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Potential novel role of asthma biologics as rescue therapy in the intensive care unit for life-threatening asthma exacerbations: a systematic review

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Abstract

Severe asthma exacerbations have high morbidity and mortality. The management can be challenging, and the optimal strategy for patients admitted to the intensive care unit (ICU) with life-threatening and near-fatal asthma has not been fully defined. An interesting area of research is represented by the rescue or compassionate use of biological drugs when all treatments fail, including advanced interventions such as extracorporeal membrane oxygenation. This systematic review analyzes the cases described in the literature and discusses characteristics, treatments, and outcomes of patients who received asthma-approved monoclonal antibodies as rescue therapy following admission to the ICU due to near-fatal asthma exacerbations or status asthmaticus refractory to conventional treatments. A total of 14 studies (13 case reports and 1 case series) were included according to the prespecified inclusion and exclusion criteria. Various monoclonal antibodies were administered, most commonly benralizumab and omalizumab. Treatment was generally initiated within the first week of ICU admission, with nearly half of the patients receiving therapy within 5 days. Further research, including randomized controlled trials, is required to assess if this therapeutic option impacts ICU outcomes, which specific biologics could be used, and their eventual optimal timing and dosage.

Key words: biologics, asthma, life-threatening exacerbations, ICU, rescue therapy.

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Introduction

The Global Initiative for Asthma (GINA) defines severe asthma exacerbations (SAEs) as episodes characterized by progressive worsening of symptoms, such as breathlessness, cough, wheezing, and chest tightness, accompanied by declining lung function [1]. These episodes may be triggered by environmental factors (like pollen or pollution), respiratory tract infections, and/or poor adherence to inhaled therapy.

Inflammatory cascade activation leads to bronchospasm, mucus plugging, airway obstruction, and dynamic hyperinflation, which, in severe cases, may progress to respiratory failure and cardiopulmonary arrest.

Exacerbations may require evaluation and treatment in the clinic, emergency department (ED), or ultimately admission to the intensive care unit (ICU) to reduce the risk of serious complications or death associated with severe respiratory failure [1].

Standard treatment includes short-acting β agonists (SABA), ipratropium bromide, inhaled corticosteroids (ICS), and systemic corticosteroids. Additional therapies, such as magnesium sulfate, epinephrine, terbutaline, methylxanthines, and leukotriene receptor antagonists (LTRA), represent options that may also be considered despite limited evidence for their efficacy [2,3].

Correction of hypoxemia and hypercapnia is essential in managing life-threatening asthma events [2,4]. A trial of non-invasive ventilation may be beneficial for patients at low risk of major complications who did not respond to medical therapy, but evidence remains insufficient, and the latest European Respiratory Society/American Thoracic Society guidelines do not include a recommendation for or against its use [5]. Thus, endotracheal intubation and invasive mechanical ventilation are indicated if the respiratory failure is progressing and should not be delayed if clinical improvement is not achieved with pharmacological therapy. Extracorporeal membrane oxygenation (ECMO) can be considered in patients who remain severely acidotic and hypercapnic despite conventional therapy [3,4].

An interesting area of research is represented by the rescue or compassionate use of biological drugs for patients admitted to the ICU due to SAEs unresponsive to standard and advanced therapies.

Despite indications from regulatory agencies not to use these drugs for relief of acute bronchospasm and status asthmaticus, the

"off-label" administration has been described in rapidly deteriorating patients at high risk of death.

Materials and Methods

This systematic review analyzes the current literature describing the use of biological drugs for SAEs leading to ICU admission. The study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines, and the protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) before the study was conducted (registration number: CRD42024571257).

Focused question

A PICO specialized framework was used to define the search strategy considering:

- P (population): patients admitted to ICU with near-fatal asthma exacerbations or status asthmaticus and refractory to conventional treatments;
- I/E (intervention/exposure): rescue use of asthma biologics;
- C (comparison): it was not applicable in this study;
- O (outcomes): patients' characteristics, treatment, and outcomes.

This review aimed to answer the following focused question: what are the characteristics, treatments, and outcomes of patients admitted to ICU for near-fatal asthma exacerbations or status asthmaticus refractory to conventional treatments who received asthma-approved monoclonal antibodies as rescue therapy?

Search strategy

The search was conducted on the online databases MEDLINE (PubMed), Scopus, ClinicalTrials.gov, Cochrane Library, and Google Scholar, from inception to April 2025, and was followed by manual literature searches in the reference lists of the included articles to identify potential additional articles about this topic. The research string was as follows: (benralizumab OR dupilumab OR mepolizumab OR omalizumab OR reslizumab OR tezepelumab) AND (refractory status asthmaticus OR near-fatal asthma OR Life-threatening Asthma OR acute asthma exacerbation OR severe asthma exacerbation).

Study selection

We included clinical trials, observational studies, case series, case reports, letters to the editor, correspondence, and commentaries describing patient presentations that met the following inclusion criteria: i) adult patients (>18 years); ii) patients with a known history of asthma or fully diagnosed after the acute event; iii) patients admitted to ICU who received asthma-approved monoclonal antibodies as rescue therapy for near-fatal asthma exacerbations or status asthmaticus refractory to conventional treatments; iv) articles written in English. Studies unavailable as full-texts, abstract-only papers, or studies describing nonadult patients were classified as ineligible for inclusion. Articles describing the cases of patients who received asthma-approved monoclonal antibodies during asthma exacerbations but were not admitted to the ICU were not considered for inclusion.

Data extraction

Two researchers (LC and AC) independently searched the data, selected and extracted them. If the extracted data from both researchers did not match, the original text was reviewed by another researcher (SI) to reach a consensus. Extracted data included the following items: author/year, study design, patient characteristics (including age, sex, comorbidities, previous therapy for asthma), other treatments received in ICU, asthma biologic used, timing of utilization of the biologic, and patient outcomes (including timing of response, interruption of other treatments, discharge).

Evaluating the risk of bias

The Critical Appraisal Checklist for Case Reports developed by Moola *et al.* was used to perform a quality check of the included studies [6]. Two authors (LC and AC) independently assessed the quality of individual studies, and disagreements were resolved by discussion with a third author (SI).

Data synthesis

Data from original papers were extracted and reported *via* qualitative synthesis. Because of the limited number of reports and the restricted total number of patients, also in consideration of the design of the studies and the heterogeneous nature of outcome measures, a quantitative analysis was not conducted.

Results

The initial literature search generated 1607 potentially eligible articles from the aforementioned databases, plus 10 records identified additionally by manual search. A total of 172 duplicates were identified and removed. After excluding 1427 articles, 14 articles were included in this review according to the prespecified inclusion and exclusion criteria. A flow chart showing the study selection is presented in Figure 1.

Risk of bias

Table 1 shows the risk of bias of the studies included in the review, evaluated using the Critical Appraisal Checklist for Case Reports. Quality assessment of the eligible studies revealed that, on average, all of the recommended elements were fulfilled and thus, these were considered as low risk of bias. Only three studies did not attain a perfect score.

Study characteristics

Overall, 13 articles included in the systematic review were case reports [7-19], and 1 article was a case series [20]. Across all studies, a total of 17 patients were identified; 11 (65%) were male, and 6 (35%) were female. The median age was 41 years (range 23 to 69 years), and 4 (24%) patients were 25 years old or younger. Table 2 describes demographic characteristics of the patients, including age and sex, and summarizes comorbidities and previous therapies for asthma. A total of 6 patients (35%) were on treatment with medium/high dose ICS-long-acting β2-agonists (LABA), 2 patients (12%) with high dose ICS-LABA-long-acting muscarinic antagonists (LAMA). Of these patients, 2 were additionally assuming LTRA and 1 patient was on chronic oral corticosteroids (25 mg/day). 5 patients (29%) were assuming SABA or long-acting muscarinic antagonists (SAMA)-SABA as needed, 1 patient was not assuming any therapy, and for another patient no information was reported by the authors. One patient had received different monoclonal antibodies for severe asthma (namely omalizumab, mepolizumab, and benralizumab) but was not under any biologic during the adverse event.

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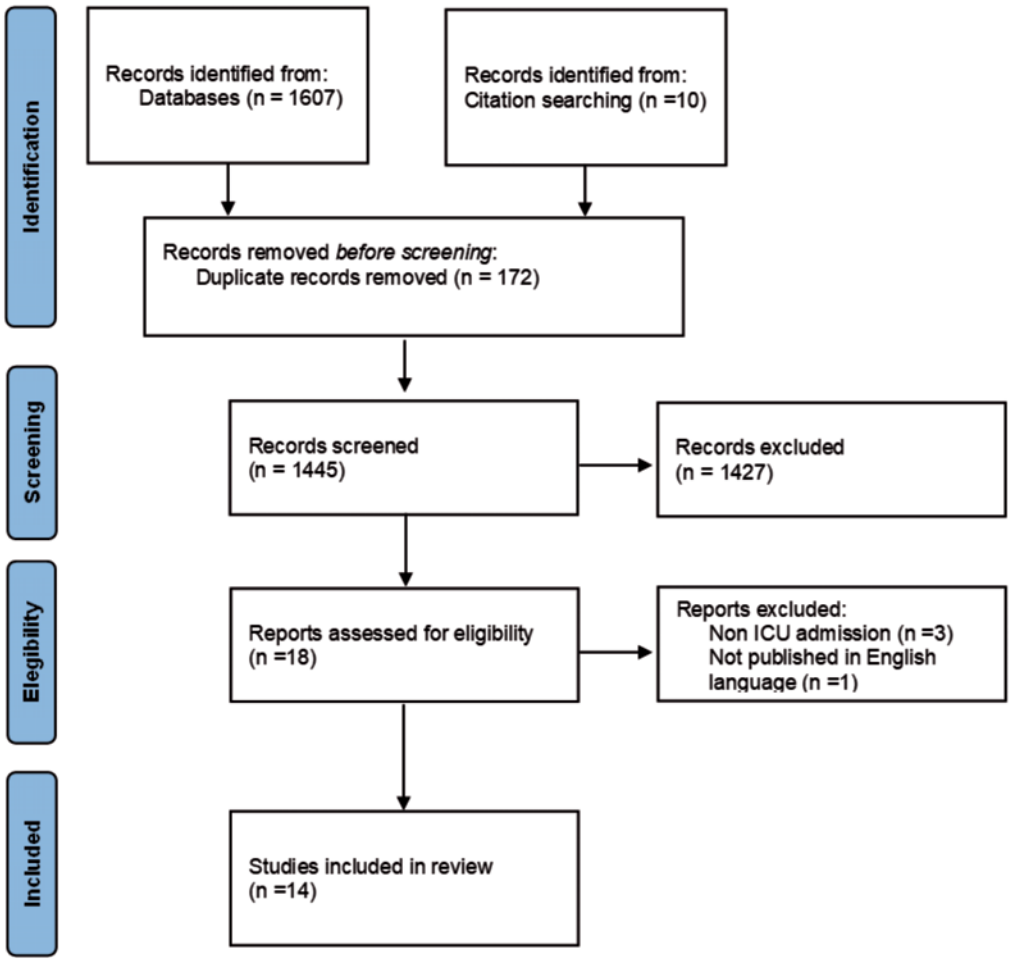


Figure 1. PRISMA 2020 flowchart diagram of the selected articles.

Table 1. Quality assessment of the included studies.

Author, year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8
Tello *et al.*, 2019 [7]	•	◦	•	•	•	•	•	•
Renner *et al.*, 2019 [8]	•	•	•	•	•	•	•	•
Milger *et al.*, 2019 [9]	•	•	•	•	•	•	•	•
Pérez de Llano *et al.*, 2021 [10]	•	•	•	•	•	•	•	•
Benes *et al.*, 2021 [11]	•	•	•	•	•	•	•	•
Barbarot *et al.*, 2022 [12]	•	•	•	•	•	•	•	•
Slevogt and Brauer, 2022 [13]	•	◦	•	•	•	•	•	•
Shanmukhappa *et al.*, 2023 [14]	•	•	•	•	•	•	•	•
Rodrigues *et al.*, 2023 [15]	•	•	•	•	•	•	•	•
Coghlan *et al.*, 2024 [16]	•	•	•	•	•	•	•	•
Granda *et al.*, 2024 [17]	•	•	•	•	•	•	•	•
Grasmuk-Siegl *et al.*, 2024 [18]	•	•	•	•	•	•	•	•
Montagnolo *et al.*, 2024 [19]	•	•	•	•	•	•	•	•
Conemans *et al.*, 2025 [20]	•	◦	•	◦	•	•	•	•

Q1, were patients' demographic characteristics clearly described?; Q2, was the patient's history clearly described and presented as a timeline?; Q3, was the current clinical condition of the patient on presentation clearly described?; Q4, were diagnostic tests or methods and the results clearly described?; Q5, was the intervention(s) or treatment procedure(s) clearly described?; Q6, was the post-intervention clinical condition clearly described?; Q7, were adverse events (harms) or unanticipated events identified and described?; Q8, Does the case report provide takeaway lessons?
•, yes; ◦, no.

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Comorbidities included allergies to pollens, house dust mite, animal fur or food (4, 24%), obesity (2, 12%), atopic dermatitis (2, 12%), obstructive sleep apnea syndrome (1), tuberculosis (1), laryngeal cancer (1), asthma and chronic obstructive pulmonary disease (COPD) overlap (1), use of drugs (1), and alcohol abuse (1). Three patients (18%) had no comorbidities, and 6 patients (35%) were active smokers. Overall, 2 patients had already experienced asthma exacerbations without the need for hospital admission, 2 patients had required hospitalization, and 1 patient even ICU admission but without invasive mechanical ventilation. Table 2 also describes which asthma biologic has been used and the timing of administration of the biologic agent. In the ICU, all patients were sedated and intubated, and invasive mechanical ventilation was administered. Regarding medical therapy, the normal differences in treatment for administered drugs, doses, and time of administration between multiple centers made a statistical analysis impossible to perform. Advanced procedures following standard treatment failure were also taken into consideration, as shown by the use of ECMO, which was

Table 2. Patient characteristics (including demographics, comorbidities and previous therapies for asthma, biologic used and timing of administration in the intensive care unit).

Author(s), year	Patient age	Patient sex	Patient comorbidities	Previous therapies for asthma	Asthma biologic used	Timing of administration of the biologic
Tello *et al.*, 2019 [7]	43 yo	F	NA	Budesonide-formoterol, Tiotropium	Mepolizumab 100 mg s.c.	7 days after admission to ICU
Renner *et al.*, 2019 [8]	53 yo	F	Asthma-chronic obstructive pulmonary disease overlap, chronic smoker	ICS, LAMA, LABA, oral corticosteroids (25 mg prednisolone/day)	Reslizumab 3 mg/kg IV	3 days after admission to ICU
Milger *et al.*, 2019 [9]	41 yo	M	Pollen allergy	SABA	Omalizumab 600 mg s.c.	8 days after admission to ICU
Pérez de Llano *et al.*, 2021 [10]	23 yo	M	Active smoker, occasionally used cocaine and marijuana, allergy (house dust mites)	Maintenance ICS LABA stopped during the preceding 6-8 weeks and replaced by albuterol several times a day	Benralizumab 30 mg s.c.	4 days after admission to ICU
Benes *et al.*, 2021 [11]	25 yo	F	Pollen allergy, atopic eczema, food allergies and oral allergic syndrome, occasional smoker	Ipratropium/fenoterol as needed	Omalizumab 600 mg s.c.	8 days after admission to ICU
Barbarot *et al.*, 2022 [12]	31 yo	M	Atopic dermatitis, active smoker	SABA on demand	Mepolizumab 100 mg s.c.	20 days after admission to ICU
Slevogt and Brauer, 2022 [13]	41 yo	M	NA	NA	Omalizumab 600 mg s.c.	Days 3, 6, 7, 10 and 11 after admission to ICU
Shanmukhappa *et al.*, 2023 [14]	30 yo	M	No comorbidities	ICS LABA, Montelukast, fexofenadine as needed	Omalizumab 600 mg s.c.	4 days after admission to ICU
Rodrigues *et al.*, 2023 [15]	25 yo	F	No comorbidities	No maintenance therapy	Mepolizumab 100 mg s.c.	4 days after admission to ICU
Coghlan *et al.*, 2024 [16]	69 yo	M	Pulmonary tuberculosis and resection of early-stage laryngeal cancer	ICS LABA	Benralizumab 30 mg s.c. and Omalizumab 300 mg s.c.	2 weeks after admission to ICU
Granda *et al.*, 2024 [17]	36 yo	M	Obesity, active smoker, heavy drinker	ICS LABA	Reslizumab 3 mg/kg IV	12 days after admission to ICU
Grasmuk-Siegl *et al.*, 2024 [18]	43 yo	M	Allergy (house dust mite, animal hair, pollen), obesity, obstructive sleep apnea	High-dose ICS/LABA, antihistaminic therapy, oral theophylline, nasal mometasone. Previous biological therapies with omalizumab in 2011, followed by mepolizumab in 2017, and benralizumab in 2019	Tezepelumab 210 mg, s.c.	12 days after admission to ICU
Montagnolo *et al.*, 2024 [19]	24 yo	F	No comorbidities	ICS/LABA, LTRA	Benralizumab 30 mg s.c.	2 days after admission to ICU
Conemans *et al.*, 2025 [20]	48 yo	F	Active smoker	Formoterol		7 days
	65 yo	M	Former smoker	N.A.	Benralizumab	5 days
	62 yo	M	Former smoker	ICS/LABA	30 mg s.c.	7 days
	61 yo	M	NA	Salbutamol		5 days after admission to ICU

NA, not available; ICS, inhaled corticosteroids; LAMA, long-acting muscarinic antagonist; LABA, long-acting β2-agonist; SABA, short-acting β agonists; LTRA, leukotriene receptor antagonists; ICU, intensive care unit.

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performed in 9 patients (53%). A total of 4 patients (23%) received omalizumab, 3 patients (18%) received mepolizumab, 2 patients (12%) received reslizumab, 6 patients (35%) received benralizumab, 1 patient (6%) received tezepelumab, and 1 patient (6%) received a combination of benralizumab and omalizumab. The median time of administration following admission to ICU was 7 days (2-20 days). 8 patients (47%) received the monoclonal antibody within 5 days of admission. One patient treated with omalizumab received multiple administrations of the monoclonal antibody during the stay in ICU following an updosed scheme. The clinical response to the administration of the biologic agent was interpreted as reduced need for mechanical ventilation following improvement of ventilatory parameters and arterial blood gas analysis, and as the possibility to stop or decrease the intensity of other concomitant therapies. Table 3 summarizes patient outcomes, including timing and clinical response to treatment, discontinuation of concomitant therapies, discharge details, and follow-up when reported.

Discussion

The use of biologic therapies in the ICU for life-threatening asthma exacerbations is an emerging area of interest. This is supported by growing evidence on the safety and effectiveness of biologics in reducing symptom burden and exacerbation rates in severe asthma patients in outpatient settings. Biologics, which target specific immune pathways, may reduce circulating cytokine levels or antagonize immune cells responsible for inflammation, thereby potentially stabilizing critically ill patients. The possibility of administering asthma-approved monoclonal antibodies to patients with asthma exacerbations admitted to the ICU was suggested by Bourdin *et al.* in 2021 [21]. Besides the mechanism of action, rapid modulation of inflammation is a key factor; therefore, pharmacokinetics plays a critical role. Monoclonal antibodies for severe asthma are high-molecular-weight compounds. When administered subcutaneously, they require 6-8 days on average to reach peak plasma concentrations in healthy individuals. This happens because absorption into the systemic circulation first requires transport of the drug through the interstitial space into the lymphatic system [22]. Consequently, subcutaneous administration takes longer for the peak plasma concentration to be reached than with intravenous administration. Thus, pharmacokinetic characteristics may affect the effectiveness of biologics within the ICU. However, despite the immediate availability of intravenous monoclonal antibodies such as reslizumab, there is no study suggesting the superiority of one biologic over another [21], primarily due to the scarcity of such cases. Pharmacological profiles of biologics approved for asthma are presented in Table 4. This review provides an

Table 3. Clinical response, discontinuation of concomitant therapies, and discharge.

Author(s), year	Timing of clinical response	Discontinuation of concomitant treatments	Discharge and follow-up
Tello *et al.*, 2019 [7]	Marked improvement after 2 days (better decarboxylation, pH, reduced PEEP)	Weaned and extubated after 8 days	Not available
Renner *et al.*, 2019 [8]	Improvement within 24 hours	Extubated the next day, transferred to ward	Discharged on day 13 post-intubation
Milger *et al.*, 2019 [9]	Rapid improvement in ventilation	ECMO off by day 12, ventilator weaning over 2 weeks	Discharged to rehab 5 weeks after onset
Pérez de Llano *et al.*, 2021 [10]	Improvement after 4 days (normalized pH, reduced airway resistance)	Extubated on ICU day 13; steroids tapered	Discharged after 25 days
Benes *et al.*, 2021 [11]	Ventilatory improvement within 90 minutes	ECMO off within 24h; extubated on day 10	Discharged on day 25
Barbarot *et al.*, 2022 [12]	Improvement at 48h (resolved bronchospasm, normalized PEEP, ↓eosinophils)	ECMO off after 7 days; extubation on day 30	Discharged 7 days post-ICU
Slevogt and Brauer, 2022 [13]	Slight improvement on day 4; improved ventilation and ↓IgE	Fully weaned 2 weeks later	Long-term omalizumab; normal lung function at follow-up
Shanmukhappa *et al.*, 2023 [14]	Improvement within hours (↓O2 needs, resolved bronchospasm)	Extubated day after treatment; ICU exit on day 6	Discharged on day 9; continued omalizumab
Rodrigues *et al.*, 2023 [15]	Clinical improvement at 48h (normalized PaCO2, ↓auto-PEEP)	Extubated on ventilation day 11; steroids tapered	Discharged from ICU on day 19; ongoing biologic therapy
Coghlan *et al.*, 2024 [16]	Gradual ventilatory improvement	Rapid weaning and tracheostomy decannulation	Discharged within 2 weeks; tapered oral steroids
Granda *et al.*, 2024 [17]	Improvement in 2 days (ventilation and oxygenation)	ECMO off day 14; second reslizumab on day 39	Discharged 2 months later
Grasmuk-Siegl *et al.*, 2024 [18]	Improvements within 24h (expiratory flow)	ECMO off by day 7; ventilation weaned over 13 days	Transferred to ward; ongoing pulmonary rehabilitation
Montagnolo *et al.*, 2024 [19]	Significant improvement after ~5 days; ↓eosinophils >90% by 48h	ECMO and IMV stopped on day 5	Discharged on day 19; benralizumab prescribed long-term
Conemans *et al.*, 2025 [20]	All four patients showed clinical improvement with reduced ventilator pressures	Extubation occurred between 4 and 18 days. 1 patient developed ventilator-associated pneumonia but recovered	ICS/LABA and benralizumab maintained asthma control in 2 patients; 1 remained OCS-dependent; 1 had stable asthma without biologics

PEEP, positive end-expiratory pressure; IgE, immunoglobulin E; ECMO, extracorporeal membrane oxygenation; IMV, invasive mechanical ventilation; ICU, intensive care unit; ICS, inhaled corticosteroids.

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Table 4. Currently available monoclonal antibodies used against severe asthma, mechanism of action and pharmacological characteristics.

Biologic agent	Mechanism of action	Route of administration	Peak concentration time	Bio-disponibility	Half life	Elimination
Omalizumab	Anti IgE	Subcutaneous	7-8 days	62%	26 days	Complexes with IgG and IgE
Mepolizumab	Anti IL-5	Subcutaneous	4-8 days	74-80%	16-22 days	Proteolytic enzymes
Reslizumab	Anti IL-5	Intravenous	Immediate	100%	24 days	Proteolytic enzymes
Benralizumab	Anti IL-5R	Subcutaneous	4-7 days (eosinophilic depletion seen after 24 hours)	59%	15 days	Proteolytic enzymes
Dupilumab	Anti IL-4/IL-13	Subcutaneous	3-7 days	64%	10-13 weeks	Proteolytic enzymes
Tezepelumab	Anti TSLP	Subcutaneous	3-10 days	77%	26 days	Proteolytic enzymes

IgE, immunoglobulin E; IgG, immunoglobulin G; IL, interleukin; TSLP, thymic stromal lymphopoietin.

insight into the clinical characteristics, comorbidities, and management of patients with SAEs requiring ICU admission, with a focus on the potential role of biologic therapies in an acute setting. The described cohort predominantly includes young adult patients with variable asthma severity and different therapeutic backgrounds, underscoring the heterogeneous nature of SAEs. In fact, despite being more frequent in severe asthma patients, any asthmatic patient may suffer a severe exacerbation, and mild asthmatics have been shown to carry a considerable risk of exacerbations, including severe, life-threatening exacerbations [23,24]. 5 out of 13 patients were using SABA or SAMA-SABA as needed. This is consistent with the recent evidence that has indicated a higher risk of exacerbations with SABA monotherapy and its overuse. For this reason, SABA-only treatment is no longer recommended, and as-needed combination ICS-formoterol is the preferred reliever therapy in adults and adolescents [1]. Comorbid conditions, particularly allergies and obesity, were prevalent, consistent with known risk factors that may exacerbate asthma or complicate its management [25,26]. The high rate of active smokers (38%) may have further compromised treatment efficacy, given the adverse effects of smoking on respiratory health and response to asthma therapies [27]. In the ICU, all patients received standard emergency management for asthma exacerbations. Nearly half (47%) required ECMO. This highlights the severity of respiratory compromise and the need for advanced interventions beyond typical asthma exacerbation management. An analysis of the Extracorporeal Life Support Organization registry showed that ECMO use in patients admitted for near-fatal asthma has increased, since it can improve gas exchange and prevent lung injury induced by mechanical ventilation, being a lifesaving adjunct for the most refractory cases or a bridging strategy to avoid aggressive ventilation [28]. However, careful management is required to avoid complications. The majority of patients included in the analysis received benralizumab, an anti-interleukin (IL)-5 receptor α antibody. It prevents the interaction between IL-5 and its receptor and promotes antibody-dependent cell-mediated cytotoxicity, enhancing eosinophil apoptosis [29]. Benralizumab can cause rapid and near-complete depletion of eosinophils, with a speed of onset of effect very similar to that seen with oral prednisolone [30]. Following the antagonism of IL-5/IL-5R, targeting immunoglobulin E (IgE) with omalizumab was the second most used approach. It was used in status asthmaticus patients with very high IgE levels. It is also interesting that one patient treated with omalizumab received multiple doses in an up-dosing regimen [13], suggesting that, in extreme cases, intensified biologic administration could be beneficial, although evidence on efficacy and safety is limited in this context. Tezepelumab, recently approved, targets thymic stromal lymphopoietin (TSLP), an epithelial-derived cytokine released in response to multiple triggers, preventing its interaction with the receptor and thus inhibiting multiple downstream inflammatory pathways, and at the moment it is the only monoclonal antibody approved for patients with either high or low levels of T2 biomarkers [31]. It has been used as rescue therapy in one patient who had already received different monoclonal antibodies without benefit, who suffered a near-fatal exacerbation triggered by an influenza A infection, all characteristics that suggest epithelial barrier dysfunction [32]. No cases of dupilumab rescue use in ICU were found in the literature. Nevertheless, despite its 3-7 day timeframe to reach peak plasma levels, dupilumab has shown rapid clinical effects [33]. The blockage of IL-13, which has a broad spectrum of action in asthma, including increased mucus production, proliferation of airway smooth muscle and stimulation of airways hyper-responsiveness [34], could offer therapeutic benefit in this setting. One patient in the cohort received a combination of biologics. While such dual biologic therapy has been described in uncontrolled severe asthma with overlapping allergic and eosinophilic phenotypes, it remains unendorsed by guidelines due to insufficient evidence and high cost [35]. Its application in the ICU has not been previously reported and may suggest potential synergy from targeting multiple inflammatory pathways. The median time to biologic administration post-ICU admission was 7 days (range: 2-20), with 47% receiving the biologic within 5 days. These data suggest that earlier administration may enhance outcomes when conventional therapies fail. Given the pharmacokinetics of biologics, early use could optimize long-term benefits even if immediate effects are limited. Nonetheless, delayed onset of action remains a major limitation. Although this review focuses on ICU patients, there are reports of biologics being used for acute exacerbations in ED and hospital wards when patients do not respond to conventional treatment or have contraindications or do not want to assume corticosteroids. These cases were excluded due to study criteria. Noteworthy is the case by Nolasco *et al.* [36], where benralizumab alone was used to manage an acute exacerbation without corticosteroids, antibiotics, or intensive bronchodilation, allowing a clearer assessment of benralizumab effects on eosinophil counts and pulmonary function. Similarly, Kim *et al*. described clinical and functional improvements following dupilumab administration after failure of conventional treatments [37]. The ABRA study further supports this approach, demonstrating that subcutaneous benralizumab (100 mg) rapidly depletes eosinophils and reduces treatment failure risk during acute eosinophilic exacerbations of asthma and COPD [38]. An ongoing phase 2B trial (NCT04617171) is evaluating the effi-

cacy of benralizumab initiated during acute exacerbations requiring hospitalization, assessing its impact on exacerbation recurrence, ICU admissions, healthcare utilization, and readmissions [39]. No randomized controlled trials (RCTs) specifically examining biologic use in ICU settings were found on ClinicalTrials.gov. Existing literature has several limitations. It is limited to case reports, with no prospective studies or RCTs available. Small sample sizes, variable treatments, heterogeneous follow-up, and potential publication bias limit generalizability and the ability to draw definitive conclusions on safety and efficacy. RCTs are urgently needed to assess whether biologics can improve prognosis in ICU patients with near-fatal exacerbations or refractory status asthmaticus. Relevant parameters should include inflammatory biomarkers (*e.g.*, eosinophil counts) before, during, and after biologic administration, correlated with clinical outcomes. Potential indicators of response include reduced need for respiratory support on mechanical ventilation, shorter duration or lower dosage of systemic corticosteroids and bronchodilators. Average improvement time and length of hospital stay are two other key factors to consider.

Conclusions

Biologic agents have revolutionized the management of severe asthma and are considered effective add-on maintenance therapies for uncontrolled severe asthma [40]. Even if they have not been intended for acute interventions, their potential role in the ICU setting is a fundamental topic of clinical research, particularly for patients who are suffering from life-threatening exacerbations and are refractory to standard treatments. Future research is required to assess if this therapeutic option impacts ICU outcomes, which specific biologics could be used, and their eventual optimal timing and dosage, also in consideration of pharmacokinetics profiles.

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