10 Cyclosporine A

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Cyclosporine A (CsA) is a neutral lipophilic compound that was first isolated in the 1970s from the fungal species *Tolypocladium inflatum gams*. CsA is a cyclic polypeptide that consists of 11 amino acids and that has a molecular weight of 1202 daltons.[1] It was found to have potent immunosuppressive properties and was initially used in the late 1970s to prevent organ rejection following transplantation. CsA first became available for general use in North America in 1983 and is now perhaps the most widely used drug to prevent graft rejection in transplantation medicine. The spectrum of conditions for which CsA is now being used has broadened, with recent reports of its benefit in several autoimmune and cutaneous diseases.

Pharmacology

The oral route is the most common form in which CsA is presently prescribed in dermatology. The intramuscular route may result in poor absorption with subsequent wide variations in serum CsA levels,[2] and the intravenous mode is rarely used for the treatment of cutaneous diseases. The topical and intralesional routes have been reported to be of some efficacy in selected disorders[3-13] and are not discussed in this article. CsA is absorbed from the gastrointestinal tract and metabolized by the liver. There is subsequent enterohepatic circulation of CsA. The bioavailability of oral, absorbed drug is approximately one-third,[14] with peak levels occurring about 3 hours following ingestion. The average half-life is 19 hours (range, 8–24).[15]

After CsA has been taken orally, there are wide variations in CsA pharmacokinetics among patients, resulting in a range of CsA trough levels for the same ingested CsA dose.

The CsA dosage does not correlate with peak CsA levels, trough CsA levels at 24 hours, or peak minus trough levels.[16] Although the actual peak level may not correlate with the incidence of adverse reaction, a low peak-to-trough ratio of CsA levels may be associated with an accumulation of CsA, which may subsequently result in more severe side effects.[17]

At present, suggested guidelines for the short-term use of oral CsA in dermatology are as follows: oral CsA dose should be under 5 mg/kg/day; serum creatinine levels should not become 50% greater than the baseline value while the patient is on CsA; and trough blood CsA levels, high-performance liquid chromatography (HPLC) or monoclonal radioimmunoassay (RIA), must be kept under 250 ng/ml (or polyclonal RIA under 500 ng/ml).

Supported in part by the Babcock Endowment Fund.

Some common drug interactions with CsA are given in Table 10-1.[18-20] Certain drugs induce hepatic cytochrome P450, thereby decreasing CsA levels. Other drugs inhibit cytochrome P450 and other hepatic enzymes, resulting in elevated CsA blood levels. Because CsA can cause renal dysfunction, drugs that may cause synergistic nephrotoxicity should be used with caution.

TABLE 10-1. Common Drug Interactions with Cyclosporine

A. Induced hepatic cytochrome P_{450} enzymes and therefore decrease CsA blood levels
rifampin
isoniazid
phenytoin
phenobarbitone
carbamazepine
sulfadimidine plus trimethoprim—only when given intravenously
B. Inhibit metabolism of hepatic cytochrome P_{450} and therefore increase CsA blood levels
erythromycin
doxycycline
ketoconazole
amphotericin B
cimetidine
ranitidine
corticosteroids
calcium-channel blockers (diltiazem, verapamil, nicardipine)
oral contraceptives
danazol
C. Synergistic nephrotoxicity
aminoglycosides
nonsteroidal anti-inflammatory drugs
melphalan
amphotericin B
trimethoprim plus sulfamethoxazole—oral
cotrimoxazole—oral

Dermatologic Applications

In CsA-responsive dermatoses, CsA may have an effect by inhibiting T-cell activation and lymphokine production. At present the cutaneous condition for which CsA has been most widely used is psoriasis. Mueller and Herrman[21] treated four patients with psoriasis and psoriatic arthritis with oral CsA (300-400 mg/day). All patients responded within 1 week but worsened upon discontinuation of drug. The beneficial results of CsA in psoriasis and psoriatic arthritis were confirmed by several open studies and two double-blind studies using oral CsA (1-14 mg/kg/day).[21-37] The details of these studies are given in Table 10-2. Both the rate of response of psoriasis vulgaris and the incidence of side effects appear to be dose dependent. At the moment, the authors are carrying out a double-blind, placebo-controlled study to determine the most suitable dosage for the treatment of psoriasis vulgaris.

Use of oral CsA has also been reported for various other cutaneous diseases. Pemphigus (vulgaris, foliaceous, and erythematosus forms) and bullous pemphigoid have generally responded to CsA alone or to a combination of CsA and corticosteroids. (Table 10-2).[38-45] Dermatomyositis and polymyositis have responded to CsA alone or in combination with corticosteroids, with improvement usually occurring within the first few weeks of therapy (Table 10-2).[46-52] CsA alone or in conjunction with prednisone or other immunosuppressive agents has been used for the therapy of lupus erythematosus. CsA may have a role as a corticosteroid-sparing agent, but it will probably not be effective monotherapy in this condition.[53-57] In open studies, Behçet's disease appears to be CsA responsive, with improvement in both ocular and nonocular symptoms (Table 10-2).[58-62] Most patients with mycosis fungoides who have been treated with CsA have had advanced disease. Generally, there has been some initial improvement in erythema and pruritus, but the long-term response has been poor (Table 10-2).[63-68] In open studies, atopic dermatitis patients have demonstrated clinical responses to CsA,[69,70] but flares can clearly occur in patients who have previously improved using the drug. One patient with ichthyosis vulgaris improved with CsA therapy,[71] but we found it to be ineffective in five patients with lamellar ichthyosis.[72] Alopecia areata appears to be a CsA responsive disorder,[73-75] and further double-blind studies are needed to confirm its efficacy. Except for one case of rapidly progressing scleroderma,[76]

TABLE 10-2. Summary of Studies of Cyclosporine A

Study, Year of Publication	Disease No. of patients	Therapy Regimen	Outcome	Reported Side Effects
Psoriasis (Psoriasis vulgaris = PV) and Psoriatic Arthritis (PA)				
Muller and Hermann,[21] 1979 Switzerland	PA and PV (4)	CsA 300-900 mg/day (oral)	Improvement in PA and psoriasis.	
Muller and Graf,[22]1981 Switzerland	PA and PV (4)	CsA 750-900 mg/day initially (oral). After 2 weeks, CsA 200-400 mg/day	Improvement in psoriasis. Improvement of PA in two patients after 7-9 weeks of therapy.	Nausea, paresthesiae, tremors, renal dysfunction. Herpes zoster in one patient
Harper et al.,[23] 1984, U.K.	PV and PA	CsA (5 mg/kg/day; oral). After 4 weeks, CsA raised to 6 mg/kg/day	Psoriasis—clear at 75 days. PA improvement at 6 weeks	
Van Hoof et al.,[24] 1985, Netherlands	PV (1)	Renal transplant patient on prednisolone and CsA	Almost complete clearing of psoriasis within days of starting CsA.	
Ellis et al.,[25] 1986, U.S.A. (double-blind)	PV (21)	CsA 14 mg/kg/day (oral; mean dosage) for 4 weeks	Total clearing or moderate to marked improvement in 17 patients.	Hypertension, headache, fatigue, paresthesiae, gingival hyperplasia, joint pain, hirsuitism, tremor.
van Joost et al.,[26] 1986, Netherlands	PV (5)	CsA 5 mg/kg/day (oral; mean dosage) for 4 weeks	Remission—three patients. Significant improvement—two patients.	Hypertension, diarrhea, renal dysfunction
Marks,[27,28] 1986, U.K.	PV (n = 9) Pustular Psoriasis (1)	CsA started with 1 mg/kg/day. Increased every 2 weeks by 1 mg/kg/day to a maximum of 5 mg if response not observed. Clearance noted at mean dose 3.3 mg/kg/day	Clearance—seven patients. Improvement—two patients after 23 weeks. Pustular psoriasis—no response	
Griffiths et al.,[29] 1986, U.K.	PV (10)	Eight subjects, initial CsA-2 mg/kg/day; two subjects, initial CsA-3 mg/kg/day. According to clinical response, CsA maximum 4 mg/kg/day	By 8 weeks: Total clearance—5 subjects. Up to 85% clearance—5 subjects. Therapeutic dose of CsA 3 mg/kg/day. 12-week study	Hypertension, renal dysfunction, hypertrichosis. All reversible when CsA stopped
Brooks,[30] 1986, U.K.	PV (7)	CsA 1-3 mg/kg/day (oral)	Six of seven patients cleared. One dropout—found CsA mixture unacceptable	Renal dysfunction
Bencini et al.,[31] 1986	Erythro-dermic psoriasis (2)	Psoriatics receiving CsA post-transplant	Marked improvement	
Wentzell et al.,[32] 1987, U.S.A.	PV, PA erythro-dermic & pustular psoriasis (14)	CsA 5-15 mg/kg/day (oral) over mean of 4 weeks (range 2.5-8 weeks).	Clear—three patients. Markedly improved —10 patients. Dropout—one patient	Increased appetite, weight gain, tremulousness, diarrhea, renal dysfunction, fatigue, nausea
Picascia et al.,[33] 1987, Netherlands	Psoriasis erythrodermic (2)	CsA 7.5-8.5 mg/kg/day (oral) initially, then CsA reduced	All four patients completely clear within 3 weeks.	Renal dysfunction, hypertrichosis, tremors.

TABLE 10-2. (Continued)

Study, Year of Publication	Disease No. of patients	Therapy Regimen	Outcome	Reported Side Effects
Meinardi et al.,[34] 1987, Netherlands	Psoriasis (generalized pustular—von Zumbusch) and PA (1)	CsA 12 mg/kg/day (oral) initially	Third day—clearance of pustules. Later improvement of arthralgias. Before complete remission—elevation of serum creatinine. CsA decreased to 5 mg/kg/day—new psoriatic lesions. Steroids added. 4 months later creatinine normal. CsA raised to 9 mg/kg/day. Steroids discontinued. Remission 9 months later. Patient on CsA 4 mg/kg/day. No recurrence	Renal dysfunction
van Joost et al.,[35] 1988, Netherlands (double-blind)	PV (20)	CsA mean dose 5.5 mg/kg/day (oral)	Improvement—greater than 75% PASI score in 15 of 18 patients on active drug within 4 weeks	Hypertension (mild, reversible), renal dysfunction (reversible), myalgias, fatigue, hypertrichosis, headaches, mild gynecomastia, tremor, gastrointestinal upset
Zachriae et al.,[36] 1987, Denmark	Pustular psoriasis (acrodermatitis continua type) (1)	CsA (14-5 mg/kg/day) (oral) 14 mg/kg/day. Response to disease was dose dependent	Clearing within 1 week on CsA	Hypertension
Gupta et al.,[37] 1988, U.S.A.	PA, PV (6)	CsA 6 mg/kg/day (oral) for 8 weeks	Clearing of psoriasis in all patients. Improvement in certain parameters of PA. Worsening of disease upon discontinuation of therapy	Nausea, headache, fatigue, flushing, hypertension (mild, reversible), gingival hyperplasia
Pemphigus Vulgaris (PV) and Bullous Pemphigoid (BP)				
Thivolet et al.,[38] 1985, France	PV (2)	CsA 6 mg/kg/day (oral) plus prednisone 1 mg/kg/day	Healing of lesions after 10-15 days of CsA	None
	BP (1)	CsA 6 mg/kg/day (oral) plus prednisone	Lesions healed over 3 weeks	None
	PV (1)	CsA 6 mg/kg/day (oral)	Lesions cleared within 4 weeks	None
Barthelemy et al.,[39] 1986, France	BP (4)	CsA 6-8 mg/kg/day (oral)	Two responded; two failures for whom prednisone 0.5 mg/kg/day added with subsequent response in one patient	None
	BP (3)	No response to steroids. Started CsA 6-8 mg/kg/day (oral)	Responded to CsA	None
	PV (4)	CsA 6-8 mg/kg/day (oral)	One responded. Three nonresponders, in whom prednisone 0.5 mg/kg/day added, with successful response	None
	PV (4)	Patients steroid resistant	Responded to CsA	None

TABLE 10-2. (Continued)

Study, Year of Publication	Disease No. of patients	Therapy Regimen	Outcome	Reported Side Effects
Balda et al.,[40] 1986	Pemphigus Foliaceous (1)	CsA 3.5-6.5 mg/kg/day (oral) combined with Prednisone (7.5-10 mg every 2 days)	Responded to CsA	None
	Pemphigus Erythematosus (n = 1)			
Cunliffe,[42,43] 1987, U.K.	BP (n = 1)	CsA (approx. 150 mg/day; oral) with prednisone (8-15 mg/day)	Good response over 2 months	Hypertrichosis
	Pemphigus Foliaceous (1)	Unresponsive to azathioprine 50 mg tid and prednisone (100 mg/day). CsA 250 mg/day (oral) added	Good response. After 3 months, CsA reduced to 150 mg/day, later reduced azathioprine to 50 mg/day. Corticosteroids discontinued	
Trappeiner and Groh,[44] 1985, Austria	PV (1)	CsA (approx. 10 mg/kg/day; oral)	No response	
Barthelemy et al.,[45] 1988, France	PV (9)	CsA 6-8 mg/kg/day (oral) prednisone 0.5-1 mg/kg/day added in some cases.	One patient responded to CsA alone. Five patients responded to combination therapy of CsA prednisone. Three patients no response to CsA alone. Two of these responded when prednisone added.	Gingivitis, hypertrichosis, hypertension, renal and hepatic dysfunction
Dermatomyositis (DM) and Polymyositis (PM)				
Zabel et al.,[46] 1984, W. Germany	DM (1)	CsA 3 mg/kg/day (IV)	Within a few days—clinical improvement, decrease of serum creatine kinase to normal	
Bendtzen et al.,[47] 1984, Denmark	PM (2)	CsA 7.5-10 mg/kg/day (oral)	Improvement within 1 week	
Van der Meer et al.,[48] 1986, Netherlands	PM (2)	Patient required prednisolone 100 mg/day for control. Resulting side effects were severe. Started on CsA 10 mg/kg/day (oral)	Within a few weeks of starting CsA, able to reduce steroids	
Ejstrup,[49] 1986, Odense	DM (1)	Lack of response to prednisone 75 mg/day and azathioprine 150 mg/day. Started on CsA 7.5 mg/kg/day	Improvement within weeks. Prednisone reduced 80 mg to 12.5 mg/day while on CsA	
The et al.,[50] 1985, Netherlands	PM (1)	CsA 10 mg/kg/day (oral). After 4 weeks, CsA reduced to 5 mg/kg/day. Maintenance dose: 5 mg/kg/day (at 1 yr)	Improvement within 2 weeks. Two months after start of CsA, muscle enzymes normal. After 1 yr. of therapy complete remission	Gastrointestinal complaints, renal dysfunction. Both responded to dosage reduction
Jones et al.,[51] 1987, U.K.	PM (2)	Patient 1: CsA 7.5 mg/kg/day (oral) with prednisolone 10 mg and 60 mg on alternate days	No response in 7 weeks	Renal dysfunction
		Patient 2: CsA 5 mg/kg/day (oral) plus prednisolone 10 mg/kg/day	Unresponsive to steroids and CsA (3 months therapy)	Nausea, tremors, hirsutism

TABLE 10-2. (Continued)

Study, Year of Publication	Disease No. of patients	Therapy Regimen	Outcome	Reported Side Effects
Girardin et al.,[52] 1988	DM (1)	CsA 5 mg/kg/day (oral), plus prednisone 0.1 mg/kg/day. After 8 months of CsA, patient still in remission	Good response. CsA adjusted to keep CsA whole blood (level approx. 300 ng/ml)	
Behçet's Disease and Inntraocular Inflammatory Disease				
Nussenblatt et al.,[58] 1983, U.S.A.	Bilateral, posterior uveitis of non-infectious origin (8)	CsA 10 mg/kg/day (oral) Behçet's disease. Improvement of nonocular symptoms also	Seven of eight improved.	Renal dysfunction, paresthesiae, fatigue, gingival hyperplasia flushing
French-Constant et al.,[59] 1983, U.K.	Behçet's (1)	CsA 10 mg/kg/day (oral)	Remission in 1 week. CsA stopped after 10 days following elevation of creatinine. Within 7 days, creatinine back to normal. CsA restarted at 5 mg/kg/day. Complete remission in 7 days. After 3 weeks, disease flared. CsA raised to 10 mg/kg/day with control of symptoms. Rising creatinine and CsA discontinued. Disease flared	Renal dysfunction
Sanders et al.,[60] 1983, U.K.	Posterior uveitis and retinal vasculitis. Behçet's, sarcoidosis, idiopathic (1)	CsA	Beneficial effect	
Nussenblatt et al.,[61] 1985, U.S.A.	Behçet's (n = 7)	CsA 10 mg/day (oral)	CsA abrogated acute phase of ocular attack. Recurrences totally prevented or markedly reduced. Improvement also noted in nonocular complications of Behçet's	Gingivitis, hypertrichosis, fatigue, paresthesiae, renal dysfunction
Wechsler et al.,[62] 1986, France	Behçet's	CsA 10 mg/kg/day (oral)	Suppression of disease, hypertension, nephrotoxicity	Hirsutism, gynecomastia
Mycosis Fungoides (MF)				
Puttick et al.,[63] 1983, U.K.	Sezary syndrome (1)	CsA 17.5 mg/kg/day (oral)	Within 1 week clearing of erythema and relief of pruritus. Able to reduce dosage of prednisolone being taken concurrently	Renal and hepatic dysfunction
Moreland et al.,[64] 1985	MF (ulcerated tumor stage) (1)	CsA 300 mg/day (intravenous route) initially. After 14 days changed to CsA 200 mg twice daily (oral)	Initial response in 10 days. Improvement continued for first 12 weeks then deterioration	

TABLE 10-2. (Continued)

Study, Year of Publication	Disease No. of patients	Therapy Regimen	Outcome	Reported Side Effects
Totterman et al.,[65] 1985, Sweden	Sezary syndrome (1)	CsA (oral) for 14 months	Pruritus responded 2-3 days. Decrease in erythema, number of tumor cells in skin and lymph nodes. Number of circulating Sezary cells largely unaffected	Renal dysfunction
Maddox et al.,[66] 1985, U.S.A.	MF (1)	CsA 5 mg/kg/day intravenous	Within a few days, marked improvement in pruritus. Skin lesions improved. After 4 months, while still on CsA, pruritus and infiltration recurred	
Jensen et al.,[67] 1987, Denmark	MF (2)	Patient 1: Stage III MF CsA 12.4 mg/kg/day (intravenous), then changed to oral CsA. Then disease flared	After a few days—marked decrease in pruritus. Later dimunition in size of skin tumors. After 8 weeks drug discontinued	
Kreis et al.,[68] 1988, U.S.A.	MF (3)	Patient 1: Generalized erythroderma, inguinal lymphadenopathy CsA 5 mg/kg/day. After 2 weeks, CsA increased to 7.5 mg/kg/day	After week 1—complete resolution of pruritus. Marked decrease in erythroderma. After 7 weeks, increased BUN and CsA decreased to 5 mg/kg/day	Renal dysfunction

For other diseases see text.

this disease has generally *not* demonstrated significant response to CsA.[77]

Pyoderma gangrenosum has responded well to oral CsA therapy (6–10 mg/kg/day), with improvement occurring within 1.5–3 weeks of starting therapy.[78-80] Oral CsA (7.5–9 mg/kg/day) has also been reported to be of benefit in three patients with epidermolysis bullosa acquisita.[81-83] A patient diagnosed as being a persistent light reactor demonstrated some improvement while on oral CsA (6 mg/kg/day); there was worsening of disease upon discontinuing CsA.[84] Picascia and Roenigk[85] have reported one patient with male-pattern alopecia and psoriasis treated with oral CsA (7.5 mg/kg/day). Hair regrowth in areas of baldness was noticed while on CsA, with hair loss occurring upon discontinuation of CsA. In one case of cutaneous sarcoidosis, there was clearing of skin lesions within 2 weeks of starting oral CsA (10 mg/kg/day).[86] Miller et al.[87] reported the use of oral CsA in three patients with chronic, steroid-dependent erythema nodosum leprosum. Two patients demonstrated an excellent response, with a partial response in the third patient.

Adverse Effects

CsA has a spectrum of side-effects, many of which are dose dependent (Table 10-3). The following discussion focuses on the side effects that may occur during low-dose oral CsA in a nontransplant patient. The incidence of side effects can be minimized by careful patient selection, using the lowest CsA dose possible for short periods and monitoring blood trough levels of CsA. The triad of side effects that should be kept in mind is renal dysfunction, hypertension, and possible development of malignancy.

TABLE 10-3. Side Effects of Oral Cyclosporine A

Nephrotoxicity (see also electrolyte disturbances)	*Elevation of serum BUN and creatinine *Decreased glomerular filtration rate *Hypertension Hyperchloremic acidosis
Electrolyte disturbances	*Hyperkalemia, *hypomagnesemia *hyperuricemia
Neoplasms	Also see Cutaneous Noncutaneous: Non-Hodgkins lymphomas, lymphomas, others (see text) Benign tumors: benign breast tumors, papillary adenomas, fibroplasia of heart and kidneys
Neurologic	*Paresthesias, *dysesthesias, *hand tremors, muscle weakness, depression/psychosis, seizures, headache, encephalopathy
Dental	*Gingival hyperplasia
Gastrointestinal	*Nausea, *diarrhea/constipation Anorexia, indigestion, weight loss Elevated triglycerides and cholesterol
Liver (see also Gastrointestinal)	*Elevation of total and direct bilirubin Elevation of alkaline phosphatase Elevation of transaminases
Cutaneous	*Hypertrichosis Neoplasms-SCC, BCC, Kaposi's sarcoma, others axillary hidradenitis, acne, folliculitus, skin thickening, epidermal cysts, sebaceous hyperplasia, breast tenderness, gynecomastia
Musculoskeletal	*Fatigue, myalgias, joint pains
Hematologic	Anemia, thrombocytopenia, elevation of ESR Leukopenia, erythremia, recurrent hemolytic uremic syndrome, increased risk for thromboembolic complications
Infections	Viral infections (eg, CMV, EBV, opportunistic infections such as pneumocystis pneumonia) Bacterial and fungal infections
Miscellaneous	*Flushing sensation, breast lumps, aseptic meningitis, myocardial infarction, angina, fluid retention, visual impairment, diabetes

*Relatively common side effects that may occur in treatment of cutaneous diseases.

Renal dysfunction is the most common side effect we have encountered and is dose-dependent. It is generally reversible upon lowering the dosage of CsA or upon discontinuing the drug. A dermatologist treating a patient with oral CsA in an outpatient setting can monitor for renal dysfunction by obtaining regular measurements of serum blood urea nitrogen, serum creatinine, creatinine clearance, CsA blood trough levels, and blood pressure.

The use of CsA blood trough levels as a means of determining a safe therapeutic dose of CsA has not proved to be as successful as originally anticipated. There are multiple methods by which CsA blood levels can be measured. These include RIA, HPLC, and

fluorescence polarization immunoassay (FPIA).[88,89] The RIA method is a rapid and sensitive method for estimating the concentration of CsA and its metabolites. Both monoclonal and polyclonal antibodies are available. Some can distinguish between the parent compound and metabolites. HPLC is more time consuming, but it can detect the parent drug and its metabolites separately with great precision. FPIA has been introduced recently to measure CsA blood levels; further details are given elsewhere.[89] Nonetheless, a rough correlation between CsA blood trough levels and nephrotoxicity exists.

Two important points that need to be addressed are whether short-term, low-dose CsA can result in chronic renal dysfunction upon discontinuation of drug. To date this has not occurred in our experience. Whether long-term, low-dose oral CsA can lead to irreversible renal dysfunction still needs to be determined, but at low doses of CsA currently being used, available evidence suggests that this is unlikely.

The development of hypertension is also dose dependent and is more likely to develop in patients with preexisting hypertension or renal dysfunction. In nontransplant patients receiving oral CsA, hypertension has been reported in approximately 25% patients.[25,90] In our experience with low-dose, oral CsA (6 mg/kg/day), if hypertension develops it is generally mild and can be controlled by dose reduction or discontinuation of CsA or by other standard medical measures. Blood pressure normalizes upon discontinuation of CsA.

The majority of the information about the development of malignancy with CsA is available at transplantation doses of CsA, usually when CsA has been used in conjunction with other immunosuppressive therapy. The incidence of lymphomas in patients treated with transplantation doses of CsA is similar to that seen with other immunosuppressive agents.[91-94] It is felt that in these transplant patients lymphomas develop as a result of their depth of immunosuppression rather than as a consequence of being on any particular immunosuppressive drug; long-term studies are needed to compare the effect of low-dose, single-agent CsA with conventional immunosuppressive therapy. In otherwise healthy patients treated with low-dose oral CsA for a short period, the risk of lymphoma should be close to that of the general population. In view of the above, the lowest possible dose of CsA should be used.

Other side effects that may be seen with oral CsA therapy are summarized in Table 10-3. Hypertrichosis is a common side-effect, occurring in 30-95% of transplant patients receiving CsA.[95-97] With low-dose CsA, hypertrichosis was not found to be of clinical significance. Resolution normally occurs within 1-2 months of discontinuing oral CsA. In a study performed by the present authors, gingival hyperplasia occurred in 33% of 21 psoriatic patients who received oral CsA 14 mg/kg/day for 4 weeks.[25] The gingival changes were usually mild and resolved when CsA was discontinued. The clinical and histologic changes seen with gingival hyperplasia induced by CsA and phenytoin are essentially identical.[98,99] Fatigue is a relatively common side effect, but it may improve with continued therapy. A flushing sensation, especially in the upper half of the body, may occur early in therapy; this also usually subsides with continued therapy.

Electrolyte abnormalities include hyperkalemia, hypomagnesemia, and hyperuricemia. Electrolytes should be monitored regularly, especially when patients have other medical problems. Transiently occurring gastrointestinal side-effects consisting of nausea, anorexia, upper abdominal discomfort, and diarrhea are common, but these usually subside with continued therapy or upon lowering the dose of CsA. CsA metabolities are excreted mainly in the bile via the enterohepatic circulation. Excretion of CsA is reduced as a result of hepatic, pancreatic, or bowel dysfunction.[100] In view of the above, patients with cutaneous disease who have significant preexisting hepatic dysfunction may not be suitable candidates for oral CsA therapy. With low-dose CsA, in otherwise healthy patients who have cutaneous disease, hepatic dysfunction consisting of elevated total and

direct bilirubin may occur but is usually mild, and it responds to lowering or discontinuing CsA.

Neurologic side effects consisting of paresthesias, dysesthesias, and hand tremors may be seen soon after starting CsA therapy and usually subside with continued therapy or following CsA dose reduction. Other less frequent neurologic side effects are given in Table 10-3. No increased risk of infection was seen with low-dose CsA given for short periods to otherwise healthy patients. This may be a serious side effect in already immunosuppressed patients receiving higher doses of CsA. A mild normochromic, normocytic anemia has been reported with CsA therapy.[101] We have not found this to be of clinical significance.

Conclusions

Oral CsA is an immunosuppressive agent that is increasingly being considered for treatment of various cutaneous conditions. The dermatoses most responsive to CsA appear to be psoriasis, Behcet's disease, alopecia areata, psoriatic arthritis, pyoderma gangrenosum, and atopic dermatitis. Some other diseases such as pemphigus, bullous pemphigoid, dermatomyositis, and lupus erythematosus, have also demonstrated a response to therapy. The side effect profile of CsA may limit widespread use of this drug. Many of the side effects are dose dependent, and studies must be performed to determine the lowest effective dose in the CsA-responsive dermatoses. In any patient being considered for oral CsA, possible side effects should be weighed carefully against the benefits of therapy.

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