

## Response to Wirostko et al. Re: “Cross-Linked Hyaluronic Acid as Tear Film Substitute” by Posarelli et al. (*J Ocul Pharmacol Ther* 2019;35(7):381–387)

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Dear Editor,

**W**E REALLY APPRECIATE THE relevance of the letter by Wirostko et al.;<sup>1</sup> the authors highlighted the importance of thiolated carboxymethyl hyaluronic acid (CMHA-S), called Ocular Bandage Gel (OBG), not only as a tear film substitute but also in protecting the ocular surface and accelerating corneal wound healing.<sup>2,3</sup>

The aim of our review<sup>4</sup> was primarily to explain the structure of crosslinked hyaluronic acid (HA) and its use as a tear film substitute in dry eye disease; based on its physical properties this molecule displays greater stability and better resistance on the ocular surface. Hence, the possible role of crosslinked HA in repairing damaged ocular surface is undoubtable.<sup>2,3</sup>

The role of HA in wound healing process seemed to be associated with 2 mechanisms: the first one, observed at short term (15 h), seemed related with an increased corneal cell proliferation, the second one, observed at longer term (12–16 days), should involve cells migration.<sup>2</sup>

HA's effect on epithelial cell proliferation was similar to that of epidermal growth factor and superior to fibronectin.<sup>5</sup> Moreover, HA is a ligand of a cell surface adhesion molecule (CD44) expressed by normal human corneal epithelial cells. During wound healing processes, the interaction between CD44 on the cells and HA may facilitate a rapid migration of cells and consequently a rapid closure of the wound.<sup>6</sup>

Crosslinked HA, through formation of covalent bonds between the chains of the molecule, displays a 3-dimensional network, with greater viscoelasticity and consequently a better resistance to degradation in stress conditions, such as during wound healing processes. Another relevant property involved in healing processes of crosslinked molecules is to show a superior resistance to enzymatic degradation.<sup>4</sup> Therefore, the ability of ocular bandage gel (OBG) to accelerate corneal re-

epithelialization after photorefractive keratectomy<sup>3</sup> validates the role of CMHA-S not only in dry eye disease but also after trauma or surgery. Finally, gel viscosity can be modulated via crosslinking processes; this feature is fundamental for human application. Blurred vision is a common complaint of patients suffering from dry eye and using gel formulation eyedrops.<sup>7</sup>

In conclusion, preliminary reports about the use of cross-linked HA in humans both as a tear supplement and in ocular wound care are encouraging in terms of efficacy and safety; further clinical studies will increase the relevance of these initial and promising pieces of evidence.

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