Effective treatment for rare sight-threatening infection: Clinical trial

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A new drug candidate, based on pioneering UCL and Moorfields Eye Hospital research and currently under development by SIFI S.p.A., has been found to be highly effective in treating a rare sight-threatening eye infection in a new international clinical trial.

The findings, published in *Ophthalmology*, describe the efficacy and safety of the first drug candidate for the treatment of Acanthamoeba keratitis (AK), applying a novel and evidence-based treatment protocol.

AK is one type of microbial keratitis (corneal infection)—a condition that results in inflammation of the cornea (the eye's clear protective outer layer). AK can cause extreme levels of pain as well as light sensitivity.

AK is relatively uncommon, affecting about one in 37,000 contact lens wearers per year in the UK, but it is responsible for about half the cases of sight loss in this group. Contact lens wearers face an increased risk of the disease; a UCL and Moorfields team recently found that people who wear reusable contact lenses face nearly four times the risk of those wearing daily disposables, while showering with lenses in and wearing lenses overnight also each raised the risk by more than threefold.

The treatment being studied, low concentration polihexanide (PHMB 0.02%), was first compounded and used in the 1990s to treat AK, introduced by a team co-led by this latest study's lead author, Professor John Dart, and is widely recommended as a treatment for AK, but it is not a licensed drug, and treatment outcomes have been variable.

Professor John Dart (UCL Institute of Ophthalmology and Moorfields Eye Hospital NHS Foundation Trust) said, "Acanthamoeba keratitis in contact lens users can be prevented by following safe use advice: Do use daily disposables if possible, wash and dry hands before handling lenses, maintain good lens and lens case hygiene, and don't use them when bathing swimming or showering, or use goggles and renew the lens after use, don't wear them overnight, and don't use them every day.

"Unfortunately, when the disease does develop the course is prolonged, and in the recent past, one-third of patients have had poor visual

outcomes with one quarter requiring surgery at some stage.

"PHMB 0.02% is an effective and widely recommended unlicensed therapy, but many clinicians have trouble accessing it, mistakes in formulation can sometimes lead to poor results, and the lack of a proven treatment protocol has resulted in wide variations in how the drug is used and in treatment outcomes. We hope that our new robust findings with polihexanide 0.08% will be a game changer for AK treatment, by improving access and the consistency of treatment, addressing currently unmet patient needs."

The Phase 3 randomized controlled double blind clinical trial followed a Phase 1 trial in healthy volunteers which showed that a significantly higher concentration (0.08%) of polihexanide was safe to use. The Phase 3 trial was run in accordance with European Medicines Agency scientific advice and compared the efficacy and safety of a high concentration of polihexanide (0.08%) as a monotherapy to a widely used dual therapy, combining a lower dose of PHMB (0.02%) with propamidine.

The study involved the analysis of 127 people being treated for AK at six hospitals across Europe (in England, Italy and Poland).

The researchers found both formulations to be highly effective when used with the detailed drug delivery protocol, with medical cure rates of 110/127 (87%) overall and for each treatment individually, meaning 87% of people were cured of AK without needing surgery, one of the highest ever reported for AK. The treatment failure rate was 17/127 (13.4%), nearly half of whom required therapeutic corneal transplant surgery. The overall transplant surgery rate of 8/127 (6.3%) is one of the lowest reported in any case series of AK.

The researchers say that the widely recommended dual therapy was more effective than usual in this trial because clinicians were strictly following

a set treatment protocol. In addition, the new monotherapy has advantages over dual therapy, as the simplicity reduces the risk of errors in practice.

Dr. Vincenzo Papa (Head of Scientific Affairs at SIFI), a co-author of the study, said, "This publication in *Ophthalmology* ... further encourages our continued efforts to make polihexanide 0.08% (Akantior) available to patients with AK, as the first approved orphan medicinal product. Given the extreme burden of the disease and the high unmet medical need, we are proud of the high efficacy outcomes in the robust setting that the trial created, especially when compared with the efficacy rates of 60% reported with the current best treatment."

Based on the comprehensive quality, preclinical and clinical data package generated over 15 years of research, SIFI is now seeking regulatory approvals for polihexanide 0.08% in Europe, the UK and the US.

Juliette Vila Sinclair Spence, Rare Disease Patient Advocate & Chairwoman, Acanthamoeba Keratitis Eye Foundation, commented, "Exciting news: AK Warriors (aka patients) are now one step closer to receiving the first-ever product with a standardized protocol for Acanthamoeba keratitis. This is starting to bring light to the end of the tunnel."

AK causes the front surface of the eye, the cornea, to become painful and inflamed, due to infection by Acanthamoeba, a cyst-forming microorganism. The most severely affected patients (a quarter of the total) end up with less than 25% of vision or become blind following the disease, and face prolonged treatment. Overall, 25% of people affected require corneal transplants to treat the disease or restore vision.

Contact lens use is now the leading cause of microbial keratitis in

patients with otherwise healthy eyes in countries in the global north. Sight loss resulting from microbial keratitis is uncommon but Acanthamoeba, although a rare cause, is one of the most severe and is responsible for about half of those contact lens users who develop sight loss after keratitis. Approximately 90% of AK cases are associated with avoidable risks. In recent years a UCL and Moorfields team has found AK to be on the rise in South-East England.

More information: John K.G. Dart et al, The Orphan Drug for Acanthamoeba Keratitis (ODAK) trial: PHMB (polihexanide) 0.08% and placebo versus PHMB 0.02% and propamidine 0.1%, *Ophthalmology* (2023). DOI: 10.1016/j.ophtha.2023.09.031

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