

Biologics in allergic rhinitis

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Abstract. – This paper aims to review biologics in allergic rhinitis (AR). Biologic agents of Omalizumab, Dupilumab, Mepolizumab, Reslizumab, and Benralizumab are reviewed in detail.

The search is performed in “Pubmed,” “Google,” “Google Scholar” and EBSCO Academic Search Ultimate (EKUAL) database of Kırıkkale University Library from 2021 to 2000, and randomized and/or placebo-controlled studies, review papers, meta-analysis, and reports are taken into consideration. The search was performed with the keywords of “allergic rhinitis,” “biologics,” “biologic agents,” “Omalizumab,” “Dupilumab,” “Mepolizumab,” “Reslizumab,” “Benralizumab,” “Anti IgE,” “Anti-IL-4/IL-13,” “Anti IL-5”. Search is also performed in the “U.S. Food and Drug Administration” (FDA) and “European Medicines Agency” (EMA) web systems.

Biological agents such as monoclonal antibodies (Mab) in treatment are called biological therapy or biotherapy. Omalizumab is a humanized Anti-IgE monoclonal antibody. Omalizumab treatment improved the Daily Nasal Rescue Medication Score (DNSSS) and decreased the use of antiallergic drugs in seasonal and perennial AR and rhino-conjunctivitis. Omalizumab is also used in specific immunotherapy patients with allergic rhinitis and reduced allergic reactions associated with allergen immunotherapy, such as anaphylaxis. Dupilumab is an Anti-IL-4/IL-13 biologic agent. Dupilumab treatment significantly improved sino-nasal Outcome Test (SNOT-22) total scores in perennial allergic rhinitis. Anti-IL-5 monoclonal antibodies of Mepolizumab, Reslizumab Benralizumab reduce the number of eosinophils in the blood and tissue, corticosteroid addiction and asthma attacks are reduced, and their use in the treatment of severe eosinophilic asthma has been approved.

Biologics, especially Omalizumab, and Dupilumab, may be used more in allergic rhinitis.

Key Words:

Biologics, Anti-IgE monoclonal antibody, Anti-IL-4/IL-13, Anti-IL-5, Omalizumab, Dupilumab, Mepolizumab, Reslizumab, Benralizumab.

Biological Agents and Biological Treatment

The use of biological agents such as monoclonal antibodies (Mab) in treatment is called biological therapy or biotherapy¹⁻⁴.

Monoclonal Antibodies

Monoclonal antibodies are produced by animals (i.e., mouse) cell sequences/clones that are immunized to a specific antigen. Their structure can also be chimeric, which contains a part of the antibody obtained from the mouse in the variable region and part of the human antibody in the rest of the regular part. Humanized ones contain only the antibody part obtained from the mouse in the hypervariable region. Human ones contain only human antibodies¹⁻⁴.

The naming of the monoclonal antibodies is performed according to the syllables used before the last appendix – mab¹⁻⁴:

- If the last appendix – “o” arrives before – mab (-omab), it is considered that is a mouse antibody.
- If there is a “u” before – mab (-umab), it is considered that is a human antibody.
- If there is a “xi” before – mab (-ximab), it is considered that is a chimeric antibody.
- If there is “zu” before – mab (-zumab), it is necessary to consider that it is humanized antibody.

Biologics

In this review, the following biologics will be mentioned (Table I):

- Omalizumab (Anti IgE)
- Dupilumab (Anti-IL-4/IL-13)
- Mepolizumab (Anti IL-5)
- Reslizumab (Anti IL-5)
- Benralizumab (Anti IL-5)

Methods

The search is performed in “Pubmed,” “Google,” “Google Scholar” and EBSCO Academic Search Ultimate (EKUAL) database of Kırıkkale Uni-

Table I. Biologics.

Biologics	Mechanism of effect	Drug name
Omalizumab	Anti IgE	XOLAIR®
Dupilumab	Anti-IL-4/IL-13	DUPIXENT®
Mepolizumab	Anti IL-5	NUCALA®
Reslizumab	Anti IL-5	CINQAIR®, CINQAERO®
Benralizumab	Anti IL-5	FASENRA®

IgE: Immunoglobulin E, IL: Interleukin.

versity Library from 2021 to 2000, and randomized and/or placebo-controlled studies, review papers, meta-analysis, and reports are taken into consideration. The search was performed with the keywords of “allergic rhinitis,” “biologics,” “biologic agents,” “Omalizumab,” “Dupilumab,” “Mepolizumab,” “Reslizumab,” “Benralizumab,” “Anti IgE,” “Anti-IL-4/IL-13,” “Anti IL-5”. Search is also performed in the “U.S. Food and Drug Administration” (FDA)⁵ and “European Medicines Agency” (EMA)⁶ web systems.

Anti-IgE-Based Monoclonal Antibodies: Omalizumab

Mechanisms

Omalizumab is a humanized Anti-IgE monoclonal antibody (IgG1 kappa) produced by hybrid technology and is the first confirmed biological agent in asthma. It connects to the third part (ce3) of the constant part of IgE’s heavy chain¹⁻³.

Omalizumab binds the free IgE and prevents IgE from being connected with the FcεRI receptor on mast cells and basophils, to which it is connected with high affinity and the secretion of mediators from these cells. Omalizumab prevents degranulation and allergic reaction/inflammation with its effect on mast and basophil cells¹⁻³.

FcεRI receptors are gradually downregulated in eosinophils, mast cells, B lymphocytes, and dendritic cells. FcεRI expression is reduced. Eosinophils proceed to apoptosis. Omalizumab also prevents antigen presentation of dendritic cells and IgE antibody production of B cells, making them anergic¹⁻³.

Information for Medication

- Drug Name: Xolair®. Active substance: Omalizumab 150 mg/Vial.
- FDA approval: 2003⁷; EMA approval: 2005⁸.

Indications by FDA⁷

- Adult moderate-severe persistent asthma; over six-year-old children, having positive skin test or showing in vitro reactivity to perennial aeroallergens and symptoms are not sufficiently controlled with inhaled corticosteroids.
- In adult nasal polyp patients over 18 years, if there is not enough response to nasal corticosteroid, it is added to the treatment.
- In adults with chronic idiopathic urticaria and in those who remain symptomatic despite H1 antihistamine treatment over 12 years.

Indications by EMA⁸

- Treatment of allergic asthma, chronic idiopathic urticaria, and chronic spontaneous urticaria.
- Severe persistent asthma in children ≥ six years (allergic asthma caused by IgE): Positive skin test for allergens (mite, pollen, or mold); symptoms are present throughout the day, morning, or evening; severe asthma attacks (in those who use high doses of inhaled corticosteroids and long-acting beta-agonists).
- In patients 12 years and older, if their respiratory function is less than 80% of the standard value.
- Chronic (long-term) spontaneous urticaria (itchy rash). Over 12 years, patients who do not benefit sufficiently from antihistamine treatment.
- Adult patients with severe chronic rhinosinusitis and nasal polyps (inflammatory nose and sinuses, swelling due to inflammation in the nose). Patients who receive corticosteroid treatment to the nose and this treatment does not work enough.

Application ways and warnings

It is applied subcutaneously (s.c.). Doses are divided into 150 mg; no more than 150 mg is applied in 1 region⁷.

In asthma: XOLAIR® 75-375 mg S.C. (every 2 or 4 weeks)^{7,9}.

Serum total IgE level (I.U./mL) and weight are measured, and the dose is determined according to them^{7,9}.

Nasal Polyp: XOLAIR® 75-600 mg S.C. (every 2 or 4 weeks)^{7,9}.

Serum total IgE level (I.U./mL) is measured, and dose and frequency are determined accordingly^{7,9}.

It is not applied in acute bronchospasm and status asthmatics. It is not indicated in other allergic conditions and other urticaria forms. In FDA documents, anaphylaxis (0.2%) and malignancies (0.5%) (20/4,127 patients) have been warned (FDA-2021). Malignancies in the placebo group are 0.2% (5/2,236 patients)^{7,9}.

Use of Omalizumab in allergic rhinitis

Tsabouri et al¹⁰'s meta-analysis included 11 randomized controlled trials (RCTs) and 2,870 patients with seasonal and perennial A.R. and rhino-conjunctivitis. They reported that Omalizumab treatment improved the Daily Nasal Rescue Medication Score (DNSSS) and decreased the use of antiallergic drugs. Omalizumab dose is 0.016 mg/kg per I.U./mL of IgE and given subcutaneously every 2-4 weeks. Treatment was performed for 8-24 weeks (an average of 16 weeks). 90% of the patients used Omalizumab for 12 weeks. Treatment began 4-14 weeks before pollen season. No significant adverse effects have been observed.

In the meta-analysis of Yu et al¹¹, 16 randomized controlled trials; and 3,458 patients (1,931 in the study group, 1,527 in the control group) were included. After Omalizumab treatment, daily symptom score, daily ocular score, daily nasal medication symptom score, emergent drug use, and rhino-conjunctivitis-specific QoL questionnaire, and in its entirety, statistically significant improvement was reported.

Birch pollen-induced seasonal allergic rhinitis

In 2000, Adelroth et al¹² conducted a study to compare the effectiveness of 300 mg of Omalizumab. Patients with basal IgE: 30-150 IU/mL were applied Omalizumab at 0th and fourth weeks (2 doses), and those with basal IgE of > 150 IU/mL were given Omalizumab at 0th, 3rd, and sixth weeks (3 doses). In this study, mildly localized urticaria was observed in 3 patients. Nasal and ocular symptom severity scores, quality of life, and medication scores differed significantly.

Seasonal allergic rhinitis induced by Japanese cedar tree pollen

Okubo et al¹³ applied a 150-375 mg dose of Omalizumab to 100 patients with moderate/severe seasonal

allergic rhinitis induced by Japanese cedar tree pollen. Nasal, ocular, and medication scores decreased in post-treatment evaluation. Symptom reduction and low free IgE levels were found to be directly related.

Perennial allergic rhinitis (PAR)

Chervinsky et al's¹⁴ randomized placebo-controlled study used s.c. Omalizumab or placebo for 16 weeks on 289 patients (12-70 years) with moderate-to-severe PAR lasting two years. These patients had sensitivity to one of the perennial allergens (mite, dog, or cat). Basal total serum IgE level was between 30-700 IU/mL. Omalizumab is used with a dose of 1 or 2 times per month, and 0.016 mg/kg for each IgE I.U./mL was given. Nasal symptom intensity, medication, and rhinitis quality of life scores differed significantly from the control. Omalizumab treatment was found to be effective when patients were asked. It has also been effective in patients not responding to immunotherapy or nasal corticosteroid treatment.

Perennial allergic rhinitis and concomitant allergic asthma (SOLAR study)

In the Vignola et al¹⁵ randomized placebo-controlled study, called "SOLAR", they tried the effectiveness of Omalizumab treatment in 405 adults and adolescents with moderate-severe PAR lasting for two years and concomitant uncontrolled persistent allergic asthma. In these patients, basal IgE levels were between 30-1,300 IU/mL, and there are indoor allergen atopies. During treatment, scores of Rhinitis Quality of Life (RQoL), which assessed the quality of life in rhinitis, and Asthma Quality of Life (AQoL), which assessed the quality of life in asthmatics, showed that they had moderate to severe disease. For 28 weeks, this group of patients was given Omalizumab every four weeks at a dose of 0.016 mg/kg per IgE I.U./mL. In the post-treatment evaluation, asthma exacerbations were lower, asthma and rhinitis symptom scores were lower, and quality of life scores were better. Patients and researchers have described the treatment effectiveness of omalizumab in asthma-rhinitis as good or flawless.

Effect of Omalizumab on specific immunotherapy (SIT) in the treatment of allergic rhinitis

Treatment of Omalizumab is used in specific immunotherapy patients with allergic rhinitis for the following reasons^{1,16}:

- To reduce the side effects of specific immunotherapy (SIT).
- To ensure that it can be applied to risky groups.

- To extend SIT treatment effectiveness.
- It is used to help develop tolerance.

Omalizumab was used as a biological agent with SIT. In patients receiving immunotherapy, Omalizumab treatment helps with IgE neutralization, reducing IgE expression in mast cells and basophils and reducing allergic reactions associated with allergen immunotherapy, such as anaphylaxis¹⁷.

In Kuehr et al¹⁸'s randomized placebo-controlled study, 221 patients with moderate-to-severe seasonal allergic rhinitis between the ages of 6 and 17 received SIT against birch and grass pollen allergy, Omalizumab was added to the treatment, and effects were observed. Symptoms and medication scores were improved in groups receiving omalizumab.

Kopp et al¹⁹ in their randomized, double-blind, placebo-controlled, multicenter study, 140 patients (adolescent and adult) with seasonal grass pollen allergic rhino-conjunctivitis and asthma, Omalizumab or placebo treatment started two weeks before allergen immunotherapy (AIT) started, and this treatment was continued for 18 weeks. Adding Omalizumab to AIT was reported to increase disease control during the first pollen season. Local reactions were higher in the placebo group than in the Omalizumab group (16.8% vs. 12.3%), but this difference was not statistically significant.

In Casale et al²⁰ randomized, double-blind, placebo-controlled, multicenter study, 155 adult patients with ragweed allergy were given Omalizumab treatment before ragweed allergen immunotherapy. Patients received a placebo or omalizumab for nine weeks; after one day of gapping, they received a 12-week AIT+placebo or AIT+Omalizumab. AIT+Omalizumab combination therapy was found to have lower allergy scores ($p = 0.044$) and fewer adverse effects than those who received only AIT+placebo ($p \leq 0.05$). In addition, in the Omalizumab+AIT group, the risk of anaphylaxis decreased five times compared to the placebo+AIT group AIT (OR, 0.17; $p = 0.026$).

Anti-IL-4/IL-13-Dupilumab

Mechanisms

Dupilumab is a human IgG monoclonal antibody. IL-4 and IL-13 act on the same receptors in type 2 inflammation. Type 1 receptor has an IL-4R α sub-unit, and type 2 receptor has IL-4R α and IL-13R α 1 subunits²¹⁻²³. These two cytokines play an essential role in T2 inflammation^{1,23,24}.

- Differentiation of T cells to Th2 cells.
- IgE production from B cells (IL-4).
- Remodeling the airways.
- Production of mucus from the Goblet cells.
- Causes effects such as flat muscle contractivity (IL-13).
- In addition, IL-13 directly affects the production of exhaled nitric oxide fraction (FeNO) in the airway epithelium.
- Plays an essential role in eosinophil migration by activating vascular adhesion molecules.

Dupilumab binds to IL-4 receptor alpha subunits and blocks IL-4 and IL-13 signal pathways as they connect to the common receptor. It prevents the effects of IL-13 and IL-4 *via* IL-4R α , a common receptor, and reduces IgE levels by an average of 40%^{1,23}. Beneficial effects on asthma, atopic dermatitis, and nasal polyps (N.P) have been reported. There is more effectiveness in eosinophilic asthmatics. It has been shown to improve the quality of life in asthmatics accompanied by chronic rhinosinusitis and nasal polyposis *via* its positive effects on the upper and lower airways^{22,23,25-28}.

Information for Medication

- Drug name: Dupixent[®]. Active substance: Dupilumab 150 mg/mL injectable.
- FDA approval: 2017²⁹; EMA approval: 2017³⁰.

Indications by FDA²

- In 6 years and above patients, having moderate-to-severe atopic dermatitis (which cannot be controlled with topical treatments, or these treatments were not recommended), Dupixent can be used in combination with corticosteroids or alone.
- 12 years and above moderate-to-severe asthma (in asthma patients with eosinophilic type or dependent to oral corticosteroids) (FDA).
- In chronic rhinosinusitis with nasal polyps (CRSwNP), which cannot be adequately controlled with treatment.

Indications by EMA²⁹

- 12 years and above moderate-to-severe atopic dermatitis (in patients with systemic treatment candidates).
- Severe atopic dermatitis between the ages of 6 and 11 (in patients with systemic treatment candidates).
- Severe asthma of 12 years and above [patients characterized by type 2 inflammation, increased blood eosinophils, increased exhaled nitric oxide fraction (FeNO), ina-

dequate control with a high dose of inhaled corticosteroids and other drug treatments].

- In adult patients with chronic rhinosinusitis with nasal polyps (CRSwNP), patients who use intranasal corticosteroids, who cannot be adequately controlled by systemic corticosteroids and/or surgery.

Application ways and warnings

It is applied subcutaneously (s.c.)^{28,29}.

Applications by FDA

Atopic dermatitis (FDA)^{28,30}:

In adults: first 600 mg (300 mg, two injections, injected from different locations), followed by 300 mg every two weeks^{28,30}.

Asthma: 12 y and over (FDA)^{28,30}.

- 400 mg initial dose (2 x 200 mg injection), then 200 mg/once every two weeks (12 y and over children).
- 600 mg initial dose (2 x 300 mg injections), then 300 mg/once every two weeks (adults).
- If there is asthma (need to use oral steroids) or co-morbid moderate-severe atopic dermatitis, an initial dose of 600 mg (2 x 300 mg injections), then 300 mg/once every two weeks.

Chronic rhinosinusitis with nasal polyps (CRSwNP) (FDA)

- Adults, 300 mg/once every two weeks^{28,30}.

Applications by EMA

Atopic dermatitis (EMA)²⁹:

- In adolescents of 60 kg or more and adults, 600 mg (2 injections of 300 mg) are performed on different sites, then a 300 mg injection is given every two weeks²⁹.
- In adolescents, if it is less than 60 kg, injections are made with 200 mg. If there is no recovery after 16 weeks, the drug will be stopped²⁹.

Asthma (EMA)²⁹:

- In severe asthma (using oral corticosteroids or also with co-morbid atopic dermatitis), the first dose is 600 mg (2 doses of 300 mg), applied to different regions. Then, 300 mg is injected every two weeks²⁹.
- In all other asthma patients, the first dose is applied to 2 different regions of 200 mg (2 doses of 200 mg), after which a 200 mg injection is given every two weeks²⁹.

It is not applied in acute bronchospasm and status asthmatics²⁸.

Adverse reactions

Hypersensitivity reactions (urticaria, rash, erythema nodosum, anaphylaxis, serum disease (FDA)²⁸.

Serum disease (allergy to foreign proteins) and serum disease-like reactions (EMA)²⁹.

Dupilumab in PAR and co-morbid asthma

In the study of Weinstein et al³¹, 465 patients were included. 241 (61%) patients had Perennial allergic rhinitis (PAR). One hundred fifty patients were given 200 mg Dupilumab every two weeks; 157 patients were given 300 mg Dupilumab every two weeks; and 157 patients were given a placebo every two weeks. In patients with Astma+PAR, 300 mg (every two weeks) Dupilumab treatment led to significant improvement of SNOT-22 total scores ($p = 0.009$), nasal congestion, discharge, sneezing, and postnasal drainage symptoms ($p < 0.01$). Dupilumab 200 mg (every two weeks) was also reported to provide non-statistically significant improvement in SNOT total and associated symptoms.

Anti-IL-5 Monoclonal Antibodies: Mepolizumab

Mechanisms

Mepolizumab is a humanized Anti-IL-5, a monoclonal antibody (IgG1 kappa). Interleukin 5 (IL-5) is produced by Th2 lymphocytes, innate lymphoid cells (ILC-2), and mast cells. It is the basic cytokine involved in eosinophils' activation, regeneration, and life process. Anti-IL-5 agents suppress eosinophilic airway inflammation. There is significant experience with anti-IL-5 in diseases such as asthma, and so far, it shows a favorable safety profile^{1,32,33}.

Information for Medication

- Drug name: NUCALA[®]
- Active substance: NUCALA[®] (MEPOLIZUMAB) injectable; subcutaneous 100 MG/ML.
- FDA approval: 2019³⁴.
- EMA approval: 2019³⁵.
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Indications by FDA

At six years and over, severe asthma (eosinophilic phenotype); in adults, eosinophilic granulomatosis and poly-angiitis (EGPA) in adults; at 12 years and over, pediatric hypereosinophilic syndrome (HES) (\geq six months, non-hematological secondary cause undetectable)³⁴.

Indications by EMA

Severe refractory eosinophilic asthma (in adults, adolescents, and children aged six years and over)³⁵.

Application ways and warnings

It is applied subcutaneously (s.c.).

Adverse reactions: anaphylaxis, angioedema, bronchospasm, hypotension, urticaria, rash³⁴.

Applications by FDA³⁴

- Severe asthma at 12 y and above 100 mg s.c./every four weeks.
- 6 to 11 y severe asthma: 40 mg s.c./every four weeks.
- EGPA: 300 mg (3 separate 100 mg s.c.) injection/every four weeks.
- HES: 300 mg (3 separate 100 mg s.c.) injections/every four weeks³⁴.

Applications by EMA^{35,36}

S.c. The injection is performed every four weeks in the upper arm or abdomen.

- 100 mg over 12 y and 40 mg from 6-11 y are recommended.

Long-term treatment can be done with Nucala^{35,36}.

Anti-IL-5 Monoclonal Antibodies: Reslizumab

Mechanisms

Reslizumab is a humanized IL-5 antagonist monoclonal antibody (IgG4κ), an anti-IL-5 agent. IL-5 contributes to eosinophil activation, maturation, and survival. Therefore, anti-IL-5 treatment can suppress inflammation of eosinophil origin^{1,37}. The agent directly targets IL-5, reducing circulating eosinophils^{25,38}.

Information for Medication

- Drug name: CINQAIR[®] 100 MG/10 ML INJECTABLE; INJECTION (FDA)³⁹, CINQAERO[®] 10 mg/mL (EMA)⁴⁰.
- Active substance: RESLIZUMAB^{39,40}.
- FDA approval: 2016³⁹.
- EMA approval: 2016⁴⁰.

Indications by FDA

18 y and above severe asthma (eosinophilic phenotype)³⁹.

Indications by EMA

Severe eosinophilic asthma (not sufficiently controlled with high doses of inhaled corticosteroids and other medical treatments). It is used in adults⁴⁰.

Application ways and warnings

It is applied intravenously (IV)^{39,40}. It is not indicated in other eosinophilic conditions, acute bronchospasm, and status asthmaticus³⁹.

Reslizumab patients' most common side effects are nasopharyngitis, headache, and upper airway infections^{25,38}. Anaphylaxis (0.3%) and malignancies (0.6%) (6/1,028 people) were reported. In the placebo-receiving group, malignancies are 0.3%. Malignancies were detected after less than six months of use³⁹.

Applications by FDA

3 mg/kg (every four weeks), i.v. Infusion (given in 20-50 minutes) (FDA)³⁹.

Applications by EMA

Under 35 and over 199 kg, 3 mg/kg, in people between 35-199 kg, according to the dosing schema published by EMA⁴⁰.

Anti-IL-5 Monoclonal Antibodies: Benralizumab

Mechanisms

Benralizumab is humanized IL-5 receptor alpha-effective cytolytic monoclonal antibody (IgG1, kappa). Like Mepolizumab and Reslizumab, it is a monoclonal antibody that binds to the IL-5 receptor α (IL-5R α) unit located on the surface of eosinophils. It shows pro-eosinophilic action. It also binds to natural killer cells, leading to cellular cytotoxic action and apoptosis on eosinophils^{25,41}.

Information for Medication

- Drug name: FASENRA[®]; ACTIVE SUBSTANCE: BENRALIZUMAB 30 MG/ML INJECTABLE; INJECTION^{42,43}.
- FDA approval: 2017⁴²; EMA approval: 2018⁴³.
It is produced with recombinant DNA technology in Chinese hamster ovarian (CHO) cells⁴³.

Indications by FDA

12 y and above, severe asthma (eosinophilic phenotype)⁴².

Indications by EMA

For children aged 6-18 years, there is not enough data on safety and efficacy. It is used in adults with severe eosinophilic asthma, which cannot be adequately controlled despite high doses of inhaled corticosteroids and long-acting β -agonist use⁴³.

Application ways and warnings

It is applied subcutaneously (s.c.)^{42,43}.

It is not indicated in other eosinophilic conditions, acute bronchospasm, and status asthmaticus⁴².

Applications by FDA and EMA

30 mg/s.c. Applied every four weeks (first three doses), then applied every eight weeks^{42,43}.

Adverse reactions

Anaphylaxis, angioedema, bronchospasm, hypotension, urticaria, and rash are reported⁴².

Overall Effects of Anti-IL-5 Agents

Mepolizumab, reslizumab, and Benralizumab reduce the number of eosinophils in the blood and tissue, corticosteroid addiction and asthma attacks are reduced, and their use in the treatment of severe eosinophilic asthma has been approved^{1-3,44,45}.

The use of anti-IL-5 in chronic rhinosinusitis with nasal polyps (CRSwNP) has been raised. These agents are thought to be effective by causing eosinophil apoptosis and reducing tissue eosinophilia^{1-3,44,45}.

Side Effects of Biological Therapies

Simple and common problems with Omalizumab are urticaria, headaches, and problems at the injection site^{1,7,8,46-49}. Anaphylaxis (0.2%) and malignancies (0.5%) have been warned by FDA⁸. It is emphasized that after the first three injections of omalizumab, the patient should wait for at least 2 hours, and in subsequent injections, patients should wait at least 1/2 hour^{1,7,8,46-49}.

Hypersensitivity and anaphylaxis have been reported in all biological agents. Reslizumab (0.6% vs. Placebo 0.3%)^{37,38} and Omalizumab (0.5% vs. Placebo 0.2%)^{8,9} have been reported to increase the risk of malignancies theoretically. Dupilumab can cause serum disease and serum disease-like reactions^{28,29}. Follow-up of patients is also required for opportunistic infections (herpes zoster⁵⁰ and helminthic infections)^{51,52}.

Conclusions

Biologics, especially Omalizumab and Dupilumab, may be used more in allergic rhinitis. Omalizumab

treatment led to an improvement in Daily Nasal Rescue Medication Score (DNSSS), and reduced allergic reactions associated with allergen immunotherapy, such as anaphylaxis. Dupilumab treatment led to significant improvement of SNOT-22 total scores in perennial allergic rhinitis.

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None.

Conflict of Interest

The authors declare no conflict of interest.

Ethics Approval

Ethics approval was waived due to the narrative nature of the study.

Authors' Contributions

Nuray Bayar Muluk: Planning, designing, literature survey, interpretation of the results, active intellectual support, writing, submission. Cemal Cingi: Planning, designing, literature survey, interpretation of the results, active intellectual support, English editing.

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Informed Consent

Not applicable.

Availability of Data and Materials

All data are presented in the text.

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