ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Review Article

Management of the adverse effects of dupilumab in atopic dermatitis and prurigo nodularis

Manejo dos eventos adversos do dupilumabe na dermatite atópica e no prurigo nodular

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ABSTRACT

Atopic dermatitis (AD) and prurigo nodularis (PN) are inflammatory skin diseases characterized by various lesions such as eczema, papules, and nodules, with marked pruritus and, in severe cases, significant impairment of quality of life for patients and their families. Dupilumab is approved in Brazil for the management of both moderate/severe AD and PN that does not respond to topical treatments. The efficacy and safety of dupilumab have been extensively established for both conditions in clinical trials and real-world studies. This article aims to review the main adverse events (AEs) associated with the use of dupilumab in AD and PN and assist in their management. Since the introduction of dupilumab a few years ago, the main reported AEs have been injection site reactions, ocular surface disease (non-infectious conjunctivitis, blepharitis, dry eyes), eosinophilia, and facial/neck erythema. Other manifestations have also been observed in patients with AD on dupilumab, but without proven association: psoriasis, arthralgia, and alopecia areata. Although AEs very infrequently lead to discontinuation of dupilumab, it is crucial that physicians prescribing it for these conditions, dermatologists, and immunologists know how to detect and manage its possible adverse effects.

Keywords: Atopic dermatitis, prurigo nodularis, dupilumab, drug-related side effects and adverse reactions, management.

RESUMO

A dermatite atópica (DA) e o prurigo nodular (PN) são doenças inflamatórias da pele que cursam com lesões variadas, como eczemas, pápulas e nódulos, acompanhados de intenso prurido e, nos casos graves, de importante prejuízo da qualidade de vida para os pacientes e seus familiares. O dupilumabe está aprovado no Brasil para o manejo das duas condições: DA moderada/grave e PN que não responde aos tratamentos tópicos. A eficácia e segurança do dupilumabe foram amplamente estabelecidas para ambas as condições em ensaios clínicos e estudos de vida real. Este artigo tem como objetivo revisar os principais eventos adversos (EAD) associados ao uso do dupilumabe em DA e PN, e auxiliar no seu manejo. Desde o início do uso da medicação, há alguns anos, os principais EAD reportados foram: a reação no local da injeção, a doença da superfície ocular (conjuntivite não infecciosa, blefarite, olhos secos), a eosinofilia e o eritema de face/pescoço. Outras manifestações também foram observadas em pacientes com DA em uso de dupilumabe, mas sem associação comprovada: psoríase, artralgia e alopecia areata. Apesar de muito infrequentemente levarem à suspensão do dupilumabe, é fundamental que os médicos prescritores deste medicamento para estas condições, dermatologistas e imunoalergistas, saibam detectar e manejar seus possíveis eventos adversos.

Descritores: Dermatite atópica, prurigo nodular, dupilumabe, eventos adversos, manejo.

Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease, with eczematous lesions of typical location depending on age and severity of pruritus.[1,2] The prevalence of AD is approximately 15% in children and 5% in adults, and is increasing.[3,4] AD is the primary cause of skin complaint in childhood and the second in adolescence leading patients to seek specialist care, as shown in a Brazilian

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study.[5] Living with AD can be a burden, especially for those requiring long-term systemic treatment, because the immunosuppressants used sometimes fail to control the condition and may lead to serious adverse reactions. Itch and skin lesions cause sleep disturbances, anxiety, depression, low self-esteem, and inability to perform physical, school, and work activities, compromising the quality of life of patients and family members.[6] Disease severity is associated with decreased quality of life, both for patients and their family.[7]

Prurigo nodularis (PN) is also a chronic inflammatory skin disease, very itchy and characterized by firm, isolated or confluent papules and/or nodules, most commonly seen in middle-aged patients and women. Systemic diseases such as nephritis, type 2 diabetes, and HIV infection may be associated with PN. The pathogenesis is still unclear, but immune dysregulation and neural circuits play an important role in the vicious cycle of skin itching and scratching.[8]

Traditional treatment for both diseases includes topical corticosteroids, topical calcineurin inhibitors, emollients, phototherapy, gabapentinoids, and immunosuppressants, with a wide range of adverse effects.[3,6] A few years ago, dupilumab proved to be highly effective and safe for AD, with numerous studies demonstrating its efficacy and safety in both clinical trials and real-world settings.[9-12] Recently, dupilumab was also approved as a treatment for PN in the United States[13] and in Brazil.[14] Two phase 3 randomized clinical trials (LIBERTY-PN PRIME and PRIME2) showed statistically significant improvements in itch and skin lesions in PN with dupilumab vs placebo. Adverse events were consistent with the known safety profile.[15]

Dupilumab was the first immunobiologic agent approved for the treatment of moderate-to-severe AD and PN unresponsive to topical treatments in Brazil. It is a fully human IgG4 monoclonal antibody that directly targets the shared alpha subunit of the interleukin (IL)-4 and IL-13 receptors.[16] These 2 cytokines are involved in type 2 helper T-cell (Th2) immune response, inducing allergen sensitization, promoting atopic inflammation, and reducing the function and structure of the skin barrier. The antibody inhibits the action of these cytokines and promotes changes in gene expression in AD lesions, improving their molecular signature.[17] Several studies have shown the impressive efficacy and safety of dupilumab in the treatment of AD, in different settings and age groups.[10,18,19] This new personalized treatment approach is based on the pathogenesis of the disease and is a milestone in the treatment of AD, and more recently, PN.

Potential adverse events of dupilumab

Adverse events associated with the use of dupilumab include injection site reaction, ocular surface disease (noninfectious conjunctivitis, blepharitis, dry eye), eosinophilia, and facial/neck erythema, which have been known for some years, since the beginning of medication use. A recent real-world Dutch study also included Meibomian gland dysfunction as a new drug-related adverse event in patients with AD.[20]

Injection site reaction

Local reactions were present in 11.4% of 1888 patients using dupilumab, with erythema being most common, followed by unspecified reaction, pain, and itching at the injection site. There are no reports of drug discontinuation due to local reactions, and, when necessary, treatment is symptomatic, with analgesics or oral anti-inflammatory drugs and topical corticosteroids for a few days.[21]

Ocular surface disease (conjunctivitis, blepharitis, dry eye)

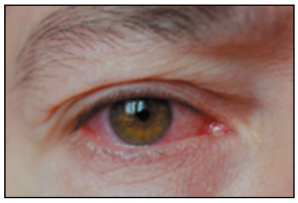
Figure 1 illustrates the differential diagnoses of ocular surface disease. Regardless of the use of dupilumab, patients with AD often present with other associated atopic diseases, such as asthma, rhinitis, food allergy, and allergic conjunctivitis, including a more chronic and severe phenotype called atopic keratoconjunctivitis. A study conducted in the United States to evaluate the association between AD and conjunctivitis in adult patients, between 2001 and 2015, compared the frequency of conjunctivitis events in patients with AD and without AD. The risk of conjunctivitis was 4 times higher in adults with AD (odds ratio [OR] = 4.38; 95% CI, 1.39-13.79; p = 0.012) and, specifically, 8 times higher for allergic conjunctivitis (OR = 8.03; 95% CI, 1.76-36.58; p = 0.007). The conclusion is that adults with AD are significantly more likely to have allergic conjunctivitis than adults without AD.[22] It is essential that physicians who care for these patients be aware of this issue and learn to recognize and manage allergic conjunctivitis. Other studies of adult patients in Iran[23] and the Netherlands[24] also showed similar results, as did other studies of pediatric patients[25-27].

Conjunctivitis is an inflammation of the conjunctiva, a thin, transparent membrane that covers the anterior part of the sclera and the inner surface of the eyelids. Allergic conjunctivitis has an estimated prevalence of 20% worldwide.[28] Symptoms include itching, tearing, hyperemia, and conjunctival edema (chemosis), as well as blurred vision in more severe cases.[29] The association between AD and allergic conjunctivitis can be explained by the fact that these diseases share common pathophysiologic mechanisms. Both involve type II immune response, most often triggered by an allergic process, but also show impairment of physical barrier functions. In addition to skin barrier dysfunction, studies suggest the existence of defects in the ocular surface epithelium in individuals with AD, which would predispose them to conjunctivitis.[30,31]

However, dupilumab-associated conjunctivitis has an unknown pathophysiology. The mean time for the development of dupilumab-associated conjunctivitis ranged from 2 to 8 weeks in clinical trials, and the number of new cases increased over time and appeared to level off around weeks 20-24.[32]

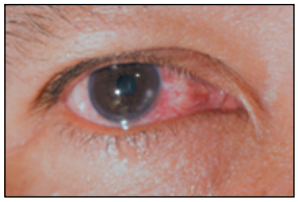
Treatment includes topical agents such as antihistamines, mast cell stabilizers, nonsteroidal anti-inflammatory drugs, and corticosteroids. Avoiding allergens is also essential, and contact lens wearers should avoid putting on lenses during episodes to prevent contamination with infectious agents and complications.[22]

In studies on the safety and efficacy of dupilumab in AD, conjunctivitis was one of the most commonly reported adverse reactions. In pivotal studies, the incidence of conjunctivitis was statistically higher in the dupilumab-treated group (8.6%-22.1%) than in the placebo group (2.1%-11.1%). A recent real-world study, which included 29 French centers and 241 patients, showed a higher conjunctivitis rate of 38%. In this study, the development of conjunctivitis was significantly associated with a personal medical history of allergic conjunctivitis, and in 4% of cases



CONJUNCTIVITIS (inflammation of the conjunctiva)

It may be acute (red eye) or chronic (pink eye). It affects the entire conjunctiva, including the inner surface of the eyelids. The diagnosis is based on ocular discharge: serous, purulent, or mucopurulent. Infections, allergies, and physicochemical irritation are the most common causes. Foreign body sensation, burning, and itching, but no pain.

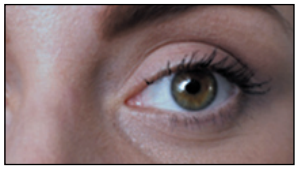


KERATITIS (inflammation of the cornea)

Always associated with severe pain. Other symptoms include foreign body sensation and photophobia. Signs: red eye, watery or purulent discharge, and decreased visual acuity (due to loss of corneal transparency). Penlight examination may reveal corneal ulceration or opacification.

BLEPHARITIS (inflammation of the eyelid)

It corresponds to inflammation of the margin of the eyelid. It is classified as anterior, with sticky plaques or scaly crusting along the eyelashes (typical of staphylococcal or seborrheic dermatitis), or posterior due to Meibomian gland dysfunction (chalazion or oily secretion). Symptoms include a sandy or gritty feeling in the eyes, which may be associated with photophobia and/or increased tear production.



DRY EYE

Due to either insufficient tear production or excessive tear evaporation.

Symptoms include foreign body sensation or eye roughness. The conjunctiva appears normal, but it may be red. Paradoxically, a perception of increased tear flow may occur. Keratoconjunctivitis sicca (Sjögren's syndrome) is characterized by filaments containing mucus with epithelial cells.

Figure 1

Examples of common ocular surface diseases in patients with atopic dermatitis

Adapted from Guex-Crosier Y, et al.[47].

it was a reason for dupilumab discontinuation.[12] In studies on PN, conjunctivitis was the most common adverse event (12.6%; n = 15/119).[8]

Therefore, physicians prescribing dupilumab should be aware of the signs, symptoms, and treatment options in cases where conjunctivitis develops. A suggested algorithm for management of dupilumab-associated ocular surface disease is shown in Figure 2.

Eosinophilia

Eosinophilia is not uncommon in patients treated with dupilumab. Approximately 20% of real-world AD cases experience an increase in eosinophil counts from baseline. Hypereosinophilia (above 1500/mm^3) occurs in 9%-11% of patients. The proposed mechanism is that the drug inhibits eosinophil migration into the tissue, but not eosinophil production in the bone marrow, thus leading to their accumulation in the blood. Eosinophilia is usually transient without clinical consequences.

Dupilumab-associated facial and neck erythema

Dupilumab-associated facial/neck erythema refers to the appearance of erythema on the face and/or neck in patients with AD who did not have lesions in these areas or whose lesions developed characteristics that are different from those of preexisting lesions. The cause remains unclear, but possible etiologies are rosacea, contact dermatitis, *Malassezia furfur* skin

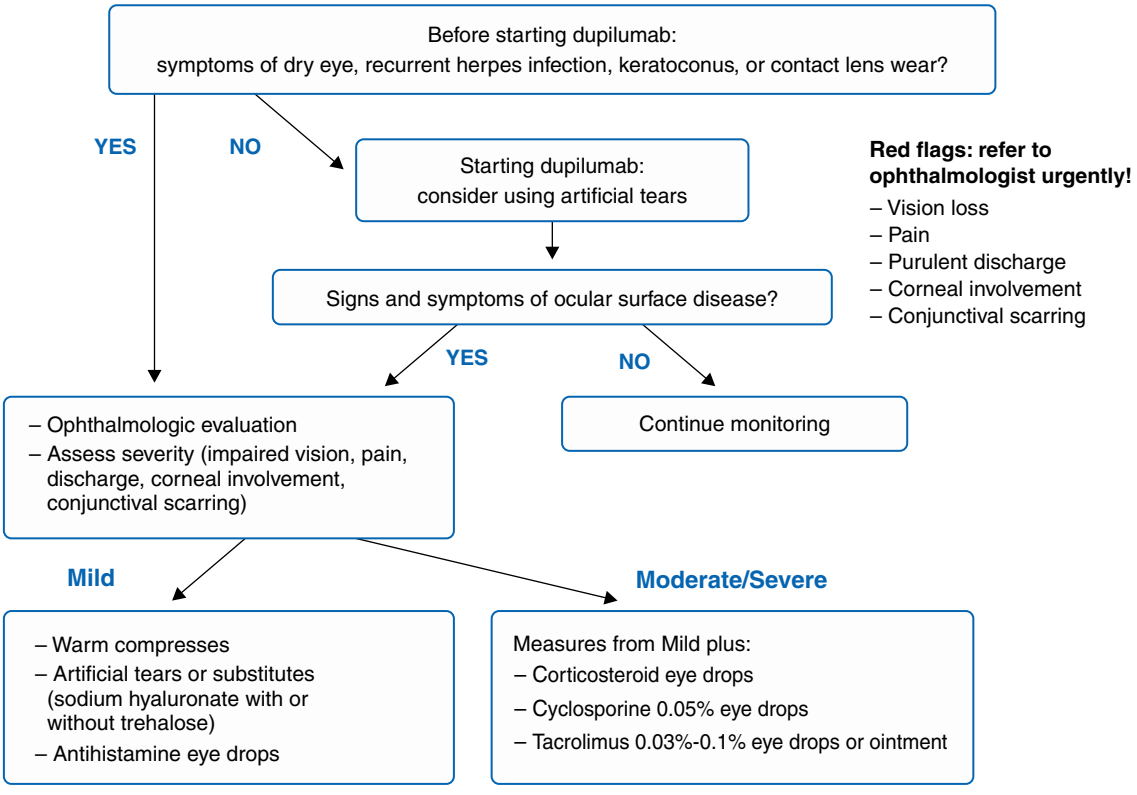


Figure 2
Algorithm for the management of dupilumab-associated ocular surface disease in atopic dermatitis and prurigo nodularis
Adapted from Guex-Crosier Y, et al.[47].

colonization, adverse effects of calcineurin inhibitors, or the discontinuation of topical corticosteroids leading to a worsening of the condition. It should be noted that the vast majority of patients with AD and preexisting lesions on the face improved with dupilumab. A study of 162 dupilumab-treated patients with AD and facial lesions showed improvement in 88.3%, whereas 6.6% remained unchanged and 4.3% experienced exacerbation.[33] In another study of 101 patients diagnosed with facial or neck erythema, 45% reported different skin symptoms from preexisting dermatitis. The most commonly used treatments were topical corticosteroids, topical calcineurin inhibitors, antifungal agents, and topical or oral ivermectin. In this study, 11% of 101 patients with facial/neck erythema discontinued dupilumab owing to this adverse event.[34] In another study of 916 dupilumab-treated patients with AD, facial/neck erythema occurred in 82 (9%).[35]

Other manifestations reported in dupilumab-treated patients with AD, but with no proven association, include psoriasis[36,37], arthralgia[38], and alopecia areata.[35]

Psoriasis

The occurrence of paradoxical psoriasiform reactions (P-PRs) in dupilumab-treated patients has been recently reported. Conversely, cases of eczema in patients treated with immunobiologic agents for psoriasis have also been described. One study identified 42 patients who developed P-PRs, 41 with *de novo* psoriasis and 1 with worsening preexisting psoriasis. All patients responded well to AD treatment with dupilumab before the development of P-PRs, which occurred, on average, 22.65 weeks after starting dupilumab. Treatment options were topical corticosteroids in 38.5%, or systemic therapy in 38.5%, or discontinuation of dupilumab in 32.5%.[36] Another study included 112 patients with AD who developed P-PRs, 101 with *de novo* psoriasis and 11 with worsening preexisting psoriasis. In the first group, patients more frequently developed lesions on the scalp and extremities, on average, 5 months after starting dupilumab, against 4 months after starting dupilumab in the second group. In the *de novo* group, dupilumab was discontinued in 38/101 patients (38%). Discontinuation and/or treatment led to complete remission of psoriasis in 30/63 (48%), incomplete remission in 3/63 (5%), recurrence in 1/63 (1.5%), persistence in 5 /63(8%), and worsening in 6/63(10%). In the second group, 50% discontinued dupilumab.[37]

Arthralgia

Cases of arthralgia as a potential adverse effect of dupilumab treatment in patients with AD have been reported, although they have not occurred during clinical trials. The onset of arthralgia ranged from days to months after the first dose. A real-world study of 4000 patients treated with dupilumab for 6 months showed no increased risk of arthralgia compared with other patients with AD using cyclosporine or mycophenolate mofetil. Therefore, the study concluded that there is no reason for growing concerns about the emergence of new cases of arthralgia associated with dupilumab treatment.[38]

Alopecia areata

In a retrospective study of 916 patients using dupilumab, 11 reported alopecia areata as an adverse event (1.2%).[35] However, other case reports indicate that dupilumab may even be effective in the treatment of concomitant alopecia areata and AD.[39,40]

Conclusion

Conjunctivitis is one of the most common adverse reactions in the treatment of patients with AD using dupilumab, and these same patients, with moderate-to-severe disease, are those who are statistically more likely to develop allergic conjunctivitis. It is important for physicians to be aware of these issues and, if possible, learn to manage conjunctivitis minimally until the ophthalmologist is consulted, according to the algorithm presented here. Several case reports have demonstrated that increasing the spacing between dupilumab injections tends to reduce this adverse effect.[41-45] However, dupilumab discontinuation due to conjunctivitis in patients who respond well to the drug is not at all desirable. Fortunately, this has rarely been required, as early diagnosis and proper treatment of conjunctivitis are often effective measures to control it, allowing patients to continue with AD treatment and to achieve the much-desired disease control.[46]

As for the other adverse events reported here, we can observe that eosinophilia, despite being relatively common, is transient and has no clinical consequences. Local reactions, if present, can be easily managed. Facial/neck erythema remains unclear, as it can have different etiologies and there are many empirical treatment options. Paradoxical reactions of *de novo* psoriasis or worsening preexisting psoriasis have been reported and, albeit infrequent,

reinforce the importance of obtaining personal and family history of autoimmune diseases in patients with AD. Arthralgia does not appear to be a concern because its association with dupilumab treatment has not been confirmed. Alopecia areata associated with AD requires further studies, as it can either be preexisting or develop after the initiation of dupilumab, or even, dupilumab may assist in hair regrowth in alopecia areata.

In conclusion, there is abundant evidence showing the efficacy and safety of dupilumab, and, in daily practice, we are pleased to see the potential improvements achieved with this drug in the lives of patients with moderate-to-severe AD and PN.

References

1. Wollenberg A, Barbarot S, Bieber T, Christen-Zaech S, Deleuran M, Fink-Wagner A, et al. Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part II. J Eur Acad Dermatol Venereol. 2018;32(6):850-78.
2. Wollenberg A, Barbarot S, Bieber T, Christen-Zaech S, Deleuran M, Fink-Wagner A, et al. Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part I. J Eur Acad Dermatol Venereol. 2018;32(5):657-82.
3. Kay J, Gawkrodger DJ, Mortimer MJ, Jaron AG. The prevalence of childhood atopic eczema in a general population. J Am Acad Dermatol. 1994;30(1):35-9.
4. Silverberg JI, Hanifin JM. Adult eczema prevalence and associations with asthma and other health and demographic factors: a US population-based study. J Allergy Clin Immunol. 2013;132(5):1132-8.
5. Giavina Bianchi M, Santos AP, Cordioli E. The majority of skin lesions in pediatric primary care attention could be managed by Teledermatology. PLoS One. 2019;14(12):e0225479.
6. Silverberg JI, Gelfand JM, Margolis DJ, Boguniewicz M, Fonacier L, Grayson MH, et al. Symptoms and diagnosis of anxiety and depression in atopic dermatitis in U.S. adults. Br J Dermatol. 2019;181(3):554-65.
7. Campos ALB, Araújo FM, Santos MALD, Santos AASD, Pires CAA. Impact of atopic dermatitis on the quality of life of pediatric patients and their guardians. Rev Paul Pediatr. 2017;35(1):5-10.
8. Cao P, Xu W, Jiang S, Zhang L. Dupilumab for the treatment of prurigo nodularis: A systematic review. Front Immunol. 2023;14:1092685.
9. Wollenberg A, Beck LA, Blauvelt A, Simpson EL, Chen Z, Chen Q, et al. Laboratory safety of dupilumab in moderate-to-severe atopic dermatitis: results from three phase III trials (LIBERTY AD SOLO 1, LIBERTY AD SOLO 2, LIBERTY AD CHRONOS). Br J Dermatol. 2020;182(5):1120-35.
10. Simpson EL, Bieber T, Guttman-Yassky E, Beck LA, Blauvelt A, Cork MJ, et al. Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis. N Engl J Med. 2016;375(24):2335-48.
11. Stingeni L, Bianchi L, Antonelli E, Caroppo ES, Ferrucci SM, Ortoncelli M, et al. Moderate-to-severe atopic dermatitis in adolescents treated with dupilumab: A multicentre Italian real-world experience. J Eur Acad Dermatol Venereol. 2022;36(8):1292-9.
12. Faiz S, Giovannelli J, Podevin C, Jachiet M, Bouaziz JD, Reguiai Z, et al. Effectiveness and safety of dupilumab for the treatment of atopic dermatitis in a real-life French multicenter adult cohort. J Am Acad Dermatol. 2019;81(1):143-51.
13. Sanofi. Press Release: Dupixent® (dupilumab) approved by FDA as the first and only treatment indicated for prurigo nodularis [Internet]. Available from: https://www.sanofi.com/en/media-room/press-releases/2022/2022-09-28-22-05-26-2524764 .
14. Brasil, Ministério da Saúde, Agência Nacional de Vigilância Sanitária (Anvisa). DUPIXENT (dupilumabe): nova indicação [Internet]. 2023. Available from: https://www.gov.br/anvisa/pt-br/assuntos/medicamentos/novos-medicamentos-e-indicacoes/dupixent-dupilumabe-nova-indicacao-3#:~:text =)%3A%20nova%20indica%C3%A7%C3%A3o-,DUPIXENT%20(dupilumabe)%3A%20nova%20indica%C3%A7%C3%A3o,estes%20tratamentos%20n%C3%A3o%20s%C3%A3o%20aconselhados.
15. Yosipovitch G, Mollanazar N, Ständer S, Kwatra SG, Kim BS, Laws E, et al. Dupilumab in patients with prurigo nodularis: two randomized, double-blind, placebo-controlled phase 3 trials. Nat Med. 2023;29(5):1180-90.
16. Wenzel S, Ford L, Pearlman D, Spector S, Sher L, Skobieranda F, et al. Dupilumab in persistent asthma with elevated eosinophil levels. N Engl J Med. 2013;368(26):2455-66.
17. Guttman-Yassky E, Bissonnette R, Ungar B, Suárez-Fariñas M, Ardeleanu M, Esaki H, et al. Dupilumab progressively improves systemic and cutaneous abnormalities in patients with atopic dermatitis. J Allergy Clin Immunol. 2019;143(1):155-72.
18. Simpson EL, Paller AS, Siegfried EC, Boguniewicz M, Sher L, Gooderham MJ, et al. Efficacy and Safety of Dupilumab in Adolescents With Uncontrolled Moderate to Severe Atopic Dermatitis: A Phase 3 Randomized Clinical Trial. JAMA Dermatol. 2019.
19. Blauvelt A, de Bruin-Weller M, Gooderham M, Cather JC, Weisman J, Pariser D, et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. Lancet. 2017;389(10086):2287-303.
20. Musters AH, van Lookeren FL, van der Gang LF, Middelkamp-Hup MA, Bosma AL, Jessurun NT, et al. Real-world reported adverse events related to systemic immunomodulating therapy in patients with atopic dermatitis: Results from the TREAT NL (TREatment of ATopic eczema, the Netherlands) registry. J Eur Acad Dermatol Venereol. 2023.
21. Kim PJ, Lansang RP, Vender R. A Systematic Review and Meta-Analysis of Injection Site Reactions in Randomized-Controlled Trials of Biologic Injections. J Cutan Med Surg. 2023;27(4):358-67.
22. Wu KK, Borba AJ, Deng PH, Armstrong AW. Association between atopic dermatitis and conjunctivitis in adults: a population-based study in the United States. J Dermatolog Treat. 2019:1-5.
23. Shokouhi Shoormasti R, Pourpak Z, Fazlollahi MR, Kazemnejad A, Nadali F, Ebadi Z, et al. The prevalence of allergic rhinitis, allergic conjunctivitis, atopic dermatitis and asthma among adults of Tehran. Iran J Public Health. 2018;47(11):1749-55.
24. Thyssen JP, Toft PB, Halling-Overgaard AS, Gislason GH, Skov L, Egeberg A. Incidence, prevalence, and risk of selected ocular disease in adults with atopic dermatitis. J Am Acad Dermatol. 2017;77(2):280-6.e1.
25. Schneider L, Hanifin J, Boguniewicz M, Eichenfield LF, Spergel JM, Dakovic R, et al. Study of the Atopic March: Development of Atopic Comorbidities. Pediatr Dermatol. 2016;33(4):388-98.
26. Henriksen L, Simonsen J, Haerskjold A, Linder M, Kieler H, Thomsen SF, et al. Incidence rates of atopic dermatitis, asthma, and allergic rhinoconjunctivitis in Danish and Swedish children. J Allergy Clin Immunol. 2015;136(2):360-6.e2.
27. Stensballe LG, Klansø L, Jensen A, Haerskjold A, Thomsen SF, Simonsen J. The validity of register data to identify children with atopic dermatitis, asthma or allergic rhinoconjunctivitis. Pediatr Allergy Immunol. 2017;28(6):535-42.
28. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Lancet. 1998;351(9111):1225-32.

29. Cronau H, Kankanala RR, Mauger T. Diagnosis and management of red eye in primary care. Am Fam Physician. 2010;81(2):137-44.
30. Yokoi K, Yokoi N, Kinoshita S. Impairment of ocular surface epithelium barrier function in patients with atopic dermatitis. Br J Ophthalmol. 1998;82(7):797-800.
31. Mantelli F, Mauris J, Argüeso P. The ocular surface epithelial barrier and other mechanisms of mucosal protection: from allergy to infectious diseases. Curr Opin Allergy Clin Immunol. 2013;13(5):563-8.
32. Akinlade B, Guttman-Yassky E, de Bruin-Weller M, Simpson EL, Blauvelt A, Cork MJ, et al. Conjunctivitis in dupilumab clinical trials. Br J Dermatol. 2019;181(3):459-73.
33. Ahn J, Lee DH, Na CH, Shim DH, Choi YS, Jung HJ, et al. Facial erythema in patients with atopic dermatitis treated with Dupilumab - a descriptive study of morphology and Aetiology. J Eur Acad Dermatol Venereol. 2022;36(11):2140-52.
34. Jo CE, Finstad A, Georgakopoulos JR, Piguet V, Yeung J, Drucker AM. Facial and neck erythema associated with dupilumab treatment: A systematic review. J Am Acad Dermatol. 2021;84(5):1339-47.
35. Napolitano M, Fabbrocini G, Patruno C. Dupilumab-associated cutaneous adverse events among adult patients with atopic dermatitis: A retrospective study. J Dermatol. 2023;50(7):880-7.
36. Li Y, Liu H, Zhang F. Biologics-Induced Immunophenotypic Cross-Switching in Patients with Psoriasis and Atopic Dermatitis. Indian J Dermatol. 2023;68(2):186-91.
37. Trave I, Salvi I, Burlando M, Cozzani E, Parodi A. "De Novo" Psoriasis and Relapse of Psoriasis Induced by Dupilumab: Three New Cases and Review of the Literature. J Clin Med. 2023;12(19):6291.
38. Schneeweiss MC, Wyss R, Schneeweiss S, Anand P, Jin Y, Dicesare E, et al. Joint pain in patients with atopic dermatitis receiving treatment with dupilumab: A US nationwide cohort study. J Am Acad Dermatol. 2024;90(1):134-7.
39. Yan X, Tayier M, Cheang ST, Liao Z, Dong Y, Yang Y, et al. Hair repigmentation and regrowth in a dupilumab-treated paediatric patient with alopecia areata and atopic dermatitis: a case report. Ther Adv Chronic Dis. 2023;14:20406223231191049.
40. Bur D, Kim K, Rogge M. Dupilumab Induced Hair Regrowth in Alopecia Totalis. J Drugs Dermatol. 2023;22(4):410-2.
41. Treister AD, Kraff-Cooper C, Lio PA. Risk Factors for Dupilumab-Associated Conjunctivitis in Patients With Atopic Dermatitis. JAMA Dermatol. 2018;154(10):1208-11.
42. Maudinet A, Law-Koune S, Duretz C, Lasek A, Modiano P, Tran THC. Ocular Surface Diseases Induced by Dupilumab in Severe Atopic Dermatitis. Ophthalmol Ther. 2019;8(3):485-90.
43. Ivert LU, Wahlgren CF, Ivert L, Lundqvist M, Bradley M. Eye Complications During Dupilumab Treatment for Severe Atopic Dermatitis. Acta Derm Venereol. 2019;99(4):375-8.
44. Barnes AC, Blandford AD, Perry JD. Cicatricial ectropion in a patient treated with dupilumab. Am J Ophthalmol Case Rep. 2017;7:120-2.
45. Levine RM, Tattersall IW, Gaudio PA, King BA. Cicatrizing Blepharoconjunctivitis Occurring During Dupilumab Treatment and a Proposed Algorithm for Its Management. JAMA Dermatol. 2018;154(12):1485-6.
46. Agnihotri G, Shi K, Lio PA. A Clinician's Guide to the Recognition and Management of Dupilumab-Associated Conjunctivitis. Drugs R D. 2019;19(4):311-8.
47. Guex-Crosier Y, Di-Lucca J, Häusermann P, Laffitte E, Saulite I, Schmid-Grendelmeier P, et al. Management of dupilumab-associated ocular surface diseases in atopic dermatitis patients. Swiss Med Wkly. 2021 Aug 20;151:w30020. doi: 10.4414/SMW.2021.w30020.

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