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# Risks and safety of biologics: A practical guide for allergists

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## ABSTRACT

Biologic agents are a rapidly expanding class of medications, and several options are now available for the management of allergic and immunologic disorders. The risks of biologic therapy need to be understood in order to adequately counsel patients and appropriately monitor for potential adverse events. We sought to provide a comprehensive review of the risks and adverse effects reported for the current FDA-approved biologics used in management of allergic and immunologic disorders, including omalizumab, benralizumab, dupilumab, mepolizumab, reslizumab, tezepelumab and tralokinumab. Our review focuses on the risk of hypersensitivity reactions, pregnancy-specific considerations, risk of infection and risk of malignancy. We also highlight drug-specific adverse events and unique safety issues identified in case reports.

**Keywords:** Biologics, Safety, Adverse events, Risks, Allergy

## INTRODUCTION

Biologic agents are a rapidly expanding class of medications accounting for more than 20% of all drugs approved annually by the U.S. Food and Drug Administration (FDA) since 2014.[1] Monoclonal antibodies constitute the majority of biologic agents approved, and several options are now available for the management of allergic and immunologic disorders, including moderate to severe-persistent asthma, chronic sinusitis with nasal polyps, chronic spontaneous urticaria, hypereosinophilic syndrome, and eosinophilic esophagitis. Although monoclonal antibodies have demonstrated efficacy and transformed clinical care for these multiple conditions, several factors must be considered when initiating and monitoring therapy.[2] In this clinical-decision process, risks of biologic therapy need to be understood in order to adequately counsel patients and to appropriately monitor for potential adverse events.

In this review, we provide a comprehensive summary of risks and adverse effects reported for the current FDA-approved biologics used in management of allergic and immunologic disorders, including omalizumab, benralizumab, dupilumab, mepolizumab, reslizumab, tezepelumab, and tralokinumab (Fig. 1). Please see Fig. 1 and Table 1 for a complete list of FDA-approved indications and mechanisms of these agents. Our review focuses on the risk of hypersensitivity reactions, pregnancy-specific considerations, risk of infection, and risk of malignancy. Where relevant, we highlight drug-specific issues, such as the potential development of eosinophilia in patients receiving dupilumab. We include recommendations provided by expert consensus groups and/or pharmaceutical companies regarding mitigation of the potential risks associated with use of these

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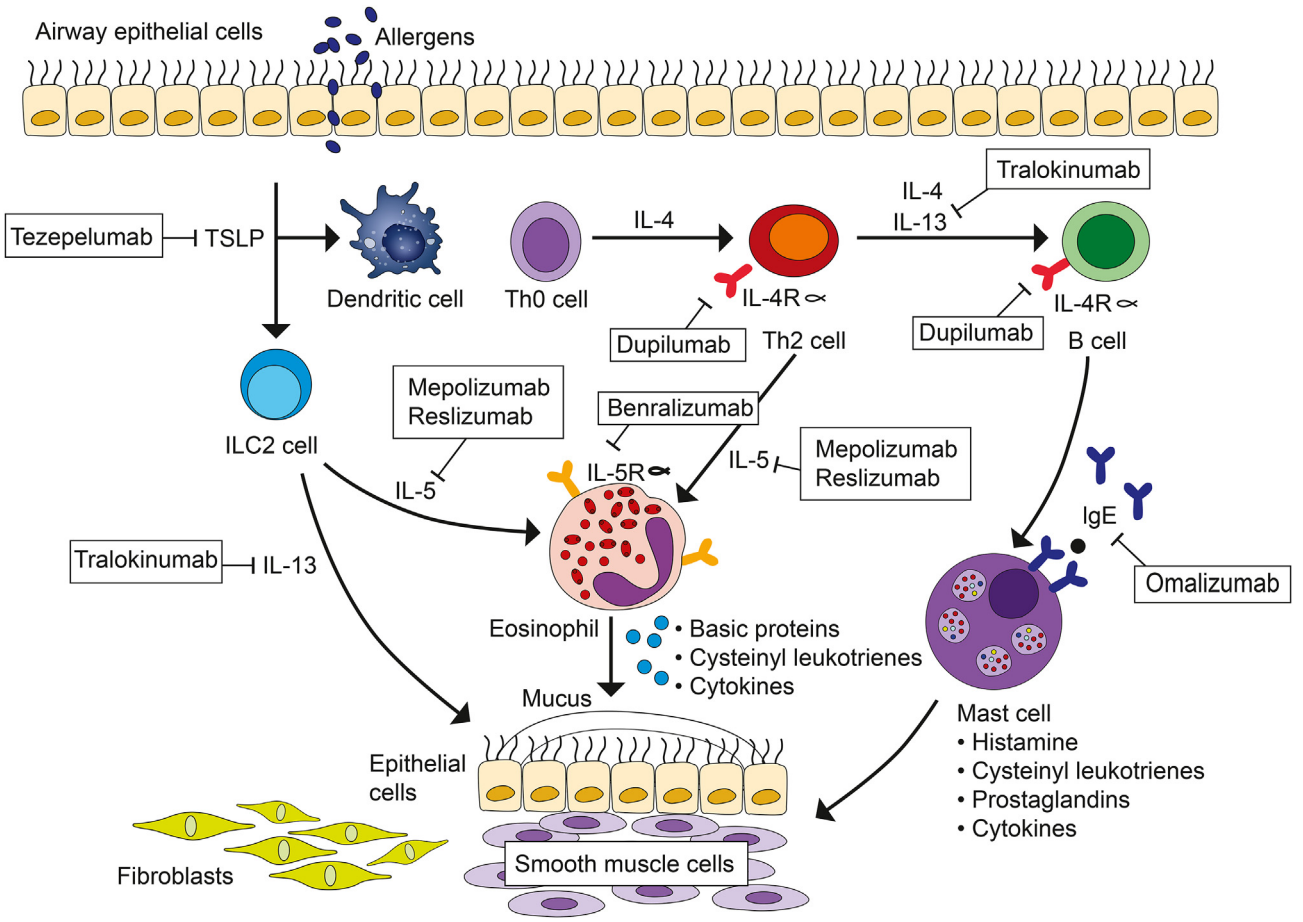


**Fig. 1** Mechanisms of Biologics FDA-Approved for Use in Allergic and Immunologic Disorders. Adapted from Fig. 1 in Krings JG et al. J Allergy Clin Immunol Pract. 2019 May–Jun; 7 (5):1379–1392. TSLP: thymic stromal lymphopoietin; ILC2: Type 2 Innate Lymphoid Cells; IL-4: Interleukin-4; IL-13: Interleukin 13; IL-4Rα: IL-4 receptor alpha subunit; IL-5: Interleukin 5

biologics. We also provide a summary of unique safety issues identified in select case reports.

## OMALIZUMAB

### Systemic reactions

Anaphylaxis has been associated with omalizumab since its initial FDA approval for allergic asthma in 2003, and the product label includes a black box warning for anaphylaxis (Table 1).[3,4] The overall rate of omalizumab-related anaphylaxis is low, occurring in approximately 0.1–0.2% of patients.[3,4]

A joint task force between the American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI) Executive Committees examined omalizumab clinical trials data on anaphylactic reactions and reported a rate of 0.09%.[4] The majority of patients who experienced anaphylaxis were female (84%), with a mean age of 40.5 (range 9–86) years.[5] Risk factors for developing anaphylaxis to omalizumab include prior history of anaphylaxis to other agents [odds ratio of 8.1 (95% CI, 2.7–24.3)].[5,6] The most common symptoms of omalizumab related anaphylaxis were respiratory (96%), though the majority of patients experienced both respiratory and cutaneous symptoms (69%).[5] Cardiovascular involvement occurred less frequently (9%).[5]

The majority of reactions (72%) occurred after the first 3 doses.[5] Over half (63%) occurred within an hour of omalizumab administration, and 43% of episodes occurred within 30 min of administration.[5] Many patients experienced delayed anaphylaxis, with symptom-onset later than 6 h after administration in 11% of patients.[5,6] According to a retrospective review of the US FDA

| Biologic | FDA-Approved Indication | Dosing and Route | Black Box Warning |
|---|---|---|---|
| Omalizumab | • CSU refractory to H1 antihistamine, ≥12 years<br>• IgE-mediated allergic asthma, not controlled by ICS, ≥6 years<br>• Nasal polyps, not controlled by inhaled corticosteroid, ≥18 years | • CSU: 150 or 300 SC every 4 weeks<br>• Asthma: dose determined by serum IgE level, ranging from 150 to 375 mg SC every 2–4 weeks<br>• Nasal polyps: dose determined by serum IgE level, ranging from 75 to 600 mg SC every 2–4 weeks | Anaphylaxis |
| Mepolizumab | • EGPA, ≥18 years<br>• HES, ≥18 years<br>• Nasal polyps, ≥18 years<br>• Severe eosinophilic asthma, ≥6 years | • EGPA: 300 mg SC every 4 weeks<br>• HES: 300 mg SC every 4 weeks<br>• Nasal polyps: 100 mg SC every 4 weeks<br>• Asthma: 100 mg SC every 4 weeks for (≥12 years old); 40 mg SC every 4 weeks (6–11 years old) | None |
| Reslizumab | • Severe eosinophilic asthma, ≥18 years | • 3 mg/kg IV infusion every 4 weeks | Anaphylaxis |
| Benralizumab | • Severe eosinophilic asthma, ≥12 years | • 30 mg SC every 4 weeks for the first 3 doses, then 30 mg every 8 weeks | None |
| Dupilumab | • Moderate to severe eosinophilic or steroid-dependent asthma, ≥6 years<br>• Moderate to severe AD, not controlled with topical therapies, ≥6 years<br>• CRSwNP, ≥18 years<br>• EoE, ≥12 years | • Asthma: 400–600 mg SC loading dose, followed by 200–300 mg SC every 2 weeks<br>• AD: 600 mg SC, followed by 300 mg SC every 2 weeks<br>• CRSwNP: 300 mg SC every 2 weeks<br>• EoE: 300 mg SC every week | None |
| Tezepelumab | • Severe asthma, ≥12 years | • 210 mg SC every 4 weeks | None |
| Tralokinumab | • Moderate to severe AD not controlled by topical therapies, ≥18 years | • 600 mg SC loading dose, followed by 300 mg SC every 2 weeks | None |

**Table 1.** FDA-approved indications and dosing of biologics used in allergic and immunologic disorders *CSU: chronic spontaneous urticaria; ICS: inhaled corticosteroid; EGPA: eosinophilic granulomatosis with polyangiitis; HES: hypereosinophilic syndrome; CRSwNP: chronic rhinosinusitis with nasal polyposis; EoE: eosinophilic esophagitis; AD: atopic dermatitis; SC: subcutaneous; IV: intravenous.*

Adverse Event Reporting System database, anaphylaxis to omalizumab has reporting odds ratio of 24.19 (23.02, 25.41).[7] This study found that 5 (0.28%) cases of anaphylaxis-related death have been reported, and hospitalization for management of anaphylaxis has been required in 511 (28.92%) cases.[7]

Because of the association between omalizumab and anaphylaxis, the AAAAI/ACAAI Joint Task Force recommends the following prior to administering omalizumab: obtain informed consent; provide patient education on the signs and symptoms of anaphylaxis; prescribe an epinephrine auto-injector; educate on the proper use of auto-injectors and perform a preinjection health assessment.[3,4] The AAAAI/ACAAI Joint Task Force initially recommended that all patients be observed after each injection, for 2 h after the first 3 injections and 30 min after all subsequent

injections.[3,4] For patients with no prior history of anaphylaxis, including to drugs, foods, etc., the US FDA allows for omalizumab to be self-administered at home if the patient receives the initial 3 doses under observation with no hypersensitivity reaction.

### Pregnancy

Omalizumab is designated pregnancy category "fetal risk cannot be ruled out" by the US FDA. This designation was informed by a prospective observational study (EXPECT), that assessed the rate of major congenital anomalies, prematurity, low birth weight or small size for gestational age among pregnant women exposed to at least one dose of omalizumab within 8 weeks of conception or anytime during pregnancy.[8] Nearly all (98.4%) patients were exposed to omalizumab in the first trimester, and 81.8% continued omalizumab throughout pregnancy (median exposure, 8.8 months).[8]

Results demonstrated no increased risk of major congenital anomalies, prematurity, low birth weight or small size for gestational age among pregnant patients receiving omalizumab.[8] In a subsequent disease-matched comparator cohort, adverse outcomes were similar between omalizumab-exposed and disease-matched cohorts. The prevalence of major congenital anomalies was 8.1% in the omalizumab cohort and 8.9% in the comparator cohort.[9] There were 99.1% live births versus 99.3% in the comparator cohort; premature birth in 15% versus 11% and small for gestational age in 9.7% versus 15.8%. The strength of these results is limited by the small size of the cohorts; approximately 200 pregnant patients were included in each study.

In general, because monoclonal antibodies transport across the placenta in a linear fashion as pregnancy progresses, it is thought that potential effects on a fetus are likely to be greater during the second and third trimesters of pregnancy. In animal reproduction studies, no evidence of fetal harm has been observed.[10]

### Malignancy

Malignant neoplasms (breast, non-melanoma skin, prostate, parotid) occurred in 0.5% of patients receiving omalizumab compared to 0.2% of controls, and the package insert warns about the association between malignancy and omalizumab use.[11] In a phase IV 5-year safety study (EXCELS), malignancy rate per 1000 patient years was found to be 16 in omalizumab group (95% CI, 14.2–17.9) and 19.1 in the non-omalizumab group (95% CI, 16.5–22.0), with a hazard ratio of 1.09 (95% CI, 0.87–1.38).[12] An analysis of pooled data from randomized, double-blind, placebo-controlled asthma trials found no association between omalizumab use and malignancy.[11]

### Infection and vaccination

There are insufficient data to make conclusions about the risk of parasitic infections in patients receiving omalizumab.[13] One double-blind, placebo-controlled study assessed the risk of helminth infection among individuals treated with omalizumab who were deemed high risk of helminth infection. All individuals received antihelmintic treatment, followed by 52 weeks of omalizumab or placebo. Those receiving omalizumab did not have significantly higher risk of helminth infection (OR 1.47, 95% CI 0.74–2.95).[14] The package insert recommends vigilant monitoring for helminth infection in patients who are at high-risk for helminth infection; this recommendation is based on theoretical risk. There is no evidence to suggest omalizumab leads to increased susceptibility of other types of infection, and studies have not demonstrated increased risk of opportunistic or serious infection. There are no published contraindications or recommendations regarding vaccination.

### Case reports

Several case reports describe the onset of arthralgia after use of omalizumab. Specifically, serum sickness-like reactions and rheumatoid arthritis-like joint pain have been described.[15–17] Multiple case reports describe identification of eosinophilic granulomatosis with polyangiitis (EGPA) in patients receiving omalizumab.[18–23]

## MEPOLIZUMAB

### Hypersensitivity reactions

There were no episodes of anaphylaxis reported among mepolizumab users in 5 double-blind, placebo-controlled studies. Hypersensitivity reactions occurred at a rate of 1%, though the types of reactions designated as hypersensitivity reactions was not

clearly defined in all cases.[24–27] These reactions were all mild to moderate in severity. In 1 study, 2 patients experienced hypersensitivity reactions: the first reported malaise and headache, and the second reported dizziness and lightheadedness.[28] Both patients received additional doses of mepolizumab without adverse effect.

In three open-label extension trials, the rate of hypersensitivity reactions was reported at 1–2%.[28–30] There were no reports of anaphylaxis considered to be related to mepolizumab treatment, and there were no fatalities. A review of US FDA AERS database from January 2004 to September 2020 revealed 104 reported cases of anaphylaxis on mepolizumab; this study found a reporting odds ratio of anaphylaxis on mepolizumab of 4.65 (95% CI, 3.85–5.65).[7]

### Pregnancy

There are currently insufficient data on the use of mepolizumab in pregnant or breastfeeding patients to inform drug-associated risk to the fetus or newborn. An ongoing prospective, observational study (Study 200 870) assessing the risk of mepolizumab use in pregnancy began in 2016 and includes 3 cohorts of patients: patients exposed to at least 1 dose of mepolizumab 8 weeks prior to last menstrual period or any time during pregnancy; patients with asthma and no mepolizumab exposure; and non-asthmatic patients with no exposure to teratogens or mepolizumab.[31] The primary end point is major structural defects among live born infants.

Preliminary results demonstrate that 20 pregnant women with asthma and exposure to mepolizumab and 136 pregnant women with asthma and no exposure to mepolizumab enrolled in the study between November 2016 and August 2021. The outcome of the pregnancy was known for 17 of the 20 women exposed to mepolizumab: 12 of 17 pregnancies (70.6%) resulted in live birth, 1 resulted in spontaneous abortion and 3 were lost to follow-up.[31] Major birth defects occurred in 0 of 12 reported live births.[31] Of those unexposed to mepolizumab, the outcome of pregnancy was known for 129 of the 136 participants: 103 of 129 resulted in live birth, 2 resulted in spontaneous abortion and 24 were lost to follow-up. Major birth defects occurred in 7 of 103 (6.8%) of live births.[31] No conclusions have yet been drawn from this data. The study is expected to conclude in 2023.

### Malignancy

There is no evidence to suggest that patients receiving mepolizumab are at increased risk of developing malignancy. In open-label extension trials, approximately 2% of patients receiving mepolizumab developed malignancy.[28,29] In one study (COLUMBA), 6 (2%) patients reported malignancy, including basal cell carcinoma (3), prostate cancer, (2) and breast cancer (1).[29] The authors do not comment on whether these malignancies were attributed to mepolizumab use. Duration of the open-label extension trials ranged from 4 weeks to 4.5 years, which may not be long enough to detect signals in malignancy risk.

### Infection and vaccination

In double-blind, placebo-controlled trials, there was no difference in rate or severity of infection between placebo and mepolizumab groups. In 2 open-label extension trials, opportunistic infection occurred in 4–7% of patients receiving mepolizumab; most of these cases were herpes zoster infections, though candida and pulmonary tuberculosis were also reported. Only 1 episode of herpes zoster was considered serious; all other episodes were nonserious and resolved despite continuation of mepolizumab.[28,29] There were no reported helminth infections.[24–30] The mepolizumab package insert recommends that those eligible for Herpes zoster vaccine consider receiving it prior to starting therapy.[32]

### Case reports

There are a limited number of case reports describing unique adverse events in patients on mepolizumab. Two reports describe adverse outcomes in patients receiving mepolizumab for asthma: one patient developed alopecia and another developed non-cardiac chest pain.[33,34]

## RESLIZUMAB

### Anaphylaxis

Reslizumab features a black-box warning for anaphylaxis. In placebo-controlled studies, 4 cases of anaphylaxis occurred with reslizumab

administration (3%).[35] One patient was treated with epinephrine; the other patients were treated with antihistamines and corticosteroids. No patient experienced respiratory failure, circulatory collapse, or death.[35] In open-label extension trials, no anaphylaxis was reported, and there were no other hypersensitivity reactions thought to be related to reslizumab use. Review of US FDA AERS database from January 2004 to September 2020 identified 4 reported cases of anaphylaxis to reslizumab with an odds ratio of 5.74 (95% CI, 2.14–15.41). The package insert recommends observation after reslizumab infusion for "an appropriate period of time." There are no specific guidelines regarding the length of observation period or need for patients to maintain epinephrine prescription. We favor a 30-min observation period after infusion and require patients to keep epinephrine on-hand.

### Pregnancy

There is insufficient data regarding the risk of reslizumab in pregnancy. At present, there are no clinical trials designed to assess the outcomes of pregnant patients receiving reslizumab.

### Malignancy

At present, there is no evidence to suggest that patients receiving reslizumab are at increased risk of developing malignancy. In randomized-controlled trials, malignancy was reported in 6 of 1028 (0.58%) patients on reslizumab compared to 2 of 730 (0.27%) on placebo. Reported malignancies in the reslizumab group included colon cancer (1), teratocarcinoma (1), lung adenocarcinoma (1), lung neoplasm (1), plasmacytoma (1), prostate cancer (1), squamous cell carcinoma, (1) and patients with greater than 1 malignancy (6).[35] There was no statistically significant difference between the groups (odds ratio, 2.14 [95% CI, 0.38–21.70]).[35]

### Infections and vaccinations

The incidence of infection in was low (2%) among patients receiving reslizumab in randomized-controlled trials, and there was no increased risk in patients receiving reslizumab compared to placebo (relative risk 0.77, 95% CI 0.70–0.85). There were no reported helminth infections or opportunistic infections. There are no published contraindications or recommendations regarding vaccination.[35]

### Case reports

In our literature review, we found no case reports describing unique reslizumab-related adverse effects.

## BENRALIZUMAB

### Hypersensitivity reactions

Hypersensitivity reactions occurred in 1–3% of patients in placebo-controlled trials.[36–38] Nearly half of hypersensitivity reactions were urticarial; 1 patient developed eosinophilic granulomatosis with polyangiitis.[37] Anaphylaxis occurred in 1 patient in the open-label extension trial.[39] This patient developed anaphylaxis while continuing benralizumab from a prior study; the timing of anaphylaxis and number of doses received prior to reaction are not reported.

### Pregnancy

There are insufficient data on the use of benralizumab in pregnant or breastfeeding patients to inform on drug-associated risk to the fetus or newborn. A benralizumab pregnancy exposure study (NCT02794999) began in March 2019 and is currently enrolling patients who were exposed to benralizumab anytime during pregnancy or within 8 weeks prior to the first day of the last menstrual period. The study will conclude in February 2026.

Information about benralizumab exposure in pregnancy is currently limited to case reports. In 1 such report, a 36-year-old female with hypereosinophilic syndrome was found to be pregnant after 138 weeks of benralizumab therapy. Benralizumab was continued throughout pregnancy, and the infant was delivered by cesarean section at 38 weeks gestation for failure to progress. No major birth defects are described.[40]

### Malignant neoplasms

There is insufficient evidence to suggest a causal relationship between benralizumab and malignancy. In an open-label extension study, 1 patient developed malignancy that was felt by the investigator to be related to benralizumab. This patient had a history of prostatic hypertrophy and

elevated prostate specific antigen and developed prostate cancer 3 days after their second dose of benralizumab.[39]

### Infections and vaccination

Across all trials, patients receiving benralizumab had no increased risk of infection, and there were no reported helminth infections.[36–39] There was 1 reported case of herpes zoster.[36] Subsequently, a case report published in 2019 describes a 61-year-old patient who developed disseminated herpes zoster after initiation of benralizumab.[41] There are no published contraindications or recommendations regarding vaccination.

### Special considerations

One death related to benralizumab was reported in an open-label extension trial. This patient developed hepatitis, Aspergillus pulmonary infection and multiorgan failure.[39]

### Case reports

Several case reports describe the development of inflammatory disorders in patients receiving benralizumab, including cytokine-release hypersensitivity reaction and cystitis.[42,43]

## DUPILUMAB

### Hypersensitivity reactions

No anaphylactic events have been reported in any trial.[44–48] Three trials reported hypersensitivity reactions in approximately 1% of participants, with no significant difference in rates of hypersensitivity reaction between placebo and dupilumab. Dupilumab's package insert states that hypersensitivity reactions occur in less than 1% of patients, including generalized urticaria, serum sickness, rash, erythema nodosum and anaphylaxis.[49]

### Malignancy

There is insufficient evidence to suggest a causal relationship between dupilumab and malignancy. In an open-label extension trial, 5 patients developed malignancy. Two were felt to be related to the study drug, including 1 patient with Hodgkin disease and 1 patient with prostate cancer.[46] In another open-label study, treatment-emergent events included malignancy in 2 patients (metastatic lung cancer and gastric adenocarcinoma), and both diagnoses led to death.

### Pregnancy

An analysis of the World Health Organization (WHO) safety reporting database identified 36 reports of pregnancy-related adverse drug reactions in patients receiving dupilumab.[50] With the exception of 1 reported case of heterotopic pregnancy (OR 21.66 [95% CrI 2.95–159.02), the authors found no association between reported adverse outcomes and dupilumab use.[50] The majority of reported adverse events (58.3%) were spontaneous abortion (OR 0.57 [95% CrI 0.37–0.88]).[50]

Pregnant or breastfeeding individuals were excluded from enrollment in dupilumab clinical trials; however, pregnancy outcomes are reported for some participants who became pregnant while participating in clinical trials. In the TRAVERSE open-label extension study, 9 participants receiving dupilumab for asthma became pregnant: 3 spontaneous abortions occurred in the dupilumab/dupilumab arm and none occurred in the placebo/dupilumab arm.[51]

An ongoing retrospective cohort study (Dupi PODS) aims to identify the incidence of adverse pregnancy and infant outcomes in women who are receiving dupilumab for atopic dermatitis compared to those with atopic dermatitis not on dupilumab. The trial began enrolling patients in September 2019 and is expected to conclude in July 2027.

### Infections and vaccinations

There was no evidence of increased infection incidence in any trial, and there were no reported helminth infections.[44–48,52] Approximately 0.4–1% of patients developed herpes zoster infection, and 0.4–2% of patients developed eczema herpeticum.[53,54]

Patients with recent live vaccination were excluded from initial placebo-controlled trials in patients with atopic dermatitis (SOLO 1 and SOLO 2). Thus, it is recommended that patients avoid exposure to live vaccines while on dupilumab. There is no explicit evidence indicating that live

vaccination is risky among patients receiving dupilumab.

## Eosinophilia

Eosinophilia was reported as adverse event in the Liberty Asthma Quest trial; 52 (4.1%) of patients who received dupilumab developed eosinophilia compared to 4 (0.6%) of placebo.[55] Only a few patients (0.2%) developed symptomatic eosinophilia.[55] Eosinophilia with absolute eosinophil counts >3000/mm$^3$ occurred in 1.2% of patients in the combined dupilumab groups and 0.3% in the combined placebo groups. The highest mean percent change in eosinophils from baseline occurred between 16 and 20 weeks, and the greatest change occurred in patients receiving dupilumab 300 mg every 2 weeks.[55]

Four patients developed symptomatic eosinophilia. One such patient was a 50-year-old male with asthma and chronic rhinosinusitis with nasal polyposis who received dupilumab 300 mg every 2 weeks. On day 16 of the trial, he developed fever, chills, myalgia, and arthralgias, and on day 30, his absolute eosinophil count was 10,280/mm$^3$. Another patient was a 56-year-old male with an eosinophil count of 2080/mm$^3$ on day 113 who developed chronic eosinophilic pneumonia. A 28-year-old female was found to have an increase in absolute eosinophil count from 45 at baseline to 2310 at day 367. She developed myositis and radiculopathy; however, she was able to continue dupilumab without interruption, and her symptoms were managed with NSAIDs. The final patient was a 52-year-old female who developed pneumonitis after her absolute eosinophil count increased from 1210/mm$^3$ at baseline to 3040 at day 105.

In the Liberty Asthma Venture trial, eosinophilia was reported as an adverse event in 14% of patients receiving dupilumab versus 1% placebo.[44] The eosinophil count increased beyond 3000/mm$^3$ in 13% of dupilumab users and 1% of placebo. There were no clinical consequences of eosinophilia in this trial.

In the SOLO 1 and SOLO 2 trials, transient and small increases in eosinophil counts were noted at weeks 4 and 8. The eosinophil counts returned toward or below baseline by week 16.[54] Liberty NP Sinus-24 and Sinus-52 studies found transient, non-significant increases in eosinophil counts excepting 4 patients who developed symptomatic eosinophilia. One patient was diagnosed with EGPA; the others discontinued dupilumab due to symptoms of arthralgia (1), asthma exacerbation (1) and insomnia (1).[45]

In 1 open-label extension trial, patients had greater eosinophilia at follow-up compared to baseline, and absolute eosinophil counts were >1500/mm$^3$ in 15.8% of patients with a max of 7800/mm$^3$.[56] In TRAVERSE open-label trial, 1.4–6.4% of patients developed asymptomatic eosinophilia, and 5 of these patients were diagnosed with EGPA. By week 96, mean blood eosinophil counts had decreased to below baseline for all groups. The mechanism underlying the development of EGPA in this population is not well-established, though it may reflect the severity of disease among patients selected for participation in clinical trials.

Results of clinical trials suggest that eosinophil counts tend to be highest between 4 and 16 weeks of therapy, returning to baseline thereafter for most patients. Additionally, if the eosinophilia is asymptomatic, patients can continue dupilumab therapy without interruption.

## Conjunctivitis

Conjunctivitis is a common adverse effect among patients receiving dupilumab. In the SOLO 1 and SOLO 2 trials, conjunctivitis was reported in 3–5% of patients receiving dupilumab, compared to 1% of patients receiving placebo.[54] In the Liberty Ad Chronos Trial, the reported rate was higher for both groups, occurring in 14–23% of patients on dupilumab and 9% of patients receiving placebo.[53]

In open-label extension trials, 10.7–18% of patients developed conjunctivitis (ie, allergic conjunctivitis, bacterial conjunctivitis, viral conjunctivitis).[56,57] Most cases of conjunctivitis were mild or moderate, resolving without discontinuing treatment. Some patients with moderate conjunctivitis required topical eye treatment during the study. In 1 open-label trial, 5 patients (0.3%) developed severe conjunctivitis, and 3 of the 5 patients discontinued dupilumab. In the Liberty Ad Chronos trial, one patient discontinued dupilumab after developing atopic

keratoconjunctivitis. In the Traverse open-label extension study, conjunctivitis events occurred less frequently over time: 8.5% of events occurred during weeks 0–12 and 0.7% of events occurred between weeks 48 and 60. Among patients with atopic dermatitis who receive dupilumab, underlying barrier defects may contribute to the development of conjunctivitis.[47]

Based on results of clinical trials, mild conjunctivitis can be managed conservatively without discontinuation of treatment. A low threshold for referral for ophthalmologic evaluation is appropriate for patients non-responsive to conservative therapy or for patients with moderate to severe symptoms.

### Case reports

A wide variety of inflammatory conditions have been associated with dupilumab in case reports, including uveitis, blepharoconjunctivitis, inflammatory arthritis, and ulcerative colitis.[58–64] Numerous dermatologic conditions have also been reported, include psoriasis, rosacea, seborrheic dermatitis, alopecia areata, erythema nodosum, and facial flushing.[65–72]

## TEZEPELUMAB

### Hypersensitivity reactions

In the NAVIGATOR study, no patients randomized to receive tezepelumab reported anaphylaxis during the 52-week study period, and no other hypersensitivity reactions were described.[73] Similarly, no anaphylaxis or hypersensitivity reactions were reported in the CASCADE trial.[74]

### Pregnancy

There are currently no available data on the use of tezepelumab in pregnant or breastfeeding patients, and at present, there is no trial actively recruiting pregnant patients.

### Malignancy

In the NAVIGATOR study, the incidence of malignancy and benign neoplasm did not differ between tezepelumab and placebo groups (5 patients [0.9%] in each group).[73] Reported malignancies included malignant melanoma in situ (2), basal cell carcinoma (3), prostate cancer (1), squamous cell carcinoma (1), endometrial cancer (1), and squamous cell carcinoma of the oral cavity (1).[73] In the CASCADE study, no patients receiving tezepelumab developed malignancy during the trial period.[74]

### Infection and vaccination

In the CASCADE and NAVIGATOR studies, there were no severe infections reported in patients receiving tezepelumab over the 52-week study periods.[73] The risk of helminth infection is unknown, and the package insert recommends vigilance in monitoring for helminth infections in patients receiving tezepelumab. The package insert also recommends avoidance of live vaccines, as the concomitant use of tezepelumab and live vaccines has not been studied.

### Case reports

In our literature review, we found no case reports describing unique tezepelumab-related adverse effects.

## TRALOKINUMAB

### Hypersensitivity reactions

The package insert warns about a possible risk of hypersensitivity reaction to tralokinumab, including anaphylaxis and angioedema; however, the frequency of hypersensitivity or anaphylactic reaction occurrence is uncertain.[75] No anaphylactic or hypersensitivity reactions were reported among patients receiving tralokinumab for atopic dermatitis in any of the phase 3 clinical trials (ECZTRA 1, ECZTRA 2 and ECZTRA 3).[76,77]

### Pregnancy

There is currently no available data on the use of tralokinumab in pregnant or breastfeeding patients. At present, there is no trial actively recruiting pregnant patients.

### Malignancy

The impact of tralokinumab on malignancy risk is not known. There was 1 reported case of malignancy among those receiving tralokinumab in the ECZTRA 2 trial and 1 case in the ECZTRA 3 trial.[76,77] One of these patients developed prostate cancer and discontinued treatment as a result.[77] The authors

do not comment on whether the malignancy was attributed to tralokinumab use.

### Infection and vaccination

There is no increased risk of serious or opportunistic infection described among patients receiving tralokinumab for atopic dermatitis in phase 3 clinical trials.[76,77] Specifically, patients receiving tralokinumab did not seem to be at higher risk of eczema herpeticum compared to placebo.[76,77] Patients with known helminth infections were excluded from all trials; the risk of helminth infection is unknown. The package insert recommends discontinuing tralokinumab if patients do develop helminth infection.[75] Avoidance of live vaccines is also recommended, based on lack of data to demonstrating tolerance to live vaccines.

### Conjunctivitis

During 16-week initial treatment period for safety analysis in both the ECZTRA 1 and ECZTRA 2 trials, conjunctivitis was reported more frequently among patients receiving tralokinumab compared to placebo.[76,77] For instance, 60 (10%) patients receiving tralokinumab in ECZTRA 1 developed conjunctivitis, compared to 7 (3.6%) of patients receiving placebo.[76] All cases were reported to be mild to moderate in severity. Two patients ultimately discontinued tralokinumab due to conjunctivitis.[76,77]

### Eosinophilia

In the ECZTRA 1 and ECZTRA 2 trials, patients treated with tralokinumab for atopic dermatitis developed a greater increase in baseline eosinophil counts during the first 16 weeks of the study compared to those receiving placebo.[76] The increase in eosinophil counts did not seem to result in other adverse outcomes, and eosinophil counts returned to baseline with continued treatment.

### Case reports

There is 1 published case report describing vernal keratoconjunctivitis in a patient receiving tralokinumab for atopic dermatitis.[78]

## SUMMARY

Anaphylaxis is uncommon among the biologics reviewed in this paper, with reported rates ranging from 0 to 1%. There is an explicit black box warning for the risk of anaphylaxis with use of both omalizumab and reslizumab.

There is insufficient evidence to determine risks associated with biologic use in pregnant or breastfeeding patients. The most studied agent in the context of pregnancy is omalizumab, and results indicate no increased risk of major congenital anomalies, prematurity, low birth weight, or small size for gestational age among pregnant patients receiving omalizumab. Studies available at present are limited by small sample size.

There is no definitive evidence for increased risk of malignancy associated with any of the biologics reviewed. Studies are limited by the duration of extension trials peaking at 4.5 years, which may not be sufficient time to detect a signal in malignancy risk.

There is no definitive evidence for increased risk of parasitic infections associated with biologics. However, patients at high risk of developing helminth infection or with recently diagnosed helminth infection were excluded from all clinical trials. Thus, vigilance in identifying and treating potential helminth infection is recommended to providers using these biologic agents. A small percentage of patients receiving dupilumab, mepolizumab and benralizumab reported developing herpes zoster infection. For dupilumab, this occurred in 0.1% of patients. Disseminated herpes zoster was uncommon. The development of serious and/or opportunistic infections were otherwise not found to be associated with the agents reviewed.

It has been recommended by their respective package inserts that patients receiving dupilumab, tezepelumab, and tralokinumab avoid live vaccines. This recommendation is based on a lack of data confirming the safety of concomitant use of these agents and lives vaccines, rather than a known true risk.

### Abbreviations
US FDA: United States Food and Drug Administration; AAAAI: American Academy of Allergy, Asthma, and Immunology; ACAAI: American College of Allergy, Asthma, and Immunology; OR: odds ratio; CI: confidence interval; EGPA: eosinophilic granulomatosis with polyangiitis; AERS: Adverse Events Reporting System; NSAIDS: non-steroidal anti-inflammatory drugs.

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The authors declare that they have no conflict of interest.

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