

# Inflammatory Response in Dry Eye

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**PURPOSE.** Dry eye is a major ocular pathology worldwide. Although dry eye is a multifactorial disease, recent studies have shown that chronic immunologic processes have a pivotal role in its pathogenesis, characterized by the infiltration of immune cells in the lacrimal glands, elevated levels of tear inflammatory cytokines, and increased density of immune cells in the cornea and conjunctiva. This review describes the recent advances in understanding the relationship between dry eye and inflammation.

**METHODS.** This narrative review is based on searches of recent international literature using terms related to the immune response in dry eye, and includes clinical trials, animal experiments, and expert reviews.

**RESULTS.** Although dry eye presents clinically as tear film instability associated with corneal/conjunctival epithelial disorders, Meibomian gland dysfunction, and decreased visual function, recent laboratory and clinical studies have indicated inflammation in the lacrimal glands, Meibomian glands, conjunctiva, cornea, and aqueous tears. Furthermore, inflammation at these locations leads to conjunctival goblet cell apoptosis, corneal epithelial barrier disruption, and corneal nerve damage. These inflammatory outcomes can be exacerbated by intrinsic and extrinsic factors, such as aging, sex steroid hormone, autoimmune diseases, contact lens use, visual display terminals, and dry environment.

**CONCLUSIONS.** Recent advances in dry eye research have revealed the inflammatory process and its pathogenesis, which has been proposed as an “inflammatory vicious cycle” of dry eye. Comprehensive assessment of dry eye based on inflammation will improve the selection of treatments and help break the inflammatory cycle in clinical settings.

**Keywords:** tear, dry eye, lacrimal gland, immune response, inflammation

Dry eye is a prevalent ocular disorder characterized by bilateral reduced aqueous tear production and tear film instability. It is a multifactorial disease of the tear film, which affects 5% to 40% of adults older than 40 years.<sup>1–4</sup> The prevalence of dry eye is higher in women than men,<sup>4</sup> and a higher body mass index (BMI) is shown to be a preventive factor for dry eye.<sup>3</sup> Based on a recent study, 16.4 million people were estimated to have dry eye in the United States in 2013.<sup>4</sup> Dry eye causes eye irritation, hyperemia, glare, eye fatigue, and blurred vision. Vision impairment in dry eye is due to the increased higher-order aberrations,<sup>5,6</sup> or superficial punctate keratitis,<sup>7</sup> and in severe cases, such as graft-versus-host disease (GVHD) or Stevens-Johnson syndrome (SJS), blindness from corneal opacification or ulceration may result.<sup>8,9</sup> Tear instability in dry eye is caused by a variety of conditions; aqueous deficiency due to lacrimal gland atrophy, lipid abnormalities associated with Meibomian gland dysfunction (MGD), and excessive tear evaporation.

A variety of clinical tests currently are used in clinical practice to diagnose dry eye and assess its severity and clinical endpoints, including Schirmer's test, tear break-up time (TBUT), tear osmolarity, and vital dye staining of the cornea, such as Rose Bengal and Lissamine Green. However, to use the knowledge of dry eye mechanism in its treatment, an understanding of the pathologic processes of the disease is essential. The components of tears, such as clusterin,<sup>10–12</sup> mucin,<sup>13–16</sup> galectin,<sup>17</sup> and lipid,<sup>18–20</sup> also are important in understanding the homeostasis of the tear film and ocular

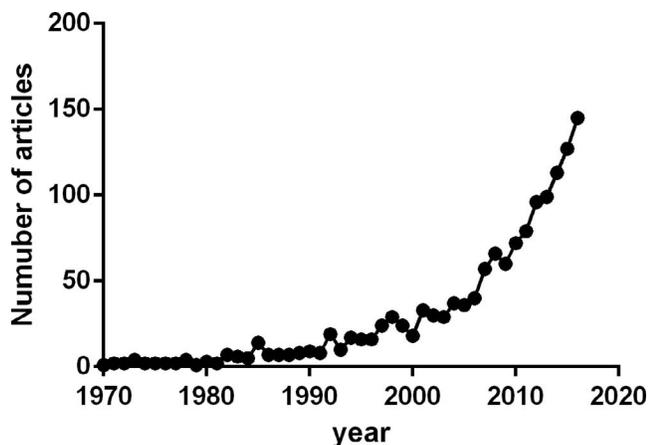
surface. Recent studies have used inflammatory parameters, such as tear cytokines or dendritic cells (DCs) density as biomarkers to assess the efficacy of treatments.<sup>21</sup> Moreover, the number of articles on “inflammation and dry eye” has increased, especially in the last 10 years (Fig. 1), and a detailed pathogenesis of dry eye is being elucidated by immunologic research and intravital imaging technologies. The United States Food and Drug Administration recently approved two drugs, cyclosporine and lifitegrast, for the treatment of dry eye, which inhibit T-cell activation and cytokine production. These drugs represent a major advance in dry eye treatment.<sup>22</sup> This review highlights the immune response in dry eye diseases, based on recent studies.

## RECENT INTERNATIONAL PROGRESS IN DRY EYE—ASSOCIATED INFLAMMATION

### Inflammatory “Vicious Cycle” in Dry Eye

Recently, dry eye was defined as “a multifactorial disease of ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities have etiologic roles” at the Dry Eye Workshop (DEWS II).<sup>23</sup> Baudouin et al.<sup>24</sup> proposed the concept of a “vicious cycle of inflammation” (Fig. 2) as a core driver in dry eye and breaking the cycle was reported to be an important step in the treatment of dry eye.<sup>25</sup>





**FIGURE 1.** The number of articles on “inflammation and dry eye.” The annual number of articles has increased between 1970 and 2016 when our PubMed search was conducted with the keywords of “inflammation and dry eye”.

The inflammatory vicious cycle includes tear film instability, tear hyperosmolarity, apoptosis of corneal/conjunctival cells, and inflammation in the ocular surface. Intrinsic and extrinsic factors cause stress to the ocular surface, which accelerates the cycle and, in turn, exacerbates dry eye.

### Inflammatory Mechanism in Experimental Dry Eye Models

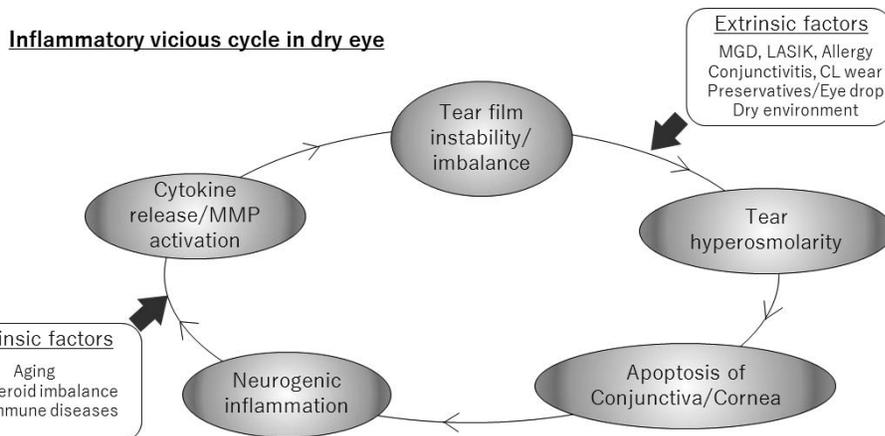
Experimental dry eye models have shown that the inflammatory changes associated with dry eye have an important role in its pathogenesis. First, CD4<sup>+</sup> T cells from mice with dry eye were adoptively transferred to T-cell-deficient nude mice, which led to severe inflammation in the lacrimal glands, cornea, and conjunctiva, resulting in decreased tear production and conjunctival goblet cell loss.<sup>26</sup> Second, topical cyclosporine, a T-cell immunomodulatory agent, was effective in inhibiting conjunctival epithelial apoptosis in an experimental dry eye model.<sup>27</sup> Third, in mouse models, aqueous tear deficiency increased the level of IFN- $\gamma$  in tear, which exacerbated goblet cell (GC) apoptosis.<sup>28</sup> Fourth, pathologic Th17 cells resistant to regulatory T cells mediate the ocular surface autoimmunity and its blockade of IL-17 decreases the

severity and suppresses the progression of experimental dry eye.<sup>29,30</sup> Collectively, these findings from experimental research have identified the immune system as a critical factor in dry eye.

### Immune Cell Infiltration Into Multiple Locations in Dry Eye

Ocular surface inflammation sometimes can appear to be absent or subclinical, especially in patients with mild cases of dry eye. However, evidence for inflammation in dry eye has been well documented in people with various types of dry eye (such as aqueous-deficient dry eye and MGD), and includes infiltration of the conjunctiva and lacrimal glands by immune cells,<sup>31-36</sup> an increase in the density of DCs in the cornea,<sup>36-39</sup> and elevated levels of tear cytokines.<sup>21,40-42</sup> Histopathologic examination of the lacrimal glands and conjunctiva showed lymphocytic infiltrates from patients with and without Sjögren's syndrome.<sup>33-35</sup> Conjunctival cells from dry eye patients overexpressed inflammatory/apoptosis markers, such as HLA-DR (dendritic cell maturation marker), Fas (CD95, apoptosis-related marker), CD40 (costimulatory protein on antigen-presenting cell [APC]),<sup>43</sup> IFN- $\gamma$ , and TNF- $\alpha$ .<sup>44</sup> Brignole et al.<sup>45</sup> reported a reduced expression of these markers in the conjunctiva following a 6-month treatment of topical cyclosporine in patients with keratoconjunctivitis sicca.

Among the immune cells, APCs induce T-cell activation, resulting in the inflammatory cascade in dry eye.<sup>46</sup> Previous studies on corneal APCs showed that its density in the center cornea increased in inflammatory conditions, such as herpes simplex keratitis, corneal graft rejection, vernal keratoconjunctivitis, and bacterial keratitis, compared to normal eyes and eyes after photorefractive keratectomy.<sup>47-49</sup> Various types of immune cells, such as macrophages, monocytes, and DCs, have been demonstrated to be important in the pathogenesis of dry eye.<sup>36-39</sup> Lin et al.<sup>50</sup> reported an increase in corneal inflammatory cells in Sjögren's syndrome (approximately 10-fold) and non-Sjögren's syndrome (approximately 3-fold), which was correlated with results from clinical dry eye diagnostic parameters, such as the Schirmer test, corneal staining score, and TBUT. Kheirhah et al.<sup>38</sup> evaluated morphologic parameters of corneal DCs, such as DC size, number of dendrites, and DC field (the area DCs cover) in eyes with aqueous-deficient dry eye and evaporative dry eyes using *in vivo* confocal microscopy (IVCM), and reported that all of these parameters were significantly increased in eyes with dry



**FIGURE 2.** Inflammatory vicious cycle in dry eye. The inflammatory vicious cycle associated with dry eye that consists of tear instability, tear hyperosmolarity, apoptosis of the conjunctival/corneal cells, neurogenic inflammation and cytokine release (Fig. 2 is adapted from Pflugfelder et al. 2017).<sup>22</sup> The cycle can be initiated and amplified by intrinsic and extrinsic factors.

eye compared to those in normal eyes. Villani et al.<sup>51</sup> showed that topical steroid treatment for dry eye not only improved the ocular surface conditions, but also significantly decreased corneal DC density detected by IVCN. Thus, intravital imaging of altered corneal DCs using IVCN may enable assessment of immune system activity and the inflammatory response in the cornea and, therefore, help tailor treatments through patient stratification.<sup>32</sup>

### Elevated Levels of Proinflammatory Cytokines in Dry Eye

Recent studies have suggested that proinflammatory cytokines in tears may have a key role in the pathogenesis of several corneal diseases, including dry eye disease,<sup>52</sup> as was found in keratoconus,<sup>53,54</sup> GVHD,<sup>55</sup> conjunctivitis,<sup>56</sup> as well as in the development of corneal neovascularization (NV).<sup>57</sup> Pflugfelder et al.<sup>41,58,59</sup> first showed elevated levels of proinflammatory cytokines in dry eye. They demonstrated increased levels of proinflammatory cytokines, such as IL-1, IL-6, and IL-8, and decreased epidermal growth factor (EGF) levels in eyes with Sjögren's syndrome.<sup>41</sup> They also showed that the tear cytokine levels are strongly correlated with dry-eye-related clinical parameters. Hyperosmolar stress also has a direct proinflammatory effect on the ocular surface that increases the tear cytokine levels.<sup>60</sup> Villani et al.<sup>61</sup> reported a correlation between corneal DC density and tear inflammatory cytokines in dry eye with rheumatoid arthritis (RA) and found that IL-1 and IL-6 concentrations decreased after the systemic treatment of RA. Other studies reported reduced tear cytokine levels as an inflammatory biomarker for the effectiveness of topical steroids<sup>62</sup> or intense pulsed light<sup>21</sup> in treating dry eye due to MGD. In these reports,<sup>21,61,62</sup> inflammatory cytokine levels correlated well with ocular surface parameters.

In severe ocular surface diseases, such as SJS, chemical burns, and ocular cicatricial pemphigoid (OCP), destruction of the corneal epithelial stem cells located at the corneal limbus results in conjunctival invasion, corneal NV, chronic inflammation, and stromal scarring, leading to major impairment of vision. Such ocular surface conditions not only cause corneal epithelial damage, but also can result in severe dry eye and glaucoma.<sup>63-66</sup> Among these comorbidities, the presence of severe dry eye leads to a poor prognosis of surgical intervention, causing postoperative persistent epithelial defects and corneal melts.<sup>67</sup> Regarding changes to tears, previous studies have shown elevated cytokine levels in tears in patients with SJS,<sup>68</sup> trachoma,<sup>69</sup> OCP,<sup>70</sup> and Graves' ophthalmopathy with exposure keratitis,<sup>71</sup> compared to normal controls. The tear cytokine levels can be improved with treatment, such as intensive steroid therapy in the acute phase of the disease,<sup>72</sup> or mucosal membrane grafting<sup>73</sup> in the chronic phase. In addition, IVCN revealed increased immune cell counts in the cornea and conjunctiva in severe ocular surface diseases.<sup>37,74</sup> Vera et al.<sup>59</sup> evaluated corneal DCs using IVCN and reported that SJS patients with dry eye had larger numbers of DCs and more severe nerve damage.

### RECENT PROGRESS ON DRY EYE-ASSOCIATED INFLAMMATION RESEARCH IN JAPAN

#### Inflammatory Response in Dry Eye

Regarding the inflammatory response in dry eye, Hikichi et al.<sup>53</sup> demonstrated novel findings in the lacrimal glands, conjunctiva, cornea, and tear film, and have made important contributions to the advances of this field. They demonstrated lymphocyte infiltration in lacrimal glands in Sjögren's

syndrome and Sato et al.<sup>75</sup> later duplicated these findings using IVCN in human subjects. Recently, Fukui et al.<sup>76</sup> found that lacrimal gland inflammation in patients with IgG4-related Mikulicz's disease caused epithelial-mesenchymal transition (EMT)-like fibrosis in the lacrimal glands. Uchino et al.<sup>77,78</sup> showed that the oxidative stress caused multifocal inflammation and lacrimal gland fibrosis, which leads to dry eye-associated ocular symptoms using transgenic Tet-mev-1 knockout mice. Kojima et al.<sup>79</sup> used Cu, Zn-superoxide dismutase (SOD)-1 knockout mice and also showed inflammation in the lacrimal glands, leading to decreased tear secretion. Tsubota et al.<sup>80</sup> reported upregulation of chemokine CXCL1 in the lacrimal glands of thymectomized NFS/sld mice, leading to lymphocyte infiltration and decreased tear secretion.

Regarding conjunctival/corneal inflammation, Tsubota et al.<sup>44</sup> also evaluated the expression of inflammatory markers of conjunctival cells in Sjögren's syndrome. They showed that IFN- $\gamma$  and TNF- $\alpha$  are factors for HLA-DR upregulation in conjunctival cells.<sup>44</sup> Later, Wakamatsu et al.<sup>81</sup> reported increased density of DCs in the conjunctiva using IVCN in patients with Sjögren's syndrome,<sup>36</sup> which was correlated strongly with the oxidative stress markers of the ocular surface lipid in the tear film. The investigators postulated that oxidative stress can be an inciting factor in the generation of ocular surface inflammation.<sup>81</sup> Recently, He et al.<sup>37</sup> found an increased density of corneal DCs in patients with GVHD-induced dry eye using IVCN, which was correlated strongly with the results from a variety of dry eye assessments, such as TBUT, Schirmer's test, and ocular surface disease index (OSDI). They also found an increased density of nerve branching points and tortuosity of subbasal nerves in GVHD-induced dry eye.<sup>37</sup> These morphologic changes have been reported in autoimmune diseases, such as rheumatic arthritis<sup>82</sup> and Graves's ophthalmology.<sup>83</sup> Yagi et al.<sup>72</sup> reported a proinflammatory cytokine storm in the tears of patients with SJS, which was suppressed by therapeutic modalities, such as those using intensive steroids therapy. Their group showed that tear cytokine levels can decrease after ocular surface reconstruction by limbal stem cell transplantation in patients with SJS.<sup>68</sup> They observed the time-course alteration of tear cytokine levels and found that tear cytokines decreased to baseline levels after the conjunctival epithelium regenerated and healed completely.<sup>72</sup>

Regarding MGD, Matsumoto et al.<sup>84</sup> first identified inflammatory cells in the eye lids of patients with obstructive MGD using IVCN in 2009. They also showed its reduction after anti-inflammatory treatment. Ban et al.<sup>85</sup> also found infiltration of inflammatory cells in the Meibomian glands of patients with GVHD using IVCN, suggesting that the inflammatory response caused excessive fibrosis and atrophy of these glands. In a laboratory study, Ibrahim et al.<sup>86</sup> reported decreased tear secretion, Meibomian gland atrophy, and increased proinflammatory cytokine levels in the tear film, leading to MGD in an experimental model of (SOD)-1 knockout mice.

#### Non-Inflammatory Process of Dry Eye in Office Workers

These previous studies demonstrated the inflammatory response in humans and murine models with dry eye. The Asia Dry Eye Society (ADES) defined dry eye as "a multifactorial disease characterized by unstable tear film causing a variety of symptoms and/or visual impairment, potentially accompanied by ocular surface damage."<sup>87</sup> Compared to the international definition,<sup>88</sup> the ADES definition highlight "unstable tear film" as the pivotal mechanism of dry eye.<sup>87</sup> Uchino et al.<sup>89</sup> reported that short

tear-film break-up-time (TFBUT)-type dry eye (unstable tear film) was more prevalent than other types of dry eye in a survey among visual display terminal (VDT) workers. Therefore, their colleagues conducted basic research on dry eye in VDT workers. Nakamura et al.<sup>90</sup> created a novel rat model of dry eye, by placing a rat on a balance swing in combination with air exposure to produce an evaporative environment as a model of VDT users. They first showed decreased tear secretion in office workers, which was dependent on the number of years of VDT use. Next, they demonstrated lacrimal gland dysfunction as a decrease in tear secretion, which recovered after cessation of the swing activity.<sup>90</sup> Kamoi et al.<sup>91</sup> evaluated the morphologic changes in secretory vesicles in the lacrimal glands and found no infiltration of immune cells in VDT users, whereas the number of immune cells in the lacrimal gland of Sjögren's syndrome significantly increased. From these findings, they proposed a new "non-inflammatory" mechanism for VDT work-related dry eye, in which a tear secretion disorder, probably related to a decreased blinking rate, leads to an excessive accumulation of secretory vesicles, while tear production is intact. In contrast, the mechanism of dry eye in Sjögren's syndrome is impaired tear production and secretion due to inflammation in the lacrimal gland.<sup>91</sup>

## FUTURE DIRECTIONS: COMPREHENSIVE APPROACH TO UNDERSTANDING OCULAR SURFACE INFLAMMATION

### Corneal Nerve and Immune Homeostasis

The corneal nerve is reduced or altered in patients with ocular surface diseases.<sup>37,38</sup> The cornea is the most innervated tissue in the body with a nerve density of 300 to 600 times that of the skin.<sup>92,93</sup> Corneal nerves penetrate the peripheral corneal stroma and form the subbasal nerve plexus between Bowman's layer and the basal epithelium in a radial distribution.<sup>93</sup> Corneal innervation regulates corneal sensation, provides protective and trophic functions and promotes epithelial integrity, proliferation, and wound healing.<sup>94,95</sup> Regarding corneal nerve alteration in human subjects, specific changes occur to the corneal subbasal nerve density and morphology in dry eye,<sup>96,97</sup> as reported in patients with keratoconus,<sup>98,99</sup> diabetes,<sup>100</sup> and infectious keratitis,<sup>49,101</sup> and as a result of corneal surgery.<sup>102-104</sup> Recent studies have revealed that the peripheral nervous system (PNS) not only mediates information exchange between the central nervous system and peripheral tissues, but also regulates innate immune responses through hormonal and neuronal routes as a nonspecific response to pathogens.<sup>105,106</sup> In contrast, dysfunction of the PNS may result in proinflammatory innate immune responses, termed "neurogenic inflammation."<sup>107-110</sup> Further, adrenergic nerves have been identified as regulators of leukocyte recruitment to and within tissues.<sup>111,112</sup> In the cornea, Cruzat et al.<sup>101</sup> evaluated the density of DCs and corneal nerve loss in eyes affected by infectious keratitis, such as bacterial, fungal, and Acanthamoeba keratitis, using *in vivo* confocal microscopy. They found the concomitant increase in DC density and pronounced decrease in corneal nerve density, whereas less DC infiltration occurred in eyes with moderate corneal nerve loss. They concluded that the increased density of DC was correlated with the decreased corneal nerve density, suggesting a potential interaction between the immune and nervous system in infectious keratitis.<sup>101</sup> Their research team also found that the tear cytokine levels are positively correlated with the density of corneal immune cells and inversely correlated with the corneal nerve density in eyes with

infectious keratitis,<sup>49</sup> suggesting that tear cytokine levels can signify inflammation of the ocular surface.

### Dry-Eye-Associated Inflammation and the Corneal Microenvironment

Dry-eye-associated inflammation may change the corneal microenvironment. It has been well documented that the inflammation occurs in the subbasal cornea, conjunctiva, and Meibomian and lacrimal glands. Recently, Kheirkhah et al.<sup>113</sup> reported reduced corneal endothelial cell density (CECD) and nerve density in patients with dry eye. They speculated that a lower CECD is due to the reduction of corneal nerves in dry eye, because a concomitant decrease in corneal nerve and CECD has been reported in other etiologies, such as herpetic keratitis,<sup>114,115</sup> and Fuchs' endothelial corneal dystrophy.<sup>116</sup> Further, Kheirkhah et al.<sup>117</sup> showed that low corneal nerve density is associated with a higher reduction rate of CECD in patients with dry eye. We recently found elevated levels of aqueous cytokines in chronic ocular surface diseases, which suggests the existence of chronic inflammatory conditions in the anterior chamber, leading to cataract formation or reduction of CECD, if the corneal epithelial barrier function breaks down.<sup>63</sup> Furthermore, we demonstrated a connection among iris pigment damage, elevated cytokine levels in the aqueous humor and CECD in eyes with various ocular conditions, including bullous keratopathy and post-penetrating keratoplasty,<sup>118-121</sup> providing evidence that a "chronic inflammatory" microenvironment in the anterior segment of the eye supports the pathogenesis of these conditions. With chronic inflammation, various changes occur: loss of goblet cells in the conjunctiva, limbal stem cell loss, aqueous tear deficiency, immune cell infiltration into the corneal stroma, decreased CECD, corneal nerve loss and elevated cytokine levels in the tears and aqueous humor. The cornea, lacrimal glands, tears, conjunctiva, iris and aqueous humor are anatomically close and the pathogenic alteration of one can affect another. Goblet cells, for example, maintain DCs in an immature state and modulate the local immune response.<sup>122</sup> They also present antigens to underlying APCs via goblet cell associated antigen passages without a break in epithelial integrity.<sup>123,124</sup> Research on the aqueous humor found that the inflammatory cytokine levels increased by a 1000-fold in some eyes, compared to those of healthy controls, which influences not only IOP, but also corneal neovascularization, tear composition, and the condition of the corneal nerves, corneal immune cells and epithelium. In other words, in normal eyes, there appears to be some mechanism for orchestrating homeostasis among tear production, nerves, and immune cells in the cornea. Although the results of these articles can be influenced by confounding factors, such as prior intraocular surgery and preexisting iris damage, future studies on their association with dry eye will be important to understand their physiologic and pathologic impacts. Because dry eye presents as tear film instability, future studies on how ocular surface inflammation changes the corneal microenvironment through its etiopathogenesis, especially in eyes with severe types of dry eye, such as SJS, OCP, or chemical burn, despite the absence of apparent and subclinical inflammation, will be valuable.

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