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Case report: Concomitant use of nightly vitamin A ointment with daily PROSE wear for ocular surface disease associated with chronic Stevens-Johnson syndrome

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ABSTRACT

Purpose: To describe a case of chronic ocular surface disease associated with Stevens-Johnson Syndrome (SJS) in which the addition of nightly topical ophthalmic preservative free vitamin A ointment to the daily use of a customized ocular surface prosthetic device (PROSE) appears to mitigate disease progression.

Observations: A 51-year-old female with SJS secondary to lamotrigine use presented for follow up evaluation. Ocular history was significant for acute SJS twenty-four years prior with chronic ocular surface sequelae predominantly affecting the left eye. The condition had been stabilized without progression by utilizing long term PROSE daytime wear along with nightly application of topical ophthalmic vitamin A ointment. The patient reported non-compliance with vitamin A ointment use for the prior three months. The ocular surface examination of the left eye was notable for significantly progressed inferior keratinization and neovascularization which had been unchanged over the course of the three prior annual exams. After restarting nightly topical ophthalmic vitamin A ointment and continuing regular PROSE use, there was no further ocular surface disease progression in the ensuing 4 years of follow up.

Conclusion and Importance: The use of nightly topical ophthalmic vitamin A ointment may be a viable adjuvant therapy alongside daily PROSE use for progressive chronic SJS ocular surface disease.

1. Introduction

Stevens-Johnson syndrome (SJS) and its more severe variant, toxic epidermal necrolysis (TEN), are acute inflammatory reactions of the skin and mucous membranes which are most frequently a result of an adverse drug reaction.[1] Chronic ocular surface involvement is common and is characterized by cicatricial disease, including but not limited to trichiasis, symblepharon, keratitis, cornea neovascularization and ocular surface keratinization.[2,3] The role and utilization of topical lubricants, topical and systemic immunosuppressants, amniotic membrane grafts, and scleral lenses have been deeply investigated for treatment of these ocular sequelae. On the contrary, the use of nightly preservative free topical ophthalmic vitamin A ointment in this context has had minimal evaluation. Despite this paucity of evidence, vitamin A ointment has recently become a more commonly prescribed intervention. Although two prospective clinical trials have inferred topical vitamin A may reverse histologic squamous metaplasia of the cornea in patients with SJS and other cicatricial disease, evidence for its clinical efficacy is mixed. These studies did not control for additional dry eye treatments and no patients received topical vitamin A as an adjunct therapy to daily scleral lens or customized ocular surface prosthetic device (PROSE), (BostonSight, Needham, MA) use.[4–6] Literature over the last 25 years has otherwise remained at the level of small case series and does not specifically address currently available formulations of preservative free topical ophthalmic vitamin A ointment (Ocunox, Candorvision, Montreal, Canada) (Vita-POS, AFT Pharmaceuticals, Auckland, New Zealand) (Hylo Night with Vitamin A, New York City, United States).[7–9]

PROSE is a commonly used treatment modality for patients with SJS, with the goals of ocular surface support, pain reduction and best corrected visual acuity (BCVA). Persistent and progressive ocular surface signs and symptoms can still occur despite the use of PROSE in SJS patients. Anecdotally, in chronic SJS patients with daily PROSE use,

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some clinicians have reported improved symptoms and reduction in ocular surface neovascularization and keratinization with the addition of nightly topical ophthalmic vitamin A ointment. To our knowledge, however, there is no currently published literature on this combination therapy. Here we report on a chronic SJS case with long term daily PROSE use where the addition of nightly topical vitamin A ointment appeared to play a role in mitigating progressive ocular surface disease.

2. Case report

A 51-year-old female long term PROSE wearer (6 years of consecutive daily wear) with a remote past ocular history significant for SJS secondary to lamotrigine use, presented for a yearly follow up consultation to reevaluate the function and fit of the PROSE device in her left eye. The patient reported the left eye felt "a little bit drier" recently. Her past ocular history was notable for initial acute SJS twenty-four years prior, with significantly greater chronic signs and symptoms in the left eye compared to the right eye, and a past medical history significant for a non-specific seizure disorder and chronic migraines. Current ocular medication regimen included lubricating gel drops as needed in both eyes and lubricating ointment used each night in the left eye. The patient stated that 3 months prior to this visit she had discontinued her nightly vitamin A ointment (Ocunox [250 I·U./g retinol palmitate (vitamin A)], Candorvision, Montreal, Quebec) which was prescribed 3 years earlier in an effort to help mitigate progressive ocular surface scarring and neovascularization. In the years prior to initiation of vitamin A ointment, there was progressive ocular surface keratinization and neovascularization as well as frequent episodes of ocular surface inflammation, which were managed acutely with topical tobramycin 0.3%-dexamethasone 0.1%.

BCVA in the left eye was 20/25, only slightly reduced from the BCVA of 20/20-2 at the prior evaluation one year earlier. Slit lamp examination was notable for significantly progressed inferior keratinization and neovascularization, which had been without changes at the three prior annual exams (Fig. 1A and B). The patient was instructed to restart nightly vitamin A ointment to the left eye and to follow up for close observation. Additionally, the patient was instructed to start cyclosporine A 0.05% (Restasis, Abbvie, North Chicago, IL) one drop twice a day in the left eye.

At follow up examination, two months later, the patient noted noncompliance with the prescribed cyclosporine A 0.05%, with very rare usage, but reported regular nightly compliant use of vitamin A ointment in the left eye. The slit lamp examination was stable with no progressive neovascularization or keratinization.

This pattern of very rare, inconsistent use of cyclosporine A 0.05% (including only rare irregular once a day use and extended periods of months with no usage), along with compliant regular nightly use of vitamin A ointment continued over the next 4 years of care. Three years into this time period, an optical prescription change and a material change was made to the PROSE device, adjusting the Dk from 127 to 180, due to the availability of a new rigid gas permeable (RGP) polymer. Over the ensuing 4-year time period of observation following re-initiation of vitamin A ointment, there was no progressive corneal keratinization or worsened neovascularization and BCVA remained stable at 20/20-2 (Fig. 2). Additionally, no ocular surface inflammatory flares occurred and no treatment with ocular topical steroids was required during this time period.

3. Discussion

Ocular surface inflammation with progressive corneal and conjunctival scarring is a common finding in chronic SJS.[10] Damage to the cornea and conjunctiva from acute SJS results in acute complications in 77% of patients, and adult patients suffer chronic SJS ocular surface sequalae in 27–59% of cases.[11,12] Loss of corneal limbal stem cells, damage to conjunctival goblet cells and severe meibomian gland involvement are the most common etiologies of ocular surface damage. These factors, along with chronic inflammation, result in conjunctival cicatrization, a high risk for corneal epithelial breakdown, progressive corneal neovascularization, and ultimately vision loss.[13]

Because of disease severity, chronic ocular SJS patients wearing a PROSE device or scleral lens often require adjuvant therapies. Unfortunately, the data regarding such therapies is limited. There is evidence that systemic corticosteroids may decrease systemic SJS biomarkers of inflammation (such as interferons and interleukin-6). However, this must be balanced with the knowledge that chronic use of steroids increases patient risk of serious complications such as poor wound healing and infection.[14] Systemic cyclosporine may be effective in slowing disease progression, however, it still remains relatively less studied in comparison with corticosteroids, and immunosuppression remains a concerning risk.[15,16] The use of topical bevacizumab applied in the fluid reservoir of a PROSE device has also shown promise to reduce corneal neovascularization in chronic ocular SJS. In a retrospective case series of 12 patients treated for corneal neovascularization, of whom 7 had SJS, addition of topical bevacizumab led to regression of corneal neovascularization in 92% of cases and improved visual acuity in 77% of cases.[17] Of note, topical bevacizumab may carry a risk of corneal epithelial breakdown and requires more investigation.[18] The notable risk profile of the above treatments, such as poor wound healing, infection, immunosuppression, and ocular surface breakdown, may stand in stark contrast to the presumed low risk profile of nightly preservative free topical vitamin A ophthalmic ointment, though more studies are needed.[19]

To date, there is a scarcity of evidence to support the use of topical vitamin A ophthalmic ointment in the management of chronic SJS, with or without concomitant use of a PROSE. Current utilization is predominantly based on anecdotal reports. Vitamin A therapies may halt or reverse epithelial metaplasia and keratinization seen in SJS, however the duration of this effect has not been explored. A case series following 8 patients, one of which had SJS, suggested that topical all-trans retinoic

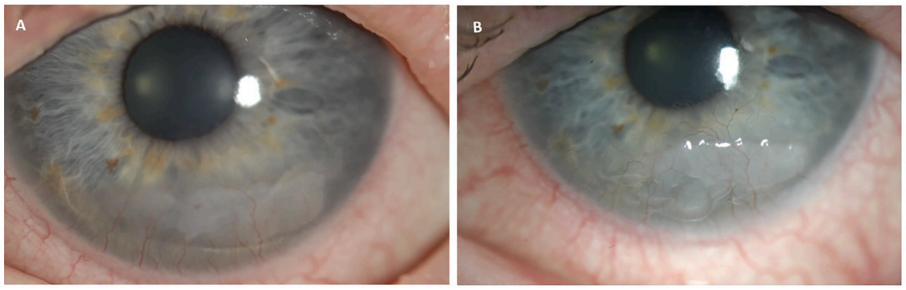

Fig. 1. Fig. 1A: Ocular surface, left eye: inferior neovascularization and early keratinization. Stable ocular surface appearance over three consecutive annual slit lamp examinations during period of compliant nightly topical ophthalmic vitamin A use preceding a 3-month period of non-compliance. Fig. 1B: Ocular surface, left eye: progressive inferior neovascularization and dense keratinization at examination following 3 months without nightly topical ophthalmic vitamin A ointment.

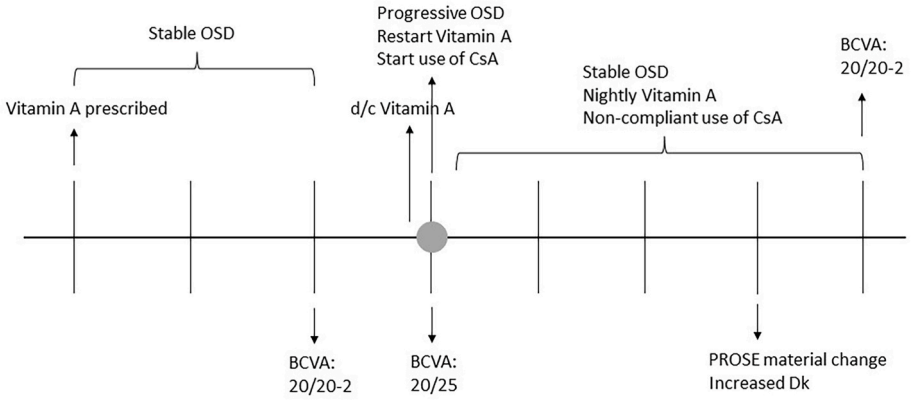

Fig. 2. Timeline of events, left eye. Gray circle represents exam immediately following 3-month period without the use of topical ophthalmic vitamin A ointment. Hash marks each represent one year prior to or after this visit. OSD = ocular surface disease. Vitamin A = Vitamin A ointment. CsA = Cyclosporine A 0.05% eye drops. BCVA = best corrected visual acuity. Dk = oxygen permeability. PROSE = customized ocular surface prosthetic device. d/c = discontinued.

acid (an active form of vitamin A), may be beneficial for the treatment of squamous metaplasia and keratinization of the conjunctiva, however, local irritation developed in some.[7–9] None of these studies utilized vitamin A as an adjuvant nightly regimen with daily PROSE or scleral lens wear, a protocol that is currently being utilized in clinical care.

There are inconsistencies in the formulation and dosage of topical vitamin A ointment used in current published literature. Some studies used varying concentrations of vitamin A drops[20] while others used ointment.[19,21] Alanazi et al. presented data that suggested oral vitamin A supplements may improve quality but not quantity of tears.[22] How the pharmacokinetics of different routes of administration and dosing affect vitamin A bioavailability to the ocular surface must be investigated in order to better standardize its use.

The mechanism of action of vitamin A supplementation on the ocular surface remains unclear. Vitamin A deficiency induces and aggravates inflammation and is associated with abnormal cell metabolism, cell degeneration and loss.[23] A lack of vitamin A in corneal tissue has been shown to result in abnormal differentiation of epithelial cells, resulting in keratinization and epithelial squamous metaplasia.[19] Vitamin A supplementation, therefore, may ameliorate ocular surface inflammation by either its effect on the immune system or on epithelial integrity.[23]

In this report, we share one case where the addition of nightly topical vitamin A ophthalmic ointment to a regimen of daily PROSE wear appears to mitigate progressive chronic SJS ocular surface disease. With this regimen, the ocular surface condition was stable for years, but on self-discontinuation of the vitamin A treatment, disease progression was apparent on examination. When the patient was restarted on vitamin A ointment she was found to have no further disease progression over four years of follow up. We acknowledge the patient was started on topical cyclosporine A 0.05% at the same time as re-initiation of nightly vitamin A application, however, the cyclosporine was taken rarely, if at all, and the patient typically came to appointments noting that no cyclosporine had been instilled for months. The oxygen permeability of the PROSE fluorosilicone acrylate material was altered during the course of the treatment, but there was no disease progression for three years prior to that change.

Future studies are necessary to understand the potential utility of vitamin A as an adjunctive nightly regimen to daytime PROSE wear for chronic SJS. Longitudinal prospective analysis of supplemental vitamin A in varying concentrations and routes of administration could confer a better understanding of the potential effects on the SJS ocular surface. Vitamin A ophthalmic ointment may represent a lower risk, efficacious alternative to other standard regimens, such as topical steroids.

4. Conclusion

Progressive ocular surface disease in chronic SJS may occur despite the use of a PROSE device. Such progression is a challenge to clinicians due to limited treatment options with variable efficacies and often notable risks. This case introduces a patient with daily PROSE use who was found to have ocular surface disease progression following a three-month period of vitamin A ophthalmic ointment non-compliance. Stabilization of the ocular surface condition was demonstrated during periods of compliance. Further study of the concomitant use of nightly preservative free vitamin A ophthalmic ointment along with daily PROSE wear is necessary to better elucidate the possible benefits and risks in individuals with chronic SJS.

Data availability

N/A.

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Authorship

All authors attest they meet the current ICMJE criteria for authorship.

Patient consent to publication

Consent to publish the case report was not obtained, as this case report does not contain any identifiable health information or identifiable personal information that could lead to the identification of the patient. All guidelines were followed to ensure HIPAA compliance, and we adhered to the Declaration of Helsinki, as well as applicable federal and state laws.

Declaration of competing interest

The authors report no financial conflicts of interest in this work. Daniel Brocks is a salaried clinical employee of BostonSight, Needham, MA. None of the authors have a propriety or financial interest in PROSE (BostonSight, Needham MA) or the prosthetic devices used in PROSE treatment.

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