Topical use of arthritis drug provides relief for dry eye disease

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Dry eye disease (DED) is a common condition that causes discomfort, visual disturbance and potentially damaging ocular surface inflammation that greatly impacts a person's quality of life. An estimated nine million people in the United State alone suffer from significant DED; millions more may have milder forms or experience discomfort when exposed to low humidity or contact lens use. DED, the most common reason people visit ophthalmologists, is estimated to cost $55 billion in annual direct and indirect costs to society in the nation alone.

In a new study, researchers from the Massachusetts Eye and Ear, Harvard Medical School, and Brigham and Women's hospital show that topical anakinra (Kineret; Amgen Inc.), a recombinant version of human IL-1Ra approved for treatment of rheumatoid arthritis, significantly reduced dry eye symptoms. Topical use of a protein-based biologic agent in treatment of DED is unprecedented and may herald a new era of highly targeted topical molecular treatments for ocular surface disease. The results of this clinical trial are described online first in *JAMA Ophthalmology*.

"We began looking at the possible therapeutic effects of IL-1Ra over 10 years ago in my laboratory," said Reza Dana, M.D., MSc., M.PH., senior author. "This clinical trial was a significant milestone in our research. The results clearly show us not only that we can possibly help the millions of people affected by dry eye disease worldwide, but that biologics such as this have the potential to provide targeted therapies for other ocular ailments, as well."

Early studies have shown that DED is associated with significant overexpression of inflammatory cytokines, including interleukin 1 (IL-1), in the eye. However the options to treat the inflammatory component of DED have been limited and some of these involved adverse effects. Anti-inflammatory medications such as tetracycline derivatives, topical corticosteroids, and cyclosporine A that have been successfully used in the treatment of DED downregulate the production of IL-1 and upregulate the production of IL-1 receptor antagonist (IL-1Ra) at the ocular surface. The IL-1Ra suppresses IL-1-mediated inflammation by completely inhibiting the binding of IL-1a and IL-1b to IL-1 receptor I. Topical IL-1Ra has been successfully used to treat experimental rodent models of corneal transplant rejection, dry eye disease, allergic conjunctivitis and alkali burn-associated ocular inflammation.

The researchers performed a randomized, double-masked clinical trial designed to assess the safety of efficacy of topical IL-1Ra in patients with DED. Seventy-five participants in the 16-week study were randomly allocated in the 2:2:1 ratio to receive eye lubricant (artificial tear), 2.5% of anakinra or 5% of anakinra. Patients found the anakinra was well tolerated and was significantly more effective than the eye lubricant in improving the signs and symptoms of DED. Anakinra at 2.5% was four times more likely than the eye lubricant to bilaterally eliminate corneal staining, a clinical measurement of ocular surface disease. Topical anakinra also significantly reduced dry eye symptoms six times more effectively than the eye lubricant, which is capable of independently improving the signs of DED. Moreover, termination of anakinra (but not the lubricant) application at week 12 lead to a clear trend toward increased symptoms between weeks 12 and 16, confirming the therapeutic effect of the drug.

"We have never seen results such as this before in a trial to treat dry eye disease. We possibly have found a safe, well tolerated eye drop that can

treat the underlying cause of dry eye rather than just temporarily mask the symptoms. We are excited about the positive results we saw in the data and with our patients who found relief in their symptoms and were able to return to some of their normal daily activities," Dr. Dana said.

Provided by Massachusetts Eye and Ear Infirmary