This baseline dose

**Table 2: Comparison of the Therapeutic Efficacy of Cyclosporine versus Cyclosporine and Ketoconazole (Mean ± S.E.M.): n = 6.**

<table>
<thead>
<tr>
<th></th>
<th>Cyclosporine</th>
<th>Cyclosporine + Ketoconazole</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Follow-up Interval (months)</strong></td>
<td>13.3 ± 6.6</td>
<td>32.7 ± 8.3 (Range: 3 - 45)</td>
<td>0.155</td>
</tr>
<tr>
<td><strong>Δ Visual Acuity (number of letters)</strong></td>
<td>-0.50 ± 6.3</td>
<td>-1.33 ± 1.5 (Range: 3 - 58)</td>
<td>0.875</td>
</tr>
<tr>
<td><strong>Number of Flare-ups</strong></td>
<td>1.8 ± 0.8</td>
<td>0.3 ± 0.2</td>
<td></td>
</tr>
<tr>
<td><strong>Flare-up by months of treatment</strong></td>
<td>0.2 ± 0.1</td>
<td>0.008 ± 0.005</td>
<td>0.055</td>
</tr>
</tbody>
</table>

* Mean ± standard error of the mean.
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Table 3: Comparison of the Side Effects and Dosage Modifications between Cyclosporine and Cyclosporine/Ketoconazole at Baseline and at End of Treatment (Mean ± S.E.M.):

<table>
<thead>
<tr>
<th></th>
<th>Cyclosporine</th>
<th>Cyclosporine + Ketoconazole</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ Cyclosporine (mg/kg/day)</td>
<td>-2.1 ± 0.7</td>
<td>-0.8 ± 0.2</td>
<td>0.125</td>
</tr>
<tr>
<td>Ketoconazole (mg/day)</td>
<td>-</td>
<td>200</td>
<td></td>
</tr>
<tr>
<td>Δ Prednisone (mg/day)</td>
<td>-5.8 ± 4.2</td>
<td>2.1 ± 5.0</td>
<td>0.098</td>
</tr>
<tr>
<td>Δ Serum Creatinine (mg/mL)</td>
<td>0.27 ± 0.09</td>
<td>0.13 ± 0.05</td>
<td>0.137</td>
</tr>
<tr>
<td>Δ Creatinine Clearance (mL/min)</td>
<td>-15.8 ± 3.5</td>
<td>-3.67 ± 7.0</td>
<td>0.247</td>
</tr>
<tr>
<td>Δ Systolic Blood Pressure (mm Hg)</td>
<td>8.0 ± 4.6</td>
<td>0.2 ± 4.7</td>
<td>0.376</td>
</tr>
<tr>
<td>Δ Diastolic Blood Pressure (mm Hg)</td>
<td>11.0 ± 2.4</td>
<td>-9.3 ± 5.4</td>
<td>0.033</td>
</tr>
</tbody>
</table>

* Mean ± standard error of the mean.

was determined in both study periods 3 weeks to 1 month after entry. This time was selected as it allowed for a readjustment in the cyclosporine dose after starting combination treatment.

The follow-up interval is somewhat longer in the second study period with a mean of 32.7 months (range 3 to 58 months) as compared to 13.3 months (range 3 to 45 months) for cyclosporine alone. However, this difference was not statistically significant. On average, the change in visual acuity was similar for both periods (table 2). A notable difference was seen in the observed number of flare-ups of uveitis. A total of 11 flare-ups were observed over a cumulative 80 month period with cyclosporine alone, while 2 flare-ups were noted over a cumulative 196 months of combined treatment. When the data is analysed per patient (table 2) a significant trend is observed particularly when comparing the risk of a flare-up per month of treatment.

Dosage adjustments were required in both study periods. The dose was adjusted according to ocular response and adverse side effects. In both periods, the cyclosporine dose could be lowered further. Adjustments were also made to the prednisone dose. However, the overall need for steroids remained about the same during both study periods. At the time of the last evaluation while on cyclosporine alone, patients were receiving a mean cyclosporine dose of 4.7 mg/kg/day and a mean dose of prednisone of 13 mg/day. At the time of the last evaluation on cyclosporine/ketoconazole, the mean cyclosporine dose was 0.6 mg/kg/day and the mean prednisone dose was 16 mg/day. The final cyclosporine concentration in the latter study period represents less than 10% of the initial cyclosporine dose or about 13% of the final cyclosporine concentration prior to entering combination therapy.

During the initial study period, 3 patients showed signs of renal toxicity as defined in the methods section. Two patients had a transient rise in hepatic transaminases and bilirubin that responded to a cyclosporine dose reduction. Three patients had an increase in systolic and diastolic blood pressures. While on combination treatment, 2 of the 3 patients with signs of renal toxicity progressed. Renal function did not significantly recover following a cyclosporine dose reduction and they were taken off cyclosporine therapy. The other patient maintained his serum creatinine and creatinine clearance within a normal range. No hepatic toxicity was observed. Patients showed no further change in systolic blood pressure, and the diastolic pressure decreased in all affected patients (table 3).
Discussion

The systematic coadministration of ketoconazole and cyclosporine appears to provide several advantages to patients suffering from chronic uveitis. In our initial study, we were able to show that the combination was both safe and effective over a 3 month period. In several cases, the cyclosporine dose could be lowered by more than 80%, while still providing adequate if not superior immunosuppression. However, we did not know the long term effects of combining both drugs. In this study, we followed the same cohort of patients for up to 5 years on combination therapy. The combination in the majority of patients was well tolerated. Only two patients showed renal toxicity which required a switch to an alternate form of treatment. In both cases, renal toxicity had been evident before combination therapy was instituted. In another two patients, early signs of renal, hepatic and hemodynamic changes were normalized on cyclosporine/ketoconazole without any subsequent recurrence of the problem. Such results were possible because of careful and frequent measurements of both hepatic and renal functions throughout the follow-up period. Frequent cyclosporine levels were obtained in the early stages, until a stable level within the therapeutic range was achieved. This is particularly indicated in cases where ketoconazole is added some time after cyclosporine therapy is started. In such cases, cyclosporine should initially be reduced by 70%, with further adjustments being made over the next 2 to 3 months based on the serum cyclosporine levels. The lack of renal toxicity observed in the present and other similar studies, cannot be explained on the basis of a cyclosporine dose reduction alone. Several factors are probably responsible including a reduction in the number of circulating metabolites, a lessening of the maximum cyclosporine concentration, and possibly a direct inhibition of cyclosporine induced toxicity mediated through cytochrome P450. At higher in vitro concentrations above 100 nM, cyclosporine can block its own hydroxylation through cytochrome P450 and can lead to the generation of superoxide free radicals. These free radicals in turn cause an increase in lipid peroxidation, an important mediator of both renal and hepatic CSA toxicity. Since ketoconazole prevents O₂ fixation and activation by P450, it can effectively inhibit both the metabolism of cyclosporine and the generation of superoxide free radicals which mediate CSA related toxicity.

Ketoconazole was well tolerated, with no adverse effects related to its long term use being noted in our patients. Hepatic injury associated with ketoconazole therapy has been reported but appears to be due to an idiosyncratic drug reaction. It is hepatocellular in nature, leading to an increase in transaminases. Combination of CSA and ketoconazole can occasionally lead to an increase in bilirubin and alkaline phosphatase levels, but these usually normalize upon reducing the CSA dose. Ketoconazole requires an acid medium for effective absorption, and therefore should not be given at the same time as antacids or drugs that increase the gastric pH. High dose ketoconazole can lower serum testosterone and lead to a reduction in sexual function. In a group of heart transplant patients, it was observed that the mean testosterone level decreased from 4.1 ± 1.2 ng/mL before ketoconazole to 3.2 ± 1.3 ng/mL at the end of follow-up (mean of 10.7 months). Nothing is known about the effect of this combination on children, and its use in this age group should be carefully monitored, if used at all.

The addition of ketoconazole did not have a deleterious effect on cyclosporine's immunosuppressive activity. Patients appeared to be in tighter control when on combination therapy as compared to cyclosporine alone (table 2). The difference nearing statistical significance between the two groups. The number of patients in our study is limited, and a larger number would be necess-
sary to fully assess the immunosuppressive effect of combined therapy. While all patients were stable at the time ketoconazole was added, all patients were still considered to have active disease. All patients had experienced a flare-up of uveitis in the 4 months preceding the initiation of ketoconazole. A similar beneficial effect has also been noted in a randomized heart transplant study. Patients on combined therapy suffered fewer episodes of rejection requiring OKT3 treatment. The exact mechanism responsible for this observation is not known. Ketoconazole is known to have some immunomodulatory effect of its own. It is able to block the synthesis of leukotrienes and thromboxanes, and it can potentiate the effect of steroids by inhibiting microsomal degradation through 6b-hydroxylation. All of our patients were on low to moderate doses of steroids at the time of the trial (table 3).

As a consequence of the reduced oral requirements for cyclosporine following the coadministration of ketoconazole, the mean daily cost of cyclosporine is sharply decreased. In our case, patients were able to reduce their daily cyclosporine requirements by 90%. In heart transplant patients, this can represent a 73% reduction in cost, even when taking the additional cost of ketoconazole into account. Such savings can be of considerable importance in the face of increasing pressures for cost containment. However, these savings must be partially offset by the increased need for cyclosporine blood monitoring. This is particularly important shortly after instituting combination therapy, as we and others have found that the degree of inhibition varies somewhat between patients.

In the future, the coadministration of ketoconazole and cyclosporine may become an important practical consideration in patients with endogenous uveitis. It appears to offer both significant cost savings and a favorable pharmacodynamic profile.

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