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Adverse effects of monoclonal antibodies in the treatment of moderate-to-severe asthma: a narrative review

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Abstract

Introduction and purpose: Over the past two decades, the management of severe asthma shifted from high doses of inhaled and oral corticosteroids to targeted biologic agents. Adverse effects of treatment with monoclonal antibodies are not yet fully characterised. The aim of this paper is to provide a comprehensive review of the adverse effects of the FDA-approved monoclonal antibodies in the treatment of moderate-to-severe asthma, including omalizumab, benralizumab, dupilumab, mepolizumab, reslizumab, tezepelumab.

Material and methods of research: A thorough literature review was performed using PubMed Web of Science and Embase, employing key words related to monoclonal antibodies, asthma and adverse effects.

Description of the state of knowledge: Omalizumab and mepolizumab have black box warning on the risk of anaphylaxis. Due to scarcity of data, no causal association between the use of monoclonal antibodies and risk of malignancy can be established. The most common adverse effects of biologic agents in severe asthma include upper respiratory tract infections, nasopharyngitis and asthma worsening.

Conclusions: Overall, monoclonal antibodies have a favourable safety profile, with certain risk of side effects remains present, and is variable for the different molecules. More studies of asthmatic patients treated with monoclonal antibodies are needed to spot rare adverse events and those developing over longer time.

Key words: monoclonal antibodies; asthma; biologics; adverse events; allergy

1. Introduction

Asthma is a heterogenous disease, defined by airway inflammation, airway hyper-responsiveness, and mucus hypersecretion, all contributing to variable airflow obstruction, but with heterogeneous underlying inflammatory mechanisms (1). Asthma is characterized by symptoms such as dyspnea, tightness of the chest, wheezing, cough, that vary over time and in intensity. Asthma might present differently in terms of the age at onset, the severity of asthma, the clinical presentation and the underlying pathological mechanism (1). Deeper understanding of asthma mechanisms and endotypes allowed the development of selective monoclonal antibodies, targeting specific cytokines or its receptors.

Over the past two decades, the management of severe asthma shifted from high doses of inhaled and systemic corticosteroids to targeted biologic agents. In this review, we will focus on the risk of anaphylaxis, risk of malignancy, risk of infections, (e.g. helminth and opportunistic), influence on cardiovascular health and safety of drug use in pregnancy. We also provide insight into drug-specific adverse effects and rare incidences identified in case reports.

2. Materials and methods

A comprehensive literature search was conducted using electronic databases including PubMed Web of Science and Embase. The search strategy utilized a combination of keywords related to specific monoclonal antibodies, asthma and adverse effects. The search was limited to articles published in English from inception to 2024. Additional studies were identified through manual searches of reference lists of relevant articles.

3. Description of the state of knowledge

Several monoclonal antibodies are currently available for the treatment of moderate-to-severe including omalizumab, benralizumab, dupilumab, tezepelumab, mepolizumab and reslizumab. Each has different mechanism and target distinct immune pathway, but all reduce asthma exacerbations and improve lung function, asthma control and quality of life. Biologic agents are also available in the treatment of other allergic diseases including chronic sinusitis with nasal polyps, chronic spontaneous urticaria and eosinophilic esophagitis.

Monoclonal antibodies are usually well-tolerated and safe; however, some adverse effects are rare or not fully characterized.

4. Molecular targets in the pathophysiology of asthma

4.1. Epithelial cell derived cytokines - alarmins

Epithelial cells are able to produce alarmins in response to exogenous, environmental stimuli e.g. allergens or indigenous stimuli e.g. cellular damage (2). Alarmins include thymic stromal lymphopoietin (TSLP), interleukin 25 (IL-25) and interleukin 33 (IL-33). The blockage of TSLP, IL-25, IL-33 attenuates local type 2 inflammation and decreases airway remodelling (2). Epithelial cell derived cytokines vary in structure and have different roles in asthma pathophysiology.

TSLP is a member of the IL-2 family of cytokines and signals through a heterodimer of TSLPR and IL-7Ra (3). TSLP is produced in two isoforms with distinct immune functions - long isoform TSLP (lfTSLP) and short isoform TSLP (sfTSLP) (3). The long isoform TSLP initiates and propagates T2 inflammatory responses, induce epithelial damage and airway remodelling (4). The short isoform is produced constitutively and has homeostatic, anti-inflammatory properties (3, 4). IL-33 is a member of the IL-1 family and induces T2 immune responses. IL-33 is produced by bronchial epithelial cells is response to allergens, pollutants, viral and fungal pathogens. IL-33 is elevated in airway epithelial cells, bronchoalveolar lavage and airway smooth muscle of asthmatics and correlate with disease severity (5). IL-25 (also known as IL-17 E) is a member of the IL-17 family but has distinct biological effects compared with the rest of the IL-17 family (5).

Tezepelumab is anti-TSLP monoclonal antibody, FDA-approved in the management of moderate-to-severe asthma in patients ≥12 years. Tozorakimab, monoclonal antibody targeting IL-33, is currently being investigated in phase 2 clinical trials in patients with asthma (NCT04570657). In case of IL-25, the blockage this cytokine is studied in animal models and preclinical investigations (6). Monoclonal antibodies targeting alarmins e.g. TSLP inhibits multiple downstream inflammatory pathways and reduces biomarkers and cytokines associated with inflammation including blood eosinophils, airway submucosal eosinophils, FeNO, IgE, IL-5 and IL-13 (3). The blockage of upstream cytokine such as TSLP can be potentially more effective than targeting downstream cytokines e.g. IL-5, IL-4, IL-13.

4.2. Down-stream cytokines

Epithelial cell-derived cytokines (e.g. TSLP, IL-33, IL-25) lead to the infiltration of lung tissue with type 2 helper cells, type 2 innate lymphoid cells (ILC2s), M2-polarized macrophages and eosinophils (7). Subsequently, activated T2 lymphocytes produce principal type 2 cytokines e.g. IL-4, IL-13 and IL-5, propagating T2 immune inflammation. IL-4 and IL-13 can activate B cells via IL-4Rα, further leading to IgE class-switch recombination, B cell maturation and the production of IgE-allergen specific antibodies. IL-4 and IL-13 act on goblet cells to induce mucus secretion.

IL-5 is responsible for eosinophil recruitment to the airways. IL-5 drives eosinophil differentiation, proliferation, survival, activation, adhesion, extravasation, recruitment to airways and degranulation (7). Currently available monoclonal antibodies blocking IL-5 are reslizumab and mepolizumab. Benralizumab is a monoclonal antibody directed against the alpha subunit of the IL-5 receptor, also blocking the activity of IL-5. The blockage of IL-5 leads to eosinophil depletion, however without long-term bone marrow suppression after the medication withdrawal (8).

Table 1. Overview of the monoclonal antibodies used in moderate-to-severe asthma with molecular targets, FDA-approved indications and black box warnings

Monoclonal antibody	Molecular target	FDA-approved indication	Black box warning
Omalizumab	Target IgE antibodies	• **Chronic spontaneous urticaria (CSU) refractory to H1 antihistamine, ≥12 years** • **IgE-mediated allergic asthma, not controlled by inhaled corticosteroids (ICS), ≥6 years** • **Nasal polyps, not controlled by inhaled**	Anaphylaxis

		corticosteroid, ≥18 years,	
Dupilumab	Target the interleukin-4 receptor α, blocking the interaction of IL-4 and IL-13 with the receptor	• **Moderate to severe eosinophilic or steroid-dependent asthma, ≥6 years** • **Moderate to severe atopic dermatitis (AD), not controlled with topical therapies, ≥6 years** • **Chronic rhinosinusitis with nasal polyps (CRSwNP) ≥18 years** • **Eosinophilic esophagitis (EoE), ≥12 years**	None
Tezepelumab	Target TSLP, blocking the TSLP-TSLPR interaction	• **Severe asthma, ≥12 years**	None
Benralizumab	Target the alpha subunit of the IL-5 receptor, blocking the activity of IL-5	• **Severe eosinophilic asthma, ≥12 years**	None
Reslizumab	Target IL-5	• **Severe eosinophilic asthma, ≥18 years**	Anaphylaxis
Mepolizumab	Target IL-5	• **Severe eosinophilic asthma, ≥6 years** • **Eosinophilic granulomatosis with**	None

		polyangiitis (EGPA), ≥18 years • **Nasal polyps, ≥18 years** • **Hypereosinophilic syndrome (HES) ≥18 years**	

5. Omalizumab

Omalizumab is an anti-IgE fully human monoclonal antibody indicated for moderate-to-severe persistent asthma, nasal polyps and chronic idiopathic urticaria.

5.1. Systemic reactions

There is a risk of systemic reaction; anaphylaxis, occurring in approximately 0.1-0.2% of patients (9). In a study on 1773 patients that experienced omalizumab-related anaphylaxis, 511 (28.92%) required hospitalization for the management of anaphylaxis and 255 (14.43%) patients experienced life-threatening reactions (10). Death was reported in 5 (0.28%) cases and disability in 14 (0.79%) patients (10). Omalizumab product label includes a black box warning with the risk of anaphylaxis. Patients receiving omalizumab need a detailed clinical history and close monitoring after the first drug administration. Medical professionals should inform patients on the signs and symptoms, management of anaphylaxis and should prescribe an epinephrine auto-injector for patients self-administering omalizumab at home (11).

5.2. Risk of malignancy

Monoclonal antibodies can interfere with the immune system, and possibly could increase the risk of cancer. It has been suggested that absent or very low serum Immunoglobulin E levels can increase malignancy development (12). In a 5-year observation study (EXCELS) no significant association was found between omalizumab use and risk of cancer (13). The pooled analysis of 32 RCTs the observed cancer incidence in the study group (4.14 and 4.45 per 1000 person-years for omalizumab and placebo groups, respectively) was in the range of the incidence reported from a population-based cohort study of asthmatic patients (5.9 per 1000 person-years) and nonasthmatic patients (4.1 per 1000 person-years) (14). Due to observational nature of studies and short period of observation, no causal association can be established between omalizumab use for asthma and malignancy risk (13).

5.3. Other adverse events

In terms of rare adverse events, 15 cases of drug-induced sarcoidosis following omalizumab treatment have been reported (15). Several case reports described the onset of eosinophilic granulomatosis with polyangiitis (EGPA) in patients treated with omalizumab (16).

6. Benralizumab

Benralizumab is a monoclonal antibody directed against the alpha subunit of the IL-5 receptor, blocking the activity of IL-5. Benralizumab is indicated for patients with severe asthma and blood eosinophil counts of 350 cells per μL or greater at baseline.

6.1. Systemic reactions

In a phase 3 extension study enroling 1926 patients, anaphylaxis was reported in one patient (8).

6.2. Risk of malignancy

In the same study, new cases of malignancy was reported in 12 patients (1%), including hematologic cancers (n=4), colon cancer (n=2), pancreatic cancer (n=1), basal cell carcinoma (n=2), nasal cavity cancer (n=1) and prostate cancer (n=2) (8). Only one case of malignancy (prostate cancer) was considered to be related benralizumab treatment by study investigators. There is insufficient evidence on the causal relationship between malignancy and benralizumab use.

6.3. Infections

The most common adverse events in three randomized clinical trials (SIROCCO, CALIMA and BORA) were nasopharyngitis (in 1% of patients in BORA and 12–21% of patients in SIROCCO or CALIMA) and viral upper respiratory tract infection (in 15–16% of patients in BORA and no patients in SIROCCO or CALIMA) (8, 17). 1–2% of patients treated with benralizumab experienced serious adverse events associated with infections (8, 17). The treatment with benralizumab leads to eosinophil depletion, however without the increased risk of infections. 1–2% of patients experienced serious adverse events associated with infections during the 1-year period in BORA, which was similar to the percentages in the SIROCCO and CALIMA trials.

7. Dupilumab

Dupilumab is a fully human anti–interleukin-4 receptor α monoclonal antibody that blocks both interleukin-4 (IL-4) and interleukin-13 (IL-13) signalling. In a phase 3 randomized controlled

trial the incidence of adverse events was similar in patients treated with dupilumab (81.0%) and patients receiving placebo (83.1%) (18).

7.1. Systemic reactions

No anaphylactic reaction was reported in any randomized controlled trial assessing dupilumab use in patients with asthma (19, 20). Low risk of anaphylaxis in dupilumab is probably related to its 99% of human component of the monoclonal antibody (10).

7.2. Hypereosinophilia

Eosinophilia occurred in 4.1% of the combined dupilumab arm and in 0.6% of the combined placebo arm. 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 (18). Eosinophilia was associated with clinical symptoms in four patients receiving dupilumab, two of which had serious adverse events including worsening of hypereosinophilia and chronic eosinophilic pneumonia (18). In another study, eosinophilia was reported in 14% of patients receiving dupilumab versus 1% placebo with no clinical consequences (21). Study by Wechsler et al. reported 1.4% to 6.4% prevalence of hypereosinophilia >3000 among 2061 asthmatics over a 5-year period (22). Retrospective analysis of 100 severe asthmatics on dupilumab that developed hypereosinophilia revealed 6% of cases of symptomatic eosinophilia (23). Symptoms of hypereosinophilia included: numbness in the hands and feet that resolved after stopping dupilumab (1 patient), asthma attacks requiring emergency department (ED) visit (3 patients), fevers, dyspnea, arthralgias, and myalgias (1 patient) and eczema worsening (1 patient). Symptoms in those patients resolved after discontinuation of dupilumab and switching to another monoclonal antibody (23). Overall, eosinophilia in most cases is asymptomatic and tends to decline to baseline levels after discontinuation of the treatment with dupilumab (21, 23).

7.3. Infections

There was no evidence of increased incidence of infections in any trial, and there were no reported helminth infections (18). Conjunctivitis is a common adverse effect of patients with atopic dermatitis treated with dupilumab (24), however rarely reported in patients with asthma. Considering cardiac events, no significant difference was found between dupilumab arm and placebo arm (18).

7.4. Arthralgia

In a retrospective analysis, arthralgia occurred in 5% of patients with AERD treated with dupilumab (25).

7.5. Pregnancy

Based on a report from the World Health Organization (WHO) safety database combining approximately 38000 reports, there were 36 cases of adverse effects in pregnant women treated with dupilumab. The majority of reported adverse events (58.3%) were spontaneous abortion (OR 0.57 [95% CrI 0.37–0.88]) (26). In the TRAVERSE open-label extension study, 9 participants receiving dupilumab for asthma became pregnant; 3 patients receiving dupilumab experienced spontaneous abortions, while none occurred in the placebo arm (27).

8. Tezepelumab

Tezepelumab, a fully human monoclonal IgG2λ binding human TSLP, thereby blocking the TSLP-TSLPR interaction (3). Tezepelumab is the only FDA-approved therapy for moderate-to-severe asthma independent of the baseline eosinophil count.

8.1. Systemic reactions

In the NAVIGATOR and CASCADE study, the rate of adverse events was similar in the group of patients treated with placebo and in the tezepelumab group. Patients randomized to tezepelumab reported no anaphylaxis and no hypersensitivity reactions during the 52-week observation period (28, 29). Mostly reported adverse effects include nasopharyngitis, upper respiratory tract infections, bacterial bronchitis and headache (28, 30). In a multi-centre, real-life study none of patients had any serious adverse effects, while a minority of patients (<10-15%) reported headache, fever or muscle pain shortly after tezepelumab administration (31).

8.2. Risk of cardiovascular diseases

In the DESTINATION study, the risk of cardiac adverse effects, including many different types of cardiovascular disorders, was higher in the tezepelumab arm than in the placebo arm over 2-year observation period. However, the incidence of serious cardiac adverse events and cardiovascular deaths was similar in tezepelumab and placebo recipients (30).

According to a systematic review of seven randomized controlled trials (RCTs) there were no statistically significant difference in the proportion of patients with at least one adverse event (AE), AEs leading to discontinuation of study treatment, all-cause death, influenza, bronchitis, nasopharyngitis, headache, and hypertension between group receiving tezepelumab and placebo (32).

8. 3. Risk of malignancy

Alarmins are implicated in the development of malignancy; in some tumours TSLP appear to have pro-tumorigenic role, while in others TSLP appear to be protective (33). In the NAVIGATOR study, the incidence of malignancy and benign neoplasms did not differ between

patients treated with placebo and tezepelumab (0.9% of patients in each group) (34). In the CASCADE study no patient developed malignancy during the trial period (28).

8.4. Pregnancy

Currently, there is no data on the safety of tezepelumab in pregnant women or breastfeeding women and no actively recruiting trial on those patient groups.

9. Mepolizumab

Mepolizumab is a humanized monoclonal antibody targeting IL-5. Mepolizumab is indicated for patients with severe eosinophilic asthma, eosinophilic granulomatosis with polyangiitis (EGPA), nasal polyposis and hypereosinophilic syndrome (HES).

9.1. Most common adverse effects

The most common reported adverse events in an open label extension study of mepolizumab of asthmatic subjects include respiratory tract infection (67%), headache (29%), asthma worsening (27%), and bronchitis (21%) (35). Post-hoc analysis revealed that patients with comorbid chronic rhinosinusitis experienced respiratory tract infections and asthma worsening more often (35). Hypersensitivity reactions occurred in less than 1% of patients treated with mepolizumab (36).

9.2. Infections

Based on data from two 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 (35, 37).

9.3. Systemic reactions

In terms of systemic reactions, no case of anaphylaxis was observed in five randomized double-blind placebo-controlled trials (38). Based on a retrospective study using data from the US Food and Drug Administration Adverse Event Reporting System database from January 2004 to September 2020, 104 cases of anaphylaxis related to mepolizumab (10). Odds ratio of anaphylaxis on mepolizumab was 4.65 (95% CI, 3.85–5.65) (10). In the literature several cases of anaphylactic reaction following mepolizumab administration were reported (39). Despite low incidence of anaphylaxis, appropriate precautions should be taken when mepolizumab is administered.

9.4. Risk of malignancy

In open-label extension studies, approximately 2% treated with mepolizumab developed malignancy (35, 37). There is no evidence on the association between biologic drug use and the

increased risk of developing malignancy. However, the observation period of extension studies (up to 4.5 years) might be too short to detect increased cancer risk.

10. Reslizumab

Reslizumab is a humanized monoclonal antibody directed against IL-5. Reslizumab is indicated in the subset of patients with the evidence of eosinophilic airway inflammation.

10.1. Systemic reactions

Reslizumab includes a black box warning for anaphylaxis. The package insert recommends observing patient following reslizumab administration for an appropriate period, however without specifying the time frame. Based on pooled data from five randomized controlled trials, anaphylaxis occurred in three patients (0.3%) treated with reslizumab (40). In an open-label extension study, no case of anaphylaxis was reported (40).

10.2. Risk of malignancy

A pooled data of six clinical trials showed no significant difference in the incidence of malignancies in patients treated with reslizumab when compared with placebo or the general population (40). Based on the same analysis, the rate of infections was low in the group of asthmatics treated with reslizumab and there was no difference between placebo and reslizumab arm (relative risk 0.77, 95% CI 0.70–0.85) (40). No opportunistic nor helminth infections were reported (40).

10.3. Other adverse effects

Real-life study by Ibrahim et al. reported significant elevation of creatinine kinase level (mean increase from 94.1 U/L pretreatment level to 184.7 U/L after 3 months of therapy ($p = 0.025$), and 160.5 U/L at 1 year ($p = 0.031$) (41).

10.4. Pregnancy

Up to date, no study assessed the efficacy of reslizumab treatment in the group of pregnant or breastfeeding women. Thus, the safety of reslizumab in pregnancy is unknown.

Summary

The paper briefly outlies adverse effects of monoclonal antibodies in the treatment of moderate-to-severe asthma, based on data from randomized clinical trials, open-label trials and real-life studies. The highest risk of anaphylaxis is attributed to omalizumab (10). Two monoclonal antibodies - omalizumab and reslizumab have black box warning about the risk of anaphylaxis. Based on currently available data, no causal association between increased risk of malignancy and monoclonal antibodies use can be established.

Overall, monoclonal antibodies have a favourable safety profile and adverse reactions occur rarely. Due to scarce data on the safety of monoclonal antibodies in pregnancy, it remains a contraindication for the treatment for the majority of biologic agents.

Future perspectives

Up to date, the data on adverse reactions of monoclonal antibodies is based mainly on the randomized clinical trials, representing a homogenic study population and a relatively short period of observation (up to 2 years). More adverse reactions can be observed in 4th phases of randomized controlled trials, open label extension trials, real-life studies and pharmacovigilance studies observing more heterogenous population over longer period of time. Some adverse reactions may develop over a longer observation period e.g. malignancy and are not initially reported in randomized controlled trials.

Lately, the idea of combining treatment with two monoclonal antibodies in patients with suboptimal control arises. However, data on safety of dual biologic therapy is lacking. The first RCT of combining approved biologics for severe asthma, Study of Magnitude and Prediction of Response to Omalizumab and Mepolizumab in Adult Severe Asthma (PREDICTUMAB, NCT03476109) is currently recruiting asthmatic patients.

Questions remain regarding the long-term safety of blocking the alarmins and the benefit–risk ratio of anti-cytokine treatment compared with that of cumulative systemic corticosteroids exposure, for which the side effects can lead to significant morbidity, but are well known. Further real-life and pharmacovigilance studies of the safety monoclonal antibodies are needed to spot rare adverse events and those developing over longer period.

Author's contributions

The authors confirm contribution to the paper as follows:

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