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REVIEW

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# Safety Profiles of Biological Therapies Used in Asthma Treatment

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## ABSTRACT

The reliability of the biologics used in the treatment of severe asthma is as important as their effectiveness. There are currently six mAbs approved for the treatment of severe asthma (omalizumab, mepolizumab, benralizumab, reslizumab, dupilumab, and tezepelumab). In this review, the safety data obtained from clinical phase studies and real-life studies of these biologics are presented in detail together with our clinical experience. More real-life studies have been done with omalizumab and mepolizumab. It has been shown in these studies that their reliability profiles are quite good. A real-life study with tezepelumab has not been published so far. There are few real-life studies on benralizumab, dupilumab, and reslizumab. However, safety profiles in RCTs with these biologics have been reported similar to placebo. In clinical phase studies, it is seen that the safety profiles of all six biological treatments are quite good.

**Keywords:** Biological, Safety, Asthma

**Abbreviations**

**ADA:** anti-drug antibody
**ADR:** adverse drug reaction
**AE**: adverse event
**CPK:** creatine phosphokinase
**CRS/NP**: chronic rhinosinusitis with nasal polyp
**HSR:** hypersensitivity reaction
**HES:** Hypereosinophilic syndrome
**ISR:** injection site reaction
**IV**: intravenous
**mAB:** monoclonal antibody
**OCS:** oral corticosteroid
**SA:** severe asthma
**SAE:** severe adverse event
**SC:** subcutaneous
**SR**: systemic reactions
**TSLP:** thymic stromal lymphopoietin
**URTI**: upper respiratory tract infection

## INTRODUCTION

In the past two decades, the increase in studies on underlying immunopathobiological mechanisms in asthma, determination of endo-types and sub-endo-types, and their association with phenotypes have led to the development of targeted biological therapies through monoclonal antibodies (mAB). There are currently six biological agents approved for the treatment of severe asthma (SA) (omalizumab, mepolizumab, benralizumab, reslizumab, dupilumab, and tezepelumab). The safety profiles of these biological agents are as important as their clinical effects.

Terminologies regarding drug safety should be clear and used correctly. Therefore, the concepts of "adverse reaction", "adverse effect", "side effect", and "adverse event (AE)" will be discussed below.

### Adverse Reaction

An adverse reaction is a harmful and undesirable condition that occurs at normal doses of the drug used for the prophylaxis, diagnosis, treatment, or change of physiological function of disease in humans (1). It anticipates the potential danger from future administration and often requires avoiding drug reactions, changing the dosage regimen, or discontinuing the product (2).

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**Adverse Effect**

An adverse effect is a potentially harmful effect produced by a drug. This may or may not be associated with a clinically significant adverse reaction and/or an abnormal laboratory test. "Adverse effects" are usually determined by laboratory tests (e.g., biochemical, hematological, immunological, radiological, pathological) or clinical studies (e.g., endoscopy, cardiac catheterization), and "adverse reactions" are detected by clinical symptoms and findings (3). When adverse drug reactions (ADR) are suspected, the reaction is attributed to the drug. Ideally, the citation is accompanied by an explanation of the degree of probability of citation (certain, probable/likely, possible, unlikely, conditional/unclassified, unassessable/unclassifiable) (2,4).

**Side Effect**

Any adverse effects related to the pharmacological properties of the drug that occur at the normal doses of a drug used by a patient. Such an effect can be either positive or negative. Such effects are well known, even expected, and require little or no change in patient management (1).

**Adverse Event**

An adverse event (AE) is a drug-independent negative consequence that occurs in a person while taking a drug or at a later stage. All "ADRs" are AEs, but not all AEs are "ADRs". This distinction is important in pre-marketing clinical trials where not all events are drug-related.

## CLINICAL AND RESEARCH CONSEQUENCES

### Anti-IgE (Omalizumab) safety profile

#### *Safety data of pre-marketing clinical studies with omalizumab*

Since omalizumab is the oldest of the biologics used in SA, it is the biologic with the most long-term safety data. In pre-marketing clinical studies, the most common AEs in patients treated with omalizumab are injection site reaction (ISR), acute respiratory viral infections, sinusitis, headache, and pharyngitis. These AEs were similar for patients treated with omalizumab and the placebo group (5).

A randomized double-blind placebo-controlled phase 3 study of 546 patients, with moderate to severe allergic asthma, evaluated the clinical efficacy, steroid reducing effect, and safety of omalizumab (6). In this study;

- While 5 (1.8%) patients in the placebo group left the study due to AEs, all patients in the omalizumab group continued until the end of the study.
- The most common AE associated with the drug was fatigue and paresthesia. This rate was 1.1% in the omalizumab group, but there were no patients in the placebo group. Suspected drug-related headache was seen in 3 (1.1%) patients in both groups.
- Symptoms at the local injection site were 11.8% in the omalizumab and 7.7% in the placebo.

The efficacy and safety of omalizumab in the treatment of inhaled corticosteroid-dependent asthma was evaluated in another, placebo-controlled, double-blind phase-3 study of 525 patients (7). The frequency of AEs was similar in both groups (89.2% in the omalizumab vs 89.1% in the placebo). The number of patients with severe adverse events (SAE) was 7 (2.6%) in the omalizumab group and 6 (2.3%) in the placebo group.

#### *Safety data from real-life studies with omalizumab*

Real-life studies show omalizumab is tolerated very well in both adults and children (8, 9). Safety data from real-life observational studies appeared to be consistent with the results of randomized controlled clinical trials (10).

- In a real-life study in which 3620 patients receiving omalizumab were evaluated for 52 weeks, 32% AE and 15% SAE were reported. SAEs associated with omalizumab was <1% and anaphylaxis were reported the most (0.11%). ADR was observed in 8% of the patients and the most common ADR was fatigue (0.94%) (8).
- In a study with 91 patients, the efficacy and safety of omalizumab for a long term, such as 9 years, were evaluated. ADRs requiring discontinuation of omalizumab treatment occurred in 6 patients (6.6%) (3 patients with arthralgia/myalgia, 1 patient with urticaria/angioedema, 1 patient with metrorrhagia, and 1 patient with relapsed herpes labialis) (11).
- Long-term treatment with omalizumab appears to be quite safe and well tolerated in clinical practice. Long-term use has not been shown to increase the risk of ADR, in particular anaphylaxis (11).
- In a study in which adults and adolescents, were given omalizumab treatment for allergic asthma, 90 (11.2%)

of 801 patients developed 144 SAEs. Only 3 (0.4%) patients had an AE specifically reported, all three of which were reported as moderate anaphylaxis due to omalizumab (12).

One of the most serious possible ADRs of a drug is anaphylaxis. It was reported that the frequency of anaphylaxis attributed to omalizumab use is <0.2% (13). Anaphylaxis may develop following both the first and subsequent administrations of omalizumab. Although the majority of these reactions occur within 2 hours, a small number of them can occur after 2 hours (13, 14).

Although the course, severity, and response of the patients at risk of helminth infection did not change, the infection rate was slightly increased with omalizumab (15). If a helminthic infection develops and patients do not respond to the recommended anti-helminth therapy, discontinuation of omalizumab should be considered (5).

A study reporting an increase in cardiovascular system, and cerebrovascular system AEs has been observed in the omalizumab group compared to placebo and has raised concerns about this issue (16).

Therefore, the EXCELS study, a prospective observational cohort study, was launched to evaluate the clinical efficacy and long-term safety of omalizumab in patients with moderate to SA.

- In this study, the authors showed that the observed rates of arterial thromboembolic events were similar between the omalizumab and placebo groups.
- This study also evaluated the risk of malignancy associated with omalizumab and found that the drug was not associated with an increased risk of malignancy (17).

The effects of omalizumab on pregnancy have also been a curious subject. The results of pregnancy data of 191 patients, who received omalizumab with the EXPECT study, were published in 2015.

- This study was a prospective, observational study of pregnant women exposed to multiple doses of omalizumab in the 8 weeks before conception or at any time during pregnancy.
- Major congenital anomalies, prematurity, low birth weight, and small size ratios for gestational age were not different from other studies conducted in this asthma population.
- There was no significant increase in major or minor anomalies (18).

***Our clinical experience***

In a study conducted in our clinic in which patients with atopic SA treated with omalizumab were evaluated retrospectively. Thirty eight patients who received omalizumab treatment for >6 months between 2009 and 2017 were included in this study. It was reported that omalizumab was well tolerated in all patients during the treatment and that no patient had a systemic reaction (SR) or serious ADR during the follow-up period. Therefore, no ADRs required discontinuation of omalizumab therapy (19).

When omalizumab was evaluated in terms of ADRs between 2009 and 2020, no ADR was observed in 63 of 64 patients requiring omalizumab discontinuation. Only one of the patients developed anaphylaxis (ADR likely/possible) and therefore the patient could not continue the treatment.

**Mepolizumab (Anti-IL5) safety profile**

***Safety data of pre-marketing clinical studies with mepolizumab***

Mepolizumab has been shown to have a consistent safety profile in all randomized placebo-controlled trials in patients with severe eosinophilic asthma (SEA) (20, 21)

In the DREAM study;

- The safety profile of mepolizumab (75 mg, 250 mg, and 750 mg) was similar to placebo in patients with SEA.
- No serious life-threatening anaphylaxis has been reported.
- Serious infections were found in approximately 3% of the mepolizumab and placebo groups combined and opportunistic infections were seen in less than 1% of cases in the mepolizumab group. Herpes zoster was seen in two patients in the mepolizumab group but not in the placebo (20).

In COSMOS, a 52-week open-label extension study of MENSA and SIRIUS [a study to determine the long-term safety of 100 mg subcutaneous (SC) mepolizumab in asthmatic patients], mepolizumab was shown to have a good long-term safety profile.

- When the mepolizumab and placebo infusion/injection arms were compared, it was seen that there were similar rates of AEs and serious AEs.
- No increase in systemic and local site reactions was reported. They were slightly higher report in the placebo arm than in the mepolizumab infusion/injection arm. Anaphylaxis, thought to be associated with mepolizumab treatment, was also not detected (22).

The long-term safety and clinical benefits of mepolizumab were evaluated in patients with SEA in the COSMEX study. The long-term safety profile in COSMEX (patients receiving 100 mg SC mepolizumab every 4 weeks as add-on therapy for up to 172 weeks), which included 339 patients in an extension study of COSMOS, was similar to those seen in previous studies of mepolizumab and with no new safety concerns (23). However, the absence of a placebo-controlled arm in the design of this study makes it difficult to made strong clinical interpretations of any AE thought to be drug-related. In the COSMEX study;

- Anaphylaxis or non-allergic systemic reactions (SR) associated with mepolizumab have not been reported.
- When evaluated in terms of potential opportunistic infection AEs, herpes in eight patients, candida in three patients, and pulmonary tuberculosis in one patient were reported. Non-serious herpes zoster infections that resolved without discontinuation of mepolizumab were reported in three additional patients.

Longer-term reliability data compared to the COSMOS and COSMEX studies were revealed by the COLUMBA study. 347 patients receiving 100 mg SC mepolizumab were included in this study and safety data was recorded for a mean of 3.5 years (maximum 4.5 years). The limitation of the COLUMBA study was the lack of a placebo-controlled arm to make a strong clinical interpretation of any treatment-related adverse outcomes. Nevertheless, the data from the COLUMBA study supports the long-term safety of mepolizumab in patients with SEA (24). In the COLUMBA study;

- Serious AEs were detected as allergic/hypersensitivity SRs in 8 (2%) patients and non-allergic SRs in 1 (< 1%) patient. Anaphylaxis has not been reported with mepolizumab.
- While an opportunistic infection was detected in 24 (7%) patients during treatment, 8 (2%) of them were found to have herpes zoster infection.
- No parasitic infection was reported.
- Neutralizing antibodies were negative and anti-drug antibodies (ADA) were found to be rare positive (8%) in all samples. In most patients, ADA-positive titers were found to be low, transient, and lacking in immunogenicity increasing with the duration of treatment. No relationship was found between the frequency or hypersensitivity reactions (HSR) of AEs and the presence or absence of ADAs (24).

Clinical studies have shown that mepolizumab is a safe biological agent that is well tolerated. However, it is also known that real-life data may differ significantly from clinical studies in terms of patient characteristics, patient-physician cooperation, treatment follow-up, and outcome management (25).

***Safety data from real-life studies with mepolizumab***

Mepolizumab appears to be well tolerated in preliminary real-life reports for many AEs, including urticaria, herpes zoster, trigeminal neuralgia, fatigue, headache, and local reactions at the injection site (26, 27)

- In a study evaluating real-life reliability results of mepolizumab, AE reporting was found to be quite low (28). The most common AEs reported in this study were local ISR (4.3%); headache and myalgia/arthralgia were <1%. Hospitalization was required in only one case due to paroxysmal supraventricular tachycardia, which started a few days after the second dose of mepolizumab. However, it was concluded that this event was not related to the treatment, and drug administration continued.
- In a retrospective real-life study including 36 patients, no significant reaction at the injection site was detected. Mild herpes zoster was reported in one patient and urticaria in another. However, these events were not found to be related to mepolizumab and patients continued to take mepolizumab without any problems (27).
- In another real-life study involving 143 patients, who received at least one dose of mepolizumab, the discontinuation rate of mepolizumab was reported as 6/143 (4.2%). (Five resulted from lack of response to treatment and one discontinued due to possible treatment-related urticaria). Only mild side effects, such as headache and local ISR were reported in this study. All of these resolved spontaneously within an hour and without any medication (29).

- In a clinical prospective observational real-life study of 66 patients with SEA, no serious AEs were reported during the study period. Eleven patients (18%) reported mild AEs such as muscle pain, itching, rash, injection site pain, fever, and headache (30).

Little is known about the effects of mepolizumab in pregnancy. In one case report, no ADRs or side effects related to clinical findings for mother and child were reported (31).

Mepolizumab is approved for pediatric and adolescent patients, 12 years (United States) or 6 years (European Union), with SEA.

27 (90%) of 30 children, who received mepolizumab for 52 weeks, experienced AEs and 7 (23%) SAEs, but none of the SAEs were found to be associated with the treatment. Death was not seen in any of the cases. Long-term safety, pharmacodynamic, and efficacy data from this study support a positive benefit-risk profile for mepolizumab in children, with SA and an eosinophilic phenotype, and were similar to adult study data (32).

***Our clinical experience***

- In our clinic, an ADR that required discontinuation of treatment with mepolizumab, which we started in the population of patients with oral corticosteroid (OCS)-dependent CRS/NP eosinophilic SA, developed in one patient. Mepolizumab was discontinued due to the development of arthralgia, myalgia, weakness, and additional fever and nausea after the third dose administration of the patient, who developed arthralgia, myalgia, and fatigue in the first two doses, one day after the administration. It was observed that these complaints and symptoms did not recur in the follow-up after the treatment was discontinued. Therefore, this reaction was assessed as a probable/likely ADR (33).
- In a study involving our patients studied the mepolizumab-related adverse events and these are summarized in Table I (34). A patient with normal echocardiography (EF: 64%), who had been performed approximately one year ago, developed pitting edema in the lower extremity 10 days after the second dose of mepolizumab. Global hypokinesia in the left ventricle, elevation in Troponin T and pro-Brain Natriuretic Peptide (EF: 40-45%) were detected in the patient who applied to the cardiology clinic. In the cardiological evaluation performed 1 month after the discontinuation of mepolizumab treatment, regression was found in the signs of heart failure. AEs such as herpes zoster, herpes labialis, parasitic infection, and anaphylaxis were not observed.
- Although not explicitly recommended, it is recommended to consider the varicella vaccine in potential mepolizumab patients (5). In our clinic, we did not have varicella (chickenpox) vaccine prophylaxis for these patients, but we also closely monitoring this aspect. None of our patients developed a disease secondary to varicella.

**Reslizumab (Anti-IL5) safety profile**

***Safety data of pre-marketing clinical trials with reslizumab***

Reslizumab administered IV every four weeks in SEA was well tolerated in randomized controlled trials (35, 36).

In a randomized placebo-controlled clinical study conducted with reslizumab at a dose of 3 mg/kg by Castro et al., nasopharyngitis was found to be the most common AE (21% in the reslizumab group and 9% in the placebo group) and these AEs were reported to occur mostly in patients with nasal polyps (37). In this study;

- The overall safety profile of reslizumab was determined to be similar to placebo. AEs occurring in more than 5% of patients treated with reslizumab were reported as nasopharyngitis, upper respiratory tract infections (URTI), sinusitis, influenza infection, and headache.
- There was no difference in infections and infestations between patients receiving placebo or reslizumab, and no helminthic infestations were reported.

**Table I: Drug-related advers events seen in patients receiving mepolizumab treatment in our clinic**

| | n (%) |
|---|---|
| Local injection site reactions | 14 (16.7) AE |
| Headache | 15 (17.9) AE |
| Arthralgia/myalgia | 22 (26.2) AE |
| Heart failure with reduced ejection fraction | 1 (1) ADR (Possible) |
| Serum sickness-like picture | 1 (1) ADR (Probable) |

**AE:** Adverse event, **ADR:** Adverse drug reaction

- Infusion site reactions (pain, rash, and hematoma) were reported in <2%.
- Two patients in the reslizumab group experienced anaphylaxis.
- Approximately 3% of patients treated with reslizumab had at least one positive ADA response. The safety profile of ADA-positive patients was not different from those recorded in the general population (37).

In the phase 3 study conducted by Bjermer et al., the most common AEs were found as headache, nasopharyngitis, URTI, and sinusitis (36). In this study;

- The percentage of patients reporting treatment-related AE was 8% in the placebo, 6% in the 0.3 mg/kg reslizumab, and 12% in the 3.0 mg/kg reslizumab group.
- One patient in the reslizumab 3.0 mg/kg group dropped out of the study due to mild myalgia.
- Reslizumab 0.3 mg/kg and 3.0 mg/kg groups had ADA responses in 12% and 11% of patients, respectively, but reported low titers (36).

In a pooled analysis of placebo-controlled asthma studies, the tolerability profile of reslizumab (n = 1028) for treatment up to 52 weeks, treatment-related AEs (Reslizumab: 12%, placebo: 13%), treatment discontinuation rates due to AEs (in each group 5%) were reported at similar rates to the placebo (n = 730) (38). In this study;

- Treatment-related AEs were generally detected to be mild or moderate, while treatment-related SAEs were reported as < 1% in both the reslizumab and placebo groups.
- In both groups, the most common treatment-related AE was headache (2% for each).
- All other treatment-related AEs were reported as < 1% in the reslizumab and placebo groups, including increased blood creatine phosphokinase (CPK) (0.27% versus 0.58) and myalgia (0.29% versus 0.27%). Blood CPK elevations with reslizumab were asymptomatic, transient, and did not result in cessation of therapy.
- Serious treatment-related anaphylactic reactions not observed in the placebo group were reported in 0.3% of reslizumab recipients (all were ADA negative)
- In this analysis, malignancy was observed in six reslizumab patients (0.6%) and two placebo patients (0.3%) during treatment. Since the malignancies occurring in the group receiving reslizumab were not from any particular tissue group, it was reported that the likelihood of the malignancies being drug-related was low.

Although there is no increased risk of malignancy attributed to the drug, close monitoring is still recommended about the effect of significant suppression of eosinophils (39).

In an open-label extension study of 1051 patients with moderate-to-SEA (up to two years), 66% of patients had at least one AE in the reslizumab infused arm and 75% of the placebo arm (40). In this study;

- The most common AEs were reported as worsening asthma, nasopharyngitis, URTI, sinusitis, and headache. Among these AEs, asthma worsening was less common in the reslizumab infusion arm than in the placebo (28%, 46%, respectively), while other common AEs were found at similar rates in the reslizumab and placebo infusion arms.
- SAEs affected 78 (7%) of 1051 patients (placebo 7%, reslizumab 8%), 18 (2%) of 1051 people discontinued treatment due to SAEs (placebo 1%, reslizumab 2%).
- There were three deaths (one in the placebo group, two in the reslizumab group) but none was associated with treatment.
- No helminthic or suspected opportunistic infection was detected.
- No cases of anaphylaxis were reported.
- The ADA was similar at baseline between patients in the placebo and reslizumab groups (4% positive for each group). During the study period, 5% of the patients in both groups showed ADA response that emerged with treatment, but it was determined that ADA positivity did not affect the rapid and continuous reduction of blood eosinophils by reslizumab (40).

***Safety data from real-life studies with reslizumab***

There are a few real-life studies with reslizumab.

- In a 2019 study by Ibrahim et al. reslizumab was well-tolerated. The most common side effects were fatigue

and the authors observed elevations in CPK levels. Only one patient discontinued treatment due to an AE - an allergic skin rash that disappeared after cessation of reslizumab (41).

- In a study from Spain, 208 participated in the study and reslizumab showed an adequate safety profile. Of the 28 patients who discontinued treatment, four were discontinued due to AEs (arthromyalgias in three cases and elevated CPK levels in one). AEs occurred in 20 patients (9.6%). The most frequently reported AEs were arthromyalgia (5.3%) followed by headache (1.9%) (42).
- In another study among the 78 (36.3%) patients who discontinued reslizumab, four patients (5.1%) discontinued due to non-serious AEs; none were due to serious AEs (43).

No information is available regarding the safety of reslizumab during pregnancy or breastfeeding.

**Benralizumab (Anti-IL5R) safety profile**

***Safety data of pre-marketing clinical trials with benralizumab***

Three major clinical trials, SIROCCO, CALIMA, and ZONDA were conducted with benralizumab. The frequency of AEs was similar between the benralizumab and placebo groups (44-46).

The efficacy and safety results of benralizumab in uncontrolled SEA were evaluated in the randomized, double-blind, parallel-group, placebo-controlled, multicenter SIROCCO phase 3 study (44). In the SIROCCO study;

- Similar percentages of SAEs were reported, and the most common SAE in all patients was the worsening of asthma (8% in the placebo group, 5% in the benralizumab every four weeks group, and 6% in the benralizumab every eight weeks group).
- ISR was seen in 33 patients [every 4 weeks in the benralizumab group: 16 (4%), every eight weeks in the benralizumab group: 9 (2%), and in the placebo group: 8 (2%)]
- Five patients died during the study period. None of the deaths was reported to be related to the drug.
- A positive ADA response was noted in 13% of the patients in the benralizumab groups. There was no data in the study that a positive ADA response is associated with hypersensitivity or efficacy results.

In a multi-center randomized, double-blind, parallel group, placebo-controlled, phase 3 CALIMA study, the efficacy and safety data of benralizumab in add-on therapy in patients aged 12-75 years, with uncontrolled SEA, were investigated. Patients were randomized to 30 mg SC benralizumab every four weeks, 30 mg SC benralizumab every eight weeks or SC placebo for 56 weeks (45). In the CALIMA study;

- Most of the AEs were mild and moderate. Nasopharyngitis was reported most frequently (20%) and was found at similar rates in benralizumab and placebo injection arms. ISR developed in 28 (2%) patients, HSR developed in 43 (3%) patients, and the most common HSR was reported as urticaria (22 patients, 2%). All these reactions were found at a similar rate in the benralizumab and placebo groups.
- The most frequently reported SAE during treatment was worsening asthma. Death was reported in 4 (< 1%) patients during the treatment period. However, none of the deaths was reported to be related to the study drugs.
- ADA positivity was detected in 127 (15%) of 866 patients, who were given benralizumab.

In the 28-week randomized controlled trial by ZONDA, the drug safety of benralizumab (at a dose of 30 mg administered as SC every four weeks or every eight weeks), as well as its effects on the reduction of OCS dose, was also evaluated in severe OCS-dependent asthma (46). In the ZONDA study;

- The most frequently reported AEs were reported as nasopharyngitis and asthma worsening.
- SAE was reported as 19% in the placebo group, 10% in the benralizumab group every four weeks, and 10% in the benralizumab group every eight weeks. Two patients in the group who received benralizumab every eight weeks were reported to have died during the study period. No deaths were reported in the groups, who received placebo or in the benralizumab group every four weeks. The causes of death were acute heart failure (the patient had hypertension and coronary

artery disease at the study entry) and pneumonia (The patient had atrial fibrillation while in the hospital. This patient had a history of concomitant hypercholesterolemia, hypertension, angina pectoris, congestive heart failure, dyslipidemia, and atrial fibrillation at the start of the study).

- ADA was positive in 12 (8%) of 145 patients, who received benralizumab, and 10 were positive for neutralizing antibodies. Among patients with a positive ADA response, one out of five patients in the group receiving benralizumab every four weeks and three out of seven patients in the group receiving benralizumab every eight weeks were reported to have an increase in blood eosinophil count compared to baseline.

The BORA study, a long-term efficacy and safety study of benralizumab in severe uncontrolled asthma, is a phase 3 extension study for eligible patients, who completed SIROCCO and CALIMA (47). In the BORA study:

- The most common AEs in all groups were reported as viral URTI (14-16%) and worsening of asthma (7-10%).
- The most common SAEs were reported as worsening asthma (3-4%) and pneumonia caused by a bacterial infection (0-1%).
- The number of patients, who experienced any AE, SAE, or AE leading to discontinuation during treatment, was similar in the placebo and benralizumab injected arms.
- Overall, 107 (13%) of 809 patients treated with benralizumab at the recommended dosage regimen during the treatment period of 48 to 56 weeks developed a treatment-emergent ADA response. A total of 12% (94/809) of patients treated with benralizumab developed neutralizing antibodies. High ADA titers have been associated with increased clearance of benralizumab and increased blood eosinophil levels. However, no evidence was observed regarding the efficacy or safety relationship of these antibodies against the drug.

***Safety data from real-life studies with benralizumab***

Real-life studies are important for evaluating the effect of a treatment in usual clinical conditions. Few real-life studies have been conducted with benralizumab so far.

- In a real-life study, the efficacy and safety results of benralizumab were evaluated in 10 patients with SEA, who completed one year of treatment. Nine patients continued benralizumab administration without any problem and it was reported that only one patient developed mild fever with paracetamol response (48).
- In another real-life study with benralizumab, 42 patients, with SEA treated with benralizumab for at least six months, were evaluated and benralizumab was found to be well tolerated. Among the side effects experienced by nine patients (21.4%), arthralgia, headache, and dystermia were reported most frequently. It was reported that all these effects were mild and did not lead to cessation of treatment (49).

No increased risk of malignancy was observed in any of the benralizumab clinical trials. There were no cases of thromboembolic AE (5). No information is available regarding the safety of benralizumab during pregnancy or breastfeeding.

**Dupilumab (Anti-IL4Rα) safety profile**

***Safety data of pre-marketing clinical studies with dupilumab***

The safety profile of dupilumab was similar to placebo in all RCT. AEs include ISR, URTI, headache, nasopharyngitis, bronchitis, and sinusitis (50).

In a randomized, double-blind, placebo-controlled, parallel group, multicenter pivotal phase 2b clinical trial, the efficacy and safety of dupilumab were evaluated (51). In this study;

- The AE rates occurring during the treatment process were found to be similar among the treatment groups (75-83% with dupilumab and 75% with placebo) and the most frequently reported AE was URTI (placebo 14%, dupilumab groups 18%).
- Dupilumab was not found to increase the incidence of bacterial or opportunistic infections.
- In the dupilumab groups, two patients died during the treatment process, but the causes of death were not associated with the treatment drug.
- Transient elevations in blood eosinophils were observed in those with a higher baseline eosinophil count. Although there were significant differences in change by basal eosinophils between the dupilumab

groups and placebo from week 4 to week 16, this difference was shown to decrease after week 16. Approximately seven weeks after the application of the study drug (dupilumab 300 mg dose regimen every two weeks), a hypereosinophilic syndrome (HES) AE was observed in a patient with a history of high eosinophils (especially when not using corticosteroids). After the initiation of methylprednisolone, the eosinophil count decreased rapidly, but the study treatment was discontinued in the patient due to the occurrence of HES.

In the efficacy and safety study of dupilumab conducted by Rabe et al., 210 patients were enrolled in the study and the frequency of AE was found to be similar between the dupilumab and placebo groups (52). In this study;

- The most common AE was reported as viral URTI.
- ISRs were more common in the dupilumab group than in the placebo group (9% versus 4%).
- Eosinophilia (> 3000 cells / μl) was detected in 13% of the group receiving dupilumab and this rate was found to be 1% in the placebo group. However, eosinophilia-related clinical findings or AEs were not detected in the patients.
- ADA was seen in five patients in both groups, but no significant effect of dupilumab on efficacy and safety was detected.

The clinical significance of eosinophilia remains unclear, and rare SAEs have been reported. The mechanism of eosinophilia associated with dupilumab is thought to be likely due to the blockade of eosinophils' transfer to tissue by this biological (53). Therefore, clinicians should be mindful of potential eosinophilic diseases that can be triggered by dupilumab.

***Safety data of real-life studies with dupilumab***

Results from a limited number of real-life studies are available on dupilumab safety data.

- Dupilumab efficacy and safety data were reviewed in patients with SA in a multicenter retrospective real-life cohort study. In this study, the most common AEs were reported as ISRs (14%), asthenia (6%), infection (3%), and headache (5%). Since spontaneous bruising occurred during menstruation in an AE case, treatment had to be discontinued. Three deaths were reported during the treatment period, none of which, were associated with treatment by the investigators (54).
- Increases in the frequency of ocular AEs including dry eye disease, conjunctivitis, or keratitis have been reported in patients treated with dupilumab for atopic dermatitis indication. However, there was no increase in the frequency of ocular AEs in the use of dupilumab in SA (55).

To date, no association between dupilumab and increased cardiovascular or neoplastic risk has been reported. However, long-term and large-scale real-life studies are needed to obtain more reliable data (53).

No studies have been conducted on the use of dupilumab in pregnant women and the data obtained from clinical use is very limited. Human IgG antibodies are known to cross the placental barrier. Therefore, it should be kept in mind that dupilumab can be passed from mother to child (5).

**Tezepelumab (Anti-TSLP) safety profile**

***Safety data of pre-marketing clinical trials with Tezepelumab***

Tezepelumab is the latest biological approved for SA.

In CASCADE, a double-blind, randomized, placebo-controlled, phase 2 trial, 116 patients were randomly assigned (59 to tezepelumab – 210 mg/4 weeks, 57 to placebo). The percentage of AEs in both the tezepelumab and the placebo was 90%, and there were no safety findings of concern. Three (5%) patients in the tezepelumab group and seven (12%) patients in the placebo groups had serious AEs. The most common AEs were nasopharyngitis, post procedural complications (Injection-site reactions occurred in seven (12%) patients in the tezepelumab group and two (4%) in the placebo group) and headache (56).

A phase 3, RCT evaluates the efficacy of tezepelumab in adults and adolescents with severe, uncontrolled asthma. 77.1% of the patients in the tezepelumab group and 80.8% of those in the placebo group reported an AE, and 9.8% and 13.7% reported a serious AE, respectively. The most common AEs were nasopharyngitis, URTI, headache, and asthma. ISR occurred in 3.6% of the patients in the tezepelumab group and 2.6% of those in the placebo group (57). In the PATHWAY study by Corren et al. (phase 2, randomized, double-blind, placebo-controlled trial), the overall incidence of AEs was similar across the 210 mg/4 week

tezepelumab and placebo. The most common AEs were nasopharyngitis, bronchitis, and headache. ISR occurred in 3.6% of the patients in the placebo group and 2.9% of the patients in the 210 mg/4 week tezepelumab group (58).

Data on the safety profiles of these biologics are summarized in Table II.

## CONCLUSION

### Safety profile results of biologicals

The reliability of the biologics used in the treatment of SA is as important as its effectiveness. The safety results of these six biologic agents approved for use in SA are summarized below.

- Omalizumab has the most safety data, as it is the oldest of the biologics used in SA.
- Since mepolizumab was the first anti-IL5 licensed for clinical use, it has more and longer-term data on its efficacy and safety than other anti-IL5 and anti-IL5Rs, including initial real-life studies.
- In clinical phase studies, it is seen that the safety profiles of all six biological treatments are quite good.
- More real-life studies have been done with omalizumab and mepolizumab mAbs. It has been shown in these studies that their reliability profiles are quite good. A real-life study with tezepelumab has not been published so far. Additionally, real-life studies on benralizumab, reslizumab, and dupilumab are very few.
- Although blood eosinophilia can be seen after dupilumab, its clinical significance is still unclear. However, caution should be exercised in terms of potential eosinophilic diseases.
- Treatment-related anaphylaxis has been reported in asthmatic patients receiving omalizumab/reslizumab and usually developed early after administration of the drugs. Therefore, one should be alert for anaphylaxis.

**Table II: Safety profiles of biologics on clinical trials**

| | | | Safety profile |
|---|---|---|---|
| OMALIZUMAB | Premarketing clinical trial | Solèr M, et al., (6) | The most common AE: fatigue and paresthesia<br>Drug-related headache: 3 (1.1%) patients in both groups<br>Symptoms at the local injection site were 11.8% at the omalizumab and 7.7% at the PL. |
| | | Busse W, et al., (7) | The frequency of AEs: 89.2% in the omalizumab vs 89.1% in the PL.<br>The number of patients with SAE was 7 (2.6%) in the omalizumab group and 6 (2.3%) in the PL group. |
| | Real-life studies | Adachi M, et al., (8) | 32% AE and 15% SAE were reported.<br>SAEs associated with omalizumab was <1% and anaphylaxis were reported the most (0.11%)<br>ADR was observed in 8% of the patients and the most common ADR was fatigue (0.94%) |
| | | Di Bona D, et al., (11) | ADRs requiring discontinuation of omalizumab treatment occurred in 6 patients (6.6%) (3 patients with arthralgia/myalgia, 1 patient with urticaria/angioedema, 1 patient metrorrhagia, and 1 patient with relapsed herpes labialis) |
| | | Casale TB, et al., (12) | 90 (11.2%) of 801 patients developed 144 SAEs. Only 3 (0.4%) patients had an AE specifically reported, all three of which were reported as moderate anaphylaxis due to omalizumab |
| | | Baker DL, et al., (13) | The frequency of anaphylaxis attributed to omalizumab use is <0.2% |
| | | Cooper PJ, et al., (15) | The helmintic infection rate was slightly increased with omalizumab |
| | | Iribarren C, et al., (17) | The observed rates of arterial thromboembolic events were similar between the omalizumab and PL groups.<br>Omalizumab was not associated with an increased risk of malignancy |
| | | Namazy J, et al., (18) | Major congenital anomalies, prematurity, low birth weight, and small size ratios for gestational age were not different from other studies conducted in this asthma population.<br>There was no significant increase in major or minor anomalies |
| | | Türk M, et al., (19) | No patient had a systemic reaction (SR) or serious ADR during the follow-up period.<br>Omalizumab was well tolerated. |

**Table II continue**

| | | | |
|---|---|---|---|
| **MEPOLIZUMAB** | Premarketing clinical trial | Pavord ID, et al., (20) | The safety profile of mepolizumab was similar to PL in patients with SEA.<br>No serious life-threatening anaphylaxis has been reported. |
| | | Lugogo N, et al., (22) | There are similar rates of AEs and serious AEs between PL and mepolizumab<br>No increase in systemic and local site reactions was reported. |
| | | Khatri S, et al., (23) | Anaphylaxis or non-allergic systemic reactions (SR) associated with mepolizumab have not been reported.<br>When evaluated in terms of potential opportunistic infection AEs, herpes in eight patients, candida in three patients, and pulmonary tuberculosis in one patient were reported. |
| | | Freemantle N, et al., (24) | Serious AEs were detected as allergic/hypersensitivity SRs in 8 (2%) patients and non-allergic SRs in 1 (< 1%) patient. Anaphylaxis has not been reported with mepolizumab.<br>While an opportunistic infection was detected in 24 (7%) patients, 8 (2%) of them were found to have herpes zoster infection.<br>A parasitic infection has not been reported |
| | Real-life studies | Strauss RA, et al., (27) | No significant reaction at the injection site<br>Mild herpes zoster was reported in one patient and urticaria in another. |
| | | Bagnasco D, et al., (28) | The most common AEs: local ISR (4.3%); headache and myalgia/arthralgia |
| | | Lombardi C, et al., (29) | The discontinuation rate of mepolizumab was reported as 6/143 (4.2%) (Five resulted from lack of response to treatment and one discontinued due to possible treatment-related urticaria).<br>Only mild side effects, such as headache and local ISR were reported. |
| | | Pertzov B, et al., (30) | No serious AEs were reported during the study period. Eleven patients (18%) reported mild AEs such as muscle pain, itching, rash, injection site pain, fever, and headache |
| | | Gupta A, et al., (32) | 27 (90%) of 30 children experienced AEs and 7 (23%) SAEs, but none of the SAEs were found to be associated with the treatment |
| | | Yılmaz I, et al., (33) | Mepolizumab was discontinuedin one patient due to the development of arthralgia, myalgia, weakness, and additional fever and nausea after the third dose administration. This reaction was assessed as a probable/likely ADR<br>AEs such as herpes zoster, herpes labialis, parasitic infection, and anaphylaxis were not observed. |
| **RESLIZUMAB** | Premarketing clinical trial | Bjermer L, et al., (35) | The most common AEs were found as headache, nasopharyngitis, URTI, and sinusitis<br>Reslizumab 0.3 mg/kg and 3.0 mg/kg groups had ADA responses in 12% and 11% of patients, respectively, but reported low titers |
| | | Castro M, et al., (36) | Nasopharyngitis was found to be the most common AE<br>AEs occurring in more than 5% of patients treated with reslizumab were reported as nasopharyngitis, upper respiratory tract infections (URTI), sinusitis, influenza infection, and headache.<br>Infusion site reactions (pain, rash, and hematoma) were reported in <2%.<br>Two patients in the reslizumab group experienced anaphylaxis |
| | | Deeks ED, et al., (37) | Treatment-related AEs (Reslizumab: 12%, PL: 13%), treatment discontinuation rates due to AEs (in each group 5%) were reported at similar rates to the PL<br>The most common treatment-related AE was headache |
| | | Murphy K, et al., (39) | The most common AEs were reported as worsening asthma, nasopharyngitis, URTI, sinusitis, and headache<br>There were three deaths (one in the PL group, two in the reslizumab group) but none was associated with treatment.<br>No helminthic or suspected opportunistic infection<br>No cases of anaphylaxis |
| | Real-life studies | Ibrahim H, et al., (40) | Reslizumab was well-tolerated. The most common side effects were fatigue and the authors observed elevations in CPK levels |
| | | de Llano LAP, et al., (41) | AEs occurred in 20 patients (9.6%). The most frequently reported AEs were arthromyalgia (5.3%) followed by headache (1.9%) |
| | | Wechsler ME, et al., (42) | Among the 78 (36.3%) patients who discontinued reslizumab, four patients (5.1%) discontinued due to non-serious AEs; none were due to serious AEs |

**Table II continue**

| | | | |
|---|---|---|---|
| **BENRALIZUMAB** | Premarketing clinical trial | Bleecker ER, et al., (43) | The most common SAE was the worsening of asthma Injection site reaction (ISR) was seen in 33 patients [every 4 weeks in the benralizumab group: 16 (4%), every eight weeks in the benralizumab group: 9 (2%), and in the PL group: 8 (2%)]<br>Five patients died during the study period. None of the deaths was reported to be related to the drug. |
| | | FitzGerald JM, et al., (44) | Nasopharyngitis was reported most frequently AE(20%)<br>similar between benralizumab and PL.<br>The most frequently reported SAE during treatment was worsening of asthma. |
| | | Nair P, et al., (45) | The most frequently reported AEs were reported as nasopharyngitis and asthma worsening.<br>ADA was positive in 12 (8%) of 145 patients, who received benralizumab, and 10 were positive for neutralizing antibodies |
| | | Busse WW, et al., (46) | The most common AEs in all groups were reported as viral URTI (14-16%) and worsening of asthma (7-10%).<br>The most common SAEs were reported as worsening asthma (3-4%) and pneumonia caused by a bacterial infection (0-1%). |
| | Real-life studies | Miralles Lopez JC, et al., (47) | One patient (10%) developed mild fever with paracetamol response |
| | | Padilla-Gallo A, et al., (48) | Among the side effects experienced by nine patients (21.4%), arthralgia, headache, and dystermia were reported most frequently.<br>It was reported that all these effects were mild and did not lead to cessation of treatment |
| **DUPILUMAB** | Premarketing clinical trial | Wenzel S, et al., (50) | The most frequently reported AE was URTI (PL 14%, dupilumab groups 18%).<br>Dupilumab was not found to increase the incidence of bacterial or opportunistic infections.<br>Transient elevations in blood eosinophils were observed in those with a higher baseline eosinophil count. |
| | | Rabe KF, et al., (51) | The most common AE was reported as viral URTI.<br>ISRs were more common in the dupilumab group than in the PL group (9% versus 4%).<br>Eosinophilia (> 3000 cells / µl) was detected in 13% of the group receiving dupilumab and this rate was found to be 1% in the PL group. |
| | Real-life studies | Dupin C, et al., (53) | The most common AEs were reported as ISRs (14%), asthenia (6%), infection (3%), and headache (5%). |
| | | Touhouche AT, et al., (54) | There was no increase in the frequency of ocular AEs in the use of dupilumab in SA |
| **TEZEPELUMAB** | Premarketing clinical trial | Diver S, et al., (55) | The most common AEs were nasopharyngitis, post procedural complications (Injection-site reactions occurred in seven (12%) patients in the tezepelumab group and two (4%) in the PL group) and headache |
| | | Menzies-Gow A, et al., (56) | The most common AEs were nasopharyngitis, URTI, headache, and asthma. ISR occurred in 3.6% of the patients in the tezepelumab group and 2.6% of those in the PL group |
| | | Corren J, et al., (57) | The most common AEs were nasopharyngitis, bronchitis, and headache. ISR occurred in 3.6% of the patients in the PL group and 2.9% of the patients in the 210 mg/4 week tezepelumab group |

**AE:** Adverse event, **ADA:** Anti-drug antibody, **SAE:** Severe adverse event, **ISR:** Injection site reaction, **URTI:** Upper respiratory tract infection, **SR:** Systemic reaction, **PL:** Placebo

- Treatment-related AEs should be reported as ADRs in both clinical trials and real-life studies. If suspected ADRs are associated with the drug, accompanying an explanation of the possibility of this association (such as certain, probable, probable, unlikely) will provide a better evaluation of these AEs.

**Authorship Contributions**

Concept: **İnsu Yılmaz,** Design: **Gülden Paçacı Çetin, İnsu Yılmaz,** Data collection or processing: **Gülden Paçacı Çetin, Bahar Arslan, İnsu Yılmaz,** Analysis or Interpretation: **Gülden Paçacı Çetin, İnsu Yılmaz,** Literature search: **Gülden Paçacı Çetin, Bahar Arslan, İnsu Yılmaz,** Writing: **Gülden Paçacı Çetin, Bahar Arslan, İnsu Yılmaz,** Approval: **Gülden Paçacı Çetin, Bahar Arslan, İnsu Yılmaz.**

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