NOVEL USES FOR CYCLOSPORINE A

Cyclosporine A (CSA) is an immunomodulating agent whose mechanism of action is related to its dampening effect on the function of helper T-lymphocytes. The drug has been found useful in clinical settings other than transplantation, such as certain hematologic, dermatologic, and connective tissue diseases. Because it has a high incidence of acute and chronic toxicity, CSA should be used only after more conventional measures have failed.

HEMATOLOGIC INDICATIONS

Although most beneficial in solid organ transplantation, CSA also has been successful in the prophylaxis of acute graft-versus-host disease (GVHD) in bone marrow transplantation. CSA combined with methylprednisolone or methotrexate is more effective than any single agent in the prevention of GVHD.

CSA in combination with antithymocyte globulin and methylprednisolone is beneficial in the treatment of aplastic anemia, according to the interim analysis of a German trial. Small trials have shown that CSA may benefit patients with pure red cell aplasia. Case reports indicate benefit in other hematologic diseases, including refractory idiopathic thrombocytopenic purpura, Hodgkin's disease (amelioration of the "B" symptoms), reduction of the titer of factor VIII inhibitors in the hemophilias, and autoimmune neutropenia of Felty's syndrome.

DERMATOLOGIC INDICATIONS

CSA was first reported as treatment for psoriasis in 1979. Subsequent publications confirmed its benefit in the treatment of severe psoriasis—namely plaque, erythrodermic, and pustular forms of the disease. Most investigators use a dosage of 5 mg/kg/day to 6 mg/kg/day to avoid acute toxicity. In one study, all 17 patients treated with 5 mg/kg/day improved, and 12 cleared completely within 3 months. The 41% relapse rate among these 12 patients 6 months after discontinuing CSA was no different than the rate expected with other antipsoriatic therapies.

Because CSA might favor the expansion of antigen-specific suppressor T-lymphocytes, it has been studied and found useful in recalcitrant atopic dermatitis, in which patients show a decreased number of suppressor cells. Case reports suggest that it may be useful in severe actinic dermatitis that has failed to respond to corticosteroids, PUVA, or azathioprine. Other potential uses include generalized cutaneous lichen planus, oral erosive lichen planus, alopecia areata, pemphigus vulgaris, and pyoderma gangrenosum.

TREATMENT OF CONNECTIVE TISSUE DISEASE

CSA has been studied in open, uncontrolled and blinded, controlled trials involving patients with rheumatoid arthritis (RA), Behcet's syndrome, juvenile dermatomyositis, systemic lupus erythematosus, Sjogren's syndrome, uveitis, primary biliary cirrhosis, and chronic active hepatitis.

CSA has been evaluated most extensively in RA, and at least three controlled trials demonstrate its efficacy. In all patients, CSA was used only after the failure of more conventional measures, including gold and d-penicillamine. All CSA-treated patients showed reduction in the number of swollen joints and improved global assessments. Although CSA has little effect on the erythrocyte sedimentation rate, C-reactive protein was significantly lowered in treated patients. Unfortunately, acute toxicity resulted in the discontinuation of CSA in up to 45% of treated patients within 6 months.

In trials of patients with Behcet's syndrome, control of uveitis was better with CSA, 10 mg/kg/day, than with colchicine or with prednisolone combined with chlorambucil. Fourteen chronically ill children with juvenile dermatomyositis who had failed combination therapy with corticosteroids and immunosuppressive agents responded to a maintenance dose of CSA ranging from 2.5 mg/kg/day to 7.5 mg/kg/day. The addition of CSA also allowed the reduction of maintenance prednisolone from a mean of 14 mg/day to 3 mg/day.

ADVERSE EFFECTS

Hypertension and renal dysfunction are the greatest cause for concern in CSA-treated patients. Nearly every rheumatoid arthritis patient treated with CSA has some rise in serum creatinine, and hypertension often accompanies renal impairment. The mechanisms of renal damage include primary vascular effects with resulting decreased renal blood flow, direct renal tubular injury, stimulation of interstitial cell proliferation which leads to fibrosis, and inhibited production of protective renal prostaglandins. These renal effects appear to be dose-related and may be less troublesome if a dosage of 3 mg/kg/day to 5 mg/kg/day is used to maintain a trough level below 200 ng/ml. Drugs that can produce synergistic toxicity, such as nonsteroidal anti-inflammatory