Comparison of Efficacy of Two Different Topical 0.05% Cyclosporine A Formulations in the Treatment of Adenoviral Keratoconjunctivitis-Related Subepithelial Infiltrates

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Key Words
Adenoviral keratoconjunctivitis · Cyclosporine A · Subepithelial infiltrates

Abstract
Subepithelial infiltrates secondary to adenoviral keratoconjunctivitis may persist for years and cause blurred vision, halos, glare, and photophobia. These infiltrates arise from immune reaction against the virus, and few studies have reported topical cyclosporine A to be effective in the treatment of subepithelial infiltrates. Herein, we describe a patient with adenoviral keratoconjunctivitis-related subepithelial infiltrates who did not respond to treatment with a new topical cyclosporine A emulsion prepared with castor oil (Depores 0.05%; Deva İlaç, Kocaeli, Turkey), while the FDA-approved nanoemulsion formulation provided improvement in symptoms and reduced the inflammatory reaction (Restasis 0.05%; Allergan, Irvine, Calif., USA).

Introduction
Adenoviridae are icosahedral, nonenveloped, double stranded DNA viruses that can cause an array of diseases including conjunctivitis, gastroenteritis, hepatitis, myocarditis and pneumonia. This family of viruses is the most common cause of acute viral infection of the conjunctiva, accounting for up to 75% of all conjunctivitis cases. The most frequent manifestation of ocular adenoviral infection is epidemic keratoconjunctivitis (EKC) [1].
The incubation period of EKC varies between 4 and 24 days, and the symptoms tend to last for 7–21 days. The patient may remain infectious for 10–14 days. The most common symptoms are red eyes, excessive tearing, foreign body sensation, and photophobia. In more severe cases, patients can present with ocular or periorbital pain and decreased visual acuity. Decreased visual acuity is generally seen as a result of multifocal subepithelial infiltrates (SEIs) which are observed in up to 50% of the cases.

These SEIs represent a cellular immune reaction against viral antigens deposited in the corneal stroma under the Bowman’s membrane and can persist for weeks to years. Topical steroids are effective in the treatment of SEI; however, after stopping steroid eye drops, recurrences may develop, and the patient may become steroid dependent. With long-term treatment, side effects of steroids such as intraocular pressure (IOP) increase, and cataract can develop. Therefore, topical cyclosporine A (CsA) has been proposed as a means of long-term treatment of SEIs [2, 3].

In this paper, a patient with adenoviral keratoconjunctivitis-related SEIs is reported who did not respond to a new topical CsA formulation, an emulsion prepared with castor oil (Depores 0.05%; Deva İlaç, Kocaeli, Turkey), while treatment response could be achieved by an FDA-approved nanoemulsion formulation (Restasis 0.05%; Allergan, Irvine, Calif., USA).

**Case Presentation**

A 48-year-old female presented with the complaint of blurry vision and photophobia in her right eye. Previous medical history revealed the use of topical antibiotics, corticosteroids, and preservative-free artificial tears for 3 months with the diagnosis of adenoviral keratoconjunctivitis. At the time of presentation, she had been using topical 0.05% CsA emulsion in castor oil (Depores) six times daily and preservative-free artificial tears eight times daily for 1 month. Her visual acuities were 20/20 in both eyes. Slit-lamp biomicroscopy revealed mild conjunctival hyperemia, several centrally located corneal SEIs (fig. 1), and superficial punctate epitheliopathy in the right eye. Other ophthalmologic findings, including IOP measurements, were normal in both eyes.

In vivo corneal confocal microscopy (IVCM; Heidelberg Retina Tomograph II Rostock; Heidelberg Engineering GmbH, Heidelberg, Germany) was performed for detailed examination. Langerhans cells with typical pseudopods were detected at the subepithelial nerve plexus level of the corneas of both eyes, predominantly in the right eye (fig. 2). Corneal stroma and endothelial cells were normal in morphology and cell counts.

The treatment regimen was changed from topical 0.05% CsA emulsion in castor oil (Depores) six times daily to topical %0.05 CsA nanoemulsion (Restasis) two times daily, and the patient was recommended to continue her preservative-free artificial tears. At the 1-month visit following initiation of the nanoemulsion formulation, her symptoms improved, SEIs appeared less active at slit-lamp biomicroscopy, and there was no corneal staining (fig. 3). IVCM did not reveal Langerhans cells anymore (fig. 4). The patient was advised to continue her eye drops and come for a follow-up examination 1 month later; however, she was lost to follow-up.

**Discussion**

Adenoviridae cause EKC, which can have profound effects on patients’ quality of life for weeks. Subepithelial infiltrates are seen in 50% of these patients and cause decreased visual acuity.
acuity, blurred vision, halos, glare, and photophobia [1]. Immune response against viral replication in subepithelial keratocytes is responsible for SEIs. Histologically, these infiltrates are composed of lymphocytes, histiocytes, and antigen-presenting Langerhans cells [4]. Hence, topical corticosteroids and topical CsA are considered effective treatment regimens [2, 3, 5].

In our patient, treatment of SEIs with topical 0.05% CsA emulsion in castor oil failed to provide symptomatic relief or inactivation of SEIs. Moreover, Lanhergans cells were observed using IVCMA despite ongoing treatment for 1 month. After changing the treatment to topical 0.05% CsA nanoemulsion, at the 1-month visit after the treatment, there was significant improvement in symptoms at slit-lamp biomicroscopy, SEIs appeared inactive, and there were no inflammatory cells at IVCM.

Previously, Levinger et al., [3] reported on 12 eyes of 9 patients with adenoviral keratoconjunctivitis-related SEIs unresponsive to topical corticosteroids or developing IOP increase with topical corticosteroids. The treatment was switched to topical 1% CsA in aqueous vehicle and carboxyl methyl cellulose gel drops twice daily. This formulation was well tolerated by patients and provided improvement in symptom score and visual acuity.

Okumus et al., [5] reported successful treatment of SEIs with 0.05% topical CsA nanoemulsion 4 times daily for the first 15 days and then twice daily in 22 eyes of 16 patients who were again either unresponsive to topical corticosteroids or developed secondary IOP increase. Decrease in SEI activity score and IOP was achieved with this treatment over a mean follow-up of 5 months.

Lack of response to the topical CsA castor oil formulation in our patient may be due to the low bioavailability of CsA in this particular emulsion formulation. On the other hand, a favorable treatment response could be achieved with the use of the FDA-approved nanoemulsion CsA formulation in the same patient.

Corneal tissue penetration of CsA is low because of its hydrophilic structure [5]. To improve tissue penetration of CsA, in different dry-eye studies, peanut oil, castor oil, and olive oil had been used as solvents. However, tolerability of these solutions was low, and effective doses could not be achieved at the tissue level. Later, cyclodextrins, penetration enhancer agents, colloidal carriers, and micelles were investigated, but none of these solutions could provide an effective tissue dose or the desired tolerability [6, 7]. None of the described topical systems has really succeeded in achieving therapeutic concentrations on the corneal surface. Following long-term preclinical formulation studies, the 0.05% nanomicelle formulation (oil-in-water emulsion produced by nanotechnology) of CsA (Restasis; Allergan) was approved by the FDA and is currently the only FDA-approved topical CsA formulation.

Restasis 0.05% CsA is a castor oil-in-water nanoemulsion, which is stabilized by polysorbate 80. During phase II studies, this nanoemulsion was solubilized up to 0.4% w/w CsA and was observed to cause only mild discomfort in rabbits when applied eight times daily for 7 days. After administration of a single dose of the 0.05% CsA nanoemulsion formulation, an acceptable concentration was detected at the corneal tissue level (C_{max} = 955 ng/g in rabbits), and high concentrations (>300 ng/g) could still be detected in the cornea 96 h after administration [8]. Depores 0.05% formulation, on the other hand, is a new formulation of topical CsA developed as a castor oil emulsion. However, no preclinical/clinical studies are available on the bioavailability and/or efficacy of this formulation.

In conclusion, in our patient, the castor oil formulation of CsA (Depores 0.05%; Devallac) was not effective in the treatment of adenovirus-related SEIs, while a favorable treatment response could be achieved with the nanoemulsion formulation (Restasis 0.05%; Allergan). Therefore, clinicians should be aware of the possibility of different efficacy profiles of different topical CsA formulations having the same concentration. Larger-scale controlled
studies are required to evaluate the safety and efficacy of different topical CsA formulations in adenoviral keratoconjunctivitis.

**Statement of Ethics**

Written informed consent was obtained from the patient.

**Conflict of Interest**

The authors declare that they have no conflicts of interest.

**References**


**Fig. 1.** Slit-lamp biomicroscopy image of the right eye. Adenoviral keratoconjunctivitis-related SEIs in the central part of the cornea.
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Fig. 2. IVCM image of the right eye. Subepithelial Langerhans cells with characteristic pseudopods (depth: 41 µm).

Fig. 3. Slit-lamp biomicroscopy image of the right eye after the use of 0.05% CsA nanoemulsion formulation for 1 month. SEIs appear less active.
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Fig. 4. IVCM image of the right eye. No visible subepithelial Langerhans cells are present after 1 month of treatment with the 0.05% nanoemulsion formulation (depth: 40 µm).