Observations in clinical and experimental ocular autoimmunity

de Smet, M.D.

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Chapter 14

Combined Use of Cyclosporine and Ketoconazole in the Treatment of Endogenous Uveitis

Marc D. de Smet, Benjamin I. Rubin, Scott M. Whitcup, Juan S. Lopez, Howard A. Austin, Robert B. Nussenblatt

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Combined Use of Cyclosporine and Ketoconazole in the Treatment of Endogenous Uveitis

Marc D. de Smet, M.D., Benjamin I. Rubin, M.D., Scott M. Whitcup, M.D., Juan S. Lopez, M.D., Howard A. Austin, M.D., and Robert B. Nussenblatt, M.D.

Ten patients with endogenous uveitis were in clinical remission attributable to treatment with cyclosporine and prednisone. After the cyclosporine dose was reduced by two thirds, these patients were randomly assigned to treatment with or without ketoconazole, a potent inhibitor of cytochrome P-450, in a double-masked placebo-controlled study. The dose was reduced over three days. During a three-month follow-up, no patients treated with ketoconazole had a relapse of uveitis, while four of six (66%) control subjects had a flare-up. Toxicity in the ketoconazole-treated group was limited to a transient decrease in glomerular filtration rate (20% from baseline) at one month in two of six (33%) patients. Renal function was stabilized by further reduction of the cyclosporine dose.

Several studies have shown that many forms of endogenous uveitis can be successfully treated with a combination of cyclosporine and corticosteroids. One major drawback to the disseminated use of cyclosporine has been its considerable cost. Reducing the metabolism of cyclosporine would allow a dose reduction and thereby diminish the cost. Cyclosporine metabolism is mediated almost exclusively by the liver cytochrome P-450 microsomal enzymes. The antifungal ketoconazole inhibits this enzyme system both in vivo and in vitro, resulting in increased blood concentrations of cyclosporine that may become toxic if the dose is not reduced. Recently, First and associates used 30% of their standard cyclosporine dose (8 mg/kg of body weight) in connection with ketoconazole to prevent graft rejection in patients who had undergone renal transplantation. None of their 18 patients developed any marked toxicity in up to 13 months of follow-up. This combination has not yet been tried in autoimmune diseases. We tested this drug combination in patients with endogenous uveitis whose conditions had been stabilized using our standard dose of cyclosporine and prednisone for at least three months.

Patients and Methods

Patients whose endogenous uveitis was controlled with cyclosporine (5 mg/kg of body weight/day) and prednisone (0 to 0.5 mg/kg of body weight/day) signed an informed consent approved by the Institutional Review Board, and had their cyclosporine dose decreased by 70% in two increments over three days. At the time of the initial reduction in the cyclosporine dose, patients were randomly assigned in a masked fashion to treatment with or without ketoconazole. Patients were monitored for three months or until the development of a flare-up (defined as a decrease in best-corrected visual acuity by two lines as measured by the Early Treatment of Diabetic Retinopathy Study eye chart or an increase by two steps in vitreal haze as defined previously). Patients were also monitored at regular intervals for development of hepatic or renal toxicity. A doubling of the hepatic enzymes, a 30% increase in serum creatinine concentration, or a 30% decrease in the 24-hour urinary creatinine clearance led to a further reduction in the dosage of cyclosporine. Hydrated clearance studies using technetium Tc 99m diethylene triaminopenta-acetic acid and iodohippurate sodium I 131 were per-
formed at days 0, 30, and 90 to obtain an accurate measurement of the true glomerular filtration rate.11

**Results**

Ten patients were entered in the study; ketoconazole was administered to four patients and placebos were administered to six patients (Table). Use of corticosteroids at the time of entry into the study was determined. The dose was not modified during the study. None of the patients treated with ketoconazole developed a flare-up, as compared to four of six patients administered placebos who did develop flare-ups (P = .035, chi square). All of the flare-ups developed within three weeks of random assignment to treatment and the decrease of the cyclosporine dose. All flare-ups were caused by a decrease in visual acuity by two lines or more. After flare-up of their ocular disease, three patients elected to be treated with ketoconazole while maintaining the same reduced cyclosporine dose. In these three patients, the ocular inflammation resolved with no further flare-up in the next three months. Patient 4 had a severe ocular attack of Behçet's disease after reduction in the cyclosporine dose. To achieve rapid control, it was in the patient's best interest to be treated with standard doses of cyclosporine and no ketoconazole. None of the patients initially administered placebos had a permanent decrease in visual acuity. Two of the four patients who were treated with ketoconazole had an improvement in visual acuity although their visual acuities had been considered stable before entering the study.

A 30% increase in serum creatinine concentration was noted in two patients while they were being treated with ketoconazole. This was paralleled by a decrease in the glomerular filtration rate, which is a more sensitive measure of change in renal function than creatinine clearance or serum creatinine (by 20% in one patient and 30% in the other patient). In both patients, a dosage reduction led to a normalization of the serum creatinine concentration by the next clinic visit, two months later. The glomerular filtration rate returned to the baseline value in one patient, whereas it remained at the lower
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value in the other patient. At three months in most patients, the renal and hepatic profiles were unchanged as compared to baseline values (Figure).

Discussion

We demonstrated the efficacy of treatment with coadministered ketoconazole, cyclosporine, and prednisone in patients with autoimmune disease. Ketoconazole proved to be a potent inhibitor of cyclosporine metabolism. Cyclosporine doses should be reduced quickly during a two- to three-day period to prevent development of markedly increased levels of circulating cyclosporine. Cyclosporine-related toxicity can be avoided if the cyclosporine whole blood levels are maintained in the lower ranges of the normal values (500 to 1,000 ng/l). This was achieved in these patients by reducing the orally administered cyclosporine dose to between 10% and 30% of the baseline dose.

The exact extent of the dose reduction varies between patients, but by maintaining whole blood cyclosporine levels in the lower range of the normal values, one can avoid toxicity and achieve a good treatment effect. The dose should initially be decreased to 30% of the original dose. Once the patient has been treated with this lower dose for several days (minimum, four half-lives), a cyclosporine whole blood level should be obtained. If the level remains high, the cyclosporine dose can safely be reduced further. When starting treatment with ketoconazole, a patient should be carefully monitored for clinical signs of acute cyclosporine toxicity. These would manifest as an increase in the blood pressure, an increase in the blood urea nitrogen concentration, serum creatinine concentration, or an increase in liver enzyme concentration. Manifestation of any of these clinical signs should prompt further reduction of the cyclosporine dose.

Some patients who were treated with the ketoconazole-cyclosporine combination had a further improvement in visual acuity even though their clinical remission was considered stabilized before entering the study. This possibly indicates that sustained levels of cyclosporine are better at maintaining a remission than is the usual treatment schedule in which drug concentration changes dramatically in a given day. The addition of ketoconazole to the regimen of coadministered reduced-dose cyclosporine (5 mg/kg of body weight/day or less) and prednisone seemed to be effective in maintaining remissions in patients with uveitis. Clearly, further studies are needed to determine the long-term toxicity of this combination therapy for newly diagnosed patients as well as for patients with chronic uveitis and severe, bilateral sight-threatening disease.

References


