DED TREATMENTS ON THE HORIZON: TOLERABILITY AND EFFICACY OF THE MELANOCORTIN AGONIST PL9643

Reviewing the results of a Phase 2 study.

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Recognizing and treating dry eye disease (DED) before anterior segment surgery is one of the most important things a clinician can do during the preoperative evaluation. When detected, DED should be treated prior to surgical intervention in order to maximize not only postoperative outcomes but also patient comfort and quality of life. Patients who experience DED preoperatively are more likely to be dissatisfied with their visual outcomes if the condition is left untreated, even if they are 20/20.

DED is multifactorial, affecting the cornea, conjunctiva, and the entire ocular surface. Most often, it is characterized by ocular irritation. It can, however, also cause visual impairment in severe cases.[1,2] The signs and symptoms of DED do not always correlate, and they can fluctuate over time.[3,4] Basic lifestyle changes such as minimizing alcohol intake, ensuring adequate fluid intake, using humidifiers, and getting adequate sleep can help to minimize the effects of DED. Another firstline treatment option is prescribing artificial tears.[5,6] When these options do not adequately control the DED symptoms, therapy becomes more complicated. Likewise, corticosteroid eye drops, for example, can improve the signs and symptoms of moderate to severe DED, but they are recommended for short-term use only. Supplementation with omega-3 fatty acids works to block proinflammatory cytokines and the inflammatory process,[6,7] but some report insufficient improvement with current formulations.[6,8,9]

NEW OPTION ON THE HORIZON

Melanocortins, a family of neuropeptide hormone agonists first discovered in pituitary tumor cells, are present in numerous tissues including the eye.[10] Melanocortin hormones act through binding to melanocortin receptors (MCRs) types 1 through 5,[11-16] and MCR agonists have been found to play an important role in resolving inflammation.[13,14]

Endotoxin-stimulated neutrophils or macrophages binding endogenous a-melanocyte-stimulating hormone (a-MSH) or a synthetic MCR agonist results in inhibition of transcription factor nuclear factor kappa B. This suppresses the production of proinflammatory cytokines interleukin 1 (IL-1), IL-6, and IF-8.[13,17] As a result, there is an increase in the production of the antiinflammatory cytokine IL-10 possibly through extracellular signal-regulated kinase and activating protein-1 activation within the leukocytes and monocytes (Figure).

Melanocortin agonists that target MCR1 and MCR5 in particular have been shown to treat ocular conditions such as DED and diabetic retinopathy with at least the same efficacy as glucocorticoids but with a better safety profile.[18,19]

Palatin Technologies has designed two classes of peptide agonists—pan

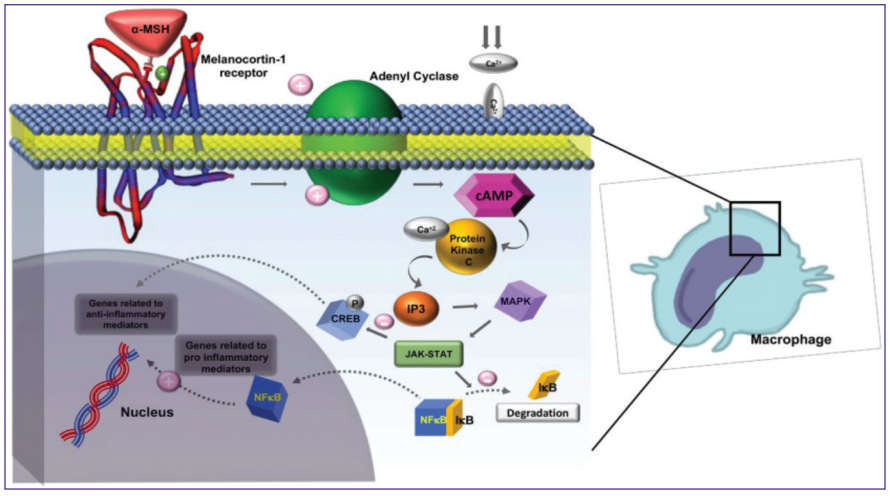

Figure. Melanocortin receptor pathway and inflammation inhibition in macrophages. The binding of a-melanocyte-stimulating hormone (a-MSH) to melanocortin 1 receptor (MC1r) activates adenyl cyclase and generates cAMP response element-binding protein (CREB). This activates protein kinase C, leading to elevation of Ca2+ into the cell and the production of inositol triphosphate (IP3). IP3 then activates the mitogen-activated kinase (MAPK) and Janus kinase-signal transducer and activator of transcription proteins (JAK-STAT) pathways, inhibiting the degradation of inhibitor of nuclear factor kappa B (IkB) and activating CREB to produce downstream antiinflammatory effects.

From Moscowitz AE, Asif H, Lindenmaier LB, Calzadilla A, Zhang C, Mirsaeidi M. The importance of melanocortin receptors and their agonists in pulmonary disease. *Front Med (Lausanne)*. 2019;6:145.

agonists, which bind to multiple MCRs (not MCR2), and selective agonists of MCR1—that emulate the activity of endogenous a-MSH. In preclinical animal models, these compounds reversed the pathology in inflammatory and autoimmune diseases, including rheumatoid arthritis, inflammatory bowel disease, DED, uveitis, and diabetic retinopathy.

PHASE 2 STUDY

Study design. My colleagues and I were involved in a prospective, randomized, placebo-controlled, double-masked multicenter trial to evaluate the efficacy and tolerability of PL9643 (Palatin Technologies), a MCR pan-agonist, in adults with mild, moderate, or severe DED. The study duration was 12 weeks.[20]

A total of 160 patients were randomized one-to-one in a double-masked vehicle-controlled manner to receive either 1 µg/mL PL9643 ophthalmic solution or vehicle, topically, three times daily. All patients received placebo during a 2-week run-in period; 99 had mild DED and 61 had moderate or severe DED. Clinical assessments were performed at 2, 4, 8, and 12 weeks after randomization. The median age in the PL9643 and vehicle groups was 69.5 years (range, 51-80 years) and 69 years (range, 51-84 years), respectively, and 71% and 70% of patients, respectively, were women.

The co-primary objective endpoint to indicate signs of DED was inferior corneal fluorescein staining, and the co-primary subjective endpoint to indicate the presence of symptoms was ocular discomfort using a single-question scale (0 = no discomfort to 4 = constant discomfort). Secondary endpoints included fluorescein staining, lissamine green dye staining, tear breakup time (TBUT), and the patient-reported symptoms of burning, dryness, eye discomfort, foreign body sensation, grittiness, ocular discomfort, itching, and stinging.

Results. In the subset of patients with moderate or severe DED, PL9643 showed statistically significant improvements in both objective and subjective primary endpoints over vehicle. In the overall population, however, the differences were not significant.

At week 12, PL9643 had reduced inferior corneal and conjunctival fluorescein staining (LS mean difference [SEM], -0.55 [0.2], $P<.01$) and total conjunctival lissamine green staining (LS mean difference [SEM], -0.81 [0.29], $P<.01$). There was also a significant reduction in total conjunctival lissamine green staining at week 2 (LS mean difference [SEM], -0.67 [0.30], $P<.03$), and TBUT improved significantly from baseline at week 12 ($P<.05$).

Patients with moderate to severe DED who received PL9643 showed improvement in ocular discomfort over placebo (LS mean change from baseline, -0.2 at week 2 and -0.1 at week 12). Statistically significant improvements and trends toward improvement were seen at week 2 with PL9643 compared with placebo for ocular discomfort (LS mean difference [SEM], -0.4 [0.19], $P<.02$), ocular burning (LS mean difference [SEM], -0.6 [0.32], $P<.06$), and eye discomfort (LS mean difference [SEM], -7.4 [4.59], $P<.01$).

The safety and tolerability profile of PL9643 was positive. There were 39 treatment-emergent adverse events (TEAEs), 16 and 23 of which occurred in patients receiving PL9643 and placebo, respectively. Nine ocular adverse events were reported, but only one (chalazion) in patients receiving PL9643. This, however, was not considered related to study drug.

CONCLUSION

Overall, PL9643 provided significant subjective and objective benefits at weeks 2 and 12 for patients with moderate or severe DED. This ophthalmic solution was well tolerated, and there was no ocular TEAEs or pain related to the instillation of the eye drops. These positive results, which were seen across multiple signs and symptoms of DED, support continued development of PL9643 as a novel therapy for DED. A Phase 3 trial comparing PL9643 to vehicle in more than 300 patients with moderate to severe DED is planned. ■

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