The FDA Guidelines for the Treatment of Psoriasis Using Cyclosporine A: Are They Adequate?

Herschel S. Zackheim, MD

I present a review of the current US Food and Drug Administration (FDA) guidelines for using cyclosporine A (CSA) to treat psoriasis, with particular emphasis on the period for which CSA may be administered. My concern is that, without violating the guidelines, CSA could be given for a prolonged period with only very brief time-outs. I also review the risks for renal toxicity, malignancy, and other side effects from prolonged administration.

Cyclosporine A (CSA) is a widely used short-term treatment for severe or resistant psoriasis. Guidelines for the prevention of renal toxicity, hypertension, and other toxicities are given in the *Physicians' Desk Reference* (*PDR*). In this article, I focus on a statement that appears in the *PDR* and on a Neoral® (CSA) package insert: "Long-term experience . . . in psoriasis patients is limited and continuous treatment for extended periods greater than one year is not recommended."[1]

Not included in the *PDR* are the number of CSA courses that can be given, the minimum length of the between-course time-out, a definition of *extended periods* (2, 5, 10 years?), and the permissible maximum lifetime cumulative dose.

Thus, without violating *PDR* guidelines, a patient could take CSA continuously for 12 months, stop for 1 month, and then take another 12-month course, ad infinitum. Because a considerable amount of CSA could be taken over a prolonged period—and because patients who have benefited from using CSA are likely to pressure physicians to continue prescribing it—physicians need to become familiar with the risks associated with prolonged use of CSA.

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Reprints: Herschel S. Zackheim, MD, 2327 Branner Dr, Menlo Park, CA 94025 (e-mail: hszackheim@orca.ucsf.edu).

Renal Toxicity

Grossman et al[2] used 2.5 to 5.0 mg/kg per day of CSA to treat 122 patients with psoriasis for 3 to 76 months. Serum creatinine (SC) levels increased more than 30% from baseline in 43% of patients after a median treatment period of 23 months, and hypertension occurred in 24% after a median treatment period of 53 months.

Lowe et al[3] treated 42 patients with an initial CSA dosage of 5 to 6 mg/kg per day. A subset of 14 patients was maintained on a minimum dosage of 3 mg/kg per day for 3.5 years. After 2.5 years, 2 patients showed moderate interstitial fibrosis and tubular atrophy. After 3.5 years, results of repeated biopsies in 9 patients showed slight increases in structural changes. These changes correlated with increasing age and medication-induced hypertension.

Zachariae et al,[4] performed renal biopsies in 30 patients with psoriasis treated with CSA 2.5 to 6 mg/kg per day for 6 months to 8 years. They noted mild renal lesions in the first year. After 2 years, 17 of 25 patients exhibited features of nephropathy despite completely normal pretreatment specimens. After 4 years, all but one patient had arteriolar hyalinosis, with interstitial fibrosis pronounced in 5 patients and moderate in 6 patients. Glomerular sclerosis was significant. A decrease in glomerular filtration rate (GFR) and an increase in SC level correlated with severity of structural lesions. In general, SC levels increased during the first year and thereafter stabilized, but a significant decrease in GFR was noted at all later times.

Powles et al[5,6] reported on a series with long follow-up. Mean CSA dosage was 2.8 mg/kg per day (range, 1–5 mg/kg per day). Two groups were followed. In one group, 7 patients used CSA for a mean of 10 years. In all 7 patients, an SC level increase of more than 30% persisted, and in 4 of these patients

the increase was greater than 50%. GFR at 10 years decreased more than 30% in 2 patients and more than 50% in 1 patient. Stable renal function was noted in 3 of the 7 patients. Two patients had repeated renal biopsies for investigation of deteriorating renal function; results of these biopsies, compared with results of the 5-year biopsies, showed further evidence of nephrotoxicity. Two of 9 patients had discontinued CSA because of renal toxicity.[6]

In the other group, 20 patients used CSA for a mean of 6 years. In 9 of these patients, an SC level increase of more than 30% persisted, and in 5 of these the increase was greater than 50%. A GFR decrease of more than 30% persisted in 7 patients, and in 2 of these the decrease was greater than 50%. After CSA was discontinued, renal function improved with time. Powles et al[6] concluded, "Providing renal function is monitored with GFR and renal biopsies in addition to SC, then long-term (5–10 years) CSA can be justified in severe psoriasis not responsive to other treatments."

One month after medication was discontinued, Pei et al[7] examined GFR, renal plasma flow, and kidney biopsies of 15 patients with psoriasis treated with CSA 5 mg/kg per day for 25 to 35 months. Seven patients had a decreased GFR, and 4 of these also had a reduced renal plasma flow below the 2.5 percentile of normal. Four patients had moderate tubulointerstitial scarring and arteriolopathy; the other 11 had mild structural abnormalities. The researchers concluded that low-dosage CSA can be associated with chronic renal injury.

de Rie et al[8] used CSA at dosages of less than 2 to greater than 3 mg/kg per day to treat 26 patients with severe psoriasis for 7 to 37 months (mean, 19.5 months). CSA treatment was discontinued in 12 of the 26 patients because of nephrotoxicity or development of hypertension. One patient developed 2 squamous cell carcinomas (SCCs) of the skin.

Described in the *PDR* is the case of a 27-year-old man who developed renal deterioration but continued using CSA.[1] Progressive renal failure led to the man's death. No further details are given. Ho et al[9] reported on a study of psoriasis treated with intermittent short courses of CSA given for as long as 2 years. No significant changes in blood pressure or SC level were noted. However, mean duration of treatment was 322 days, which is within FDA guidelines even for continuous treatment.

Lymphoma and Other Malignancies

Koo et al[10] reported the case of a 67-year-old man whose psoriasis was treated with CSA for a total of 8 months. The initial dose was 5 mg/kg per day for 6 weeks, which was then reduced to 3 mg/kg per day for an additional month. The patient was then randomly assigned to placebo, but his psoriasis soon flared. He requested resumption of CSA, which was restarted after he gave informed consent. CSA was resumed at 3 and 2 mg/kg per day. However, because of poor response and borderline renal function, CSA was discontinued after 8 months. Fifteen months after the patient started using CSA (or 7 months after he discontinued using CSA), a large intraoral mass was detected. The mass, a destructive tumor in the left maxillary sinus, extended into adjacent structures and was diagnosed as a B-cell lymphoma. Despite chemotherapy and radiation therapy, the patient developed systemic disease and died after a subdural hematoma.[10]

For this patient, the latent period between starting to use CSA and developing the lymphoma was 15 months—consistent with a mean latent period of about 10 months for transplant patients.[11] Before CSA, the patient had been treated with methotrexate, psoralen plus UVA light (PUVA), etretinate, hydroxyurea, and tar plus UVB light. However, these were discontinued at least 4, 3, 3, 2, and 1 year, respectively, before the diagnosis of lymphoma. Thus, CSA is the medication most likely related to the onset of the lymphoma.

Massouye et al[12] described a patient whose keratosis lichenoides chronica was treated with CSA 5 mg/kg per day for 5 months. Four months later, the patient developed generalized adenopathy and was found to have a B-cell immunoblastic lymphoma.

Cliff et al[13] reported the case of a patient with psoriasis who developed a large-cell B-cell lymphoma after 6 years of using CSA at a mean dosage of 4 mg/kg per day. This patient also used methotrexate for a short period.

Bagot and Dubertret[14] reported the case of a 59-year-old man who had psoriasis and who developed erythroderma after 6 weeks of using CSA 2.5 mg/kg per day. Results of blood tests showed leukocytosis of 15,500/mm^3 and 29% Sézary cells. The patient's erythroderma cleared within a few weeks after CSA was discontinued.

Yamamoto et al[15] reported the case of a patient who had psoriasis and who developed oral adenocarcinoma 3 months after starting CSA (maximum, 3 mg/kg per day). Grossman et al[16] reported the development of cervical intraepithelial neoplasia after 43 months of treating psoriasis with CSA 3 mg/kg per day.

In a recent study, Marcil and Stern[17] found that the risk for developing cutaneous SCCs is increased by using CSA for patients with psoriasis who were previously treated with PUVA. In the 5 years before first use, 6 (21%) of 28 CSA users developed a total

of 20 SCCs. After CSA use (mean follow-up, 6 years), 13 (46%) of the 28 CSA users developed a total of 169 SCCs. Thus, after adjustment for the amount of PUVA and methotrexate treatment, the incidence of SCCs was 7 times higher after the first CSA use than in the previous 5 years. Marcil and Stern also estimated that the risk for developing an SCC after any use of CSA is close to that for at least 200 PUVA treatments.[17]

CSA has been designated as a human carcinogen in the US National Toxicology Program's Eighth Report on Carcinogens.[18]

Conclusion

Clearly, using CSA for long-term treatment of psoriasis poses a considerable risk for development of serious complications. Although the risk vis-à-vis current 1-year guidelines seems low, *PDR* wording allows for prolonged use of CSA with only brief time-outs, and the possibility of severe consequences exists. Guidelines for the use of repeated courses of CSA are urgently needed, but their development requires extensive, long-term, multi-institutional studies.

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