Stem cell therapy for dry eye disease

On December 8, 2023, Michael Møller-Hansen defended his thesis "Mesenchymal stem cell therapy in aqueous deficient dry eye disease" at the Graduate School of Health and Medical Sciences, University of Copenhagen. The PhD project was conducted at the Dept. of Ophthalmology, Rigshospitalet. The supervisors were Prof. Steffen Heegaard, MD, DMSc, and Associate Prof. Anne Katrine Wiencke, MD, PhD, from the Dept. of Clinical Medicine, University of Copenhagen, Denmark.

Michael Møller-Hansen
University of Copenhagen, Denmark

Dry eye disease is characterized by ocular dryness, irritation, and blurred vision and can have a significant impact on the patient's quality of life. This condition can be particularly severe in patients with aqueous-deficient dry eye disease (ADDE) from Sjögren's syndrome (SS), an autoimmune disease that affects the salivary and lacrimal glands (LGs). Current ADDE treatments are often limited to symptomatic relief. I conducted a literature review to explore the current surgical interventions for ADDE in humans. These included procedures involving the eyelids and tear ducts, transplantation of amniotic membrane or salivary glands, injections around the tear ducts, and cell-based injections into the LG. Mesenchymal stem cells (MSCs) have shown promise in regenerating damaged tissue and reducing inflammation in various diseases. Previous studies in animal models have suggested that MSCs could be effective in treating ADDE. Thus, this thesis aimed to investigate the safety and efficacy of injecting MSCs into the LG as a treatment option for patients with ADDE secondary to SS. MSCs derived from healthy donors' adipose tissue (ASCs) were cultured in a laboratory, frozen, and thawed ready for use. In the safety study, we performed the first human trial involving the administration of a single injection of ASCs into the LG of one eye in seven patients with severe ADDE. The primary objective was to test the safety of this treatment, with the secondary objective of assessing improvements in subjective and objective signs of dry eye. The results of the trial showed no serious side effects within 4 months of follow-up. On average, we found a 40% reduction in dry eye symptoms assessed with the Ocular Surface Disease Index (OSDI) questionnaire. Additionally, in the treated eye, we found a significant decrease in tear osmolarity, an increase in tear film stability, and an increase in tear production. To further investigate the efficacy of this treatment, we performed a randomized clinical trial comparing the ASC injection into the LG with the injection of a vehicle (the excipient in which the ASCs are dissolved) and observation (no intervention). The study included 20 participants receiving ASC injections, 20 receiving vehicle injections, and 14 observed without intervention. All injections were performed transcutaneously using ultrasonic guidance (**Figure 1**). The participants were assessed for 12 months following treatment. Both intervention groups showed a significant reduction of approximately 40% in subjective symptoms. This improvement was evident at the 1-week follow-up and persisted until the 12-month follow-up. The observation group did not experience any change in OSDI score. The ASC group exhibited a significant mean increase in non-invasive tear break-up time (NIKBUT) of 6.48 s (149%) at the 4-week follow-up, which was significantly higher than that in the vehicle group ($p=0.04$). Moreover, the ASC group showed a significant increase in NIKBUT compared to the observation group at the 12-month follow-up ($p=0.004$). In both the ASC and vehicle groups, we observed a significant increase in Schirmer test scores at the 4- and 12-month follow-ups. This thesis contributes valuable findings and a new treatment option for patients with ADDE due to SS. Injection of ASCs into the LG was shown to be safe and improve subjective dry eye symptoms and tear film stability.

Key points:

- New therapeutic options are needed to target severe aqueous-deficient dry eye disease.
- Injection of adipose-derived mesenchymal stem cells (ASCs) into the lacrimal gland is safe and feasible, without significant adverse effects.
- Injection of ASCs reduced symptoms and signs of severe dry eye.

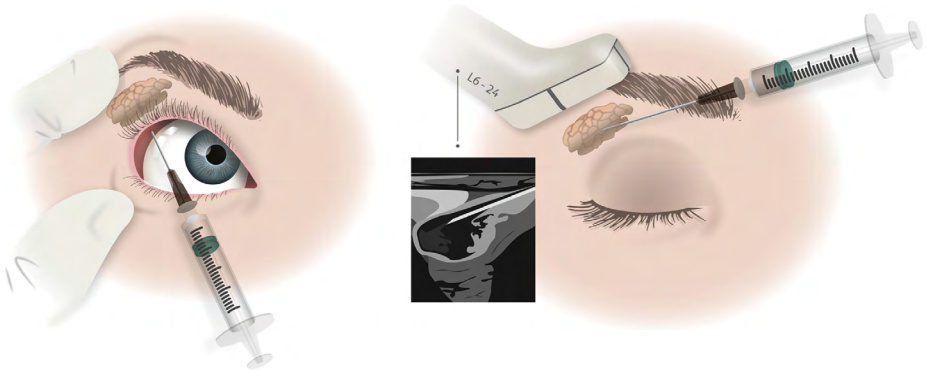

Figure 1. Injection methods into the lacrimal gland (LG). Left: Transconjunctival injection as performed in the safety study. Right: Transcutaneous injection using ultrasound imaging in which the LG can be identified as performed in the randomized clinical trial.

Future directions:

- Further studies may determine the mode of action for ASCs and vehicle treatments.
- Research should assess whether ASCs could be used as an anti-inflammatory therapeutic option for other eye diseases.

References

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