SHORT COMMUNICATION

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Anaphylactic risks associated with immunobiological agents in asthma therapy

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Specific monoclonal antibodies (mAbs) have been increasingly used in the management of patients with severe asthma. As of October 2022, six mAbs (omalizumab, reslizumab, benralizumab, mepolizumab, dupilumab, and tezepelumab) have been approved by the Food and Drug Administration (FDA) and are currently available for asthma management in North America[1]. Several adverse effects have been reported with the administration of these mAbs in clinical trials, which had often shown a similar incidence in the placebo-treated groups. Of particular concern are the risks of hypersensitivity/allergic reactions and anaphylaxis, as these drugs may demonstrate antigenic properties. Symptoms typically associated with these severe side effects include bronchospasm, hypotension, syncope, urticaria, angioedema of the throat/tongue, dyspnea, cough, chest tightness, cutaneous angioedema, and generalized pruritus. Anaphylaxis, a systemic and life-threatening immune reaction, may also occur, requiring immediate medical assistance and specific interventions, such as intramuscular epinephrine injection[2].

Hypersensitivity/allergic reactions due to mAbs are fundamentally driven by the immunogenic properties of their protein component. Thus, fully human mAbs, which consist of 99% human components, are usually associated with a significantly lower risk of anaphylaxis compared to humanized mAbs, as those can carry up to 10% of murine elements[3]. However, sensitization and hypersensitivity/allergic reactions may also be driven by excipient chemicals, such as polysorbates, which are usually present in mAbs formulations. Interestingly, the female sex also seems to be a potential risk factor for anaphylaxis related to mAbs used in asthma. A history of anaphylactic reactions, regardless of the etiology, is also of clinical relevance when prescribing any mAbs. Even more concerning is that asthma patients appear to have a higher risk of severe allergic reactions, including anaphylaxis, compared to those suffering from chronic urticaria during treatment with the same mAb[3].

Overall, the estimated incidence of anaphylactic reactions related to mAb therapy for severe asthma is low[3,4]. Nevertheless, according to clinical trial and post-marketing surveillance data, the risk of developing anaphylaxis may differ according to the mAb in use. It is important to consider that mAbs that have been on the market for longer periods are more likely to be associated with hypersensitivity/allergic reactions.

Omalizumab is the first mAb specifically developed for asthma management and has been in commercial use since 2003, with an incidence of anaphylaxis estimated at 0.1–0.2%. Most of these reported cases occurred within 2 h after its administration, though some delayed-onset cases have also been reported up to 24 h. Of note, anaphylaxis may be triggered by any dose of omalizumab, regardless if previous doses had been well tolerated[5,6].

Reslizumab may also cause anaphylaxis, as 0.3% of patients randomized to this mAb also experienced this side effect during phase 3 clinical trials, which was more likely to occur as early as the second dose, either during infusion or within 20 min[4].

Given these observations, it is not surprising that FDA has included a black box warning on both omalizumab and reslizumab's labels recommending in-office infusion and close monitoring after these injections. For the first three doses of omalizumab, the monitoring period recommended is 2 h, which can be decreased to at least 30 min with subsequent doses. Conversely, there are no current clear recommendations for how long patients on reslizumab should be monitored after its infusion.

Benralizumab phase 3 clinical trials reported hypersensitivity/allergic reactions in approximately 3% of subjects treated with this drug[4]. In a previous 1-year phase 3 extension study, out of 518 patients treated with this drug, only

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Table 1. Suggested recommendations for administration of monoclonal antibodies in asthma.

• All patients must sign an informed consent form prior to treatment commencement.	
• All patients must be warned regarding the potential related risks and advised to seek prompt medical assistance should they experience any symptoms suggestive of anaphylaxis.	
• These drugs must be administered in a healthcare setting capable of providing urgent and intensive care support.	
Group	**Monitoring**
Low risk Omalizumab* Reslizumab Benralizumab	• Direct medical supervision during administration and observation for at least 2 h after injection for the first three doses. Personnel should be able to recognize anaphylaxis and treat it accordingly. • Direct medical supervision during administration and observation for at least 30 min from the fourth dose onward.
Very low risk Mepolizumab	• Direct medical supervision during administration and observation for at least 30 min, regardless of the dose number.
Extremely low risk Dupilumab Tezepelumab?	• Direct medical supervision during administration and observation for at least 30 min. Dupilumab can be considered for self-administration at home, especially if no hypersensitivity/allergic reactions occur during the first three doses[3].

*Ideally, patients would be trained for using epinephrine auto-injectors.

one case of anaphylaxis was described (0.19%)[7]. However, a recent study based on post-marketing reports supports that the risk of anaphylaxis associated with benralizumab seems to be similar to that observed with omalizumab and reslizumab[3]. In this study, the risk of hospitalization due to anaphylaxis was significantly higher in patients treated with benralizumab compared to their counterparts receiving omalizumab.

For mepolizumab, while no cases of drug-related anaphylaxis were described in clinical trials, post-marketing data have reported few cases of anaphylaxis following its administration[3,8]. Hypersensitivity/allergic reactions due to dupilumab (a fully human mAb), despite being estimated in 0.1–1.0%, consist mainly of generalized urticaria[4], and no cases of anaphylaxis have been reported with this drug based on post-marketing reports[3]. Similarly, no anaphylactic reaction was described among 528 asthma patients treated with tezepelumab, another fully human mAb, in a phase 3 clinical trial[9]. However, post-marketing data on tezepelumab are still scarce, as this drug has been on the market for a short period (approved for use in the United States since December 2021).

Therefore, based on the currently available data, we propose to classify the mAbs employed in severe asthma management according to their anaphylaxis risk into the following categories: *low risk* (omalizumab, reslizumab, and benralizumab), *very low risk* (mepolizumab), and *extremely low risk* (dupilumab and, probably, tezepelumab). Specific recommendations for the administration of these mAbs are listed in Table 1. These immunobiological agents must be administered in a healthcare setting capable of providing urgent and intensive care support, including administration of epinephrine, oxygen, bronchodilators, intravenous corticosteroids, and proceed with emergency orotracheal intubation and/or initiate cardiopulmonary resuscitation if needed. All patients on immunobiological therapy for asthma should be also warned about the risk of anaphylaxis with these drugs and advised to seek prompt medical attention in case they experience any hypersensitivity/allergic side effects. Ideally, patients on omalizumab should be able to initiate anaphylaxis treatment outside hospital facilities, which mostly relies on the use of an epinephrine auto-injector[5,6]. However, this recommendation is not feasible in Brazil, given that epinephrine auto-injectors, especially in public settings, are not available to be offered to our patients. Out of the six mAbs described here, given the good safety profile of dupilumab, we agree with the possibility of its self-administration at home after no occurrence of any hypersensitivity/allergic reactions during the first three doses administered under medical supervision[3].

The recommendations presented here should and will need to be updated as new evidence becomes available. Finally, to ensure accurate pharmacovigilance, it is essential that healthcare professionals report any adverse events related to these mAbs to local health authorities.

AUTHORS' CONTRIBUTIONS

JBM: Conceptualization, Methodology, Resources, Writing – original draft, Writing – review & editing. **FSLF**: Conceptualization, Writing – review & editing. **LSBC**: Conceptualization, Writing – review & editing.

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