Corneal Neovascularization and the Utility of Topical VEGF Inhibition: Ranibizumab (Lucentis) Vs Bevacizumab (Avastin)

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ABSTRACT Corneal avascularity is necessary for the preservation of optimal vision. The cornea maintains a dynamic balance between pro- and antiangiogenic factors that allows it to remain avascular under normal homeostatic conditions; however, corneal avascularity can be compromised by pathologic conditions that negate the cornea's "angiogenic privilege." The clinical relevance of corneal neovascularization has long been recognized, but management of this condition has been hindered by a lack of safe and effective therapeutic modalities. Herein, the etiology, epidemiology, pathogenesis, and treatment of corneal neovascularization are reviewed. Additionally, the authors' recent findings regarding the clinical utility of topical ranibizumab (Lucentis®) and bevacizumab (Avastin®) in the treatment of corneal neovascularization are summarized. These findings clearly indicate that ranibizumab and bevacizumab are safe and effective treatments for corneal neovascularization when appropriate precautions are observed. Although direct comparisons are not conclusive, the results suggest that ranibizumab may be modestly superior to bevacizumab in terms of both onset of action and degree of efficacy. In order to justify the increased cost of ranibizumab, it will be necessary to demonstrate meaningful treatment superiority in a prospective, randomized, head-to-head comparison study.

KEY WORDS angiogenesis, bevacizumab, cornea, corneal angiogenic privilege, hemangiogenesis, lymphangiogenesis, neovascularization, ranibizumab, vascular endothelial growth factor, VEGF

I. INTRODUCTION

Corneal transparency and optimal vision require an avascular cornea.[1] The cornea possesses redundant antiangiogenic mechanisms that actively maintain corneal avascularity, collectively accounting for corneal angiogenic privilege.[2] Although the human cornea is avascular under normal homeostatic conditions, corneal angiogenic privilege is not absolute. Corneal neovascularization (**NV**) is a sight-threatening condition that can develop in response to inflammation, hypoxia, trauma, or limbal stem cell deficiency.[1] A variety of therapeutic modalities have been employed in the treatment of corneal NV with variable, and often limited, clinical success.[3]

Vascular endothelial growth factors (**VEGF**s) regulate the development and maintenance of blood and lymphatic vessels.[4] VEGF neutralizing agents have proven invaluable in the treatment of pathologic conditions such as neovascular age-related macular degeneration and diabetic retinopathy; furthermore, recent findings suggest that VEGF inhibition may be an effective therapeutic modality for corneal NV.[5-7] Because systemic anti-VEGF exposure is associated with severe and potentially life-threatening adverse events, it is prudent to pursue the route of administration that minimizes systemic exposure.[8] Herein, we present a brief review of corneal NV; additionally, we summarize our recent findings regarding the clinical utility of topical ranibizumab (Lucentis®; Genentech, Inc.; San Francisco, CA) and bevacizumab (Avastin®; Genentech, Inc.) in the treatment of corneal NV.

Accepted for publication January 2012.

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Supported in part by NIH grants EY-12963 (RD) and EY-19098 (RD).

The authors have no proprietary or commercial interests in any concept or product discussed in this article.

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OUTLINE

Abbreviations

Ang	Angiopoietin
CD	Cluster of differentiation
FasL	Fas ligand
FGF	Fibroblast growth factor
FND	Fine-needle diathermy
HSV	Herpes simplex virus
IA	Invasion area
IL	Interleukin
MMP	Matrix metalloproteinase
MT-MMP	Membrane-type MMP
mVEGFR	Membrane-bound VEGF receptor
NA	Neovascular area
NSAID	Nonsteroidal anti-inflammatory drug
NV	Neovascularization
PDGF	Platelet-derived growth factor
PD-L1	Programmed death-ligand 1
PDT	Photodynamic therapy
PEDF	Pigment epithelium-derived factor
PlGF	Placental growth factor
sVEGFR	Soluble VEGF receptor
TGF	Transforming growth factor
TIMP	Tissue inhibitor of metalloproteinases
TNF	Tumor necrosis factor
TSP	Thrombospondin
VC	Vessel caliber
VEGF	Vascular endothelial growth factor
VEGFR	VEGF receptor
WHO	World Health Organization

II. BACKGROUND

A. Etiology and Epidemiology

According to the World Health Organization (**WHO**), approximately 285 million people are visually impaired worldwide; of these, approximately 39 million are blind.[9] Corneal disease is second only to cataract as the leading cause of nonrefractive visual impairment worldwide.[10] Despite aggressive international prevention efforts, corneal disease remains the most common cause of blindness in some developing countries.[11] Corneal NV is a potential sequela of numerous conditions, including infection, injury, surgery, autoimmune disease, limbal stem cell deficiency, neoplasm, dystrophy, and contact lens use.[2] Over a decade ago, it was estimated that there are up to 1.4 million cases of corneal NV in the USA alone.[12] The clinically evident pattern of vessel invasion (eg, vascular pannus, superficial stromal NV, or deep stromal NV) is often indicative of the etiology of corneal NV; for example, deep stromal NV generally develops in response to interstitial keratitis (eg, herpetic stromal keratitis) or significant ocular trauma (Figure 1).[2,12] Corneal NV ultimately alters visual acuity by inducing stromal edema, cellular infiltration, lipid deposition, hemorrhage, and scarring.[13]

Corneal NV is a potential complication of numerous bacterial, parasitic, and viral infections. Trachoma is the world's leading infectious cause of blindness.[14] The WHO estimates that there are 146 million cases of *Chlamydia trachomatis* infection worldwide, and 5.9 million people are blind or at immediate risk of blindness from trachomatous trichiasis.[14] Recurrent episodes of trachoma can damage the eyelid, resulting in eyelash-induced corneal abrasions, ulcerations, NV, and scarring.[15] Onchocerciasis, commonly referred to as river blindness, is the second most common infectious cause of blindness worldwide.[16] The causative filarial nematode, *Onchocerca volvulus*, infects an estimated 37 million people, and 270,000 cases of