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Immunosuppressive and Immunomodulatory Drugs

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## Chapter 234

# Immunosuppressive and Immunomodulatory Drugs

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There has been significant progress in the search for selective immunomodulation; the most significant advance in immunotherapy has been the reduction in systemic glucocorticoids exposure along with early or concomitant introduction of immunosuppressive and immunomodulatory adjuvants. Unlike immunomodulators, immunosuppressants are characterized by (1) a low therapeutic index (narrow window between the toxic and the therapeutic range) and (2) intra- and interindividual variation of the pharmacokinetics of these agents. These obstacles are usually overcome by precise drug dosing (ideal/lean body weight and body surface area) as well as close monitoring of drug levels (parent and metabolite serum peak and trough levels) and organ toxicity.

The main goals in immunotherapy therapy are “safety and effectiveness,” which currently are accomplished by the use of “combination therapy.”<sup>1,2</sup> The ideal immunotherapy combination is the one that combines drugs that have different mechanisms of action and different toxicity profiles. Thus, an additive or synergistic therapeutic effect will be obtained along with a significant reduction in dose-dependent side effects.

A comprehensive knowledge of the pathophysiology of the treating disease as well as of the pharmacokinetics and pharmacodynamics concepts is crucial for delineating the most effective and safest therapeutic regimens for autoimmune and inflammatory skin disorders (see eFig. 234-0.1 in on-line edition; Fig. 234-1).

### ▪ MACROLACTAM DRUGS

Macrolactam drugs are immunomodulators derived from microorganism fermentation products that include calcineurin inhibitors (CNIs) [e.g., cyclosporine, tacrolimus (TCL), and pimecrolimus] and mammalian target of rapamycin inhibitors (mTORIs) [e.g., sirolimus (SRL) and everolimus (EVL)]. Macrolactams are versatile immunomodulators that selectively suppress T-cell response and have synergistic therapeutic effects when they are combined with virtually any other immunosuppressive drug.<sup>1,2</sup>

### *Calcineurin Inhibitors*

#### MECHANISM OF ACTION

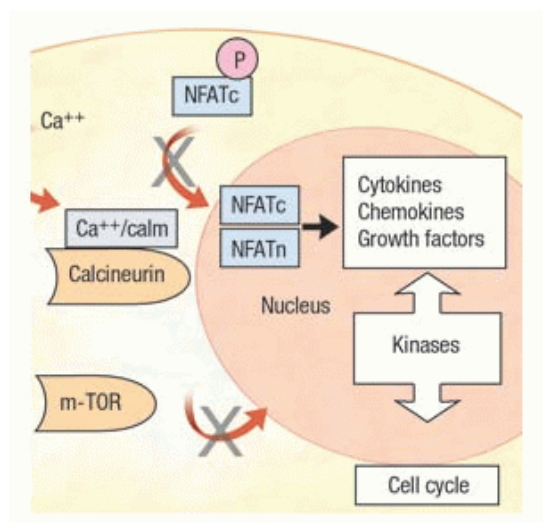
CNIs inhibit T-cell stimulation initiated by several pathways, of which the T-cell receptor (TCR) CD3 is the

best understood.<sup>3</sup> Mechanisms involving B-7 and CD28/cytotoxic T lymphocyte antigen-4, and other co-stimulatory pathways seem not to be affected by cyclosporine A (CsA) or other CnIs. The high-affinity receptor for CsA is a 17-kd immunophilin called *cyclophilin A (CyPA)*. The other CnIs (TCL and pimecrolimus) bind a structurally unrelated, different immunophilin called *macrophilin-12* also known as *FK-506 binding protein-12 (FKBP-12)*. The drug-immunophilin complex binds to calcineurin (Cn), a serine/threonine protease composed of two subunits: CnA and CnB. CnA constitutes the catalytic unit possessing binding sites for CnB and calmodulin. Cn activity strictly correlates with interleukin 2 (IL-2) production via CD3 activation. Cn is also involved in the induction of apoptosis and degranulation of cytotoxic T lymphocytes. Experimental data show that the CsA, TCL, and pimecrolimus/Cn complex inhibits the nuclear translocation of the nuclear factor of activated T cells c molecule by blocking its dephosphorylation. This is thought to be the key step by which these drugs uncouple TCR activation from IL-2 transcription. TCL is 10- to

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100-fold more potent than CsA in vitro in the inhibition of Cn activity.

### IMMUNOSUP-PRESSIVE AND IMMUNOMODU-LATORY DRUGS AT A GLANCE



- The main goals in immunotherapy are safety and effectiveness.
- Unlike immunomodulators, immunosuppressive drugs are all characterized by a narrow therapeutic window requiring precise dosing and close side-effect monitoring.
- The highest level of safety and effectiveness in immunotherapy therapy is currently accomplished by the use of combined regimens.
- An additive or synergistic combined immunotherapeutic regimen allows significant reduction of dose-dependent drug side effects maintaining or improving the effectiveness, respectively.
- A comprehensive knowledge of the pathophysiology of the treating disease as well as of the pharmacokinetics and pharmacodynamics concepts is crucial for delineating the most effective and safest therapeutic regimens.

In summary, CsA inhibits the T-cell activation mediated by antigen, but it does not inhibit the early phases of lymphocyte signal transduction occurring after antigen-mediated activation. The immunomodulatory effects of these drugs are intricate and subject to constant discoveries. A simplified explanation of the mechanism of action of these drugs is presented in the following sections and is illustrated in Fig. 234-2.

## CYCLOSPORINE A

CsA is a hydrophobic lipophilic undecapeptide extracted from fungi.

### *Pharmacokinetics.*

The microemulsion-based formulation of CsA has an improved bioavailability giving the drug more predictable absorption.<sup>3,4</sup>

#### **Modified median effect formula for combined therapeutic effect**

$$C_{ix} = \frac{A \text{ combined with } B}{A} + \frac{B \text{ combined with } A}{B}$$

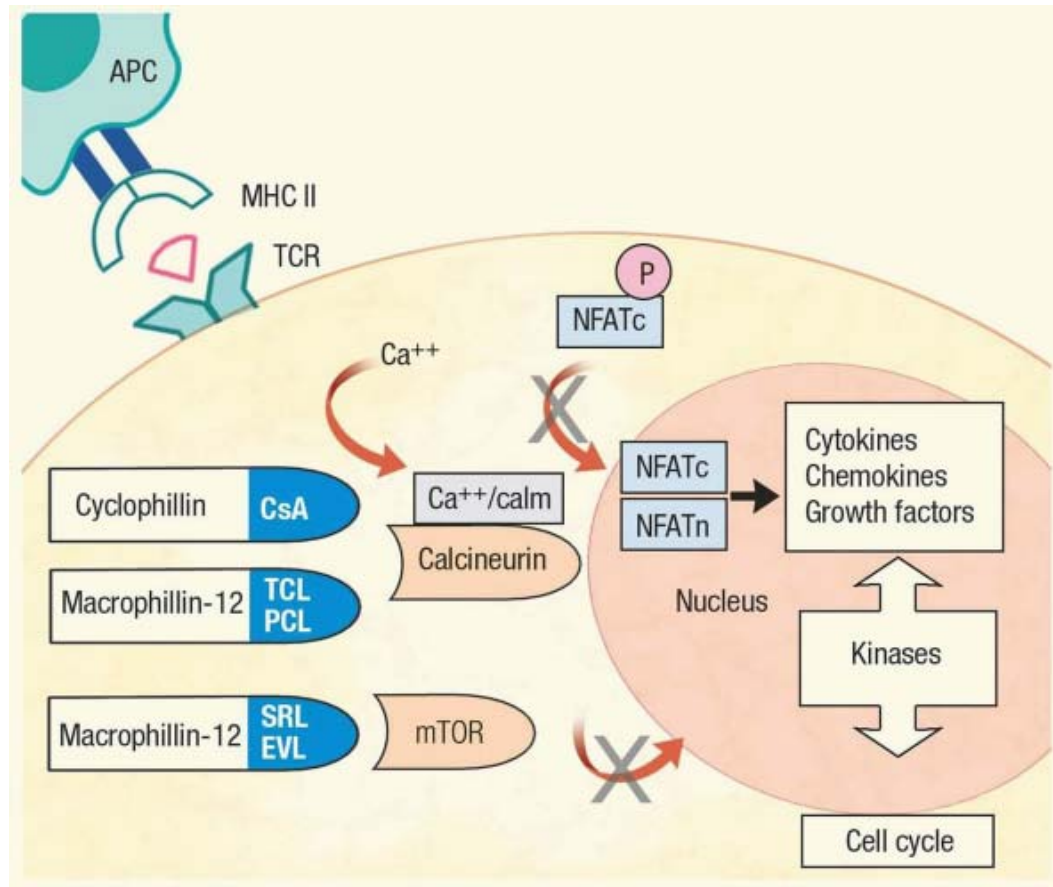
C<sub>ix</sub>: index inhibition (Igs, disease activity, etc)

C<sub>ix</sub>: = 1 additive

< 1 synergistic

> 1 antagonistic

**FIGURE 234-1** A modified, median-effect formula is widely used in organ transplant, which helps in finding the therapeutic windows of immunosuppressive drugs as well as the synergistic, additive, or antagonistic effect of a postulated drug combination. Igs = immunoglobulins. (From Chou TC, Talalay P: Quantitative analysis of dose-effect relationships: The combined effects of multiple drugs or enzyme inhibitors. *Adv Enzyme Regul* 22:27, 1984.)



**FIGURE 234-2** This diagram outlines the key mechanisms by which calcineurin (Cn) inhibitors and mammalian target of rapamycin (mTOR) inhibitors inhibit T-cell activation triggered by presentation of antigen via the T-cell receptor (TCR). The first step in antigen presentation involves presentation of a peptide that is bound within the peptide-binding groove of the major histocompatibility complex (MHC) class II molecule. This complex is then presented to the TCR. This causes transmembrane signaling that increases intracellular calcium concentrations. The liberated calcium, bound to calmodulin, interacts with Cn, a calcium-dependent serine/threonine phosphatase that dephosphorylates nuclear factor of activated T cells (shown here as NFATc), and this causes NFAT to translocate to the nucleus. There it binds to other nuclear components of NFAT (shown here as NFATn). This complex regulates the transcription of many cytokine genes, shown in the diagram. Cyclosporine (CsA), tacrolimus (TCL), and pimecrolimus (PCL) diffuse freely into the cytoplasm of T cells and bind with their respective immunophilins. This drug/immunophilin complex binds to Cn and blocks its ability to dephosphorylate NFAT, and thereby inhibits the production of cytokines, chemokines, and growth factors [interleukin 2 (IL-2), IL-3, IL-4, tumor necrosis factor- $\alpha$ , interferon- $\gamma$ , granulocyte-macrophage colony-stimulating factor, etc.] that would normally be induced after T-cell activation via the TCR. Sirolimus (SRL) has a more complex intracellular mechanism of action. Although SRL and everolimus (EVL) bind macrophilin-12 (also known as *FKBP-12*), the immunophilin of TCL and PCL, its mechanism of action does not appear to be mediated by Cn inhibition. mTOR inhibitors block cell kinases that would have a direct effect on the cell cycle by also an indirect effect in chemokine, cytokine, and growth factor synthesis. APC = antigen-presenting cell.

CsA can also be administered intravenously as a 50 mg/mL solution made up in an ethanol-polyoxyethylated castor oil mixture. The accumulation of CsA in erythrocytes and leukocytes is the reason that whole-blood monitoring of CsA levels is much more accurate than measurement of plasma levels. Peak levels occur from 1.3 to 4.0 hours after oral administration. After gaining access to the circulation, CsA distributes widely and has a large apparent volume of distribution (13 L/kg). CsA is metabolized into greater than 30 cyclic, partly active metabolites by the liver cytochrome P<sub>450</sub> 3A enzyme (CYP 3A).<sup>5,6</sup> Thus, drugs that compete for binding to CYP 3A will increase CsA levels, and drugs that induce P<sub>450</sub> will accelerate metabolism and decrease blood levels. Certain foods rich in bioflavonoids, especially grapefruit, seem to increase the drug's bioavailability through an interaction with cytochromes. Its elimination half-life is 6 to 12 hours in the absence of severe hepatic disease, and biliary excretion accounts for more than 90 percent of its elimination. CsA solution does have some penetration of mucosal surfaces, but this is not true of cornified epithelium. Intralesional injections of CsA do provide some local effects in psoriasis, but they are not widely used.

### **Indications**

- Psoriasis
  - Moderate to severe psoriasis
  - Part of combined therapy
  - Failure of conventional treatment
- Graft-versus-host disease
  - Prophylaxis
- Pyoderma gangrenosum
  - Moderate to severe disease
  - Part of combined therapy
  - Failure of other treatments
- Paraneoplastic pemphigus
  - Part of combined therapy, namely in lichenoid forms
- Lichen planus
  - Mucosal and/or cutaneous forms
  - Moderate to severe cases
  - Solo or part of combined therapy
- Atopic dermatitis
  - Moderate to severe cases
- Behçet disease

- Ocular and mucocutaneous forms
- Moderate to severe cases
- Dermatomyositis
  - Moderate to severe forms
- Alopecia areata
- Recurrent aphthous stomatitis
- Epidermolysis bullosa acquisita

### **Dosing Regimen. (Table 234-1)**

	ORAL	INTRAVENOUS
Adults	2.5-5.0 mg/kg/day	2-3 mg/kg/day
Children	5-7 mg/kg/day	3-5 mg/kg/day

### **Initiating Therapy.**

Doses higher than 5 mg/kg/day are not advisable. The U.S. Food and Drug Administration has approved CsA for psoriasis in doses up to 4 mg/kg/day, with a recommended starting dose of 2.5 mg/kg/day. Dosage increases should be performed after 4 weeks of therapy, and dose reductions are permitted at any time. Dosage increases should not exceed 0.5 to 1.0 mg/kg/day at 2- to 4-week intervals. Intravenous CsA formulation can be infused slowly over a period of 2 to 6 hours at about one-third of the usual oral dose, or about 2 to 3 mg/kg per day.<sup>7</sup>

### **Monitoring Therapy.**

With psoriatic patients going into remission, defined as a reduction in the psoriasis area and severity index of greater than 75 percent, the CsA dose should be down-titrated at 4-week intervals. The two most common assays for trough levels are high-performance liquid chromatography (HPLC) and radioimmunoassay are performed in EDTA-containing whole blood. The recommended range is 200 to 400 ng/mL. Children have comparable bioavailability of orally ingested CsA, but have a higher renal drug clearance rate (11.8 mL/min per kg vs. 5.7 mL/min per kg in adults), and a correspondingly shorter blood level half-life (7.3 hours vs. 10.7

hours in adults). Children may therefore require somewhat higher dosages and more frequent administration to achieve comparable trough levels to adults.

### ***Risks and Precautions.***

Serum creatinine levels should be carefully monitored during CsA therapy. If creatinine levels increase more than 30 percent above baseline, the dosage should be reduced for 1 to 2 weeks. If, after that time, the creatinine levels decrease below the 30 percent elevation mark, continuation at the lower dose is advisable. In cases where the creatinine remains elevated by more than 30 percent, discontinuation of CsA is recommended until the creatinine returns to levels within 10 percent of pre-treatment levels. More accurate studies monitoring the glomerular filtration rate clearance are used in individualized cases. From a practical standpoint, adequate monitoring of CsA dosage can be achieved by the avoidance of CsA doses higher than 5 mg/kg/day, evaluation of clinical response, and vigilance for signs of toxicity. This requires a detailed physical examination, including blood pressure monitoring with threshold concern triggered by a persistent diastolic blood pressure above 90 mm Hg, a complete history with emphasis on concomitant drug ingestion and medical conditions that may potentiate CsA toxicity, and laboratory evaluations for complete blood count, creatinine and blood urea nitrogen, uric acid, liver enzymes, serum electrolytes and magnesium, and a urinalysis. In patients receiving long-term CsA therapy (> 6 months), the serum creatinine and its clearance may not be a reliable predictor of altered renal function, and potentially irreversible chronic cyclosporine nephrotoxicity may ensue. In such circumstances, more reliable studies for the evaluation of renal function may be indicated.

### ***Complications.***

#### **RENAL FUNCTION, LIVER, AND NEUROLOGIC.**

Overall, one in four patients taking CsA develops clinical and laboratory evidence of altered renal function, including hypertension. Two types of CsA-induced nephrotoxicity are encountered in dermatologic patients. The first type usually starts within 2 to 3 weeks after drug initiation, and it is usually associated with high CsA blood levels. In this toxicity, there is an insidious decrease in glomerular filtration rate along with hypertension, and tubular dysfunction in association with a complete recovery of renal function upon dose-lowering or discontinuing therapy. The second type is likely a result of cumulative sub-clinical chronic renal toxicity. This may occur in the absence of any detectable elevation of creatinine or blood pressure. Histologic changes include interstitial fibrosis, tubular atrophy, and some degree of vasculopathy. Although renal function can improve somewhat after discontinuation of the drug, this type of toxicity is generally irreversible. In psoriatic patients receiving 5 mg/kg/day CsA, elevation of serum creatinine may persist

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for more than 4 months after discontinuation of the drug. Several mediators, including endothelin-1, angiotensin II, osteopontin, and transforming growth factor- $\beta$ 1, have been implicated in the pathogenesis of CsA-associated nephrotoxicity and hypertension. Calcium channel antagonists exert beneficial effects on CsA-induced hypertension and nephrotoxicity, presumably through the inhibition of endothelin-1. Other drugs, including angiotensin converting inhibitors (enalapril, lisinopril, etc.) and angiotensin receptor blockers (losartan, valsartan, etc.), are also effective mainly when used in combination with other antihypertensive drugs. New drugs, such as endothelin A receptor blockers (bosentan, darusentan, etc.) and renin inhibitors (aliskiren), appear to be promising for CsA-treated patients.<sup>8, 9, 10</sup> Diuretics and nephrotoxic drugs should be used with caution in CsA-treated patients. Another uncommon adverse renal complication is the development

of thrombotic microangiopathy/hemolyticuremic syndrome,<sup>11,12</sup> especially in allogeneic bone marrow transplant patients receiving CsA for acute graft-versus-host disease. Hypomagnesemia and hyperkalemia or hypokalemia are not uncommonly encountered.

Nausea, vomiting, anorexia, and diarrhea commonly occur with the use of CsA. Elevations of liver enzymes greater than 100 percent over baseline should be managed by reduction of the CsA dose by 25 percent weekly, until enzyme levels normalize.

Headache is a common complaint, especially in patients with a history of migraines. It tends to resolve spontaneously as therapy continues. CsA-induced seizures appear to be associated with hypomagnesemia and concomitant use of high doses of systemic corticosteroids. Thus, serum magnesium levels should be always monitored and kept above the lower normal range in CsA-treated patients. Cortical blindness, lethargy, confusion, seizures, hemiplegia, tremors, and paresthesias have also been described in patients receiving CsA.<sup>8</sup>

There is evidence of impaired fibrinolysis and endothelial damage and proliferation associated with CsA. Hypercoagulability seems to contribute to the progression of atherosclerosis and glomerular damage in CsA-treated patients. Significant cytopenias have rarely been reported with the use of CsA.

Hypercholesterolemia, elevation of low-density lipoproteins, and hypertriglyceridemia may be seen with CsA.

## **CANCER.**

CsA-treated transplant recipients have a relative risk for all skin cancers of 6.8 versus 2.2 to 5.5 in patients receiving other immunosuppressive therapies. CsA-treated dermatologic patients also have a higher risk of skin cancers, including squamous cell carcinomas, basal cell carcinomas, human papilloma virus-associated anogenital carcinoma, and Kaposi sarcoma. The high incidence of squamous cell carcinoma in psoriatic patients treated with CsA could be biased by previous exposures to psoralen and ultraviolet A light or ultraviolet B. Approximately 25 percent of non-visceral Kaposi sarcomas can be expected to undergo complete or partial remission following cessation or reduction of immunosuppressive therapy. Epstein-Barr virus-associated post-transplant lymphoproliferative disorder (PTLD) is quite rare in dermatologic patients. PTLD frequently usually fails to respond to chemotherapy, but it may regress spontaneously after reduction and/or cessation of immunosuppression. The incidence of lymphoma in CsA-treated dermatologic patients appears to be less than 0.2 percent. The incidence of lymphoma in transplant patients receiving CsA alone or in combination with corticosteroids is less than 1 percent, whereas for those receiving CsA in conjunction with other immunosuppressive drugs is as high as 8 percent. In contrast to the high mortality rate attributed to lymphomas arising in immunosuppressed patients, lymphomas developing in CsA-treated patients seem to carry a better prognosis despite of having a shorter latency period seems.<sup>13, 14, 15</sup> In rheumatoid arthritis patients treated with CsA, there was no increase in malignancies in comparison with a matched control group of patients with rheumatoid arthritis who were not treated with CsA. Other neoplasms, including melanoma, are also reported in CsA-treated patients, although their true incidence is unknown.

## **OTHER ADVERSE EFFECTS.**

Hypertrichosis occurs in virtually all patients on long-term CsA therapy. It is not limited to androgen-dependent, hair-bearing areas, and shows no tendency to spontaneous remission. Gingival hypertrophy is reported in up to 70 percent of CsA-treated patients; it is more common in children, individuals with poor oral hygiene and concomitant use of calcium channel drugs. Improvement of this gingival complication with

topical or systemic azithromycin and metronidazole can be seen. An acneiform eruption, indistinguishable from that seen in steroid-induced acne, is frequently reported. A disseminated comedonal or cystic acneiform eruption can also occur. These side effects can appear at any time during CsA therapy, although they are more commonly described at the time of initiation of CsA therapy. Keratosis pilaris, sebaceous hyperplasia, warts, and epidermal inclusion cysts occur in up to one-third of CsA-treated patients.

Osteoporosis seems to result from the CsA's action on osteoblasts and osteoclasts, and by altering lymphokine release. CsA can induce hyperuricemia in up to 15 percent of patients, and it is also an indicator of early CsA-induced nephrotoxicity. Myopathy has been reported in transplant patients receiving high doses of CsA, and thus, caution should be used with the concomitant use of statins.

## PREGNANCY.

CsA does not seem to be mutagenic or teratogenic, although there is a high incidence of preterm newborns, fetal growth retardation, abortions, preeclampsia, and hypertension in mothers taking CsA, and these occurrences are magnified in transplant patients. There are no reports of neonatal complications in children born to fathers receiving CsA. Adequate contraceptive measures are recommended in women of childbearing potential. CsA crosses the placenta and is excreted in breast milk. CsA-treated transplant patients seem to have a relative risk for infectious, life-threatening complications that is much lower than that seen in patients receiving azathioprine and prednisolone. However, increased vigilance for infectious complications is recommended in CsA-treated patients.

## TACROLIMUS

TCL, a Cnl formerly known as *FK506*, is a macrolactam drug first isolated from *Streptomyces tsukubaensis*.

### ***Mechanism of Action.***

The postulated mechanisms of action of TCL are similar, if not identical, to the ones described for CsA (see Macrolactam Drugs).<sup>16</sup>

### ***Pharmacokinetics.***

TCL can be administered orally, topically, and intravenously. The pharmacokinetics of systemic TCL are characterized by a two-compartment model with a rapid initial drop and a long elimination half-life of 12 to 21 hours. TCL is metabolized in the liver with less than 1 percent of the drug excreted intact. TCL has not proved to be more effective than CsA, but it appears

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to have a better bioavailability. The topical formulations have a concentration of 0.3 percent and 0.1 percent in an ointment vehicle, and for more detailed information, see Chap. 221.

**TABLE 234-2 Tacrolimus Dosing Regimen**

ORAL

INTRAVENOUS

Adults	150-200 µg/kg/day	25-50 µg/kg/day
Children	200-300 µg/kg/day	50-100 µg/kg/day

### **Dosing Regimen. (Table 234-2)**

#### **Initiating Therapy.**

The dosage of systemic TCL should be reduced in the presence of hepatic dysfunction by 10 percent to 30 percent of the standard dosing.

#### **Monitoring Therapy.**

There is a good correlation between enzyme-linked immunosorbent assay and HPLC mass spectrometry measurements in monitoring of whole blood concentrations of TCL. Enzyme-linked immunosorbent assays may also detect metabolites of the drug, and thus, caution should be taken in patients with liver diseases or with concomitant use of CYP4503A-binding drugs. Blood levels of 5 to 15 ng/mL are recommended.

#### **Risks and Precautions.**

The risks and precautions are quite similar to the ones applied for CsA. However, neurotoxicities and glucose intolerance are somewhat higher than with CsA use, and thus, close monitoring of magnesium and glucose serum levels and, if indicated based on personal or family history, glucose tolerance tests are strongly recommended. The risk for PTLD seems to be higher in children with hepatic transplants who received both TCL and anti-OKT3, but it has not been definitively proved in dermatologic patients or in different clinical scenarios. Dose reduction and close monitoring of TCL levels by HPLC mass spectrometry in patients with liver diseases are strongly recommended. A less graft-versus-leukemia effect in comparison with the one seen with CsA is observed in bone marrow transplant patients. A great deal of concern has been raised regarding the potential risk of lymphoproliferative diseases with this drug, which led to a highly controversial placement of a black box warning by the U.S. Food and Drug Administration with the topical formulation (see Chap. 221).

#### **Complications.**

Mucocutaneous and metabolic side effects seem to be less frequent with the use of TCL. However, nephrotoxicity seems to be comparable to that seen with the use of CsA. The rest of the side effects are comparable with those seen with CsA use.

## **Indications**

- Psoriasis
- Pyoderma gangrenosum
- Atopic dermatitis
- Graft-versus-host disease
  - Prophylaxis
  - Therapy
- Lupus erythematosus
  - Systemic
  - Chronic cutaneous

Systemic TCL can be used virtually in any inflammatory and autoimmune skin disease in which systemic CsA has proved effective.<sup>17-21</sup> For topical use of TCL, see Chap. 221.

## **PIMECROLIMUS**

Pimecrolimus, also known as *ASM 981*, is a derivative of the parent compound ascomycin originally isolated from the fermentation products of *S. hygroscopicus* var. *ascomyceticus*. Pimecrolimus has a similar mechanism of action as that of other CnIs. Pimecrolimus is formulated in vehicle cream at concentrations of 0.2 percent, 0.6 percent, and 1.0 percent (see Chap. 221).

## ***Mammalian Target of Rapamycin Inhibitors***

### **MECHANISM OF ACTION**

SRL and its derivatives EVL and temsirolimus are most widely known as *mTORIs*. Although mTORIs bind to FKBP-12 (macrophilin-12), this drug-immunophilin complex inhibits gene transcription through a complex mechanism that is independent from the one involving Cn.

**TABLE 234-3 Sirolimus Dosing Regimen**

	DAILY ORAL DOSE
Adult—African and Asian descents	3-10 mg
Adult—Caucasians Children	0.5-3.0 mg 1.5 mg/m <sup>2</sup>

## PHARMACOKINETICS

African and Asian descent patients require a higher initial and maintenance dose of SRL than Caucasians. EVL bears a stable 2-hydroxyethyl chain substitution at position 40 on the SRL structure, which has given a greater polarity than SRL, improving the pharmacokinetic and particularly its oral bioavailability. Oral EVL is absorbed rapidly and reaches peak concentration after 1.5 hours. In adults, EVL pharmacokinetic characteristics do not differ according to age, weight, or sex, but body weight-adjusted dosages are necessary in children.<sup>25, 26</sup> The target trough concentration of EVL should range between 3 and 15 ng/dL. SRL topical formulation (2.2 percent and 8.0 percent) has been use in psoriasis patients (see Chap. 221).

## INDICATIONS

- Graft-versus-host disease
  - Prophylaxis
  - Refractory chronic
- Psoriasis
  - Severe
  - Solo therapy
  - Combination therapy with Cn inhibitors
  - mTORIs have a potential use in any inflammatory dermatosis in which CnIs play a therapeutic role.

## DOSING REGIMEN (Tables 234-3 and 234-4)

### INITIATING THERAPY

As mentioned in Table 234-3, due to ethnic differences, the SRL recommended oral loading dose is 6 mg and

oral maintenance dose is 2 mg per day for Caucasian patients, and the oral loading dose is 10 mg and oral maintenance dose is 5 mg per day for African Americans. Asians also appears to require higher doses of this drug. EVL starting dose are the same regardless of sex and race. The usual dosing for adults is 0.75 to 1.5 mg bid and for children 0.8 to 1.2 mg/m<sup>2</sup>.

## MONITORING THERAPY

Due to significant intra- and interindividual variability, measuring

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trough levels is critical with the use of mTORIs. Through levels for SRL and EVL are 5 to 20 ng/dL and 3 to 15 ng/mL, respectively. Complete blood cell count, electrolytes, liver function test, and a lipid profile, along with a comprehensive clinical examination with periodic blood pressure measurement, are mandatory.

**TABLE 234-4 Everolimus Dosing Regimen**

DAILY ORAL DOSE	
Adults	0.8-1.2 mg/m <sup>2</sup>
Children	0.75-1.5 mg/bid

## RISKS AND PRECAUTIONS

Concomitant use of antimetabolite drugs, including mycophenolate mofetil (MMF) and azathioprine in patients with mTORIs of upper normal or higher trough blood levels (e.g., SRL: equal or higher than 20 ng/dL or EVL: equal or higher than 5 ng/mL), raises the risk of cytopenias, namely thrombocytopenia. Concomitant use of CnIs, namely TCL, may increase the risk of thrombotic microangiopathy/hemolytic uremic syndrome, and thus, monitoring of blood cell count, dyslipidemia, electrolyte abnormalities, edema, and increase of liver function tests are also associated with high trough levels of these drugs. Patients with extensive psoriasis treated with SRL should be monitored closely for capillary leak syndrome, a rare complication reported only in one series.<sup>27</sup>

## COMPLICATIONS

Cytopenias, namely thrombocytopenia, hypertriglyceridemia, hypercholesterolemia, arthralgias, edema, and impaired wound healing, have been frequently associated with the use of mTORIs. Occurrence of cytomegalovirus appears to be lower that observed with the use of CnIs. No gingival hyperplasia has been observed with SRL. Tremor or any other neurologic complications are not frequent. Hypertension and malignancies are significantly reduced in comparison with the use of CnIs. This is most likely related to the

endothelial, mesangial antiproliferative and antineoplastic properties of mTORIs.

## ▪ **MYCOPHENOLATE MOFETIL**

MMF is an ethyl ester of its active metabolite, mycophenolic acid (MPA) a product of several *Penicillium* species.

### ***Mechanism of Action***

MMF is the reformulated product of MPA, but with enhanced bioavailability. MPA inhibits the type II isoform of inosine monophosphate dehydrogenase in the de novo pathway of purine synthesis. Lymphocytes are quite susceptible to this drug effect, because they minimally use the hypoxanthine-guanine phosphoribosyl transferase salvage pathway for purine synthesis. Other less understood mechanisms have also been reported.

### ***Pharmacokinetics***

The drug is rapidly absorbed after oral administration, and antacids and cholestyramine may decrease its absorption. Approximately 5 percent of the drug is bound to albumin. It is nearly completely metabolized by glucuronyl transferase, and more than 90 percent of the drug is eliminated by the kidneys. The MMF glucuronide metabolite, which is increased in renal failure, increases MMF clearance by competing for its binding sites on albumin. MMF pharmacokinetics seems not to be affected by the concomitant administration of CsA. As with many other immunosuppressive agents, doses up to 20 percent higher may be required for children due to a physiologic increased liver metabolism. A new oral formulation of MPA, mycophenolate sodium enteric coating (MP-EC), has been proved to be as effective as MMF at conversion dose as follows: 250 mg of MMF = 180 mg of MP-EC and 500 mg of MMF = 360 mg of MP-EC. This new formulation is less expensive and appears to have less gastrointestinal side effects.

### ***Indications***

- Atopic dermatitis
- Autoimmune blister diseases
- Chronic actinic dermatitis
- Connective tissue diseases
- Graft-versus-host disease
- Lichen planus
- Psoriasis
- Pyoderma gangrenosum
- Vasculitic syndromes

### ***Dosing Regimen (Table 234-5)***

### ***Initiating Therapy***

MMF is commonly used in synergistic and safe combination with CsA and glucocorticoids.

MMF is commonly used with systemic corticosteroids as adjuvant therapy. The full therapeutic effect of MMF or MP-EC, namely on antibody-mediated diseases, shouldn't be expected until 2 or 3 months after therapy initiation. The therapeutic and toxic profiles of MMF have led this drug to be the substitute of azathioprine.

**TABLE 234-5 Mycophenolate Mofetil Dosing Regimen**

	DAILY ORAL DOSE
Cytotoxic T-cell mediated diseases	25-35 mg/kg
Antibody-mediated diseases	35-55 mg/kg

Note: 180 mg of mycophenolate sodium enteric coating is the equivalent of 250 mg of mycophenolate mofetil; 360 mg of mycophenolate sodium enteric coating is the equivalent of 500 mg of mycophenolate mofetil.<sup>27,28</sup>

### **Monitoring Therapy**

Measurement of serum levels of MPA shows inconsistent predictive value to monitor effectiveness and toxicity in MMF-treated patients. Complete cell count and a liver function test are recommended to be monitored on a monthly basis.

### **Risks and Precautions**

Gastrointestinal side effects, occasionally with intractable diarrhea, namely in elderly patients, are common, but in the vast majority of the cases they disappear with continuation of therapy, dividing the total daily dose (e.g. three or four times a day), and taking the drug with food. Increased risk of herpes zoster virus re-activation is rather common, namely in elderly patients and patients with autoimmune blistering disease (author's personal observation). Significant cytopenias could be expected when combined with mTORIs. Dose reduction should be made for patients with liver diseases.

### **Complications**

Expected toxicities include nausea, upset stomach, vomiting, and diarrhea. There is no increase in nephrotoxicity, hepatotoxicity, hypertension, or neurotoxicity when MMF is used in conjunction with CsA and corticosteroids. The hematologic and gastrointestinal side effects are dose dependent and usually clinically insignificant. An increased incidence of lymphoproliferative diseases and lymphoma is reported with its use, as well as predisposition for infectious complication, usually non-life-threatening.<sup>30, 31, 32, 33, 34, 35, 36, 37, 38</sup>

Other antimetabolite and immunosuppressive agents are discussed in Chap. 228.

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