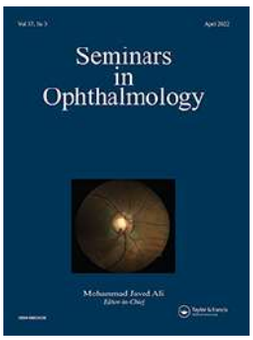

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Lacrimal Gland Insufficiency in Aqueous Deficiency Dry Eye Disease: Recent Advances in Pathogenesis, Diagnosis, and Treatment

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ABSTRACT

Background: Aqueous deficiency dry eye disease is a chronic and potentially sight-threatening condition, that occurs due to the dysfunction of the lacrimal glands. The aim of this review was to describe the various recent developments in the understanding, diagnosis and treatment of lacrimal gland insufficiency in aqueous deficiency dry eye disease.

Methods: A MEDLINE database search using PubMed was performed using the keywords: "dry eye disease/syndrome", "aqueous deficient/deficiency dry eye disease", "lacrimal gland" and "Sjogren's syndrome". After scanning through 750 relevant abstracts, 73 eligible articles published in the English language from 2016 to 2021 were included in the review.

Results: Histopathological and ultrastructural studies have revealed new insights into the pathogenesis of cicatrising conjunctivitis-induced aqueous deficiency, where the lacrimal gland acini remain uninvolved and retain their secretory property, while significant ultrastructural changes in the gland have been observed. Recent advances in diagnosis include the techniques of direct clinical assessment of the lacrimal gland morphology and secretion, tear film osmolarity, tear film lysozyme and lactoferrin levels, tear film interferometry and lacrimal gland confocal microscopy. Developments in the treatment of aqueous deficiency dry eye disease, apart from the nanoparticle-based tear substitutes, include secretagogues like diquafosol tetrasodium and rebamipide, anti-inflammatory topical agents like nanomicellar form of cyclosporine and lifitegrast, scleral contact lenses, neurostimulation, and acupuncture for increasing the amount of tear production, minor salivary gland transplantation, faecal microbial transplantation, lacrimal gland regeneration and mesenchymal stem cell therapy.

Conclusions: Significant advances in the understanding, diagnosis and management of lacrimal gland insufficiency and its role in aqueous deficiency dry eye disease have taken place within the second half of the last decade. Of which, translational breakthroughs in terms of newer drug formulations and regenerative medicine are most promising.

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Introduction

Dry eye disease (DED) is a major cause of chronic ocular morbidity, affecting millions of individuals worldwide.[1,2] It is estimated that about 40% of the Indian urban population or close to 270 million people would be affected by DED in the next decade.[1] The second Tear Film and Ocular Surface Society dry eye workshop (TFOS DEWS II) has defined DED as "a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage and neurosensory abnormalities play an etiological role".[2] Old age, female sex, medication use, dry environment or extended screen time on electronic devices are the known risk factors which lead to the development of DED.[1,3] DED has been classified into evaporative dry eye (EDE), and aqueous-deficient dry eye (ADDE) disease, based on Meibomian or lacrimal gland involvement, respectively, although the DEWS II guidelines suggest that these variants may lie along the continuum of the disease.[2] Irrespective of the underlying cause, instability of the tear film leads to ocular surface inflammation which is responsible for the clinical features characteristic of the disease.[4] Among the two broad categories, ADDE due to lacrimal gland insufficiency accounts for about a third of all cases of DED[1] but is the more serious and potentially blinding condition, since it can cause severe ocular surface inflammation and chronic keratopathy. This review summarizes the significant advances in the understanding, diagnosis and management of lacrimal gland insufficiency and its role in ADDE that have taken place within the second half of the last decade.

Methodology

A MEDILINE search using PubMed was performed with the keywords: "dry eye", "dry eye disease", "dry eye syndrome", "aqueous deficient dry eye", "aqueous deficiency dry eye", "Sjögren's syndrome" and "lacrimal gland" for articles published between 2016 and 2021. The search revealed a total of 20,945 articles. Articles not having abstracts, not in the English

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language, not relevant to the topic of interest and repetitive articles were excluded. A total of 750 abstracts were scanned, and 73 relevant articles were included in the review.

Etiology and pathogenesis of lacrimal gland insufficiency in ADDE

Aqueous deficiency dry eye disease can occur if the lacrimal gland is congenitally absent, developed incompletely or there is an acquired damage to the gland and its periductular tissue due to the ongoing inflammation. Depending on the underlying etiology, ADDE is classified into Sjögren's and non-Sjögren's type (Figure 1).[2]

Sjögren's Syndrome-Associated ADDE

Sjögren's syndrome (SS) is a systemic autoimmune condition wherein lymphocytic infiltration of the exocrine glands including the lacrimal gland occurs, leading to persisting inflammation and symptoms of dry eye and dry mouth, besides various other systemic manifestations such as arthritis. For its diagnosis, the American-European Consensus Group 2012-revised classification criteria are the most commonly used (Figure 1).[5–7] The pathogenesis of SS is multifactorial. Genetic susceptibility, female sex, viral infections, overactivation of B cells, role of Th1 and Th17 cells and increase in the pro-inflammatory cytokines such as matrix metalloproteinases (MMPs) are known to play a role in its pathogenesis.[8] Role of ocular and gut microbiome in the pathophysiology of SS has been recently reported. The gut microbiota is closely related to the immune system during development.[9] It maintains a balance between the immune responses and is said to play a crucial role of immune regulation. Any dysbiosis in the gut microbiome may lead to auto-immune diseases such as SS.[10–12]

Non-Sjögren's Type of ADDE

This can further be classified into congenital and acquired types (Figure 1). Congenital alacrima is a rare condition of absence of tear production from birth. There is abnormal or deficient development of the lacrimal gland or its ductal tissues. It is associated with a multitude of systemic disorders and is an important and rare cause of paediatric dry eye disease.[13] Presentation can vary from congenital absence or hyposecretion of tears, developmental delay, to severe multi-systemic involvement.[14–16]

Acquired causes of non-Sjögren's-type ADDE include immune-mediated conditions such as Stevens–Johnson syndrome (SJS), mucous membrane pemphigoid (MMP) and graft versus host disease (GVHD).[3,17,18] Stevens-Johnson syndrome is a chronic mucocutaneous blistering disease, which is triggered by drugs or viral infections.[19–22] It is said to occur as a result of dysregulated immune response, mainly pertaining to innate immunity.[23,24] It is a cytokine-mediated response, which leads to the deposition of neutrophils in the conjunctiva of these patients.[25] In both SJS and MMP, there is chronic inflammation of the ocular surface, which if not treated in time, leads to cicatrising conjunctivitis, ultimately causing ADDE. Graft versus host disease (GVHD) is an adverse immunological event following allogeneic hematopoietic stem cell transplantation. It includes a T cell-mediated immune response which causes infiltration and inflammation of ocular structures such as the lacrimal glands and conjunctiva, leading to ADDE.[26,27] Other acquired causes

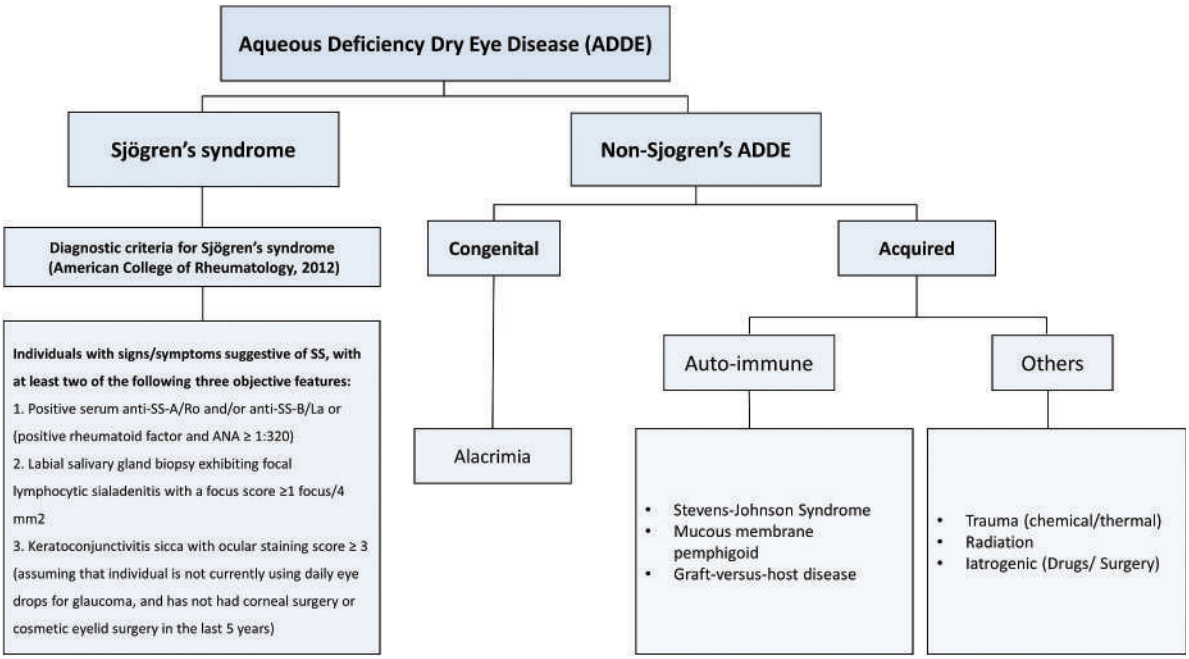

Figure 1. Classification of aqueous deficiency dry eye disease into Sjögren's and non-Sjögren's dry eye disease. Non-Sjögren's ADDE can further be classified into congenital form such as in cases of alacrimia and acquired form seen in various auto-immune diseases and other conditions such as chemical/thermal trauma, radiation and iatrogenic damage.

of non-Sjögren's-type ADDE include ocular chemical burns, iatrogenic causes such as kerato-refractive surgeries, long-term use of topical and systemic medications and radiation therapy for head and neck cancers. Some of these conditions, like radiation therapy, cause direct damage to the lacrimal gland and the ocular surface, while others, like topical anti-glaucoma medications, cause chronic inflammation and fibrosis of the ocular surface leading to cicatrising changes.

Normal anatomy of healthy lacrimal glands

Gross and Applied Anatomy

The main lacrimal gland is located in the supero-temporal orbit, behind the orbital rim, in the lacrimal gland fossa. It extends from the lateral edge of superior rectus muscle to the frontozygomatic suture and posteriorly upto the posterior aspect of the globe.[28,29] The lacrimal gland is seen as an almond-shaped, concavo-convex bilobed structure, divided into two lobes by the lateral horn of levator aponeurosis.[29–32] The larger lobe being the orbital lobe constitutes about 60–70% of the gland, weighs about 600–700 g and is located behind the orbital septum.[28,31–34] Hence, the orbital lobe cannot be clinically visualized. The smaller palpebral lobe, located beneath the levator aponeurosis, is relatively flat and can be examined clinically in the superior fornix by elevation or eversion of the lateral part of the upper eyelid. It appears as a pale, pinkish, lobulated structure.[28,32,35] Although lacrimal gland secretions are thought to mainly contribute to reflex tearing, recent reports suggest that the gland has an important role in basal tear secretion as well.[36–38]

There are two types of accessory lacrimal glands, the glands of Wolfring (along the tarsal border) and Krause (in the substantia propria of fornices). Glands of Wolfring are more in number, present mainly in the upper eyelid, while the Gland of Krause are larger in size. These glands, like the main lacrimal gland, are serous in nature and of eccrine variety. Parasympathetic nerves and hormones stimulate the accessory lacrimal glands, which contribute to both basal and reflex secretions.[39]

Microscopic Structure

Microscopically, the lacrimal gland is formed of acinar epithelial cells forming lobules draining into intralobular ducts. The ducts are lined by tubular columnar cell, surrounded by myoepithelial cells.[39,40] The intralobular ducts further merge into interlobular ducts which are lined by cuboidal cells and open in the superior and inferior fornix as 3–12 excretory ductules.[39–42] Recently, the role of columnar cells of ducts in the secretion of tears have also been found; however, this still requires further studies for confirmation.[43] The intervening interstitial connective tissue contains lymphocytes, plasma cells, mucosa-associated lymphoid tissue, fibroblasts, blood vessels and nerve fibres.[29,32,39] Accessory lacrimal glands are similar to the main lacrimal gland microscopically.

Pathological and ultrastructural changes in lacrimal gland insufficiency

Sjögren's-Associated ADDE

In SS, the lacrimal gland undergoes progressive fibrosis and hence gradually loses its secretory function. The histological examination of the lacrimal gland has revealed acinar dilation, interstitial fibrosis, with inflammatory aggregates and atrophy with fibrosis of the gland.[44]

Cicatrising Conjunctivitis-Associated ADDE

In chronic cicatrising conjunctivitis such as SJS, MMP, and chemical burns, there is an ongoing sub-conjunctival fibrosis, leading to the destruction of the lacrimal ductules, both in the palpebral and orbital lobes, which on histological examination is seen as peri-ductular, interlobar and interlobular lymphocytic infiltration and fibrosis. The acini, particularly in the orbital lobe, may remain uninvolved and retain their secretory property.[44,45] These changes are in stark contrast to the diffuse glandular atrophy and inflammatory aggregation that is seen in SS. However, despite the relative preservation of acinar structure on histopathology, significant ultrastructural changes have also been observed, showing disturbance in productivity and secretory activity of the glands in cicatrising disease like SJS.[46]

Diagnostic modalities of lacrimal gland insufficiency in ADDE

The traditional standard basic tests for the diagnosis of DED include ocular surface disease index score (OSDI), Schirmer's test, tear film height and tear film break up time (TBUT). Since this review focuses mainly on ADDE due to the lacrimal gland insufficiency, for the simplicity of discussion, the recent advances in diagnostic modalities have been classified into direct assessment of the lacrimal gland and indirect assessment of lacrimal gland insufficiency by tests based on tear film parameters.

Direct Clinical Assessment of Lacrimal Gland and Its Function

Morphometry

Clinically, on slit lamp bio-microscopy, one can assess the lacrimal gland by asking the patient to look inferonasally and lifting the upper eyelid to observe the contour, size and appearance of the palpebral lobe of the lacrimal gland. Recently a study by Singh et al. showed that in normal individuals and those with EDE, the palpebral lobe is bilaterally symmetrical, having a convex pinkish appearance. However, in cases of ADDE, the palpebral lobe size is bilaterally asymmetrical, appears flatter than normal and loses its convexity. Further, in SJS, the palpebral lobe appears smaller and there is a presence of symblepharon along with scarring.[35] Therefore, clinical assessment of the palpebral lobe morphology can not

only help us in diagnosing ADDE but can also help us in differentiating between the underlying etiological causes of SS and SJS.

Tear Flow Rate or Tear Secretion

Direct assessment of tear secretion (DATS) from the excretory ducts on the surface of the palpebral lobe of lacrimal lobe was first described in 1986.[41] It was developed on the concept of the Seidel's test, wherein a point of leak appears as a stained flow of fluid from the focal source. Similarly, simply touching the surface of the palpebral lobe with a fluorescein strip shows the appearance of the fluid at the duct openings and its rate of flow and washout.[45] Recent studies have shown its utility in diagnosing the subtype of ADDE. Singh et al. showed the difference in the number of ductular opening and flow rate between patients of cicatrising conjunctivitis, SS and normal healthy individuals. The patients of cicatrising conjunctivitis had reduced number of ductular opening and tear flow rate as compared to the patients of SS.[35] Also the latency for the initiation of the tear flow and the rate of flow can be assessed. The time lag is maximum in the cicatrising group followed by the SS group. The advantage of both lacrimal gland morphometry and DATS is that they can be performed in the clinic and can aid clinicians to diagnose the subtype of DED.

Indirect Assessment of Lacrimal Gland Function (Tear Film-Based Tests)

Tear Film Breakup (TBFU) Patterns

Due to the ongoing inflammation and subsequent injury to the epithelial cells and microvilli, ocular surface shows positive staining after the topical application of fluorescein. In 2017, Yokoi et al. described the characteristic tear film breakup patterns in the various subtypes of DED, thereby proving an aid for diagnosis. They described five main patterns. As per their report, an area break of ocular surface staining points towards severe grade of ADDE, a line and dimple break indicate mild-to-moderate grade of ADDE, while a spot break determines decreased wettability of the surface.[47] Based on this pattern, DED can be classified into three independent subtypes, ADDE, decreased wettability DE (DWDE), and increased evaporation. Hence, based on the pattern, it is possible to identify which component of the tear film should be supplemented. This novel concept of a layer-by-layer diagnosis and therapy is known as "tear film-oriented diagnosis" (TFOD) and "tear film-oriented therapy" (TFOT).[48]

Non-Invasive Tear Film Breakup Time (NIBUT)

Instillation of fluorescein dye is considered invasive in nature since it is associated with chances of transmission of infection; hence, a newer method known as non-invasive tear film break up time (NITBUT) was introduced.[49] It is a placido disc-based assessment of the tear film, which determines the tear film stability based on the reflection of mires from the ocular surface. The reflection gets altered when the tear film stability is compromised.[50,51] However, there appears to be significant difference in the values measured by TBUT and NITBUT. Average value of 3–4 NIBUT measurements provides a more accurate result, and hence the average value should be preferred over a single measurement.[52]

Tear Meniscus Height

An objective way of assessing the tear film volume is by using the anterior segment optical coherence tomography (OCT)-based measurement of tear meniscus height (TMH). Time domain (TD-OCT) was the first OCT used for this purpose. Recent advances in spectral domain and swept source OCT have proven to be more useful, since it has the added benefit of helping in distinguishing the subgroup of DED.[53–56] The TMH is lowest in Sjogren's syndrome, followed by non-Sjogrens ADDE.[57]

Tear Strip Meniscometry

This device uses a water absorbing material similar to the Schirmer's test. It has the added benefit that it is quick, providing results within 5 seconds, and is a non-invasive method to quantify the tear volume.[58,59]

Tear Osmolarity

In case of ADDE and EDE, due to the insufficient aqueous secretion and normal or excessive evaporation, the ocular surface remains in a chronic state of inflammation. This inflammation of ocular surface results in outpouring of inflammatory products and cytokines into the tear film. This results in increasing the tear film osmolarity. The TearLab Osmolarity System (TearLab Corporation, San Diego, California, USA) is currently the only FDA-approved commercially available in-office device for measuring tear film osmolarity.[60] It collects a sample of 50 nL of tear film and gives results within just a few seconds.[61] The normal tear osmolarity has a value of 302 mOsm/L with an inter-eye difference of 8 mOsm/L.[60,62] It is worth noting that tear osmolarity is variable depending on the time of the day, or food intake, and hence must never be considered as a static value.[61,63]

MMP-9

Due to the evidence of increase in the pro-inflammatory cytokines such as MMP-9 in tear film of patients with DED, MMP-9 assessment has turned a useful aid for diagnosis. MMP-9 is an important endopeptidase released in the tear film during the extracellular matrix remodelling and facilitating leukocyte migration and chronic state of inflammation.[64–66] Currently, InflammaDry test (RPS, Inc., Sarasota, Florida, USA) is the only FDA-approved device for the detection of MMP-9 in patients. However, the test is non-specific for DED since the MMP-9 levels can be elevated even in other inflammatory ocular conditions such as keratitis.[67]

Lactoferrin and Lysozyme

These are the normal constituents of the tear film, which are said to have a protective mechanism in the form of antibacterial, antitumor and immunomodulatory property. Lactoferrin levels in tear fluid are mainly reduced in autoimmune conditions such as SS.[68–70]

Lacrimal Gland Imaging

CT scan, MRI scan and PET scan are some of the known modalities used for lacrimal gland imaging. Recently, the role of in vivo confocal microscopy of the lacrimal gland has been demonstrated in DED patients.[71] It can assess the acinar unit density, acinar unit diameter and inflammatory cell density in both the Meibomian and lacrimal glands.[72] This is a relatively unexplored area and there is enormous scope for further research in the field of lacrimal gland imaging.

Treatment of lacrimal gland insufficiency

Pharmacological Treatment

Lacrimal gland insufficiency manifests mainly as a reduction in the tear volume which further leads to increased tear hyperosmolarity, resulting in chronic ocular surface inflammation and disease sequelae. (Figure 2). Hence, the pharmacological treatment of ADDE includes topical tear supplements, punctal plugs, secretagogues and anti-inflammatory agents such as corticosteroids, cyclosporine and tacrolimus. There is also an important role of controlling the underlying systemic disease, particularly in immune-mediated conditions like SS and GVHD.

Tear Supplements

These have been the first line of management in patients with ADDE, regardless of the disease severity. They are known to improve the ocular surface lubrication, tear retention, tear osmolarity and TBUT and reduce the ocular surface staining. However, there are various types of artificial tears available which differ in its constituents.[73,74] Preservatives such as benzalkonium chloride should be avoided as it causes stinging sensation and ocular surface toxicity with long-term use. The pH of the human tear is between 6.9 and 7.5. Any compound having a higher pH causes burning sensation upon instillation. These factors further worsen the pre-existing symptoms of a patient with DED. Current recommendations are that a preservative-free compound having a lower pH should be preferred. Due to the varied compositions, the drops need to be individualized in every patient.

Secretagogues

This is a new class of drugs, which mainly acts on the receptors of the lacrimal gland and helps in increasing the tear production. This class of drugs include diquafosol tetrasodium, rebamipide, cevimeline and oral pilocarpine. Diquafosol tetrasodium is available as a 3% ophthalmic solution. It acts on P2Y2 receptors, which are found on the conjunctiva, meibomian and lacrimal gland. It increases the intracellular calcium and thereby helps in increasing the tear secretion.[75–82] Rebamipide is a quinolinone derivative, which has a dual effect. It acts on goblet cells and increases the mucin production, thereby improving the tear film stability and epithelial regeneration. It also has an added benefit in increasing the levels of PGE2 and PGI2 and reducing the level of TNF-A, thereby preventing macrophage infiltration in the conjunctiva and reducing the amount of ocular surface inflammation and improving the tear film stability.[82–86] Cevimeline hydrochloride is a cholinergic agonist that binds to muscarinic acetylcholine receptors, especially to the M3 receptor, producing an increase in glandular secretions. Oral pilocarpine is also known to be having similar mechanism and helps in increasing both the salivary and aqueous tear production in patients of SS.[87–90]

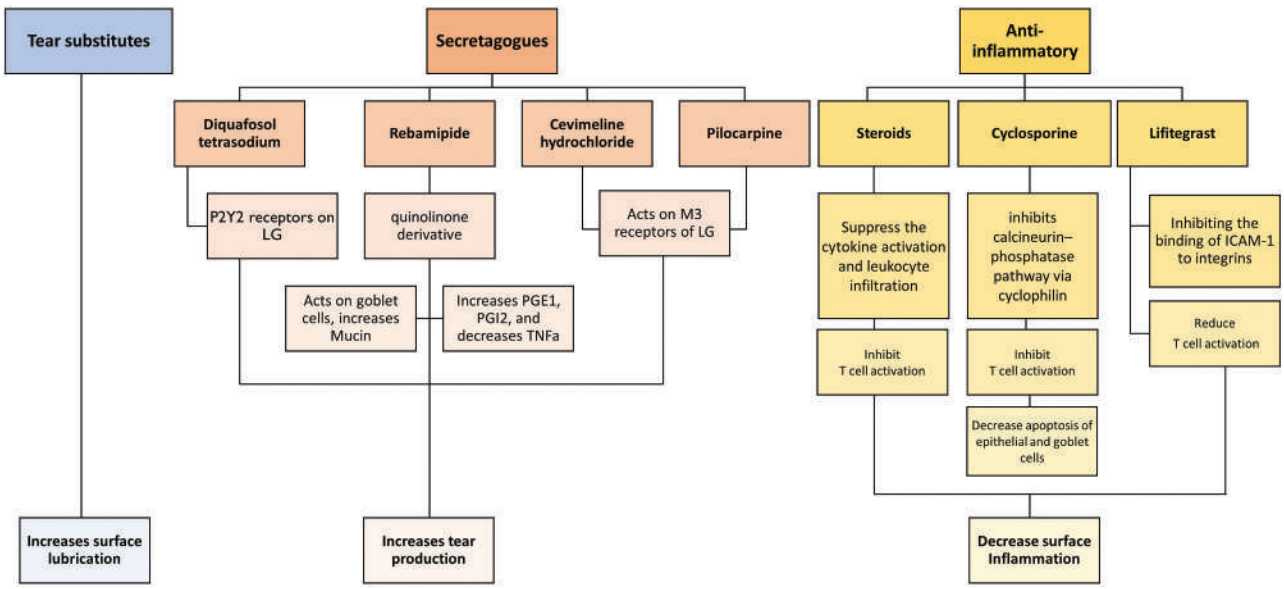

Figure 2. Classification, mechanism of action and the effect on ocular surface of various topical drugs used in the treatment of ADDE. LG, lacrimal gland; PG, prostaglandins; TNF, tumor necrosis factor; M3, muscarinic receptor and ICAM-1, intercellular adhesion molecule.

Anti-inflammatory Agents

The pathogenesis of DED[90] and molecular interaction of various anti-inflammatory agents have been illustrated in Figures 3 and 4. Topical corticosteroids help in reducing the ocular surface inflammation by interrupting the inflammatory cycle. They mainly suppress the cytokine activation and leukocyte infiltration, thereby controlling the ongoing inflammation. However, in view of the various side effects, their continued long-term use is not recommended. Topical cyclosporine acts by inhibiting the calcineurin–phosphatase pathway via cyclophilin. It is also said to increase the goblet cell density and increase tear production. It is said to inhibit T cell activation and decrease apoptosis of epithelial and goblet cells.[91] FDA has approved 0.05% cyclosporine emulsion (Restasis, Allergan Inc. Irvine, CA, USA), which has anti-inflammatory property and in addition is also known to increase the tear production.[92–94] It is said to give better results than the use of lubricants alone in the treatment of DED.[95]

Cequa (CEQUA, Sun Pharmaceutical Industries, Inc., Cranbury, NJ), a preservative-free nanomicellar form of cyclosporine, has also recently been approved by FDA. It has the advantage of better drug penetration and rapid onset of action.[96] Lifitegrast (XiidraTM, Novartis, USA) was approved in 2016 to treat DED.[97] It is a nanoparticle, which prevents the inflammatory cascade by inhibiting the binding of ICAM-1 to any integrins. It inhibits binding of leukocyte-associated antigen-1 (LFA-1) on T cells to its ligand intercellular adhesion molecule-1 (ICAM1) on antigen presenting, epithelial and vascular endothelial cells and prevents the formation of the immunological synapse that is required for full T cell activation. It is available for topical use as 5% ophthalmic solution.[98–102] Metformin, a first-line drug used in type 2 diabetes, has also emerged as an effective anti-inflammatory drug useful in patients of SS.[103] Multiple other treatment modalities to promote body's natural anti-inflammatory mechanism are described which include oral supplementation with Omega-3 polyunsaturated fatty acids (PUFAs), curcumin and anti-oxidants, which suppress interleukins and the inflammatory cascade.[104,105]

Contact Lenses

Soft bandage contact lenses are known to improve the symptoms of patients with DED. Many recent studies have shown the role of scleral and PROSE (Prosthetic Replacement of Ocular Surface Ecosystem) lenses in terms of improving symptoms and visual acuity, particularly in cases with severe ADDE in patients with chronic ocular sequelae of SJS.[106,107] These lenses are filled with fluid, which provide lubrication to the ocular surface. It improves the quality of vision as well as improved the symptoms of patients. However, the limitation is its availability, expense and need of training for its application and removal.[108–110]

Neuronal Stimulation Therapy

Acupuncture is a form of Chinese traditional medical therapy, wherein needles are applied at specific points on the body for neuronal stimulation. It has shown to be effective in treating DED. However, further studies are needed to gauge its efficacy.[111–113] Role of anterior ethmoidal nerve stimulation being better than lacrimal nerve stimulation for increasing the aqueous production is also known.[114] Intranasal Tear Neurostimulator (TrueTear, Allergan plc) is a similar device

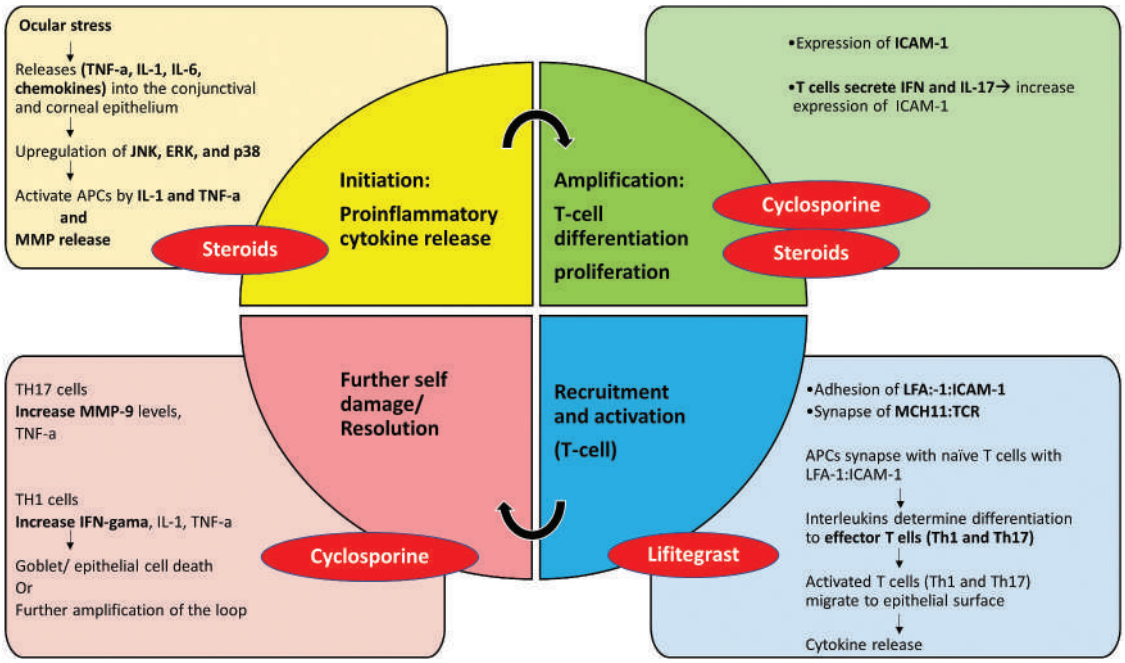

Figure 3. Mechanism of action of the anti-inflammatory agents such as steroids, cyclosporine, and Lifitegrast used in ADED. TNF-α, tumor necrosis factor alpha; IL-, interleukin; JNK, c-Jun N-terminal kinase; ERK, extracellular signal–related kinase; APC, antigen presenting cells; MMP, matrix metalloproteinase; ICAM-1, intercellular adhesion molecule 1; LFA-1, lymphocyte function-associated antigen 1; MHCII, major histocompatibility complex II; TCR, T cell receptor; IFN-γ, interferon gamma. Adapted from Periman et al.[90]

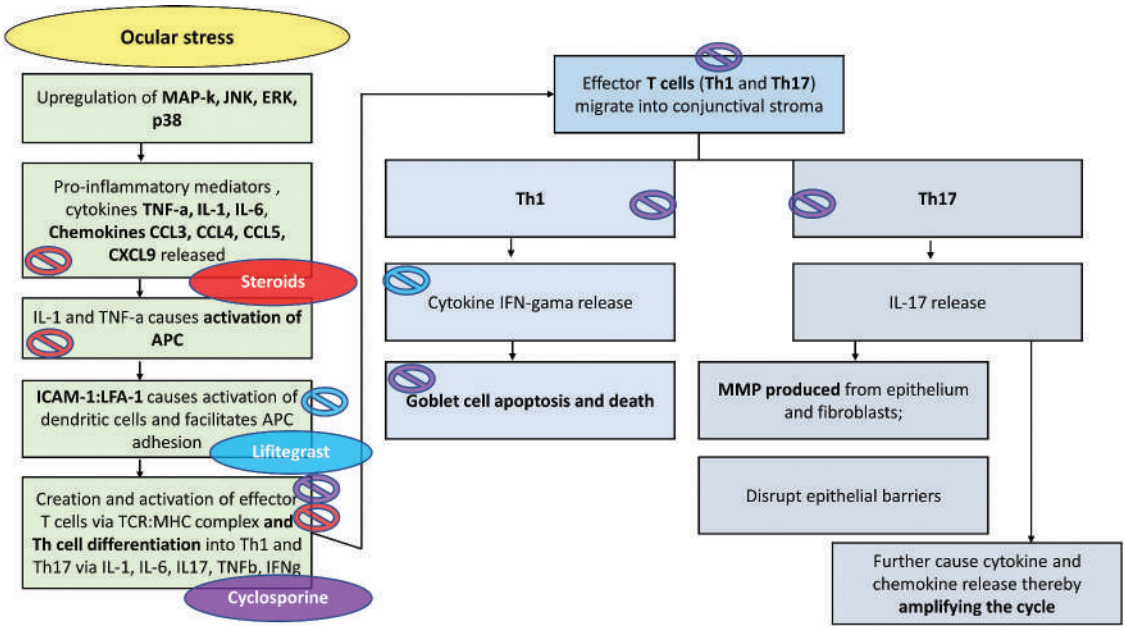

Figure 4. Site of action during the pathophysiology of ADED-induced inflammatory cascade and the molecular interaction of the various anti-inflammatory agents used in ADED. MAP-K, mitogen-activated protein kinase; JNK, c-Jun N-terminal kinase; ERK, extracellular signal–related kinase; TNF-α, tumor necrosis factor alpha; IL-, interleukin; CCL,CXCL- chemokines; ICAM-1, intercellular adhesion molecule 1; LFA-1, lymphocyte function-associated antigen 1; TGF-β, transforming growth factor beta; IFN-γ, interferon gamma and MMP, matrix metalloproteinase. Adapted from Periman et al.[90]

designed to deliver microcurrents to the nasal cavity, stimulating the nasolacrimal pathway. It has recently received FDA approval to temporarily increase tear production. It has shown significant improvements in ocular dryness and discomfort compared along with a good safety profile and hence appears to be a promising new management strategy for these patients.[115] The iTEAR®100 device is a similar device; however, unlike TrueTear, this stimulates the anterior ethmoidal nerves at the tip of the nose. Further clinical trials for its efficacy and safety are awaited.

Surgical Management

Minor Salivary Gland Transplantation (MSGT)

This surgical option has shown to be useful and effective in patients with certain types of severe ADDE. The surgery was first described in 2008.[116] The graft tissue is obtained from under the oral labial mucosa and transplanted onto the posterior eyelid lamella. It increases the tear secretions in patients of non-Sjögren's type of ADDE.[117–119] Recently, a modified technique has also been described, wherein the graft is taken en-bloc, retaining the overlying mucosa and submucosal tissue to act as a barrier against post-operative sub-conjunctival fibrosis. In the modified technique the graft is placed over the superior bulbar surface of the eye.[119] Certain clinical tests have been described to help selecting the donor site and in assessing the functionality of the transplanted glands post-operatively.[120–122] The test is similar to the DATS test, wherein a fluorescein strip is applied onto the labial mucosa, and based on the number of excretory duct openings, the donor site can be selected.[120,121,123,124] Similarly, the test can be used to objectively assess the number of functional openings and secretory rate in the transplanted graft on the ocular surface.[122] It is important to remember that MSGT is not recommended in Sjögren's type of DED because the underlying disease process affects both the salivary and the lacrimal glands.

Mesenchymal Stem Cell Transplantation

Mesenchymal/stromal stem cells (MSCs) possess immunomodulatory properties and multilineage differentiation abilities. It acts by suppressing both local and systemic inflammation and inhibiting the activation and proliferation of T cells.[125] It has a potential role in treating patients with severe or refractory DED. The literature also shows its role in treating patients with steroid-resistant GVHD-induced DED.[126] Injection of MSCs derived from bone marrow or adipose tissue into the lacrimal gland has also shown efficacy.[127] Further results of randomized control trials from the same group is still awaited.

Lacrimal Gland Regeneration

Lacrimal gland regeneration using MSC, in addition to immunomodulation, is one of the main focuses of current research and is gaining popularity.[128–131] Further advances include the development of bio-engineered lacrimal glands, which can produce tears having the protein content similar to human tears.[132,133] Researchers have also described the establishment of 3D organoids of the human lacrimal gland, which can engraft and produce mature tear products after orthotopic transplantation in mice.[134] Organoids can be expanded over multiple months and recapitulate morphological and transcriptional features of lacrimal ducts. These exciting and novel approaches are awaiting clinical translation.

Faecal Microbial Transplant

The role and interaction of ocular-gut-microbiome have been found to have a major role to play in the pathophysiology of ocular surface diseases, especially in auto-immune conditions such as SS. Hence, supplementation with probiotics or metabolites of commensal bacteria could have a major role in future treatment directives for dry eye diseases.[135,136] Faecal microbial transplant showed efficacy in patients of immune-mediated DED; however, further trials would be needed to prove its efficacy and safety.[137]

Summary

Aqueous deficiency dry eye disease, although the less common form of DED as compared to EDE, is the more serious clinical sub-type that causes chronic ocular morbidity and is potentially blinding. The underlying cause of ADDE is the dysfunction of the lacrimal glands, which is mostly acquired and due to auto-immune diseases that either directly target the gland, like in SS, or the periglandular tissue and the secretory ductules, like in SJS. Recent advancements have improved our understanding of the pathological processes affecting the lacrimal gland, particularly in cicatrising non-Sjögren's type of ADDE. Developments in diagnostics include both simple clinical diagnostic techniques like direct assessment of lacrimal gland morphology and secretion, which can be performed in office settings without any specialized equipment and sophisticated, yet elegant and objective tear-film-based tests like osmolarity measurements. Introduction of newer therapeutic agents, such as secretagogues like diquafosol, anti-inflammatory agents like preservative free nanomicellar form of cyclosporine and lifitegrast, have expanded the treatment options and are likely to bring more relief to patients. Lastly, the role of the gut microbiome is being explored through faecal microbial transplantation in SS-associated ADDE, while the final frontier of lacrimal gland rejuvenation, repair or replacement is also being challenged through MSC therapy and bioengineered glands and organoids.

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Case report

Simple oral mucosal epithelial transplantation (SOMET) for ocular surface reconstruction in Stevens-Johnson Syndrome: A case report

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ABSTRACT

Introduction: We report the clinical outcome of a novel surgical technique called simple oral mucosal epithelial transplantation (SOMET) for the treatment of limbal stem cell deficiency (LSCD) in a patient with Stevens-Johnson Syndrome (SJS).

Presentation of case: An eighteen-year-old girl was diagnosed as having chronic bilateral ocular sequelae of SJS. She initially underwent mucous membrane grafting (MMG) in both eyes for lid margin keratinization. Over the course of the next decade, the ocular surface cicatrization worsened in her left eye, leading to progressive symblepharon formation with total corneal conjunctivalization. She then underwent ocular surface reconstruction using bulbar MMG and SOMET. Following SOMET, the ocular surface epithelialized within 3 weeks and remained stable throughout the follow-up period. At one-year postoperatively, the visual acuity had improved from light perception to 20/250 unaided, and to 20/100 with scleral contact lens correction in the left eye.

Discussion: Simple limbal epithelial transplantation (SLET) has been a boon for the treatment of unilateral LSCD. Allogeneic SLET and kerato-limbal allografts can be useful for patients with bilateral disease, however this exposes the patients to the risks of long-term systemic immunosuppression. SOMET combines the benefits of cultivated oral mucosal epithelial transplantation (COMET) and SLET, and is an autologous and single-staged surgical alternative for patients with bilateral LSCD.

Conclusion: This case demonstrates that SOMET is a viable surgical option in cases with bilateral LSCD, eliminating the need for an allogeneic limbal graft, systemic immunosuppression, or laboratory cell culture.

1. Introduction

Stevens-Johnson Syndrome (SJS) is a rare, life-threatening, vesiculobullous disease of the skin and mucosa, occurring due to an immune-mediated hypersensitivity reaction to a systemic drug or infection [1]. Ocular involvement is the most common chronic sequelae of SJS, which impairs the quality of life of affected individuals [1,2]. Keratopathy and limbal stem cell deficiency (LSCD) ensue due to constant friction from lid margin keratinization, long-standing ocular surface inflammation, conjunctival cicatrization, and aqueous deficient dry eye disease, leading to sight-threatening complications [2]. Treatment of lid margin keratinization involves lid margin mucous membrane grafting (MMG) or the use of prosthetic replacement of ocular surface ecosystem (PROSE) contact lenses [3–5]. The fornix and the ocular surface can be reconstructed using amniotic membrane transplantation (AMT), ocular surface MMG, or cultivated oral mucosal epithelial transplantation (COMET) [6,7]. Bilateral LSCD in these patients can be treated with allogeneic limbal stem cell transplantation or COMET [8]. Being an autologous procedure, COMET carries no risk of immunological rejection, improves visual acuity, ocular surface severity scoring, and helps treat LSCD [9]. However, it requires a sophisticated and expensive clinical-grade laboratory setup. Allogeneic limbal stem cell transplantation, on the other hand, requires long-term systemic immunosuppression. In this case report, we applied the concept of simple limbal epithelial transplantation (SLET) and combined it with the benefits of COMET, by replacing the limbal tissue with autologous oral mucosa, using a surgical technique termed simple oral mucosal epithelial transplantation (SOMET). This case report is as per the SCARE-2020 criteria [10].

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2. Presentation of case

An eighteen-year-old girl presented to us in 2012 with complaints of photophobia, redness, and discharge in both eyes (OU) for the past three years, after an episode of multiple skin eruptions and rashes over the body, which occurred as a consequence of consuming systemic medication for fever. At presentation, she had a best corrected visual acuity (BCVA) of 20/40p in OU. There were blocked meibomian orifices, thickened and keratinized lid margins, conjunctival cicatrization, and corneal scarring with vascularization noted in OU. She was diagnosed as having ocular sequelae of SJS and was started on topical steroids, and frequent application of tear substitutes. She later underwent lid margin MMG in OU. The right eye (OD) later underwent symblepharon release, amniotic membrane grafting and cataract surgery. While OD was relatively stable (Fig. 1A), in the left eye (OS) over the period of the next ten years, she developed a progressive symblepharon covering 80–90 % of the cornea (Fig. 1B) causing her visual acuity to drop from 20/40 to light perception. At this stage we intervened surgically in OS and performed symblepharon release with ocular surface reconstruction using bulbar MMG and SOMET.

Surgical procedure (Fig. 2): under general anesthesia, after painting and draping the eye, the symblepharon was released from the cornea and a 360-degree peritomy was performed (Fig. 2A, B). A combination of sharp and blunt dissection was carried out to separate the fibrovascular pannus from the underlying corneal stroma (Fig. 2C). An amniotic membrane graft (AMG) was attached over the ocular surface with fibrin glue and perilimbal 10-0 nylon continuous sutures (Fig. 2D). The oral mucosa over the lower lip was cleaned with betadine 5 % solution. The submucosal tissue was infiltrated with 5 mL of lignocaine hydrochloride 2 % and adrenaline (1:200,000) solution. The MMG was marked with tissue markers and borders incised with number 11 blade. It was then carefully excised and placed over the surgical drape (Fig. 2E). A small triangular piece of the MMG tissue (approximately 3 mm in size) was excised and kept aside for SOMET later (Fig. 2F). The submucosal tissue was debulked, and the graft was thinned to the extent possible (Fig. 2G, H). It was divided into 2 horizontally equal parts for surface reconstruction (Fig. 2I). The grafts were attached circumferentially over the sclera around the limbus using 7-0 vicryl sutures (Fig. 2J–K). The remaining triangular tissue of MMG (Fig. 2K) was thinned and divided into 10–15 tiny pieces, which were placed over the paracentral cornea (similar to SLET), using fibrin glue, over which a soft bandage contact lens (BCL) was placed (Fig. 2L).

Post-operatively, she was followed up at 1 day, 1 week, 3 weeks, 2 months, 6 months, and 1 year. She was started on low-dose oral steroids (20 mg/day) for a week, which were tapered to 5 mg/day for a month and stopped thereafter; topical tear substitutes, and ointment of steroid and antibiotic combination applied thrice a day for 1 week and later shifted to only nightly application. The cornea had completely epithelized by 3 weeks (Fig. 3A, B) and the BCL was removed. The fornices had been restored (Fig. 3C) and the ocular surface (bulbar) MMG had also integrated well (Fig. 3D–F). We encountered no epithelial instability, or any other complication during the entire post-operative period. At the final 1-year follow-up visit, the ocular surface was stable, the cornea was completely epithelized, the SOMET grafts had completely integrated, and there was residual macular to nebular grade superficial stromal scarring with vascularization (Fig. 4A, B). The uncorrected visual acuity was 20/200 and 20/250 in OD and OS, respectively. She was improving to 20/100 in OS with PROSE contact lenses (Fig. 4C, D). The Schirmer's test value had also increased from 0 mm at 5 min preoperatively to 6 mm post-operatively.

3. Discussion

Following SJS, patients usually present to an ophthalmologist after developing ocular symptoms such as foreign body sensation, dry eyes, or decrease in visual acuity, months to years after the acute episode [11]. The chronic stage may lead to sight-threatening complications due to lid margin keratinization, dry eye disease, and chronic ocular surface inflammation [2–6,11]. Since LSCD in SJS is often bilateral, surgical options include allogeneic limbal stem cell transplantation in the form of allo-SLET, or keratolimbal allografting (KLAL), or autologous COMET. Outcomes of limbal allografting in cases of SJS have not shown to be satisfactory due to high chances of failure and the need for long-term immunosuppression which have other potential side effects [11,12]. COMET has a success rate of about 70 % in cases of bilateral LSCD. It helps in rapid surface epithelization, reduces corneal opacification, and improves visual acuity [9,13,14]. Studies have shown that the cultured cells resemble the corneal epithelial cell having three to five cell layers, with small basal cells, flattened middle cells, and polygonal superficial cells. They express markers of corneal epithelial cell differentiation (cytokeratin 3 and connexin 43), and marker of progenitor stem cells (p63), similar to corneal epithelial cells [13–15].

COMET has the advantage of being an autologous procedure, and not requiring any systemic immunosuppression; while the disadvantages include it being a two-staged procedure, and the requirement of an expensive clinical-grade laboratory set-up for cell cultivation [8]. Based

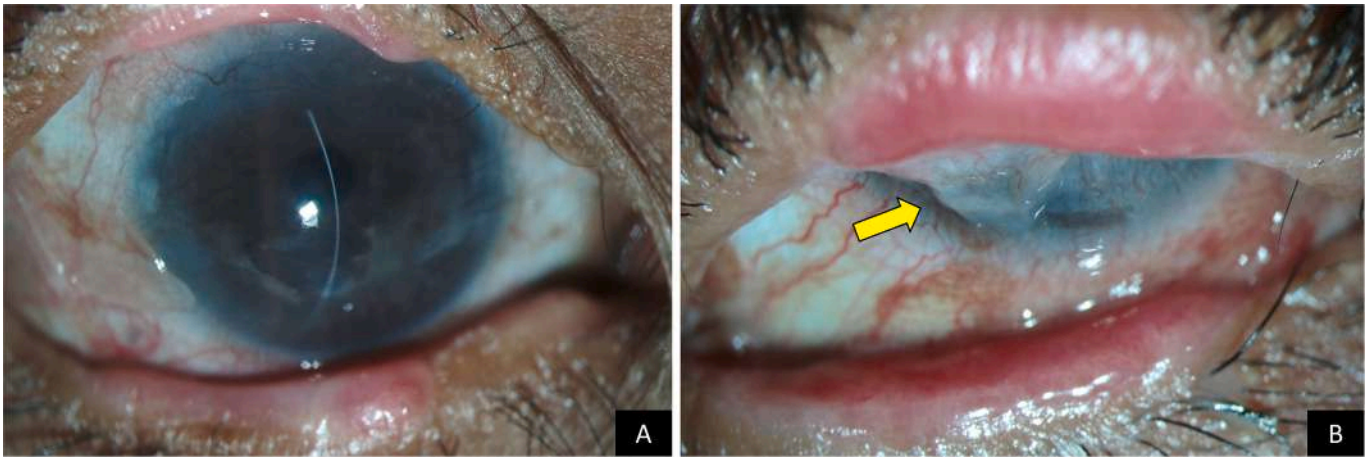

Fig. 1. Slit lamp photographs of both eyes around ten years after of undergoing eyelid mucous membrane grafting. The right eye (A), which had also undergone symblepharon release with amniotic membrane transplantation and cataract surgery two years prior shows: thickened lid margins, integrated eyelid mucous membrane grafts in both upper and lower eyelid, with nebular grade corneal scarring. The left eye (B) shows: thickened lid margins with mucous membrane grafts in place, an extensive symblepharon covering almost the entire cornea (yellow arrow), limiting eversion of the upper lid and precluding the view of the cornea. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

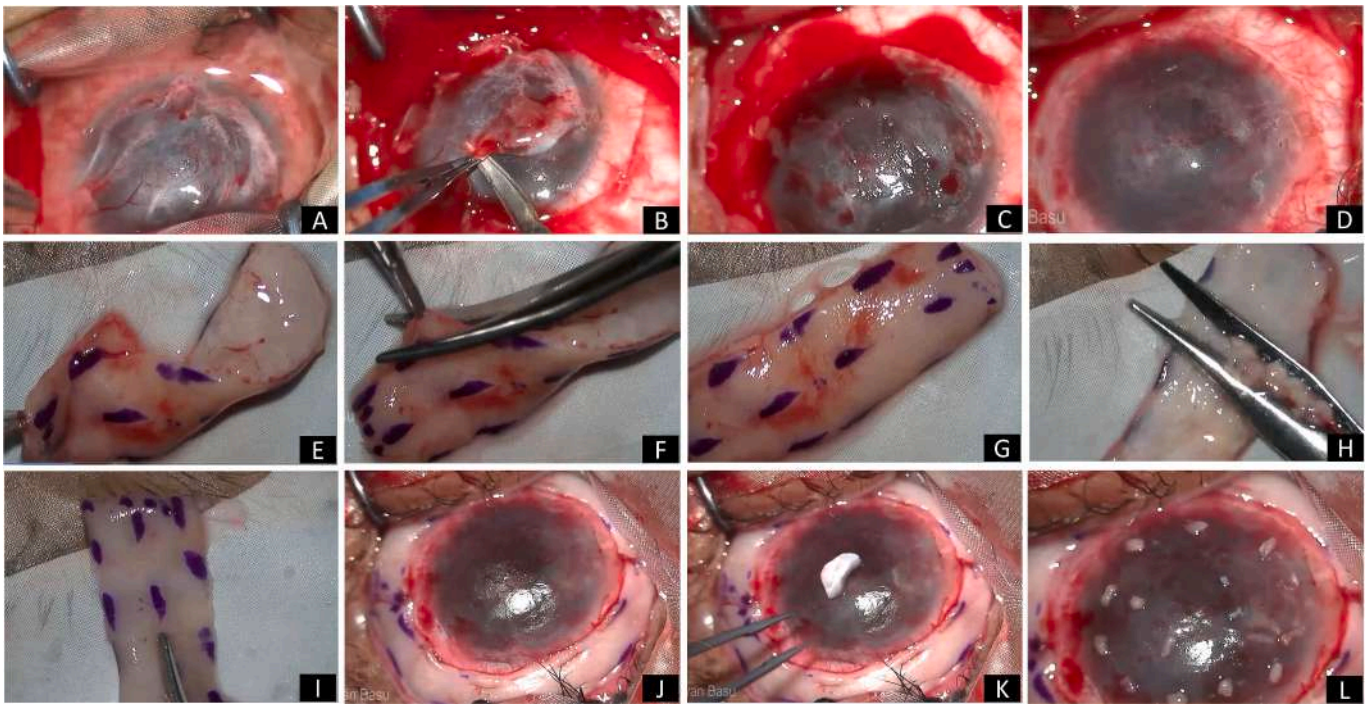

Fig. 2. Surgical technique of simple oral mucosal epithelial transplantation or SOMET (A to L). A: The symblepharon was excised (A) and the self-retaining speculum was placed to expose the cornea and ocular surface. A 360-degree peritomy was performed (B) and the fibro-vascular pannus was dissected from the underlying corneal stroma (C). An amniotic membrane graft was placed over the ocular surface using fibrin glue, along with anchoring, perilimbal, continuous sutures with 10-0 nylon (D). The oral mucous membrane graft was harvested from the lower lip (E), and a small triangular shaped tissue was excised (F, G) and kept aside, for later use as SOMET. The graft was thinned to the extent possible by excising the underlying submucosal tissue and fat (H). The tissue was then dissected into two equal parts (I). The grafts were sutured over the bulbar bare sclera, circumferentially around the limbus (J), using 7-0 vicryl sutures (K). The triangular tissue was then thinned (K) and divided into 10–15 small pieces, and placed over the cornea, using fibrin glue (L).

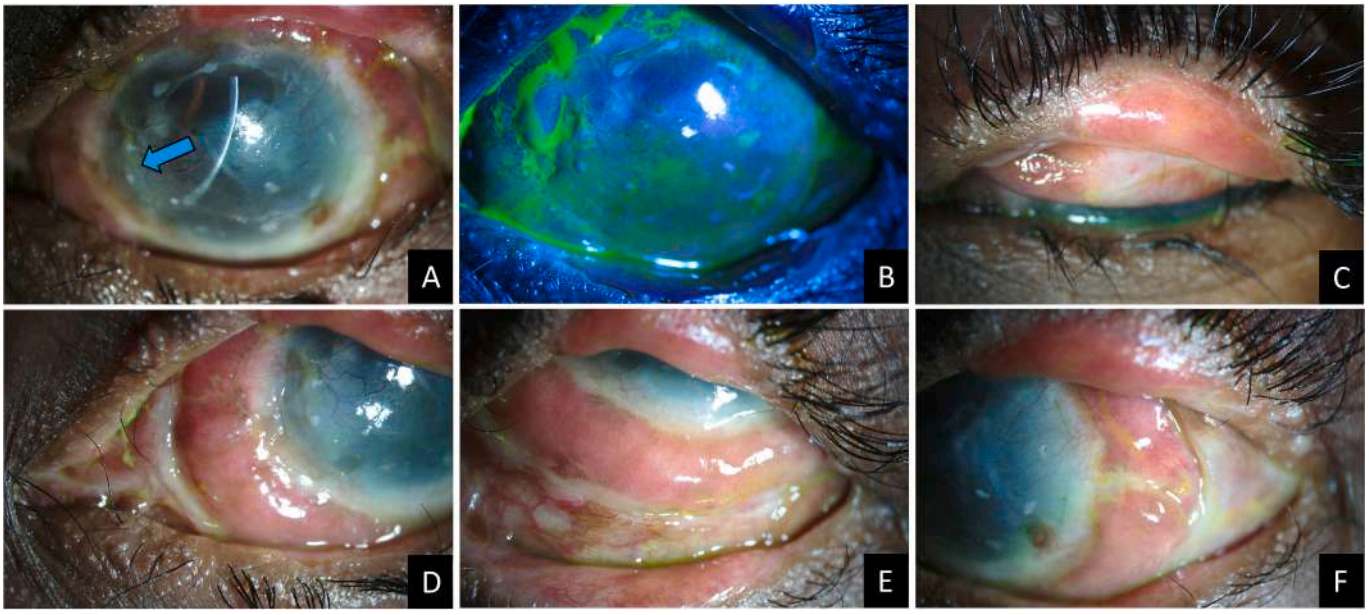

Fig. 3. Slit lamp photographs of the left eye three weeks after simple oral mucosal epithelial transplantation or SOMET (A to F). The tiny pieces of mucosal grafts (A, blue arrow) can be appreciated in the paracentral cornea. Fluorescein-stained image in cobalt blue filter (B) shows a completely epithelized corneal surface. Everted image of the left upper eyelid (C) reveals a deep upper fornix. Images in different gazes (D to F) showing 360-degree bulbar mucous membrane grafts, which are well taken up. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

on the encouraging outcomes of COMET, and combining them with the principle of SLET (where autologous limbal tissue from a healthy eye is divided into multiple small pieces and placed over the AMG in the paracentral cornea for these cells to proliferate and eventually epithelize and cover the entire corneal surface) [16,17] we decided to perform SOMET, a synthesis of both these techniques. We placed tiny pieces of the MMG, obtained from the lip mucosa, circumferentially at the para-central cornea with the help of fibrin glue over an underlying AMG.

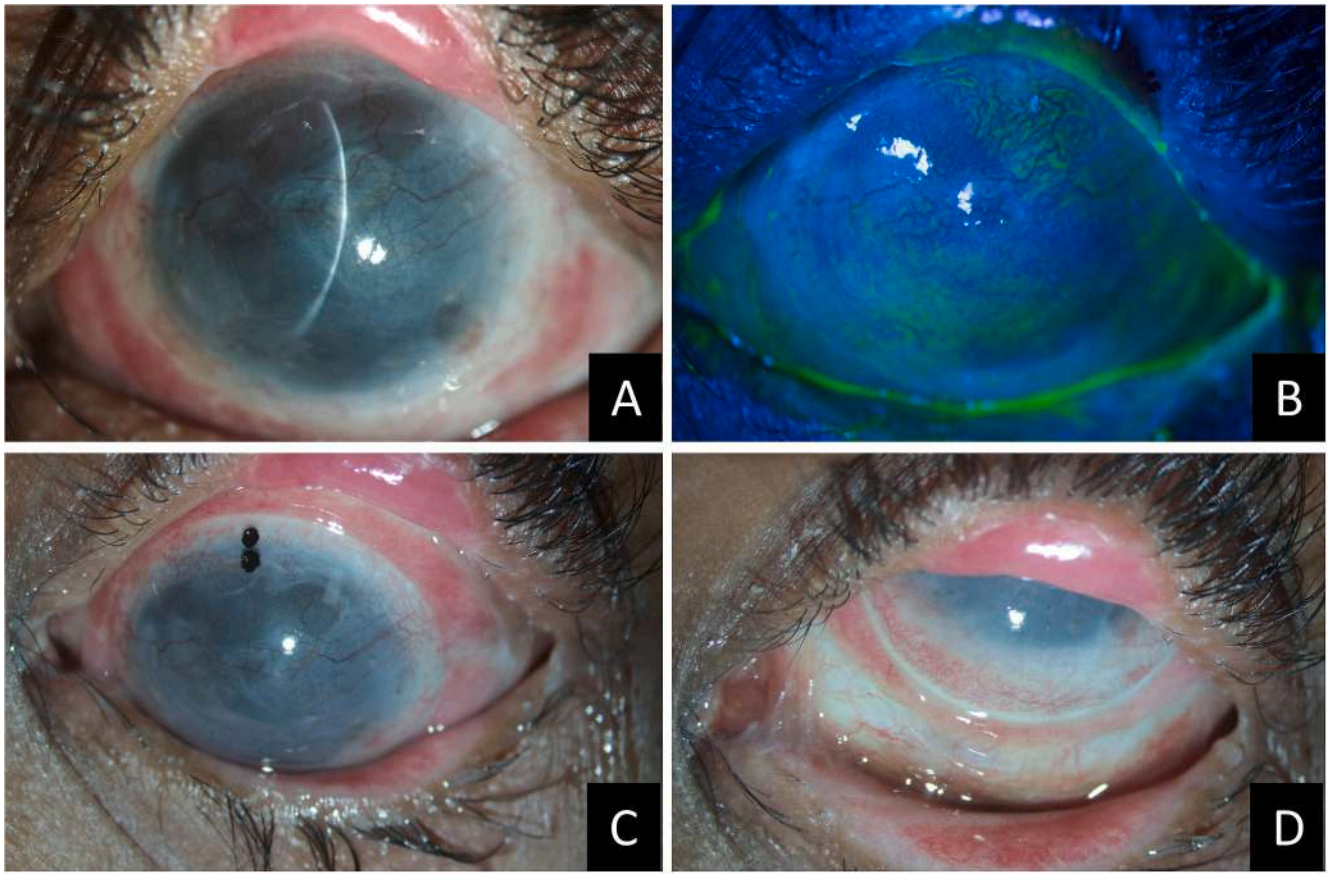

Fig. 4. Slit lamp photos of the left eye at the one-year follow-up visit after simple oral mucosal epithelial transplantation or SOMET (A to D). The corneal surface is stable (A), completely epithelized (B) with completely integrated SOMET grafts and macular to nebular grade superficial corneal scarring and vascularization. Images after wearing PROSE contact lenses in the left eye (C, D) which show acceptable fitting of the lenses over the reconstructed corneal and bulbar surface.

These transplants were seen as discrete tissue initially but later integrated and led to complete epithelization of the corneal surface by 3 weeks. Post-operatively, a well epithelized surface, improvement in visual acuity and Schirmer's value were noted at 1-year follow-up in our patient.

There are few reports of the oral mucosa being used as a tissue graft, without ex-vivo cultivation as in COMET, for the treatment of LSCD [18,19]. In a retrospective study done by Liu et al., an oral mucosal graft was used as a surrogate limbus in 7 eyes with severe LSCD (1 eye having LSCD due to SJS). They too simultaneously treated the symblepharon along with LSCD. Their results showed that all patients had improvement in symptoms and corneal scarring. They also demonstrated that initially, the peripheral corneal vascularization increased, which then decreased significantly after 3–6 months [18]. The first report of performing SOMET was in a rabbit model of LSCD by Inamochi et al. [19]. In this study a 3 × 4 mm piece or oral mucosal tissue was excised and divided into small pieces, treated with dispase II, and placed over the denuded cornea, without AMT or fibrin glue. They demonstrated that the epithelium expanded to form islands around the grafts 1 week after surgery and the corneal defect was completely epithelialized at 2 weeks, similar to the results of SLET. They went on to describe that the single surface layer of epithelial cells was CK3-positive, and basal cells were p63 positive similar to corneal epithelial cells [19]. Hence, they concluded that the direct placement of autologous oral mucosal tissue, without ex-vivo cell culture, could be a good alternative to limbal allografting in bilateral LSCD. This report is the first clinical validation of the SOMET technique proposed by Inamochi et al. The modifications from the animal study were that there was no prior treatment of the mucosal tissue with dispase, we used AMG on the cornea, and used fibrin glue to secure the transplants, analogous to SLET for the treatment of LSCD. Here the AMG would act as a scaffold for the mucosal epithelial cells to proliferate rapidly. We also performed simultaneous bulbar surface reconstruction with MMG to address the severe symblepharon, analogous to a conjunctival autograft or MMG being performed along with SLET to address the conjunctival deficiency [17]. This approach was not only effective in anatomically restoring the ocular surface but also resulted in significant functional improvement in unaided and contact lens-corrected visual acuity.

4. Conclusion

This study highlights the potential of SOMET as a surgical alternative to allogeneic limbal transplantation and COMET for the treatment of bilateral LSCD. It combines the strengths of SLET and COMET, while avoiding the need for long-term systemic immunosuppression or laboratory cell cultivation. However, a prospective study with a larger sample size is required to validate the long-term clinical outcomes of SOMET in different cases of bilateral LSCD.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Patient perspective

"I was blind and disfigured in my left eye. The surgery helped me in seeing better, but what I was most impressed with was the improvement in the cosmetic appearance of the eye. This has helped improve my self-confidence and self-esteem."

Declaration of competing interest

The authors have no conflict of interest.

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