Novel Therapy to Treat Corneal Epithelial Defects: A Hypothesis with Growth Hormone

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ABSTRACT Impaired corneal wound healing that occurs with ocular surface disease, trauma, systemic disease, or surgical intervention can lead to persistent corneal epithelial defects (PCED), which result in corneal scarring, ulceration, opacification, corneal neovascularization, and, ultimately, visual compromise and vision loss. The current standard of care can include lubricants, ointments, bandage lenses, amniotic membranes, autologous serum eye drops, and corneal transplants. Various inherent problems exist with application and administration of these treatments, which often may not result in a completely healed surface. A topically applicable compound capable of promoting corneal epithelial cell proliferation and/or migration would be ideal to accelerate healing. We hypothesize that human growth hormone (HGH) is such a compound. In a recent study, HGH was shown to activate signal transducer and activators of transcription-5 (STAT5) signaling and promote corneal wound healing by enhancing corneal epithelial migration in a co-culture system of corneal epithelial cells and fibroblasts. These effects require an intact communication between corneal epithelia and fibroblasts. Further, HGH promotes corneal wound healing in a rabbit debridement model, thus demonstrating the effectiveness of HGH in vivo as well. In conclusion, HGH may represent an exciting and effective topical therapeutic to promote corneal wound healing.

KEY WORDS corneal epithelial defect, growth factors, human growth hormone, insulin-like growth factor-1, persistent corneal epithelial defects (PCED), wound healing

I. INTRODUCTION

Corneal wound healing is a highly regulated process that requires the proliferation and migration of epithelial cells,[1] interactions between epithelial cells and stromal fibroblasts, and actions of various growth factors and cytokines.[2,3] Rapid re-epithelialization of the injured area is extremely important in reducing the risk of potentially blinding microbial superinfection and corneal opacification. When the process is altered by ocular surface disease, trauma, systemic disease, and/or surgical intervention, corneal epithelial wound healing can be delayed, leading to corneal defects that will not "close." These persistent corneal epithelial defects (**PCED**) result in corneal scarring, ulceration, opacification, corneal neovascularization, and, ultimately, visual compromise and loss of vision.[1]

There is an unmet need for a therapy that could help heal the cornea pharmaco-therapeutically. Currently, "bandage" methods are used to help re-epithelialize a cornea. These may include aggressive lubricants, debridement and patching, application of a bandage contact lens,[4] human amniotic membrane (AM),[5] use of autologous serum[6,7] as a supernatant to

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Abbreviations

AM	Amniotic membrane
bFGF	Basic fibroblast growth factor
EGF	Epidermal growth factor
GH	Growth hormone
HA	Hyaluronic acid
HGH	Human growth hormone
IGF	Insulin-like growth factor
IGFR	IGF-1 receptor
KGF	Keratocyte growth factor
LSCD	Limbal stem cell deficiency
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
PCED	Persistent corneal epithelial defect
P13K	Phosphoinositide 3-kinase
p-STAT5	Phospho—STAT5
rHGH	Recombinant HGH
STAT5	Signal transducer and activators of transcription-5

provide necessary growth factors, and suturing of the lids via a tarsorrhaphy.[8] In severe cases, a conjunctival graft may be placed over the cornea.[9] Often, PCEDs recur and are costly to the patients and the healthcare provider.

Agents that can accelerate wound closure by increasing the migration and proliferation of corneal epithelial cells are of interest because of their potential benefit for patients with persistent epithelial damage from dry eye, surgical or non-surgical trauma, refractive interventions, corneal abrasion, non-healing corneal ulcers, and neurotrophic corneas secondary to diabetes, cranial nerve palsies, and herpetic keratitis.[1] Such patients could benefit significantly from a topical preparation that could stimulate the epithelial cells to migrate and proliferate and thus heal.

II. CHARACTERISTICS OF PERSISTENT CORNEAL EPITHELIAL DEFECTS

A. Prevalence

PCED can be defined as a loss of the integrity of the corneal surface and/or a defect in the epithelium caused by injury or disease, which does not heal within the usual timeframe of several days, but persists for weeks or even months. The condition generally has a duration of less than 1 year, but it can recur years later. Underlying disease states that may result in such defects include exposure keratopathy, limbal stem cell deficiency (LSCD), previous herpes simplex or herpes zoster infection, diabetic keratopathy, neurotrophic keratopathy, and severe dry eye. The defects can also be associated with corneal transplant surgery or diabetic vitrectomy used to treat these diseases.[10,11]

The actual incidence of PCED is not known but can be estimated based on assumptions regarding the likely causes of PCED; i.e., the incidences of the underlying conditions can be used to estimate the number of cases of PCED. Overall, the estimated number of PCEDs per year in the United States (U.S.) is roughly 73,434-99,465 cases, based on a recent U.S. population of approximately 314,037,169 (http://www.census.gov/population/www/popclockus.html). Thus, the total incidence of PCEDs is less than 200,000 in the U.S. and is therefore considered an orphan disease in this region.

B. Causes

1. Exposure Keratopathy

Exposure keratopathy is the result of incomplete lid closure (lagophthalmos) that causes drying of the cornea despite normal tear production.[12] Among the causes of exposure keratopathy are cranial nerve palsy, aneurysm, herpes infection, and lid malposition. No data have been identified concerning the prevalence of PCED in patients with exposure keratopathy; however, the number of cases is expected to be quite low.

2. Limbal Stem Cell Deficiency

LSCD is a disease in which the stem cell functions of the limbus and the barrier function of the limbus fail. LSCD can result from trauma or disturbance due to autoimmune processes or infectious or neoplastic conditions. The reduced ability of limbal stem cells to divide and repopulate the cornea as epithelial cells leads to an unstable epithelial surface, pain, decreased vision, and stromal scarring.[13] Corneal epithelial defects appear and fail to heal normally.[14]

3. Herpes Simplex

The incidence of ocular herpes simplex in the U.S. is 20.7 per 100,000 person-years, and the prevalence is 149