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MINIREVIEWS

Evaluating the efficacy of stem cells in treating severe dry eye disease

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Abstract

Dry eye disease (DED) is a multifactorial disorder that disturbs ocular surface equilibrium, considerably diminishing quality of life. Present therapies only offer symptomatic alleviation. Stem cell treatment, especially mesenchymal stem cells (MSCs), has surfaced as a viable approach for tissue regeneration and immunological regulation in DED. Preclinical and early clinical investigations indicate that MSCs can improve lacrimal gland functionality, diminish inflammation, and facilitate corneal regeneration. Nonetheless, obstacles persist in enhancing MSC viability, determining the optimal MSC source, and guaranteeing sustained therapeutic effectiveness. Additional extensive randomized clinical trials are required to confirm the efficacy of MSC-based therapies for severe DED.

Key Words: Dry eye disease; Stem cell therapy; Mesenchymal stem cells; Corneal regeneration; Exosome; Cornea; Clinical trials

Core Tip: Stem cell treatment offers a potential regenerative strategy for addressing severe dry eye disease by restoring lacrimal gland function, regulating inflammation, and facilitating corneal restoration. This review incorporated current preclinical and clinical discoveries, contrasting various mesenchymal stem cell (MSC) sources and their modes of action. Notwithstanding promising outcomes, obstacles persist in enhancing MSC viability, standardizing administration techniques, and guaranteeing prolonged safety. More extensive randomized controlled studies are necessary to determine the effectiveness of MSC-based treatments in severe dry eye disease.

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INTRODUCTION

Dry eye disease (DED), also known as keratoconjunctivitis sicca, is a chronic condition characterized by diminished tear film stability and elevated tear hyperosmolarity, which may result in peripheral nerve injury[1,2]. Patients experience various symptoms, including pain, blurred vision, and discomfort and in some cases neuropathic ocular pain[1,2]. Risk factors include environmental humidity, age, sex, use of computer screens, and ethnicity[1]. Globally, the incidence of DED is between 5.5% and 22.7%, and it is one of the most common causes of referrals to ophthalmology[3]. Given how common DED is, there is unfortunately no definitive cure available. Current management is focused on the symptoms and involves a step ladder approach, commencing with artificial lubricating tears, topical steroids, and nutritional supplements[4].

The primary function of the tear film is to protect and lubricate the ocular surface[1]. DED can be divided into evaporative, aqueous deficiency, and mixed types[5]. Evaporative DED results from an unstable lipid layer, leading to tear evaporation and hyperosmolarity due to meibomian gland dysfunction (MGD). Aqueous deficiency DED (ADDE) is due to lacrimal gland (LG) damage and can be exacerbated by thyroid disease, diabetes, and rosacea[5]. Other causes of LG damage are damage or radiation to the head and neck[6]. ADDE is further divided into Sjögren's and non-Sjögren's dry eye.

In the Western hemisphere, Sjögren's syndrome (SS) is the most common cause of severe ADDE and is characterized by lymphocytic infiltration of the salivary gland and the LG, causing dry mouth and eyes[7]. Females are more likely to have SS, and the ocular sequelae can involve microbial keratitis, ulceration, vascularization, perforation, and scarring[8]. SS can be primary or associated with other autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus. The diagnosis of SS in patients with DED requires more than just clinical signs and symptoms. Primary SS is confirmed if a patient with clinical signs and symptoms of SS scores 4 or more points from Table 1. This review focused on the current research and development of clinical treatments for severe DED utilizing stem cells and their products.

PATHOGENESIS OF DED

The Tear Film and Ocular Surface Dry Eye Workshop II redefined DED in 2017 as "a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability, hyperosmolarity, ocular surface inflammation, and neurosensory abnormalities play etiological roles"[5].

Table 1 Diagnostic criteria for primary Sjogren's syndrome

Diagnostic criteria	Points
Positive anti-SSA antibody from a peripheral blood sample	3
Focal lymphocytic sialadenitis	3
Abnormal ocular staining score 5 out of 7	1
Schirmer test score ≤ 5 mm/5 minutes	1
Unstimulated salivary flow rate ≤ 0.1 mL/minute	1

SSA: Sjogren's-syndrome-related antigen A.

Recent research has shown that mesenchymal stem cells (MSCs) exhibit therapeutic benefits *via* many pathways, including the release of anti-inflammatory cytokines like interleukin (IL)-10 and transforming growth factor-beta (TGF-β), control of immune cell activity, and facilitation of epithelial regeneration[9]. Exosomes generated from MSCs include bioactive compounds that promote corneal epithelial repair and suppress apoptotic pathways. Furthermore, stem cells rejuvenate LG functionality by developing into glandular cells and releasing growth factors that facilitate tissue healing [10-14]. These strategies jointly mitigate the inflammatory and degenerative processes linked to DED.

ROLE OF CHRONIC INFLAMMATION IN DED

Chronic inflammation is a main contributing factor affecting LG dysfunction and secretion leading to ADDE[9]. SS, diabetes, chronic graft-*vs*-host disease, and aging are all risk factors for chronic inflammation. When tear cytokines in patients with DED were analysed, there were increased levels of IL-1, IL-4, IL-6, IL-8, IL-10, IL-17A, tumour necrosis factor-α, TGF-β, metalloproteinase (MMP)-3, and MMP-9 compared with controls[10-14]. The increased cytokine levels were also correlated with DED severity[10-14]. Levels of IL-6 were significantly higher in patients with DED with the release of inflammatory factors such as IL-17[15]. IL-17 also promoted MMP-3 and MMP-9 release, which are involved in wound healing and inflammation[16,17]. MMPs compromise the tight connections among epithelial cells, resulting in the deterioration of the corneal barrier. Chronic inflammation arises from the "vicious cycle" of dry eye illness (Figure 1): Several elements from the ocular and external environment contribute to tear film instability, subsequently resulting in tear hyperosmolarity. This leads to cellular death in the cornea and conjunctiva, inciting inflammation that subsequently activates the meibomian glands and LGs, negatively impacting the tear film. Thus, anti-inflammatory therapy is fundamental in the management of dry eye illness.

IMMUNE RESPONSE IN DED

The ocular surface in DED has elevated levels of C-C chemokine ligands (CCL) 3, CCL 5, CCL20, and T helper (Th) cell chemokines, which can promote proinflammatory Th cell migration to the ocular surface. CCL20 is responsible for the cellular homing of Th17 in DED. De Paiva *et al*[18] demonstrated that Th1 and Th17 cells were present in the conjunctiva with high expression of IL-17 and interferon (IFN)-γ. IFN-γ reduces the ability of goblet cells to secrete mucin, which is important for immune tolerance of the ocular surface[19,20]. Anti-inflammatory regulatory T cells ($CD4^+$) are important modulators of the immune system, maintaining self-antigenic tolerance and preventing autoimmune disease locally and systemically (*e.g.*, SS, chronic graft-*vs*-host disease) by suppressing autoreactive T cells[21]. Treatments that can target IL-17 or inhibit Th17 function can potentially reduce the progression and severity of DED[19].

NEURONAL INJURY AND DED

In neurotrophic keratitis, impaired corneal innervation leads to corneal epithelial breakdown, tear film disruption due to decreased lacrimation reflex, and increased ocular surface inflammation. The corneal nerve plexus is amongst the densest in the human body and is populated with sensory nerves. The release of inflammatory factors in the tears or any other changes within the ocular surface environment will travel through afferent signalling and stimulate efferent innervation, gland secretion, and blink activity[21]. Disruption or dysfunction in the nerve conduction pathway can lead to DED by aggravating ocular surface injury and the persistence of inflammation[22]. The peripheral sympathetic and parasympathetic nerves regulate secretion by the conjunctival goblet cells[22].

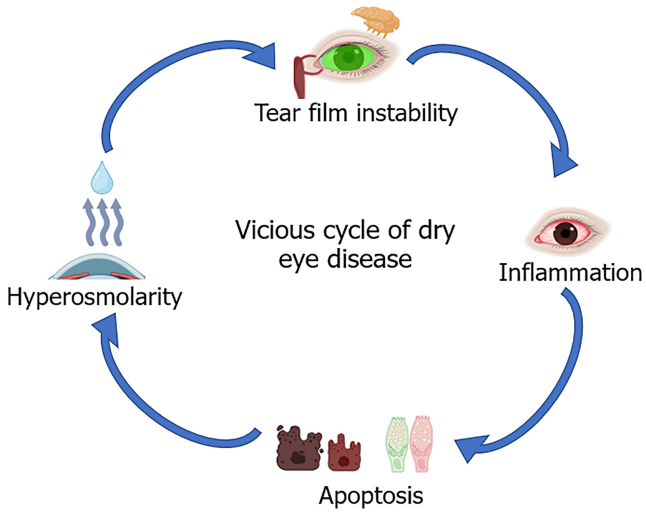

Figure 1 Vicious cycle of dry eye disease.

CURRENT TREATMENT OPTIONS FOR DED

Management of DED often begins with artificial tears to improve tear film stability, with some demonstrating clinical efficacy[23]. Patients test out different eye drop brands in a trial-and-error manner; although there are guidelines for ocular lubricant pathways, these vary depending on the locality. Patients with ADDE, especially due to SS, will have higher levels of ocular surface inflammation compared with patients with non-SS DED; artificial tears alone do not provide effective symptom relief[24]. Kim *et al*[25] have shown that topical steroids and/or cyclosporin A can significantly reduce ocular signs and symptoms of DED. Short-term topical steroids can be effective in reducing ocular surface inflammation. If a step up in treatment is needed, then serum eye drops are another efficacious option[26]. If there is MGD, then lid massage and intense pulsed light therapy can reduce ocular surface inflammation[27].

Surgical treatments such as punctal plugs and lid tarsorrhaphy (partial or complete) have been used as an adjuvant to topical therapy. More novel procedures, such as amniotic membrane transplant, have also been utilized. Amniotic membrane transplant does improve DED signs and symptoms, but the effect is temporary, with a mean relapse time of 25 days[28]. More experimental procedures, such as platelet-rich plasma (PRP) injections into the LG, have been attempted and show objective and subjective improvements in ADDE signs[29]. PRP production has no standardization. Therefore, studies may have different PRP compositions, making comparisons difficult[30]. There is a lack of randomized clinical trials comparing PRP injection with another interventional treatment and no long-term follow-up more than 3 months post-procedure. In summary, these treatments provide symptom relief only and do not target the underlying causes of DED. Hence, novel regenerative therapies are needed.

STEM CELL THERAPY IN DED

Stem cells are undifferentiated cells that have the potential to differentiate into a variety of specialized cells (differentiation) and can produce identical stem cells (self-renewal)[31]. Stem cells can be embryonic or adult, with embryonic stem cells derived from blastocysts having pluripotency (differentiating into three germ layers). This makes embryonic stem cells suitable for use in regenerative medicine. However, there are ethical issues and risks of tumorigenicity. Adult stem cells repair damage and maintain cellular turnover but have reduced differentiation ability ranging from unipotent (single specialized cell) to multipotency (differentiating in one germ layer). Adult stem cells exist in the LG and can differentiate into cells of the acinar, myoepithelium, and lacrimal ducts[32]. These can potentially be utilized to restore LG function. Alternative sources of adult stem cells in the human body include MSCs. MSCs have been studied for tissue and organ regeneration due to their wide availability and lack of cellular surface immune-stimulating markers. Allogenic use will avoid a graft-*vs*-host response[33].

Tissues within the body have some regeneration ability after injury, and adult stem cells have been found in specialized niches. Animal studies have identified stem cell niches within cultured *in vitro* LG organoids[34]. The LG stem cells (LGSCs) were isolated and identified with a variety of established techniques: Western blot; flow cytometry; immunostaining; and PCR[34-37]. Stem cell markers such as nestin and P63 were used to identify LGSCs[38,39]. These markers were found to be increased in number after leukin-1 injury, suggesting that stem cells were mobilized in response to the injury[34,40].

Different culture methods have been reported in these studies, and they can influence the characteristics and quality of identified stem cells and their phenotype. The explant culture method was utilized by many studies with cell strainers, flow cytometry, and Matrigel to isolate cells[35,39,41,42]. The cultured cells were classified by immunohistochemical staining and morphology[35,39,42]. Xiao and Zhang[39] used a serum-free medium and maintained LGSCs in a three-

dimensional culture. Three-dimensional cell culture differs from traditional two-dimensional cell culture (cells grown in a monolayer) in that it allows cell growth and interaction with the surrounding extracellular framework in three dimensions. This technique has the potential to be used as an alternative to animal models of DED and transplantation.

LG REGENERATION

The LG contributes to the aqueous component layer of the tear film and supplies numerous proteins, enzymes, antimicrobial factors, and immunoglobulins that are protective of the ocular surface[43-45]. Disruption of the LG would significantly affect the tear film and its protective role[45]. The LG acinar cells produce primary LG fluid that is subsequently modified by the ductal cells with electrolytes and water[46]. The myoepithelial cells are located around the acini and have a contractile function allowing regular fluid secretion to the ocular surface[47]. The ductal cells supply 30% of the LG fluid[43].

There are two main research areas within the field of LG regeneration. The first is to identify key signalling pathways and proteins for LG inflammation and promotion of regeneration[35,38]. The second is the development of treatments for direct *in situ* LG regeneration with cultured stem cells or stem cell products[35,36,48,49]. Studies in regenerative mechanisms of living tissues have demonstrated the importance of the epithelial-to-mesenchymal transition that allows cell proliferation and repair. You *et al*[34] found the mobilisation of nestin-positive MSCs within LG regeneration. Key regulatory proteins that coordinated the transition were snail and vimentin, which are potentially new therapeutic targets for LG repair mechanisms[34].

A signalling pathway that directs cells towards the epithelial-mesenchymal transition within the LG is the bone morphogenic protein-7 pathway[40]. This pathway has been shown to ameliorate tissue damage in an animal model of renal injury by reducing inflammation and fibrosis[50]. Therefore, the addition of exogenous bone morphogenic protein-7 to damaged LG or in combination with transplantation can potentially reduce the inflammatory process during LG regeneration.

Extracellular ATP is used as fuel during the inflammatory process. Basova *et al*[51] demonstrated that blocking Pannexin-1 reduced the import of extracellular ATP and led to reduced inflammation and improved donor cell survival during LG regeneration. Several stem cell types and products have been investigated for direct application in LG regeneration. The most promising are MSCs with human-subject clinical trials in progress (Table 2).

THE POTENTIAL OF MSCS IN DRY EYE TREATMENT

MSCs are adult stem cells with multipotency and self-renewal abilities, differentiating into osteoblasts, myocytes, adipocytes, and chondroblasts[52]. Bone marrow-derived MSCs (BM-MSCs), adipose-derived MSCs (AD-MSCs), umbilical cord-derived MSCs (UC-MSCs), and cornea-derived MSCs (C-MSCs) are frequently utilized in research. The MSCs are well-defined according to criteria set by the International Society for Cell and Gene Therapy[53]. Specific surface markers associated with MSCs include CD73, CD90, and CD105 as well as the ability to adhere to plastic surfaces [54]. Endothelial and hematopoietic markers are absent and a low expression of major histocompatibility complex molecules. This allows MSCs to have immune privilege and can be transplanted without immunosuppression.

MSCs communicate with the existing immune cells and release paracrine factors (secretomes) that maintain tissue homeostasis, immunomodulation, and regeneration[55]. When MSCs are exposed to proinflammatory factors (*e.g.*, tumour necrosis factor-α), they will differentiate into an immunosuppressive phenotype. Liu *et al*[56] found that MSCs can activate $CD4^+$ T cells and reduce IFN-γ production. Several studies have found dysregulation of the enzyme indoleamine 2,3-dioxygenase in autoimmune diseases such as SS that is induced by IFN-γ[57,58]. Indoleamine 2,3-dioxygenase modulates innate and adaptive immune responses resulting in suppression of effector T cells[59]. MSCs also can suppress the differentiation and maturation of dendritic cells, inhibit the action of natural killer cells, and neutrophil apoptosis *via* its secretome function[53]. Consequently, MSC transplantation has been used to treat SS and refractory rheumatoid arthritis[60,61].

The immunoregulatory and anti-inflammatory characteristics of MSCs render them suitable for severe dry eye illness associated with ocular surface inflammation, limbal stem cell deficiency (LSCD), and nerve injury. Adipose tissue has been a good source of MSCs and is used widely in research. Galindo *et al*[62] found good tolerance, anti-inflammatory, and anti-angiogenic effect when utilizing human AD-MSCs to treat LSCD in a rabbit model. The site of administration and concentration of AD-MSCs affect the efficacy, with Fuentes-Julián *et al*[63] giving local and intravenous AD-MSCs during keratoplasty surgery that resulted in neovascularization and inflammation. Indirect action by AD-MSCs through its paracrine signalling factors such as vascular endothelial growth factor, TGF-β, and insulin-like growth factor can improve wound healing in corneal tissues[64]. AD-MSCs were cultured with human corneal epithelial cells, and their secretomes were observed to inhibit the epithelial-mesenchymal transition in the cornea[65].

Bone marrow served as the initial source for the isolation of MSCs, and BM-MSCs have been delivered through subconjunctival and intravenous injections as well as corneal transplantation. Shukla *et al*[66] found that subconjunctival and intravenous MSC delivery had better therapeutic effects compared with other methods in a corneal injury murine model. In a proof-of-concept clinical trial, Calonge *et al*[67] found that BM-MSCs could promote corneal epithelium proliferation in LSCD.

Table 2 Comparison of different stem cell sources in dry eye disease treatment

Stem cell source	Differentiation potential	Anti-inflammatory properties	Clinical applications	Key findings
AD-MSCs [74,76,84]	Multipotent	High secretion of anti-inflammatory cytokines	Used in limbal stem cell deficiency and corneal wound healing	Show promising anti-inflammatory and regenerative effects
BM-MSCs [36,85,86]	Multipotent	Moderate secretion of anti-inflammatory cytokines	Used in severe DED and Sjögren's syndrome-related dry eye	Effective in reducing inflammation and promoting epithelial proliferation
UC-MSCs [75,86-90]	Higher plasticity than AD-MSCs and BM-MSCs	High immunomodulatory potential	Investigated for corneal and lacrimal gland regeneration	Exhibits low immunogenicity and enhances corneal healing

AD-MSCs: Adipose-derived mesenchymal stem cells; BM-MSCs: Bone marrow-derived mesenchymal stem cells; UC-MSCs: Umbilical cord-derived mesenchymal stem cells; DED: Dry eye disease.

UC-MSCs are harvested from umbilical cord blood, which is more abundant and easier to collect than other sources. Their expression profile more closely resembles embryonic stem cells with pluripotency and can differentiate into corneal epithelium, stromal, and endothelial cells. With demonstrated low immunogenicity and graft-*vs*-host disease, UC-MSCs have been used in corneal transplantation, with Coulson-Thomas *et al*[68] using human UC-MSCs to resolve corneal defects in a murine model of mucopolysaccharidosis VII. However, there is variation in the yield of harvested UC-MSCs and methods of isolation and culture can be complex, limiting clinical application in a real-world setting[69]. MSCs with multidirectional differentiation potential are also located in the anterior corneal stroma next to the limbal stem cells.

Jabbehdari *et al*[70] found that C-MSCs had greater differentiating potential to corneal cells than MSCs derived from other sources. Culture techniques that combined limbal epithelial cells with C-MSCs were superior compared with culture with only limbal epithelial cells[71]. C-MSCs from human cadaveric corneoscleral rims were successfully expanded and found to express stem cell genes[72]. Inhibition of corneal neovascularization has been demonstrated by Eslani *et al*[73] in mouse corneas that have been treated with C-MSCs. When directly engrafted into corneal wounds in mice, these autologous stem cells prevented the formation of fibrotic tissue and promoted regeneration of ablated stroma that was indistinguishable from native tissue[72].

Various sources of MSCs demonstrate distinct biological features, potentially affecting their effectiveness in the treatment of dry eye illness. BM-MSCs are well described and have significant immunomodulatory capabilities; nevertheless, their invasive extraction method restricts clinical use. AD-MSCs are readily accessible and have a high multiplication rate, rendering them appropriate for therapeutic use. UC-MSCs demonstrate less immunogenicity and enhanced pluripotency, providing benefits for tissue regeneration. C-MSCs are particularly advantageous for ocular applications, demonstrating enhanced differentiation potential into corneal epithelial cells. Future research should concentrate on direct comparison assessments to identify the most suitable MSC source for therapeutic use in DED.

THE APPLICATION OF MSCS IN SEVERE DED

The core mechanism underlying clinical DED is tear film instability. The tear film is maintained by tissues of the conjunctiva, cornea, LG, and eyelid. Numerous preclinical *in vivo* animal studies have demonstrated the potential of MSCs in DED (Table 2). MSCs have been studied in mice, canines, and rabbits[36,74-76]. Studies have used MSC-derived exosomes and other derivatives with promising results and no adverse events. Canines are used as DED models because they develop dry eyes naturally due to an immune-mediated inflammatory reaction affecting the LG, like humans[77]. Bittencourt *et al*[74] demonstrated transplantation of AD-MSCs around the LGs in 15 canines with ADDE to be safe and increased tear production significantly, resulting in clinical improvement during the 12-month follow-up. In another study, Villatoro *et al*[76] injected allogeneic adipose-derived stromal cells in 12 canines with refractory bilateral ADDE that resulted in improved tear production, and clinical signs were maintained up to 9 months after initial treatment.

The primary constituent of the lipid layer of the tear film is meibum, which is secreted by the meibomian gland. The quality and quantity of meibum will deteriorate in MGD and reduce tear film stability. MSCs have been used to treat a BAC-induced mouse model of DED resulting in improvement post-treatment[78]. The therapeutic mechanism remains unclear, despite the observable infiltration of MSCs into the meibomian gland cells. The main component of the mucoprotein layer in the tear film is mucosal protein, secreted by the conjunctival goblet cells. Diseases or processes resulting in the loss of goblet cell function will decrease tear film stability and activate the inflammatory cascade. The number of conjunctival goblet cells has been shown to increase after treatment with MSCs[78,79]. LG inflammation and atrophy can also lead to decreased tear secretion. MSCs have been shown to promote LG regeneration. Møller-Hansen *et al*[80] demonstrated the safety and feasibility of an AD-MSC injection treatment in 7 patients with ADDE with follow-up to 16 weeks in a phase I trial.

MSCs exercise their therapeutic benefits in dry eye illness by paracrine signalling, immune response regulation, and direct cellular differentiation. MSCs release trophic substances, including hepatocyte growth factor, insulin-like growth factor-1, and TGF-β, which enhance LG epithelial cell proliferation and diminish inflammatory cytokine production[56-

58]. Furthermore, exosomes produced from MSCs have been demonstrated to suppress apoptosis in corneal epithelial cells by downregulating caspase-3 activation. Moreover, the treatment efficacy of MSCs may vary between evaporative DED and ADDE. In evaporative DED, MSCs predominantly demonstrate anti-inflammatory effects *via* regulating meibomian gland activity and diminishing lipid layer instability. In ADDE, MSCs facilitate LG regeneration and augment aqueous tear output. These particular functions underscore the necessity for customized MSC-based treatments that address the underlying pathophysiology of DED.

Although numerous preclinical studies have shown the effectiveness of MSCs in DED models, there remains a lack of agreement regarding the ideal cell source and delivery method. Certain research implied that AD-MSCs demonstrate enhanced anti-inflammatory capabilities, whilst others indicate that UC-MSCs provide higher differentiating potential. Moreover, clinical studies are constrained, predominantly emphasizing safety over effectiveness. Future study must focus on direct comparisons of various MSC sources to determine optimal procedures for clinical use.

These preclinical animal studies have utilized comparatively brief follow-up durations, generally spanning only a few weeks to months. This is a substantial constraint as it precludes a thorough assessment of long-term effectiveness or possible hazards including cancer. Future investigations on MSC treatment must include prolonged follow-up periods of no less than 12 months, focusing specifically on any indications of atypical cellular proliferation or fibrosis in the treated tissues. Table 2 shows the comparison of different stem cell sources.

EVALUATION OF MSC THERAPY: CLINICAL EVIDENCE AND CHALLENGES

There are very few human clinical trials examining the use of MSCs in DED despite numerous preclinical studies (Table 3). While the phase I trial conducted by Møller-Hansen *et al*[80] indicated safety and feasibility, the limited sample size (n = 7) constrains the generalizability of the results. Limited sample numbers can result in statistical biases, unintended outcomes, and an inflation of treatment effects. Consequently, extensive randomized controlled trials with sufficient statistical power are essential to substantiate the clinical effectiveness of MSC treatment in dry eye illness. Minimum clinically important difference (MCID) has been proposed by the Tear Film and Ocular Surface Dry Eye Workshop II report as a primary endpoint in DED clinical trials. The MCID was the smallest amount of change that was significant for the patient[81,82]. OSDI score was recommended as one of the primary endpoints in DED trials for severe disease (score more than 33) with a MCID of 7.3 to 13.4 points[83].

Recently, a randomized controlled trial evaluating the safety and efficacy of AD-MSC injections into the LG of patients with ADDE was completed[80]. This double-blinded trial included 54 patients with severe ADDE secondary to SS and were randomized to AD-MSC injection (treatment; n = 20), placebo (n = 20), or an observation group (n = 14). The sample size was based on an 80% power (2-sided t-test), a significance level $P < 0.05$, and additional allowance for potential dropout for the duration of the trial. At the 12-month follow-up there was a significant reduction in primary endpoint measures (OSDI score) in the treatment group along with objective clinical signs[80]. Of interest, significant improvement in subjective OSDI scores was noted in the placebo group, who had an injection of 10% dimethyl sulfoxide (CryoStor10) with no AD-MSCs, possibly as a result of the anti-inflammatory and/or placebo effect. Clinically, only the AD-MSC treatment group showed objective clinical improvement at 4 weeks and 12 months of follow-up.

The assessment of MSC treatment in severe DED necessitates a comprehensive examination of clinical outcomes, comparative effectiveness, and constraints. Clinical investigations have indicated enhancements in corneal epithelial integrity, tear secretion, and a decrease in inflammatory markers subsequent to MSC treatment. Diversity in MSC sources, delivery methods, and follow-up lengths hinders direct comparisons. Future research must emphasize the standardization of MSC therapy techniques and the identification of appropriate MSC sources for sustained effectiveness. Table 3 shows the clinical trials in this sector.

CONCLUSION

MSC-based therapy for DED is feasible, and it has an exciting scope for the treatment of damaged tissue. Future research must concentrate on many critical domains to improve the practical use of MSC treatment for dry eye condition. Primarily, enhancing the survival rates of MSCs is a priority as transplanted MSCs frequently have restricted persistence *in vivo*. Exploration of strategies like genetic manipulation to augment MSC resilience or coadministration with biomaterials is warranted. MSC delivery strategies necessitate enhancement to optimize therapeutic effectiveness. Although topical and subconjunctival delivery have demonstrated potential, innovative biomaterial scaffolds and sustained-release formulations may enhance MSC retention at the ocular surface.

Prolonged clinical studies with extensive follow-up periods are crucial for evaluating safety issues, including cancer and immunological rejection. Moreover, discrepancies in stem cell production techniques among research hinder direct comparisons. The establishment of standardized protocols for the isolation, characterization, and growth of MSCs will be crucial for their effective therapeutic use. Examining the function of MSC-derived exosomes in DED treatment is a potential approach since exosomes may provide a cell-free therapeutic option with comparable regeneration advantages. Finally, a uniform reporting structure for adverse events in MSC treatment must be established to enable accurate comparisons among trials. Resolving these fundamental difficulties would facilitate the effective incorporation of MSC-based treatments in clinical ophthalmology.

Table 3 Registered clinical trials for mesenchymal stem cells in dry eye disease from the ClinicalTrials.gov database (July 31, 2024)

No.	Study	Diagnosis	Drug	Intervention	Patient number	Location(s)	Trial reference number (NCT)
1	Effect of UMSCs derived exosomes on dry eye in patients with cGVHD	Dry eye	UMSC-Exo	Transconjunctival injection	27	Guangzhou, Guangdong, China	04213248
2	Mesenchymal stem cell therapy of dry eye disease in patients with Sjögren's syndrome	Keratoconjunctivitis sicca, in Sjögren's syndrome	AD-MSCs	Transconjunctival injection	40	Copenhagen, DK, Denmark	04615455
3	Safety and efficacy of pluripotent stem cell-derived mesenchymal stem cell exosome (PSC-MSC-Exo) Eye drops treatment for dry eye disease post refractive surgery and associated with blepharospasm	Dry eye post refractive surgery	PSC-MSC-Exo	Topical eye drops	12	Hangzhou, Zhejiang, China	05738629
4	Treatment with allogeneic adipose-derived mesenchymal stem cells in patients with aqueous deficient dry eye disease	Aqueous deficiency dry eye disease, keratoconjunctivitis sicca	AD-MSCs	Lacrimal gland injection	7	Copenhagen, DK, Denmark	03878628
5	Allogeneic mesenchymal stem cells transplantation for primary Sjögren's syndrome (pSS)	Keratoconjunctivitis sicca, in Sjögren's syndrome	AlloMSC	Intravenous infusion (single dose)	20	Nanjing, Jiangsu, China	00953485
6	Therapeutic effect of stem cell eye drops on dry eye disease	Dry eye syndromes	MSC eye drops	Topical eye drops	10	Nanjing, Jiangsu, China	05784519

UMSC-Exo: Umbilical cord-derived mesenchymal stem cell exosome; AD-MSCs: Adipose-derived mesenchymal stem cells; PSC-MSC-Exo: Pluripotent stem cell-derived mesenchymal stem cell exosome; AlloMSC: Allogeneic mesenchymal stem cell; MSC: Mesenchymal stem cell; cGVHD: Chronic graft-*vs*-host disease; pSS: Primary Sjögren's syndrome; UMSC: Umbilical cord-derived mesenchymal stem cell.

FOOTNOTES

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