Use of Topical Cyclosporin A in a Primary Sjögren’s Syndrome Mouse Model

Kazuo Tsubota, Ichiro Saito, Naozumi Ishimaru, and Yoshio Hayashi

Purpose. A new animal model, the NFS/sld mutant mouse, was used for primary Sjögren’s syndrome to investigate the efficacy of topical and systemic cyclosporin A (CyA) in preventing inflammation of the exocrine glands.

Methods. Cyclosporin A was applied topically (0.01% and 0.1%, three times a day) or administrated orally (10 mg/kg and 100 mg/kg, once a day) to mice from 6 to 16 weeks of age, after which the mice were killed.

Results. Topical CyA reduced lacrimal gland and submandibular gland inflammation without causing pathologic changes in other organs. Flow cytometry showed that CD4 expression of CD4 T cells from the submandibular lymph nodes was downregulated, whereas that of Mel14 was upregulated. Using a reverse transcription-polymerase chain reaction assay, we determined that topical CyA significantly decreased the expression of mRNA of IL-2 and T-cell receptor-constant β-chain.

Conclusions. Topical CyA may be clinically useful in reducing the lymphocyte infiltration of lacrimal glands associated with Sjögren’s syndrome.

Sjögren’s syndrome (SS) is an autoimmune disorder primarily affecting exocrine glands, such as the lacrimal and salivary glands, by infiltration of activated lymphocytes and the consequent destruction of the glands. The major symptoms are severe dry eye and mouth, with greatly reduced tear and saliva production caused by malfunction of the exocrine glands. The disease may progress to systemic involvement and finally to lymphoid neoplasia. No effective cure has been developed, and the only available treatment is symptomatic, in the form of artificial tears or saliva, punctum plugs, or protective eyeglasses to prevent desiccation.

Cyclosporin A (CyA) is an immunomodulatory agent that suppresses activation and proliferation of T cells. It is widely used for immunosuppression in organ transplants, and its efficacy and mechanism of action are well established. Although the use of CyA in autoimmune diseases is still controversial, it may be appropriate for treating SS, in which the major infiltrating lymphocytes into the lacrimal and salivary glands are CD4 T cells, as in organ transplant rejection. Whereas some investigators have found that systemic CyA reduces infiltration of lymphocytes in salivary glands, others have found adverse effects of CyA. This discrepancy may be explained by differences in the duration of the application of CyA and the beginning point of CyA therapy. However, because CyA inhibits positive selection and delays negative selection and the final stage of SS may be lymphoid neoplasia, systemic CyA may hasten the onset of systemic SS.

Materials and Methods

Animals

Female NFS/N strain mice carrying the mutant gene sld were reared in our pathogen-free mouse colony. Thymectomy was...
performed on day 3 after birth (3-day TX), as described. We used 46 mice for the topical CyA investigation and 23 for the oral portion. All animal procedures were performed in accordance with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research.

Cyclosporin A

For the topical study, 0.01% and 0.1% CyA eye drops dissolved in 2 μl ophthalmic solution (Santen Pharmaceuticals, Osaka, Japan) was applied with a micropipette three times a day to both eyes (the CyA ophthalmic solution contained polyoxyl 40 stearate as a solubilizing agent). Treatment was initiated at 6 weeks of age and was applied 6 days a week. Five to six animals each were treated with the two CyA concentrations or with placebo (ophthalmic solution vehicle only) for 2, 6, and 10 weeks each, after which their data were excluded from the study. Thus, data from 23 animals were analyzed.

For the systemic portion of the study, CyA (Sandoz Pharmaceuticals, Basel, Switzerland) dissolved in 0.1 ml olive oil was given orally through a gavage tube. Animals were divided into three groups: control, 10 mg/kg CyA, and 100 mg/kg CyA. Treatment started at 6 weeks of age and was administered 5 days a week. The animals were killed after treatment for 4 weeks (n = 1, 10 mg; n = 2, 100 mg), 6 weeks (n = 3, 10 mg; n = 4, 100 mg), and 10 weeks (n = 4, control; n = 4, 10 mg; n = 5, 100 mg). The serum CyA trough was measured at the time of death. Thirty-nine animals were in the systemic oral CyA group; however, 16 animals died during the study, and their data were excluded from the study. Thus, data from 23 animals were analyzed.

Glandular Penetration of Cyclosporin A

We used a liquid scintillation counter (model 2100 TR; Hewlett Packard, San Francisco, CA) to measure the concentration of CyA in various organs after single and repeated instillation of 0.1% 3H-CyA ophthalmic solution. Drops were placed in both eyes of BALB/c female mice. Four animals each were treated once or three times a day for 3, 5, or 7 days. All animals were killed 16 hours after the final treatment and the following organs studied: lacrimal gland, submandibular gland, parotid gland, spleen, whole blood, thyroid, and cornea. Because the tissue volume was so small, eight specimens from four animals were measured together for thyroid and cornea.

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Single</th>
<th>3 Days</th>
<th>5 Days</th>
<th>7 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lacrimal gland</td>
<td>12.1 ± 2.3</td>
<td>67.6 ± 5.8</td>
<td>89.9 ± 15.7</td>
<td>75.5 ± 11.2</td>
</tr>
<tr>
<td></td>
<td>(0.2/18.7)</td>
<td>(1.6/24.1)</td>
<td>(1.9/21.3)</td>
<td>(1.6/20.9)</td>
</tr>
<tr>
<td>Submandibular gland</td>
<td>9.7 ± 1.3</td>
<td>29.3 ± 4.1</td>
<td>37.8 ± 7.6</td>
<td>34.3 ± 7.5</td>
</tr>
<tr>
<td></td>
<td>(1.1/108.0)</td>
<td>(3.7/125.9)</td>
<td>(4.9/131.1)</td>
<td>(4.0/118.7)</td>
</tr>
<tr>
<td>Parotid gland</td>
<td>5.9 ± 1.3</td>
<td>18.5 ± 6.3</td>
<td>27.0 ± 9.7</td>
<td>23.8 ± 6.6</td>
</tr>
<tr>
<td></td>
<td>(0.4/64.2)</td>
<td>(0.9/53.1)</td>
<td>(1.4/50.4)</td>
<td>(1.5/61.4)</td>
</tr>
<tr>
<td>Spleen</td>
<td>1.8 ± 0.2</td>
<td>6.8 ± 2.0</td>
<td>11.3 ± 2.0</td>
<td>9.5 ± 1.3</td>
</tr>
<tr>
<td></td>
<td>(0.1/78.9)</td>
<td>(0.5/83.1)</td>
<td>(0.9/82.3)</td>
<td>(0.8/80.0)</td>
</tr>
<tr>
<td>Whole blood</td>
<td>0.6 ± 0.1</td>
<td>2.4 ± 0.2</td>
<td>4.6 ± 0.7</td>
<td>3.2 ± 0.1</td>
</tr>
<tr>
<td></td>
<td>(0.1/13.2)</td>
<td>(0.1/8.7)</td>
<td>(0.2/11.6)</td>
<td>(0.1/11.7)</td>
</tr>
<tr>
<td>Thyroid gland</td>
<td>1239</td>
<td>3358</td>
<td>4457</td>
<td>4268</td>
</tr>
<tr>
<td></td>
<td>(22.3/18.0)</td>
<td>(50.4/15.0)</td>
<td>(59.7/13.4)</td>
<td>(64.5/15.1)</td>
</tr>
</tbody>
</table>

Values are means ± SD of cyclosporin A in nanograms per gram of tissue, with the mean amount of cyclosporin A in nanograms per milligram of mean tissue in parentheses.

cDNA Synthesis and Polymerase Chain Reaction Amplification

Total RNA was prepared from the lacrimal gland tissues and converted to cDNA, as described. For the polymerase chain reaction (PCR) assay, the cDNA was added to 20 μl sense and antisense primers, 1.25 mM deoxyribonucleoside triphosphate, and 1 unit of Taq polymerase (Boehringer Mannheim, Indianapolis, IN) in the buffer recommended by the manufacturer. The primers specific for interleukin (IL)-2 were 5'-ATG TAC AGC ATG CTC GCA TCC TGT GCT A3'- (sense) and 5'-AGT CAA ATC CAG AAC ATG CCG CAG AGG TCC A3'- (antisense) and yielded 398-bp PCR products. The primers specific for T-cell receptor-constant β-chain (CB) were 5'-ATC TGA GAA ATG CTC GCA TCC TGT GCT A3'- (sense) and 5'-TCA GTG CAG AGG CCT GGG-3' (antisense), and yielded 364-bp PCR products. The primers specific for β-actin were 5'-GTC GGC GCC TCT AGG CAC CA3'- (sense) and 5'-CGG TTG GCC TTA GGG TTC AGG GGG G3'- (antisense), and yielded 245-bp PCR products. The amplification reaction for IL-2, CB, and β-actin consisted of 35 cycles at 94°C for 30 seconds, 60°C for 30 seconds, and 72°C for 1 minute, followed by a final extension of 10 minutes. The products were separated by agarose electrophoresis and visualized by ethidium bromide staining. The specificity of the amplified bands was validated by their predicted size.

Histologic Study

All organs were fixed with 4% phosphate-buffered formaldehyde (pH 7.2) and prepared for histologic examination. The sections were stained with hematoxylin-eosin. Histologic grading of the inflammatory lesions (lacrimal gland, submandibular gland, and parotid gland) was performed according to the method of White and Casarett. The grading was performed in a blinded manner, as described.

Immunohistochemistry

Immunohistochemical staining with monoclonal antibodies (mAbs) was performed on freshly frozen sections (submandibular gland, 0.1% CyA group, 16 weeks old) by the avidin-biotin immunoperoxidase method. Briefly, frozen 4-μm sections were fixed in acetone for 5 minutes, rinsed in...
phosphate-buffered saline (PBS; pH 7.2), and incubated with each of the first mAbs as follows: biotinylated rat mAbs to B220, L3T4 (CD4), Thy 1.2, Mac-1, and Lyt2 (CD8) (Beckton Dickinson, Mountain View, CA). Presence of IL-2 and IL-2R (PharMingen, San Diego, CA) was also determined by immunohistochemistry. All control samples treated with normal rat and hamster sera (Cappel Laboratories, Cochranville, PA) or PBS, instead of the first mAbs, yielded negative results.

**Flow Cytometry**

Surface markers of the isolated mononuclear and spleen cells were analyzed with a cell sorter (FACScan; Becton Dickinson) by using mAbs to CD44, CD45RB, and Mel14 (PharMingen). Surface markers were identified by mAbs in conjunction with two-color flow cytometry. Irrelevant antibody activity was used as a specificity control. A thousand viable cells were analyzed by flow cytometry; dead cells were excluded from the analysis using forward- and side-scatter parameters.
TABLE 2. The Effect of Topical Cyclosporin A on Lymphocyte Infiltration of Exocrine Glands

<table>
<thead>
<tr>
<th>Age</th>
<th>Treatment</th>
<th>Parotid</th>
<th>Submandibular</th>
<th>Lacrimal</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 weeks</td>
<td>Vehicle</td>
<td>3.0 ± 0.7</td>
<td>2.8 ± 0.8</td>
<td>3.2 ± 0.8</td>
</tr>
<tr>
<td></td>
<td>0.01% CyA</td>
<td>3.0 ± 0.7</td>
<td>2.8 ± 0.8</td>
<td>3.2 ± 0.8</td>
</tr>
<tr>
<td></td>
<td>0.1% CyA</td>
<td>2.8 ± 0.5</td>
<td>2.2 ± 0.5</td>
<td>2.4 ± 1.1</td>
</tr>
<tr>
<td>12 weeks</td>
<td>Vehicle</td>
<td>3.2 ± 0.5</td>
<td>3.2 ± 0.5</td>
<td>3.2 ± 0.8</td>
</tr>
<tr>
<td></td>
<td>0.01% CyA</td>
<td>3.2 ± 0.5</td>
<td>2.8 ± 0.5</td>
<td>2.6 ± 0.6</td>
</tr>
<tr>
<td></td>
<td>0.1% CyA</td>
<td>3.0 ± 0.7</td>
<td>2.4 ± 0.6</td>
<td>2.8 ± 0.8</td>
</tr>
<tr>
<td>16 weeks</td>
<td>Vehicle</td>
<td>3.2 ± 0.5</td>
<td>3.2 ± 0.5</td>
<td>3.4 ± 0.9</td>
</tr>
<tr>
<td></td>
<td>0.01% CyA</td>
<td>2.6 ± 0.9</td>
<td>1.8 ± 0.5*</td>
<td>2.0 ± 0.7</td>
</tr>
<tr>
<td></td>
<td>0.1% CyA</td>
<td>2.7 ± 0.5</td>
<td>1.3 ± 0.5*</td>
<td>1.7 ± 0.8*</td>
</tr>
</tbody>
</table>

CyA, cyclosporin A.
Values are means ± SD (n = 5-6).
* Significantly different from vehicle (nonparametric Dunnett's test; P < 0.05).

RESULTS

Measurement of Cyclosporin A

The concentration of CyA in lacrimal gland of BALB/c mouse after a single dose and 3, 5, and 7 days of topical application was 12.1 ± 2.3, 67.6 ± 5.8, 89.9 ± 15.7, and 75.5 ± 11.2 ng/g, respectively. We confirmed that of the three exocrine glands, the highest concentration was recorded in the lacrimal gland and that this level stabilized after 5 days. The CyA concentration in all other organs except cornea was low (Table 1).

![Figure 2](https://example.com/figure2.png)

**Figure 2.** Immunohistochemical analysis of infiltrating mononuclear cells in the submandibular gland from 16-week-old NFS/sld mouse with thymectomy on day 3 of life. (A) CD4, (B) CD8, (C) interleukin (IL)-2, (D) IL-2R. Most cells were recognized as CD4+ T cells (A) and a lesser number as CD8+ cells B. Most infiltrating cells expressed IL-2 (C), whereas a small proportion of cells were positive for IL-2R (D). Immunoperoxidase; magnification, ×360.
**Figure 3.** Flow cytometry of the isolated mononuclear cells from cervical lymph nodes and spleen in control 16-week-old NFS/sld mice with thymectomy on day 3 of life (A; 3-day TX NFS/sld) and in 3-day TX NFS/sld mice treated topically with 0.01% (B) and 0.1% (C) cyclosporin A. The activation marker of CD44 decreased in treated groups, whereas that of Mel14 increased, set-gated on CD4. CD45RB CD4 remained within the same range.

**Figure 4.** Reverse transcription-polymerase chain reaction analysis of interleukin-2 and T-cell receptor--constant β-chain mRNA expression of splenic lymphocytes in NFS/sld mice with thymectomy on day 3 of life treated for 4, 6, and 10 weeks with topical 0.1% cyclosporin A.
FIGURE 5. Histologic studies of inflammatory lesions in the lacrimal glands (A), submandibular glands (B), parotid gland (C), thyroid (D), lung (E), and pancreas (F) of NFS/sid mutant mice with thymectomy on day 3 of life administered systemic 100 mg/kg cyclosporin A per day. The inflammation in each organ increased. Hematoxylin-eosin; magnification, ×80.

**Topical Cyclosporin A and Exocrine Gland Inflammation**

Topical use of 0.1% CyA for 10 weeks significantly reduced the inflammation in the lacrimal and submandibular glands (Figs. 1A, 1B, 1C, 1D), but not in the parotid gland (Figs. 1E, 1F). These findings were consistent with the histologic grading of the inflammatory lesions (Table 2).

Immunohistochemistry of the exocrine glands after application of topical CyA showed that most of the infiltrating mononuclear cells were CD4+ cells with a small number of CD8+ and B220+ cells (Figs. 2A, 2B), which did not differ significantly from pretreatment values. Topical CyA application also caused prominent staining in the lacrimal gland for IL-2 and IL-2R (Fig. 2C, 2D).

FACScan (Becton Dickinson, San Jose, CA) analysis of surface phenotype in the lymph node cells showed a significant increase in Mel4+ CD+ in both of the topical CyA groups compared with that in the control group. Both treatment groups also showed decreases in CD44+ CD4 T cells, whereas no changes were observed in CD45RB+ CD4+ cells (Fig. 3).
TABLE 3. The Effect of Systemic Cyclosporin A on Lymphocyte Infiltration of Exocrine Glands

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Treatment</th>
<th>Parotid</th>
<th>Submandibular</th>
<th>Lacrimal</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 weeks</td>
<td>10 mg (n = 1)</td>
<td>2.0*</td>
<td>3.0*</td>
<td>3.0*</td>
</tr>
<tr>
<td></td>
<td>100 mg (n = 2)</td>
<td>3.0*</td>
<td>3.0*</td>
<td>3.5*</td>
</tr>
<tr>
<td>12 weeks</td>
<td>10 mg (n = 3)</td>
<td>3.7 ± 0.6</td>
<td>3.7 ± 0.6</td>
<td>4.0 ± 0.0</td>
</tr>
<tr>
<td></td>
<td>100 mg (n = 4)</td>
<td>3.8 ± 0.5</td>
<td>3.8 ± 0.5</td>
<td>4.0 ± 0.0</td>
</tr>
<tr>
<td>16 weeks</td>
<td>0 mg (n = 4)</td>
<td>2.5 ± 0.6</td>
<td>2.8 ± 0.5</td>
<td>2.3 ± 0.5</td>
</tr>
<tr>
<td></td>
<td>10 mg (n = 4)</td>
<td>2.8 ± 1.0</td>
<td>3.0 ± 0.8</td>
<td>3.0 ± 0.8</td>
</tr>
<tr>
<td></td>
<td>100 mg (n = 5)</td>
<td>3.8 ± 0.5</td>
<td>3.6 ± 0.6</td>
<td>3.6 ± 0.6†</td>
</tr>
</tbody>
</table>

Values are means ± SD.
* No SD was calculated because sample of specimens was too small.
† P < 0.05 versus 0 mg (nonparametric Dunnett’s t test).

These results indicate that the lymph node cell activation marker decreased and the resting marker increased. There were no significant changes in these markers in spleen mononuclear cells (data not shown).

Reverse transcription-polymerase chain reaction analysis after 0.1% CyA treatment showed that neither IL-2 nor Cβ mRNA expression changed after 2 or 6 weeks, but that both were significantly inhibited after 10 weeks (Fig. 4). This inhibition corresponded to the decreased lymphoid infiltration seen in immunohistologic analysis. There were no apparent systemic effects of topical CyA, evidenced by the absence of inflammatory changes in thyroid, pancreas, bronchus, and kidney.

**Systemic Cyclosporin A and Exocrine Gland Inflammation**

We examined inflammation in the lacrimal, parotid, and submandibular glands in 3-day TX NFS/sld mutant mice (n = 23) treated with systemic CyA 10, 12, and 16 weeks after thymectomy. Lymphocyte infiltration was severe compared with that in the placebo group (P < 0.05) and was observed in all the exocrine glands (Figs. 5A, 5B, 5C, 5D, 5E, 5F; Table 3). Three of five mice treated with 100 mg/kg CyA had prominent infiltrates in the thyroid, pancreas, bronchus, lung, liver, and kidney (Table 4). Significant organ inflammation after treatment of mice with systemic CyA was not limited to the exocrine glands. Because many mice treated with systemic CyA died during the experiments, the data for the 4- and 6-week treatments were incomplete; nevertheless, there was more infiltration than in the control animals (Table 3). The 3-day TX NFS/sld mutant mice treated with placebo showed a histologic pattern similar to natural at 16 weeks.

**DISCUSSION**

In this study, topical CyA reduced the lymphocyte infiltration and inflammation of exocrine glands in the SS model mouse, 3-day TX NFS/sld. There were no apparent systemic effects. In contrast, oral CyA caused increased inflammation not only in the lacrimal glands but in such organs as the thyroid and pancreas. Moreover, it caused the deaths of many of the animals.

The lack of an animal model for SS has been a major obstacle in the development of new treatments. It has been shown that autoimmune sialadenitis develops spontaneously in autoimmune-prone mice with other autoimmune diseases and in certain strains of aged mice, and it was induced experimentally by artificial immunization. The 3-day TX NFS/sld mouse with no immunization was the first animal model in which spontaneous autoimmune lesions developed that were exclusively localized to the salivary and lacrimal glands, which resembles primary SS in humans. The lymphocyte infiltration began approximately 4 weeks after thymectomy, with slow progression in the parotid, submandibular, and lacrimal glands. We began treating the mice with topical or systemic CyA from the time they were 6 weeks old and continued for as long as 16 weeks. We showed unequivocally that lymphocyte infiltration is decreased by topical CyA but is increased by systemic treatment.

**TABLE 4. Lymphocyte Infiltration of Other Organs in NFS/sld Mice Treated with Systemic Cyclosporin A**

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Treatment</th>
<th>Thyroid</th>
<th>Pancreas</th>
<th>Bronchus</th>
<th>Kidney</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 weeks</td>
<td>10 mg (n = 3)</td>
<td>0/3*</td>
<td>1/3</td>
<td>0/3</td>
<td>0/3</td>
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<tr>
<td></td>
<td>100 mg (n = 4)</td>
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<td>16 weeks</td>
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<td>0/4</td>
<td>3/4</td>
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<td></td>
<td>10 mg (n = 4)</td>
<td>3/4</td>
<td>2/4</td>
<td>3/5</td>
<td>3/5</td>
</tr>
<tr>
<td></td>
<td>100 mg (n = 5)</td>
<td>3/5</td>
<td>3/5</td>
<td>3/5</td>
<td>3/5</td>
</tr>
</tbody>
</table>

* Number of specimens positive for lymphocyte infiltration/number of specimens examined.
The results of systemic application may be considered paradoxical, because CyA is an immunosuppressive drug that inhibits the T-cell receptor (TCR)-mediated signal transduction. Systemic CyA is widely used in organ transplantation to suppress rejection by inhibiting CD4+ and CD8+ T cells.5 Although in most situations CyA’s only serious side effects are kidney and liver cytotoxicity,6 the drug occasionally induces the sort of autoimmune reactions we observed.7,27 The mechanism has not been determined yet, but CyA may not inhibit the deletion of all self-specific T cells.12 In our animal model, systemic CyA may have inhibited deletion of self-specific T cells or the suppressor function of other T cells. That many organs were infiltrated by inflammatory cells suggests a widespread effect on the body’s T cells. Although some studies have shown that systemic CyA may reduce lymphocyte infiltration into exocrine organs,8,9 the drug may also induce autoimmunity in humans, especially in patients with SS, and may cause a lymphoproliferative disorder.

In contrast, topical CyA reduced lacrimal gland infiltration without systemic complications. Interleukin-2 and C/β mRNA decreased in the lacrimal glands of topically treated mice, indicating a decrease in the infiltrating T lymphocytes. Furthermore, the increase in lymph node Mel14 and the decrease in CD44+ CD8+ cells observed by flow cytometry reflected inactivation of CD4+ T cells. This latter effect is important, because activated T cells are believed to play a major role in lacrimal gland destruction.28

Topical use of CyA is becoming popular for the prevention of allograft rejection in corneal transplants and for controlling immunologic or allergic disorders of the ocular surface.29-38 Such use does not have systemic immune effects, and thus does not trigger an autoimmune or neoplastic response. Topical CyA has been controversial,39 because although it can reach the tarsal conjunctiva, a rejected corneal graft, and other targets on the ocular surface, it is not clear whether it reaches the lacrimal glands or lymph nodes where the infiltrating T cells are activated. However, our measurement of CyA concentration in various organs (Table 1) after topical use of CyA in the mouse model clearly showed good drug penetration, with the highest concentration in the lacrimal gland followed by the submandibular and parotid glands. Because the major infiltrating cells in the lacrimal gland have restricted T-cell receptors, especially the T-cell receptors V/β8+ and V/β6+, which may recognize the organ-specific autoantigens,16 the effect of CyA should be limited. The higher concentration of CyA in the lacrimal and submandibular glands than in the parotid gland may explain why suppression of lymphocytes was only observed in the former two glands. A minimum CyA concentration of 30 ng/g may be necessary to be clinically efficacious.

Another possible advantage of topical CyA may be a direct effect on ocular surface cells. In dry eye associated with SS, lymphocyte infiltration also occurs in the conjunctival epithelium, whose cells may undergo squamous metaplasia.40,41 Topical use of CyA may also suppress the deleterious effect of infiltrating lymphocytes in the conjunctival epithelium.39

In conclusion, our study clearly showed the efficacy of topical CyA in preventing lymphocyte infiltration into the lacrimal and submandibular glands. Systemic CyA accelerated the infiltration, indicating that it should be used carefully in patients with autoimmune disorders.

References


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