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REVIEW ARTICLE

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Ocular surface disease in moderate-to-severe atopic dermatitis patients and the effect of biological therapy

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Abstract

Atopic dermatitis (AD) is a chronic inflammatory skin disease for which new targeted therapies are currently available. Due to the increased rates of ocular surface disease (OSD) reported during treatment with these new targeted treatments, more insight into the occurrence and pathomechanism of OSD in moderate-to-severe AD patients is needed. Therefore, this review's first part highlights that most patients with moderate-to-severe AD already have characteristics of OSD before starting targeted treatment. Remarkably, not all AD patients with OSD report ocular symptoms. OSD in AD is associated with less conjunctival goblet cells (GC) compared to healthy controls. In addition, OSD severity in AD patients is associated with high AD activity, the presence of eyelid and/or facial eczema, and high levels of AD-related severity biomarkers in tear fluid. The second part of this review highlights that pre-existing ocular pathology (e.g. in combination with the use of ophthalmic medication or eyelid eczema) may be associated with the development of dupilumab-associated ocular surface disease (DAOSD). During dupilumab treatment, DAOSD (which can be new-onset OSD or worsening of pre-existing OSD) is observed in approximately one-third of the dupilumab-treated AD patients. Anti-inflammatory ophthalmic treatment improves DAOSD, and dose reduction of dupilumab may also be an effective treatment option. The pathomechanism of DAOSD is still not fully elucidated. In a prospective study low, but stable conjunctival GC numbers were observed in moderate-to-severe AD patients, before and during dupilumab treatment. However, the Mucin 5AC (MUC5AC) expression of GCs decreased during dupilumab treatment, suggesting an impairment of the GC function by dupilumab treatment. In addition, higher dupilumab tear fluid levels were found in dupilumab-treated AD patients with moderate-to-severe OSD compared to patients with no or mild OSD, whereas the dupilumab serum levels are similar. Clinicians should be aware of the frequent occurrence of OSD in

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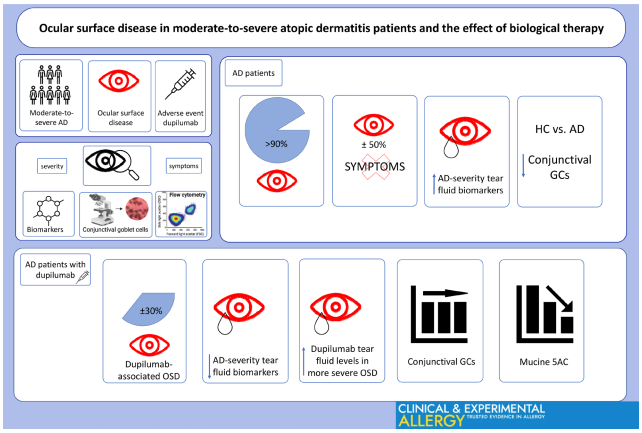
moderate-to-severe AD patients, and a low-threshold referral to an ophthalmologist is recommended.

KEYWORDS
atopic dermatitis, ocular surface diseae, dupilumab



GRAPHICAL ABSTRACT

Ocular surface disease is very common in AD patients, and not all patients reported ocular symptoms. Less conjunctival goblet cells were found in AD patients compared to healthy controls. During dupilumab treatment, approximately 30% of the dupilumab-treated AD patients developed dupilumab-associated ocular surface disease. Stable but low conjunctival goblet cell numbers were found, with a decrease in the Mucin 5AC production. Clinicians should be aware of (DA)OSD in AD patients.

1 | INTRODUCTION

Atopic dermatitis (AD), a chronic, inflammatory skin disease affecting up to 10% of the adult population, is known to be associated with ocular comorbidities.[1,2] Uncontrolled AD around the eyes can lead to chronic scratching and rubbing, contributing to the risk of developing ocular symptoms.[1] Ravn et al. found an overall prevalence of conjunctivitis of 31.7% in AD patients, compared to 13.3% among controls.[3] Other commonly reported ocular diseases in moderate-to-severe AD patients include eyelid eczema, superficial punctate keratopathy, allergic conjunctivitis, atopic keratoconjunctivitis, cataract, increased risk of retinal detachment, keratoconus, and viral ocular infections.[1,4]

The development of ocular side effects during treatment with new targeted therapies (especially biological therapy) indicated for moderate-to-severe AD highlights the importance of better understanding ocular surface disease (OSD) in AD patients and has renewed the interest in ocular comorbidity in patients with AD.[5] OSD can be used as an umbrella term for various ocular diseases (Figure 1).

Dupilumab is a fully human monoclonal antibody that targets the interleukin (IL)-4 receptor (IL-4Rα), resulting in inhibition of the T helper(Th) 2 pathway, which has demonstrated its efficacy and safety in both clinical trials and real-world studies.[6–8] Dupilumab-associated ocular surface disease (DAOSD) has been reported in up to 34% of dupilumab-treated AD patients in daily practice.[5–7] This review aims to further specify the clinical characteristics of (DA)OSD in moderate-to-severe AD patients and its pathomechanism.

Key messages

- OSD is very common in AD patients and associated with AD severity and facial involvement.
- Pre-existing ocular pathology (combined with ophthalmic medication or eyelid eczema) is associated with developing (DA)OSD.
- Clinicians should be aware of (DA)OSD in AD, low-threshold referral to an ophthalmologist is recommended.

2 | PART I: OCULAR SURFACE DISEASE IN ATOPIC DERMATITIS PATIENTS

2.1 | OSD in moderate-to-severe AD: diagnosis and severity measurement

We previously investigated OSD in moderate-to-severe AD patients ($n = 70$) who were investigated both dermatologically ophthalmologically.[9] To objectively assess the severity of OSD, we have introduced the Utrecht Ophthalmic Inflammatory and Allergic (UTOPIA) disease score.[10] This standardized ophthalmic examination includes the severity of inflammation of the ocular surface (Figure 2A).[10] An overall severity category is given per eye based on the grading of the individual characteristics (Figure 2A).[10] The higher the UTOPIA score, the more severe the patient's OSD.

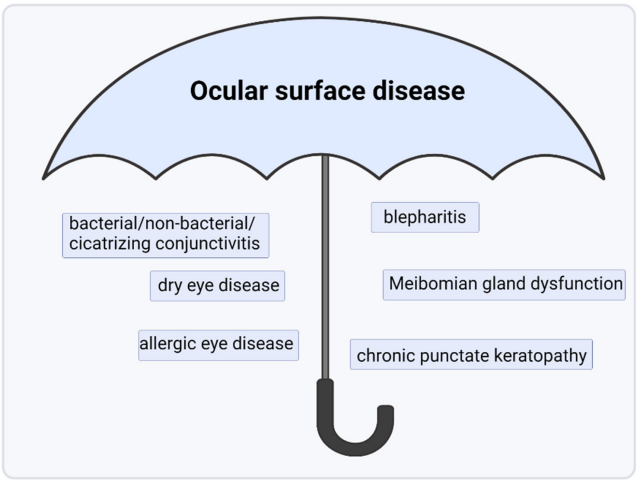


FIGURE 1 Eye conditions that fall under the term ocular surface disease.[65] Figure created in Biorender.

Current literature uses different terminology to describe diseases of the ocular surface (e.g. conjunctivitis and blepharoconjunctivitis, both of which are part of OSD), making it difficult to compare studies. In addition, the characteristics of allergic conjunctivitis are different from those of AD-related OSD (Figure 2B). Therefore, different terms are used when referring to specific studies in this review. Furthermore, several methods are used in the current literature to diagnose OSD, including patient-reported diagnosis, physician-confirmed diagnosis (without examination by an ophthalmologist), and ophthalmologist-confirmed diagnosis (with or without the use of an objective scoring system). Many studies do not describe how OSD is diagnosed, or how to differentiate between different degrees of severity of ocular inflammation. This highlights the importance of using a standardized ophthalmic examination. By using a standardized score, such as the UTOPIA score, the severity of OSD can be measured over time, and the effect of different local and systemic treatments can be evaluated in more detail.

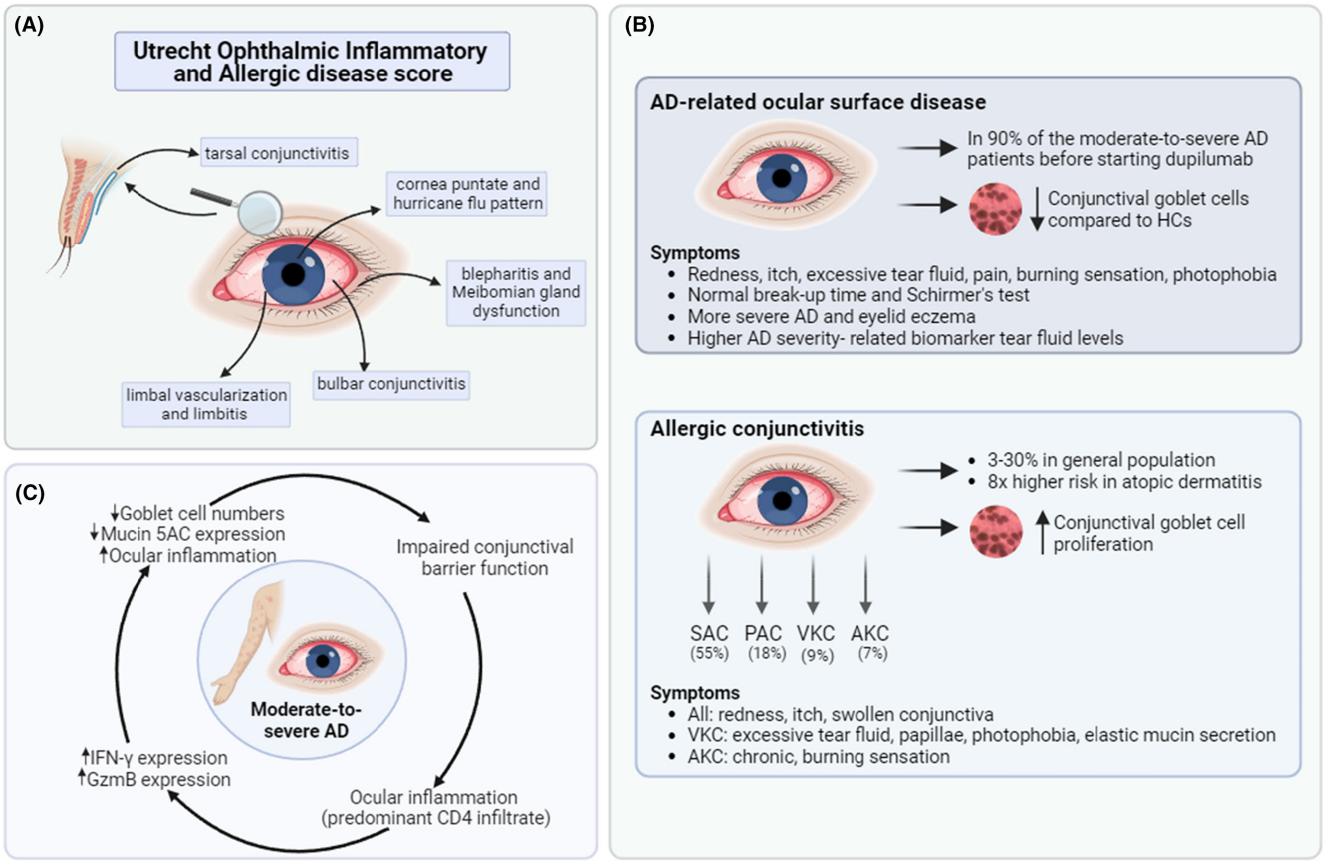


FIGURE 2 UTOPIA-score, characteristics of different ocular diseases, and its hypothesis. (A) The individual characteristics of the Utrecht Ophthalmic Inflammatory and Allergic disease score (UTOPIA-score).[10] All individual characteristics are categorized per severity: no, mild, moderate or severe inflammation, which will be combined to provide an overall severity score. (B) AD-related ocular surface disease and allergic conjunctivitis: two different entities. Characteristics of AD-related ocular surface disease compared to allergic conjunctivitis.[27,31,66–71] (C) Hypothesis regarding the decreased goblet cell numbers and the ocular inflammation found in moderate-to-severe atopic dermatitis patients. AD, atopic dermatitis; AKC, atopic keratoconjunctivitis; HCs, GzmB, granzyme B; healthy controls; IFN-γ, interferon-gamma; PAC, perennial allergic conjunctivitis; SAC, seasonal allergic conjunctivitis; VKC, vernal keratoconjunctivitis. Figure created in Biorender.

We have prospectively demonstrated that most patients with moderate-to-severe AD already have OSD before the start of biological treatment (90.0%, $n = 60/70$).[9] In line with our results, Dogru et al. described papillary hypertrophy of the tarsal conjunctiva and blepharitis in most patients with moderate-to-severe AD (76.2% and 71.4%, respectively).[9,11] A study by Touhouche et al. also performed an ophthalmic examination in moderate-to-severe AD patients before starting dupilumab.[12] Interestingly, they observed papillae (a sign of tarsal conjunctivitis) in 17/46 (37.0%) patients, which is less than our finding of tarsal conjunctivitis in 57/70 (81.4%) patients.[9,12] However, Touhouche et al. did not describe clear definitions of the ophthalmic examination and the grading of the papillary severity, making comparison with the results of our study difficult.[9,12]

The importance of performing a standardized ophthalmological examination when investigating OSD in AD patients is emphasized by the fact that only half of the patients with OSD report ocular symptoms, as we have previously described.[9] This shows that patient-reported OSD is less reliable, leading to possible underdiagnoses of OSD. Bortoluzzi et al. also found this discrepancy, as they reported a lack of correlation between the Ocular Surface Disease Index (OSDI), which focuses in part on symptoms of OSD, and the clinical evaluation of the ocular surface.[13] Low OSDI scores were observed in patients with severe ocular surface involvement.[13]

2.2 | Associations between OSD and AD

Despite the knowledge that OSD is common in moderate-to-severe AD patients, ophthalmic examination in these patients is seldom performed in daily practice.[14] However, as Foley et al. pointed out, the UTOPIA score may not be a suitable tool for the dermatologist, as this examination is performed with a slit lamp and requires ophthalmic knowledge and experience.[15] This emphasizes the need to learn more about the associations between OSD and dermatological, ophthalmological, and clinical factors to identify which patients need an ophthalmic examination and ophthalmological treatment.

Our prospective study of OSD in AD revealed that patients with moderate-to-severe OSD have more severe AD, based on a higher Eczema Area and Severity Index (EASI), higher Investigator Global Assessment (IGA), and higher serum Thymus and Activation-Regulated Chemokine (TARC) levels than patients with no or mild OSD.[9] Additionally, significantly more patients with moderate-to-severe OSD reported eyelid or facial eczema in the past year compared to patients with no or mild OSD.[9] Dogru et al. also found an association between OSD and eyelid or facial eczema in AD patients.[11] In addition, they observed higher grades of conjunctival squamous metaplasia, which may occur as a result of chronic ocular inflammation, in patients with facial atopy and suggested that this may be the basis for the clinical morbidity of corneal complications in AD patients.[11,16] In line with these results, we found in our study that the head neck EASI correlated with the UTOPIA score, indicating that patients with eyelid or facial eczema have significantly more severe OSD.[17] Altogether, the presence of eyelid or facial eczema and more severe AD may indicate an increased risk of (undiagnosed) OSD.

2.3 | Management of OSD

OSD can be treated with artificial tears, inflammatory eye drops and/or tacrolimus skin ointment. Tacrolimus skin ointment has shown efficacy in the treatment of OSD in various studies.[18,19] Therefore, we advise to treat OSD in an early stage with tacrolimus skin ointment. If this is not sufficient, referral to an ophthalmologist is recommended for additional treatment with, for example, anti-inflammatory eye drops (e.g., corticosteroids).

2.4 | Pathophysiology

2.4.1 | Conjunctival inflammation characteristics of OSD in AD

To learn more on the pathomechanism of OSD in AD, we have investigated tear fluid biomarkers in AD patients ($n = 16$).[17] Significantly higher periostin, IL-22 and TARC tear fluid levels were measured in patients with moderate-to-severe OSD compared to patients with no or mild OSD.[17] Interestingly, TARC, periostin and IL-22 are known biomarkers for clinical severity of AD.[20,21] The relationship between these biomarkers in tear fluid and the severity of AD might be explained by local production or by an impaired barrier function of the ocular surface epithelium. Yokoi et al. showed that the ocular surface barrier is impaired in AD patients with blepharoconjunctivitis (e.g., blepharitis and conjunctivitis).[22,23] As reported in our study of OSD in AD, patients with moderate-to-severe OSD had blepharitis and tarsal conjunctivitis, suggesting that these patients had a similar barrier dysfunction as described by Yokoi et al.[9,22]

Taken together, these findings show that AD patients with moderate-to-severe OSD have high levels of AD-related tear fluid biomarkers, possibly due to the AD-related impaired conjunctival barrier function and/or local production by activated conjunctival epithelial cells, which are related to the severity of AD. This indicates that these patients may be predisposed to AD-related OSD, which is different from allergic conjunctivitis.

2.4.2 | Conjunctival goblet cells and Mucin 5 AC expression in moderate-to-severe AD patients

The assumption that patients with moderate-to-severe AD are predisposed to OSD is also supported by the lower number of conjunctival goblet cells (GCs) in these patients compared to healthy controls, as demonstrated in our study of OSD in AD.[9,24] Conjunctival impression cytology (CIC), a non-invasive technique to collect the first cell layers of the conjunctival epithelium, was used to investigate the number of GCs and their function. One of

the main mucins produced by these GCs is Mucin 5AC (MUC5AC), which has a protective function for the ocular surface.[25] GCs also have an important function in the mucosal immune system through the production of immunoregulatory factors, resulting in suppression of the production of several cytokines, including interferon-gamma (IFN-γ).[26–28] In line with our findings, Dogru et al. previously reported significantly lower conjunctival GC densities in AD patients compared to controls.[9,11] In addition, results from our prospective study of OSD in AD show that conjunctival GC counts were lower in AD patients with more severe OSD, suggesting that the number of GCs in AD patients is negatively correlated with the severity of the inflammation.[9]

To investigate the function of the conjunctival GCs in AD-related OSD, we also examined the MUC5AC secretion of the GCs.[9] CIC samples from moderate-to-severe AD patients were analysed by using flow cytometry. Higher MUC5AC expression was found in patients with more severe OSD, while their GC numbers were lower compared to patients with no or mild OSD. Furthermore, our prospective study of (DA)OSD in AD patients shows a non-significant but higher expression of MUC5AC in AD patients compared to healthy controls ($n=69$).[24] Previous literature reports that increased expression of MUC5AC, in patients with reduced conjunctival GC numbers, could be a defense response to compensate for the impaired ocular surface.[29]

It has been suggested that CD4+ cells that infiltrate the conjunctival epithelium may include Th1 cells, which could induce IFN-γ secretion.[26,30] Expression of IFN-γ is inversely correlated with GC density of the bulbar conjunctiva, suggesting that increased IFN-γ expression may lead to a lower number of GCs in moderate-to-severe AD patients.[26] The initial increased MUC5AC expression could be a defense response to compensate for the lower GC numbers. Eventually, a lower number of GCs could reduce the ocular surface protection due to decreased MUC5AC secretion, which may result in an impaired conjunctival barrier function leading to ocular inflammation. We hypothesize that this results in a self-reinforcing chain of events that influence each other (Figure 2C).

In other ocular diseases, such as graft-versus-host disease, the number of GCs is also negatively correlated with the severity of inflammation.[27] In contrast, GC hyperplasia and mucin hypersecretion have been reported in conjunctival papilloma, chronic injuries, atopic keratoconjunctivitis, and allergic conjunctivitis.[27,31] The Th2 cytokine IL-13 normally increases conjunctival GC proliferation and reduces GC apoptosis.[25] It has been suggested that exposure to allergens stimulates GC proliferation and mucin secretion.[27] The low conjunctival GC densities that are observed in moderate-to-severe AD patients with OSD indicate that AD-related OSD has a different pathogenesis than allergic conjunctivitis (Figure 2B).

2.5 | Brief summary

Taken together, OSD is very common in moderate-to-severe AD patients and is associated with low conjunctival GC numbers; possibly due to their (AD-related) conjunctival inflammation. Remarkably, many patients do not report ocular symptoms, which can result underdiagnosis and undertreatment. In addition, moderate-to-severe OSD in AD patients is associated with more severe AD, eyelid eczema in the past year and higher levels of AD-related severity tear fluid biomarkers (Figure 2B).

3 | PART II: DUPILUMAB-ASSOCIATED OCULAR SURFACE DISEASE IN ATOPIC DERMATITIS PATIENTS

The aim of this second part is to provide insight into DAOSD in moderate-to-severe AD patients during dupilumab treatment by reviewing the literature on clinical risk factors contributing to the development of DAOSD, the (clinical) characteristics of DAOSD, and its underlying pathomechanism.

3.1 | Risk factors for developing DAOSD

As DAOSD is the most commonly reported side effect in dupilumab-treated AD patients, it is desirable to identify which patients are at risk of developing DAOSD. We previously identified risk factors for developing DAOSD in patients with moderate-to-severe AD ($n=469$).[32] Self-reported DAOSD was found in 152/469 (32.4%) patients, and univariate analyses showed an association between eyelid eczema in the past year and developing DAOSD, which was also found by Touhouche et al.[12]

This raises the question whether patients with pre-existing OSD are predisposed to developing DAOSD. In the above-mentioned study including 469 AD patients, it was reported that having a history of any eye disease (excluding self-reported allergic conjunctivitis) requiring ophthalmic medication before starting dupilumab treatment is a risk factor for developing self-reported DAOSD.[32] Katsuta et al. also found that AD patients with DAOSD were more likely to have a history of ocular complications, suggesting that patients who develop DAOSD may already have an (undiagnosed) ocular disease that possibly worsens during treatment with dupilumab.[33,34]

Taken together, pre-existing ocular pathology (e.g., especially when requiring ophthalmic medication or eyelid eczema) may be associated with developing DAOSD.[32]

3.2 | Signs and symptoms of DAOSD

More knowledge is needed regarding ophthalmic characteristics of DAOSD. Therefore, we recently examined the frequency and severity of DAOSD in a prospective study, in which 69 patients were investigated both dermatologically and ophthalmologically before and during dupilumab treatment.[24] Severity of (DA)OSD was assessed by the UTOPIA score (Figure 2A).[10] Our findings showed that OSD was present in 91.3% ($n=63/69$) of the patients before starting dupilumab treatment.[24] While none of the 20 patients who

developed DAOSD (i.e., ≥3 points increase in UTOPIA from baseline) had limbitis at baseline, 5/20 (25.0%) patients showed limbitis at the onset of DAOSD. Severe chronic (DA)OSD with limbal involvement, defined as limbitis, may be the result of chronic limbal inflammation. Limbitis could lead to limbal stem cell deficiency with possible irreversible long-term effects, such as conjunctivalization (i.e., conjunctival tissue covering the cornea which may lead to visual loss), requiring long-term follow-up.[35,36]

Remarkably, only half of the patients with (DA)OSD report symptoms before and during dupilumab treatment.[9,24] Therefore, the patient-reported diagnosis appears to be less reliable.[9,13,24] It is possible that low corneal sensitivity may play a role in the low symptomatic ocular surface condition in AD patients with OSD, as reduced corneal sensitivity scores have been observed in patients with atopic keratoconjunctivitis, dry eye disease, and Sjögren's syndrome.[37–39] Adita et al. stated that reduced corneal sensation was correlated with the severity and chronicity of dry eye disease in patients with Sjögren's syndrome, suggesting that subjective symptoms may decrease over time due to its chronicity.[39] Interestingly, the patient-reported diagnosis seemed to be more reliable in the case of DAOSD (e.g., new-onset DAOSD or worsening of pre-existing OSD), as 18/20 (90.0%) patients with DAOSD reported symptoms at the onset of DAOSD.[24] Therefore, we hypothesize that patients with AD-related OSD may report fewer symptoms due to its chronicity and that patients with DAOSD report symptoms more adequately due to a more acute onset. However, it is also possible that patients in our study were more focused on reporting symptoms due to the performed ophthalmic examination.[24]

3.3 | Treatment of DAOSD

We recently investigated the effect and prescription frequency of ophthalmic treatments in a study where ophthalmic treatment was started in the case of pre-existing OSD or DAOSD.[24] Only few patients were treated with ophthalmic drugs before starting dupilumab treatment, indicating that OSD in AD is often undetected and undertreated.[24] Most patients ($n=63/69$, 91.3%) in our study had OSD before starting dupilumab treatment. Half ($n=38/64$, 59.4%) of these patients started ophthalmic treatment already at baseline, which was continued after 4 weeks of dupilumab treatment.[24] After 28 weeks of treatment 55.1% ($n=38/69$) of the patients were still using ophthalmic therapy.[24] A total of 20 patients developed DAOSD during the study, which was controlled (i.e., patients with a previous increase ≥3 points in UTOPIA score from baseline but no longer at week 28) in 50.0% of the patients ($n=10/20$) at week 28, of whom 6/10 were receiving anti-inflammatory ophthalmic treatment (e.g., ophthalmic steroids, tacrolimus skin ointment).[24] This indicates that anti-inflammatory therapies can be effective in treating (DA)OSD, and suggests that early treatment reduces the severity of DAOSD. However, it might also be possible that the patients in our study had less severe (DA)OSD due to early ophthalmic treatment.[24]

Popiela et al. retrospectively observed DAOSD in 32.1% ($n=9/28$) of dupilumab-treated AD patients and found a good response to corticosteroid eye drops in 7/9 patients.[33] Nahun et al. retrospectively investigated 37 dupilumab-treated AD patients and described the rapid resolution of DAOSD (specifically with blepharoconjunctivitis) after treatment with tacrolimus skin ointment ($n=4$).[40] We have recently shown improvement of OSD in dupilumab-treated AD patients who were treated with tacrolimus skin ointment on the external eyelids, as it possibly diffuses through the eyelids to the eye.[24] Combined with our previous findings that eyelid eczema may be associated with developing DAOSD and is related to AD-related OSD, this suggests that early treatment of eyelid eczema might lead to a reduced risk of developing (DA)OSD.[9,32]

3.3.1 | Long-term follow-up of DAOSD

Overall, the long-term management of DAOSD can be challenging. Ophthalmic corticosteroids are effective in treating DAOSD but can cause long-term side effects (e.g., cataract and glaucoma). Therefore, data on the long-term follow-up of patients with DAOSD are needed.[41] In a prospective case series, we found self-reported DAOSD in 66/167 (39.5%) of the dupilumab-treated AD patients, of which 33/66 (50.0%) patients were referred to an ophthalmologist.[10] Most of these 33 patients still had mild-to-moderate DAOSD after long-term follow-up (mean duration of 17.5 months), despite anti-inflammatory ophthalmic treatment.[10] This is comparable to the findings of Popiela et al., who described that 67.0% ($n=6/9$) of the dupilumab-treated AD patients remained on ophthalmic corticosteroid medication after a mean follow-up of 16 months.[33]

However, long-term data of dupilumab trials (phases 1–3) in AD patients showed that after 3–4 years of treatment with dupilumab, the majority of DAOSD cases resolved with ophthalmic treatment (e.g., ophthalmic corticosteroids).[42–44] These results contradict our previous findings, as we found that most patients still suffered from mild-to-moderate DAOSD during long-term follow-up despite anti-inflammatory ophthalmic treatment, of which long-term use (in the case of ophthalmic corticosteroids) is not recommended.[10,41] The differences may be explained by the fact that the phase 3 trials investigated patient-reported diagnosis, which appears to be less reliable. Moreover, the studies that investigated long-term data from the dupilumab trials excluded patients who discontinued dupilumab treatment due to side effects, such as DAOSD.[42–44] However, the follow-up in the dupilumab trials was longer than the follow-up in our study, which may also explain the differences and suggest that DAOSD may improve after a longer period of treatment.[10] Long-term real-world data on DAOSD are needed to compare with data from the dupilumab trials.

3.3.2 | Effect of dose adjustment of dupilumab on DAOSD

We recently investigated the effect of dose adjustment of dupilumab on DAOSD.[10] Prolongation of the dosing interval to 300 mg dupilumab every 3–5 weeks due to DAOSD in 10/33 (30.0%) patients resulted in improvement of ocular inflammation ($n=6$) or remission ($n=1$). Dupilumab was discontinued due to ocular pathology in 3/33 (9.1%)

patients, leading to improvement or remission in all cases.[10] Patruno et al. found improvement of ocular symptoms in 46.6% ($n=7/15$) of the patients with DAOSD after prolongation of the dosing interval to 300 mg every 3–4 weeks, without worsening of AD.[45] In addition, Spekhorst et al. reported persistent AD control in patients who tapered the dosage of dupilumab due to controlled AD.[46] The beneficial effect of dose reduction on DAOSD seems in contrast to the study by Akinlade et al., who pooled data on dupilumab concentrations of phase 3 dupilumab trials from baseline to week 16 and suggested that the incidence of DAOSD may decrease with higher serum concentrations of dupilumab.[5] However, these studies reported patient-reported DAOSD, and we did not find a relationship between dupilumab concentrations and the development of DAOSD.[47] In addition, the first phase 3 dupilumab trials (SOLO 1 and 2) reported lower rates of DAOSD than other phase 3 trials and real-world data, possibly because less was known about DAOSD at that time.[5,6] Since prolongation of the dosing interval may reduce the severity of DAOSD, and does not lead to exacerbation in AD patients with controlled disease, this could be an effective strategy to reduce the severity of DAOSD.[46]

3.3.3 | Switching to a different treatment for AD due to DAOSD

If DAOSD cannot be controlled, switching to a different targeted AD therapy may be a solution. Phase 3 trials of tralokinumab, a biologic therapy that specifically targets IL-13, reported fewer OSD as adverse events compared to phase 3 trials of dupilumab (7.5% vs. 8.6–22.1%, respectively).[5,48] However, low percentages of DAOSD were also observed in the early dupilumab trials. A head-to-head trial, which would be needed to compare OSD rates between these biological therapies, has not yet been conducted. As tralokinumab specifically targets IL-13, it is hypothesized that this may lead to less OSD compared to dupilumab, which affects both IL-4 and IL-13 signalling.[48] However, the pathomechanism leading to OSD during both dupilumab and tralokinumab is yet not fully understood.[48] Our prospective case series described the effect of switching from dupilumab to tralokinumab treatment in 4 AD patients with DAOSD, and suggested that some patients with DAOSD may benefit from switching to tralokinumab.[49] Further studies are needed to learn more about the effect of tralokinumab treatment on DAOSD.

Figure 3 summarizes the recommendations for referral to an ophthalmologist in case of ophthalmic symptoms during dupilumab treatment.

3.4 | Pathomechanism of DAOSD in AD

3.4.1 | Dupilumab tear fluid levels and OSD severity in AD patients

The exact pathomechanism of DAOSD in AD patients remains unclear. Several hypotheses have been suggested, such as undertreatment of the eyes by dupilumab.[50] This hypothesis was based on an inverse relationship between serum dupilumab levels at week 16 and the development of DAOSD.[50] However, we recently measured dupilumab levels in tear fluid and serum, and related these findings to the severity of OSD during dupilumab treatment in 48 AD patients.[51] At week 28 of dupilumab treatment, median dupilumab tear fluid levels were significantly higher in patients with moderate-to-severe OSD compared to patients with no or mild OSD, while serum levels were not related to OSD severity.[51] Our results disprove the hypothesis that undertreatment of the eyes by dupilumab leads to the development or worsening of OSD during dupilumab treatment.[5]

Dupilumab is a monoclonal IgG4 antibody and elevated levels of IgG in tear fluid have been found in several ocular diseases.[52–58] It is known that IgG crosses the blood-tear barrier as a result of ocular inflammation and increased vascular permeability.[59] In addition, an impaired conjunctival barrier is found in AD patients with blepharoconjunctivitis.[22] Taken together, this may lead to leakage of IgG (including the IgG4 antibody dupilumab) from the vessels into the tear fluid, resulting in the detection of dupilumab in the tear fluid. As tear fluid IgG levels may be a marker for the extent of inflammation,[59] this may also explain why higher levels of dupilumab are found in the tear fluid of patients with more severe OSD.

3.4.2 | Relationship between serum dupilumab levels and developing DAOSD

Akinlade et al. reported that the incidence of DAOSD decreased with higher dupilumab serum concentrations.[5] This is in contrast to our study results, showing no relationship between serum dupilumab levels and DAOSD severity after 28 weeks of treatment with dupilumab.[51] A possible explanation for this difference may be that we assessed the severity of (DA)OSD by an ophthalmic examination, whereas Akinlade et al. based DAOSD on patient-reported symptoms.[5] In line with our study, Spekhorst et al. showed no relationship between serum dupilumab levels and the development of DAOSD in 295 dupilumab-treated AD patients.[47,51] Interestingly, in-vitro studies have shown that IL-4Rα is also present on conjunctival epithelial cells.[60,61] A pilot study has demonstrated that dupilumab levels were detected on conjunctival epithelial cell suspensions and reduced conjunctival IL-4Rα expression was observed after 4 weeks of treatment with dupilumab.[51] Since dupilumab-treated AD patients with more severe OSD had high levels of dupilumab in tear fluid, it is possible that this leads to complete blocking of IL-4Rα on conjunctival cells.[51] This is supported by the finding that prolonging the dupilumab dosing interval resulted in less signs and symptoms of DAOSD, possibly as a result of reduced dupilumab levels in the eyes.[10] Taken together, these results indicate that dupilumab reaches the ocular surface, and that the increased local drug availability in the eyes may play a role in the development of DAOSD. Furthermore, as Hansen et al. reported that IL-4Rα is present on conjunctival GCs, we hypothesize that local dupilumab levels could worsen (DA)OSD by interfering with the conjunctival GC development, which is normally affected by IL-13.[61]

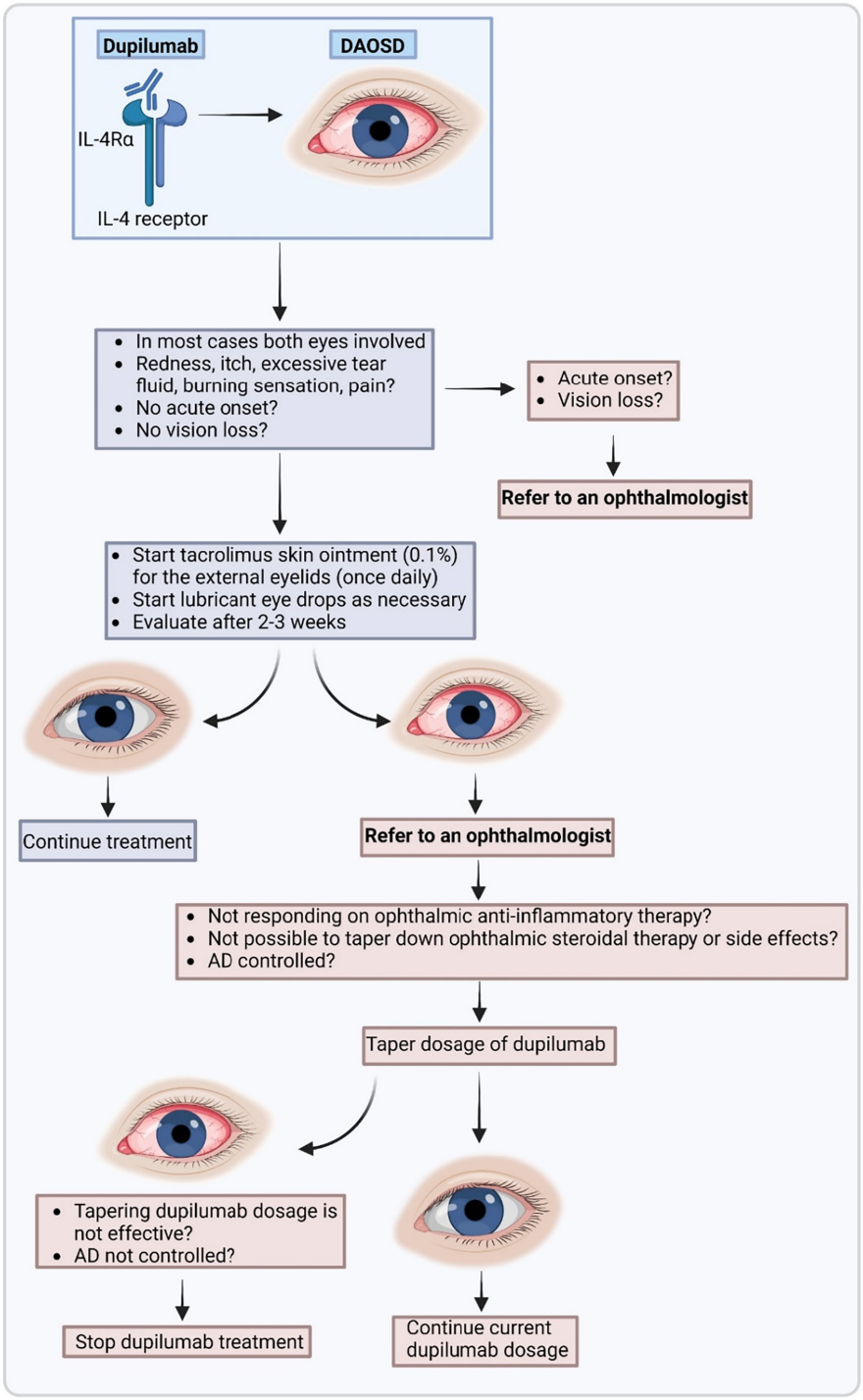


FIGURE 3 Recommendations regarding management and referral to an ophthalmologist in case of dupilumab-associated ocular pathology. AD, atopic dermatitis; DAOSD, dupilumab-associated ocular surface disease; IL, interleukin. Figure created in Biorender.

3.4.3 | Effect of dupilumab on conjunctival GCs and MUC5AC

GC scarcity may play a role in the development of DAOSD, as previous case studies reported scarcity of conjunctival GCs ($n=6$) and recurrence of GCs after discontinuation of dupilumab ($n=1$).[62,63] However, moderate-to-severe AD patients already have lower conjunctival GCs compared to healthy controls before starting dupilumab treatment.[9] Recently, we have shown in 69 dupilumab-treated AD patients that the number of conjunctival GCs increased slightly during dupilumab treatment while the percentage of Cytokeratin 19 (CK19)-CD45-MUC5AC+ cells, which is the main mucin produced by the GCs, decreased significantly.[24] In addition, DAOSD was observed in 28.9% ($n=20/69$) of the patients, in whom the number of GCs remained stable and the percentage of CK19-CD45-MUC5AC+ cells decreased at the onset of DAOSD compared

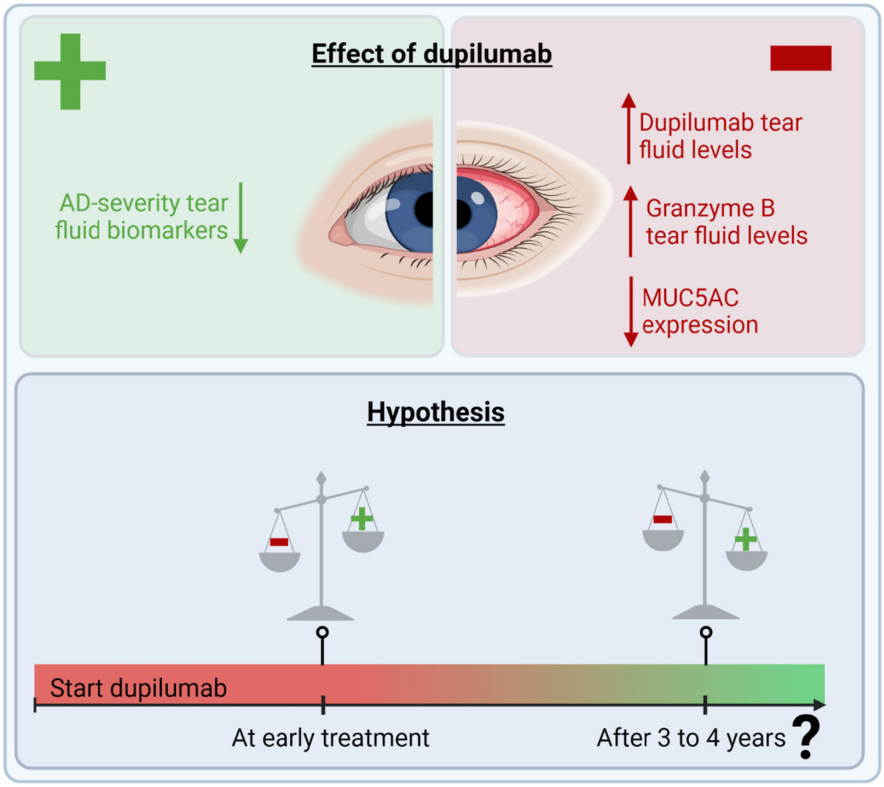


FIGURE 4 Hypothesized positive and negative ocular effects associated with dupilumab. Figure created in Biorender. AD, atopic dermatitis; MUC5AC, mucin 5AC.

to baseline.[24] A relative deficiency of MUC5AC in the tear fluid of dupilumab-treated patients was also reported by Barnett et al.[64] Taken together, these findings suggest that the function of the conjunctival GCs may be impaired as a result of dupilumab treatment, which is reflected by decreased MUC5AC expression.

3.4.4 | Conjunctival biomarkers during dupilumab treatment

AD-related severity biomarkers, such as IL-22 and TARC are used as markers for inflammation, and decrease during dupilumab treatment.[6,20] This suggests that dupilumab treatment leads to a decrease in the AD-related severity biomarkers in tear fluid, indicating a possible beneficial effect of dupilumab on AD-related OSD. On the other hand, we have observed an impairment of GC function by dupilumab, suggesting that dupilumab could have both a positive and a negative effect on OSD in AD patients. We hypothesize that this imbalance may shift in favour of the beneficial effect after a longer treatment period with dupilumab, as long-term data from the dupilumab trials showed that most cases of DAOSD resolved over time (Figure 4).[42–44]

3.4.5 | Hypothesis on the development of DAOSD

Our original hypothesis on DAOSD development is shown in Figure 5A. Dupilumab blocks IL-4 and IL-13 signalling. Blocking of IL-4 leads to less proliferation of Th2 cells and less inhibition of the proliferation of Th1 and Th17 cells. This might lead to a disbalance between these cells, leading to a Th-1 inflammatory response. The blocking effect of dupilumab on IL-13 might lead to less GC hyperplasia, leading to fewer GCs and less mucus production.

The revised hypothesis on DAOSD development including the results from this review is shown in Figure 5B. Not the number of GCs, but the Mucin 5AC production by GCs is affected by dupilumab. Blocking of IL-4 may lead to less proliferation of Th2 cells and less inhibition of the proliferation of Th1 and Th17 cells. As tear fluid biomarkers showed no differences in Th1- and Th17- related biomarkers during dupilumab treatment, the theory that blocking of IL-4 leads to less proliferation of Th2 cells, and increased proliferation of Th1 and Th17 cells could yet not be fully confirmed.

3.5 | Brief summary

DAOSD occurs in approximately one-third of the dupilumab-treated AD patients. Pre-existing ocular pathology (e.g. in combination with ophthalmic medication or eyelid eczema) is associated with the development of (patient-reported) DAOSD. We hypothesize that the blockade of IL-4 and IL-13 signalling by dupilumab leads to the impairment of GC function, contributing to the development of DAOSD.

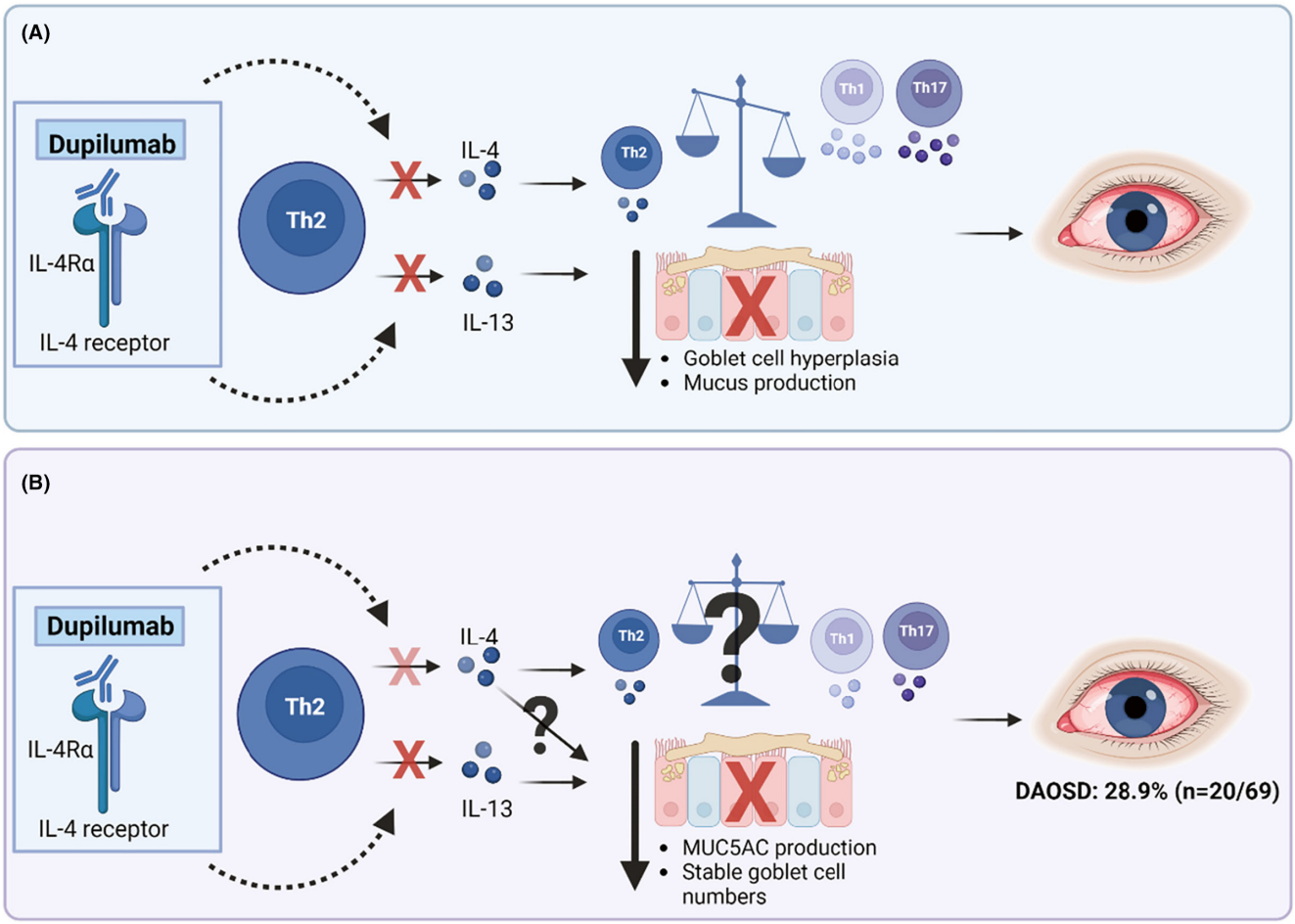


FIGURE 5 Hypothesis on the pathomechanism of dupilumab-associated ocular surface disease (DAOSD). (A) Original hypothesis on DAOSD development that was studied in the prospective studies described in this review. (B) Revised hypothesis on DAOSD development including the results of the prospective studies described in this review. AD, atopic dermatitis; DAOSD, dupilumab-associated ocular surface disease; IL, interleukin; MUC5AC, Mucin 5AC; Th, T helper. Figure created in Biorender.

AUTHOR CONTRIBUTION

All authors have been involved in drafting the manuscript or revising it critically and have given final approval for the version to be published.

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None.

CONFLICT OF INTEREST STATEMENT

Roselie Achten has nothing to disclose. Judith Thijs is a speaker for Sanofi, Janssen, Almirall, and LEO Pharma. Marlot van der Wal has nothing to disclose. Chantal van Luijk is a speaker for Sanofi and Santen. Daphne Bakker is a speaker for Sanofi, Janssen, and LEO Pharma. Edward Knol is a speaker and advisory board member for Sanofi Genzyme. Matthijs van Luin has nothing to disclose. Mohsin el Amrani has nothing to disclose. Eveline Delemarre has nothing to disclose. Ahmed Elfiky has nothing to disclose. Joke de Boer has nothing to disclose. Femke van Wijk is a speaker and/or consultant for Janssen, Johnson & Johnson, and Takeda. Marlies de Graaf is a consultant, advisory board member and/or speaker for AbbVie, Eli Lilly, Janssen, LEO Pharma, Pfizer, Regeneron Pharmaceuticals and Sanofi. Marjolein de Bruin-Weller is a consultant, advisory board member, and/or speaker for AbbVie, Almirall, Aslan, Arena, Eli Lilly, Galderma, Janssen, Leo Pharma, Pfizer, Regeneron Pharmaceuticals, and Sanofi.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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