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REVIEW

# Application of Biologics in the Treatment of Asthma in the Past Two Decades: A Bibliometric Analysis and Beyond

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**Abstract:** This study aims to demonstrate the bibliometric characteristics of articles on biologics for asthma treatment over the past two decades. There were 3395 articles published in 653 journals from 91 countries/regions from January 1, 2000 to September 30, 2023. The results showed biologics changes the course of asthma has attracted the interest of researchers and asthma remission has recently been proposed by researchers. Therefore, the goal of T2-high asthma management was shifted from controlling to complete remission. There was also growing interest among researchers in alleviating symptoms in T2-low asthma. New biological targets also need to be discovered when patients do not achieve satisfactory therapeutic outcomes with biologic agent, and one of the potential future direction for a treatment breakthrough lies in the combination of two biologics or the utilization of novel biologics that target dual sites. The development of biologics has progressed rapidly and has demonstrated their effectiveness in clinic, however, biologics still face multifaceted challenges and require further research to identify additional targets or enhance efficacy.

**Keywords:** biologics, asthma, T2 inflammation, bibliometric analysis

## Introduction

The prevalence of asthma is increasing year by year, affecting approximately 300 million people worldwide.[1] Asthma exacerbations significantly lead to a decrease in the quality of life and an increase in mortality rates for patients. Consequently, reducing asthma exacerbation is of utmost importance in the clinical treatment of asthma.[2]

Asthma is a chronic inflammatory airway disease with heterogeneity. Currently, asthma is clinically categorized into two types based on the biomarkers in serum and sputum samples: T2 (T2-high) and non-T2 (T2-low) asthma. T2-high asthma, also known as eosinophilic asthma, accounts for approximately 50% of asthma cases and can be further divided into allergic and non-allergic subtypes.[3,4] It is triggered by inhaled allergens, micro-organisms, pollutants, and other factors that stimulate the airway epithelial cells to secrete thymic stromal lymphopoietin (TSLP), interleukin-25 (IL-25), and IL-33, the alarmins.[5,6] These substances, either alone or in combination with dendritic cells, activate downstream innate immune cells, leading to the release of T2-type inflammatory factors such as IL-4, IL-5, and IL-13.[7,8] This process promotes the infiltration and activation of eosinophils, basophils, and mast cells, which further contribute to T2 inflammation. Additionally, T2 cytokines activate B cells to secrete immunoglobulin E (IgE) and stimulate smooth muscle cells in the airway, resulting in bronchoconstriction and airway hyperresponsiveness (AHR).[9] They also induce goblet cells to secrete excessive mucus and ultimately lead to airway remodeling. Absolute eosinophil counts in blood and sputum, serum IgE levels, and fractional exhaled nitric oxide (FeNO) are all important biomarkers for identifying T2 inflammation.[10,11]

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T2-low asthma includes neutrophilic asthma, mixed asthma, and paucigranulocytic asthma. The underlying disease mechanism of T2-low asthma is currently not well understood. It typically arises due to inflammation caused by neutrophils or paucigranulocytes, which leads to the activation of T1 and Th17 cells, resulting in asthma attacks.[12]

While standardized treatments can effectively control the symptoms for most asthma patients, there remains a subset of patients, approximately 5–10%, who continue to experience uncontrollable symptoms, also known as severe asthma.[13] Severe asthma is characterized by a need for high-dose inhaled corticosteroids (ICS) and long-acting bronchodilators, or an inability to adequately control symptom exacerbations even with such treatment. This subset of patients with severe asthma poses a significant burden on medical resources and has a substantial social and economic impact.[14,15] Over the past two decades, biologics have been used to treat asthma patients who struggle to manage their symptoms. The first biological agent, Omalizumab, was approved in 2003 and demonstrated promising results in the treatment of IgE-dependent allergic asthma.[16] Subsequently, biologics that target IL-4/IL-4R, IL-5, or TSLP have also been approved. Clinicians now have options to choose biologics that target different inflammatory pathways, which enhances their ability to manage asthma symptoms.[17]

However, there remains significant potential for the advancement of biologics in the treatment of asthma due to its biological heterogeneity and multitude of targets. The existing biologics available in the clinic and those currently being researched primarily focus on a limited number of inflammatory factors, indicating promising avenues for further research in the field of biologics for asthma. The objective of this article is to perform a bibliometric analysis on the scholarly literature pertaining to the utilization of biological agents for the management of asthma within the last twenty years. Additionally, this study aims to present a comprehensive overview and evaluation of the prevailing research findings, thereby offering potential avenues for future investigation by researchers in the field of asthma treatment using biologics.

## Methods

Searched in the Web of Science core collection database with the searching strategy TS = (asthma) AND TS = (biologic OR "monoclonal antibody" OR "biological therapy" OR biotherapy OR "biologic product" OR "biologic agent"). The search was limited to the time period from January 1, 2000 to September 30, 2023. Inclusion criteria included papers and reviews related to the search, while letters, briefs, book reviews, etc. were excluded. This resulted in a total of 3395 articles, which were utilized for visual analysis in terms of countries, institutions, journals, citations, and keywords.

The articles obtained were subjected to visual analysis using bibliometric techniques, employing the software of VOSviewer 1.6.18 (Centre for Science and Technology Studies, Leiden University, The Netherlands), Citespace 6.2.R5 (Chaomei Chen, China), Pajek 64 5.16 (University of Ljubljana, Slovenia), Cytoscape 3.8.2 (Cytoscape Consortium, USA) and Microsoft Excel (Microsoft Office 2021, Microsoft, Redmond, WA), and R package ComplexHeatmap 2.16.0, R package circlize 0.4.15. R package Clusterprofiler, R package enrichplot, R package ggplot2, and STRING (http://string-db.org) online platform, such as countries, journals, citations, keywords, genes, and diseases. The information pertaining to genes and diseases was sourced from CITEXS (https://www.citexs.com), a data analysis platform, and was utilized to generate pertinent visual maps for the purpose of analyzing the research status, identifying research hotspots, and tracking trends within this study.

Clusterprofiler, enrichplot and ggplot2 R packages were used to perform the extracted genes for Gene Ontology (GO) enrichment analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) Pathway Analysis.

STRING (http://string-db.org) online platform and Cytoscape 3.8.2 (Cytoscape Consortium, USA) were used to construct, analyze and visualize the Protein–Protein Interaction (PPI) Networks Analysis of the extracted proteins.

R package ComplexHeatmap 2.16.0 and R package circlize 0.4.15 were used to analyze the trend of keyword popularity over time.

VOSviewer 1.6.18 (Centre for Science and Technology Studies, Leiden University, The Netherlands) and Pajek 64 5.16 (University of Ljubljana, Slovenia) were used to analyze countries, journal publications, research fields, keyword frequencies, genes and diseases.

Citespace 6.2.R5 (Chaomei Chen, China) software was utilized for the visual analysis of countries and citations, and draw relevant visual maps. Create emergency graphs for the top 10 emerging strengths of countries. The parameter settings for CiteSpace were shown in the figures.

# Results

## Global Research Trends in Asthma Biologics (2000-2023)

Our bibliometric analysis of 3395 articles, from January 1, 2000 to September 30, 2023, revealed the growing scientific emphasis on biologic asthma therapeutics, reflecting their expanding clinical relevance and research priority (Figure 1). Geospatial analysis identified the United States as the predominant contributor, producing 1517 articles (44.68% of global output), followed by the United Kingdom (565 articles) and Italy (426 articles). The US also demonstrated exceptional international collaboration propensity, evidenced by a total link strength of 1365 - the highest among nations (Table 1). Notably, U.S.-UK collaborations formed the strongest bilateral partnership (Figure 2A). Temporal analysis revealed concentrated US research output between 2004 and 2007 (emergence strength: 22.35), significantly exceeding other nations (Figure 2B). This surge aligns chronologically with omalizumab's regulatory approval, which provided novel therapeutic options for refractory allergic asthma patients and stimulated clinical research interest through demonstrated efficacy.

### The Analysis of Journals and Citations

An analysis was conducted on journals and citations, which revealed that a total of 653 journals had published 3395 articles on the research of biologics for asthma treatment between January 1, 2000 and September 30, 2023. Among these journals, the Journal of Allergy and Clinical Immunology – In Practice emerged as the most prolific publisher with 172

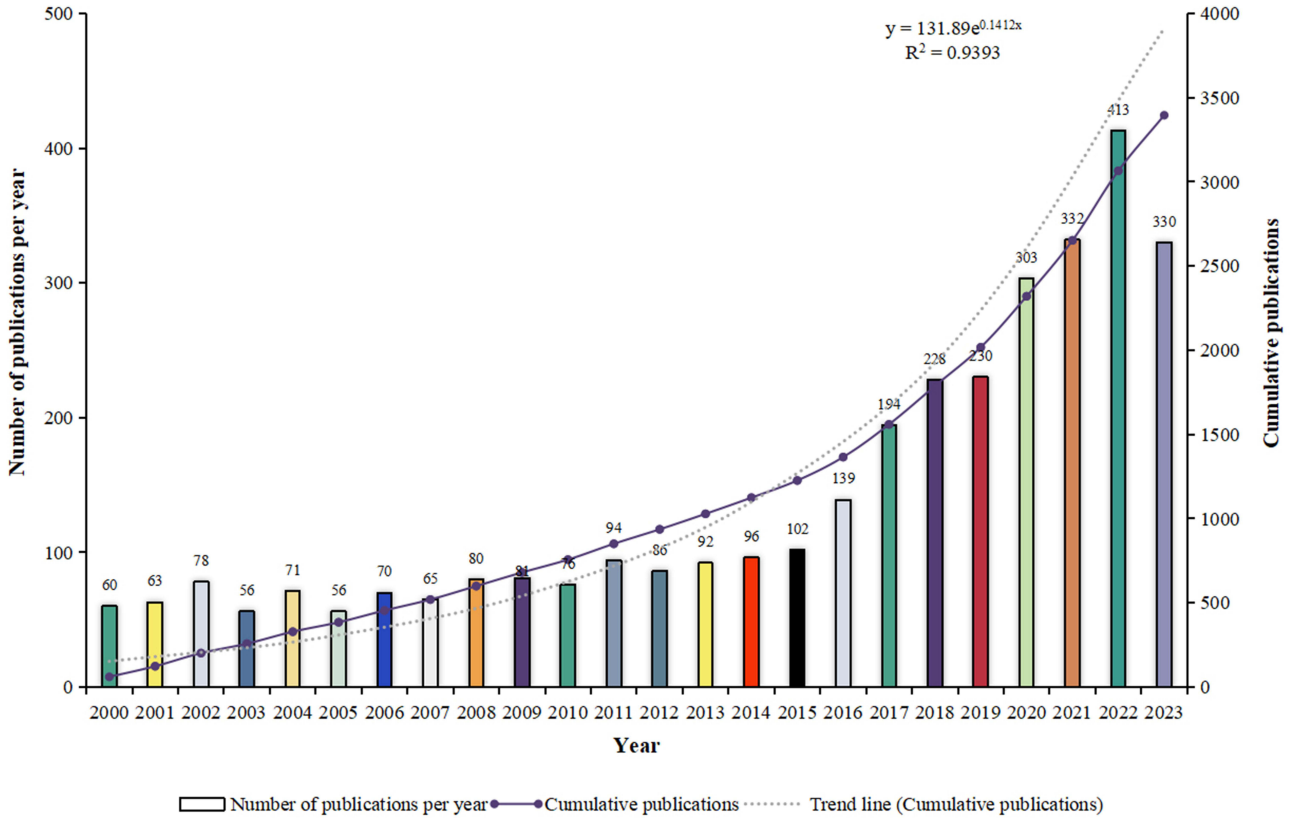


**Figure 1** The trend of publications in two decades. From January 1, 2000, to September 30, 2023, a total of 3395 publications focused on biologics for asthma treatment were recorded. The average annual number of publications during this period was calculated to be 141.46. A robust exponential function is given by y = 131.89e0.1412x (R2 = 0.9393, where x represents the year and y represents the cumulative number of publications), was developed to model the cumulative posting trend. The fitting degree of this function is considered satisfactory.


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**Table 1** The Publications of Biologics for Asthma in Regions/Countries

| ID | Regions | Published | Weight 1 | Weight 2 | Weight 3 | Weight 4 | Score 1 | Score 2 | Score 3 |
|---|---|---|---|---|---|---|---|---|---|
| 87 | USA | 1517 | 36 | 1365 | 1990.5427 | 86,809 | 1.3122 | 2015.1833 | 57.2241 |
| 85 | United Kingdom | 565 | 36 | 1073 | 1000.2587 | 42,804 | 1.7704 | 2015.9345 | 75.7593 |
| 38 | Italy | 426 | 35 | 518 | 436.4896 | 13,387 | 1.0246 | 2018.6901 | 31.4249 |
| 10 | Canada | 258 | 36 | 605 | 523.5359 | 21,141 | 2.0292 | 2016.4496 | 81.9419 |
| 28 | Germany | 237 | 35 | 703 | 536.2932 | 19,740 | 2.2628 | 2016.5612 | 83.2911 |
| 12 | China | 235 | 33 | 302 | 227.672 | 5499 | 0.9688 | 2017.5404 | 23.4 |
| 39 | Japan | 230 | 33 | 275 | 354.2293 | 11,320 | 1.5401 | 2015.3391 | 49.2174 |
| 26 | France | 196 | 32 | 602 | 451.8127 | 18,762 | 2.3052 | 2017.8724 | 95.7245 |
| 75 | Spain | 191 | 35 | 518 | 278.2705 | 7281 | 1.4569 | 2018.7906 | 38.1204 |
| 2 | Australia | 146 | 31 | 335 | 300.4296 | 9867 | 2.0577 | 2016.5753 | 67.5822 |
| 51 | Netherlands | 145 | 32 | 508 | 356.9331 | 11,865 | 2.4616 | 2017.8552 | 81.8276 |
| 7 | Belgium | 135 | 33 | 507 | 357.8277 | 10,310 | 2.6506 | 2018.1333 | 76.3704 |
| 77 | Sweden | 135 | 33 | 487 | 293.9401 | 9114 | 2.1773 | 2017.4889 | 67.5111 |
| 78 | Switzerland | 90 | 34 | 303 | 164.625 | 5492 | 1.8292 | 2017.4333 | 61.0222 |
| 74 | South Korea | 74 | 26 | 79 | 59.2781 | 1451 | 0.8011 | 2017.2027 | 19.6081 |
| 29 | Greece | 68 | 31 | 203 | 86.6615 | 1984 | 1.2744 | 2019.2206 | 29.1765 |
| 63 | Poland | 62 | 26 | 153 | 80.2183 | 2393 | 1.2938 | 2018.1613 | 38.5968 |
| 8 | Brazil | 52 | 29 | 195 | 99.1921 | 2767 | 1.9075 | 2015.9231 | 53.2115 |
| 18 | Denmark | 51 | 28 | 180 | 95.6948 | 2808 | 1.8764 | 2018.8235 | 55.0588 |
| 70 | Singapore | 49 | 27 | 147 | 68.2851 | 1391 | 1.3936 | 2019.2857 | 28.3878 |

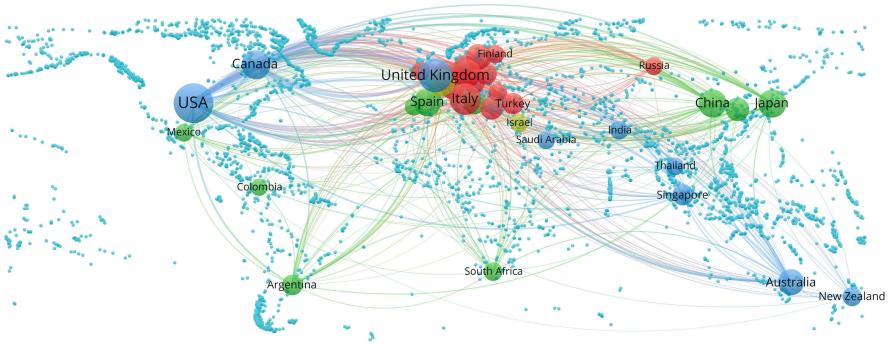
**Notes**: Weight 1 for <Links>, Weight 2 for <Total link strength>, Weight 3 for <Norm. citations>, Weight 4 for <Citations>. Score 1 for <Avg. norm. citations>, Score 2 for <Avg. pub. year>, Score 3 for <Avg. citations>.

articles, indicating its significant focus on the research of biologics for asthma treatment. This was followed by the Journal of Allergy and Clinical Immunology with 149 articles and Annals of Allergy Asthma & Immunology with 124 articles, suggesting that they both made significant contributions to the field (Figure 3A). According to the co-citation paper clustering analysis of the aforementioned articles resulted in a total of 15 citation directions, encompassing chronic rhinosinusitis and nasal polyps. These findings strongly indicated the existence of a connection between the biological agents employed in the treatment of asthma, chronic sinusitis, and nasal polyps (Figure 3B), thereby providing valuable insights and possibilities for further research into biological agents.

## Analysis of the Research Direction of Biologics

Existing biologics underwent a thorough verification process in clinic prior to their approval, which imposed limitations on research due to the known targets present. Consequently, researchers may encounter difficulties in breaking free from the existing paradigm. To address this challenge, we continued to perform analysis of research fields and keywords on the retrieved documents. All these papers could be categorized into five distinct fields: Biology and Medicine, Chemistry and Physics, Psychology and Social Sciences, Engineering and Mathematics, and Ecology and Environmental Science & Technology (Figure 4). The research covered in these articles encompasses a wide range of disciplines, including biomedicine, materials science, engineering, and environmental science, among others, which indicated the potential to conduct research on biologics from various perspectives. These results demonstrated that the development of biologics extended beyond the realm of biomedicine and garnered attention in the fields of material science and engineering technology, due to the promising prospects for the advancement of carrier materials for biologics in current research. And, the evolution of keywords in published articles may provide a potential means for subsequent research to exceed established boundaries. The findings from the literature keyword analysis indicated that “chemokines” and “bronchiolitis” emerged relatively early, whereas “real-world”, “precision medicine” and “asthma control”, as shown in the red boxes, are more recent keywords (Figure 5A). And, the prevalence of keywords such as “leukotrienes”, “chemokines”, and “lung” has gradually decreased in recent years. In contrast, the popularity of keywords such as “real-world”, “remission” and “asthma control”, as shown in the red boxes, has increased in recent years (Figure 5B). These results

A




B

**Top 10 Countries with the Strongest Citation Bursts**

| Countries | Year | Strength | Begin | End | 2000 - 2023 |
|---|---|---|---|---|---|
| USA | 2000 | **22.3** | 2004 | 2007 | |
| ENGLAND | 2000 | **6.76** | 2000 | 2001 | |
| JAPAN | 2000 | **4.8** | 2012 | 2014 | |
| GREECE | 2002 | **3.58** | 2020 | 2023 | |
| NORTH IRELAND | 2016 | **3.53** | 2021 | 2023 | |
| NEW ZEALAND | 2001 | **3.22** | 2001 | 2019 | |
| IRAN | 2015 | **3.22** | 2015 | 2019 | |
| TURKEY | 2008 | **3.11** | 2020 | 2023 | |
| POLAND | 2004 | **2.88** | 2014 | 2016 | |
| GERMANY | 2000 | **2.45** | 2007 | 2008 | |

**Figure 2** The comparison of publications in different regions/countries. (**A**). The VOSviewer software was used to conduct a visual analysis of the publication areas. In this analysis, each sphere represents a country, and the thickness of the line connecting the spheres indicates the level of collaboration between countries. Additionally, the size of the spheres exhibits a positive correlation with the number of countries that publish articles. (**B**) The timeframe spanning from January 1, 2000, to September 30, 2023, was examined using CiteSpace software. This revealed that the top ten countries had the highest volume of research publications concerning the use of biologics for treating asthma. Notably, the red area depicted in the figure indicates the specific time period during which each country experienced a surge in its publication output.

demonstrated that researchers have been focusing on the application of biologics to achieve asthma remission, allowing patients to stop medications, and the efficacy of existing biologics in real-world settings.

## Analysis of Biological Functions, Pathways, and Protein–Protein Interactions

To facilitate comprehensive research, this study employed the CITEXS data platform to extract a total of 1548 diseases and 2517 genes from a corpus of 3395 articles. Subsequently, they were subjected to the co-occurrence cluster analysis of genes, Protein–Protein Interaction (PPI) networks analysis, Gene Ontology (GO) enrichment analysis, and Kyoto Encyclopedia of Genes & Genomes (KEGG) pathway analysis, respectively. The co-occurrence cluster analysis of genes revealed that allergic cytokines, including IL-4, IL-5, IL-13, and IGHE (IgE), remained the primary focus of research of biologics for asthma. While, non-allergic cytokines such as TNF, IL-17A, IFNG (IFN-γ), and IL-6 were the principal research targets. Furthermore, in terms of alarmins and signaling molecules, TSLP, IL-33, IL-25, and CCL11 received more attention (Figure 6A). Among the proteins identified in the papers, IL6, IFN-γ, TNF, IL10, and CD4 emerged as the top five proteins, potentially serving as core proteins (Figure 6B). The GO enrichment analysis encompasses the examination of biological processes (BP), molecular functions (MF), and cellular components (CC). Within the realm of BP, genes exhibited enrichment in various biological functions, including "cytokine-mediated signaling pathways", "positive regulation of cytokine production", and "leukocyte migration". In terms of CC, genes demonstrated enrichment in biological functions such as the "external side of the plasma membrane", "vesicle lumen",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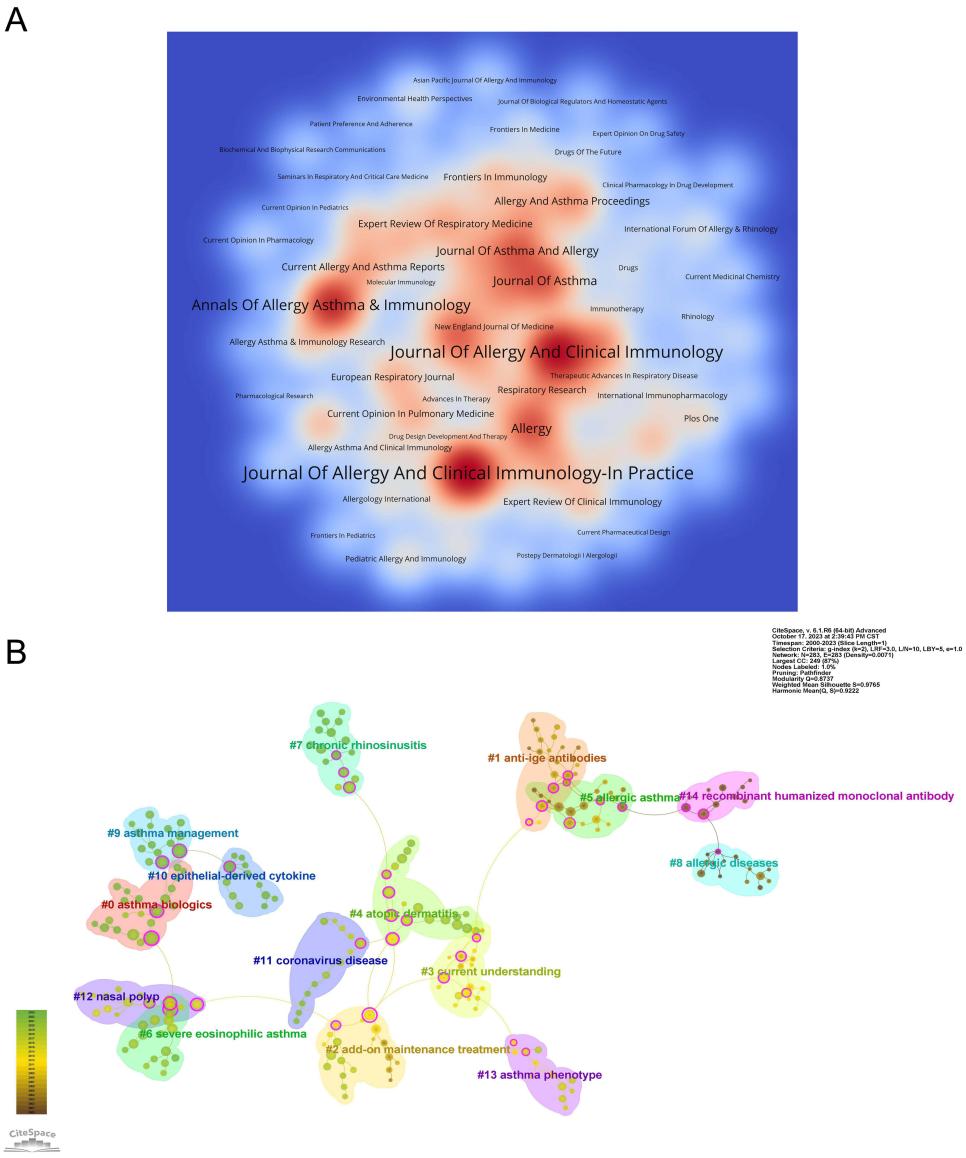


**Figure 3** The visual analysis in journals and citations. (**A**) The VOSviewer was used to perform a visual analysis of journals, where the color intensity corresponds to the quantity of published articles. (**B**) Investigated the co-citation patterns within the literature concerning biologics for asthma treatment, spanning from January 1, 2000, to September 30, 2023, utilizing CiteSpace. The magnitude of the superimposed sphere, which refers to the cumulative size of the corresponding spheres along the annual ring line, exhibits a direct correlation with the number of citations. The color brown signifies an earlier citation time, while green indicates a later citation time. The superimposed color signifies the period in which the article was cited. The years of citation are represented. The lines connecting the circles depict the co-citation relationship between the documents. The nodes highlighted in rose red are considered pivotal nodes, possessing a centrality value exceeding 0.1.

and “cytoplasmic vesicle lumen”. Concerning MF, genes showed enrichment in biological functions such as “receptor ligand activity”, “cytokine receptor binding”, and “cytokine activity” (Figure 6C). Regarding KEGG pathway analysis, the findings indicated that the investigation of the therapeutic mechanism of biologics for asthma primarily associates these agents with signaling pathways such as “Cytokine–cytokine receptor interaction” and “JAK-STAT signaling pathway” (Figure 6D). These findings suggested that the therapeutic mechanism of biologics for asthma treatment primarily targets conventional inflammatory factors, protein–protein receptor interactions, and the JAK-STAT pathway. Furthermore, current biologics predominantly inhibited classic T2 factors such as IL-4, IL-5, and IgE, there remained a lack of comprehensive research on factors like IL-6, IL-10, and IFN-γ, despite their significant involvement in asthma pathogenesis. Consequently, researchers were particularly intrigued by these inflammatory factors. This could effectively address existing knowledge gaps in the field.

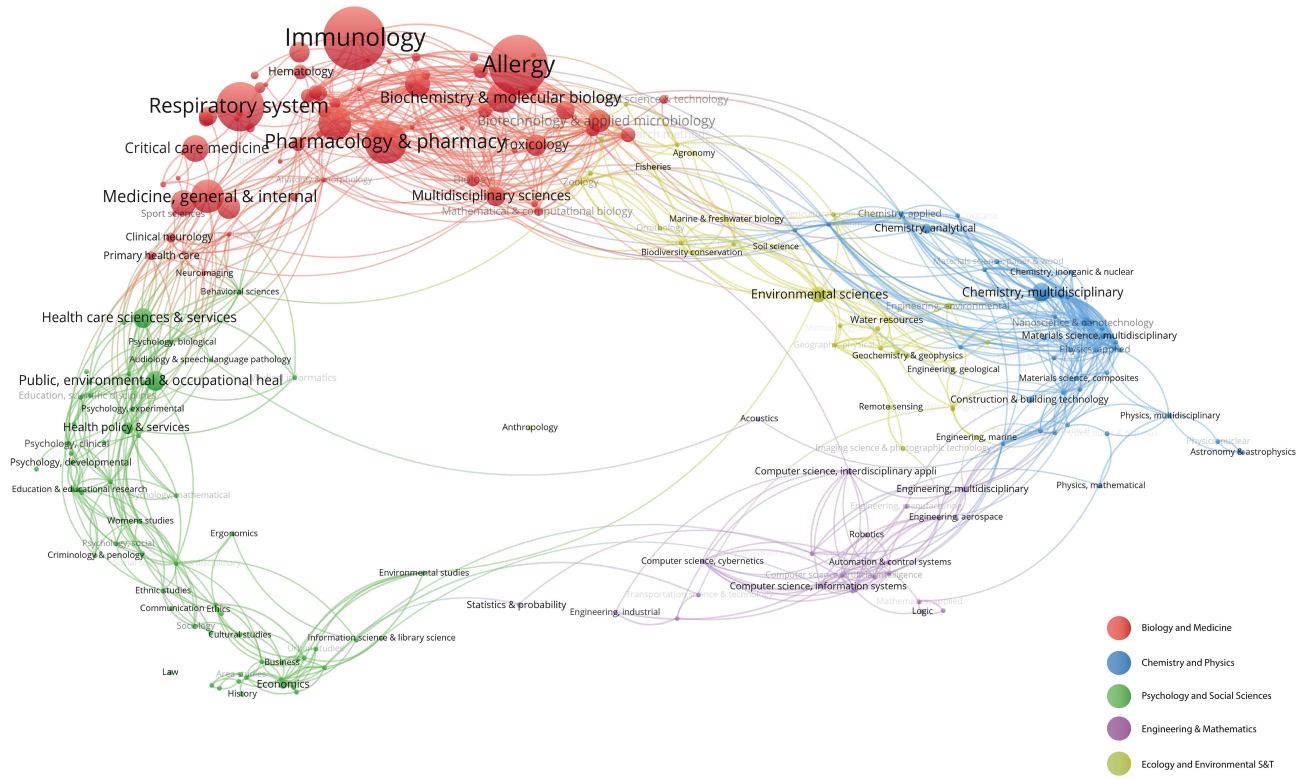


**Figure 4** The analysis of research fields. Generate statistical data regarding the 227 categories of papers acquired through a search in the Web of Science core collection database, and subsequently employ the VOSviewer software for visual analysis. The 3395 articles pertaining to research on biologics for asthma treatment are categorized into five primary fields.

# Discussion

Biologic therapies play an important role in treating asthma, especially when symptoms are not adequately controlled with traditional treatments. By selectively targeting various inflammatory pathways that are triggered by irritants such as allergens, these agents effectively impede the inflammatory response, resulting in improved control over the condition. Omalizumab,[18] the first biological agent approved for asthma treatment two decades ago, has inspired ongoing research and development of biologics that target various inflammatory factors of uncontrolled asthma. Subsequently, the approval of Mepolizumab,[19] Reslizumab,[20] Dupilumab,[21] Benralizumab,[22,23] and Tezepelumab[24] has further expanded the range of available treatment options (Table 2). Despite the existence of six biologics currently available in the market for asthma treatment, which have provided benefits to partial patients, a considerable number of individuals with asthma continue to experience challenges in symptom management due to an inadequate response to biologics. This may be attributed to the etiology of asthma, which is a heterogeneous disease. However, there are remaining questions about approved biologics:

## Can Biologics Change the Course of Asthma and Induce Complete Remission?

Most patients with asthma, unfortunately, need to apply controller medications in their lifetime, specially the patients with severe asthma, though there are 2–52% patients with mild asthma undergo remission.[25] The application of biologics in treatment has shifted the goal from controlling asthma to medication-free remission; however, there is currently no consensus on the criteria for clinical remission, and research institutions generally adopt a four domains comprehensive assessment: 1) annualized exacerbation rate, 2) daily long-term oral corticosteroid dose, 3) asthma control, 4) lung function.[26] An Italian multicenter cohort study (n=266) observed patients with severe eosinophilic asthma (SEA) who had received mepolizumab or benralizumab treatment for ≥12 months, defining clinical remission as: 1) no acute exacerbations within 12 months after discontinuation of treatment, 2) cessation of mOCS treatment, 3) Asthma


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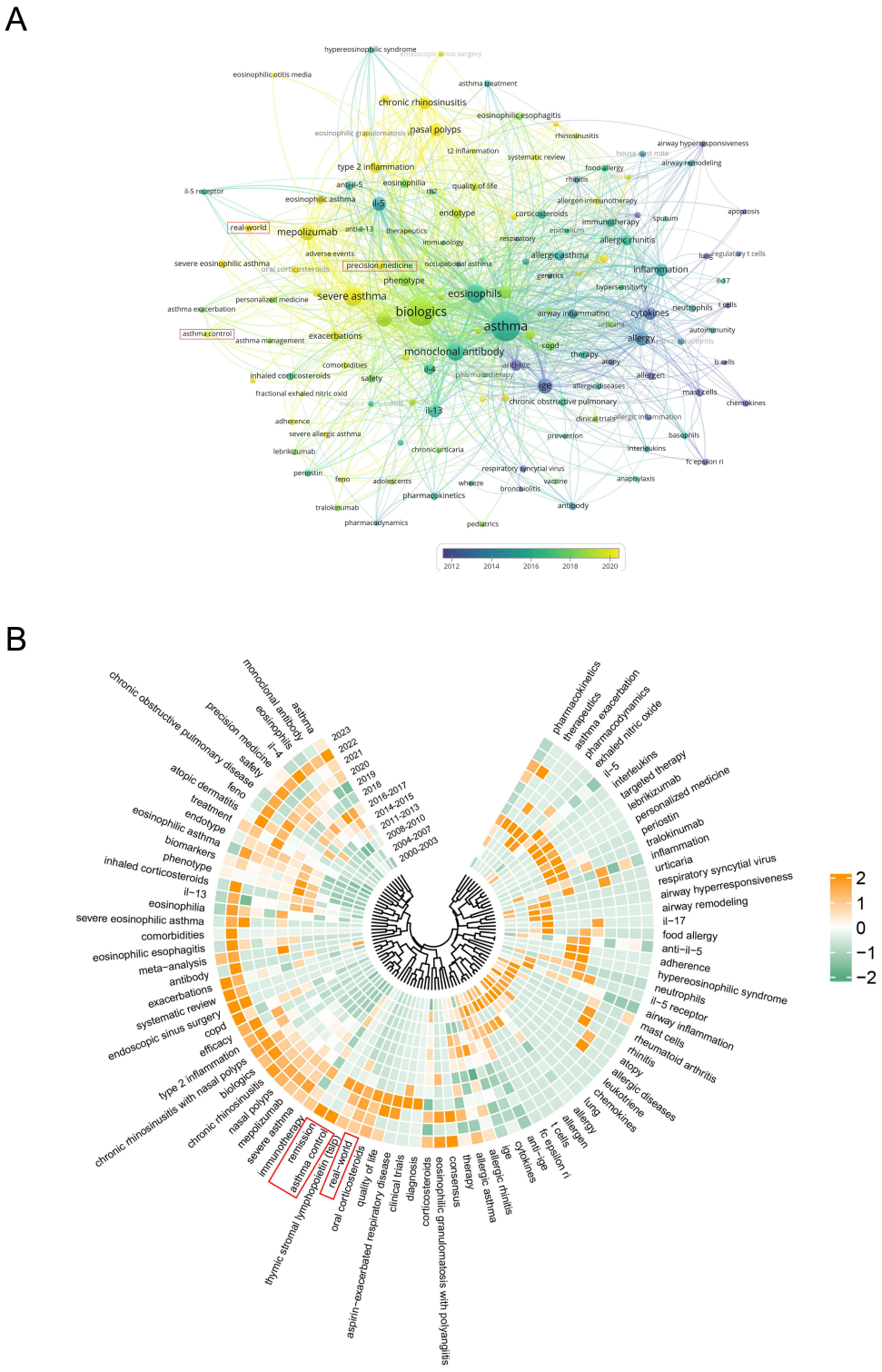


**Figure 5** The visual analysis in keywords. (**A**) The formation of a node consists of a circle and its corresponding label. The magnitude of the circle is positively correlated with the frequency of the keyword's occurrence. The chromaticity of each sphere represents the average year of occurrence, which is indicated by the color gradient located in the lower-right corner. Blue denotes keywords that emerged relatively early, while yellow signifies keywords that surfaced more recently. (**B**) A comprehensive examination of the keywords related to biological agents used for treating asthma treatment within the temporal span of 2000 to 2023 was conducted using heatmap analysis.

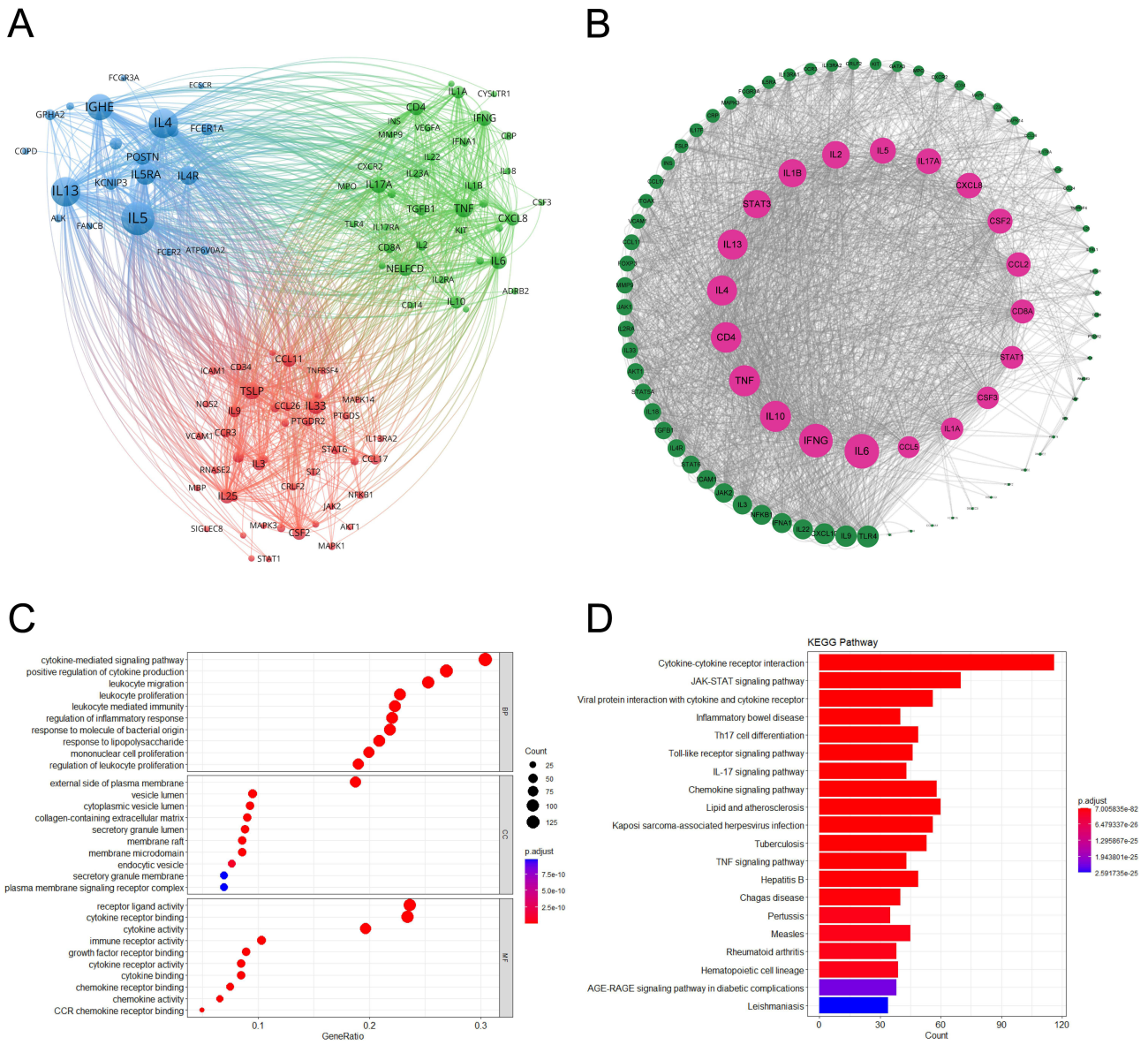


**Figure 6** The analysis of genes, pathways and proteins. (**A**) The VOSviewer software was employed to perform a co-occurrence cluster analysis of genes associated with biologics for the treatment of asthma. Each circle in the diagram represents a distinct gene, with the size of the circle denoting a positive correlation with the frequency of the gene. The thickness of the connecting lines between the circles is positively correlated with the strength of the relationship between the corresponding genes. Based on these correlations, the circles can be broadly categorized into three distinct groups, each represented by a different color. The red cluster, primarily composed of alarmins and signaling molecules, exhibits TSLP as the most prominent heat; the blue cluster, predominantly consisting of allergic cytokines, demonstrates IL5 as the highest heat; and the green cluster, primarily characterized by non-allergic cytokines, showcases TNF as the highest heat. (**B**) The top 100 proteins mentioned in the articles are extracted from CITEXS data platform and imported into the STRING platform for Protein-Protein Interaction (PPI) network construction and subsequent analysis. (**C**) The bubble chart utilized in the GO enrichment analysis visually represents each GO Term, with the size of each bubble indicating the number of genes associated with that particular function, and the color denoting the level of enrichment. The X-axis of the chart represents the GeneRatio value, while the Y-axis represents the classification or term of the GO Term. Each node within the chart corresponds to a distinct biological process, molecular function, or cellular component. (**D**) The KEGG pathway enrichment analysis identifies and prioritizes the top 20 signaling pathways, which are then visually represented in a figure. The X-axis of the figure denotes the number of genes that exhibit significant enrichment within each pathway, while the Y-axis represents the distinct signaling pathways.

Control Test (ACT) score ≥20, 4) forced expiratory volume in one second as a percentage of predicted (FEV1%) ≥80%. The study showed that 30.5% (81/266) of patients met this remission criterion.[27] A Danish nationwide cohort study (2016–2021) analyzed 501 patients with biologic therapy, and found an overall remission rate of 19% (97/501) using similar assessment criteria, with the highest remission rate of 30% in the anti-IL-4Ra monoclonal antibody (eg, dupilumab).[28] Notably, a British research team proposed differentiated remission criteria: 1) Asthma Control


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**Table 2** Biologics for the Treatment of Severe Asthma

| Target | Name | Indication | Administration & Dose |
|---|---|---|---|
| IgE | Omalizumab | Severe allergic asthma (IgE induced) | SC, 75 to 375 mg every 2 to 4 weeks according to weight and level of serum IgE |
| IL-5 | Mepolizumab | Severe eosinophilic asthma | SC, Ages>12 years: 100 mg every 4 weeks;<br>Ages 6–11 years: 40 mg every 4 weeks. |
| | Reslizumab | | IV, 3 mg/kg every 4 weeks. |
| IL-5R | Benralizumab | Severe eosinophilic asthma | SC, 30 mg every 4 weeks (first 3 dose), followed by 30 mg every 8 weeks. |
| IL-4Ra | Dupilumab | Severe eosinophilic asthma | SC, Ages>12 years: initial 400 mg, followed by 200 mg every 2 weeks;<br>Ages 6–11 years: according to weight. |
| TSLP | Tezepelumab | Severe asthma | SC, 210 mg every 4 weeks. |

**Abbreviations**: SC, subcutaneous injection; IV, intravenous injection.

Questionnaire (ACQ-5) score <1.5, 2) discontinuation of mOCS, 3) FEV1 above lower limit of normal (LLN) or no more than 100mL less than baseline, showing a remission rate of 18.3% in 1111 patients with severe asthma.[29]

The International Severe Asthma Registry (ISAR) integrated clinical data from 23 countries between 2017 and 2023 to construct three remission cutoffs: two domains: 0 exacerbations + no mOCS, three domains: 0 exacerbations + no mOCS + asthma control OR 0 exacerbations + no mOCS + percent predicted FEV1(ppFEV1)>80%, four domains: 0 exacerbations + no mOCS + asthma control + ppFEV1. The study showed a stepwise distribution of overall remission rates: four domains 20.3% (215/1059), three domains 25.8%-33.5%, two domains 50.2% (1076/2142). There were significant differences in remission rates among different biologic therapies: anti-IgE treatment 19.3%-55.1%, anti-IL-5/IL-5R treatment 20.6%-43.4%, anti-IL-4Ra treatment up to 22.6%-71%.[30]

Compared to the heterogeneity of remission criteria, predictive factors for remission have a higher degree of consistency. Multiple studies have shown that a shorter disease duration and higher baseline peripheral blood eosinophil count (BEC) strongly suggest a greater likelihood of patients achieving clinical remission. Other positive correlation factors include: low body mass index (BMI), lung function preserved, and fewer comorbidities.[27–31]

More importantly, researchers have all noted that earlier intervention with biologics for patients with severe asthma is a key to shorten the disease duration and better preserve lung function. However, currently, the use of biologics in the treatment of asthma is still the last expectation.

## Should Biological Therapy Be Exclusively Limited to Patients with Uncontrolled Symptoms of Severe Asthma?

Individuals with mild to moderate asthma may experience recurrent airway inflammation and repeated activation of airway immunity as a consequence of unforeseen circumstances beyond their control. This can lead to enduring and/or recurrent immune impairment, as well as symptoms associated with the pathological condition of reduced lung function known as airway remodeling. Despite successful management of symptoms and inflammation, the reversal of airway tissue remodeling remains challenging.[32] The utilization of biologics has shown potential in achieving partial, long-term control of inflammation and allergy levels, thereby reducing the frequency of acute asthma attacks.[33] Therefore, the administration of biologics in the early stages of asthma (eg, mild-to-moderate asthma) to block the allergen-triggered inflammatory cascade may potentially reduce irreversible airway injury caused by recurrent inflammatory insults and possibly even mitigate the development of airway remodeling. However, the hypothesis needs to be confirmed by the comprehensive analysis of clinical and laboratory data in the future.

## How Can We Strategize the Optimal Biologics Treatment for Patients with Severe Asthma, Especially Those with T2-Low Severe Asthma?

According to prevailing clinical protocols, the preferred therapeutic interventions for individuals afflicted with severe asthma characterized by airway obstruction and predominantly eosinophil-mediated asthma severity are anti-IL-5 monoclonal antibodies, such as Benralizumab, Mepolizumab, and Reslizumab.[20,34–36] Dupilumab, an anti-IL-4R

monoclonal antibody, may be considered as the optimal therapeutic option for individuals whose airway obstruction and severity are potentially influenced by factors such as mucus hypersecretion, eosinophil activation, smooth muscle contraction, or airway remodeling.[37] In cases where asthma is evidently triggered by allergens, rather than solely elevated IgE levels, the preferred treatment is anti-IgE therapy utilizing Omalizumab.[38] For patients demonstrating suboptimal response to anti-IgE therapy with significantly elevated baseline eosinophil counts (EOS ≥300 cells/μL), switching to anti-IL-5/5R therapy has demonstrated substantial clinical benefits. This therapeutic shift achieves an 81–90% reduction in annual acute exacerbation rates, accompanied by statistically significant improvements in both FEV1 measurements and Asthma Control Test (ACT) scores. Notably, multiple researches indicated that Benralizumab has a unique advantage in regulating eosinophil levels due to its unique mechanism of action that induces eosinophil apoptosis.[31,39] Furthermore, clinical observations reveal that patients presenting with elevated baseline fractional exhaled nitric oxide levels (FeNO ≥25 ppb) derive enhanced therapeutic benefits when transitioning to anti-IL-4Ra monoclonal antibody therapy (dupilumab).[39]

While, there were several patients with uncontrolled asthma that could not be alleviated by a single biologic agent. Recently, the combined use of two biologics, Omalizumab and Mepolizumab, to treat such patients showed its efficacy in some cases.[40,41] And, the novel bispecific antibodies, such as anti-IL-4Rα/IL-5[42] or anti-TSLP/IL-13,[43] were brought out by researchers. The IL-4Rα/IL-5-bispecific antibody exhibited its efficacy that inhibited goblet cell metaplasia and airway hyperresponsiveness (AHR) in a murine house dust mite (HDM) model of asthma. Nevertheless, further investigation is still required to determine the effectiveness of the anti-TSLP/IL-13 bispecific antibody. After all, the combination use of biologics and the bispecific antibody still remains a promising direction for the future treatment of uncontrolled asthma.

As the understanding of the fundamental pathogenesis of T2-high asthma has been extensively investigated, an increasing number of researchers are now directing their efforts towards the exploration of T2-low asthma. T2-low asthma is characterized by neutrophilic, paucigranulocytic, or mixed airway inflammation and is associated with adult asthma, obesity, metabolic syndrome, hypertension, and decreased sensitivity to glucocorticoid treatment.[44] Currently, there is an urgent need to clarify the pathophysiological characteristics of T2-low asthma. Numerous experiments have demonstrated the involvement of various factors, including interleukin-6 (IL-6), CXC motif chemokine ligand 8 (CXCL8), IL-17A, IL-23, IFN-γ, tumor necrosis factor α (TNF-α), IL-33, and thymic stromal lymphopoietin (TSLP), in this mechanism.[45] However, there is currently a lack of biologics specifically designed to treat severe asthma with low T2 inflammation. Among the available biologics, Tezepelumab is a monoclonal antibody that targets TSLP, which is an alarmin involved in the inflammatory response. This medication has the ability to decrease the levels of T2 inflammation markers such as IgE and FeNO, and its efficacy is not influenced by the baseline levels of blood eosinophils.[24,46] This is due to the fact that TSLP plays a role upstream in T2 inflammation.[5,47] Meanwhile, a recent study showed that Astegolimab, an monoclonal antibody specifically targets the IL-33 receptor ST2 to inhibit IL-33 signaling, exhibited noteworthy outcomes in a double-blind, placebo-controlled, dose-ranging clinical trial, even among patients with low blood eosinophil count (BEC). This study demonstrated a substantial decrease in response rates, suggesting its potential suitability for asthma patients exhibiting low T2 biomarkers.[48] Therefore, targeting the upstream of asthma inflammation and inhibiting the activation of epithelial alarmins may be the direction to solve severe asthma with low T2.

## What Is the Most Optimal Approach for the Administration of Biologics?

To the best of our knowledge, the prevailing modes of administration for biologics primarily involve subcutaneous delivery. The exception is Reslizumab, which is administered intravenously.[20,49] It is evident that both of these delivery methods possess systemic characteristics, thereby raising concerns regarding their alignment with our intended objective. Given that the target site resides within the lungs or airways, systemic administration necessitates careful deliberation on the local concentration at the specific location and potential adverse effects. Consequently, it becomes imperative to further investigate the necessity of altering the administration route to exclusively target the organ of interest with the biological agent. Currently, certain researchers have directed their attention towards the development of inhaled antibody therapies that specifically target IL-13, yielding initial findings,[50,51] though another anti-IL-13 mab, GSK679586, showed no clinically meaningful improvements in severe asthma in a randomized trial.[52] On the other hand, apart from

considering the route of administration, it is imperative to explore deeper into the investigation of drug carriers in order to enhance the efficacy. Within the realm of material science, there exist carrier technologies, such as nano particles and liposomes, which exhibit the potential to enhance the efficiency of drug absorption.[53–55] When coupled with the mentioned airway spray delivery method, these carrier technologies hold the promise of augmenting the therapeutic efficacy of locally administered monoclonal antibody therapy for asthma. Therefore, with regard to alternative administration of biologics, more investigations should be conducted by researchers in the future.

As we seen, Europeans and Americans exhibit the highest level of investment in the research of biologics for treating asthma (Figure 2B), large-scale research centers in Europe and the United States have established registry databases for asthma patients, through which statistical analysis of clinical data enables real-world evaluation of therapeutic effectiveness. The resultant evidence facilitates guideline updates, standardization of clinical practices, and advancement of long-term disease management and prognostic research. Based on the data, the prevalence of asthma is significantly higher in developed countries than in developing countries. However, it is important to acknowledge that the global prevalence of asthma is progressively increasing. This trend cannot be solely attributed to the increasing number of asthma patients in developed countries. Notably, the surge in asthma patients in developing countries, such as China, India, and others. A recent study investigating trends in asthma disease burden across Belt and Road countries revealed that China and India continue to bear disproportionately high asthma case numbers. Despite demonstrating declining age-standardized prevalence rates in both nations, China and India ranked second and first globally in absolute asthma patient counts, respectively. This phenomenon stems primarily from their substantial population bases, with contributing factors diverging between countries: population aging in China and systemic healthcare inadequacies in India.[56]

## The Limitations of Biologics in the Treatment of Severe Asthma in Children

Current biologics for asthma treatment are applicable to adults and adolescents aged ≥12 years, with selection guided by biomarkers (eg, BEC, serum IgE levels) and asthma phenotypes.[57] Despite two decades of research on biological agents for adults and adolescents, clinical investigations in children <12 years remain substantially delayed. To date, only three biologics (omalizumab, mepolizumab, and dupilumab) have been approved for severe asthma management in children aged 6–11 years.[58] Pediatric asthma exhibits high phenotypic heterogeneity, necessitating biomarker-integrated selection of biologics. However, the absence of definitive guidelines for childhood asthma phenotypes, particularly in patients <6 years, and the lack of reliable biomarkers for treatment response prediction have resulted in therapeutic decisions based on limited clinical evidence rather than precise indicators.[58,59]

Furthermore, the scarcity of safety and efficacy data for biologic therapies in younger children (<6 years) persists despite high disease prevalence.[57,60,61] This knowledge gap is partially attributable to the dynamic complexity of immune system maturation during childhood. Significant developmental changes occur in immune cell composition: CD4+ T cells, memory B cells, and NK cells progressively increase to peak levels between ages 5–9 years, while regulatory T cell populations dominant in infancy decline proportionally. This reflects the immune system's transitional process from an "infection-priority" state to a balanced defense-tolerance equilibrium.[62,63] The unpredictable consequences of directly modulating immune responses through biologics during this critical developmental window present substantial challenges in obtaining essential clinical data, further contributing to current evidence limitations.

This article presents a comprehensive bibliometric analysis, drawing upon papers from the past two decades, for examination of biologics in asthma treatment. Additionally, we investigate the functional proteins and signaling pathways that are currently under scrutiny, while offering a comprehensive overview of existing biologics. The objective is to establish a solid foundation for ongoing research and provide potential avenues for future exploration by subsequent researchers. However, this article exhibits several limitations attributed to multiple factors. Firstly, it relies solely on the analysis of existing experimental findings, thereby neglecting potential mechanisms that remain unexplored but hold higher plausibility. Despite extensive historical research and advancements in utilizing monoclonal antibodies to inhibit specific targets in T2 high asthma, the underlying pathogenesis of this condition necessitates further investigation. The identification of relevant targets in T2 low asthma remains elusive, highlighting the imperative need to identify potential avenues for future research and conduct comprehensive studies. Secondly, it is noteworthy that this article provides limited guidance pertaining to the direction of basic experiments. The prevailing papers concerning the therapeutic

management of asthma through the employment of biologics predominantly comprise clinical research, with a few basic researches. Consequently, this article endeavors to scrutinize the genes, signaling pathways, and associated literature encompassed within the retrieved sources. By conducting enrichment and interaction network analyses of proteins, the aim is to consolidate extant experimental findings and identify potential mechanisms that have yet to be explored. Lastly, the analysis findings of this article are constrained by temporal limitations. The bibliometric analysis encompassed articles published within a timeframe from January 1, 2000, to September 30, 2023, pertaining to the use of biologics for treating asthma. Biologics have garnered increasing attention, particularly in recent years, resulting in a steady growth of related literature. The outcomes presented in this article solely reflect the prevailing perspectives derived from the analysis of preceding literature. Consequently, as subsequent research findings emerge, certain analysis results may deviate from subsequent realities, necessitating cautious discernment by readers.

## Conclusion

In summary, biologics represent a promising therapy for the management of asthma in clinical settings. These medications offer a ray of hope for individuals with inadequately controlled symptoms, while also presenting extensive research opportunities. The current population of asthma patients eligible for biologics primarily consists of individuals with uncontrolled, T2-high, and severe asthma. However, as research progresses and multiple-action targets are explored, severe asthma with T2-low has drawn attention from researchers, and a few targets have already been validated. Consequently, in the future, it is possible that more biologics will likely become accessible, offering additional treatment alternatives for asthma patients, even those symptoms are not well controlled, and asthma is expected to achieve remission by biologics.

## Abbreviation

TSLP, thymic stromal lymphopoietin; IL, interleukin; IgE, IGHE, immunoglobulin E; ICS, inhaled corticosteroids; FeNO, Fractional exhaled nitric oxide; AHR, airway hyperresponsiveness; GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; PPI, Protein–Protein Interaction; BP, biological processes; MF, molecular functions; CC, cellular components; CXCL8, CXC motif chemokine ligand 8; IFN-γ, interferon-γ; TNF-α, tumor necrosis factor α; BEC, blood eosinophil count; AER, annualized exacerbation rate; mAb, monoclonal antibody; HDM, house dust mites.

## Highlight

- Summarize the characteristics of the papers on biologics for the treatment of asthma in the past two decades.
- Summarize the inflammatory factors and pathways involved in the current biologics used to treat asthma.
- Discuss the future research directions of biologics used in the treatment of asthma.

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