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REVIEW

Adverse Events of Biologics in Severe Asthma

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Abstract

Purpose of Review To summarize current evidence on the immediate and long-term safety profile of the available monoclonal biological therapy (MBT) approved for the treatment of severe asthma.

Recent Findings Clinical trials and real-world studies have shown that MBT are generally well tolerated, although certain adverse effects such as local reactions, anaphylaxis, parasitic or viral infections, malignancy, and cerebrovascular events are of special concern in these therapies or have already been reported. The frequency and severity of these effects vary depending on the specific agent and patient characteristics.

Summary MBT have significantly improved the management of severe asthma, yet continuous monitoring of their safety profile remains essential to optimize long-term outcomes and minimize risks.

Keywords Biological therapy · Asthma · Adverse effect · Omalizumab · Mepolizumab · Reslizumab · Benralizumab · Dupilumab · Tezepelumab

Introduction

Biological therapy is defined as "*medical treatments that use substances produced by living organisms or that mimic their functions to treat diseases*" [1]. According to this definition, allergen specific immunotherapy, introduced in 1911, can be considered the first biological used in asthma [2]. To discriminate between the different types of biologic therapies, this review focuses on monoclonal biologic therapies (MBT). The first MBT targeting type 2 (T2) inflammation was omalizumab, introduced in 2001 and approved for IgE-mediated asthma in 2003 [3–5].

Currently, several MBT are available for the treatment of severe asthma, including omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab and tezepelumab (Fig. 1). These agents have often multiple indications and have demonstrated high efficacy in both clinical trials and real-world studies, significantly reducing disease burden and improving patients' quality of life [6]. Moreover, recent evidence suggests that controlling T2 inflammation may have a positive effect even in non-T2 mediated diseases, likely due to broader modulation of the immune system [7–9] but also because many disorders classified previously as non-T2, do have a partly T2 inflammatory endotype.

Figure 1 Original publications (Clinical trials and observational studies) of each monoclonal biological therapy for asthma from its onset to year 2025. Original studies were included that allowed the evaluation of the efficacy, effectiveness and safety of the different molecules for a minimum period of 6 months.

Clinical trials and real-world studies have enabled the characterization of the immediate and long-term safety profile of these agents. In this review, we summarize current findings on the potential adverse effects of MBT, focusing on outcomes such as parasitic and other infections, anaphylaxis, hypereosinophilic syndromes, malignancy, stroke, and mortality.

Review Methodology

This narrative review was conducted through a comprehensive search of Phase III and IV clinical trials and real-world

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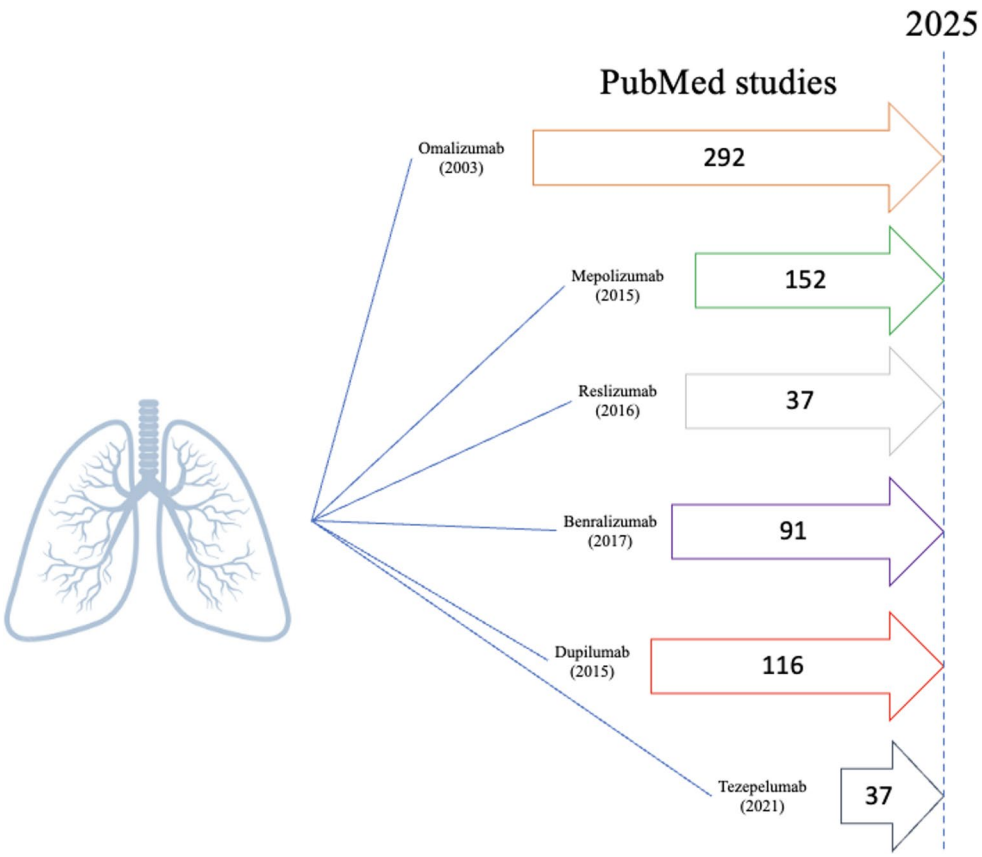

Fig. 1 Monoclonal biological therapies for asthma

studies addressing the safety profile of MBT in asthma and related T2 inflammatory diseases. The literature search was performed in PubMed and google scholar databases, using the following key terms: *Asthma*, *atopic dermatitis*, *adverse events*, *reactions*, *rhinosinusitis*, *urticaria*, *food allergy*, *eosinophilic esophagitis*, *hyper-eosinophilic syndrome*, *omalizumab*, *mepolizumab*, *reslizumab*, *benralizumab*, *dupilumab*, and *tezepelumab*. No restrictions on publication date or language were applied. Retrieved studies were screened for relevance and organized around specific research questions concerning potential adverse effects of monoclonal biologic therapy.

Results

Q1: What is the Frequency of Local Adverse Effects with MBT?

In accordance with findings from trials needed for the medication registration (pivotal studies), the frequency of local adverse reactions (LAR) showed little variation among the different MBT, ranging from 17% with omalizumab and 24% with dupilumab (variation of ± 9% maximum), with a cumulative frequency of 38% (range 24 to 41%) of treated patients per year. The most commonly reported adverse events per patients were erythema (38%), pruritus (22%), pain (18%) and edema (17%).

No association were found between the occurrence of LARs and the number of administered doses, or between reactions appeared during the initial or subsequent injections. The annual discontinuation rate due to local reactions remains low - below 0.3% (range 0.1–0.8%) (Fig. 2). Overall, these findings suggest that local adverse events are usually treatment discontinuation was not necessary.

Figure 2 Frequency of local adverse events according to original publications (pivotal trials). Original studies were

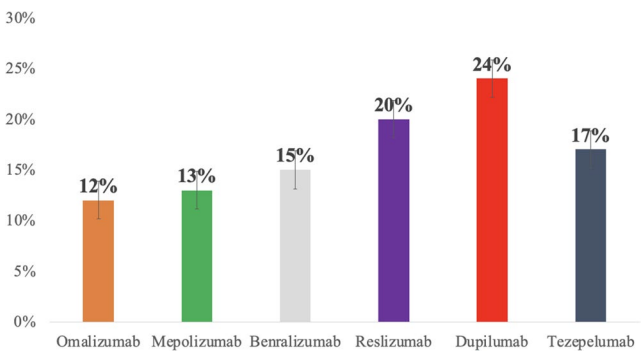

Fig. 2 Local adverse events

included that allowed the evaluation of the efficacy, effectiveness or safety of the different molecules for a minimum period of 6 months.

Q2: What is the Frequency of Anaphylaxis with MBT?

The overall risk of anaphylaxis with MBT is estimated to be less than 0.5% [10, 11] per patient. Omalizumab, the molecule with the longest post-marketing experience, accounts for the highest number of reported cases; however, its overall prevalence of anaphylaxis per patient (0.1 to 0.3%) is comparable to that reported for other MBT (Fig. 3). In the initial pivotal, randomized clinical trials, the reported prevalence was higher than in later real-world studies of omalizumab and reslizumab, which led to the original inclusion of an FDA black box warning for both agents.

The highest frequency of anaphylaxis reported with omalizumab has been reported in patients with chronic spontaneous urticaria. Nevertheless, this rate is like the background frequency of anaphylaxis among patients with severe urticaria, suggesting that disease characteristics rather than drug exposure may account for the difference. Longitudinal studies with follow-up of more than two years do not show a clear pattern between the number of injections and the frequency of anaphylaxis. Based on this observation, the EMA has granted approval for the release of omalizumab as an auto-injector for urticaria and asthma.

Anaphylaxis has also been reported, although rarely (<0.2%) with benralizumab, mepolizumab and dupilumab. At present, no cases of anaphylaxis have been reported in tezepelumab clinical trials [12–14].

Figure 3: *No significant risk*: According to Clinical trials and real word studies the incidence of this adverse event was similar to the incidence in control groups or lower than 1:500. *Potential risk*: at least one study suggests it is a risk factor, nevertheless, is important to mention that a NNH (Number need to harm) over 100 indicates a very low risk. *Potential protective factor*: at least one study suggests it is a protective factor.

Original studies were included that allowed the evaluation of the efficacy, effectiveness and safety of the different molecules for a minimum period of 6 months. The stroke risk observed for omalizumab must be interpretate with caution, as most studies compare asthma severe pateints with omalizumab and non-severe asthma patients without omalizumab.

Q3: What is the Frequency of Parasitic Infections with MBT?

The overall frequency of parasitic infections associated with MBT is below 1% [15]. In a recent pharmacovigilance analysis, Lifar P. et al. evaluated all reports of parasitic infections registered in VigiBase - the World Health Organization Global Database of Individual Case Safety

	Anaphylaxis	Parasitic infection	Cancer	Stroke	No-parasitic infection
Omalizumab	NNH 215	Risk increase in endemic zone	No significant risk	Potential risk NNH 251	Potential protective factor
Mepolizumab	No significant risk	No significant risk	No significant risk	Potential protective factor	No significant risk
Reslizumab	NNH 299	No significant risk	No significant risk	Potential protector factor	No significant risk
Benralizumab	No significant risk	Potential risk	No significant risk	Potential protector factor	Potential protective factor
Dupilumab	No significant risk	No significant risk	Potential risk NNH 281	No significant risk	Potential protective factor
Tezepelumab	No significant risk	No enough information	No enough information	No enough information	Potential protective factor

Fig. 3 Risk of serious adverse events

Reports - between 2006 and 2022 [16]. More than 90.000 patient reports of adverse events were included. The highest prevalence of parasitic infections was observed with benralizumab (0.23%), while the lowest was with dupilumab (0.03%). With indirect comparison, only benralizumab showed a statistically significant increased risk compared to control groups data (0.02%) (aOR, 9.49 [95% CI, 3.08–35.07]), and this association persisted after adjustment for endemic regions.

Earlier studies also explored the possible role of omalizumab, in suppressing the protective effects of T2 inflammation against parasitic infections. In a 2007 trial, 50% (n = 34/68) of patients receiving omalizumab experienced at least one parasitic infection compared with 41% (n = 28/69) in the placebo group (OR 2.2 CI 0.94–5.15). Importantly, omalizumab was not associated with increased morbidity, reduce time to first infection, greater infection severity, or reduced response to anthelmintic therapy [17].

Overall, available evidence indicates that parasitic infections during MBT therapy are uncommon and generally mild, though caution may be warranted when treating patients in endemic regions or with higher baseline risk (e.g., patients with immunodeficiencies).

Q4: What is the Relationship between Viral or Bacterial Infections and MBT for Asthma?

Infections caused by microorganisms other than parasites have been variably reported in patients receiving MBT for severe asthma patients. The overall incidence is heterogeneous across studies, with some suggesting a lower and others higher frequency compared with control groups [12, 18–21]. These discrepancies appear to be related to the age of the patients, infection severity and duration of follow up.

For serious infections, the risk appears to be comparable to or even lower than that of placebo groups (placebo 5% versus 3–8%). In children under 12 years of age with severe asthma, omalizumab has been associated with a reduced number and shorter duration of respiratory infections, possibly due to improved mucosal immune modulation [18, 19]. Similar results were observed with tezepelumab in adults and adolescent patients [12, 20, 21].

Evidence from pooled analysis suggest that the incidence of infections with benralizumab may decline over time, becoming similar or lower than baseline incidence of placebo after the first 12 months of therapy [22, 23]. Patients treated with dupilumab similarly showed a significantly lower use of systemic anti-infective medications compared to the placebo group [24].

In contrast, a recent real-world disproportionality analysis found an increased reporting rate of infections among mepolizumab patients (ROR = 5.12, CI 95% 5.03–5.21); predominantly affecting the upper respiratory tract with mild severity and occurring during the first six months of treatment [25]. The mechanism of this association is unknown and may be due to cofactors rather than directly to the drug.

In the NAVIGATOR study the frequency of infections with tezepelumab was 9% compared to 13% in the control group, with no severe infections reported [14]. The incidence of infections with reslizumab was generally similar to placebo in clinical trials, although some studies reported upper respiratory tract infections as a common side effect [26]. For instance, nasopharyngitis was a frequent side effect in a 16-week study, affecting 21% of patients on reslizumab versus 9% on placebo [27].

Overall, infections observed during MBT therapy are usually mild, transient, and not associated with increased serious outcomes, suggesting that these agents do not substantially compromise host defense mechanisms.

Q5: What is the Frequency of Malignancy with MBT for Asthma?

In clinical trials lasting up to 52 weeks, the frequency of malignancy among patients receiving MBT for asthma ranged from 0.2% to 0.5%), comparable to rates observed in placebo or non-biologic treatment groups (0.1–0.3%) [28]. However, the relatively short follow-up time during clinical trials limits the assessment of long-term malignancy risk, as longer exposure times are required to develop the condition.

Currently, omalizumab is the only MBT with a dedicated five-year study designed to evaluate malignancy incidence [29]. The malignancy rate was 16 per 1000 patients-years in the omalizumab group and 19.1 per 1000 patients-year in the non-omalizumab group, with a hazard ratio of 1.09 (95% CI 0.87–1.38). A pooled analysis, including placebo-controlled trials similarly found no association between omalizumab exposure and malignancy risk [30].

Sheng-Kai Ma K et al. [31], in a population-based cohort study including over 14,000 dupilumab treated patients with asthma and more than 730,000 matched controls treated with inhaled corticosteroids (ICS) and long-acting beta agonists (LABA) from 2018 to 2024, 54 new cases of lymphoma were recorded in the dupilumab group versus 43 in the ICS/LABA group, translating to a hazard ratio (HR) of 1.79 (95% CI: 1.19–2.71). Notably, the risk for T and NK cell lymphomas was significantly elevated (HR: 4.58, 95% CI: 1.82–11.53) with a number needed to harm (NNH) of 281. Other malignancies showed no significant differences between groups. However, interpretation of these findings requires caution, as most controls

had non-severe asthma. Interestingly, dupilumab-treated patients had lower all-cause mortality (HR: 0.65, 95% CI: 0.57–0.74), suggesting broader clinical benefit despite the oncological signal.

The frequency of malignancy associated with mepolizumab or benralizumab for asthma is very low, with an incidence of less than 1% in controlled studies and real-world studies, generally comparable to placebo or background rates [32–34].

The on-treatment incidence of malignancies with tezepelumab, in the NAVIGATOR and SOURCE trials was 0.65 and 0.77 per 100 patient-years respectively, compared with 0.72 and 0 per 100 patient-years in the corresponding placebo groups. These results suggest no increased malignancy risk associated with tezepelumab [12].

Overall, available data do not indicate a consistent or clinically significant increase in malignancy risk with MBT used for asthma, although continued long-term surveillance remains essential to confirm these findings. Ongoing international severe asthma registry (ISAR) studies are investigating the risks of malignancy between patients with severe asthma, who biologics, or non-biologic therapies. Data analysis in these studies is underway, and results will be published once available [35].

Q6: Do MBT Increase or Reduce the Frequency of Stroke in Asthma Patients?

A recent study suggests that use of TBM for asthma could reduce the risk for other chronic metabolic diseases like hypertension, stroke, and diabetes [36]. The real word longitudinal EXCELS study in moderate-to-severe asthma found a higher overall incidence of cardiovascular and cerebrovascular events among those treated with omalizumab (13.4 per 1000 person-years) compared to non-omalizumab patients (8.1 per 1000 person-years) [37], corresponding to a NNH of 250. Nevertheless, it is important to note that patients with severe, uncontrolled asthma inherently have an increased baseline risk of stroke, making it difficult to determine whether the increased incidence reflects the underlying disease or omalizumab treatment itself [38].

Some studies suggest that for dupilumab, the frequency of serious cardiovascular thromboembolic events -including stroke- was similar between dupilumab and placebo groups, and some studies suggest even a potential protector effect [39]. Nevertheless, one study suggests a potential risk [40].

Long-term safety data of mepolizumab do not identify stroke as a common or significant adverse event [41], however most studies have not evaluated cerebrovascular outcomes as primary endpoints. Similarly, no cases of stroke were reported in clinical trials comparing benralizumab with placebo [34, 42]. There is few information but similar to mepolizumab with reslizumab [43].

For tezepelumab, while no direct frequency rate for stroke is provided, clinical trial reports mention a single stroke event among treated patients. The overall incidence of stroke was lower in the tezepelumab-treated group compared to the placebo group [43].

In general, current evidence does not support a direct causal association between MBT and stroke. Observed cerebrovascular events appear rare and may reflect the intrinsic cardiovascular risk profile of patients with severe asthma rather than drug-specific toxicity.

Q7: What is the Relationship between Hyper-eosinophilic Syndrome and MBT for Asthma?

The incidence of hyper-eosinophilic syndrome (HES) and related eosinophilic complications in asthma patients treated with MBT for asthma is rare. Among available agents, although dupilumab may be effective in managing certain forms of HES, its use has occasionally, been linked to transient eosinophilia or HES flares, particularly early in treatment or following rapid corticosteroid tapering [44, 45].

In patients treated with omalizumab the occurrence of HES is poorly defined but considered very uncommon, with some evidence suggesting that HES appearance could be associated with the reduction of oral corticosteroid (OCS) therapy, rather than caused by omalizumab itself and even some case described off label effective use of omalizumab as therapy for HES [46].In contrast, mepolizumab, benralizumab, and reslizumab have been shown to reduce flare frequency in HES patients and do not seem to increase the risk of this complication in asthma [47–50] and in the particular case of mepolizumab can be used for HES.

Overall, MBT appear safe with respect to eosinophil-driven complications. While dupilumab may rarely precipitate HES in predisposed individuals, anti–IL-5 and anti–IL-5R therapies remain effective and well-tolerated options even in patients with eosinophilic comorbidities.

Conclusions and Summary

MBT have revolutionized the treatment of severe asthma and other diseases; reducing the morbidity, mortality and improving patient quality of life.

Current evidence indicates that monoclonal biologic therapies are generally safe and well tolerated in patients with severe asthma. Local and systemic adverse events are infrequent, typically mild to moderate in severity, and

rarely lead to treatment discontinuation. The incidence of anaphylaxis, infections, malignancy, and other serious complications remains low and comparable to that observed in placebo groups.

Continued long-term safety monitoring through real-world studies and pharmacovigilance systems is essential to detect rare adverse events and better understand patient-specific risk factors. With this information, preventive measures can be developed, allowing the lowest risk therapy to be selected for each patient. Additionally, if these effects are dose-dependent, gradual withdrawal of therapy could reduce the risk. Identifying these determinants will facilitate more personalized and safer use of biologic therapies in asthma management.

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    - ○ The study demonstrates that T2 cytokine blockade has an effect beyond traditional allergic diseases.
- Lifar P, Montastruc F, Reber LL, Magnaval JF, Guilleminault L. Parasitic Infections and Biological Therapies Targeting Type 2 Inflammation: A VigiBase Study. Am J Respir Crit Care Med. 2023;207(9):1253-5.
    - ○ The study evaluates the impact of T2 pathway blockade and the risk of parasitic infection in a large population over an extended period of time.
- Giossi R, Pani A, Schroeder J, Scaglione F. Exploring the risk of infection events in patients with asthma receiving. Heliyon. 2024;10(1):e23725.
    - ○ This study summarizes the evidence for the relationship between different biologics and the risk of infections.

Author Contributions Jorge Sánchez proposed the central idea. All authors contributed equally to the writing.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Human and Animal Rights This is a review article. This article does not contain experiments with human or animal subjects performed by any of the authors.

Competing interests The authors declare no competing interests.

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