Observations in clinical and experimental ocular autoimmunity

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Citation for published version (APA):
de Smet, M. D. (2000). Observations in clinical and experimental ocular autoimmunity

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Chapter 13

Clinical Use of Cyclosporine in Ocular Disease

Marc D. de Smet, Robert B. Nussenblatt

International Ophthalmology Clinics 33: 31-45, 1993
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Clinical Use of Cyclosporine in Ocular Disease

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Robert B. Nussenblatt, M.D.

With the advent of reliable animal models of uveitis, the factors leading to ocular inflammation have slowly been dissected and studied. Several of these models have demonstrated the key role of T cells in the development of autoimmune ocular disease and have led to the prediction that a drug with predominantly anti-T-cell activity would be of benefit in treating or preventing ocular inflammation. Cyclosporin A (CSA), the first T-cell immunosuppressant to be discovered, was quickly shown to be effective in suppressing autoimmune uveitis in both controlled and uncontrolled trials [1–3]. Also known as cyclosporine, CSA was discovered in 1969/1970 by Jean Borel and coworkers in the microbiology laboratories of Sandoz, Ltd, in Basel, Switzerland [4]. Isolated from Tolypocladium inflatum Gams, this fungal extract was first tested as an antifungal agent but proved disappointing as its spectrum of activity was too narrow. The narrow spectrum was due in part to its potent immunosuppressant effect, an effect directed virtually exclusively against T cells. In addition to this specificity, CSA was shown to be nonmyelotoxic and to have a reversible effect on the immune system. However, despite these advantages, CSA therapy requires careful guidelines, because this drug has a variety of nonimmunological toxic side effects.

Clinical Pharmacology

CSA is a neutral, lipophilic, cyclic endecapeptide (molecular weight 1,203 gm) with a unique nine-carbon amino acid in position 1 (Fig 1) [5, 6]. Its activity is very much dependent on its stereochemical configuration and, in particular, on any modification to the residues in positions 1, 2, 3, 10, and 11. It is insoluble in water. For clinical use, CSA is stabilized in castor oil for intravenous injection and in olive oil with 12.5% ethanol for

175
Chapter 13

Figure 1 Chemical structure of cyclophage A.
oral administration, which is usually accomplished by dispersing the drug in juice or milk before ingestion. The absorption rate from an oral dose is roughly 30% but is highly variable (4 to 60%), due to slow, incomplete and variable absorption of CSA from the upper small intestine according to a bile-dependent zero-order process. The peak drug level occurs approximately 2 to 4 hours after ingestion. Absorption is adversely affected by biliary diversion, slow gastric emptying, or increased gastrointestinal motility. Coadministration of food and prolonged therapy promote absorption of the drug.

Most of the CSA in circulation is associated with lipoproteins. Although some CSA circulates unbound, this fraction does not correlate with the total blood levels of CSA or with adverse clinical events. The extent of tissue deposition also varies from patient to patient, with the volume of distribution ranging from 4 to 8 liters per kilogram of body weight. However, obesity does not appear to correlate with the volume of distribution. Rather, distribution volume seems to correlate with the levels of cytoplasmic binding proteins, which are able to retain CSA for months after therapy is discontinued. The liver is the major depot of the drug, followed by the pancreas, fat, blood, heart, lung, kidney, and neural and muscular tissue.

Ocular bioavailability depends on the mode of administration and the extent to which the blood-ocular barrier is broken down. In experimental animals, systemically administered CSA does not appear to penetrate very well through intact (uninflamed) ocular tissues [7]. However, in eyes of patients with chronic flare, the concentration in the aqueous humor is approximately 40% of the plasma concentration, indicating good intraocular penetration of the drug [8]. Ocular pigment also appears to influence the intraocular drug concentration. In rabbits, a statistically greater amount of drug is present in the iris and the retina-choroid of pigmented animals as opposed to albinos [9]. Uptake from local administration is hampered by the hydrophobic nature of CSA. Topically applied CSA in oil does not appear to penetrate beyond the cornea and conjunctiva in concentrations that are therapeutically efficacious, although when the corneal epithelium is damaged, high levels are detected in the aqueous [7]. The use of collagen shields [10] or an alpha cyclodextrin vehicle [11] increases the corneal penetration five- to tenfold. Periocular injections appear to generate intraocular levels that are potentially therapeutic, but this approach has not yet been tried in humans [12].

CSA metabolism involves oxidative alterations by cytochrome P-450 into metabolites with a higher polarity. Coadministration of drugs that interfere with cytochrome P-450 will lead to a lowering of CSA metabolism. In the case of ketoconazole, this effect is strong enough to reduce the required oral dose by up to 90% [13]. Other common inhibitors of cytochrome P-450 that can influence CSA levels include erythromycin, oral contraceptives, androgens, methylprednisolone, and some calcium channel
blocks, particularly diltiazem (Table 1). Nifedipine, on the other hand, has no effect on CSA metabolism. Agents that induce cytochrome P-450 enzymes cause a decrease in CSA levels. Phenytoin, for example, will cause the CSA level to drop more than 50% within 48 hours of its administration [14]. Other agents with a similar effect include rifampin, phenobarbital, carbamazepine, and valproate.

Excretion of CSA occurs primarily through the bile and the intestines (median half-life, 6.4 to 8.7 hours), with a small amount (6%) appearing in the urine. Longer dosing intervals may be required in the presence of elevated serum levels of bilirubin or alanine aminotransferase, but not if the changes are limited to aspartate aminotransferase, lactate dehydrogenase, or alkaline phosphatase. The clearance rate in children is 45% higher than in adults, thus indicating the need for higher doses in children [15]. In contrast, drug clearance is slower in the elderly and in patients with hepatic impairment.

### Mechanism of Action

Borel [4] showed that CSA reversibly inhibits T cell-mediated alloimmune and autoimmune responses. T-cell precursors, after being generated within the bone marrow, migrate to the thymus where they mature. After maturation they disseminate throughout the body, where they can bind selectively through specific cell surface receptors to antigens that are presented by antigen-presenting cells. This immunorecognition primes T cells...
to express surface receptors for lymphokines, which act as humoral immune signals that trigger cellular maturation. A second series of T-cell recognition reactions—the activation cascade—results in the synthesis of lymphokines that will promote cell division and the acquisition of cytotoxic potential. CSA does not affect the priming reaction, but it does inhibit the activation cascade necessary for inducing specific immune functions such as lymphokine production. The synthesis and secretion of interleukin 2 (IL-2), a potent activator of T and B cells, is reduced, as is the production of interferon gamma (IFN-γ), the lymphokine that provides an amplification signal to activate macrophages and monocytes, and tumor necrosis factor alpha (TNF-α), which has a number of immune targets. In addition, cyclosporine is able to inhibit the synthesis of the alpha and beta chains of the IL-2 receptor, further reducing the possibility of T-cell activation.

The precise mechanism of inhibition by CSA is poorly understood, owing to limited knowledge of the exact activation pathways in T lymphocytes. CSA probably acts at different cellular levels. At the cell surface, it appears to act through calcium-related cytoplasmic pathways. Alternate cell surface pathways through the CD2 receptor, which activate protein kinase C, are resistant to the drug. Within the cytoplasm, CSA reduces the generation of cytoplasmic activation proteins that mediate signal transduction between the cytoplasm and the nucleus. It reduces the signal that triggers DNA synthesis by resting T-lymphocyte nuclei. The probable target is a protein called cyclophilin, whose affinity for CSA is proportional to its immunosuppressive potency. Cyclophilins are present in most tissues and exist in many isoforms, only some of which are active. The pig-kidney cyclophilin has sequence homology with peptidyl-propyl-cis-trans isomerase, an enzyme that may initiate folding of specific cytoplasmic proteins that can lead to the exposure of DNA-binding domains. The nucleus itself can be a target for the action of CSA and is the third potential site. The drug appears to bind to nuclear proteins at sites of transcription regulation. However, CSA has no effect on events that occur after gene activation. All these effects appear to occur only in helper-inducer and cytotoxic T cells. Suppressor T cells are spared the inhibitory effects of CSA, thus setting the stage for an immunoregulatory disequilibrium favoring unresponsiveness rather than immunity.

### Toxicity and Side Effects

Despite its relatively specific effects on the immune system, CSA is associated with a number of side effects and potential toxicities. Because most uveitis patients requiring CSA therapy will stay on this medication for a prolonged period of time, one must carefully weigh the risks and benefits of CSA at every stage of therapy.
Chapter 13

Nephrotoxicity

With long-term CSA use, a particular concern is the development of nephrotoxicity and hypertension. The most common effect of this drug on the kidney is characterized by increased serum creatinine and urea. This reflects a dose-dependent decrease in the glomerular filtration rate (GFR) secondary to a decrease in renal blood flow, which is a result of vasoconstriction of the afferent glomerular arteriole. The fall in GFR initially is purely functional. With a CSA starting dose of 5 mg/kg, one can expect a rise in serum creatinine of approximately 10%, but even with such a rise, the serum creatinine remains within the normal range [16, 17]. The serum creatinine level plateaus in 4 to 8 weeks and, with proper monitoring, will remain in that range provided that potentially nephrotoxic drugs are avoided. These include nonsteroidal anti-inflammatory drugs (NSAIDs), aminoglycosides, amphotericin B, ciprofloxacin, melphalan, and colchicine. The effect of NSAIDs is of particular concern because several are now available as nonprescription drugs. NSAIDs reduce the GFR by inhibiting intrarenal cyclooxygenases and adversely affecting the balance between vasodilatory and vasoconstrictor prostaglandins in the kidney. Concomitant use with CSA can lead to a transient but significant rise in serum creatinine [18], an effect that can last up to 3 weeks.

Permanent changes in renal function are rare when the dose of CSA is maintained below 5 mg/kg and when the dose is adjusted to avoid large rises in serum creatinine [19, 20]. However, the risk of irreversible structural damage to the kidney remains a major concern when using CSA in long-term treatment. Chronic CSA nephropathy, when established, is irreversible and is characterized by a striped interstitial fibrosis accompanied by focal tubular atrophy. Renal arteriolar abnormalities are also noted; these may take the form of necrosis of smooth-muscle cells, a lumpy nodular protein deposit in the vascular wall of afferent glomerular arterioles, or an arteriolar intimal hyalinosis [21]. Such changes were commonly seen in transplant patients who were on high doses of CSA and in whom the serum creatinine was permitted to remain elevated for extended periods of time. Renal arteriolar abnormalities were seen also in patients with uveitis when the initial treatment dose was 10 mg/kg/day and the serum creatinine was allowed to rise to double the pretreatment level [21]. However, multivariate logistical regression analysis of renal biopsies from 192 patients with autoimmune or inflammatory diseases revealed that the risk of permanent kidney damage is minimal if the CSA dose is maintained at or below 5 mg/kg and if increases in serum creatinine of more than 30% above baseline are avoided [20]. The duration of treatment in patients from whom biopsies were obtained ranged from 4 to 39 months. In this study, CSA nephropathy was more closely related to the maximal dose of the drug than to the dose at the time of the biopsy or to the length of time the maximal dose was administered [20]. Age also appeared to be a risk...
factor. The mean age of patients with nephropathy was 31 ± 13 years as compared to 23 ± 12 years in those patients without nephropathy. The incidence of nephropathy in children was extremely low. These results suggested that CSA-induced nephropathy may be related less to long-term, cumulative toxic effects on the arterioles and tubules than to the consequence of brief insults brought about by the administration of excessive doses of CSA.

**Hypertension**

CSA induces a dose-related rise of arterial blood pressure, resulting in an average increase of 2 to 3 mmHg (diastolic) on a 2.5-mg/kg/day dosage and of 5 mmHg on a 5-mg/kg/day dose [19]. Hypertension develops in 15 to 25% of patients. The incidence is higher if the patient has predisposing factors, particularly alterations in renal function. In most instances, hypertension occurs early, within the first few weeks of starting CSA therapy. It is responsive to dose reduction and necessitates cessation of CSA therapy in only 1 to 3% of cases. A sudden elevation of blood pressure after prolonged therapy is often indicative of impending renal toxicity and should prompt the treating physician to check serum creatinine and obtain a CSA blood level. This situation is more common in obese patients who, after months of therapy, suddenly develop hypertension and have higher circulating levels of CSA. On reducing the drug dose, the blood pressure normalizes. The practitioner should also be aware of potential drug interactions that could increase circulating levels of CSA.

Hypertension alone is not a contraindication to using CSA, provided that the hypertension is well controlled on medication [22]. Nonetheless, whether present before or while on CSA, hypertension must be aggressively treated. The best first-line agents are probably the calcium channel blockers, especially nifedipine or isradipine, because these agents do not interfere with CSA pharmacokinetics.

**Malignancies**

It is known from organ transplantation that all potent immunosuppressive therapy can lead to an increased risk of some malignancies, particularly those that are virus-associated such as B-cell lymphomas and squamous cell skin carcinomas. With CSA, the highest risk occurs in patients who require the highest level of immunosuppression. Among renal transplant patients, the risk of lymphoma is 0.4%. For patients with autoimmune disease, the incidence of lymphoma is 0.05% or less (2 of 3,700 patients studied) [19]. Early diagnosis is important because, at an early stage, the lymphoproliferative disorder may spontaneously regress after reducing or stopping the immunosuppression. There is no specific screening procedure that is of benefit other than a careful periodic clinical exami-
Chapter 13

**Table 2**  *Incidence of Side Effects due to Cyclosporine in Patients with Autoimmune Disease*

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Incidence in %*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperesthesia, paresthesia, numbness</td>
<td>50 (33)</td>
</tr>
<tr>
<td>Hypertrichosis</td>
<td>39 (50)</td>
</tr>
<tr>
<td>Gastrointestinal problems</td>
<td>37</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>31 (30)</td>
</tr>
<tr>
<td>Fatigue, weakness, malaise</td>
<td>31</td>
</tr>
<tr>
<td>Gingival hyperplasia</td>
<td>27 (34)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>16</td>
</tr>
<tr>
<td>Headache</td>
<td>16 (18)</td>
</tr>
<tr>
<td>Tremor</td>
<td>11 (6)</td>
</tr>
<tr>
<td>Hepatic dysfunction</td>
<td>9</td>
</tr>
<tr>
<td>Weight gain</td>
<td>7 (5)</td>
</tr>
<tr>
<td>Anemia (severe)</td>
<td>5</td>
</tr>
<tr>
<td>Muscle cramps, skeletal pain</td>
<td>4 (7)</td>
</tr>
</tbody>
</table>

*Data collected on patients treated at an initial dose of 10 mg/kg/day [34]. In parentheses, the percentages correspond to an initial dosage of 5 mg/kg/day in patients with multiple sclerosis [35].

Squamous cell skin carcinomas have not been seen in patients with autoimmune disease except those with psoriasis. No definite association has been made between CSA and other malignancies. CSA is known to increase serum prolactin levels, causing gynecomastia in men and promoting the development of benign breast adenomas in women. No conclusive association has been demonstrated between breast carcinoma and CSA, but older women should be closely monitored, as prolactin can promote the growth of such tumors.

**Other Adverse Reactions**

The most common side effects of CSA are listed in Table 2. Mild numbness and tingling of the extremities as well as temperature hypersensitivity are noted by 50 to 90% of patients within several days of starting on CSA [34, 35]. Nausea and gastrointestinal distress beginning with the first dose are noted in up to 40%, but only rarely does this alter a patient’s ability to use the drug. Increased hair growth on the face, arms, shoulders, and back develops in 50% of patients and is usually noted in the first few months of therapy. Gingival hyperplasia, similar to that seen in phenytoin toxicity, is noted in 25% of patients also within the first several months of therapy. Its severity is exacerbated by poor oral hygiene and can largely be controlled by careful attention to periodontal disease. A fine hand tremor occurs in the early months of treatment, but this often will improve with continued therapy. A mild normochromic normocytic anemia may be noted in 25% of patients. The hematocrit rarely falls below 30%. Hepatic toxicity has not been a major problem with CSA. There is a mild, dose-
dependent elevation of the serum transaminases and serum bilirubin and, with prolonged use, a possible increase in the incidence of cholelithiasis and choledocholithiasis [5].

An acute overdose of oral CSA does not lead to severe complications. Even the ingestion of a whole bottle of CSA (10 gm) produces only a mild syndrome of hypertension, dysesthesias, flushing, and stomach upset, which lasts no more than a few days.

Optimal Use of CSA in Autoimmune Uveitis

From the foregoing discussion, it is evident that CSA is a very useful agent to treat autoimmune ocular disease, but it also has potentially severe side effects, particularly when the drug is used over a long term. Thus only patients with a reasonable chance of responding to CSA should be selected. Optimal use of this drug implies avoiding unnecessary treatment, stopping CSA administration in patients in whom it does not appear to have the desired effect, and lowering the dose to less than 5 mg/kg/day as soon as possible in patients who show a response to the medication. Therefore, it is important to define for each patient, before treatment is initiated, the parameters that will be used to measure a positive therapeutic response.

Whenever possible, objective criteria should be selected, particularly when treating posterior pole inflammation as it is very difficult to judge improvement in cell and flare. Measuring the patient's visual acuity, particularly in the setting of macular edema, may be all that is necessary, provided that a cataract is not a major component of the visual impairment. In all cases, it is important to rule out the possibility of an infectious cause and to reconsider this possibility if the condition worsens while on therapy. There must also be potential for visual improvement. Ancillary tests such as laser interferometry or fluorescein angiography may be useful in determining the full extent of this potential [23]. Results of this evaluation should be discussed with the patient, as well as the expected benefits and side effects of therapy. The decision to use CSA should be a joint one.

Once a decision has been made to try CSA, it is important to continue the treatment long enough to notice improvement. In most cases, response will be evident within 1 month and rarely will occur beyond 3 months. Therefore, a maximal trial period of 3 months appears reasonable. If there has been no measurable improvement by the end of the third month, we discontinue therapy, even if the patient insists that there has been some subjective improvement. An abrupt stop serves two purposes: It prevents prolonged use of a potentially toxic drug, and it can also serve as a measure of CSA's efficacy. In patients who respond to CSA, the disease usually recurs in one to two weeks following treatment interruption. On reintro-
Patient with ocular inflammation that is potentially reversible

Initiate therapy with CSA 2.5 mg/kg given two times per day (5 mg/kg/day)
(Add 0.2 to 0.5 mg/kg/day of prednisone)

Response
Continue treatment for a total of 3 MONTHS or until completely resolved

No Response (1 Month)
Increase CSA to 7.5 mg/kg/day

No Response (2 Weeks)
Maximize prednisone dose (up to 1 mg/kg/day)

No Response (4 Weeks)
Stop CSA
Try Cytotoxic Agent

When remission is achieved or after 3 months:
Taper CSA by 0.5 mg/kg/day every 4–6 weeks to the minimum dose that prevents a recurrence or 2.5 mg/kg/day; then taper the steroid to about 3–10 mg/day.
Once both drugs are at a low dosage, attempt to take the patient off both medications.
If a recurrence occurs while tapering, reinstate previous CSA dosage and increase steroids until the patient is under control.

Figure 2  Treatment schedule for the use of cyclosporin A (CSA) in uveitis patients.

duction, the disease comes rapidly under control. Consequently, an abrupt cessation of therapy can serve as a therapeutic trial.

As a starting dose, we often use 2.5 mg/kg given twice daily with 0.2 to 0.5 mg/kg/day of prednisone. The therapy is continued for 2 to 3 months or until the inflammation has come under control. We then taper the steroid or the CSA, depending on the needs of the patient (Fig 2). Over the next 3 months, we taper to the minimal dose of CSA or CSA-steroid combination that will control the inflammation [24]. In situations where CSA, 2.5 mg/kg given twice daily, does not seem to be effective, we increase the dosage up to 7.5 mg/kg/day in divided doses. However, we will maintain this dosage for only a short period of time—no more than 4 to 6 weeks—and taper it back down to 5 mg/kg/day once the inflammation has been brought under control. Recently, we tried a combination of CSA and
a microsomal enzyme blocker (ketoconazole) to reduce CSA metabolism. This combination has the advantage of maintaining serum CSA levels at a more uniform level throughout the day [13], which we found led to improved visual acuity in patients who had been under marginal control. One added benefit of this approach is that a much smaller volume of CSA is needed to control the inflammation.

When switching from CSA alone to a combination of CSA and ketoconazole, the CSA dose should be reduced to one-third of the original dose, but there are considerable variations between individuals, with some patients requiring only one-tenth of the original dose. Thus one must take care in using this approach. Initially, careful monitoring of serum creatinine levels, as well as the whole blood levels of CSA, is needed.

The most effective and safe monitoring schedule for CSA is still being debated. Traditionally, both the CSA blood level and the renal function have been monitored. The clinical relevance of drug levels has recently been reviewed in patients with psoriasis and nephrotic syndrome: Frequent measurement of CSA serum trough levels did not lead to a significant gain in safety or efficacy in these patients [25]. This may be particularly true in patients whose starting dose is 5 mg/kg/day or less, as was the case in this study. Routine monitoring of the trough level probably is not necessary in most circumstances, provided that one carefully monitors renal function. However, some situations do arise in which blood monitoring is needed, such as when there is a potential for drug interaction, when there is liver dysfunction, or in cases of unexpected inefficacy (potential compliance problems). If one intends to do a trough measurement, it is important to remember that it must be taken 12 hours after the last dose and that the accuracy is poor with doses below 3 mg/kg/day. Several methods exist for measuring CSA levels, with different reference ranges for each. Each measurement must be judged using the specific reference range provided. In general, the more accurate measurements are obtained from whole blood rather than serum levels [15, 26].

Whereas it might be unnecessary to measure CSA levels on a regular basis, it is important to monitor renal function and blood pressure. An acute rise in the blood pressure may be the first indication of renal toxicity. In patients with normal renal function, serum creatinine appears to be a good indicator of renal function changes. The lag time between a change in the GFR (the gold standard for renal function) and a rise in serum creatinine is usually short. As an added safety measure, we also routinely obtain a urinary creatinine clearance every 3 to 4 months. Although not as precise as a GFR measurement by inulin clearance or with isotopes, it does give a somewhat better idea of a patient's renal reserve than the serum creatinine alone. A 30% rise in the serum creatinine or a 30% drop in the urinary creatinine clearance should prompt one to reduce the CSA dose sufficiently to normalize these values. It is further recommended that
patients have their renal function monitored every 2 weeks during the first 2 months of treatment and every 2 to 3 months thereafter.

**Clinical Use in Ocular Disease**

**Systemic CSA**

Based on observations in this and other centers, CSA appears to be particularly useful in patients with active, bilateral sight-threatening uveitis of a noninfectious nature. It is especially advantageous in patients who are unable to tolerate moderate doses of systemic corticosteroids (>25 mg prednisone) and who require steroids to control their intraocular inflammation. In a recent randomized study, one of the coauthors (RBN) has shown that CSA, when used as the sole agent, was effective in controlling inflammation in 46% of patients who were steroid-intolerant [2]. When combined with steroids, CSA was effective in an additional 35% of patients. Others have found that when used as an initial agent, it was effective in 97% of patients [17].

Nonetheless, in most cases, it is probably best to use CSA only when other more traditional forms of therapy have failed. CSA does not appear to induce a state of immune tolerance, and therefore most patients will be faced with an extended therapeutic course once CSA is started. An abrupt withdrawal of the drug before the disease has run its course can cause a rather dramatic flare-up, as was discussed earlier.

Behçet's disease is an exception to this general recommendation. Masuda and colleagues [3] have clearly demonstrated in a double-masked study that CSA as a sole therapeutic agent was superior to colchicine, the previous drug of choice, in preventing recurrences of ocular disease. In another study comparing CSA to a combination of cytotoxics and steroids in Behçet's disease, CSA was again found to be more effective at preventing recurrences ($p = 0.016$) [27]. Thus Behçet's is one disease for which CSA can be considered as the initial therapeutic agent, but only if specific diagnostic criteria are met.

There have been some indications that CSA may be useful to treat scleritis and granulomatous optic neuropathy. However, a true assessment of its efficacy in these conditions will require controlled studies.

**Topical CSA**

As discussed previously, CSA does not penetrate very well into the eye; however, it is possible to use it topically to inhibit surface immune-mediated processes. Goichot-Bonnat and associates [28] reported that a
Open a container of 50 ml cyclosporine oral solution (100 mg/ml) and leave it for 24 hours under a horizontal laminar flow hood to evaporate the alcohol.

Aseptically filter olive oil through a silo with a prefilter and a 0.22-micron filter, collecting it in a sterile 100-ml container.

Aseptically measure 73.5 ml of olive oil.

Aseptically filter the cyclosporine solution through a 0.22-micron filter for a total volume of 1.5 ml.

Mix the two solutions and aliquot as needed.

Store the vials at room temperature.

**Figure 3** Procedure for the preparation of 2% cyclosporine eye drops using commercially available systemic cyclosporine.

2% topical CSA solution in high-risk corneal grafts had an 89% success rate during a 16-month average follow-up. Similar results were obtained by Belin and coworkers [29], who reported a success rate of 91% by giving the drops preoperatively every 2 hours for 2 days followed by four times daily after the corneal graft was inserted. In a double-masked trial, 2% topical CSA was also found to be effective in treating severe vernal keratoconjunctivitis, with a significant decrease in the conjunctival hyperemia, papillary hypertrophy, and the number of Trantas' dots [30]. Improvement may be noted within the first 15 days of therapy, but relapses occurred 2 to 4 months after therapy was discontinued [31].

CSA eye drops can be prepared in a number of ways. Generally, we employ the commercial oral preparation from Sandoz using the protocol outlined in Figure 3. It is important to vent the CSA solution for at least 24 hours to remove the alcohol, which otherwise is a strong corneal irritant. Using this preparation, we were able to successfully treat a case of recurrent ligneous conjunctivitis, and we have used it in other situations as well where there was a strong suspicion of surface immune activation [32]. Topical CSA may play a role in the treatment of paracentral corneal rheumatoid ulceration. Preliminary results using a 2% solution were very encouraging [33]. However, its usefulness in this and other conditions such as oculocutaneous syndromes and Sjögren's syndrome needs to be elucidated by further studies.
Chapter 13

■ Conclusion

CSA is a useful agent in the treatment of serious inflammatory diseases of the eye. When used carefully and in patients with the appropriate indications, it is both safe and effective. In the future, we hope agents will appear that will be less toxic. Agents that might prove to be useful include FK506 and rapamycin, two drugs with a potent immunosuppressive potential against T cells. Another approach that is being investigated is to combine CSA with other immunomodulatory drugs or to cycle the use of CSA with cytotoxic agents. These newer approaches still need to be carefully evaluated in controlled settings before they can be considered as effective and safe. The ultimate goal is to control immune-mediated inflammatory disease with the minimal number of adverse side effects.

■ References
