# Retrospective analysis of adverse events with dupilumab reported to the United States Food and Drug Administration

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***Background:*** Atopic dermatitis (AD) is one of the most common inflammatory skin diseases and has aesthetic, physical, and emotional-social sequelae when left untreated.

***Objective:*** To classify the most common adverse reactions associated with dupilumab treatment in patients with AD.

***Methods:*** The United States Food and Drug Administration Adverse Event Reporting (FAERS) database was analyzed for common adverse reactions associated with dupilumab, topical pimecrolimus, and topical tacrolimus. Phase III clinical trial data were used to compare the rate of herpes infections between the treatment group and placebo group.

***Results:*** The most common adverse reaction associated with dupilumab was ocular complications. Herpes infections were extremely rare in the patients with AD being treated with dupilumab.

***Limitations:*** Prescribing information for dupilumab, topical pimecrolimus, and topical tacrolimus is not available. Adverse effects are reported by patients, health care providers, and pharmaceutical companies, they have not been corroborated.

***Conclusions:*** Ocular complications are the most common complication associated with dupilumab. The rate of herpes infection is low in patients being treated with dupilumab, topical pimecrolimus, and topical tacrolimus. There is no significant difference for the rate of herpes infection between, placebo, dupilumab, topical pimecrolimus, and the topical tacrolimus treatment group, suggesting that dupilumab does not affect herpes infection rates. (J Am Acad Dermatol 2021;84:1010-4.)

***Key words:*** adverse events; atopic dermatitis; eczema herpeticum; eczema; FAERS; FDA; herpes infection; ocular complication.

Atopic dermatitis (AD) is one of the most common inflammatory skin diseases, affecting 13% of children and 7% of adults in the United States (US).[1-3] Initiating appropriate treatment is important, because untreated AD can lead to chronic pain, intense pruritus, and a characteristic eczematous eruption.[3,4] These dermatologic symptoms can be severe and can not only greatly impact patients' quality of life but can also result in depression, anxiety, and sleep disturbance.[1,5-8]

AD causes the disruption of the skin barrier, dysregulation of the immune system, and decreases expression of antimicrobial peptide. It also increases colonization of *Staphylococcus aureus* with the development of a biofilm that increases the rate of bacteria, fungal, and viral skin infections.[9] In particular, eczema herpeticum (EH) is a feared complication of herpes simplex virus in patients with AD. EH is characterized by disseminated vesicles, skin breakdown, fever, lymphadenopathy, and potential meningitis.[10]

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The treatment of AD involves topical corticosteroids/calcineurin inhibitors and phototherapy for mild cases. For more severe cases, systemic immunomodulant/immunosuppressive agents are used.[11] In recent years, targeted therapies have also been used to treat severe cases of AD.[12] Dupilumab, a fully human monoclonal antibody against interleukin 13 and interleukin 4, approved by the US Food and Drug Administration (FDA) in 2017,[13] was shown be a safe and effective option for the treatment of mild to severe AD through multiple phase III clinical trials.[14,15]

**CAPSULE SUMMARY**

- Dupilumab is an effective treatment for atopic dermatitis. We analyzed the most commonly reported adverse events associated with dupilumab.
- Ocular complications are the most commonly reported adverse events associated with dupilumab, especially in patients with atopic dermatitis and asthma. There is no increase in herpes infection with dupilumab treatment.

Despite multiple clinical trials, however, there is still a shortage of literature on the long-term adverse events associated with dupilumab and its immune modulating effects, especially its effect on herpes infection. Therefore, our objective was to identify the most commonly reported adverse events to the US FDA Adverse Event Reporting Database (FAERS) associated with dupilumab.[16]

The rate of herpes infection associated with dupilumab use was also compared with that seen with other FDA-approved medications (topical pimecrolimus and topical tacrolimus) used for the treatment of AD. Pimecrolimus and tacrolimus are topical medications that are not associated with increased rate of herpes infections due to the lack of systemic effect and are thus used as a baseline comparison to dupilumab to see whether dupilumab use has an increased rate of herpes.

Patients in clinical trials who received placebo were used to represent general patients with AD and their baseline risk of herpes infection because these patients have an increased risk of baseline herpes infection. The lack of other FDA-approved systemic medications for the treatment of AD meant we were unable to make a comparison between dupilumab and other systemic medications.

## MATERIAL AND METHODS

We performed a retrospective analysis of adverse events associated with dupilumab (January 1, 2017, to December 31, 2020), topical pimecrolimus (January 1, 2002, to December 31, 2019) and topical tacrolimus (Protopic, LEO Pharma Inc) (January 1, 2001, to December 31, 2019) reported to FAERS, a deidentified database of medication adverse event reports filed by prescribers, consumers, and manufacturers.[16] Because tacrolimus has many different formulations, which are grouped in FAERS, adverse reactions reported for the trade name, Protopic, were used exclusively.

Adverse events in FAERS are classified by reaction terms. A list of the 20 most commonly reported reaction terms for dupilumab was recorded. For each of the medications, the number of oral herpes, herpes simplex infection, EH, and herpes zoster cases were also recorded.

Because dupilumab and topical tacrolimus have other indications, only adverse events associated with the treatment of AD were recorded.

The phase III clinical trial data were obtained from the Study of Dupilumab Monotherapy Administered to Adult Patients With Moderate-to-Severe Atopic Dermatitis (SOLO 1) and Study of Dupilumab (REGN668/SAR231893) Monotherapy Administered to Adult Patients With Moderate-to-Severe Atopic Dermatitis (SOLO 2) clinical trials published in the *New England Journal of Medicine*[15] and the Study to Assess the Efficacy and Long-term Safety of Dupilumab (REGN668/SAR231893) in Adult Participants With Moderate-to-Severe Atopic Dermatitis (LIBERTY AD CHRONOS) clinical trial published *The Lancet*.[14]

## RESULTS

The most common adverse events associated with dupilumab are ocular complications, including conjunctivitis (4.96%), eye pruritus (4.95%), ocular hyperemia (4.30%), dry eye (3.87%), eye irritation (3.06%), and increased lacrimation (2.80%) (Table I).

The rate of reported herpes infections is low among patients with AD treated with dupilumab, topical pimecrolimus, and topical tacrolimus, including oral herpes, herpes zoster, herpes simplex, and EH. The rate of all herpes infection is less than 2% for all 3 medications (Table II). An analysis of variance (ANOVA) test used to compare the rate of all herpes infections among the 3 medications showed that the rate of herpes infection is not significantly different between the medications ($P = .92$).

In the SOLO 1 trial, the rate of all herpes infections was low between the placebo and treatment group, including oral herpes, herpes zoster, herpes simplex, and EH. The rate of all herpes infection was less than

*Abbreviations used:*

ANOVA: analysis of variance
AD: atopic dermatitis
EH: eczema herpeticum
FDA: Food and Drug Administration
FAERS: FDA Adverse Event Reporting Database
SOLO 1: Study of Dupilumab Monotherapy Administered to Adult Patients With Moderate-to-Severe Atopic Dermatitis
SOLO 2: Study of Dupilumab (REGN668/SAR231893) Monotherapy Administered to Adult Patients With Moderate-to-Severe Atopic Dermatitis
Th2: T helper 2
US: United States

4% for all patients in the study.[15] An ANOVA test used to compare the rate of herpes infection among the 3 medication groups showed that the rate was not significantly different between the medications ($P$ = .24).

In the SOLO 2 trial, the rate of all herpes infections was low among the placebo and treatment group, including oral herpes, herpes zoster, herpes simplex, and EH. The rate of all herpes infection was less than 4% for all patients in the study.[15] An ANOVA test used to compare the rate of herpes infection between all 3 groups showed that the rate was not significantly different between the medications ($P$ = .94).

In the LIBERTY AD CHRONOS trial, the rate of all herpes infections was low among the placebo and treatment group, including oral herpes, herpes zoster, herpes simplex, and EH. The rate of all herpes infection was less than 5% for all patients in the study.[14] An ANOVA test used to compare the rate of herpes infections between all 3 groups showed that the rate was not significantly different between the medications ($P$ = .52).

## DISCUSSION

The most common adverse reaction associated with dupilumab is ocular complications such as conjunctivitis, eye pruritus, ocular hyperemia, dry eye, eye irritation, and lacrimation increase. Ocular complications associated with dupilumab have been well documented in numerous published studies[9,17-21] and clinical trials.[14,15] In all clinical trials, patients receiving dupilumab had a significant increase in conjunctivitis (8.6%-22.1%) vs the placebo group (2.1%-11.1%).[18] Patients with more severe baseline AD are more likely to develop conjunctivitis and other ocular complications. Interestingly, patients receiving dupilumab for the treatment of asthma do not have a higher rate of conjunctivitis (0%-1.7%) compared with placebo (0%-3.3%),[18] suggesting that an interaction between AD and dupilumab causes ocular complications.

Although there is no current consensus on the pathogenesis of the reported ocular complications, numerous hypotheses have been proposed, such as dupilumab treatment unmasks pre-existing atopic or allergic ocular inflammation,[22] causes a failure in tear production,[23] or causes a local immunosuppressant effect that increases bacterial and viral infection.[20] Most ocular complications associated with dupilumab are mild and have been shown to improve within 2 months of finishing a course of the

**Table I.** Top 20 adverse reactions associated with dupilumab reported to the United States Food and Drug Administration

| | Patients | |
|---|---|---|
| **Adverse reaction (N = 23,537)** | **Number** | **%** |
| Rash | 2326 | 9.88 |
| Pruritus | 2146 | 9.12 |
| Dermatitis atopic | 1487 | 6.32 |
| Conjunctivitis | 1168 | 4.96 |
| Eye pruritus | 1165 | 4.95 |
| Ocular hyperemia | 1012 | 4.30 |
| Erythema | 961 | 4.08 |
| Dry eye | 910 | 3.87 |
| Eczema | 870 | 3.70 |
| Injection site pain | 844 | 3.59 |
| Dry skin | 832 | 3.53 |
| Arthralgia | 724 | 3.08 |
| Eye irritation | 721 | 3.06 |
| Skin exfoliation | 658 | 2.80 |
| Lacrimation increased | 506 | 2.15 |
| Injection site erythema | 452 | 1.92 |
| Fatigue | 445 | 1.89 |
| Headache | 442 | 1.88 |
| Alopecia | 402 | 1.71 |
| Nasopharyngitis | 400 | 1.70 |

**Table II.** Comparison of the percentage of herpes infection cases reported to the Food and Drug Administration among dupilumab, pimecrolimus, and tacrolimus

| **Herpes infection*** | **Dupilumab (Dupixent)† (N = 23,537)** | **Pimecrolimus (Elidel)‡ (N = 1698)** | **Tacrolimus (Protopic)§ (N = 1589)** |
|---|---|---|---|
| Oral herpes | 378 (1.61) | 7 (0.4) | 4 (0.3) |
| Herpes zoster | 128 (0.54) | 19 (1.1) | 19 (1.2) |
| Herpes simplex | 36 (0.16) | 20 (1.2) | 22 (1.4) |
| Eczema herpeticum | 1 (<0.1) | 1 (<0.1) | 0 (0.0) |

*Data are presented as n (%).
†Sanofi and Regeneron Pharmaceuticals.
‡Valeant Pharmaceuticals North America.
§LEO Pharma Inc.

medication; however, some are severe enough to warrant the early discontinuation of the medication.[24] Early prevention and management in patients with severe AD can help them to complete the treatment without early discontinuation.[18] Hyaluronic acid eye drops, topical tacrolimus eye ointment, topical corticosteroid eye drops, and artificial tears have been used with success to treat ocular complications associated with dupilumab.[17,20,21] An ophthalmologist consult is important for the management of any ocular complications during dupilumab treatment to avoid inappropriate discontinuation before completion of the medication course.[17,20,21]

One of the most feared complication of AD is EH, which occurs in 3% of patients with AD.[1-3,10] While herpes simplex virus is present in 60% of the adult population in the US and in 16% of the pediatric population, EH only affects approximately 3% of patients with AD, suggesting a genetic predisposition or other biological factor may contribute to the development of EH in some patients with AD.[25]

AD is characterized by an inflammatory dermatosis due to T helper 2 (Th2) cell hyperactivation and systemic inflammation.[2,3] Dupilumab works by systemically inhibiting interleukin 4 and interleukin 13 signaling, thus reducing the Th2 response.[22] As a result of the reduction in the Th2 response, which is necessary for viral immunity, there is concern for an increase in viral infection among patients receiving dupilumab, especially herpes simplex infections, which can lead to EH.

When the adverse events associated with dupilumab in FAERS are examined, herpes infections, including oral herpes, herpes zoster, herpes simplex, and EH, represent a very small percentage of all adverse events reported (Table I). In a comparison of the percentage of reported cases of herpes infection between dupilumab, topical pimecrolimus, and topical tacrolimus, ANOVA shows that there is no statistically significant difference in the incidence of infections among the 3 medications ($P$ = .92). Between January 1, 2017, and December 31, 2019, only 1 case of EH was reported to the FDA associated with dupilumab. In addition, the percentage of cases reported for herpes zoster and herpes simplex is lower in the dupilumab group than in the topical pimecrolimus or topical tacrolimus groups, whereas oral herpes is higher in the dupilumab group than in the topical pimecrolimus or topical tacrolimus groups.

Despite dupilumab being a systemic medication, it does not appear to cause a higher rate of herpes infection or EH compared with topical medications. These data are supported by all of the phase III clinical trials analyzed, which showed no significant difference between the placebo group, dupilumab every other week group, and dupilumab every week group (SOLO 1, $P$ = .25; SOLO 2, $P$ = .93; and CHRONOS, $P$ = .94).[11,14,15] The reported cases of herpes infection might represent an underlying susceptibility to viral infection due to AD rather than dupilumab.

Although overall, the percentage of patients with AD who develop EH is 3% in general, patients with more severe AD and those with other atopic disease, such as food allergies and asthma, have a higher chance of developing EH.[10] Patients with AD who develop EH tend to have a higher Th2 polarization characterized by higher levels of immunoglobulin E.[26] The cytokines released by the overactive Th2 cells in patients with AD have been shown to decrease their immune response to viral infection.[27] Because dupilumab decreases the inflammatory Th2 response in patients with AD, it can help decrease the rate of herpes infection. A meta-analysis that looked at 138 studies with a combined patient population of 2178 found that dupilumab not only did not increase the rate of herpes infection in patients with AD but also did not increase the overall viral infection rate in the dupilumab group compared with the placebo group.[28] Overall, the evidence suggests that the rate of herpes infection does not increase with dupilumab treatment.

This study has several limitations. Prescribing information for dupilumab, topical pimecrolimus, and topical tacrolimus is not available, so the absolute percentage of adverse reactions is unknown for all 3 medications. In addition, because tacrolimus comes in different formulations and concentrations, we were unable to use the generic name tacrolimus to search the FAERS database. Instead, we opted to search for only the brand name Protopic, which resulted in more precise but less ample data. Furthermore, because these adverse effects are reported by patients, health care providers, and pharmaceutical companies, they have not been corroborated.

## CONCLUSION

The most common adverse events associated with the medication are ocular complications, which are sometimes severe enough to discontinue the medication. Preventive measures and treatment with various eye drops can help the patient finish the medication course; however, an ophthalmologist should be consulted. The data in the clinical trial and our analysis of FAERS suggest that treatment with dupilumab does not increase the rate of

herpes infection among patients with AD. For future research, when Janus kinase inhibitors are approved by the FDA for the treatment of AD, comparisons can also be made between dupilumab and other systemic medications for the rate of herpes infection.

**Conflicts of interest**

None disclosed.

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