SZEWCZYK, Kamila, SZEWCZYK, Bartłomiej, KRZESŁOWSKA, Wiktoria Julia, PYTEL, Paulina, WIŚNIEWSKI, Szymon and HOŁOWNIA, Weronika. Biologic Therapies: Targeting Severe Asthma at the Molecular Level. Journal of Education, Health and Sport. 2024;74:51552. eISSN 2391-8306.
https://dx.doi.org/10.12775/JEHS.2024.74.52570
https://apcz.umk.pl/JEHS/article/view/52570

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).
The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 25.04.2024. Revised: 10.05.2024. Accepted: 17.06.2024. Published: 19.06.2024.

Biologic Therapies: Targeting Severe Asthma at the Molecular Level

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Introduction:
Severe asthma is a chronic respiratory condition that affects a significant number of individuals, causing persistent inflammation of the airways and leading to recurrent symptoms such as wheezing, coughing, and shortness of breath. While conventional asthma treatments, including inhaled corticosteroids and bronchodilators, are generally effective for most asthma patients, they may not always provide sufficient relief for individuals with severe asthma. In such cases, the use of biologic agents licensed specifically for severe asthma can be a valuable treatment option.

Aim of the study:
This article aims to explore the different biologic agents licensed for severe asthma and delve into their effectiveness in managing this complex and challenging condition.

Material and methods:
Literature available in the PubMed database was reviewed using the following keywords: biologic agents for asthma; omalizumab; mepolizumab; bernalizumab; tezepelumab; monoclonal antibodies.

Conclusions:

These medications are designed to target the underlying mechanisms of severe asthma, addressing the root causes of the condition rather than just managing the symptoms. As a result, they have shown promising results in improving symptoms and reducing exacerbations in individuals with severe asthma. By understanding the potential benefits of these medications, healthcare professionals can make informed decisions when it comes to treating patients with severe asthma.

Keywords: biologic agents for asthma; omalizumab; mepolizumab; bernalizumab; tezepelumab; monoclonal antibodies.

Introduction

In the evolving landscape of severe asthma management, asthma biologics represent a paradigm shift towards precision medicine, offering new hope for patients whose conditions are poorly controlled by conventional therapies. The utilization of these targeted therapies, including monoclonal antibodies like dupilumab, omalizumab, mepolizumab, benralizumab, and the more recently approved tezepelumab, underscores a move towards individualized treatment protocols. By targeting on specific inflammatory pathways and biomarkers implicated in asthma, such as IgE and eosinophils, these biologic agents provide a mechanism to significantly reduce exacerbations, improve asthma control, and enhance quality of life for patients with severe asthma. Their development and approval underscore the critical importance of understanding the molecular underpinnings of asthma and the role of targeted therapy in managing complex cases.

This article will delve into the intricacies of severe asthma, elucidating the role and mechanisms of asthma biologics in its treatment. It will explore the approved biological treatments available to patients, including the asthma biologics criteria for their use, and the current research expanding the possibilities of these therapies. Additionally, we want to emphasize the efficacy and safety of these agents, the challenges and considerations in their

application, and the future directions of research aimed at further improving outcomes for patients with severe asthma. Through this comprehensive exploration, the article aims to provide a detailed overview of how biologic therapies are transforming the management of severe asthma at the molecular level, offering insights into their potential to significantly improve patient quality of life.

Understanding Severe Asthma

Asthma is a chronic respiratory condition that affects millions of people worldwide. [1] This chronic respiratory condition is characterized by inflammation and narrowing of the airways, leading to recurring episodes of wheezing, shortness of breath, chest tightness, and coughing. These symptoms can vary in frequency and severity and are often triggered by factors such as allergens, exercise, cold air, or respiratory infections. This disease is managed through the use of medications, such as inhaled corticosteroids and bronchodilators, and by avoiding known triggers. [2] Asthma presents in various forms and severities. One such form is severe asthma, a condition that poses significant challenges to healthcare professionals and patients alike due to its complexity and the high level of care required for management.

According to the latest Global Initiative for Asthma (GINA) guidelines, severe asthma is a form of the disease that needs treatment at GINA step 4 or 5. This includes using at least high doses of inhaled corticosteroids (ICS) with a long-acting β-agonist (LABA), or other additional control medications (like theophylline or leukotriene receptor antagonists). It may also require the use of systemic corticosteroids for more than half the days in a year to maintain control of the disease. Alternatively, it could be asthma that remains uncontrolled even with the intensive treatment described above. [2], [3] The incidence of severe asthma is estimated to be between 5% and 10% of the population of patients with bronchial asthma.

Uncontrolled asthma represents a severe manifestation of the condition, marked by specific criteria indicating inadequate management and heightened risk of complications. Various criteria define uncontrolled asthma, including poor symptom control, which is assessed through tools such as the Asthma Control Questionnaire (ACQ) and the Asthma Control Test (ACT). Scores above 1.5 on the ACQ or below 20 on the ACT indicate insufficient control. Additionally, experiencing more than two exacerbations per year, each lasting at least three days, serves as a clear indicator of uncontrolled asthma. Severe exacerbations necessitating hospitalization or systemic corticosteroids reflect the seriousness of the disease. Furthermore,

a forced expiratory volume in one second (FEV1)/forced vital capacity (FVC) ratio below 70% or an FEV1 less than 80% after bronchodilation suggests persistent airway obstruction. Lastly, asthma that deteriorates when high doses of inhaled corticosteroids (ICS) or systemic corticosteroids are reduced also signifies uncontrolled asthma. [4]

The GINA guidelines introduce several key terms and concepts in the management of severe asthma. One such term is the "anti-inflammatory reliever" (AIR), which refers to a reliever inhaler containing a low-dose ICS plus a rapid-acting bronchodilator. These include combinations such as budesonide–formoterol, beclometasone–formoterol, and ICS–salbutamol. These medications provide both immediate relief from symptoms and long-term control of inflammation. Another important concept is "maintenance and reliever therapy" (MART), a treatment regimen in which a patient uses a combination ICS–formoterol inhaler every day for maintenance and also uses the same ICS–formoterol inhaler as-needed for relief of symptoms. This approach ensures that patients receive adequate anti-inflammatory treatment while also having access to immediate symptom relief. For children aged 6–11 years with severe eosinophilic asthma, the GINA guidelines recommend the use of the anti-IL-5 antibody mepolizumab, given by subcutaneous injection, as one of the preferred maintenance options in step 5 to reduce severe exacerbations. This highlights the evolving understanding of asthma phenotypes and the development of targeted therapies. [2] As understanding of asthma continues to evolve, these guidelines will undoubtedly undergo further refinement to ensure the provision of the best possible care for patients with severe asthma.

Glucocorticoids play a central role in managing severe asthma due to their potent anti-inflammatory effects. These medications work by increasing the production of interleukin-10 (IL-10), which helps suppress inflammatory cytokines and reduce activity of various immune cells, leading to decreased inflammation and improved lung function. [5]

Phenotyping and Personalized Treatment Approaches

Recent advances in the understanding of asthma have led to the identification of different asthma phenotypes, which can inform more personalized treatment strategies. Severe asthma can be categorized into phenotypes such as eosinophilic or non-eosinophilic asthma, each associated with distinct inflammatory pathways and responses to treatment. For instance, eosinophilic asthma is often characterized by an elevated eosinophil count and may respond well to treatments targeting specific interleukins like IL-5 or IL-13. Molecular phenotyping has

further refined the approach to treating severe asthma by identifying specific inflammatory markers that can be targeted with biologic therapies. These targeted treatments, such as monoclonal antibodies against IL-5 or immunoglobulin E (IgE), offer new avenues for reducing exacerbations and improving control in patients with severe, treatment-resistant asthma. [6] In addition to eosinophilia, blood-assessed neutrophil inflammation is associated with distinct features of asthma. Evaluating both neutrophilic and eosinophilic inflammation simultaneously can help clarify the complexities of the disease. [7] A treatment approach aimed at normalising eosinophil counts in induced sputum can decrease asthma exacerbations and hospitalisations without the need for extra anti-inflammatory medication. [8]

Recognizing severe asthma involves acknowledging the complex interplay of symptoms, triggers, and inflammatory processes that define this condition. By employing a combination of trigger avoidance, pharmacological treatment, and personalized therapeutic approaches based on asthma phenotypes, healthcare providers can offer effective management strategies that significantly improve outcomes for patients with severe asthma.

What Are Monoclonal Antibodies?

Monoclonal antibodies (mAbs) represent a revolutionary advancement in medical science, characterized by their precise specificity and wide range of applications. These antibodies are produced by a single clone of cells or a cell line, ensuring that all molecules in a given batch are identical. This uniformity is key to their effectiveness and reliability in various medical and research contexts. The hallmark of monoclonal antibodies is their specificity. Each monoclonal antibody is designed to bind to a single epitope on an antigen, allowing for targeted action against specific molecules or cells. This specificity makes them invaluable in both diagnostics and therapeutics. [9]

Mechanisms of Biological Agents in Treating Asthma

Biologic therapies target specific inflammatory pathways involved in the pathogenesis of asthma, particularly in patients with an endotype driven by systemic T helper 2 (TH2)-type responses, (specifically interleukin IL-4, IL-5, and IL-13). [5] These therapies are designed to interrupt the cascade of cellular events that lead to asthma symptoms, offering a targeted approach to managing severe asthma. Furthermore, prevalence of Type 2 inflammation is

observed in most individuals diagnosed with severe asthma. [10] Studies have highlighted the heterogeneity of asthma and identified subsets of patients who benefit from these interventions. The discovery of prominent type 2 inflammation in atopic dermatitis and the success of dual IL-4 and IL-13 blockade underscore the central role of these cytokines in mediating allergic diseases. The efficacy of targeting the IL-4–IL-13 pathway across different diseases with varied tissue manifestations supports the idea that immunological diseases can be more accurately defined and treated based on their underlying driver pathways, rather than their outward symptoms. This approach opens the door to more effective, tailored therapies for a range of allergic and inflammatory conditions. [11], [12]

Monoclonal Antibodies and Their Specific Targets

All licensed biologics - omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab, and Tezepelumab are prescribed as adjunctive therapies for individuals with severe asthma who often experience exacerbations and exhibit signs of T2 inflammation. Additionally, tezepelumab is recommended for treating patients without T2 airway inflammation. [13]

Monoclonal antibodies treat severe asthma by blocking specific molecules that contribute to the inflammatory process in the lungs. For instance, mepolizumab and reslizumab target interleukin-5 (IL-5), which plays a crucial role in the life cycle of eosinophils. [5] Benralizumab targets the IL-5 receptor, affecting the same pathway but at a different interaction point. [14] Dupilumab targets the interleukin-4 receptor alpha chain, which is involved in the pathways of both interleukins 4 and 13, key players in several inflammatory responses. [15] Omalizumab targets immunoglobulin E (IgE), which is involved in allergic reactions that can lead to asthma symptoms. Lastly, tezepelumab targets thymic stromal lymphopoietin (TSLP), a molecule implicated in multiple inflammatory pathways.

Omalizumab

Omalizumab is a monoclonal antibody that binds to immunoglobulin E (IgE). Omalizumab is globally approved as a personalized treatment option for patients with moderate-to-severe allergic asthma. [16] It binds to free IgE a key antibody in the allergic response. IgE is responsible for initiating a chain reaction that leads to the tightening of airways when an individual is exposed to allergens. By blocking that mechanism, omalizumab prevents from attaching IgE to its high-affinity receptor (FcεRI) on mast cells and basophils.

Omalizumab promotes Fc€RI downregulation on basophils. These mechanisms prevent the allergic response and inhibit proinflammatory cascade. [17]

Mepolizumab and Reslizumab

Mepolizumab and Reslizumab are anti-interleukin-5 (IL-5) monoclonal antibodies that block a key cytokine in the proliferation and survival of eosinophils. By binding to IL-5, these drugs prevent it from interacting with its receptor on eosinophils. Mepolizumab and reslizumab block the IL-5 pathway, preventing the activation and migration of eosinophils to the airways, thereby reducing inflammation and symptoms. Main indication of anty-IL-5 antibodies are severe eosinophilic asthma unresponsive to other GINA step 4–5 therapies. [5]

Benralizumab

Benralizumab binds directly to the α subunit of the IL-5 receptor on eosinophils and basophils. Benralizumab has a slightly different mechanism compared to mepolizumab and reslizumab. It binds directly to the IL-5 receptor on eosinophils and basophils, blocking the action of IL-5 and leading to a reduction in eosinophil levels. Benralizumab promotes interaction with FcγRIIIa on natural killer cells, promoting antibody-dependent cellular cytotoxicity and leading to the apoptosis of eosinophils. [14]

Dupilumab

Dupilumab targets the IL-4α receptor, blocking the signaling pathways of both interleukin-4 and interleukin-13, which are crucial in the synthesis of IgE and recruitment of inflammatory cells. Dupilumab block Th2 cell inflammatory mechanism. Th2 response lie at the heart of allergic inflammatory response. [15] Additionally Dupilumab decrease mucus production, and improve overall lung function in patients with eosinophilic and corticosteroid-dependent asthma. [18]

Tezepelumab

Tezepelumab is the newest addition to the arsenal of biologic treatments for asthma. It targets thymic stromal lymphopoietin (TSLP), an upstream molecule that plays a significant role in connection between airway structural cells and immune cells. [19] Tezepelumab can be effective in treating various pathogenetic types asthma. [20]

Biologic therapies targeting T2 inflammatory pathways have significantly advanced the treatment of severe asthma. These therapies are particularly effective in patients with elevated fractional exhaled nitric oxide (FENO) levels or high blood eosinophil counts, which are markers of greater clinical efficacy. The choice of biologic therapy depends on individual patient characteristics and preferences, as all available biologics have demonstrated excellent safety profiles. Many patients with severe asthma qualify for multiple biologics, but the absence of head-to-head trials makes the selection process challenging. Additionally, the presence of allergic or eosinophilic comorbidities, such as atopic dermatitis, nasal polyposis, or eosinophilic granulomatosis with polyangiitis, should be considered, as these conditions may also benefit from specific biologics. [21]

Impact on Patient Management

The use of biologic treatments can significantly lower the risk of exacerbations in patients with eosinophilic or severe allergic asthma, reduce the dependency on oral steroids, and thus decrease the associated side effects. These treatments have also been shown to improve overall asthma control, enhance quality of life, and in some cases, improve lung function. [13] A Cochrane systematic review showed that Omalizumab effectively reduces asthma exacerbations and hospitalizations when used with inhaled steroids and during steroid tapering in clinical trials. It was significantly better than a placebo in helping participants reduce or stop inhaled steroids and was generally well tolerated, though more injection site reactions occurred. [22] The SHAMAL study provides compelling evidence of the efficacy of benralizumab in reducing the need for high-dose inhaled steroids, which are often associated with severe side effects like osteoporosis and diabetes. This study demonstrated that 92% of patients could reduce their steroid dosage, and over 60% could cease using steroids altogether, marking a significant breakthrough in asthma management. [23] However, access to these treatments can be challenging and may involve significant waiting times and logistical considerations, such as travel to specialized asthma clinics. Biologic treatments for asthma represent a significant advancement in the personalized management of this complex disease, offering hope for improved outcomes in patients with severe, treatment-resistant forms of asthma.

The targeted action of these biologic agents significantly reduces the inflammatory processes in the airways. By disrupting the interaction between cytokines and their receptors,

these therapies prevent the recruitment and activation of immune cells that contribute to airway inflammation. This mechanism not only helps in controlling acute asthma symptoms but also plays a crucial role in managing airway remodeling, a long-term consequence of chronic asthma inflammation. Biologics like dupilumab and omalizumab modify the underlying disease processes by altering the signaling pathways that lead to inflammation and structural changes in the airway tissues. This targeted approach provides a more personalized treatment option, aligning with the principles of precision medicine in asthma management. [5] Evidence suggests that omalizumab improves asthma control and reduces the incidence and frequency of exacerbations in patients with severe allergic asthma. It is also effective in reducing corticosteroid use and healthcare utilization, while it also seems to improve lung function. [16]

Efficacy and Safety of Biological Agents

Biological agents have demonstrated significant efficacy in reducing exacerbations in patients with severe asthma. Studies have shown that omalizumab may reduce exacerbations at various intervals, with a risk ratio (RR) of 0.52 at 12 weeks, 0.69 at 24 weeks, and 0.62 at 52 weeks, indicating a substantial decrease in exacerbation risk compared with placebo. [24] Furthermore, all evaluated biologicals, including benralizumab, dupilumab, mepolizumab, omalizumab, and reslizumab, have been associated with reduced exacerbation rates. For instance, benralizumab has an incidence rate ratio (IRR) of 0.53, dupilumab 0.43, mepolizumab 0.49, omalizumab 0.56, and reslizumab 0.46, all indicating a significant reduction in exacerbation rates with high certainty of evidence. [25]

The use of biological agents in treating severe asthma has also been associated with improvements in quality of life (QoL). Patients have reported profound but heterogeneous improvements beyond asthma symptoms and exacerbations, including significant benefits to social and family life. These improvements have been attributed to reductions in daily symptoms, the frequency and severity of colds and chest infections, and mental health improvements such as increased confidence and decreased fear/anxiety. Furthermore, patients were able to resume physical activities, which was considered the second most important treatment outcome for individuals with severe asthma . [26]

While biological agents offer promising results in the treatment of severe asthma, they are not without potential side effects. The most common reactions are local and general. Systematic reviews of the literature, both past and present, indicate that omalizumab has a good

safety and tolerability profile, with the risk of serious adverse reactions being comparable to placebo. In addition to the relatively common injection site reactions associated with dupilumab, a less frequently described adverse effect is an increased number of peripheral eosinophils, while maintaining a reduction in tissue eosinophilia. The most serious immediate reaction directly related to the administration of biological drugs can be anaphylaxis. For example, based on post-marketing studies, the overall risk of anaphylaxis with the use of omalizumab has been estimated at 0.2%. [27]

Current Research on Biological Treatments

Recent advancements in biologic therapies for severe asthma have significantly shifted treatment paradigms, emphasizing the role of monoclonal antibodies (mAbs) in maintenance therapy. Since 2014, following updates in clinical guidelines by GINA, mAbs have increasingly replaced traditional treatments like corticosteroids in managing uncontrolled severe asthma (UCSA). This shift highlights the evolution toward personalized medicine, utilizing targeted therapies to enhance patient outcomes. The development of mAbs targeting new therapeutic markers has been pivotal in advancing asthma treatment. These biologics are tailored to interfere with specific inflammatory pathways, making treatment more effective for individual patients based on their unique inflammatory profiles. [28]

The ongoing research underscores the need for further studies to establish the long-term safety and effectiveness of reducing or eliminating steroid use in severe asthma management using other biologic therapies. SHAMAL study represents a significant advancement in severe asthma care, demonstrating the potential of biologic therapies to minimize steroid-related harm. Benralizumab, by targeting eosinophils, offers a promising avenue for managing severe asthma with fewer adverse effects. However, further studies akin to SHAMAL are imperative to establish robust recommendations regarding the safety and efficacy of reducing or eliminating high-dose steroid usage with other biologic therapies. [23]

Future Directions and Research

Research continues to identify and evaluate small molecules that target specific inflammatory pathways in asthma. The chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2) is one such molecule that binds to prostaglandin D2 (PGD2)

and is involved in allergic inflammation. It is expressed on eosinophils, mast cells, and basophils, which are key players in the allergic response. This pathway presents a potential target for new therapies that could modulate severe asthma more effectively, particularly in patients with specific phenotypes. [29]

Another promising area of research involves the STAT5/6 Src homology 2 domains. PM-43I, a small-molecule inhibitor of the STAT6 Src homology 2 domain, has shown potential in preclinical studies. This inhibitor prevents the recruitment to the IL-4Rα docking site and phosphorylation of Tyr641, effectively inhibiting STAT5- and STAT6-dependent allergic airway disease and even reversing preexisting conditions in mouse models. These findings suggest a significant potential for developing new treatments that could better manage asthma symptoms and progression. [30]

A systematic review of the literature on biologic treatments for asthma over the past two decades highlights the increasing focus on certain keywords such as "benralizumab," "severe asthma," and "omalizumab." This bibliometric analysis provides valuable insights into the trends and shifts in research focus, which can guide future studies and help in identifying under-researched areas that may hold the key to new therapeutic discoveries. [31]

The development of molecular phenotyping and new biomarkers is crucial for advancing personalized asthma treatments. Recent studies, including trials on mepolizumab in children and adolescents, have shown that molecular profiles may predict treatment efficacy better than traditional biomarkers like blood eosinophils or fractional exhaled nitric oxide (FeNO). This shift towards molecular phenotyping could significantly enhance the precision of asthma treatments Research into non-invasive biomarkers such as urinary bromotyrosine is ongoing. This biomarker, which results from eosinophil degranulation, has been associated with asthma exacerbations and could provide a non-invasive method for monitoring disease progression and response to treatment, particularly in pediatric populations. [28] These future directions highlight the dynamic and evolving nature of asthma research, underscoring the importance of continued exploration and innovation in the field to improve patient outcomes and quality of life.

Epidemiological data from Poland highlights a concerning trend: a small percentage of severe asthma patients are accessing biologic therapies through the National Health Fund's program. The barriers to access span patient, physician, and treatment center domains. Patients

face challenges such as limited awareness of biologic therapies, restricted access, fear of new treatments, and resistance to change from established therapies. Physicians may contribute to underutilization due to lack of awareness of biologic therapy benefits, adherence to familiar treatments, time constraints during consultations, and difficulties in qualifying patients for biologic therapy programs. To address these barriers and increase access to biologic therapies, efforts should focus on patient and physician education, streamlining qualification processes, and improving coordination between care providers. These steps can enhance treatment options and improve outcomes for severe asthma patients. [27]

Conclusion

The exploration of biologic therapies in severe asthma management embodies a promising frontier in personalized medicine, reflecting a substantial leap from traditional treatment methods to those that target the disease at the molecular level. Asthma, particularly severe forms, has long posed a challenge to clinicians due to its heterogeneity and variable response to standard treatments. However, recent years have witnessed significant advancements in understanding the underlying mechanisms driving severe asthma, paving the way for more targeted therapeutic interventions.

Central to this progress are monoclonal antibodies, a class of biologic drugs designed to selectively bind to specific molecules involved in the inflammatory cascade of asthma. By precisely targeting key components of the immune response, these biologics offer a tailored approach to managing severe asthma, addressing the diverse underlying pathways that contribute to the disease's complexity.

Among the notable biologics approved for severe asthma, omalizumab stands out for its ability to target immunoglobulin E (IgE), a pivotal mediator in allergic asthma. By intercepting IgE before it can trigger allergic reactions, omalizumab helps reduce asthma exacerbations and improve symptom control in individuals with allergic asthma that is refractory to conventional therapies. Similarly, biologics such as mepolizumab, reslizumab, and benralizumab target interleukin-5 (IL-5), a cytokine crucial for the maturation and survival of eosinophils, specialized immune cells implicated in eosinophilic asthma. By inhibiting IL-5 or its receptor, these medications effectively decrease eosinophil levels in the airways, thereby attenuating airway inflammation and reducing asthma exacerbations in patients with severe eosinophilic

asthma. Dupilumab fanother noteworthy biologic, targets the interleukin-4 receptor alpha (IL-4Rα), which plays a central role in the signaling pathways of both IL-4 and IL-13, two cytokines associated with allergic inflammation and airway remodeling in asthma. By blocking IL-4Rα, dupilumab disrupts these inflammatory cascades, offering a therapeutic option for severe asthma phenotypes characterized by type 2 inflammation.

The clinical benefits of biologic therapies extend beyond symptom control, encompassing improvements in lung function, reductions in oral corticosteroid dependence, and enhancements in overall quality of life for patients burdened by severe asthma. Moreover, by addressing specific molecular targets implicated in the pathogenesis of asthma, biologics herald a new era of precision medicine, where treatment decisions are informed by an individual's unique disease profile and biomarker status.

In conclusion, the emergence of biologic therapies represents a critical evolution in asthma care, offering targeted interventions that mitigate disease severity, minimize exacerbations, and optimize outcomes for individuals with severe asthma. As our understanding of asthma pathophysiology continues to deepen, further innovations in biologic therapy hold the promise of unlocking new avenues for personalized management and improved long-term control of this chronic respiratory condition.

Author's contribution

Conceptualization, Wiktoria Julia Krzesłowska and Kamila Szewczyk; methodology, Weronika Hołownia, Kamila Szewczyk, Paulina Pytel; software, Szymon Wiśniewski, Bartłomiej Szewczyk; check, Weronika Hołownia, Szymon Wiśniewski; formal analysis, Wiktoria Julia Krzesłowska and Paulina Pytel; investigation, Bartlomiej Szewczyk; resources, Szymon Wiśniewski, Bartłomiej Szewczyk, Weronika Hołownia; data curation, Weronika Hołownia, Szymon Wiśniewski; writing - rough preparation, Kamila Szewczyk; writing - review and editing, Kamila Szewczyk; project administration, Wiktoria Julia Krzesłowska, Bartłomiej Szewczyk. visualization, Kamila Szewczyk, Weronika Hołownia; supervision, Kamila Szewczyk, Paulina Pytel; All authors have read and agreed with the published version of the manuscript.

Funding Statement

Study did not receive special funding.

Institutional Review Board Statement

Not applicable

Informed Consent Statement

Not applicable

Data Availability Statement

Not applicable

Acknowledgments

Not applicable

Conflict of Interest Statement

The authors of the paper report no conflicts of interest.

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