

Applying personalized medicine to adult severe asthma

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ABSTRACT

Background: Severe asthma is a heterogeneous disease that consists of various phenotypes driven by different pathways. Associated with significant morbidity, an important negative impact on the quality of life of patients, and increased health care costs, severe asthma represents a challenge for the clinician. With the introduction of various antibodies that target type 2 inflammation (T2) pathways, severe asthma therapy is gradually moving to a personalized medicine approach.

Objective: The purpose of this review was to emphasize the important role of personalized medicine in adult severe asthma management.

Methods: An extensive research was conducted in medical literature data bases by applying terms such as “severe asthma” associated with “structured approach,” “comorbidities,” “biomarkers,” “phenotypes/endotypes,” and “biologic therapies.”

Results: The management of severe asthma starts with a structured approach to confirm the diagnosis, assess the adherence to medications and identify confounding factors and comorbidities. The definition of phenotypes or endotypes (phenotypes defined by mechanisms and identified through biomarkers) is an important step toward the use of personalized medicine in asthma. Severe allergic and nonallergic eosinophilic asthma are two defined T2 phenotypes for which there are efficacious targeted biologic therapies currently available. Non-T2 phenotype remains to be characterized, and less efficient target therapy exists.

Conclusion: Despite important progress in applying personalized medicine to severe asthma, especially in T2 inflammatory phenotypes, future research is needed to find valid biomarkers predictive for the response to available biologic therapies to develop more effective therapies in non-T2 phenotype.

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Despite progress in its management and therapeutics, severe asthma (SA) remains a major health problem, with a high personal and socioeconomic impact.^{1,2} According to the definition of the European Respiratory Society/American Thoracic Society, SA is “asthma which requires treatment with high dose inhaled corticosteroids (ICS) plus a second controller (and/or systemic corticosteroids) to prevent it from becoming ‘uncontrolled’ or which remains ‘uncontrolled’ despite this therapy.”³ This definition implies that the diagnosis of asthma has been established, based on the clinical history and lung function tests, after the exclusion of other diagnoses that may masquerade asthma, the checking of therapeutic adherence, and correct inhaler technique as well as the management of the possible comorbidities or aggravating factors, *e.g.*, smoking.^{4–6}

Uncontrolled asthma includes at least one of these criteria: poor symptom control (recurrent symptoms or reliever use, nocturnal symptom, and activity

limitation by asthma), a high risk of exacerbation (frequent exacerbations, two or more times a year, that require oral corticosteroids; or serious exacerbation, one or more times a year that require hospitalization) and airflow limitation, *e.g.*, forced expiratory volume in 1 second (FEV₁) < 80% predicted with reduced FEV₁-to-forced vital capacity ratio, defined as less than the lower limit of normal) after a withholding of both short- and long-acting bronchodilators.^{3,7}

The World Health Organization described three categories of SA: (1) untreated SA, including patients who cannot receive treatments because of inaccessibility and socioeconomic problems (more frequently in underdeveloped countries); (2) difficult-to-treat SA in patients treated for their asthma but nonresponsive for many reasons, such as poor adherence and compliance, inadequate inhaler technique, the presence of smoking and comorbidities, or incorrect diagnosis; and (3) treatment-resistant SA, which remains uncontrolled despite the highest level of recommended treatments being taken (steps 4 and 5 of the Global Initiative for Asthma [GINA] guidelines) or requires these doses to maintain the control.^{7,8} The group with treatment-resistant SA includes the patients with uncontrolled asthma refractory to treatment despite good compliance and a correct inhaler technique.⁹

Usually, for the patients with uncontrolled asthma in primary, secondary, or tertiary care, a diagnosis of treatment-resistant SA is ultimately made. The patients

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with SA must be addressed in a specialist center for evaluation because establishing an appropriate diagnosis and treatment of confounders could improve their condition.¹ The European Respiratory Society/American Thoracic Society guidelines³ recommend three steps in reaching the diagnosis of SA. The first step is the confirmation of the diagnosis of asthma and identification of difficult-to-treat asthma; the second step is the differentiation of SA from mild-moderate asthma, and the final step is to determine the level of control.³ When following this protocol, after at least 3 months of monitoring, an asthma specialist may then establish the diagnosis of SA.¹

This review summarized the progress in applying personalized medicine in adult SA by using a biomarker-driven approach to identify people who could have a good response to specific biologic therapies that target type 2 inflammation (T2-asthma), mainly eosinophilic, with high levels of T-helper type 2 cytokines (*e.g.*, interleukin [IL] 4, 5, 13) as well as the current therapeutic possibilities to treat the non-T2 phenotype.

METHODS

This review examined the literature data published in public data bases (PubMed, Medline, U.S. National Library of Medicine®, USA) on adult SA between 2002 and 2020. The following key terms were used: “severe asthma” associated with “structured approach,” “comorbidities,” “biomarkers,” “phenotypes/endotypes,” and “biologic therapies.” Original studies were selected in priority followed by systematic reviews and metaanalyses. Results were limited to publications in English. Preference was given to articles published the past 5 years.

Clinical Characteristics of Patients with SA

The recent results from the International Severe Asthma Registry, including ~5000 patients from the United States, United Kingdom, South Korea, Italy, and Australia identified several characteristics for SA.¹⁰ The average age was 55 ± 15.9 years, with an average age for the asthma onset at 30.7 ± 17.7 years. The patients were predominantly women (59.3%), non-smokers (60.5%), white (72.6%), and who were overweight or obese (70.4%). The average exacerbation rate was 1.7 ± 2.7 per year. Nearly 35% of the patients were at GINA step 5 treatments,⁷ with 72.6% of them receiving biologics. Despite this, 57.2% of the patients had poorly controlled disease and more than half needed regular intermittent oral corticosteroids (OCS).¹⁰

Achieving good disease control with a minimum of controller medications and a low rate of adverse effects is the goal in all patients with asthma but is particularly difficult to obtain in patients with SA.¹¹ The systematic assessment of this population (Table 1) in a specialist SA center has been recommended by current

Table 1 Systematic assessment of severe asthma

1. Confirm the asthma diagnosis: clinical history plus lung function variability
2. Exclude other conditions that masquerade as asthma
3. Assess the severity of the disease: symptom control, airflow obstruction, number of exacerbations, and hospitalizations
4. Optimize treatment according to current guidelines
5. Assess adherence to therapy and inhaler technique
6. Check and adapt the self-management plan
7. Identify and avoid trigger factors
8. Manage the comorbidities
9. Assess the phenotype according to clinic-physiologic-inflammatory parameters
10. Individualize the management plan

guidelines because this strategy improves patients’ outcomes in terms of symptom control, quality of life, exacerbation rates, and health care utilization, respectively, systemic corticosteroid use.^{3,12} Annual influenza vaccination reduces the risk of asthma exacerbations, so this prophylactic measure is recommended by current guidelines in patients with SA.⁶

Comorbidities in SA

After the diagnosis confirmation, an important component in the systematic assessment of SA is the identification and management of comorbidities.^{7,11,13} Comorbidities have a negative impact on asthma outcomes, with poor asthma control by aggravating symptoms, increasing exacerbations, and decreasing lung function and quality of life.^{11,13,14} The most common comorbidities are sinonasal diseases (allergic rhinitis, chronic rhinosinusitis with or without nasal polyposis), vocal cord dysfunctions, dysfunctional breathing, gastroesophageal refluxes (GERD), obstructive sleep apnea, and anxiety and/or depression, and could be screened by validated questionnaires (summarized in Table 2).^{4,13,14}

In the European Unbiased Biomarkers in Prediction of Respiratory Disease Outcomes (U-BIOPRED) cohort,¹⁵ the most frequent comorbidities in patients who are non-smokers and with SA were allergic rhinitis (59%), GERD (47%), and nasal polyposis (35%). A recent study, in a similar Asiatic population, found a similar prevalence for the allergic rhinitis (59%) but a lower prevalence for GERD (13%) than in the European cohort,¹⁵ which suggests a possible influence of the genetic background and the life style.¹⁶ Several comorbidities in SA (obesity, osteoporosis, depression, GERD) could be iatrogenic related to the use of OCS.¹¹ A study in a SA population that required OCS showed that 93% of the patients had

Table 2 Validated questionnaires available to screen asthma comorbidities

Comorbidity	Questionnaire
Chronic rhinosinusitis and allergic rhinitis	Sinonasal Questionnaire
Gastroesophageal reflux	Gastroesophageal reflux disease questionnaire
Obstructive sleep apnea	Berlin questionnaire
Vocal cord dysfunction	Pittsburgh vocal cord dysfunction index
Dysfunctional breathing	Nijmegen questionnaire
Anxiety and depression	Hospital anxiety and depression score

iatrogenic comorbidities, such as type II diabetes, osteoporosis, and dyspepsia.¹⁷ A structured multidisciplinary approach coupled with their specific management improve control of key comorbidities and asthma outcomes.¹⁸

Phenotypes of SA

SA is a heterogeneous condition that represents several phenotypes likely driven by diverse molecular mechanisms.^{1,14,19} Phenotyping is becoming an important step in the management of SA in the era of personalized medicine to help the clinician choose the most adapted treatment for each patient.^{1,19} By using the statistical clustering approaches of cohorts with SA, various phenotypes were identified based on the age of onset, the presence of atopy, obesity, and airflow limitation; smoking status; disease activity; the nature of airway inflammation; and response to treatments.^{20–22}

In the American Severe Asthma Research Project (SARP) cohort, three clusters were associated with SA: early onset atopic asthma with preserved lung function but increased medication requirements; late-onset non-atopic asthma, more frequent in females and in patients who are obese, with airflow limitation and frequent exacerbations that require OCS, respectively, SA with important airflow obstruction and daily OCS.²² In the U-BIOPRED cohort, four clusters were characterized: one cluster associated with well-controlled moderate-to-severe asthma and three clusters associated with SA. The first SA cluster was associated with a late-onset SA with a history of smoking, persistent airflow obstruction, and a high blood eosinophil count; the second cluster was associated with non-smoking SA, persistent airflow obstruction, and the high use of OCS; and the third cluster was associated with obese SA, a greater proportion of females, a high exacerbation rate but with normal lung function.²³

In the Leicester cohort,²¹ according to sputum eosinophilia and the presence of the symptoms, two clusters were specific to the refractory asthma: the first cluster was characterized by early onset, symptom-predominant, minimum eosinophilic inflammation, a high prevalence of atopy, and female gender; the second cluster was characterized by late-onset, few symptoms,

a greater proportion of males, nasal polyposis, eosinophilic inflammation, and frequent exacerbations. Although the Leicester eosinophilic phenotype may correspond to the late-onset asthma phenotype from the SARP study²⁴ in the U-BIOPRED cohort study, a higher prevalence of nasal polyposis, a higher use of regular OCS, and a more important airflow obstruction were associated with mixed granulocytic disease.²⁵

In the Cohort for Reality and Evolution of Adult Asthma in Korea (COREA) identified four phenotypes: smoking asthma, severe obstructive asthma, early onset atopic asthma, and late-onset mild asthma.^{26,27} In a cohort from China, including patients hospitalized for an acute exacerbation, four clusters were defined: cluster 1, with early onset, neutrophilic asthma, predominantly female patients, and mild airflow obstruction; cluster 2, with eosinophilic asthma, predominantly female, and very important airflow obstruction; cluster 3, with a moderate degree of obstruction; and cluster 4, with male patients who are smokers and with poor lung function.²⁸

Biomarkers

To apply personalized medicine, it is important to be able to phenotype the condition in an unbiased way and to define biomarkers able to predict the course of the disease and the response to therapy.^{29–31} A biomarker is a measurable indicator that would have several characteristics: to distinguish between disease and health, to provide information about disease prognosis and clinical outcomes, to change with disease activity and “normalize” with successful treatment, to be reliable and reproducible in the clinical setting, to be easy to collect in the “real-world” setting, to be quantifiable in an analytical system with well-defined performance, and to be cost-effective.^{31–33}

Only a few biomarkers indicative of T2-asthma have been described (*e.g.*, immunoglobulin E [IgE] level, eosinophils in the blood and/or sputum, fractional exhaled nitric oxide FeNO level, periostin), and their utility in diagnosis, prognosis, and therapy is still controversial.^{29,31,34} The ability of the biomarkers in predicting cluster association was very poor in published studies.^{35,36} A recent analysis showed that T2-SA can be predicted by high levels of FeNO (≥ 30 ppb), and

blood and sputum eosinophil counts but not by serum IgE or periostin, which were relatively poorer predictors.³⁷

FeNO originates from nitric oxide production by the airway epithelium as a result of inducible nitric oxide synthase upregulation during the process of allergic inflammation.³² A level of <25 ppb is considered normal in adults.³⁸ High FeNO levels (≥ 50 ppb) were associated with more asthma symptoms, a high rate of exacerbations and/or asthma-related emergency department visits, an accelerated decline in lung function, and better response to ICS.^{39–43} FeNO measurements could be used as a diagnostic tool in patients who are ICS naïve, to monitor ICS therapy adherence but also to step down the ICS treatment.^{40,44,45} Despite its advantages (noninvasive technique, easy to collect in the clinical setting, with a minimal patient effort), the current guidelines for the treatment of SA do not recommend the use of FeNO in the routine for the management of these patients.^{3,6}

The blood eosinophil count is not useful for the diagnosis of asthma, but it can serve as a prognostic biomarker and to predict several therapeutic responses in T2 phenotypes.^{29,31} The cutoff to define blood eosinophilia is variable according to the different guidelines and clinical trials. A recent study in the general population found on average 0.1×10^9 cells/L for males, respectively, 0.12×10^9 cells/L the value for females to define the normal blood eosinophil count.⁴⁶ Current guidelines for SA associates T2 inflammation with a blood eosinophils count of $\geq 0.15 \times 10^9$ cells/L,⁶ whereas the cutoff used in most of the clinical trials was $\geq 0.3 \times 10^9$ cells/L.^{29,31,47,48}

Analysis of recent data showed that patients with a blood eosinophil count of $\geq 0.4 \times 10^9$ cells/L had more severe exacerbations, lower odds of achieving asthma control,⁴¹ important airflow obstructions, and enhanced longitudinal declines in lung function independent of smoking status.⁴⁹ The blood eosinophil count can predict the response to corticosteroid therapy⁴² and the up dosing of ICS is associated with a decrease in blood eosinophilia.⁵⁰ Studies about the interest to monitor blood eosinophils to adapt the dose of ICS to maintain asthma control are lacking for the moment. Blood eosinophilia has been frequently used in clinical trials for biologic therapies (anti-IL-5 antibody: mepolizumab, reslizumab; anti-IL-5 receptor [anti-IL-5R] antibody: benralizumab; anti-IL-4 receptor [anti-IL-4R] antibody: dupilumab; and anti-IgE antibody: omalizumab). In these trials, patients with blood eosinophilia (generally $\geq 0.3 \times 10^9$ cells/L) responded better to biologic therapies.^{31,51} The blood eosinophil count is easy to obtain in a practice and correlates well with sputum eosinophilia.^{52–54}

The sputum quantitative cell count is the reference standard to reflect the airway inflammation in asthma.²⁹ Induced sputum is the noninvasive method to obtain a

sputum sample but currently is performed in specialized centres.⁵⁵ The cutoff to define sputum eosinophilia is $\geq 2\%$ of the total cell count in the SARP study and $\geq 3\%$ in the U-BIOPRED study.³¹ Sputum eosinophilia $\geq 3\%$ predicts a response to ICS.⁴² Targeting a sputum eosinophil count of <3% in adults with asthma reduced the exacerbation rate compared with usual care.^{56,57} Sputum eosinophilia was also used as a predictive biomarker for the response to biotherapies in clinical trials.⁵⁵

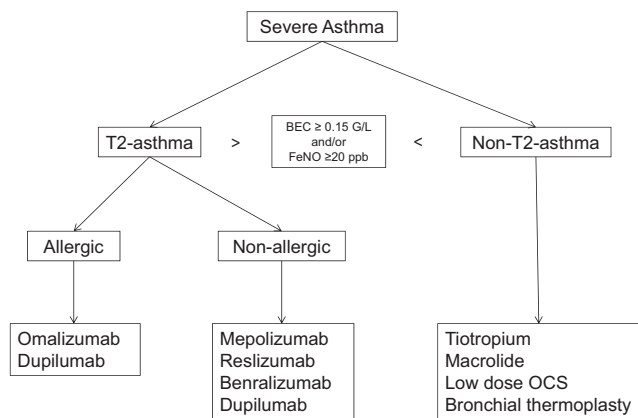
The serum IgE level is easy to measure and identify the patients who could be treated by omalizumab for their severe allergic asthma.¹⁵ Serum periostin is a useful biomarker for predicting airway eosinophilia, asthma exacerbation, and airflow obstruction but currently is not available in clinical practice.^{13,48} Biomarkers that reflect non-T2 phenotype are lacking.¹ However, a previous study showed that sputum neutrophilia of >61% in patients with SA treated by macrolides is associated with greater improvements in quality-of-life scores.⁵⁸ Exhaled breath analyses by “electronic noses” seem promising in terms of finding a useful predictive biomarkers, but these data need validation.¹⁹

Treatment

The current guidelines⁶ recommend that patients with difficult-to-treat asthma must be referred for investigation in specialized centers for consideration of add-on treatment at step 4 and 5, such as the long-action cholinergic antagonist, tiotropium, a low dose of OCS, or biologic therapies. Macrolide antibiotics and bronchial thermoplasty could also be options in selected patients with refractory SA.^{3,6} Currently available therapeutic options for SA treatment are shown in Fig. 1.

One of the novelties of the GINA guidelines 2019 was the option to use the association low-dose ICS-formoterol as maintenance and reliever therapy Symbicort® Maintenance and Reliever Therapy (SMART) for steps 3–5 of treatment.⁷ For adult patients with a history of one or more exacerbations in the previous year, the SMART strategy significantly reduces the risk of exacerbations compared with the same or higher dose of ICS–long-acting β -2 agonists (LABA) as maintenance therapy or a higher dose of ICS alone, all regimens with a reliever treatment by using short-acting β -2 agonists⁵⁹ with similar symptom control.⁷ A recent network meta-analysis in mild-to-severe asthma confirmed the benefits and the safety of the SMART strategy, which suggests that budesonide-formoterol maintenance and reliever therapy is also a suitable choice for the most severe patients.⁶⁰ However, the maximum accepted daily dose of formoterol is 48 μ g for beclomethasone-formoterol, respectively 72 μ g for budesonide-formoterol.⁷

When added to ICS and LABA, tiotropium, a long-acting muscarinic antagonist used as bronchodilator



> Mepolizumab should be the first choice if asthma related to eosinophilic granulomatosis with polyangiitis.
 > Dupilumab should be the first choice if comorbid atopic dermatitis.
 > Reslizumab or Dupilumab should be the first choice if comorbid nasal polyposis.

Figure 1. Therapeutic options in severe asthma (SA) according to the inflammatory phenotype. BEC = blood eosinophil count; OCS = oral corticosteroids.

therapy for chronic obstructive pulmonary disease, showed a beneficial effect in SA by increasing the time to the first exacerbation, which required OCS, prevention of asthma worsening, improvement of asthma control, and FEV1 level.^{51,61,62} A recent study that compared the addition of tiotropium 1.25 µg (two puffs once daily) to the increasing the ICS-LABA dose in patients with asthma ages ≥12 years showed a lower risk for asthma exacerbation (hazard ratio 0.65 [95% confidence interval CI, 0.43–0.99]; $p=0.044$), a decreased rate of asthma-related emergency department visits and hospitalizations as well as a reduction of short-acting β -2 agonists refills at 6 and 12 months in the first group treated by tiotropium + ICS-LABA.⁶³ In addition, analysis of more recent data demonstrated that the effectiveness of the tiotropium Respimat (Boehringer Ingelheim International GmbH, Ingelheim am Rhein, Germany) 5 µg daily is independent of a T2 phenotype.^{61,64} Umeclidium and glycopyrronium have not yet been approved by the U.S. Food and Drug Administration for the treatment of asthma or been evaluated as adjunct therapy for SA, but analysis of current data suggests beneficial effects on symptom control and lung function in mild-moderate asthma.^{51,65,66}

The addition of allergen immunotherapy (subcutaneous and sublingual) in adult patients with house-dust mite (HDM) driven allergic asthma could improve symptom control, airway hyperresponsiveness (AHR), time to first moderate-severe asthma exacerbation, quality of life, and decrease the medication use (more evidence for ICS treatment needs).⁶⁷ However, more of the safety data are issues from studies that enrolled patients with well- or partially controlled asthma and $FEV_1 > 70\%$ of predicted. Uncontrolled asthma is a major contraindication for allergen immunotherapy due to the high risk for severe reactions. Patients with controlled HDM-driven SA may be

eligible for HDM immunotherapy in selected cases but need careful monitoring.⁶⁷

The introduction of biologic therapies for SA has opened up the era of personalized medicine in asthma because, for the first time, treatments are directed toward specific groups by using biomarkers (Table 3).¹⁹ Patients with severe allergic asthma (positive serum-specific IgE level to at least one perennial aeroallergen) with total serum IgE levels between 30 and 700 IU/mL (up to 1300 IU/mL for 6–11 years) are selected to be treated by omalizumab.¹ IgE is a biomarker used in practice to stratify patients because those are more likely to respond to therapy.¹⁵ Blood eosinophil counts $\geq 0.26 \times 10^9/L$ and FeNO level ≥ 19.5 ppb seem to be predictive factors for a good response to this treatment.⁵¹

For most of the anti-IL-5 and anti-IL-5R α monoclonal antagonists, a blood eosinophil count of $\geq 0.3 \times 10^9/L$ is associated with a therapeutic response in patients with SA and with two or more exacerbations per year.^{68–71} The efficacy of the anti-IL-4R α monoclonal antibody dupilumab, which blocks the effects of T2 cytokines, IL-4 and IL-13, is greater in patients with a baseline blood eosinophil count $\geq 0.15 \times 10^9/L$ or FeNO level ≥ 25 ppb.^{51,69} All of these biologic therapies decrease asthma exacerbation rates, improve the quality of life, and have a positive impact on the airflow obstruction.¹⁹ Analysis of recent data suggests that patients with SA treated by available biologic therapies do not have an increased risk for COVID-19 (coronavirus disease 2019) infection, in comparison with age- and geography-matched non-asthma population.^{72–74} Current recommendations are to continue the administration of these treatments during the COVID-19 pandemic in patients for whom such therapies are clearly indicated and have been effective.⁷³ The eligibility criteria and effectiveness of currently available biologic therapies for SA are summarized in Table 3.

At the moment, personalized medicine is limited to the use of the blood eosinophil count and FeNO level as biomarkers for T2 phenotype in determining the treatment with biologic therapies. However, the blood eosinophil count is not a perfect predictor of T2-asthma, and this may not be the best biomarker for selecting the responders to these biologic treatments.³⁷ A better definition of molecular phenotypes, the development of biomarkers to delineate endotypes and to predict the response to specific therapies should be the next step in this process.¹⁹

The severe eosinophilic asthma phenotype⁴⁷ can overlap with the severe allergic asthma phenotype, but, currently, it is unknown which antibody treatment would be preferable in such patients.¹⁹ There are no clinical studies that directly compared the efficacies of these biologics, so taking into consideration the mode and/or timing of administration and the comorbidities to select a treatment becomes mandatory. For example,

Table 3 Current biologic therapies, eligibility criteria and effectiveness

Biologic Therapy	Target	Eligibility Criteria	Administration	Effects on Asthma Outcomes*
Omalizumab	IgE	≥6 years; total serum IgE level; allergies	SQ every 2 or 4 weeks; dose based on IgE level and weight	Decreases exacerbations rate; reduces airflow obstruction; improves ACQ and AQLQ scores; oral corticosteroid sparing
Mepolizumab	IL-5	≥6 years; exacerbations ≥2/year; blood eosinophils $\geq 0.15 \times 10^9/L$	SQ every 4 weeks; 40 mg (6–11 years) or 100 mg (≥12 years)	Decreases exacerbations rate; improves ACQ and AQLQ scores; oral corticosteroid sparing
Reslizumab	IL-5	≥18 years; exacerbations ≥1/year; blood eosinophils $\geq 0.4 \times 10^9/L$	IV 3 mg/kg every 4 weeks	Decreases exacerbations rate; improves ACQ and AQLQ scores
Benralizumab	IL-5R α	≥12 years; exacerbations ≥2/year; blood eosinophils $\geq 0.3 \times 10^9/L$	SQ 30 mg every 4 weeks 3× (three times), then every 8 weeks	Decreases exacerbations rate; improves ACQ and AQLQ scores; oral corticosteroid sparing
Dupilumab	IL-4R α	≥12 years; exacerbations ≥1/year; blood eosinophils $\geq 0.15 \times 10^9/L$	SQ 400 mg or 600 mg loading dose, then 200 or 300 mg every 2 weeks	Decreases exacerbation rates; reduces airflow obstruction; improves ACQ and AQLQ scores; oral corticosteroid sparing

IgE = Immunoglobulin E; SQ = subcutaneous; ACQ = asthma control questionnaire; AQLQ = asthma related quality of life questionnaire; IL = interleukin; IV = intravenous; IL-5 = interleukin 5; IL-5R α = IL-5 receptor alpha subunit; IL-4R α = IL-4 receptor alpha subunit.

*According to Ref. 51.

patients with comorbid nasal polyposis should be treated by using rezlizumab or dupilumab, whereas those with atopic dermatitis should be treated with dupilumab. At the moment, mepolizumab is the only anti-IL-5 approved treatment for eosinophilic granulomatosis with polyangiitis in patients with SA.⁴⁸ Not all patients respond well to biologic therapies, despite the presence of eligibility criteria, which suggests the involvement of non-T2 pathways in association with T2 pathways in SA.

Non-T2 target therapies have not shown a significant benefit in SA. Brodalumab, an anti-IL-17RA antibody, and golimumab, an anti-tumor necrosis factor α antibody, together with a CXC chemokine receptor 2 (CXCR2) antagonist (AZD5069), which blocks the effects of CXCL8, had no effects on asthma control scores, symptom-free days, and lung function in uncontrolled

moderate-to-severe asthma treated by using ICS.^{75–77} The absence of effectiveness may be due to an inappropriate patient selection, which reflected the lack of valid biomarkers for non-T2-asthma and the probable coexistence of T2 pathways.¹⁹

Macrolide treatment could be an interesting option in patients with SA and frequent exacerbations without criteria for a biologic therapy. It has been shown that clarithromycin administration (500 mg twice daily) in patients with refractory asthma reduced the airway neutrophil counts and improved the quality of life in patients who were undergoing active treatment.⁵⁸ The recent trial, AMAZES,⁷⁸ confirmed the benefit of macrolides in asthma (without differences between eosinophilic and neutrophilic phenotypes), with a reduction in the exacerbation rate and quality-of-life improvement in patients treated by using azith-

romycin 500 mg three times per week for 48 weeks. However, macrolides have many interactions with others drugs, which can be a limitation in their use in patients with SA and with comorbid conditions that require many medications.⁷

Bronchial thermoplasty is the first treatment that targets airway remodeling and could be suggested as a nonpharmacologic treatment in patients with asthma that remained uncontrolled despite high doses of ICS. At 6 months, bronchial thermoplasty trials for SA showed an improvement of asthma control, lung function, a decrease in the number of asthma exacerbations and reliever treatment,⁷⁹ whereas the long-term benefit (3 years) was a reduction of severe exacerbations, emergency visits, and hospitalizations.⁸⁰ However, it is unclear how this treatment works mechanistically and which patients are the best candidates for this treatment.

CONCLUSION

There has been important progress in the management of SA over the past 10 years with the introduction of biologic therapies that mostly target T2 inflammation. An increasing number of molecular phenotypes in the non-T2 phenotypes are being described, but no efficient treatments that targeted these phenotypes have emerged. The description of a range of SA endotypes with distinct treatable mechanisms and clinically available biomarkers is necessary to predict which patients will benefit and have improved outcomes with biologic therapies. It is important for patients with SA to be evaluated in specialized SA centers that can offer a multidisciplinary approach and a holistic management plan, which include treatment of comorbidities, accurate phenotyping, and precision therapy.

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