



# A Literature Review of Real-World Effectiveness and Safety of Dupilumab for Atopic Dermatitis

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Atopic dermatitis (AD) is a chronic inflammatory skin disease with pruritus, characterized by recurrent eczema with exacerbations and remissions. AD impairs patients' QOL and places a heavy burden on patients. Recently, dupilumab, an anti-IL-4R $\alpha$  antibody, was approved for the treatment of patients with moderate-to-severe AD who are refractory to topical agents and/or conventional systemic therapy. Clinical trials of dupilumab for AD demonstrated high efficacy and tolerable safety profiles. Furthermore, real-world evidence of dupilumab for AD is accumulating. Most of these data show favorable effectiveness and safety profile; however, they also clarified issues, including conjunctivitis and facial redness. There are still a certain number of patients with significant failure. In this article, we review real-world evidence of dupilumab for AD, identify concerns specific to dupilumab, and discuss unmet needs and issues to be addressed in the future.

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## INTRODUCTION

Dupilumab, an anti-IL-4R $\alpha$  antibody, demonstrated efficacy for patients with moderate-to-severe atopic dermatitis (AD) who are refractory to topical agents and/or conventional systemic therapy with tolerable safety in clinical trials (Blauvelt et al., 2017; de Bruin-Weller et al., 2018b; Simpson et al., 2016b). Real-world evidence of dupilumab for AD has been accumulating. Most of those data show favorable effectiveness and safety profile; however, the gap between results of clinical trials and real-world data has been revealed, including effectiveness, the frequency of conjunctivitis, and facial redness. This article mainly focuses on and discusses those issues raised especially by real-world data. Furthermore, although results of clinical trials and real-world data demonstrated that dupilumab is effective in most patients with AD, there is still a significant number of patients

with significant failure. For instance, in the LIBERTY AD SOLO 1 clinical trial, the percentage of patients receiving dupilumab who attained improvement of at least 50% on the Eczema Area and Severity Index (EASI), that is, EASI-50, from baseline to week 16 was 69% in patients receiving dupilumab every other week (q2w) (Simpson et al., 2016b). It reciprocally represents that around 30% of patients were refractory to dupilumab, which is still a large number. We also discuss the possible causes of inadequate response to dupilumab in certain patients with AD.

## EFFICACY AND SAFETY OF DUPILUMAB FOR AD IN CLINICAL TRIALS

### Efficacy and safety of dupilumab for adult patients with AD in clinical trials

Four major randomized, placebo-controlled, phase 3 trials of dupilumab in adult patients with moderate-to-severe AD whose disease was inadequately controlled by topical treatment were conducted: LIBERTY AD SOLO 1, SOLO 2, CHRONOS, and CAFÉ (Blauvelt et al., 2017; de Bruin-Weller et al., 2018b; Simpson et al., 2016b). LIBERTY AD SOLO 1 and SOLO 2 trials were monotherapy dupilumab trials, in which patients did not receive concomitant topical corticosteroid (TCS) and/or calcineurin inhibitors during the time that they were receiving dupilumab. In the LIBERTY AD CHRONOS trial, patients received TCS and/or calcineurin inhibitors while they were receiving dupilumab. In the LIBERTY AD CAFÉ trial, patients with an inadequate response or intolerance to cyclosporin A (CsA) or in whom CsA treatment was medically inadvisable were included. Concomitant TCS was allowed. Those clinical trials demonstrated efficacy of dupilumab for AD with tolerable safety. Generally, the incidence of conjunctivitis was higher in patients with AD receiving dupilumab. The long-term safety and efficacy of dupilumab in adult patients with moderate-to-severe AD were demonstrated in an open-label study of up to 76 weeks (Deleuran et al., 2020) or 3 years of duration (Beck et al., 2020). Analysis of clinical laboratory findings in three trials (LIBERTY AD SOLO 1 and 2 and CHRONOS) (Wollenberg et al., 2020) and investigation on 2,677 adult patients who were treated with dupilumab for up to 3 years (Beck et al., 2021) demonstrated no clinically meaningful changes in mean laboratory parameters, supporting continuous long-term use of dupilumab without laboratory monitoring. Clinical trials reported long-term efficacy of dupilumab with acceptable safety for children with moderate-to-severe AD (Cork et al., 2021, 2020b; Paller et al., 2020; Simpson et al., 2020).

### Efficacy of dupilumab by ethnic subgroup

Katoh et al. (2020) reported the efficacy and safety of dupilumab in Japanese patients with moderate-to-severe AD by analyzing the results of a 16-week, phase IIb dose-finding

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Abbreviations: AA, alopecia areata; AD, atopic dermatitis; CsA, cyclosporin A; EASI, Eczema Area and Severity Index; HSV, herpes simplex virus; IGA, Investigator's Global Assessment; LDH, lactate dehydrogenase; q2w, every other week; qw, weekly; TCS, topical corticosteroid; Th, T helper type

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trial (AD-1021), the LIBERTY AD SOLO 1 trial, and the LIBERTY AD CHRONOS trial. Baseline disease severity was numerically higher in the Japanese cohort than in the overall study population. For instance, in the SOLO 1 trial, the median EASI of Japanese adult patients treated with placebo, dupilumab 300 mg q2w, and dupilumab 300 mg weekly (qw), was 40, 37, and 36, respectively; the scores of the overall population were 31.8, 30.4, and 29.8, respectively. Generally, dupilumab significantly improved signs and symptoms of AD, including pruritus and patients' QOL, compared with the placebo in the Japanese cohort, consistent with the results in the overall study population. The proportion achieving EASI-75 of Japanese adult patients treated with placebo, dupilumab 300 mg q2w, and dupilumab 300 mg qw was 0%, 25.0%, and 51.4%, respectively, at week 16 in the SOLO 1 trial; 22.2%, 62.5%, and 63.8% at week 16, and 24.1%, 50.0%, and 70.2% at week 52 in the CHRONOS trial. The combined safety profile of dupilumab in the Japanese cohort was similar to that in the total study populations. [Alexis et al. \(2019\)](#) reported the results of post hoc analysis from three phase 3 trials, LIBERTY AD SOLO 1, SOLO 2, and CHRONOS, assessing the efficacy and safety of dupilumab versus placebo by ethnic subgroup (White, Asian, Black/African American). A total of 2,058 patients (White, n = 1,429; Asian, n = 501; Black/African American, n = 128) were included. Dupilumab significantly improved all assessed outcomes compared with the placebo in the White and Asian subgroups (LS mean percent changes in EASI were -44.5%, -77.7%, and -78.0% in patients treated with placebo, dupilumab 300 mg q2w, and dupilumab 300 mg qw, respectively, in White patients and -32.5%, -73.8%, and -75.6%, respectively, in Asian patients). In the smaller Black/African American subgroup, dupilumab significantly improved the EASI endpoints (LS mean percent changes in EASI were -39.1%, -70.8%, and -69.5% in patients treated with placebo, dupilumab 300 mg q2w, and dupilumab 300 mg qw, respectively) and mean changes in Peak Pruritus numerical rating scale and Dermatology Life Quality Index compared with the placebo, with positive numeric trends favoring dupilumab in all other endpoints, suggesting that dupilumab 300 mg qw may provide incremental benefits over the q2w regimen in Black/African American patients; however, the interpretation is limited by the small sample size of the Black/African American cohort and variations in mean body weight between ethnic subgroups (the median body weights of patients treated with placebo, dupilumab 300 mg q2w, and dupilumab 300 mg qw were 76.4 kg, 77 kg, and 77 kg, respectively, in White patients; 65.55 kg, 64 kg, and 65.3 kg, respectively, in Asian patients; and 82 kg, 84.2 kg, and 81.9 kg, respectively, in Black/African American patients).

#### **Withdrawal of dupilumab**

[Worm et al. \(2020\)](#) reported that longer dosage intervals and withdrawal after the initial 16-week successful treatment resulted in a diminution of response and induced a higher incidence of treatment-emergent antidrug antibody. They concluded that the approved regimen of 300 mg of dupilumab every 2 weeks was recommended for long-term treatment. It is known that a low trough concentration of an

antibody drug is associated with an increased risk of the formation of antidrug antibody ([Schaeverbeke et al., 2016](#)). Although the efficacy of dupilumab was not lower in patients who were positive for antidupilumab antibody than in patients who were negative for this antidrug antibody, longer intervals and repeated withdrawal and resumption may eventually induce the formation of neutralizing antidrug antibody or non-neutralizing antidrug antibody that can form immune complexes, resulting in increased clearance of the drug ([Carrascosa, 2013](#); [Jahn and Schneider, 2009](#); [Yin et al., 2015](#)). In terms of immunogenicity, the approved regimen of 300 mg of dupilumab every 2 weeks was recommended for long-term treatment. Furthermore, dupilumab targets not a cytokine (IL-4 and IL-13) but a receptor (IL-4R $\alpha$ ). Therefore, right after initiating dupilumab, IL-4 and IL-13 are possibly still abundant in the skin of the patient even if the skin looks clear clinically. Abrupt withdrawal of dupilumab at an early phase may result in exacerbation. Indeed, abrupt cessation of brodalumab, an IL-17RA antibody for psoriasis, is associated with a rapid relapse of psoriasis, with some patients experiencing a rebound ([Masson Regnault et al., 2017](#)). They concluded that it is not advisable to stop treatment with brodalumab abruptly even in patients who experience complete clearance of psoriasis. Likewise, withdrawal of dupilumab at an early phase is not recommended. Recently, [Bangert et al. \(2021\)](#) revealed specific immune cell populations, mature dendritic cells, TH2A, and Tc2 cells, that persisted for up to 1 year after clinical amelioration obtained by dupilumab while being absent from healthy controls. Their data suggest that it takes more than 1 year for treatment with dupilumab to bring immunological remission even after having achieved clinical amelioration. Considering these data and its sustained efficacy and tolerable safety in clinical trials, abrupt cessation of dupilumab is not recommended and long-term use of dupilumab can bring sustained improvement.

### **EFFECTIVENESS AND SAFETY OF DUPILUMAB FOR AD IN THE REAL WORLD**

#### **Real-world evidence of the effectiveness and safety of dupilumab for AD**

Accumulating real-world evidence has ensured the effectiveness and tolerable safety of dupilumab both in the short term and in the long term. The articles searched in PubMed and Google Scholar are shown in [Table 1](#) ([Ariëns et al., 2021, 2020](#); [Armario-Hita et al., 2019](#); [Faiz et al., 2019](#); [Fargnoli et al., 2020, 2019](#); [Ferrucci et al., 2020](#); [Jang et al., 2020](#); [Jo et al., 2020a, 2020b](#); [Kim et al., 2020](#); [Kreeshan et al., 2021](#); [Matsutani et al., 2020](#); [Nettis et al., 2020b, 2020c](#); [Olesen et al., 2019](#); [Patrino et al., 2021a, 2021b](#); [Quint et al., 2020](#); [Ribero et al., 2020](#); [Sears et al., 2021](#); [Tauber et al., 2019](#); [Tavecchio et al., 2020](#); [Uchida et al., 2021, 2019](#); [Wang et al., 2020](#); [Yamauchi et al., 2021](#)). [Patrino et al. \(2021a, 2021b\)](#) reported the effectiveness and safety of dupilumab in elderly patients with AD in real life. [Halling et al. \(2021\)](#) reported a systematic review and meta-analysis of real-world data on the efficacy and safety of dupilumab in patients with AD. Generally, the real-world data demonstrated that dupilumab was a successful and well-tolerated

**Table 1. Real-World Evidence of the Effectiveness and Safety of Dupilumab Treatment for AD**

Publication	Country	Time (wk)	Number of Patients	EASI-75, %	Other Outcomes
Ariëns et al. (2020)	The Netherlands	16	138	62	The most frequently reported side effect was conjunctivitis, occurring in 47 patients (34%).
Ariëns et al. (2021)	The Netherlands	52	210	70.3	The most frequently reported adverse effect was conjunctivitis (34%).
Armario-Hita et al. (2019)	Spain	24	70	ND	EASI decreased to 6.5 (79.3% reduction), SCORAD diminished to 15 (69.3% reduction), and pruritus VAS decreased to 2.4 (69.9% reduction). The safety profile was favorable, with six reported cases of mild conjunctivitis.
Faiz et al. (2019)	France	3.8 mo (median)	241	48.8	Conjunctivitis was reported in 84 (38.2%) of 241 patients.
Fargnoli et al. (2019)	Italy	16	109	60.6	Adverse events were experienced by 19.2% (21/109) of the patients and they were all mild in intensity, conjunctivitis being the most common side effect.
Fargnoli et al. (2020)	Italy	48	1009	81.9	Conjunctivitis was diagnosed in 20.5% (21/102) at wk 24 and 8.1% (8/98) at wk 48, suggesting remission in most cases.
Ferrucci et al. (2020)	Italy	16	117	72.7	The majority of adverse events were mild in severity and included blepharoconjunctivitis (n = 14; 11.9%), facial redness (n = 6; 5.1%), and paradoxical psoriasis (n = 1; 0.8%).
Jang et al. (2020)	Korea	16	101	63.6	Adverse events from treatment included facial erythema (9.9%) and conjunctivitis (5.0%).
Jo et al. (2020b)	Canada	16	93	ND	A total of 51 (55%) patients reached IGA of 0/1, and 38 (41%) experienced ≥1 adverse events.
Jo et al. (2020a)	Canada	52	52	ND	IGA 0/1 was achieved by 28 (54%) of 52 patients at wk 52, similar to the proportion of patients achieving IGA 0/1 at wk 16 (30/48, 63%). Conjunctivitis (n = 4, 8%) was the most commonly reported adverse event.
Kim et al. (2020)	Canada	ND	34	ND	Of 34 patients, 33 showed some clinical improvement on initiating dupilumab. The most frequently reported adverse events were nasopharyngitis (n = 4, 11.8%) and conjunctivitis (n = 4, 11.8%).
Kreeshan et al. (2021)	United Kingdom	30	164	75.31	The most common side effects were eye symptoms, occurring in 43.1% of patients, with 16.3% developing conjunctivitis.
Matsutani et al. (2020)	Japan	16	53	ND	EASI score, DLQI, and POEM decreased by 73.1%, 73.6%, and 72.1%, respectively. Conjunctivitis was the most common side effect (15/53 patients, 28%).
Nettis et al. (2020c)	Italy	16	123	65.6	The median percentage change from baseline in the EASI score was -81.6. A total of 35 patients (28.5%) developed conjunctivitis during the study period.
Nettis et al. (2020b)	Italy	16	543	81.5	Overall, 12.2% of the patients developed conjunctivitis.
Olesen et al. (2019)	Denmark	3 mo	43	63.3	Seven patients (18.4%) developed conjunctivitis.
Patruno et al. (2021b)	Italy	16	276	ND	Data of elderly patients (aged ≥ 65 years) with severe (EASI ≥24) AD were retrospectively collected. The mean percentage reduction in EASI score was 68.84% (from 29.2 at baseline to 6.3 at 16 wk). No statistically significant difference regarding efficacy was found in elderly patients compared with the group of patients with AD aged 18–64 y. A total of 61 patients (22.51%) reported adverse events, conjunctivitis and flushing being the most frequent adverse events.
Patruno et al. (2021a)	Italy	52	105	ND	Data of elderly patients (aged ≥ 65 years) with severe (EASI ≥24) AD treated with dupilumab were studied. The mean EASI percentage improvement from baseline was 56.0%, 83.9%, and 87.2% after 16, 32, and 52 weeks, respectively. Adverse events were recorded in 30 (28.6%) of 105 patients, with conjunctivitis and injection-site reaction being the most frequent.
Quint et al. (2020)	Austria	52	94	71.4% (25/35) at wk 24, 71.4 (5/7) at wk 52	After 24 wk of treatment, the median IGA and EASI showed significant reductions compared with baseline (3.9 ± 0.7 vs. 1.4 ± 0.8 and 26.5 ± 12.5 vs. 6.4 ± 6.5). Similar values for all parameters were also observed after 52 weeks of treatment. Rosacea-like folliculitis was an unexpected side effect in 6.4% of patients.
Ribero et al. (2020)	Italy	4 mo	128	88	The most frequent adverse event was conjunctivitis (12%).
Sears et al. (2021)	United Kingdom	1 y	100	63.3	A total of 94% of patients had experienced an adverse event by 1 y. Ophthalmic adverse events were most common (76%),

(continued)

Table 1. Continued

Publication	Country	Time (wk)	Number of Patients	EASI-75, %	Other Outcomes
Tauber et al. (2019)	France	16	19	ND	predominantly allergic/dupilumab-associated conjunctivitis (32%), conjunctivitis (unspecified, 7%), or dry eyes (23%). The median SCORAD decreased by 55%. Overall, 22% of patients achieved a reduction in SCORAD of $\geq 75\%$ . The ophthalmological examination showed worsening of conjunctivitis in 5 of 10 patients, stability in 4 of 10 patients, and improvement in 1 patient. Three patients developed de novo conjunctivitis.
Tavecchio et al. (2020)	Italy	52	221	83.33	None.
Uchida et al. (2019)	Japan	3 mo	22	ND	The EASI score significantly decreased by 44% on average at 1 month and by 69% at 3 months. Conjunctivitis was observed in eight patients (36%).
Uchida et al. (2021)	Japan	1 y	61	ND	The EASI score significantly decreased by a mean of 47.1% at 1 mo, 70.4% at 3 mo, 75.6% at 6 mo, and 76.5% at 12 mo. Conjunctivitis was observed in 13 patients (21.3%).
Wang et al. (2020)	United States	ND	77	ND	In 66 patients (86%), dupilumab improved clinical disease severity, with 23 patients (30%) experiencing complete clearance on dupilumab. Dupilumab was generally well tolerated and caused no serious adverse events. The most common side effects included dry eyes (n = 8), conjunctivitis (n = 6), and keratitis (n = 3).
Yamauchi et al. (2021)	Japan	32	40	72.5	Of the 40 patients, 5 (12.5%) developed conjunctivitis.

Abbreviations: AD, atopic dermatitis; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; ND, not described; POEM, Patient-Oriented Eczema Measure; SCORAD, SCORing Atopic Dermatitis.

therapy for AD in the real world as in clinical trials; however, several reports indicate that dupilumab was slightly less effective in the real world than in clinical trials. In routine clinical practice, long-term effectiveness is related to persistence on therapy, which is generally defined as "the duration of time from initiation to discontinuation of therapy" (Cramer et al., 2008). Dal Bello et al. (2020) and Silverberg et al. (2021a) reported high persistence of dupilumab in the real world, indicting patients' satisfaction with its effectiveness, tolerability, and treatment regimen. In some countries, there are still many patients who receive dupilumab injections at a clinic or hospital. Ito et al. (2020) described an increase in compliance rate by introducing self-injection of dupilumab at home.

Real-world data also highlighted that ocular adverse events commonly occur. Some real-world experiences raised the issue of facial redness during dupilumab treatment. We discuss these topics in the next chapter. Furthermore, psoriasisiform reaction during dupilumab treatment has been reported (Fowler et al., 2019; Napolitano et al., 2019; Schrom et al., 2020) with increased expression of IL-23A in the lesional skin (Napolitano et al., 2021). Arthritis and enthesitis during dupilumab treatment have also been reported (Bridgewood et al., 2021; de Wijs et al., 2020c; Ishibashi et al., 2020; Komaki et al., 2021; Willsmore et al., 2019). Development of alopecia areata (AA) after initiating dupilumab has also been reported (Kanda et al., 2019; Maloney et al., 2019; Ständer et al., 2020). As one of the plausible hypotheses, suppressing T helper type (Th) 2 by dupilumab could skew Th1/2/17 balance with subsequent relative upregulation of Th1 or Th17, which may result in the development of AA or psoriasisiform eruption.

#### Gap in effectiveness and safety between clinical trials' data and real-world evidence

Some real-world data indicate that dupilumab was not so effective in the real world as in clinical trials. Because there is overlap in the clinical appearance of moderate-to-severe AD and mycosis fungoides (Silverberg, 2020), patients with mycosis fungoides can be misdiagnosed with AD (Chiba et al., 2019; Lazaridou et al., 2020; Newsom et al., 2021). Furthermore, some clinical features of allergic contact dermatitis and psoriasis are similar to those of AD. Those patients misdiagnosed with AD who received dupilumab might have been evaluated as non-responders. Moreover, although Investigator's Global Assessment (IGA) and EASI are frequently used as evaluation tools for effectiveness of dupilumab, those results vary according to individual physicians. Objective evaluation tools could be useful to address this issue. Olesen et al. (2019) analyzed 43 patients with AD at a Danish tertiary referral center, which revealed a positive correlation between reduction in EASI score and reduction in serum lactate dehydrogenase (LDH) levels from baseline to 3-month follow-up ( $r = 0.70$ ,  $P = 0.003$ ). Matsutani et al. (2020) also reported a positive correlation of the change in EASI with the change in serum LDH levels from baseline to week 16 ( $r = 0.67$ ,  $P < 0.0001$ ). Those results suggest that a change in LDH level is one potential objective way to assess effectiveness of dupilumab. In addition, the differences in effectiveness of dupilumab among real-world reports and clinical trials may be accounted for by the difference of patients' background, including prior systemic therapy such as cyclosporine, and characteristics, including patients' weight and ethnicity as described earlier.



### Predictors of the effectiveness of dupilumab for AD in the real-world studies

Predictors of the efficacy of dupilumab for AD have not been reported in clinical trials. Meanwhile, Kato et al. (2020) analyzed real-world data and advocated that serum LDH levels at baseline could be a negative predictor of the effectiveness of dupilumab for AD among biomarkers of AD. They retrospectively investigated the associations of baseline demographics and baseline laboratory results with the percentage reduction in EASI at 1, 3, 6, and 12 months after initiating dupilumab (Kato et al., 2020). The baseline serum LDH level was negatively correlated with the percentage reduction in EASI at 3, 6, and 12 months after initiating dupilumab but not at 1 month. Baseline serum levels of TARC and IgE and the number of circulating eosinophils were not associated with the percentage reduction in EASI at any of the studied time points. Patients with AD with allergic diseases tended to have a lower percentage reduction in EASI at 1 month but had a higher percentage reduction in EASI in the long term than patients without allergic diseases. These data suggest that a higher baseline serum LDH level is associated with poor effectiveness of dupilumab in the long term in patients with AD. Furthermore, it takes a longer time for patients with AD with allergic diseases to respond to dupilumab, but these patients respond better to dupilumab in the long term than patients without allergic diseases. Nakahara et al. (2020) have been exploring biomarkers that predict clinical improvement of AD in patients treated with dupilumab, including the percentage of eosinophils in blood cell count, LDH, total IgE, soluble IL-2 receptor, CCL17, CCL18, CCL22, CCL26, CCL27, IL-13, IL-22, IL-24, IL-25, IL-31, IL-33, thymic stromal lymphopoietin, periostin, and squamous cell carcinoma antigen-2. Biomarkers predicting the effectiveness of dupilumab will possibly be revealed in the future.

### SPECIFIC CONCERNS WITH DUPILUMAB TREATMENT IN PATIENTS WITH AD

#### Conjunctivitis

**Gap in the incidence of conjunctivitis between clinical trial data and real-world evidence.** Results of clinical trials revealed that dupilumab is associated with increased incidence of conjunctivitis only in patients with AD but not in those with asthma, chronic rhinosinusitis with nasal polyps, or eosinophilic esophagitis (Akinlade et al., 2019; Bachert et al., 2016; Blauvelt et al., 2017; Castro et al., 2018; de Bruin-Weller et al., 2018b; Hirano et al., 2020; Rabe et al., 2018; Simpson et al., 2020; Thaçi et al., 2016; Wenzel et al., 2016, 2013). In the real world, dupilumab-associated conjunctivitis has also been reported (Achten et al., 2021; Armario-Hita et al., 2019; de Wijs et al., 2020a; Faiz et al., 2019; Fargnoli et al., 2019; Jo et al., 2020a; Liberman et al., 2020; Nahum et al., 2020; Nettis et al., 2020a; Ribero et al., 2020; Ruiz-Villaverde et al., 2019; Touhouche et al., 2021; Uchida et al., 2020; Wang et al., 2020). The incidence of conjunctivitis seems to be higher in the real world (up to 62%) than in clinical trials (8.6–22.1%).

The incidence of conjunctivitis was lower especially in the first two phase 3 clinical trials, LIBERTY AD SOLO 1 and SOLO 2 (2.2% in placebo, 9.7% in dupilumab q2w, 7.3% in

dupilumab qw in the pooled data) (Thaçi et al., 2019). Because conjunctivitis during dupilumab treatment is mild in most cases, dermatologists may have overlooked mild cases in these early clinical trials. Another possibility is that TCS was not allowed in those two clinical trials, whereas TCS was allowed in the later clinical trials, including LIBERTY AD CHRONOS and CAFÉ, and TCS is usually accompanied by dupilumab in the real world. The use of TCS might affect the incidence of conjunctivitis, although the mechanism is unknown. Because a lower percentage of patients suspected of having conjunctivitis by dermatologists were confirmed as having conjunctivitis by an ophthalmologist (Faiz et al., 2019), there might be a slight overestimation of dupilumab-associated conjunctivitis by dermatologists in the real world (Ferreira and Torres, 2020).

**Characteristics of dupilumab-associated conjunctivitis.** In most patients suffering from dupilumab-associated conjunctivitis, the severity is mild to moderate (Achten et al., 2021; Nahum et al., 2020; Nettis et al., 2020a; Touhouche et al., 2021), but severe cases or those with persistent conjunctivitis have been reported (Barnes et al., 2017; Li et al., 2020; Paulose et al., 2019; Popiela et al., 2021; Vingopoulos and Lazzaro, 2020). Dose adjustment or discontinuation of dupilumab is needed in certain cases (Achten et al., 2021). According to Bohner et al. (2021), the most common ocular symptoms were irritation/pain (97%), redness (83%), pruritus (62%), discharge (62%), and light sensitivity (21%). The most frequent signs were conjunctival injection (62%), superficial punctate keratitis (55%), and papillary reaction (28%). Achten et al. (2021) reported that the most frequently reported ophthalmological characteristics were tarsal and bulbar conjunctivitis and blepharitis (84.8%, 75.8%, and 66.7% of patients, respectively). Overall, 18.2% of patients presented with limbitis (Achten et al., 2021). Keratitis (Akinlade et al., 2019) is also reported. The timing of the onset of conjunctivitis after initiating dupilumab in patients with AD differed from 2 weeks to 4 months in individual reports (Nahum et al., 2020; Nettis et al., 2020a; Popiela et al., 2021; Uchida et al., 2020).

**Risk factors for dupilumab-associated conjunctivitis.** Focusing on risk factors for the development of conjunctivitis, analysis of the data of the clinical trials revealed that baseline disease-related factors, including AD severity, prior conjunctivitis history, and certain biomarkers (TARC, IgE, eosinophils), are associated with an increased incidence of conjunctivitis irrespective of treatment (in placebo-treated patients as well as in dupilumab-treated patients) (Akinlade et al., 2019). Increased biomarker levels (TARC, IgE and eosinophils) were associated with increased incidence of conjunctivitis in both groups. Although the data from the clinical trials could not identify risk factors specific for dupilumab-associated conjunctivitis, the real-world data suggest possible risk factors. Uchida et al. (2020) reported that dupilumab-associated conjunctivitis was associated with higher baseline serum levels of IgE and TARC but not with the clinical severity of AD and that a history of conjunctivitis and eosinophils showed its tendency. Nahum et al. (2020) and Nettis et al. (2020a) reported that the main predictor for the

development of dupilumab-associated conjunctivitis was a history of conjunctivitis. [Touhouche et al. \(2021\)](#) reported that dupilumab-induced ocular adverse events were associated with pre-existing dry eye disease with superficial punctate keratitis, eyelid eczema, history of food allergy, and IgE serum level >1,000 kU/l.

Consistently, prior conjunctivitis history is a risk factor of developing conjunctivitis after initiating dupilumab in both clinical trial data and real-world data. Reports on biomarkers as predictors for dupilumab-associated conjunctivitis are limited. [Uchida et al. \(2020\)](#) reported that only baseline serum TARC and IgE levels were significantly higher in patients who developed conjunctivitis, whereas TARC, IgE, and eosinophils were associated in clinical trials, which indicates that TARC and IgE are more sensitive predictors than eosinophils and possibly more useful in practice. Furthermore, baseline clinical severity did not demonstrate any association with incidence of conjunctivitis in the real world, whereas clinical trials have demonstrated that baseline AD severity was associated with an increased incidence of conjunctivitis. However, even in data from clinical trials, the difference in the incidence of conjunctivitis between patients with AD with a baseline score of 3 on the 5-point IGA scale and those with a baseline of 4 was quite small in CHRONOS (0.06 vs. 0.09 per 100 patient-years) and in CAFÉ (0.22 vs. 0.23). Distinguishing the subtle differences in disease severity of AD among patients with moderate-to-severe AD (not including mild AD) is difficult for physicians.

#### **Hypotheses of the pathomechanism of dupilumab-associated conjunctivitis.**

The pathomechanism of the development of dupilumab-associated conjunctivitis remains to be elucidated. However, several hypotheses have been proposed ([Ferreira and Torres, 2020](#); [Wohlrab et al., 2019](#)) as follows: unmasking of pre-existent subclinical atopic or allergic inflammatory processes ([Gooderham et al., 2018](#)); qualitative tear production failure ([Fujishima et al., 1995](#)); local immunodeficiency and resulting local infections with bacteria, viruses, chlamydia, or mycoplasma; increased expression of costimulating, proinflammatory molecules (i.e., OX40L) based on alterations in the immunological milieu; colonization of the Meibomian glands at the lid rim with Demodex mites ([de Bruin-Weller et al., 2018a](#)); eosinophilia, which plays a role in the occurrence of allergic eye conditions ([Thyssen et al., 2017](#); [Treister et al., 2018](#)); reduced IL-13-related mucus production ([Barnett and Afshari, 2020](#)); disruption of an immune-mediated response of conjunctival-associated lymphoid tissue ([Akinlade et al., 2019](#)); and focal scarcity of conjunctival goblet cells ([Bakker et al., 2019](#)). [Wohlrab et al. \(2019\)](#) postulated another hypothesis that a lower bioavailability at the conjunctiva caused by the decreased diffusion of mAb and increased elimination via nFcR-dependent mechanisms ([Fujishima et al., 1995](#)) may cause quantitative and kinetic reduction in the local bioavailability of dupilumab, resulting in a shorter duration of the effect of the mAb in the respective part of the eye ([Wohlrab et al., 2019](#)), although it does not provide a coherent explanation for the described scarcity of goblet cells in patients with AD treated with dupilumab. [Utine et al. \(2021\)](#) advocate the hypothesis that because Th1-mediated

inflammation is predominant in atopic keratoconjunctivitis, blocking the Th2 pathway with dupilumab therapy might result in a shift toward Th1, causing the ocular findings associated with dupilumab ([Utine et al., 2021](#)). Multiple factors may be involved in dupilumab-associated conjunctivitis. Further investigation is needed to clarify the pathomechanism of the development of dupilumab-associated conjunctivitis.

#### **Facial redness**

Real-world evidence raised the issue of facial redness that developed in some patients after initiation of dupilumab, although facial redness was not focused on as an adverse event in the clinical trials. To date, some case series of facial redness in dupilumab-treated patients with AD have been reported ([Albader et al., 2019](#); [de Beer et al., 2019](#); [de Wijs et al., 2020b](#); [Heibel et al., 2021](#); [Herz et al., 2019](#); [Igelman et al., 2020](#); [Nakanishi et al., 2021](#); [Okiyama et al., 2020](#); [Quint et al., 2020](#); [Seok et al., 2020](#); [Soria et al., 2019](#); [Stout and Silverberg, 2019](#); [Suresh and Murase, 2018](#); [Waldman et al., 2020](#); [Yamane et al., 2019](#); [Zhu et al., 2019](#)).

[Waldman et al. \(2020\)](#) characterized dupilumab facial redness by retrospectively reviewing medical records at several institutions. Dupilumab facial redness developed in 9 of 85 patients with AD (10.6%). Dupilumab facial redness often occurred by the time of the patient's 2-month follow-up visit after drug initiation. Four theories have been proposed; dupilumab facial redness may represent a hypersensitivity reaction to dupilumab, site-specific treatment failure, a seborrheic dermatitis-like reaction to facial *Malassezia* species, paradoxical flaring of allergic contact dermatitis, or a combination of these. However, there is supporting and refuting evidence for each theory.

[Jo et al. \(2021\)](#) conducted a systematic review of facial and neck erythema associated with dupilumab treatment. They analyzed data on a total of 101 patients from 16 studies who were reported to have dupilumab-associated facial or neck erythema. Baseline AD on the face or neck was observed in 52 of the 101 patients (52%). The mean time to onset of facial or neck erythema after dupilumab initiation was 11 weeks. Almost half (45/101) of the patients reported that symptoms were different from their typical AD symptoms. Treatments that were commonly used to manage facial or neck erythema were TCSs (n = 43), topical calcineurin inhibitors (n = 32), and topical and oral antifungals (n = 18). Of the 57 patients with data on the course of the adverse event, treatment resulted in clearance in 4, improvement in 29, no response in 16, and worsening in 8. A total of 11 of 101 patients (11%) discontinued dupilumab owing to this adverse event. Proposed etiologies include rosacea, alcohol-induced facial flushing, allergic contact dermatitis, and seborrheic dermatitis (in which *Malassezia furfur* is possibly involved).

We should be aware that facial redness is not a diagnosis but a sign. Physicians need to determine the underlying diagnosis by making the most use of their clinical acumen. Facial redness in most cases is possibly accounted for by residual or poorly controlled facial AD, although the diagnosis is seborrheic dermatitis, allergic contact dermatitis, or rosacea in some cases. TCS withdrawal should also be considered. The amount of TCS use considerably decreases

by improving pruritus after initiating dupilumab in most patients. Because facial redness is caused by different factors in individual patients, revealing the underlying diagnosis is the first step to address this issue.

### IMPACT OF DUPILUMAB ON COMORBIDITIES AND DISEASE BURDEN OF AD

AD not only is a skin disease but also is associated with various comorbidities and burdens (Arima et al., 2018; Eckert et al., 2019; Silverberg, 2019). In this section, we focus on the impact of dupilumab on other comorbidities and burdens caused by AD.

Boguniewicz et al. (2021) reported that dupilumab improved asthma and/or chronic sinonasal conditions in adult patients with moderate-to-severe AD by analyzing the data obtained from four randomized, double-blinded, placebo-controlled trials.

Analyses of clinical trial data revealed that dupilumab brought improvement in pruritus, pain/discomfort, anxiety/depression, QOL, and usual activities of patients with AD (Cork et al., 2020a; de Bruin-Weller et al., 2018b; Silverberg et al., 2020; Simpson et al., 2016a) as in the real-world evidence (Ferrucci et al., 2020).

Patients with AD are susceptible to developing a variety of cutaneous infections, including infections by bacteria, viruses, and fungi (Langan et al., 2017; Simpson, 2012). A meta-analysis of eight randomized controlled trials in four publications with 2,706 participants revealed decreased risks of skin infection, including eczema herpeticum, in patients who received dupilumab compared with placebo (Fleming and Drucker, 2018). No significant associations were found for dupilumab with overall herpesvirus infections and overall infections. Regarding the reason for decreased risk of eczema herpeticum (Fleming and Drucker, 2018), it is known that IL-4 and IL-13 reduce epidermal LL-37, an antimicrobial peptide active against herpes simplex viruses (HSVs) (Franzen-Röhl et al., 2017; Howell et al., 2006), and that IL-4 and IL-13 enhance HSV-1 replication (Kim et al., 2013). Thus, blocking IL-4 and IL-13 may have specific antiviral effects. Furthermore, dupilumab increased gene expression of proteins associated with epidermal barrier function, including FLG, LOR, and claudins (Guttman-Yassky et al., 2019). Restoration of barrier function by dupilumab may contribute to reduced risk of cutaneous infection.

AD is associated with AA (Andersen et al., 2017; Mohan and Silverberg, 2015). Concomitant AA was improved by dupilumab in some reports, whereas AA developed after initiating dupilumab in others, as described previously (Harada et al., 2020; Marks et al., 2019; Sachdeva et al., 2021). Although AA has historically been classified as a primarily Th1-driven process, findings of genomic susceptibility loci and cytokine activation support involvement of the Th2 pathway (Renert-Yuval and Guttman-Yassky, 2016). In patients with improvement of AA, dupilumab, by inhibiting IL-4 and IL-13, dampens the downstream effect of inflammatory mediators, potentially leading to concomitant improvement of AA and AD (Marks et al., 2019; Sachdeva et al., 2021). However, these pathways warrant further investigation.

### ISSUES TO BE ADDRESSED AND THE POSITIONING OF DUPILUMAB IN THE TREATMENT OF AD

#### Inadequate responders to dupilumab

Although results of clinical trials and accumulating real-world evidence of dupilumab have demonstrated higher efficacy and effectiveness than conventional therapy, there are still a certain number of patients with significant failure, as in other systemic therapies (Silverberg et al., 2021b). In AD, heterogeneity is identified by race (Noda et al., 2015), biomarkers (Sims et al., 2021), and severity of itch and skin lesions (Chovatiya et al., 2021). A variety of genetic and environmental factors are involved in the development and exacerbation of AD. The pathogenesis of AD is not so simple as to be explained merely by IL-4 and IL-13. This heterogeneity and compilation of the pathogenesis could account for a certain number of patients with significant failure for dupilumab. Clinical trials of upadacitinib and abrocitinib, Jak1-selective inhibitors, that can inhibit a wider range of the cytokine-signaling pathway than dupilumab, indicated the superior efficacy in patients receiving a high dose of them daily compared with dupilumab (Bieber et al., 2021a; Reich et al., 2021). In nonresponders to dupilumab, cytokines other than IL-4 and IL-13 could contribute more dominantly to the development of AD. Identifying the characteristics of such populations will lead to a smarter selection of drugs in the future.

#### Positioning dupilumab in the treatment of AD

Dupilumab demonstrated higher efficacy with a favorable safety profile for refractory patients with moderate-to-severe AD than conventional therapy. Recently, baricitinib, a Jak1/2-selective inhibitor, has been approved for the treatment of AD in some countries and will be in more countries in the near future. Upadacitinib and abrocitinib will be also available soon. Those Jak inhibitors inhibit the pathway of AD pathogenesis more specifically than conventional drugs, such as CsA and azathioprine, which enables higher efficacy in eruption and pruritus with tolerable safety. We herein discuss an optimal use of dupilumab and Jak inhibitors based on the current evidence.

Dupilumab has evidence of reducing the risks of cutaneous infection (Fleming and Drucker, 2018) and improving depression and anxiety (Cork et al., 2020a) and is approved for asthma (Castro et al., 2018), but Jak inhibitors do not, at least based on the current evidence. Therefore, dupilumab is more suitable for patients who have suffered from cutaneous infection, including eczema herpeticum; those suffering from depression and/or anxiety; and those with asthma than Jak inhibitors.

Regarding safety, dupilumab generally demonstrated more favorable safety profiles because dupilumab blocks only the IL-4 and IL-13 pathway. In prioritizing safety, dupilumab is a better option. Jak inhibitors have some contradictions, and potential increased risks of certain diseases are concerned. Patients with particular complications, such as malignancy, severe renal dysfunction, embolism/thrombosis, and cardiovascular diseases, should avoid Jak inhibitors. We should also be aware that the safety profile is different in individual Jak inhibitors (Bieber et al., 2021a, 2021b; Reich et al., 2021).



Jak inhibitors are preferable to dupilumab for patients who prefer an oral drug to injection or cannot perform self-injection. Because repeated withdrawal and resumption of dupilumab is not recommended in terms of immunogenicity as mentioned previously, Jak inhibitors are suitable for patients who want to receive it for the short term, for instance, owing to economic reasons or seasonal flares.

The unmet needs of dupilumab are conjunctivitis, facial redness, and certain population of nonresponders. Regarding conjunctivitis, Jak inhibitors do not increase its risks (Bieber et al., 2021a, 2021b; Reich et al., 2021). Patients suffering from dupilumab-induced severe conjunctivitis may want to change their treatment to Jak inhibitors. Evidence of facial redness and effectiveness of Jak inhibitors for inadequate responders to dupilumab has never been reported. The accumulation of evidence is needed.

## CONCLUSION

Dupilumab demonstrated high efficacy, high effectiveness, favorable safety, and improvement in comorbidities caused by AD. Accumulating real-world data has uncovered the differences between the real world and clinical trials and revealed some issues to be addressed, including conjunctivitis and facial redness. There are still a certain number of patients with significant failure. Further investigation is needed to elucidate them.

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