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Review Article

Therapeutic Use of Mesenchymal Stem Cells in Ophthalmology: A Review of Clinical Evidence

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Abstract

Degenerative ocular disorders, glaucoma, cataracts and age-related macular degeneration, are major contributors to global blindness and visual impairment. Other conditions, such as limbal stem cell deficiency, dry eye disease and retinitis pigmentosa, lead to significant ocular distress and progressive vision loss, profoundly affecting patients' quality of life. Conventional therapies primarily focus on symptom management and slowing disease progression, offering limited potential for tissue restoration. In recent years, stem cell therapy and regenerative medicine have emerged as promising strategies to address these limitations. Mesenchymal Stem Cells (MSCs) induced Pluripotent Stem Cells (iPSCs) and other progenitor cells have demonstrated the capacity to differentiate into ocular-specific cell types, modulate inflammation, secrete neurotrophic factors and promote tissue repair. Preclinical studies and early clinical trials have shown encouraging results in corneal regeneration, retinal repair and optic nerve protection, highlighting the translational potential of these therapies. Despite these advances, challenges remain, including optimizing cell sourcing, delivery methods, immune compatibility and long-term safety. This review provides a comprehensive overview of current stem cell-based approaches in ophthalmology, discussing underlying mechanisms, preclinical and clinical evidence and future directions for regenerative interventions aimed at restoring visual function. Stem cell therapy offers a transformative approach with the potential to shift ophthalmic care from palliative management to true tissue regeneration, offering hope for patients with previously untreatable ocular disorders.

Keywords: Ophthalmology; Stem Cell; Stem Cell Therapy; Clinical Trial; Secretome

Definition of Mesenchymal Stem Cells

Stem Cells (SCs) are specialized cells characterized by self-renewal and the capacity to differentiate into one or more lineages with varying potency [1]. Stem cell-based strategies have become central to regenerative medicine because they can, in principle, replace damaged cells or modulate hostile tissue microenvironments. Embryonic Stem Cells (ESCs) originally derived from the inner cell mass of pre-implantation blastocysts, are pluripotent and can generate derivatives of all three germ layers [2,3]. Their

self-renewal capacity, pluripotency and relative genomic stability make them attractive candidates for cellular therapies [4]. However, ethical considerations and translational constraints have limited their clinical adoption.

Induced pluripotent stem cells (iPSCs) are generated by reprogramming somatic cells through overexpression of transcription factors (Oct4, Sox2, Klf4 and c-Myc), yielding cells that closely resemble ESCs in differentiation potential and self-renewal [5-7]. Despite strong therapeutic promise, concerns persist regarding genetic and epigenetic stability, tumorigenic risk and manufacturing standardization, particularly when scaled for clinical use.

Mesenchymal stem/stromal cells (MSCs) were initially described as fibroblast-like, plastic-adherent colony-forming cells isolated from bone marrow, capable of differentiating into mesodermal lineages [8]. MSCs are now recognized as multipotent stromal populations present in many adult tissues and perivascular niches [9]. Their translational appeal is driven by relative ease of isolation and expansion, limited ethical concerns and potent immunomodulatory and trophic effects that extend beyond classical "replacement" biology.

Because MSCs are heterogeneous and lack a single definitive marker, the International Society for Cellular Therapy (ISCT) proposed minimal criteria: plastic adherence; expression of CD73, CD90 and CD105; absence of CD14, CD34, CD45 and HLA-DR; and trilineage differentiation into adipocytes, chondrocytes and osteoblasts *in-vitro*. Importantly, these criteria support phenotypic identification, but do not fully capture functional potency, which varies by tissue source, donor factors, culture conditions and manufacturing protocols.

Secretome of Mesenchymal Stem Cells

MSCs can be isolated from multiple tissues, including bone marrow, adipose tissue, placenta, dental pulp, synovium, endometrium and other sources [10]. Under defined conditions they can exhibit differentiation capacity across mesodermal and, more controversially, non-mesodermal lineages. Clinically, however, the predominant therapeutic rationale for MSCs in many indications has shifted from durable differentiation to paracrine signaling and immunomodulation.

Over the past two decades, autologous and allogeneic MSC-based interventions have been explored for inflammatory and degenerative diseases. MSCs may modulate immune responses and promote tissue repair by reshaping local cytokine environments, increasing regulatory cell populations and supporting cell survival under stress [11]. Nonetheless, cell-based therapies raise translational concerns including ectopic tissue formation, immune incompatibility, pro-tumor signaling in permissive settings, pulmonary microvascular trapping after systemic delivery and inconsistent potency across products.

These limitations have driven interest in MSC secretome as a cell-free therapeutic alternative. The MSC secretome includes soluble factors (cytokines, chemokines, growth factors, immunoregulatory mediators) and Extracellular Vesicles (EVs), potentially enabling more standardized dosing and safety testing, easier storage/administration and reduced risks associated with living cell persistence [12]. Preclinical and early clinical studies have evaluated MSC secretome approaches across multiple disease areas, with reported benefits in musculoskeletal repair, dermatologic disorders and degenerative conditions [13]. However, secretome effects appear highly context-dependent: depending on microenvironmental cues, secretome components may promote tissue protection or contribute to pathological remodeling, underscoring the need for controlled manufacturing and indication-specific evaluation [14].

EVs are commonly classified by size and biogenesis [15]. Small EVs (often termed exosomes, ~30-200 nm) typically express markers such as CD63, CD9, CD81, TSG101, Alix and flotillin and carry proteins, lipids and nucleic acids (including miRNAs) capable of modulating recipient cell pathways [15]. Medium EVs (microvesicles/ectosomes, ~200-1000 nm) bud from the plasma membrane and share overlapping cargo profiles; large EVs include apoptotic bodies and oncosomes, the latter associated with cancer cell-derived biomarkers [16]. For ocular applications, EV-based delivery is increasingly investigated as a strategy to harness MSC paracrine benefits while reducing surgical burden and long-term cell persistence risks.

Ophthalmological Diseases and the Rationale for Regeneration

Visual impairment affects more than two billion people globally [17]. Age-related conditions and refractive errors account for a substantial share and epidemiologic projections indicate increases in glaucoma and Age-related Macular Degeneration (AMD)

over coming decades, alongside rising cataract burden with population aging [18]. Many chronic eye diseases progress silently for years (e.g., glaucoma) and delayed presentation is compounded by low public awareness, misattribution to "normal aging", and limited access to routine screening [19,20]. Modifiable lifestyle risk factors (smoking, metabolic disease, nutritional deficiency and UV exposure) contribute to multiple ocular pathologies and remain important targets for prevention strategies [21,22].

Despite major therapeutic advances, many ophthalmic disorders remain limited by irreversible loss of specialized retinal or optic nerve cells and by chronic inflammatory and oxidative microenvironments that drive progressive degeneration. Regenerative medicine aims to restore structure and function by promoting cell survival, replacing lost cells and/or modulating pathological tissue environments. Approaches include gene therapy, scaffolds, soluble factors, tissue engineering and cell-based or cell-free interventions.

Multiple cell platforms have been investigated in ophthalmology, including MSCs, ESCs/iPSCs, retinal progenitor cells and Retinal Pigment Epithelium (RPE)-directed therapies. In this review, we focus on MSC-based interventions and related regenerative strategies for ocular disease, emphasizing mechanisms of action, delivery considerations, clinical evidence quality and translational barriers rather than providing an extended description of conventional therapies.

Mesenchymal Stem Cells in Retinal and Optic Nerve Disease

Retinal degenerative diseases (including glaucoma-associated optic neuropathy, retinitis pigmentosa, AMD and diabetic retinopathy) are leading causes of vision loss and blindness. In many of these conditions, conventional therapies primarily slow progression or treat complications, but do not restore lost neuronal or photoreceptor populations. MSCs are proposed as therapeutic candidates due to immunomodulatory activity, secretion of neurotrophic factors, anti-apoptotic effects and the potential, still debated *in-vivo*, for limited differentiation toward retinal-like phenotypes [23].

However, the clinical evidence base for MSCs in ophthalmology remains heterogeneous and largely early-phase. Variability in MSC source (bone marrow, adipose, umbilical cord/Wharton's jelly), manufacturing and expansion protocols, dosing, delivery route and outcome definitions complicates cross-study comparisons. Moreover, several studies report improvements that may be transient, emphasizing the need to evaluate durability beyond short follow-up windows (typically 6-12 months in many early reports). These considerations should shape interpretation of the current literature.

Preclinical work suggests MSCs can protect retinal ganglion cells, reduce inflammatory injury and support axon regeneration in optic nerve injury models [24,25]. MSCs and MSC-derived factors have been associated with expression of retinal markers *in-vitro*, but whether functional integration and stable neuronal replacement occurs *in-vivo* remains insufficiently demonstrated in most models [26]. Safety data from broader clinical fields suggest no definitive association with malignancy or mortality in aggregate analyses, yet ocular delivery introduces distinct risks that require dedicated discussion [28].

Why the Retina is a Suitable Target for MSC-Based Strategies?

The retina provides unique advantages for regenerative interventions:

1. Direct visualization through transparent optical media and precise multimodal imaging enables early detection of adverse events and objective monitoring
2. Partial immune privilege behind the blood-eye barrier may support survival of transplanted materials
3. Standardized animal models facilitate mechanistic and proof-of-concept testing
4. Ophthalmic microsurgical techniques enable targeted delivery to specific retinal compartments

At the same time, the immune-privileged environment does not eliminate risk and perturbation of ocular compartments can induce inflammation, fibrosis or Proliferative Vitreoretinopathy (PVR), particularly with intravitreal or surgical approaches.

Delivery Options and Comparative Risks

MSCs can be delivered systemically (intravenous) or locally (intravitreal, subretinal or periocular routes) (Table 1). Delivery route strongly influences both efficacy and safety profiles.

Subretinal delivery can position cells or cell products near the outer retina and RPE and bypass the inner limiting membrane

barrier that restricts intravitreal integration [29,30]. However, subretinal injection often requires vitrectomy and surgical expertise, with risks including retinal tears, detachment and inadvertent dispersion of cells into the vitreous cavity. Importantly, minimizing vitreous disruption may reduce the risk of PVR, but this remains a key safety consideration whenever intraocular surgery is performed [31].

	Local Administration (Intravitreal / Subretinal)	**Periocular Administration (Sub-Tenon / Suprachoroidal)**	**Systemic Administration (Intravenous)**
Advantages	• High local bioavailability at target tissue with limited systemic dilution • Compartment-specific targeting (intravitreal for inner retina; subretinal for outer retina and RPE) • Reduced systemic exposure and off-target systemic effects	• Less invasive than subretinal surgery • Avoids direct entry into vitreous cavity in some approaches • Lower intraocular manipulation compared to intravitreal or subretinal delivery • Potentially reduced risk of intraocular complications such as endophthalmitis	• No intraocular manipulation • Potential access to bilateral ocular tissues via systemic circulation • May be relevant in diseases with systemic inflammatory components
Limitations / risks	• Procedure-related risks (endophthalmitis, hemorrhage, lens injury) • Subretinal delivery requires surgical expertise and carries risk of retinal tear or detachment • Intravitreal delivery limited by internal limiting membrane, reducing retinal integration • Risk of inflammation, fibrosis, traction and proliferative vitreoretinopathy • Possible immune or inflammatory reactions, especially with allogeneic or repeated dosing	• Variable and potentially limited penetration to the retina depending on tissue diffusion • Less precise control of final intra-retinal dose • May not achieve sufficient concentration in advanced retinal degeneration • Limited long-term safety data compared to established intravitreal procedures	• Limited ocular delivery due to blood-retinal barrier • Pulmonary first-pass effect and variable biodistribution reduce effective retinal dose • Less control over local retinal concentration • Potential systemic adverse effects requiring monitoring
Most suitable contexts	• Localized retinal or optic nerve disease requiring targeted therapy • Trials emphasizing structural and functional retinal endpoints (OCT, ERG, perimetry)	• Early-stage retinal disease where paracrine modulation may be sufficient • Situations where intraocular surgery is undesirable or high risk	• Exploratory adjunctive therapy • Conditions where systemic immune modulation is relevant

Table 1: Comparison of MSC delivery routes for retinal and optic nerve indications.

Intravitreal delivery is less invasive and widely used for anti-VEGF injections; it can be performed outpatient and may be more relevant for inner retinal targets. Nonetheless, the internal limiting membrane limits retinal integration and intravitreal cell persistence or aggregation raises theoretical risks of traction, inflammation and fibrosis in susceptible settings [32]. Systemic delivery may be limited by pulmonary trapping and restricted ocular access due to the blood-retinal barrier, potentially reducing effective delivery to target tissues while increasing systemic exposure.

Fig. 1 summarizes the major mechanistic domains through which MSCs are proposed to exert therapeutic benefit in retinal disease. Importantly, most evidence supports a predominantly paracrine mode of action rather than stable structural integration

of transplanted cells into functional retinal circuitry. Immunomodulation is mediated through soluble factors such as PGE2 and IDO and through downstream effects on regulatory T-cells and macrophage polarization. Neuroprotection appears linked to secretion of trophic factors and attenuation of TLR4-associated inflammatory cascades. Antioxidative effects may involve activation of AKT-dependent survival signaling and enhancement of endogenous antioxidant responses, while angiogenic modulation may be beneficial in ischemic microvascular degeneration but potentially detrimental in proliferative neovascular stages. The relative dominance of these mechanisms is likely disease-stage dependent (Table 2-6).

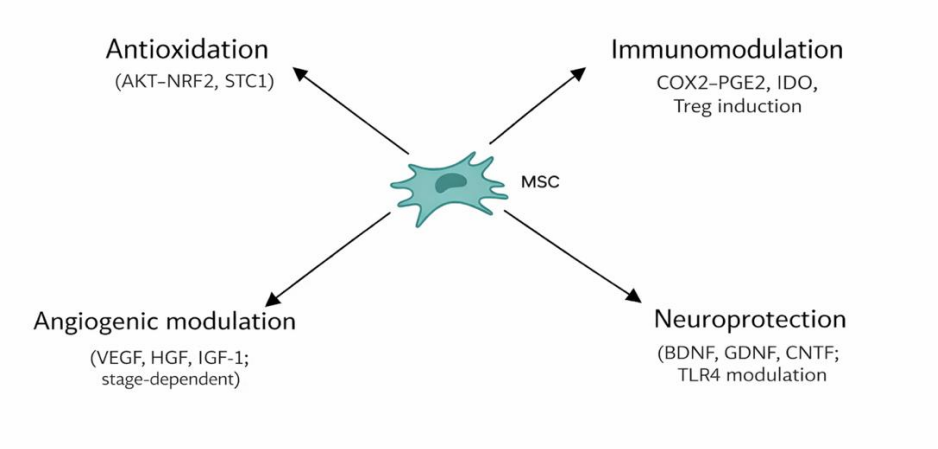

Figure 1: Principal paracrine mechanisms by which mesenchymal stem cells exert therapeutic effects in retinal and optic nerve diseases.

Ref	Design	Phase/Stage (As Reported)	N (Pts) / Eyes	MSC Source	Route	Follow-Up	Primary Endpoints (Reported)	Key Outcomes	Durability Signal	Key Limitations	LoE
(131)	Non-randomized prospective clinical trial (PCT)	Stage 3	82 / 124	UC-MSC	Suprachoroidal	6 mo	BCVA, VF	Statistically significant BCVA and VF improvement; BCVA: 46% improved, 42% stable, 12% worsened	Short-term only (6 mo)	Generalizability to early-stage RP questioned; no control/sham	2
(132)	Non-randomized PCT (open-label)	Stage 1	15 / 15	Spheroidal UC-MSC	Suprachoroidal	6 mo (1/3/6 mo checks)	BCVA, VF, mfERG	Improved BCVA, VF, mfERG; no complications reported	Short-term only (6 mo)	Small n; no control; short follow-up; mutation heterogeneity	2
(133)	Non-randomized PCT	Stage 1	11 / 11	AD-MSC	Subretinal	6 mo (dense early monitoring)	BCVA, ERG	No significant change in BCVA/ERG overall; 1 pt improved markedly; 3 pts subjective light/color improvement	Limited; largely no objective change	Ocular complications (CNM, ERM) requiring additional surgeries	2
(134)	Retrospective clinical study (LRRT)	Stage 1	25 / 34	AD-MSC (autologous)	Deep scleral pocket above choroid (LRRT)	6 mo	BCVA + "visual parameters"	Group with thicker fovea tended to improve more; not statistically significant	Short-term; unclear	Retrospective; heterogeneity; limited molecular characterization; short follow-up	3
(129)	Prospective clinical study	Stage 3	32 / 34	WJ-MSC	Sub-tenon	6 mo	BCVA, VF, OCT thickness	BCVA ↑ (70.5→80.6 letters), VF MD improved, outer retinal thickness ↑	Short-term only (6 mo)	Short follow-up; no control group	2

(128)	Prospective clinical study (extension)	Stage 3	32 / 34	WJ-MSC	Sub-tenon	1 year	BCVA, ERG, OCT metrics, perimetry	Improvements in OCT metrics, BCVA, perimetry deviation, flicker ERG vs baseline	1-year signal; still limited	No control; small n; durability beyond 1 year unknown	2
(130)	Prospective open-label non-randomized clinical trial	Stage 3	30 / 30	Autologous BM Lin− cells	Intravitreal	12 mo	BCVA, mfERG, QoL	Improvements in BCVA and mfERG response densities; better in symptoms <10 yrs	12-mo signal; unclear after	No randomization; variable disease stage; inconsistent testing equipment/conditions	2
(135)	Prospective open-label non-randomized	Stage 1	5 / 5	Autologous BM mononuclear cells	Intravitreal	10 mo	BCVA, ERG, VF, OCT	No adverse events; 4 pts +1 line BCVA maintained; structure stable	10-mo signal only	Very small n; short follow-up; autologous genetic defect concern	2
(127)	Non-randomized PCT	Stage 1	14 / 14	Autologous BM-MSC	Intravitreal	12 mo (+ subset 1.5-7 yrs)	BCVA (reported)	BCVA improvements temporary; returned to baseline at 12 mo; decline over time	**Transient**	Small n; non-randomized; long-term follow-up inconsistent across pts	2

Table 2: Clinical studies of MSC-based therapy for Retinitis Pigmentosa.

Ref	Model	Product	Source	Route	Primary Outcomes	Key Fndings	Key Limitations	LoE
(136)	Mouse glaucoma model	SSC-ESC-derived RGCs	SSC→ESC→RGC	Intravitreal	RGC survival/markers	Survived 10 days; expressed Brn3b; suggested RGC replacement	Ethical/translational limits; very short survival window	4
(137)	Rat glaucoma model	Exosome-rich conditioned media (ERCM)	AMMSC/AMESC	Intravitreal	IOP + retinal layer integrity	IOP normalized; retinal layers preserved; oxidative/hypoxic protection	Exosome yield and stability concerns	4
(138)	OHT-induced rat	Live hUC-MSC	UC-MSC	Intravitreal	Apoptosis, inflammation, thickness	↓ apoptosis/neuroinflammation via TLR4; ↑ inner retinal thickness	Limitations not specified	4
(139)	ONC *in-vivo* + RGC *in-vitro*	Exosomes	BM-MSC	Intravitreal	RGC survival, axon regen, RNFL	Promoted survival + regeneration; preserved RNFL	Some RGC subtypes resistant; regeneration limits	4
(140)	Mouse genetic glaucoma model	Secretome ± cells	Trabecular meshwork stem cells	Periocular (secretome); intracameral (cells)	IOP, TM regeneration, RGC protection	COX2-PGE2 axis; ECM modulation; ↓ IOP and protected RGCs	Limitations not specified	4
(142)	DBA/2J mouse glaucoma	sEV	BM-MSC sEV	Intravitreal monthly	RGC function, axonal damage	Preserved function; reduced axonal damage; ↑ RGC survival markers	Poor OCT image quality; behavior confounded testing	4
(144)	Chronic OHT rat	Live hUC-MSC	UC-MSC	Intravitreal	RGC loss/apoptosis; cell survival	Migrated to damaged retina; ↓ RGC loss; survived ≥8 weeks	Limited retinal integration; ILM penetration barrier	4

Table 3: MSC-based strategies for Glaucoma (Preclinical + Clinical separated).

Ref	Design	Product	Route	Key Outcomes	Safety Signals	Limitations	LoE
(141)	Phase I clinical trial (PCT)	Autologous BM-MSC	Intravitreal	No visual improvement; stable ERG; no major IOP/OCT changes	**1 retinal detachment + PVR**	Single/few cases; efficacy not shown; serious ocular complication noted	2
(143)	Retrospective clinical study (GON; LRRT)	AD-MSC (LRRT)	Suprachoroidal (as listed)	Reported improvement in BCVA + sensitivity at 6 mo vs controls	Not detailed	Sample size limited (25)	

Table 4: Human clinical studies (Glaucoma).

Ref	Model	Product	Source	Route	Primary Outcomes	Key Findings	Key Limitations	LoE
(145)	Rat DR	sEV + anti-VEGF (bevacizumab)	MSC-sEV	Intravitreal	VEGF, leakage, leukostasis	Reduced VEGF/exudates/leukostasis >2 mo; lower cell death vs bevacizumab alone	Injection burden context; translational dosing unclear	4
(146)	Rat DR	Hypoxia-induced exosomes	hUC-MSC Exs	Intravitreal (pars plana)	Vascular leakage/microvasculature	Reduced leakage; prevented microvascular changes	Complex extraction; limited yield; no proliferation/differentiation	4
(147)	Diabetic athymic nude rat	Live ASC	Adipose stromal cells	Intravitreal	Function + leakage + inflammation	Improved function; ↓ leakage; ↓ inflammatory genes; ASC resistant to HG	Limitations not specified	4
(151)	Rat DR	ERCM	Amniotic MSC	Subconjunctival	DR progression; ERG; inflammation	Delayed progression; fewer cataracts/uveitis; improved ERG signals	Notes risks: rejection, malignant transformation, vitreoretinal proliferation	4
(152)	Rat DR	ATRA-treated UC-MSC	UC-MSC	Intravitreal	Damage/apoptosis + cytokines	Reduced damage/apoptosis; regulated angiogenesis/inflammation	Limitations not specified	4
(153)	Rat DR	sEV	MSC-sEV	Intravitreal	Oxidative stress/apoptosis + pathways	NEDD4→PTEN ubiquitination→AKT→NRF2; ↓ oxidative stress/apoptosis	Unclear effect on injured RPE *in-vivo*	4
(154)	Rat DR	sEV	hUCMSC-sEV	Intravitreal	Leakage + inflammation + miRNA	↓ leakage/inflammation; miR-18b targets MAP3K1	Limitations not specified	4

Table 5: MSC-based strategies for diabetic retinopathy preclinical *in-vivo* studies.

Ref	Model	Cells	Key Outcomes	Key Findings	Key Limitations	LoE
(148)	*In-vitro* BRB model	HRECs + ASCs + pericyte-like P-ASCs	TEER/BRB integrity	P-ASCs preserved BRB and reduced HG inflammatory response	Limitations not specified	5
(149)	*In-vitro* angiogenesis	ASC vs HRMVPC	Tube formation/paracrine	ASC pro-angiogenic; pericytes anti-angiogenic	Limitations not specified	5
(155)	*In-vitro* HG stress model	HRMVECs + ASCs	Angiogenic potential	ASCs resist HG; HRMVEC tube formation reduced; stage-dependent risk noted	Timing/stage risk in late neovascular DR	

Table 6: Preclinical *in-vitro* studies (DR / BRB / angiogenesis).

Strategies for Treating Retinal Diseases with MSCs

Immunomodulation and Immune Re-programming

Conventional immunosuppression for ocular inflammatory disease (e.g., corticosteroids and systemic immunosuppressants) can be effective but carries systemic and ocular adverse effects. MSCs have been proposed as alternatives or adjuncts because they can suppress multiple immune effector pathways and promote regulatory immune phenotypes [33,34].

Mechanistically, MSCs act largely through secreted mediators that influence T-cells, B-cells, NK cells, macrophages and dendritic cells [35]. Key pathways include COX2, PGE2, IL-6, dependent signaling and Indoleamine 2,3-Dioxygenase (IDO) induction in inflammatory milieus [36]. MSC apoptosis followed by macrophage efferocytosis has been proposed as an immunoregulatory mechanism, with downstream IDO-mediated suppression contributing to reduced immune activation [37,38]. MSCs also support expansion of regulatory T-cells, polarization toward M2-like macrophages and promotion of tolerogenic dendritic phenotypes while inhibiting NK cell proliferation [39].

Cell-free MSC products may also reduce inflammatory recruitment signals. For example, MSC-derived exosomes have been associated with downregulation of MCP-1, a chemokine involved in monocyte recruitment [40]. In inflammatory models, intravitreal MSC administration has been associated with reduced expression of cytokines such as IL-1β, TNF-α and IFN-γ and decreased macrophage infiltration [41,42]. Importantly, many mechanistic findings are derived from animal models with acute inflammatory induction; translation to chronic human retinal degenerations requires cautious interpretation.

Neuroprotection and Neuronal Survival Pathways

MSC neuroprotective activity is commonly attributed to trophic support and inflammation control rather than durable neuronal replacement. MSCs can reduce retinal apoptosis, preserve inner retinal thickness and mitigate neuroinflammation partly through modulation of innate immune signaling such as TLR4-linked pathways, alongside suppression of TNF-α, IL-1β, oxidative stress mediators and reactive oxygen species [43]. MSCs secrete neurotrophic factors including NGF, GDNF, CNTF, bFGF and BDNF, which collectively support retinal neuron survival and stress resistance [44]. Conditioned medium studies suggest photoreceptor survival benefits *in-vitro*, supporting a paracrine mechanism. *In-vivo*, subretinal MSC injection has been associated with preservation of photoreceptor layers in genetic degeneration models [47]. However, whether transplanted MSCs functionally integrate as retinal neurons remains insufficiently established; many studies detect marker expression without demonstrating synaptic integration and sustained function. Early clinical reports (e.g., in retinitis pigmentosa and optic neuropathies) suggest potential functional improvements but interpretation is limited when studies are open-label, non-randomized, underpowered or have short follow-up. Future trials should standardize endpoints (BCVA, microperimetry, ERG, OCT metrics), include masking/sham controls where feasible and assess durability beyond 12 months [45,46].

Angiogenesis: Repair vs Pathologic Neovascularization

Pathologic neovascularization contributes to complications such as vitreous hemorrhage and tractional retinal detachment. Ocular vascular disease includes ischemia-driven retinal neovascularization (e.g., DR, ROP, vein occlusions) and subretinal neovascularization common in AMD and high myopia [48].

MSCs can secrete angiogenic mediators (VEGF, FGF, HGF, TGF-β1, IGF-1) that may support vascular repair in ischemic settings [49]. Conversely, the same pro-angiogenic profile could theoretically exacerbate pathological neovascularization depending on disease stage and microenvironment. Therefore, pro-angiogenic MSC effects should be interpreted as stage-dependent and may be more appropriate for early microvascular degeneration and pericyte loss than for active proliferative neovascular phases. In DR, hyperglycemia drives oxidative stress, microvascular degeneration, pericyte dysfunction and inflammation. MSCs may reduce ROS and inflammatory mediators and potentially support pericyte-like functions while promoting neurotrophic support [54,55]. However, much of this evidence is preclinical; clinical translation requires careful safety monitoring for proliferative responses.

Oxidative Stress and Antioxidant Defense

Oxidative stress is implicated in retinal degeneration through ROS-mediated damage, inflammation and cellular dysfunction. MSCs may mitigate oxidative injury via free radical scavenging, enhancement of endogenous antioxidant systems, mitochondrial support (including mitochondrial transfer in some models) and activation of survival pathways [56]. Mechanistically, evidence across systems points to pathways such as AKT-linked cytoprotection and downstream antioxidant responses (commonly discussed with NRF2-associated transcriptional programs in broader literature), although the specific causal chain should be clearly linked to retinal models when stated. Overexpression of Stanniocalcin-1 (STC1) has been associated with increased survival of oxidatively stressed cells [57]. In ocular models, adipose-derived MSCs delivered subretinally have been reported to protect RPE and photoreceptors under oxidative stress [58]. Overall, MSC-mediated antioxidant effects likely interact with immunomodulation and trophic support rather than acting as a single isolated pathway.

Conventional Therapies: Brief Context and Limitations

Conventional therapies remain essential for managing major retinal diseases, but most approaches do not replace lost neurons or photoreceptors and often require repeated treatments or invasive procedures. For retinitis pigmentosa, gene-based strategies (including ASOs, genome editing such as CRISPR/Cas9 and optogenetic approaches) represent important advances, especially when targeting specific mutations or restoring light sensitivity in surviving retinal cells [59-63]. Nutritional supplements (vitamin A, lutein, DHA) and pharmacologic approaches (including calcium channel modulation) have shown variable and sometimes conflicting evidence and generally do not provide restorative therapy [64,65].

For glaucoma, treatment focuses on intraocular pressure reduction through topical medications, laser trabeculoplasty and surgical interventions including MIGS and filtering/tube procedures [66-84]. These modalities slow progression but do not regenerate retinal ganglion cells or reverse optic nerve damage.

For diabetic retinopathy and DME, systemic metabolic control and ocular treatments (anti-VEGF, steroids, laser, vitrectomy in selected cases) have strong evidence for reducing vision loss and managing complications, but long-term burden, incomplete responses and progression in some patients persist [85-117]. These limitations motivate regenerative approaches aimed at neurovascular protection and microenvironmental modulation. Rationale for inclusion in this review: Conventional therapies are summarized here solely to define the unmet need that MSC-based and regenerative strategies seek to address, rather than to provide a comprehensive therapeutic manual.

Emerging MSC-Based Therapies for DR (Keep, but make analytical)

Recent studies suggest MSC-derived EVs may provide cell-free strategies for DR by reducing oxidative stress, inflammation and apoptosis in diabetic models. For example, MSC-sEV delivery of NEDD4 has been associated with reduced retinal oxidative stress and apoptosis in diabetic rats [153]. Human umbilical cord MSC-derived sEVs have also shown anti-inflammatory and anti-apoptotic activity in rat DR models, with microRNA-18b implicated through MAP3K1 targeting [154]. Additionally, adipose-derived MSCs may preserve pro-angiogenic repair capacity under high glucose conditions and restore endothelial angiogenesis via secreted factors [155]. While these studies are promising, most are preclinical and outcomes may depend heavily on EV isolation methods, dosing, biodistribution and disease stage. Translation requires standardized manufacturing, clear primary endpoints and long-term ocular safety evaluation.

Safety, Regulatory and Translational Challenges

Although MSC approaches are often described as "safe," intraocular and periocular delivery raises distinct risks that should be explicitly addressed:

- Proliferative Vitreoretinopathy (PVR) and fibrosis: Intraocular manipulation and cell presence in the vitreous may increase risk of traction, membrane formation and retinal detachment in susceptible contexts. Risk may vary by delivery route, product type (cells vs EVs) and surgical disruption
- Ectopic tissue formation and inappropriate differentiation: Particularly relevant for living cell products; risk is influenced by manufacturing controls and local microenvironment signals
- Tumorigenicity and long-term surveillance: While many studies report no signal of malignancy in short follow-up, long-term surveillance is limited and genomic instability risks differ by product type (e.g., iPSCs vs MSCs)
- Immune reactions and inflammation: Even "immune-privileged" ocular compartments can mount inflammatory responses and allogeneic products may carry additional immunologic considerations
- Product heterogeneity: MSC source (BM-MSC vs UC-MSC vs AD-MSC), donor characteristics, passage number, cryopreservation, potency assays and contamination controls are major determinants of reproducibility
- Regulatory and ethical concerns: The field is complicated by unregulated "stem cell clinics" offering ocular injections without rigorous evidence, which has contributed to safety incidents and public mistrust. High-quality clinical translation requires adherence to regulated manufacturing and clinical trial oversight (FDA/EMA-aligned pathways and local regulatory equivalents)

Evidence Hierarchy and Critical Appraisal

Current clinical evidence for MSC-based ophthalmic therapies is predominantly early-phase and frequently limited by:

- Small sample sizes

- Non-randomized designs
- Open-label protocols
- Inconsistent endpoints
- Short follow-up (commonly 6-12 months)
- Variable manufacturing/dosing/delivery protocols

Accordingly, the literature should be framed as preliminary, with an explicit statement that robust phase III randomized controlled trials remain limited or lacking in most indications and that reported functional improvements may be transient or influenced by bias without masking/sham controls. This critical framing will directly address the reviewer's "descriptive vs analytical" concern.

Conclusion

Mesenchymal stem cells and MSC-derived products, particularly extracellular vesicles, represent promising regenerative strategies for ophthalmic disease through immunomodulatory, neuroprotective, antioxidant and microenvironment-stabilizing effects. However, the strength of clinical evidence remains preliminary in many indications due to small early-phase studies, heterogeneity in product manufacturing and delivery and limited long-term follow-up. Future progress will depend on standardized potency and safety assays, rigorous controlled trial designs with durable functional endpoints and clear regulatory pathways that distinguish validated therapies from unregulated interventions. With these advances, MSC-based approaches may evolve from experimental interventions into reproducible, safe adjuncts or, in select contexts, transformative therapies, for preserving and restoring vision.

Conflict of Interest

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Data Availability Statement

Data can be made available upon reasonable request.

Ethical Statement

Written informed consent was obtained from the patient for publication of this case report and accompanying images. Institutional ethics approval was deemed exempt for a single case report according to institutional guidelines.

Informed Consent Statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Authors' Contributions

All authors contributed equally to this paper.

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