Mr. Allen W. Hill  
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Re: Corneal Endothelial Wound Healing

Dear Allen:

INTRODUCTION

The integrity of corneal endothelium is essential for long-term maintenance of corneal clarity. Therefore, recovery of the corneal endothelial monolayer from the mechanical trauma effects of surgery is important to understand. Endothelial cells are resilient as a function of several factors. Irrespective of this layer of cells being amitotic after birth, the cells also have a remarkable ability to enlarge during loss, arising from any cause, thereby initiating a reasonably well understood sequence of events in the wound healing process.

THE RESILIENCY OF THE CORNEAL ENDOTHELIUM

Corneal endothelium exhibits resiliency which is due to:

- the increased peripheral endothelial cell number, for migration,
- the ability of the endothelial cells to form tight junctions to maintain the endothelial barrier,
- the increase in pump sites under stress and
- the ability of the endothelial cell to shift their metabolism for membrane repair.
During corneal endothelial wound repair, the 3 stage process includes initial coverage of the injured area by elongated endothelial cells, forming a functional but incomplete barrier and minimal pump density. As the cells enlarge, and form irregular polygons, there is an increase in pump sites. The final stage of the wound healing is the remodeling of the cells into stable hexagons, where the pump sites balance the endothelial leakage, and where the corneal thickness returns to normal.

In cases of intraocular surgery\textsuperscript{7,8,9,10,11,12} the increased number of paracentral and peripheral endothelial cells allow endothelial cell spreading (peripheral to central) and remodeling to maintain the central endothelium and physiological function\textsuperscript{1,2,4,11,12}. The second method corneal endothelial cells use to withstand stress is to maintain their tight junctions. The tight junctions are the last to break down and are the first to reform during wound healing. The third mechanism that the corneal endothelial cells use to withstand stress is their ability to increase their pump site density. All mechanisms, in combination, provide for the cornea's resilience and stability in the face of surgical insult from surgery. Keratoplasty provides one of the best examples of the resiliency of corneal endothelium\textsuperscript{5,6}, since the viability of the endothelial layer of donor corneas has been demonstrated in transplantations over the past 50 years, using many preservation conditions for the donor tissue. After transplantation, the endothelial cells undergo a progressive wound healing response of migration of endothelial cells over the wound edge to the periphery, the development of tight junctions to establish the endothelial barrier, and once the barrier is formed the cells increase the pump sites. Post-transplantation, the corneas may experience significant loss of cell density. In the published clinical series on PKP over the long-term (10-15 years), decrease of ECD is significant without corresponding clinically meaningful shifts in CV or % Hex. This suggests that the long term corneal grafts with low ECD are stabilizing and have a reasonable potential to outlast the life expectancy of the recipients. ECD at 700-800 cells/mm\textsuperscript{2} or slightly below are adequate to maintain corneal transparency provided the CV and % Hex are within normal limits\textsuperscript{5,6,12}. Similarly, in eyes with glaucoma\textsuperscript{2}, decreases in endothelial cell density were observed, while the CV and % Hex were determined to be normal, which indicates endothelial stability.

Thus one can observe that the corneal endothelium responds to surgery, which is undertaken for many different reasons, in a similar wound healing manner:

- Migration of cells from peripheral reserve
- Re-establishment of barrier tight junctions
- Establishment of increased pump site density
- Adjustment of metabolism for cell repair
- Remodeling of the endothelial monolayer to a stable configuration (hexagons)\textsuperscript{12}

**REVIEW OF THE IMT CLINICAL RESULTS**

The behavior of the endothelium in eyes with the IMT device implanted show the same response pattern. The CV and % Hexagonality data from the VisionCare IMT002 clinical trial supports that the endothelial morphology/morphometry is stable, and
ongoing endothelial cell remodeling contributes to changes in endothelial cell density in the context of this stable monolayer environment. The data from the patients implanted with the IMT models WA 2.2Y and 3.0Y support a corneal endothelium that shows a stable endothelium without continual stress.

REFERENCES


Sincerely yours,

[Signature]

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HFE/pn