Eosinophilic and Allergic Asthma Phenotype and Therapeutic Possibilities

5.3

Ljiljana Bulat Kardum[1,2]

Abstract

Despite optimal treatment according to GINA guidelines, some patients with asthma have an uncontrolled, severe disease with significantly reduced lung function, an increased risk of exacerbations and disproportionate use of asthma-related health resources. The identification of specific phenotypes of asthma with unique pathophysiologic mechanisms such as T2-high and T2-low immunological pathways and clinical characteristics enabled the discovery of new and more effective treatments for severe asthma. The emergence of novel biologic treatments, including monoclonal antibodies as anti-IgE, anti IL-5/anti IL-5Rα and anti IL-4/IL-13 are has led to an enhanced understanding of the pathogenesis of asthma and highlighted the importance of patient-specific treatment dependent on phenotypic characteristics.

Keywords: severe asthma, phenotypes, T2 asthma, non-T2 asthma, biologic treatment, anti-IgE, anti IL-5/anti IL-5Rα, anti IL-4/IL-13

1 Clinic of Internal Medicine, Clinical Hospital Centre Rijeka, Rijeka, Croatia

2 Faculty of Medicine, University of Rijeka, Rijeka, Croatia

More than 300 million people worldwide suffer from asthma and it is estimated that 400 million people will suffer from asthma by 2025. It is present in all regions of the world regardless of their socioeconomic level, although its prevalence varies. In the United States, the prevalence of asthma is 7.6% and 8.4% for adults and children, respectively; in the European Union the prevalence is about 8.2% and 9.4%, respectively.[1,2,3] Most patients can achieve good disease control and a satisfactory quality of life with conventional treatment according to international guidelines such as the Global Asthma Initiative (GINA)[3].

How Common is Severe Asthma?

Despite optimal treatment, some patients with asthma have uncontrolled severe asthma with an increased risk of exacerbations and overuse of asthma-related health resources including frequent hospital care and significantly reduced lung function with a risk of further deterioration over time.[3] In this group of patients, it is necessary to identify those who manifest uncontrolled asthma and in whom accurate diagnosis or adequate treatment will significantly improve the current control of the disease ("difficult-to-treat asthma"). It is estimated that about 24% of asthma patients have GINA treatment of 4th or 5th step, 17% of all asthma patients have "difficult to treat asthma", while 3.7% of asthma patients have severe asthma.[4]. The systematic review of 195 articles reporting on severe asthma studies found the prevalence of severe uncontrolled asthma to be as high as 87.4%.[5]

https://doi.org/10.26493/978-961-293-157-5.115-123

Evolving Concepts of Severe Asthma: Personalized Asthma Management

Asthma is a complex respiratory disorder characterized by pronounced heterogeneity in disease triggers and individual responses to therapy. It is a heterogeneous disease with different phenotypic characteristics that arise from the complex interrelationship of genotypic characteristics and environmental factors. Therefore, a standard therapeutic approach is not as effective as unique pathophysiological mechanisms underlying a particular disease subtype which alter the response to conventional therapy.[8-10]

Severe asthma is defined as an asthma that requires treatment of level 4 or 5 according to GINA guidelines (high doses of ICS/LABA and/or tiotropium, leukotrienes or theophylline) in the previous year or treatment with systemic corticosteroids (CS) 50% of the previous year to prevent the development of "uncontrolled" disease or it remains uncontrolled despite this therapy. The next therapeutic step is to consider the indication for biological therapy, while oral corticosteroids according to the latest GINA guidelines revision are a backup therapeutic option to consider.[3,9]

Treating asthma with biological agents is the first step towards personalized therapy. Such approach is made possible by an increase in the understanding of the pathophysiological pathways in asthma and paved the way for new asthma treatments based mainly on T2-high pathway cytokines and associated certain phenotypes of severe asthma. Therefore, with the help of better identification of asthma phenotypes, we can select an effective targeted therapy (biological) that will allow us to achieve disease control in patients with severe asthma, in whom standard therapy has not been effective.[10-13]

Two Different Pathways Lead to Eosinophilic Airway Inflammation in Asthma

In the same time as the recognition of phenotypes of severe asthma, new knowledge about the pathophysiological and inflammatory mechanisms in asthma has advanced, which has further contributed to the differentiation of certain phenotypes and endotypes of asthma.[13] Two separate pathophysiological pathways cause eosinophilic inflammation in asthma:

1. In *allergic asthma*, dendritic cells after a contact with the allergen as well as alarmins IL-25, IL-33 and thymic stromal lymphopoietin (TSLP) from exposed epithelial cells of the airway mucosa, present antigen to Th0-naive CD4 + lymphocytes and induce their transformation into activated Th2 cells, which produce IL-4, IL-5 and IL -13. In this process, B lymphocytes were also activated to produce IgE antibodies, airway eosinophilia, and hypersecretion of mucus.[13-15]
2. In *nonallergic eosinophilic asthma*, air pollution, microbes, and glycolipids induce the release of cytokines from epithelial cells, including alarmins IL-25, IL-33 and TSLP, which activate naive lymphoid cells (ILC2) in an antigen-independent manner. Activated ILC2 cells produce high amounts of IL-5 and IL-13 causing eosinophilia, mucosal hypersecretion and airway hyperreactivity. The importance of Th2 lymphocytes in this process was highlighted through the cytokines IL-4, IL-5 and IL-13 involved in eosinophilic inflammation and IgE production, in an asthma phenotype called T2-asthma (T2-high asthma).[15-17]

Th17 cells with cytokines IL-17, IL-8 and growth factor participate in neutrophilic inflammation in non-T2 asthma (T2-low asthma).[14]

Implications of T2-High and T2-Low Pathway on Asthma Phenotypes

Several strategies have been proposed for the identification of severe asthma phenotypes, based on different clinical characteristics or

in relation to the types of cellular airway infiltration. Although the stratification of asthma phenotypes by blood eosinophils is relatively easy, it does not allow a deeper/more detailed identification of clinical phenotypes. Therefore, cluster analysis is used to identify groups of patients with asthma who share specific clinical characteristics, e.g., cluster analysis using clinical characteristics of patients such as asthma onset age, lung function value, bronchodilator reversibility and demographics. The Severe Asthma Research Program (SARP) identified five clinical groups of asthma in adults, in which four groups showed eosinophilia of varying degrees.[18]

In order to identify severe asthma phenotypes, ADEPT study[19] was conducted and identified four clusters of asthma, which were also present in the UBIOPRED study.[20] Three of these four asthma clusters were associated with eosinophilia.

In the evolution of knowledge of clinical phenotypes, Saly Wenzel and her co-workers have made a definition as follows: early-onset allergic, late-onset eosinophilic and exercise-induced phenotype, all identified by biomarkers of Th2 asthma; and three phenotypes of non-Th2 asthma, obesity- related, neutrophilic and asthma in smokers. No biomarkers of non-Th2 asthma have been identified so far as a basis for new biologics and markers of a positive response to that treatment.[21,15] This is due to the lack of knowledge of the non-T2-High (T2-Low) immune response associated with the activation of Th1 and/or Th17 cells and IL-17, IL-8 cytokines and the mechanisms underlying the recruitment and maintenance of neutrophilic inflammation.[22]

Biological Agents Targeting Airway Inflammation in Asthma: The Rational Choice

Biomarkers can warn of the severity of the disease and predict the response to a particular treatment. Some of the biomarkers, alone or in combination, will be useful in identifying patients for targeted type 2 asthma treatment. Blood eosinophils due to its high predictive value of ≥300/μL is used as an initial biomarker to predict treatment responses targeting IL-4, IL-5, and IL-13.[15,23]

Consistent with its central role in the development of allergic asthma, serum value of IgE is a good biomarker of an atopic status. Serum IgE levels are positively correlated with the severity of asthma in adults and children. Serum total IgE is used to predict responses to anti-IgE therapy, but is not useful for monitoring responses.[15,24]

The role of periostin and FENO in tailoring the biologic therapy targeting type 2 asthma is less clear. Periostin is an extracellular matrix protein secreted from IL-4 and IL-13-induced airway epithelial cells, but has not been shown to be a good biomarker in routine use. Changes in FENO after dupilumab therapy (anti IL-13/IL-4) correlate well with improvement in FEV1.[25-27]

Allergic and Eosinophilic Asthma Phenotype

The decision to choose biological therapy is preceded by a process of asthma phenotyping based on the identification of clinical characteristics and driving mechanisms of inflammation. Biomarkers help us in the rational choice of biological and predict a positive response of patients to the selected treatment:

1. The "Early-onset allergic asthma" phenotype usually begins before the age of 12. Triggers are allergens and other allergic diseases, and/or a positive family history is associated too. Specific biomarkers are elevated total IgE, specific IgE and cytokines of T2 inflammation.[9,10,13, 21]
2. In the "Late-onset persistent eosinophilic asthma" phenotype, symptoms begin in adulthood, often are associated with chronic sinusitis and nasal polyposis. Biomarkers of this phenotype are elevated eosinophils of peripheral blood and

sputum. In some patients, "aspirin exacerbated respiratory disease" is also present.[21,28,29]

While IgE is involved early in the inflammatory cascade and can be considered a cause of allergic asthma, eosinophilia can be considered a consequence of the whole process. Hence the different roles of the IgE pathway and the IL-5 eosinophil pathway in the pathogenic mechanisms of airway inflammation occurring in asthma, and thus the reason for choosing anti-IgE monoclonal antibody or anti-IL-5/IL-5Rα treatment.[30]

Mechanisms of Action of Anti-IgE Treatment in Allergic Asthma Phenotype

Omalizumab is an anti-IgE treatment. It binds to free IgE and thus reduces the binding of IgE to mast cells, basophils and eosinophils. In addition, omalizumab reduces the expression of high-affinity FcεRI receptors for IgE on these cells, thereby further reducing IgE binding to them. This reduces the release of mediators from the cells, reduces allergic inflammation, prevents the exacerbation of asthma and reduces symptoms.[31,32] Omalizumab is indicated for adults and children over six years of age with uncontrolled moderate to severe allergic asthma with elevated total IgE antibodies, a positive skin allergy test, or specific IgE antibodies to perennial allergens.[33A]

Omalizumab statistically significantly reduced daily symptoms, reduced exacerbations, and the dose of inhaled corticosteroids. Omalizumab has improved asthma control and reduced the need for other asthma medications. All these effects are visible after 12 weeks of therapy.[32,34,35] In the STELLAIR study, the rate of exacerbation reduction was similar in patients with severe allergic asthma with high (≥ 300 cells/μL) and low (< 300 cells/μL) eosinophils. Patients with higher serum IgE levels, shorter disease duration and higher blood eosinophils may benefit from delayed omalizumab therapy.[33,36]

Mechanism of Action of Anti IL-5/Anti IL-5Rα and Anti IL-4/IL-13 Treatments in Eosinophilic Asthma Phenotype

IL-5 is a key factor in the eosinophil maturation, mediates eosinophil mobilisation, activation and survival. It achieves its effects by binding to a specific subunit of the IL-5 receptor, which is IL-5Rα. The IL-5Rα subunit binds only IL-5. Eosinophils express up to three times more IL-5Rα on their cell membrane than basophils. Th2 cells, mast cells, innate lymphoid cells (ILC 2), CD34 + progenitor cells, natural killer (NK) T cells and eosinophils themselves are the main cellular source of IL-5[37] Therefore, targeting IL-5 or IL-5Rα is a logical approach to treat patients with severe eosinophilic asthma.

Two different anti-IL-5 monoclonal antibodies, mepolizumab and reslizumab, bind to different epitopes of IL-5 by interfering with its binding to IL-5R expressed on the eosinophil membrane by reducing the IL-5 signaling pathway that impairs eosinophil maturation and survival.

Mepolizumab is a humanized monoclonal IgG4 antibody, administered subcutaneously at a dose of 100 mg every 4 weeks. Criteria for introducing mepolizumab into treatment are: forced expiratory volume in 1 second (FEV1) less than 80% of predicted value, at least two exacerbations of asthma in the previous year treated with systemic glucocorticoids while the patient was treated with high doses of inhaled corticosteroids with a long-acting beta2-agonist, and at least with an additional controller and an eosinophil count of at least 150 cells per microliter in peripheral blood at screening or at least 300 cells per microliter at some point during the previous year. Mepolizumab reduces the rate of exacerbations by 53% compared to placebo (P<0.001), reduces exacerbations requiring an emergency visit and hospitalization

by 61%. It also improves the quality of life and lung function, which is reflected in the average increase in FEV1 compared to placebo (P=0.03).[33,34,38]

Reslizumab is also a humanized monoclonal IgG4 antibody, administered intravenously at a dose of 3 mg/kg body weight every four weeks. Reslizumab is indicated in patients with uncontrolled severe asthma despite treatment with high doses of inhaled corticosteroids with a long-acting beta2-agonist, with the addition of one or more controllers and/or with additional OCS therapy. The blood eosinophil counts of ≥150 cells/μL at screening or ≥ 300 cells/μL within 12 months prior to treatment of ≥300 cells/μl i had to be present. Reslizumab reduces the incidence of asthma exacerbations compared to those receiving placebo, In two studies of Castro et al, patients receiving reslizumab had a significant reduction in the frequency of asthma exacerbations - in study 1. exacerbation rate was reduced by 50%; in study 2 exacerbation rate reduced by 59%; both p<0·0001) compared with those receiving placebo. Lung function (FEV1) , asthma control (ACQ) and quality of life (AQLQ) have been improved over placebo.[32-34,39]

Benralizumab has a dual effect: it is a blocker of the IL-5Rα receptor on the eosinophil membrane and thus prevents the binding of activated IL-5, while binding NK cells that cause accelerated eosinophil apoptosis. This effect is associated with a rapid reduction in eosinophilia in the blood. It is administered subcutaneously at a dose of 30 mg every four weeks for the first three doses and then every eight weeks. Benralizumab significantly reduced asthma exacerbations and consequently progressively reduced daily OCS intake, improved ACT questionnaire value and an increase in lung function.[33,34,40]. Benralizumab is indicated in patients 12 years or older and in adults with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus long-acting β-agonists, with baseline blood eosinophil counts ≥300 cells/μL.

Dupilumab is the only biologic that has dual inhibitory activity; inhibits the signaling pathways of IL-4 and IL-13 by blocking the alpha chain of the IL-4 receptor, thus acting on two separate pathophysiological pathways cause eosinophilic inflammation in asthma:allergic and non-alergic eosinophilic patways. So, effects are not limited to those patients who have eosinophilia[28]. Dupilumab improved lung function and reduced severe exacerbations in patients with an uncontrolled severe asthma, regardless of the initial number of eosinophils and had a favorable safety profile, and therefore with inhaled corticosteroids and long-term therapy with β2-agonists could improve the life of patients with uncontrolled asthma in standard treatment.[34,41,42] Therefore, dupilumab is indicated in adults and adolescents 12 years and older with severe asthma characterised by blood eosinophil count of >150 cells/μL and/or raised fraction of exhaled nitric oxide (FeNO) >25 ppb, inadequately controlled with high dose ICS and one of more controlers.

Looking into the Near Future: Anti-epithelial Cytokine Antibodies

The epithelial cytokines: thymic stromal lymphopoietin (TSLP), IL-25 and IL-33 are released from the airway epithelium in response to allergens, air pollution, and viruses triggering an inflammatory cascade in asthma. It has been hypothesized that the blockade of these cytokines, compared with biological agents aimed at T2-inflammation, could improve severe asthma outcomes in a much wider patient population. The results of recent RCTs have shown the efficiency of tezepelumab, a human monoclonal antibody which targets TSLP; itepekimab, an anti IL-33 human monoclonal antibody; and astegolimab, a human monoclonal antibody with an IL-33 receptor blockade effect in patients with severe asthma.[45-48]

In phase 3, RCT tezepelumab as add-one therapy in uncontrolled severe asthma at a dose of 230 mg administered subcutaneously every 4 weeks in adolescents and adults, has reduced the annual exacerbation rate by 56%, and among patients with blood eosinophil counts less than 300 cells/μL reduced exacerbation rate by 41%. In addition, tezepelumab has improved lung function, asthma control and the quality of life in the T2-high asthma group, but also in the T2-low asthma group. A rapid decline in blood eosinophil counts, a decrease in FeNO, a gradual reduction in serum total IgE and a reduction in bronchial hyperreactivity were observed. Safety profile of tezepelumab was similar to placebo.[45,46]

Itepekimab (anti IL-33) in phase 2 RCT at a dose of 300 mg sc every 2 weeks has reduced exacerbations and improved lung function in patients with moderate to severe uncontrolled asthma[45,47], while astegolimab (anti IL-33R) in phase 2 RCT was administered subcutaneously every 4 weeks in patients with severe asthma, including those with low peripheral blood eosinophils, reduced the rate of exacerbations, but did not improve lung function.[45,48] Positive results of phase 3 RCTs of monoclonal antibodies efficacy against epithelial cytokines are expected, especially for T2-low asthma.

Numerous elements contribute to the response to biologic treatment and individual patient responses will vary. The monitoring of lung function, the presence of symptoms, number of exacerbations and quality of life may help in early clinical assessment of response to treatment. Identifying patients with a therapeutic response and those who do not respond to biologic therapy is not easy. Suggested approach to the treatment of severe asthma beyond standard therapies involves the treatment omalizumab in case of elevated IgE and positive perennial antigen. After 4-6 months, an assessment follows and if treatment has no effect, switch to anti-IL-5 therapy in those patients with elevated eosinophils while IgE is in the reference values. If there is no effect of IL-5 therapy, bronchial thermoplasty should be considered as in those patients with low IgE and low eosinophils.[22] Patients who have an intermediate response to therapy either need to continue treatment for one year to assess response or consider switching to alternative biologic therapy if a therapeutic effect is absent. Clinical experience and new research may identify a panel of new biomarkers that will better predict a positive response to biological therapy and facilitate our therapeutic option.[43]

Unfortunately, none of the biological agents can meet the needs of patients whose asthma is not mediated by a T2 response (T2-low asthma). Due to our limited understanding of the immune response of in T2 low asthma, our therapeutic options are very limited and are a reflection of unmet needs in severe uncontrolled asthma.[22,44]

References

1. Data, statistics, and surveillance [Internet]. Atlanta, GA: Centers for Disease Control and Prevention; [updated 2021 Sep 16]. Available from: https://www.cdc.gov/asthma/asthmadata.htm.
2. Respiratory disease statistics [Internet]. Eurostat. Available from: http://ec.europa.eu/eurostat/statisticsexplained/index.php/Respiratory_diseases_statistics/.
3. Global Initiative for Asthma [Internet]. GINA; c2022. Available from: http://ginasthma.org/.
4. Hekking PP, Reinier RW, Amelink M, et al. The prevalence of severe refractory asthma. J Allergy Clin Immunol. 2015 Apr;135(4):896-902.
5. Chen S ,Golam S, Myers J, et al. Systematic literature review of the clinical, humanistic, and economic burden associated with asthma uncontrolled by GINA Steps 4 or 5 treatment. Curr

Med Res Opin. 2018 Dec;34(12):2075-88.
6. Varsano S, Segev D, Shitrit D. Severe and non-severe asthma in the community: A large electronic database analysis. Respir Med. 2017 Feb;123:131-9.
7. Wang E, Wechsler ME, Tran TN, et al. Characterization of Severe Asthma Worldwide: Data From the International Severe Asthma Registry. Chest. 2020 Apr; 157(4):790-804.
8. Skloot, GS. Asthma phenotypes and endotypes: a personalized approach to treatment. Curr Opin Pulm Med. 2016 Jan;22(1):3-9.
9. Chung KF, Wenze SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J. 2014 Feb;43(2):343-73.
10. Asthma: diagnosis, monitoring and chronic asthma management; NICE guideline [nternet]. NICE; 2017 Nov 26 [updated 2021 Mar 22]. Available from: https://www.nice.org.uk/guidance/ng80.
11. Schleicha F, Brusselleb G, Louisa R, et al. Heterogeneity of phenotypes in severe asthmatics. The Belgian Severe Asthma Registry (BSAR). Respir Med. 2014 Dec;108(12):1723-32.
12. Buhl R, Marc Humbert M, Bjermer L, et al. Severe eosinophilic asthma: a roadmap to consensus. ERJ Opens Res. 2017 May 1;49(5):1700634. doi: 10.1183/13993003.00634-2017.
13. Chung KF. Asthma phenotyping: a necessity for improved therapeutic precision and new targeted therapies. J Intern Med. 2016 Feb;279(2):192-204.
14. Fahy JV. Type 2 inflammation in asthma – present in most, absent in many. Nat Rev Immunol. 2015 Jan;15(1):57-65.
15. Tara F. Carr TF, Zeki AA, et al. Eosinophilic and Noneosinophilic Asthma. Am J Respir Crit Care Med. 2018 Jan 1;197(1):22-37.
16. F Schleicha, G Brusselleb, R Louisa, et al. Heterogeneity of phenotypes in severe asthmatics. The Belgian Severe Asthma Registry (BSAR). Respir Med. 2014 Dec;108(12):1723-32.
17. de Groot JC, ten Brinke A, Bel E. Management of the patient with eosinophilic asthma: a new era begins. ERJ Open Res. 2015 Sep 23;1(1):00024-2015. doi: 10.1183/23120541.00024-2015.
18. Teague WG, Phillips BR, Fahy JV, et al. Baseline Features of the Severe Asthma Research Program (SARP III) Cohort: Differences with Age. Allergy Clin Immunol Pract. 2018 Mar-Apr;6(2):545-54.e4.
19. Silkoff PE, Laviolette M, Singh D, et al. Longitudinal stability of asthma characteristics and biomarkers from the Airways Disease Endotyping for Personalized Therapeutics (ADEPT) study. Respir Res. 2016 Apr 23;17:43. doi: 10.1186/s12931-016-0360-5.
20. Shaw DE, Sousa AR, Fowler SJ, et al. Clinical and inflammatory characteristics of the European U-BIOPRED adult severe asthma. Eur Respir J. 2015 Nov; 46(5):1308-21.
21. Wenzel SE. Asthma phenotypes: the evolution from clinical to molecular approaches. Nature Med. 2012 May 4;18(5):716-25.
22. Ray A, Camiolo M, Fitzpatrick A, et al. Are We Meeting the Promise of Endotypes and Precision Medicine in Asthma? Physiol Rev. 2020 Jul 1;100(3):983-1017.
23. Oishi K, Matsunaga K. Three-step algorithm for biological therapy targeted IgE and IL-5 in severe asthma. Immun Inflamm Dis. 2018 Sep;6(3):374-6.
24. Matucci A, Vultaggio A, Maggi E, et al. Is IgE or eosinophils the key player in allergic asthma pathogenesis? Are we asking the right question? Respir

Res. 2018 Jun 8;19(1):113. doi: 10.1186/s12931-018-0813-0.

25. Izuhara K, Nunomura S, Nanri Y, et al. Periostin in inflammation and allergy. Cell Mol Life Sci. 2017; 74(23): 4293-303.
26. Rupani H, Chauhan AJ. Measurement of FeNO in asthma: what the hospital doctor needs to know? Br J Hosp Med (Lond). 2019 Feb 2;80(2):99-104.
27. Arnold RJ, Massanari M, Lee TA , et al. A Review of the Utility and Cost Effectiveness of Monitoring Fractional Exhaled Nitric Oxide (FeNO) in Asthma Management. Manag Care. 2018 Jul;27(7):34-41.
28. Wenzel S. Severe asthma: from characteristics to phenotypes to endotypes. Clin Exp Allergy. 2012 May;42(5):650-8.
29. Coumou H, Westerhof GA, de Nijs SB, et al. Predictors of accelerated decline in lung function in adult-onset asthma. Eur Respir J. 2018 Feb 14;51(2):1701785. doi: 10.1183/13993003.01785-2017.
30. Gauthier M, Ray A, Wenzel SE. Evolving concepts of asthma. Am J Respir Crit Care Med. 2015 Sep 15;192(6):660-8.
31. Thomson NC, Chaudhuri R. Omalizumab: Clinical Use for the Management of Asthma. Clin Med Insights Circ Respir Pulm Med. 2012;6:27-40
32. Busse WW, Morgan WJ, Gergen PJ, et al. Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. N Engl J Med. 2011;364(11):1005-15.
33. Taichman DB.Biologic therapies for severe astme. N Engl J Med. 2022 Jan 13; 386(2):157-71.
34. Edris A, De Feyter S, Maes T, et al. Monoclonal antibodies in type 2 asthma: a systematic review and network meta-analysis. Respir Res. 2019 Aug 8;20(1):179. doi: 10.1186/s12931-019-1138-3.
35. Hanania NA, Wenzel S, Rosén K, et al. Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study. Am J Respir Crit Care Med. 2013 Apr 15;187(8):804-11.
36. Humbert M, Taillé C, Mala L, et al. Omalizumab effectiveness in patients with severe allergic asthma according to blood eosinophil count: the STELLAIR study. Eur Respir J. 2018 May 10;51(5):1702523. doi: 10.1183/13993003.02523-2017.
37. Varricchia G, Giorgio W. Canonica GW. The role of interleukin 5 in asthma. Expert rev clin immunol. 2016 Sep;12(9):903-5.
38. Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. N Engl J Med. 2014 Sep 25;371(13):1198-207.
39. Castro M, Zangrilli J, Wechsler ME, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. Lancet Respir Med. 2015 May;3(5):355-66.
40. Pelaia C, Busceti MT, Vatrella A, et al. Real-life rapidity of benralizumab effects in patients with severe allergic eosinophilic asthma: Assessment of blood eosinophils, symptom control, lung function and oral corticosteroid intake after the first drug dose. Pulm Pharmacol Ther. 2019 Oct;58:101830. doi: 10.1016/j.pupt.2019.101830.
41. Wenzel S, Castro M, Corren J, et al. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium- to-high-dose inhaled corticosteroids plus a long-acting β2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b

dose-ranging trial. Lancet. 2016 Jul 2;388(10039):31-44.
42. Maselli DJ, Velez MI, Rogers L. Reslizumab in the management of poorly controlled asthma: the data so far. J Asthma Allergy. 2016 Aug 31;9:155-62.
43. Buhl R, Humbert M, Bjermer L, et al. Severe eosinophilic asthma: a roadmap to consensus.Eur Respir J. 2017 May 1;49(5):1700634. doi: 10.1183/13993003.00634-2017.
44. Sze E, Bhalla A, Nair P. Mechanisms and therapeutic strategies for non-T2 asthma. Allergy. 2020 Feb;75(2):311-25.
45. Brusselle GG, Koppelman GH. Biologic therapies for severe asthma. N Engl J Med. 2022 Jan 13;386(2):157-71.
46. Menzies-Gow A, Corren J, Bourdin A, et al. Tezepelumab in adults and adolescence with severe uncontrolled asthma. N Engl J Med. 2021 May 13;384(19):1800-9.
47. Wechsler ME, Ruddy MK, Pavord ID, et al. Efficacy and safety of itepekimab in patients with moderate-to-severe asthma. N Engl J Med. 2021 Oct 28;385(18):1656-68.
48. Kelsen SG, Agache IO, Soong W. Astegolimab (anti-ST2) efficacy and safety in adults with severe asthma:a randomized clinical trial. J Allergy Clin Immunol. 2021 Sep;148(3):790-8.