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Impact of dupilumab treatment on the ocular surface – a review of current evidence

Mateusz Kubicz[1], Julia Kucza[1], Marzena Jargiło[1], Sebastian Sirek[2,3], Ewa Mrukwa-Kominek[2,3]

[1] Students' Scientific Club, Department of Ophthalmology, Faculty of Medical Sciences in Katowice, Medical University of Silesia, Katowice, Poland
[2] Department of Ophthalmology, Faculty of Medical Sciences in Katowice, Medical University of Silesia, Katowice, Poland
[3] Department of Adult Ophthalmology, Prof. Kornel Gibinski University Clinical Center, Medical University of Silesia, Katowice, Poland

Summary: Dupilumab is a human monoclonal antibody used in the treatment of diseases associated with type 2 inflammatory responses, such as atopic dermatitis and bronchial asthma. With the increasing use of this therapy, adverse effects are being reported more frequently, including those affecting the visual system, collectively referred to as dupilumab-associated ocular surface disease. Dupilumab acts by blocking IL-4 and IL-13 signaling, which leads to the inhibition of the type 2 inflammatory response. Disruption of the IL-13 pathway can impair goblet cell function and disturb tear-film homeostasis. The most common clinical manifestations of dupilumab-associated ocular surface disease include symptoms of dry eye disease, blepharitis, and keratoretinitis. This is a significant clinical concern and may adversely affect patient quality of life. Nevertheless, with timely collaboration between allergists and ophthalmologists and the implementation of appropriate pharmacological treatment, effective symptom control is usually achievable, and complete discontinuation of dupilumab therapy is rarely required. Further studies are needed to clarify the mechanism underlying the development of dupilumab-associated ocular surface disease in order to establish appropriate preventive strategies and treatment approaches.

Key words: dupilumab, dupilumab-associated ocular surface disease (DAOSD), ocular surface, dry eye disease (DED), conjunctivitis, biologic therapy.

1. Introduction

Dupilumab is a human monoclonal antibody used in the treatment of diseases driven by the dominance of the type 2 (Th2) immune response, such as atopic dermatitis, bronchial asthma, and chronic rhinosinusitis with nasal polyps [1, 2]. Owing to its high efficacy, this agent has found widespread application in clinical practice [1]. As the number of patients treated with dupilumab continues to grow, increasing attention has been directed toward ophthalmic adverse effects [3]. The most frequently described complications include conjunctivitis, symptoms of dry eye disease (DED), blepharitis, and other alterations of the ocular surface. The mechanism responsible for the development of this condition has not yet been fully elucidated [3, 4]. The pathogenesis is believed to be multifactorial, involving goblet cell dysfunction, tear-film alterations, and localized immune response disturbances [4]. Growing attention is also being paid to the impact of these changes on quality of life and treatment adherence.

The objective of this study is to present the current state of knowledge regarding the effects of dupilumab therapy on the ocular surface, focusing on the pathophysiological mechanisms, clinical manifestations, and therapeutic management.

2. Ocular surface and tear film

2.1 Ocular surface – components

The ocular surface is an integrated system of anatomical and functional structures responsible for protecting the visual system and maintaining its homeostasis. It comprises the cornea, conjunctiva, lacrimal glands, meibomian glands, and the lacrimal apparatus. Together, they form the lacrimal functional unit, which is responsible for tear-film production, distribution, and maintenance of its properties [5]. The conjunctiva contains goblet cells responsible for secreting mucins. These cells play a specialized role in maintaining proper hydration of the ocular surface, reducing friction during eyelid movements, and providing protection against environmental factors and microorganisms [6, 7].

2.2 Tear film and its functions

Tear film plays an essential role in maintaining proper lubrication, visual quality, and the integrity of the corneal and conjunctival epithelium. It consists of three main layers: lipid, aqueous, and mucin [5]. The lipid layer, produced mainly by the meibomian glands, limits excessive tear evaporation; the aqueous layer is responsible for supplying nutrients and substances involved in antimicrobial defense; and the mucin layer enables the uniform spreading of the tear film across the ocular surface [5, 7]. Disturbances in tear-film composition or stability lead to increased friction on the ocular surface, epithelial damage, and the development of a chronic inflammatory process [7].

2.3 Immunological significance of the ocular surface

Beyond its protective function, the ocular surface contributes to the regulation of the local immune response. This process involves epithelial cells, goblet cells, tear-film components, and local immune response mechanisms. Goblet cells, in addition to their role in mucin production, possess immunomodulatory properties and participate in maintaining a healthy ocular surface environment [6]. Goblet-cell dysfunction and tear-film destabilization are recognized as important mechanisms involved in the development of the ocular surface changes observed in patients treated with dupilumab [3].

3. Dupilumab

Dupilumab is a human IgG4 monoclonal antibody directed against the alpha subunit of the interleukin-4 receptor (IL-4Rα) [1]. By binding to the IL-4Rα receptor, it blocks both IL-4 and IL-13 signaling via type 1 and type 2 receptors.

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The type 1 receptor is expressed on cells including B and T lymphocytes, monocytes, eosinophils, and fibroblasts, and is a heterodimeric receptor complex consisting of the IL-4Rα subunit and the common γ chain. The type 2 receptor, found on monocytes, fibroblasts, eosinophils, activated B lymphocytes, epithelial cells, goblet cells, and smooth muscle cells, consists of the IL-4Rα subunit and the IL-13Rα1 (interleukin-13 receptor alpha-1 subunit) [8].

Dupilumab binds the shared subunit of both receptors, inhibiting the downstream IL-4 and IL-13 signaling cascade. Signaling via transcription factors such as STAT6, IL-4 and IL-13 induce the expression of TARC and eotaxin-3, and are responsible for multiple inflammatory processes such as eosinophil migration into tissues, immunoglobulin class switching, and collagen production by fibroblasts. IL-13 additionally promotes mucus production, goblet cell hyperplasia, and increased smooth muscle contractility [8, 9]. By binding to IL-4Rα and IL-13Rα1, dupilumab prevents signaling through the IL-4/IL-13 axis, which results in the suppression of pro-inflammatory cytokine signaling and the reduction of type 2 immune responses [8, 10]. Inhibition of this pathway blocks the key biological effects of the Th2 response – for example, eosinophilic infiltration in the lungs, the expression of inflammatory cytokines and chemokines, and Th2 cell-induced antigen-presenting cell activation [8].

Patients using dupilumab may experience side effects such as hypersensitivity reactions, vasculitic rash, worsening of pulmonary symptoms in asthma patients, eosinophilic pneumonia, cardiac complications, and neuropathy [10]. Ophthalmic complications most commonly affect patients with atopic dermatitis (AD). Mild complications include conjunctivitis and blepharitis. Moderate complications include keratitis, corneal ulceration, elevated intraocular pressure (glaucoma), and mild symptoms requiring pharmacological treatment for over a week. Severe adverse events include cystoid macular edema, chorioretinitis, and any adverse effects leading to vision loss [11].

4. Dupilumab-associated ocular surface disease (DAOSD)

4.1 Definition and clinical significance

Dupilumab-associated ocular surface disease is a collective term for adverse events affecting the ocular surface in patients treated with dupilumab [11, 12]. The spectrum of changes is broad and includes, among other conditions, conjunctivitis, DED symptoms, blepharitis, and keratitis [4, 11, 12].

4.2 Pathophysiology

The exact mechanism responsible for the development of DAOSD has not yet been fully understood, but current data indicate its multifactorial nature [12–14]. One of the most frequently discussed mechanisms is the impact of IL-4/IL-13 pathway blockade on conjunctival goblet cell function. IL-13 plays a role in regulating the proliferation of these cells and mucin production [6]. Inhibition of IL-13 signaling can lead to a decrease in goblet cell count and reduced mucin secretion, which in turn results in tear-film destabilization and increased susceptibility of the ocular surface to inflammatory changes [3, 15]. Disturbances in the local immune response and alterations within the ocular surface play a significant role. The imbalance between defensive mechanisms and inflammatory processes promotes the chronic persistence of ocular symptoms [11]. Available findings are not definitive, and no single mechanism explains all observed cases of DAOSD. Currently, it is accepted that the development of these changes depends on the interaction of immunological factors, tear-film disturbances, and individual patient characteristics [11, 12].

4.3 Clinical symptoms

The most frequently described manifestation of DAOSD is conjunctivitis [4, 12, 15]. Patients primarily report eye redness, pruritus, tearing, burning, and a sensation of ocular discomfort [4, 12]. Symptom severity can vary widely – from mild irritation to more severe changes requiring ophthalmic consultation [11]. Some patients also exhibit symptoms characteristic of DED, including a feeling of dryness, a foreign body or "gritty eyes" sensation, burning, and reduced visual comfort [5]. Blepharitis has also been described in the course of DAOSD, manifesting as redness, irritation, and inflammatory changes within the eyelids [12, 15]. Less common are more severe disorders involving the cornea, such as keratitis or ulceration [11, 12]. Severe adverse events occur rarely but can lead to visual impairment and require urgent ophthalmic treatment [11]. The most common clinical manifestations of DAOSD are summarized in Table I.

Clinical manifestation	Symptoms	Clinical significance
Conjunctivitis	redness, pruritus, tearing, burning	most commonly reported manifestation of DAOSD
Dry eye disease	dryness, foreign body sensation, burning, discomfort	may significantly impair comfort and quality of life
Blepharitis	redness, irritation, inflammatory changes	may exacerbate tear-film instability
Keratitis	pain, photophobia, reduced visual acuity	requires thorough ophthalmic evaluation
Severe/rare manifestations	corneal ulceration, severe visual impairment	may require urgent specialist treatment

Tab. I. Most common clinical manifestations of DAOSD.

4.4 Risk factors

Studies to date suggest that the development of DAOSD may be associated both with patient characteristics and the features of the underlying disease [12]. Adverse events affecting the ocular surface are observed more frequently in patients treated with dupilumab for atopic dermatitis than in patients treated for other indications [4, 11].

Potential factors increasing the risk of developing DAOSD include a more severe course of atopic dermatitis, pre-existing ocular surface diseases, allergic conjunctivitis, blepharitis, and DED [11, 12].

Some studies have also indicated a possible association between an increased risk of ocular alterations and elevated IgE levels or eosinophilia [11]. However, these results are not definitive and require further verification [9].

4.5 Diagnosis

The diagnosis of DAOSD is primarily based on the analysis of clinical symptoms, medical history, and an ophthalmic examination [11]. Establishing when symptoms first appeared relative to the initiation of dupilumab therapy and identifying prior ocular surface diseases is of critical importance [11, 16]. The ophthalmic examination includes a slit-lamp assessment of the ocular surface, analysis of corneal and conjunctival changes, and evaluation of signs of inflammation [11]. In patients with tear-film disturbances, additional tests may be required – measurement of tear break-up time (TBUT), the Schirmer test, and assessment of ocular surface integrity using fluorescein staining [17, 18].

To quantitatively assess symptom severity and its impact on daily functioning, standardized questionnaires such as the Ocu-

lar Surface Disease Index (OSDI) are also used [19]. In cases of persistent or severe symptoms, collaboration between the ophthalmologist and the physician managing the biologic therapy is recommended [16].

4.6 Treatment and management

The management of DAOSD depends on the severity of clinical symptoms and the extent of changes involving the ocular surface [11, 14]. In most cases, appropriately selected ophthalmic treatment allows for the continuation of dupilumab therapy [12, 16]. In mild cases, management is primarily symptomatic, encompassing artificial tears, lubricants, and eyelid-margin hygiene [14, 20]. The aim of this approach is to improve tear-film stability, reduce irritation, and alleviate the severity of reported complaints [7, 20]. Patients with more pronounced symptoms may require topical anti-inflammatory treatment with glucocorticosteroids, calcineurin inhibitors, or other immunomodulatory agents [14, 16, 20]. Despite the occurrence of adverse effects involving the ocular surface, complete discontinuation of dupilumab is rarely necessary [12, 16].

5. Conclusions

Dupilumab therapy is an effective therapy for diseases associated with Th2 responses. However, its use may be associated with adverse effects involving the ocular surface. Dupilumab-associated ocular surface disease manifests with a broad spectrum of symptoms, among which conjunctivitis, dry eye disease, and blepharitis are the most common. Although a growing number of publications address the mechanism underlying DAOSD, they have not been fully clarified, and all evidence points to a multifactorial pathogenesis. Prompt recognition and appropriate treatment enable symptom control and the continuation of biologic therapy in the majority of cases.

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Reprint requests to:
Mateusz Kubicz (e-mail: mateusz.kubicz15@gmail.com)
Students' Scientific Club, Department of Ophthalmology, Faculty of Medical Sciences in Katowice, Medical University of Silesia, Katowice, Poland,
Ceglana 35, 40-514 Katowice