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Mesenchymal stem cell-derived exosomes as new remedy for the treatment of inflammatory eye diseases

Carl Randall HARRELL[1,#]; Ana VOLAREVIC[2,#,*]; Dragica PAVLOVIC[3]; Valentin DJONOV[4]; Vladislav VOLAREVIC[4,5,*]

[1] Regenerative Processing Plant, Palm Harbor, Florida, USA
[2] Department of Cognitive Psychology, Faculty of Medical Sciences, University of Kragujevac, Kragujevac, Serbia
[3] Institute of Anatomy, University of Bern, Bern, Switzerland
[4] Department of Genetics, Faculty of Medical Sciences, University of Kragujevac, Kragujevac, Serbia
[5] Department of Microbiology and Immunology, Faculty of Medical Sciences, University of Kragujevac, Kragujevac, Serbia

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Abstract: Detrimental immune response has a crucially important role in the development and progression of inflammatory eye diseases. Inflammatory mediators and proteolytic enzymes released by activated immune cells induce serious injury of corneal epithelial cells and retinal ganglion cell which may result in the vision loss. Mesenchymal stem cells (MSCs) are regulatory cells which produce various immunosuppressive factors that modulate phenotype and function of inflammatory immune cells. However, several safety issues, including undesired differentiation and emboli formation, limit clinical use of MSCs. MSC-derived exosomes (MSC-Exos) are nano-sized extracellular vesicles which contain all MSC-derived immunoregulatory factors. Intraocular administration of MSC-Exos efficiently attenuated eye inflammation and significantly improved visual acuity in experimental animals without causing any severe side effects. As cell-free product, MSC-Exos addressed all safety issues related to the transplantation of MSCs. Therefore, MSC-Exos could be considered as potentially new remedy for the treatment of inflammatory eye diseases which efficacy should be explored in up-coming clinical trials.

Introduction

Immunopathogenesis of inflammatory eye diseases

The ocular surface is directly exposed to the environmental pathogens, allergens and hazards (Li and Zhang, 2022). Distortion of the visual axis caused by the injury or inflammation of eye elements may result in significant visual deficit and blindness (Stepp and Menko, 2021). Since visual impairment negatively affects patient's daily activities, well-being and quality of life, eye diseases are considered as the major global health concern (Lipson *et al.*, 2021). Detrimental immune response has a crucially important role in the development and progression of eye diseases (Egwuagu *et al.*, 2015). The invasion of microbial pathogens and physical or chemical injuries that provoke extensive damage of the ocular surface epithelium and cornea induce massive release of alarmins and self-antigens from injured cells, resulting in the activation of resident dendritic cells (DCs). Activated DCs capture microbial and self-antigens, migrate to the regional lymph nodes and activate antigen-specific, naive T cells (Egwuagu *et al.*, 2015). DC-derived interleukin (IL)-12 induce differentiation of naïve CD4 + T cells in effector, interferon gamma (IFN-γ)-producing Th1 cells while DC-sourced IL-1, IL-6 and IL-23 are responsible for the generation of IL-17 and IL-22-producing Th17 cells (Egwuagu *et al.*, 2015). CD4 + Th1 cells, in IFN-γ-dependent manner, induce generation of inflammatory (M1) phenotype in intraocular macrophages. M1 macrophages secrete inflammatory cytokines and chemokines that attract circulating monocytes and lymphocytes in the inflamed eyes. CD4 + Th17 cell-sourced IL-17 induce generation of reactive oxygen species and inflammatory cytokines in neutrophils, enhancing their phagocytic and anti-microbial properties (Egwuagu *et al.*, 2015). Continuous and long term activation of intraocular CD4 + Th1 and Th17 cells, M1 macrophages and neutrophils result in the creation of "inflammatory loop" that induces permanent damage of epithelial, endothelial and neural cells and meibomian glands in the eyes. Accordingly, inflammation-related signs and symptoms (dryness, grittiness,

*Address correspondence to: Ana Volarevic, ana.volarevic@medf.kg.ac.rs; Vladislav Volarevic, drvolarevic@yahoo.com
#These authors contributed equally to this work
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scratchiness, soreness, irritation, burning, watering, foreign body sensation, eye fatigue) are usually accompanied with reduced functional visual acuity and with impaired performance of vision-dependent daily activities (Yu *et al.*, 2021).

Mesenchymal stem cell-based therapy of eye diseases

Intraocular administration of immunosuppressive eye drops may efficiently attenuate on-going inflammation, enabling alleviation of inflammation-related symptoms (Wakefield *et al.*, 2017). However, the bioavailability of topical eye drops is generally low since the well-developed protective mechanisms of the eye ensure rapid clearance of incorporated drug from the pre-corneal space (Wakefield *et al.*, 2017). Therefore, there is an urgent need for the development and clinical use of newly generated eye drops which will contain immunomodulatory factors that are able to efficiently by-pass ocular surface barrier and to reach the target immune cells within the inflamed eyes.

Mesenchymal stem cells (MSCs) are adult stem cells that may be isolated from various tissues, including bone marrow (BM), adipose tissue (AT), dental pulp, peripheral blood, umbilical cord (UC), amniotic fluid, placental tissue (Suksatan *et al.*, 2021). MSCs are fibroblast like, spindle-shaped cells that express CD73, CD90, CD105, STRO1 and CD146 and lack expression of CD34, CD45, CD14, CD79a, CD11b, or CD19 (Dauletova *et al.*, 2021). Upon engraftment in injured or inflamed eyes, MSCs produce large amount of immunoregulatory factors (prostaglandin E2 (PGE2), nitric oxide, indoleamine 2,3-dioxygenase (IDO), IL-6, IL-10) and modulate phenotype and function of all immune cells that participate in the development and progression of inflammatory eye diseases (Suksatan *et al.*, 2021). MSCs suppress DC-dependent generation of inflammatory Th1 and Th17 cells and inhibit Th1 cell-driven activation of M1 macrophages. MSCs prevent Th17 cell-dependent activation of neutrophils and promote expansion of immunosuppressive T regulatory cells (Tregs) (Harrell *et al.*, 2021). Accordingly, large number of experimental studies demonstrated that intraocular administration of MSCs suppressed detrimental immune response in the eyes, attenuated on-going inflammation and improved visual acuity of experimental animals (Harrell *et al.*, 2018). Subconjunctivally applied BM-derived MSCs (BM-MSCs) and AT-derived MSCs (AT-MSCs) prevented apoptosis of corneal epithelial cells and supported wound healing in alkaline-injured eyes of experimental rats by suppressing production of inflammatory and pro-apoptotic cytokines (tumor necrosis factor alpha (TNF-α) and interleukin 1 beta (IL-1β)) in CD68-expressing macrophages (Dinç *et al.*, 2021). MSC-sourced micro RNAs (miRNA), which incorporated into the RNA-induced silencing complex and effectively inhibited gene expression, had important role in MSC-dependent corneal regeneration (Dinç *et al.*, 2021). MSC-derived miR146a inhibited inflammation and neovascularization in alkaline-injured eyes of experimental rats by down-regulating expression of interferon gamma (IFN-γ) and vascular endothelial growth factor (VEGF) in intraocular leucocytes (Luo *et al.*, 2018).

Despite of these promising results, there are several safety issues which limit MSC-based therapy of inflammatory eye diseases. Firstly, MSCs are not constitutively immunosuppressive cells (Gazdic *et al.*, 2015). MSCs may adopt phenotype and function under the influence of biological factors to which they are exposed. When MSCs engraft in the tissue with low level of TNF-α and IFN-γ, they obtain pro-inflammatory MSC1 phenotype and secrete large number of bioactive factors which aggravate on-going inflammation. On the contrary, when MSCs are exposed to the high levels of TNF-α and IFN-γ, they acquire immunosuppressive MSC2 phenotype and produce immunoregulatory factors that suppress inflammatory immune cells. Since local tissue concentration of TNF-α and IFN-γ differ in different phases of eye inflammation, there is a concern that MSCs which will be engrafted in the eyes with low level of TNF-α and IFN-γ may obtain pro-inflammatory MSC1 phenotype and may aggravate on-going inflammation (Gazdic *et al.*, 2015).

Additionally, transforming growth factor beta (TGF-β) and bone morphogenetic protein (BMPs), released by macrophages and parenchymal cells in inflamed eyes, may induce spontaneous and unwanted chondrogenic and osteogenic differentiation of MSCs (Rahman *et al.*, 2015). Possible unwanted differentiation of transplanted MSCs represents an important safety concern which limits clinical use of MSCs in regenerative ophthalmology (Volarevic *et al.*, 2018).

Therapeutic potential of MSC-derived exosomes in tissue repair and regeneration

Since the majority of MSC-dependent beneficial effects in attenuation of eye inflammation were relied on the activity of MSCs-sourced bioactive factors, intraocular administration of MSC-derived exosomes (MSC-Exos) is considered as an alternative therapeutic approach to MSC-based therapy since it addresses all safety concerns related to the transplantation of MSCs (Harrell *et al.*, 2020). MSC-Exos are nano-sized extracellular vesicles which contain immunoregulatory and growth factors secreted by their parental MSCs. Bioinformatics analyses was used to identify molecules and signaling pathways which were mainly responsible for biological effects of human BM-, AT- and UC-MSC-Exos (Wang *et al.*, 2020). Although differently sourced MSC-Exos had similar morphology (cup-shaped vesicles) and phenotype (expression of CD9, CD81, TSG101, and Calnexin), their immunomodulatory and regenerative properties were different. A detailed proteomic analysis revealed 355 common proteins, while 341, 23 and 37 proteins were unique to BM-, AT- and UC-MSC-Exos, respectively (Wang *et al.*, 2020). BM-MSC-Exos were enriched in growth factors, soluble receptors and signaling molecules that regulate skeletal remodeling, neurodevelopment and lymphocyte activation (ADAM9, ADAM10, CACNA2D1, NOTCH2, and HLA-A). AT-MSC-Exos were enriched in proteins that regulate oxidative stress (ATP2B1, ATP1A1, PRDX 1, 2, 4, and 6) while UC-MSC-Exos were enriched in proteins that promote repair and regeneration of injured tissues (WNT4, PAI-1, MMP-2 and 9) (Wang *et al.*, 2020).

Molecular Mechanisms Responsible for the Beneficial Effects of MSC-Exos in the Attenuation of Eye Inflammation

Importantly, as determined by transcriptome and multi-omics sequencing technologies, MSC-Exos from all tissue sources

possess potent immunomodulatory properties (Wang *et al.*, 2020). As shown in Fig. 1, MSC-derived IL-10, growth regulated protein gamma (GRO-γ), TGF-β, hepatocyte growth factor (HGF), prostaglandin E2 (PGE2), IDO and interleukin 1 receptor antagonist (IL-1Ra) were mainly responsible for the beneficial effects of MSC-Exos in the alleviation of eye inflammation (Harrell *et al.*, 2020).

MSC-sourced IL-10 attenuates antigen-presenting properties of DCs by suppressing production of pro-Th1 (IL-12, IFN-γ) and pro-Th17 cytokines (IL-1β, IL-6, IL-23) and by down-regulating expression of major histocompatibility complex (MHC) I and II proteins and co-stimulatory molecules on their membranes. MSC-derived GRO-γ promotes synthesis of TGF-β and IL-10 and induces generation of tolerogenic phenotype in activated DCs. Tolerogenic DCs present antigens to naïve T cells, induce expansion of immunosuppressive T regulatory cells and prevent generation of Th1 and Th17 cells (Harrell *et al.*, 2020). Therefore, by delivering IL-10 and GRO-γ, MSC-Exos inhibit DC-dependent generation of inflammatory CD4 + Th1 and Th17 cells (Harrell *et al.*, 2020).

MSC-derived TGF-β and HGF suppress Jak-Stat signaling pathway and induce G1 cell cycle arrest of activated T cells. MSC-sourced PGE2 reduces production of inflammatory cytokines (IFN-γ and IL-17) in CD4 + Th1 and Th17 cells. MSC-Exo-sourced IDO induces generation and expansion of Tregs and prevents their trans-differentiation in inflammatory Th17 cells (Volarevic *et al.*, 2017). In inflamed microenvironment, continuous antigen-driven stimulation of T cell receptor (TCR) activate protein kinase B (PKB) and mammalian target of rapamycin (mTOR) in Tregs which cause trans-differentiation of Tregs in inflammatory Th17 cells. MSC-sourced IDO activate GCN2 kinase which inhibit PKB/mTORC signaling pathway in antigen-primed Tregs and, consequently, prevent their trans-differentiation in Th17 cells (Volarevic *et al.*, 2017).

IL-1β has the highest ability to initiate ocular inflammation. The continuous overexpression of IL-1β provokes enhanced synthesis of inflammatory chemokines in intraocular macrophages, enabling massive influx of circulating leucocytes in inflamed eyes (da Cunha *et al.*, 2018). MSC-sourced IL-1Ra binds to the IL-1R on endothelial cells and prevents IL-1β:IL-1R interaction (Volarevic *et al.*, 2017). Accordingly, intraocular administration of IL-1Ra-containing MSC-Exos alleviate IL-1β-driven eye inflammation and significantly reduced influx of monocytes and lymphocytes in inflamed eyes (Harrell *et al.*, 2018).

Beneficial Effects of MSC-Exos in the Treatment of Inflammatory Eye Diseases

Therapeutic potential of MSC-Exos in the treatment of autoimmune eye diseases

Due to nano-sized dimension, MSC-Exos, easily by-pass ocular surface epithelial barrier and deliver their cargo (trophic factors, immunoregulatory cytokines, miRNAs) directly into the target immune cells. In this way, MSC-Exos alter phenotype and function of immune cells without affecting neighboring parenchymal cells. Additionally,

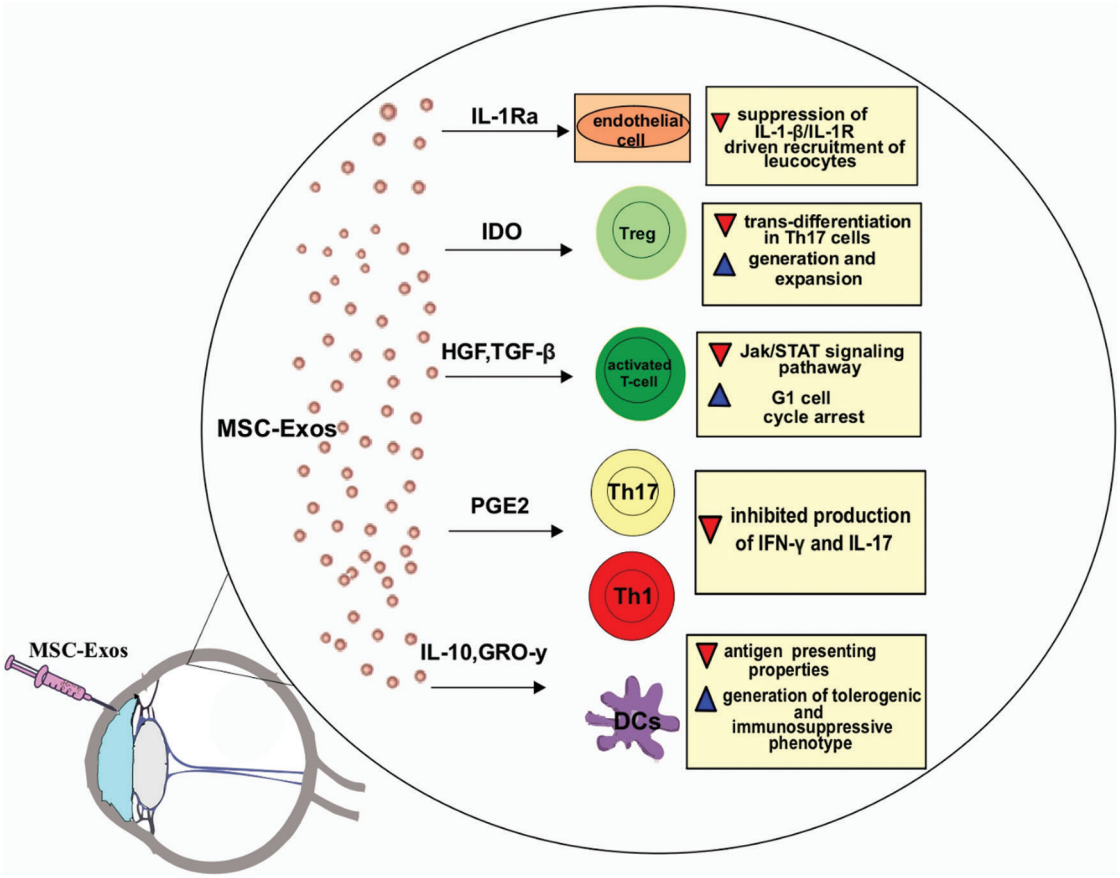

FIGURE 1. Molecular mechanisms responsible for beneficial effects of MSC-Exos in the treatment of inflammatory eye diseases.

MSC-Exos express adhesion molecules which enable their migration into the injured or inflamed eyes (Harrell *et al.*, 2018).

MSC-Exos efficiently attenuated autoimmune and inflammatory eye diseases, as shown in Table 1. Intraocular administration of MSC-Exos alleviated eye inflammation, protected retinal structure and rescued retinal function in animals suffering from autoimmune uveitis (Bai *et al.*, 2017; Shigemoto-Kuroda *et al.*, 2017). By delivering IL-10 in inflamed eyes, MSC-Exos suppressed activation of intraocular DCs and prevented generation and expansion of CD4 + Th1 and Th17 cells. MSC-Exos down-regulated production of IL-1β and IL-12 in DCs and significantly impaired synthesis of TNF-α, IFN-γ and IL-17 in Th1 and Th17 lymphocytes (Bai *et al.*, 2017; Shigemoto-Kuroda *et al.*, 2017).

Intraocular administration of MSC-Exos efficiently attenuated diabetic retinopathy in experimental rabbits. MSC-Exos protected retinal tissue by delivering mi-RNA222 in macrophages. MSC-sourced mi-RNA222 induces generation of immunosuppressive (M2) phenotype in intraocular macrophages by causing the transcriptional silencing of inflammatory genes (Zhang *et al.*, 2019).

Therapeutic potential of MSC-Exos in the treatment of dry eye disease

An ophthalmic solution "Regener-Eyes" (generic name "derived-Multiple Allogeneic Proteins Paracrine Signaling (d-MAPPS)") which contained MSC-Exos enriched with MSC-sourced IL-1Ra, soluble TNF receptors (sTNFRs) and GRO-γ efficiently attenuated eye inflammation and restored meibomian gland morphology and function in patients suffering from dry eye disease (DED) (Harrell *et al.*, 2019). MSC-sourced IL-1Ra and sTNFRs inhibited IL-1β and TNF-α-driven eye inflammation, while MSC-derived GRO-γ prevented DC-dependent generation of inflammatory Th1 and Th17 cells in the eyes of DED patients. Accordingly, Regener-Eyes significantly reduced all DED-related signs and symptoms (severe pain, dryness, grittiness, scratchiness, irritation, burning, and eye fatigue) in 131 DED patients without causing any side effects during the one year of follow-up. Importantly, significantly improved visual acuity, relieved ocular pain and complete healing of corneal epithelial defects were also noticed in Regener-Eyes-treated DED patients with Sjogren's syndrome (Harrell *et al.*, 2021). MSC-Exos-dependent suppression of NF-kB signaling in intraocular macrophages and consequent reduced production of macrophage-derived inflammatory cytokines were mainly responsible for the beneficial effects of MSC-Exos in Sjogren's syndrome (Li *et al.*, 2019).

Clinical trials which are going to investigate therapeutic effects of MSC-Exos in the treatment of eye diseases

Currently, there are two registered clinical trials which are going to investigate therapeutic effects of MSC-Exos in the treatment of eye diseases, as shown in Table 2.

Clinical trial which will examine therapeutic effects of UC-MSC-Exos in alleviation of dry eye-related symptoms in patients with chronic Graft *vs.* host disease will be conducted at Zhongshan Ophthalmic Center, Sun Yat-sen University, China (NCT04213248). According to the protocol, participants will receive artificial tears for 2 weeks, followed by UC-MSC-Exos (10 μg/drop) which will be administered four times a day for 14 days. Ocular surface index score, the amount of secreted tears, tear break time, ocular redness and visual acuity will be determined in UC-MSC-Exo-treated patients during the 12 weeks of follow-up. In another registered clinical trial, which will be conducted at Tianjin Medical University Hospital, China, UC-MSC-Exos will be intravitreally injected to promote healing of large and refractory macular holes (MHs) (NCT03437759). After air-liquid exchange, UC-MSC-Exos (50 μg or 20 μg, dissolved in 10 μl of phosphate buffered saline) will be

TABLE 1

Beneficial effects of MSC-Exos in the treatment of eye diseases

Disease	MSC-Exo-sourced factors and target cells	Cellular mechanisms	Therapeutic effects	References
Autoimmune uveitis	IL-10-dependent inhibition of DCs, Th1 and Th17 cells	down-regulated production of IL-1β and IL-12 in DCs; suppressed production of IFN-γ and IL-17 in Th1 and Th17 cells	alleviated eye inflammation; rescued retinal function	(Bai *et al.*, 2017; Shigemoto-Kuroda *et al.*, 2017)
Diabetic retinopathy	MiRNA126 and miRNA222-dependent generation of M2 macrophages	transcriptional silencing of inflammatory genes in intraocular macrophages	Alleviated retinitis; Enhanced protection of RGCs	(Zhang *et al.* 2019)
Dry eye disease	IL-1Ra and sTNFRs-dependent modulation of ECs; GRO-γ-dependent suppression of DCs	reduced expression of E and P selectins on ECs; suppressed production of IFN-γ and IL-17 in Th1 and Th17 cells	reduced pain, dryness, grittiness, scratchiness, irritation, burning, and eye fatigue	(Harrell *et al.*, 2019)
Sjogren's syndrome	IL-10-dependent suppression of M1 macrophages	suppression of NF-kB signaling in intraocular macrophages; reduced production of inflammatory cytokines and chemokines	attenuated eye inflammation; improved tear secretion	(Li *et al.*, 2019)

TABLE 2

Clinical trials which will investigate therapeutic potential of MSC-Exos in the treatment of eye diseases

Source of exosomes	Aim of the trial	Route of exosome injection	Dose of exosomes	Follow-up	Monitored parameters	Clinical trials identifier
UC-MSCs	Treatment of dry eyes in patients with chronic Graft-*vs.*-host disease	Eye drops	10 μg/drop 4 times/day 14 days	12 weeks	ocular surface index score; amount of secreted tears; tear break time; ocular redness; visual acuity	NCT04213248
UC-MSCs	Healing of large and refractory macular holes	Intravitreal injection	50 μg or 20 μg, dissolved in 10 μl of PBS	6 months	physical examination; measurement of best-corrected visual acuity; fundoscopy; optical coherence tomography	NCT03437759

administered into vitreous cavity around MHs. The recruited patients will be followed up for at least 6 months. The effects of UC-MSC-Exos will be determined by physical examination, measurement of best-corrected visual acuity, fundoscopy and optical coherence tomography.

Conclusion and Future Directions

Although MSCs possess potent immunoregulatory, angiomodulatory and neuroprotective properties, results obtained in several animal studies demonstrated that, after engraftment in the immunosuppressive microenvironment, MSCs adopt pro-inflammatory phenotype and aggravate on-going inflammation (Shukla *et al*., 2019; Wen *et al*., 2021). Moreover, MSCs express major histocompatibility complex (MHC) class II molecules and may provoke strong allogeneic immune response after transplantation in MHC-miss-matched recipients (Volarevic *et al*., 2018). Accordingly, intravitreal injection of allogeneic MSCs resulted in the severe retinal inflammation, venous congestion and massive injury of retinal ganglion cells which led to the visual loss of experimental animals (Wen *et al*., 2021).

As cell-free biological product, MSC-Exos overcome all safety issues related to the MSC-based therapy. Results obtained in experimental and clinical studies showed that MSC-Exos efficiently attenuated on-going inflammation and suppressed detrimental immune response in the eyes, suggesting their potential clinical use in the therapy of inflammatory eye diseases.

However, it should be noted that there are several issues that need to be addressed before MSC-Exos could be offered as new remedy in immuno-ophtalmology. The optimal dose, frequency and route of MSC-Exos injection should be defined for each inflammatory eye disease. Up-coming studies should also determine the exact MSC-Exo-containing immunoregulatory factor(s) which is/are responsible for the beneficial effects of MSC-Exos. Administration of MSC-Exos which will be enriched with the most effective immunoregulatory factor(s) will enhance therapeutic potential and efficacy of MSC-Exos in the treatment of inflammatory eye diseases.

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