Review

Tailored therapy in severe asthma: the importance of moving beyond a disease-centric approach

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Abstract: Despite recent advances in optimizing reliever, controller and maintenance therapy in asthma, a large subgroup of asthmatic patients continues to suffer from severe asthma, affecting their psychosociological status, their quality of life and even their life expectancy. Identifying and recognizing the specific phenotypic and endotypic characteristics in asthma has provided the medical community to drive the development of targeted therapies that are proved to benefit patients in terms of symptom control, exacerbation rate, quality of life and lung function. Adopting a more tailored and targeted approach is proving to be the key factor in reforming severe asthma treatment, minimizing the patients' burden, as well as the socioeconomical impact worldwide. In this review, we are going to describe the different phenotypes and endotypes of asthma, the currently approved targeted therapies in severe asthma as imprinted in Global Initiative for Asthma (GINA) 2023, as well as other potential pharmacological agents and strategies investigated or currently under investigation for the treatment of severe asthma.

Keywords: severe asthma, phenotype, endotype, personalized medicine, targeted therapy, treatment

1. Introduction

Asthma is a common, chronic, and heterogeneous disease, affecting people of all ages. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation. These variations are often triggered by factors such as exercise, allergen or irritant exposure, change in weather, or viral respiratory infections.[1] These features can be caused by a range of underlying mechanisms that are typically, but not always, associated with airway inflammation and airway remodelling.[2] Asthma may be characterized as mild or it may range all the way to very severe disease, causing constant symptoms and severe, life-threatening episodic flare-ups (exacerbations).

A major part of the burden of asthma is caused by acute exacerbations. Poor asthma symptom control itself substantially increases the risk of exacerbations. Exacerbations have also been strongly and consistently associated with respiratory infections. Among infectious agents, human rhinoviruses are the most prevalent in regard to asthma exacerbations, while influenza viruses seem to induce severe exacerbations mostly in adults.[3] Additional independent factors that increase the patient's risk of exacerbations even if symptoms are few, include a history of ≥1 exacerbation in the previous year, poor adherence, incorrect inhaler technique, suboptimal drug regimen, obesity, gastroesophageal reflux disease, chronic sinusitis, confirmed food allergy or morbid allergic disease, allergy exposure if sensitized, smoking, air pollution, occupational exposure, low FEV1 (<60% predicted) and increased Th2 inflammatory markers (higher blood eosinophils, elevated FeNO).[1] The risk of severe exacerbations and mortality increases incrementally with higher SABA use, independent of treatment step. People with asthma may have an accelerated decline in lung function and develop airflow limitation that is not fully reversible. Independent risk factors that have been identified

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for persistent airflow limitation include exposure to cigarette smoke or noxious agents, chronic mucus hypersecretion, and asthma exacerbations in patients not taking ICS.[1]

Severe asthma is asthma that is uncontrolled despite adherence with maximal optimized high dose inhaled corticosteroids (ICS)- long-acting beta2-agonist (LABA) treatment and management of contributory factors, or that worsens when high dose treatment is decreased and requires high dose ICS-LABA to prevent it from becoming uncontrolled.[1] It is increasingly associated with different specific phenotypes and endotypes and it must be distinguished from asthma that is difficult to treat due to inadequate or inappropriate treatment, or persistent problems with adherence or comorbidities such as chronic rhinosinusitis or obesity, as there are very different treatment implications compared with if asthma is relatively refractory to high dose ICS-LABA or even oral corticosteroids (OCS).

In the era of personalized, targeted and tailored medicine, it is mandatory that we treat patients, not diseases. This is true for every disease and is particularly important in severe disease where suboptimal or non-targeted treatment may lead to disability, poor quality of life and even death. Severe asthma is such a disease, it may be life threatening and debilitating and needs a holistic and personalized approach to the patient's management. Endotyping, phenotyping, genotyping and theratyping, and biomarkers are keywords in this area and have been gaining lots of attention in the field of precision medicine, which aims to revolutionize patient care and develop better prevention and treatment strategies.[4] The benefits and the need of moving from a disease-centric approach to a more personalized, tailored, phenotypic driven treatment in severe asthma is already being imprinted in asthma management guidelines worldwide.

2. Phenotypes and endotypes of asthma

Phenotypes are observable characteristics or outward manifestations of underlying genetics and pathophysiology. Endotypes further subtype phenotypes based on pathophysiologic mechanisms underlying the disease process.[5] Both have been used to try to better categorize patients and understand their underlying mechanisms for disease, as in recent years it has become apparent that the identification of the patient's specific phenotypic and endotypic characteristics is important not only for research purposes, but also to implement a successful treatment plan[6], targeting asthma control.

Although allergic and non-allergic asthma are probably the most commonly described and studied phenotypes, the determination of additional phenotypes is recognized in the international literature. So the broad categories of phenotypes could be classified in three categories: phenotypes defined by clinical or physiological criteria, phenotypes related to environmental triggers and phenotypes defined by their pathobiology (Table 1).[7]

It is clear that there is probably substantial interaction among the groups, while in addition, a specific phenotype is unlikely to be permanently fixed and changes in the phenotypic characteristics over time is common. As the definition implies, a phenotype can vary dependent on interactions with the environment.[7]

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Table 1. Potential phenotypic categories of asthma by phenotype [7]

Clinical or physiological phenotypes	**Severity-defined** **Exacerbation-prone** **Defined by chronic restriction** **Treatment-resistant (e.g. resistance to steroids)** **Defined by age at onset**
Phenotypes related to the following triggers	Aspirin or on-steroidal anti-inflammatory drugs Environmental allergens Occupational allergens or irritants Menses Exercise Obesity
Inflammatory phenotypes	Eosinophilic (characterized by eosinophilic airway inflammation, either by sputum eosinophils, FeNO, blood eosinophils, periostin etc with different cut-off points used) Neutrophilic (non-eosinophilic with neutrophilic predomination) Pauci-granulocytic (absence of an identifiable influx of inflammatory cells such as eosinophils, neutrophils, or lymphocytes)

2.1. Common asthma phenotypes

2.1.1. Allergic Asthma

This is the largest overall and the most easily recognized asthma phenotype, which often commences in childhood, but it can present at any age. It is associated with a past and/or family history of allergic disease such as eczema, allergic rhinitis, or food and/or drug allergy. Examination of the induced sputum of these patients before treatment often reveals eosinophilic airway inflammation. Patients with this asthma phenotype usually respond well to ICS treatment, while in the severe form of the disease the use of anti-IgE monoclonal antibody treatment has proved beneficial. The presence of allergic characteristics could be associated with better overall lung function, but with more exacerbations than non-allergic asthma.[1,7]

2.1.2. Non-Allergic Asthma

Some patients have asthma that is not associated with allergy. The cellular profile of the sputum of these patients may be neutrophilic, eosinophilic or contain only a few inflammatory cells (paucigranulocytic). Patients with non-allergic asthma often demonstrate less short-term response to ICS.[1]

2.1.3. Adult-Onset (late onset) Asthma

Some adults, particularly women, present with asthma for the first time in adult life. Adult-onset asthma is more severe, has a lower remission rate and is not as frequently associated with allergy when compared with childhood-onset asthma, while, on the contrary it seems to be associated with eosinophilic non-allergic inflammation. Often higher doses of ICS or even OCS treatment are required, while it seems that people with late-onset asthma were shown to have marginally worse lung function than those with early-onset disease. Occupational asthma should always be ruled out in patients presenting with adult-onset asthma.[1,7,8]

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2.1.4. Asthma with Persistent Airflow Limitation

Some patients with long-standing asthma develop airflow limitation that is persistent or incompletely reversible. This is thought to be due to airway wall remodeling.[1] In smoking asthmatics this phenotype should be differentiated by COPD or the possible coexistence of 2 diseases should be examined.

2.1.5. Asthma with Obesity

Some obese patients with asthma have prominent respiratory symptoms and little eosinophilic airway inflammation.[1] Several studies have shown that weight loss in obese adults with severe asthma can improve asthma control, lung function, airway hyperresponsiveness and quality of life.[9,10]

Although phenotypes focus on observed or measured features, endotypes subset individuals based on distinct functional or pathophysiologic mechanisms. For this purpose, except for clinical features, various biomarkers are used to classify patients with asthma, such as blood and sputum eosinophil levels, serum periostin, fractional exhaled nitric oxide (FENO), aeroallergen skin prick testing or radioallergosorbent test and serum IgE.[11] Additionally, immune profiling enables phenotypes to be linked with endotypes.[8] This is especially useful and nowadays necessary for diagnosis, endotyping, right choice of treatment and control of asthma, especially in severe asthma.

2.2. Asthma endotypes

Two major endotypes of severe asthma have been identified: T2-high and T2-low asthma. Although T2-high asthma is easy to distinguish, there is no clear distinction or a widely accepted definition of T2-low disease.

2.2.1. T2-high asthma endotype

T2-high asthma is associated with increased epithelial expression of Th2-type cytokines, such as IL-4, IL-5 and IL-13 and although its heterogeneity, the description of this endotype has been primarily based on the presence of atopy and/or eosinophilic airway inflammation, usually identified on the basis of sputum or blood eosinophilia, yet with no universally accepted thresholds.[6] After allocating a severe asthma patient to the T2-high endotype, it is important to define the predominant endotype (i.e. allergic or eosinophilic) driving the disease by using the specific clinical features and biomarkers mentioned above, in order to assess the treatment that is more likely to be successful. “Overlap” syndrome, i.e. patients sharing the obligatory characteristics of both endotypes, may be as high as 50%.[6]

2.2.2. T2-low asthma endotype

T2-low disease may affect up to a third of severe asthmatic subjects.[12] In most cases, the T2-low endotype is defined by the absence of markers of Th2 inflammation and is usually characterized by neutrophilic or paucigranulocytic infiltration in the airways depicted in induced sputum cell counts. Other aspects of severe asthma pathophysiology, such as recurrent bacterial/viral infections, altered innate immunity responses and airway remodeling which is associated with fixed airway obstruction and lower FEV1, may also contribute mostly to T2-low asthma. However, biomarkers for T2-low asthma are still lacking. Therefore, its definition is even more elusive and requires the lack of any known biomarkers of T2-high asthma.[6] Obesity-associated asthma represents another distinct clinical phenotype often associated with the T2-low endotype in worldwide registries of severe asthma.[12-14]

Until we find a validated T2-low biomarker, a reasonable approach based on a recent study by BUSSE et al. is used to classify patients as having either a high or a low Th2 immune profile.

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According to this study IgE ⩾100 IU·mL−1, blood eosinophil count ⩾300 μL−1 and exhaled NO fraction (FENO) ⩾30 ppb are used to define high levels of Th2 immune activation. Using these thresholds, elevation in two or more Th2 biomarkers is related to T2-high asthma endotype, whether elevation in one Th2 biomarker or no elevation at all is related to T2-low asthma endotype.[15]

3. Tailored treatment of severe asthma in the current guidelines

GINA 2023 main report incorporates an algorithm on treating severe asthma based on the assessment of asthma phenotype and/or other contributing factors as well as the patients' needs and desires. Initial assessment includes determining the patient's inflammatory phenotype as Th2 or non-Th2, a more definitive and detailed description and characterization of comorbidities and ruling out differential diagnoses that can be the cause of the patient's symptoms or non-response to therapy (eg. a parasitic infection induced eosinophilia), evaluating the need of social or psychological support, as well as inviting the patient to enroll in a registry of clinical trial.[1]

As already mentioned, Th2 inflammation is characterized by eosinophilia, increased FeNO, may be accompanied by atopy and is usually responsive to regular usage of ICS. In severe asthma, GINA 2023 suggests that refractory Th2 inflammation should be considered when the patient is already on high doses of ICS or daily OCS and still, at least one biomarker of Th2 inflammation is found elevated (blood or sputum eosinophils, FeNO), or, their asthma is clinically allergen-driven. If there is evidence of Th2 inflammation, GINA suggests examining Th2 associated clinical phenotypes to drive add-on treatment. Moreover, GINA favors using non-biologic options first, due to their lower cost in comparison to biologic therapy. However, it must be stressed that regular OCS use may lead to important adverse events and prove quite costly in the long run.

Non biologic treatments include LTRAs, aspirin desensitization for aspirin-exacerbated respiratory disease (AERD), itraconazole and OCS for allergic bronchopulmonary aspergillosis (ABPA), intranasal corticosteroids and surgical management of chronic rhinosinusitis with or without nasal polyposis, as well as topical corticosteroids for atopic dermatitis.[1]

When biologic Th2 targeted treatments are available and affordable, GINA suggests the use of asthma response predictors to guide the selection of the biologic agent, especially in patients with frequent exacerbations. Currently, six biological agents are approved for the treatment of severe Th2 asthma. These agents target the most prominent factors involved in the pathophysiology of the most encountered asthmatic phenotypes.

IgE has a key role in the immuno-allergen-induced inflammation. Omalizumab is a murine monoclonal antibody, that inhibits the degranulation and activation of inflammatory mediators by binding to the IgE receptors of the basophils' and mast cells' membrane.[16] RCTs in severe asthma showed up to 34% decrease in severe exacerbations,[17] while open label studies showed a 50%-65% reduction in exacerbation rate, asthma control and quality of life, as well as a significant steroid sparing effect.[18,19]

IL-5 along with GM-CSF and IL-3 induce the maturation, recruitment, and survival of eosinophils, and possess an integral part in airway eosinophilic inflammation and remodeling in asthma.[20] Mepolizumab, a humanized N-glycosylated IgG1 kappa monoclonal antibody (mAb) and Reslizumab, a humanized recombinant mAb IgG4 kappa, are able to block IL-5 and are both approved as add-on therapies for severe, uncontrolled Th2 eosinophilic asthma. Mepolizumab is administered subcutaneously (SC) every 4 weeks. RCTs DREAM, MENSA and SIRIUS, as well as the MUSCA study have demonstrated significant clinical benefits in asthma control, exacerbations, quality of life, in addition to improvement in pre-bronchodilator FEV1 and measurable steroid sparing effects. It has an excellent safety and tolerability profile as proved by the COSMOS and

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COLUMBIA extension studies, and the clinical benefits of mepolizumab tend to be higher when baseline blood eosinophil count is >500 cells/μL.[21-23] Reslizumab is administered intravenously (IV) once every 4 weeks and has showed similar benefits to mepolizumab in eosinophilic asthma in Phase 3 studies and in a post-hoc analysis from Phase 3 BREATH RCTs. The clinical benefits of Reslizumab tends to be higher in patients with eosinophilic asthma that have also chronic rhinosinusitis with nasal polyps (CRSwNP) than in those patients without CRSwNP.[24-26] Benralizumab is a fully humanized IgG1k afucosylated mAb that can inhibit IL-5 receptor activation. The SIROCCO and CALIMA Phase 3 studies and the ZONDA phase 3 trial showed a significant reduction in exacerbations and an improvement of asthma control following subcutaneous administration of benralizumab every 4 weeks, along with a reduction in the use of oral corticosteroids and an excellent safety profile and tolerability as demonstrated in the BORA phase 3 extension trial. The clinical benefits of Benralizumab were also significantly higher in patients with CRSwNP, FVC < 65% and baseline peripheral blood eosinophil count of ≥300 cells/μL.[27-34]

IL-4 is produced by basophils and mast cells and stimulates B lymphocytes to biosynthesize allergen specific IgE, while IL-13 is a pleiotropic Th2 cytokine that has been shown to be central to the pathogenesis of asthma. Some of the most prominent effects of IL-13 include increases in goblet cell differentiation, activation of fibroblasts, elevation of bronchial hyperresponsiveness, and switching of B cell antibody production from IgM to IgE. Dupilumab is a fully humanized IgG4 monoclonal antibody capable of inhibiting both IL-4 and IL-13 signaling by binding to the α subunit of the IL-4 receptor. LIBERTY and QUEST, two phase 3 trials, demonstrated significant improvement in lung function, exacerbation rate, as well as in Asthma Quality of Life Questionnaire (AQLQ) and Asthma Control Questionnaire-6 (ACQ-6) following subcutaneous administration of dupilumab every 2 weeks compared to placebo, with the maximum efficacy of dupilumab observed in patients with baseline eosinophil blood count ≥ 150 cell/μL and basal fractional exhaled nitric oxide (FeNO) ≥ 25 parts per billion (ppb).[35-38]

Thymic stromal lymphopoietin (TSLP) is an epithelial-cell-derived alarmin which is produced along with IL-33 and IL-25 upon exposure to allergens, pollutants, viral, fungal, and bacterial components and stimulate ILC2 and Th2 cells to produce type 2 cytokines.[39] Tezepelumab is a human monoclonal antibody that targets TSLP and it was recently licensed for severe asthma. In two RCTs PATHWAY and NAVIGATOR, treatment with Tezepelumab resulted in fewer asthma exacerbations per year compared with placebo, as well as improvement in lung function, asthma control and quality of life, regardless of the patients' allergic status.[40,41] Tezepelumab could also be considered in patients with type 2-low phenotype but according to SOURCE study thera was no significant diferrence between Tezepelumab and placebo in reduction of the OCS dose in patients with OCS-dependent asthma.[42]

All these biological therapies, except from Tezepelumab which is the most recent addition in the guidelines, have proven their efficacy and safety not only in RCTs but also in numerous real-life studies, published in the last decade.[18,19,21,32,35-38]

According to the GINA 2023 guidelines, patients eligible for receiving an add-on anti-IgE agent (omalizumab) include those sensitized to inhaled allergens on skin prick testing or specific IgE and elevated total serum IgE. Blood eosinophils ≥ 260/μl, FeNO ≥ 20ppb, childhood-onset asthma and allergen driven symptoms are considered moderate good response predictors. An anti-IL5 (mepolizumab, reslizumab) or anti-IL5R (benralizumab) agent can be administered in patients with high blood eosinophils count while adult-onset asthma, nasal polyposis, higher frequency of exacerbations and higher blood eosinophils count are considered strong good response predictors. Dupilumab, an anti-IL4R is approved as an add-on to severe eosinophilic/Th2 asthma in patients with high blood eosinophils count or high FeNO, as those biomarkers are considered to be strong predictors for response to treatment. Tezepelumab, an anti-TSLP agent, could be administered in severe asthmatics with severe exacerbations during the last year, while elevated blood eosinophils

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and FeNO levels are strong predictors of response, however it may also be considered in patients without ele-vated T2 biomarkers.[1] Table 2 summarizes the main characteristics of all these biological therapies.

Table 2. Approved biological therapies in severe asthma and their characteristics.

	Target	Initial approval for SA	Patient's age	Administration	Typical patient group
Omalizumab	IgE	2003	≥6 yrs	every 2-4 weeks SC, dose based on weight and serum Ige	Allergic asthma, childhood onset
Mepolizumab	IL5	2015	≥6 yrs	100 mg SC every 4 weeks (for ≥12 yrs)	Eosinophilic asthma, adulthood onset
Reslizumab	IL5	2016	≥18 yrs	3mg/kg IV every 4 weeks	Eosinophilic asthma, adulthood onset
Benralizumab	IL5Ra	2017	≥12 yrs	30 mg SC every 4 weeks for the first 3 doses, then every 8 weeks	Eosinophilic asthma, adulthood onset
Dupilumab	IL4Ra	2018	≥6 yrs	200mg or 300mg SC every 2 weeks (for ≥12 yrs)	Eosinophilic or allergic asthma, childhood or adulthood onset
Tezepelumab	TSLP	2021	≥12 yrs	210mg SC every 4 weeks	Eosinophilic or allergic asthma, adulthood onset, type 2 low asthma

4. Other potential agents and strategies investigated for the treatment of severe asthma

4.1. Anti-IgE agents

Anti-IgE monoclonal antibody Ligelizumab has a greater affinity for IgE than omalizumab and has been shown to consistently suppress skin test responses and free IgE levels. However, it did not show any significant effect in asthma outcome compared to omalizumab in a field study of asthma patients.[43,44]

Lumiliximab, an IgG1k chimeric monoclonal antibody from Macaca irus and Homo sapiens that targets CD23 has also been studied for use in allergic asthma, without significant clinical outcomes despite its proven ability to reduce circulating IgE concentration.[45,46] This lack of efficacy could be explained by the fact that there are many other factors involved, besides total free serum IgE, to be able to predict response to anti-IgE treatment. These factors may include cellular IgE receptor expression (FcεRI and FcεRII/CD23), specific/total IgE ratios, and cellular sensitivity, as well as local tissue IgE concentrations and permeation of the drug to the tissue site.

4.2. Agents acting on Th2 lymphocytes and their cytokine pattern

Airway inflammation in asthma is associated with increased activated CD25(+) T cells, IL-2, and soluble IL-2 receptors (IL-2Rs). Their secretion is induced by Th2 activation by allergens. In NCT00028288 trial, Daclizumab, a humanized monoclonal antibody to the CD25 subunit of IL-2R, was found to moderately improve lung function and asthma control.[47] Suppressing the IL-2

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pathway though, comes with significant risks that should be taken in consideration, such as immune mediated disorders (e.g. autoimmune hepatitis), and increased risk of infections, and limits it's use in the treatment of Th2 asthma.

IL-13 presents as another potential target for treatment in severe asthma as it has various effects in the pathogenesis of asthma, including promoting IgE production, attracting eosinophil chemokines, and increasing smooth muscle cells contractility. Lebrikizumab and tralokinumab, two anti-IL-13 monoclonal antibodies were studied as a potential treatment in various trials but failed to show any significant or consistent clinical benefit compared to placebo.[48-53]

4.3. Agents acting on eosinophils, IL-5, CCR3 and CCR4

The chemokine receptor CCR3 and cytokines IL-3, IL-5, and granulocyte-macrophage colony–stimulating factor (GM-CSF) regulate migration and proliferation of eosinophils, basophils, and mast cells in the airways. CCR3 is the cognate receptor for major human eosinophil chemoattractants from the eotaxin family and correlate with disease severity. TPI ASM8 and AXP 1275 were studied as potential treatments in moderate to severe asthma. Inhaled TPI ASM8 is a drug product containing two modified phosphorothioate antisense oligonucleotides, directed against GM-CSF receptors and human CCR3 respectively. Oral AXP 1275 is a small-molecule antagonist with high specificity for binding to CCR3. NCT 00264966 trial in 2008 showed that TPI ASM8 significantly reduced the early asthmatic response with a trend for the late asthmatic response, while the results of the RCT examining the effect of AXP 1275 published in 2018 demonstrated no inhibition of allergen-induced asthmatic responses [54,55] Mogamulizumab is a defucosylated, humanized monoclonal antibody targeting CCR4 approved for the treatment of patients with relapsed or refractory CCR4+ ATL in Japan. As CCR4 has a role in maintaining T-helper cell type 2 airway inflammation, mogamulizumab was considered as a potential treatment option in the management of asthma. The NCT01514981 trial that was designed to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of mogamulizumab in subjects with asthma was terminated in 2014 with no results posted.[56]

4.4. Agents acting on the Complement system

The C5 complement pathway has a key role in immune response. It is composed of inactive proteins that are present in the circulation and can be activated through different pathways, the most vital component being the C3 fraction. Several studies have shown an increase in the C5a levels in the asthmatic bronchial airways. Eculizumab is a monoclonal antibody, which binds to the complement protein C5, inhibiting its activation and is approved for the treatment of paroxysmal nocturnal hemoglobinuria. Its ability to prevent the formation of C5a and C5b-9 complex renders eculizumab a potential treatment candidate for asthma. In a placebo-controlled trial, inhaled eculizumab in allergic asthma patients improved lung function and reduced established airway inflammation.[16,57]

4.5. Proinflammatory cytokines

IL-1 consists of a group of eleven cytokines that regulate inflammatory response, including IL-1β and IL-1Ra. IL-1β represents a high-level mediator of the inflammatory cascade and dysregulation of its activity characterizes autoimmune diseases. Canakinumab is a human anti-iL-1β monoclonal antibody that suppresses autoimmune related inflammation by neutralizing IL-1β signalinig.[58] A randomized double-blind trial of canakinumab in mild allergic asthma patients showed that inhaled canakinumab attenuated the LAR compared to pre-treatment.[59] In another study, the IL-1 receptor antagonist, anakinra, showed a reduction in neutrophilic airway inflammation. Their efficacy and safety in severe asthma remains to be examined.[60]

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4.6. Viral Infection induced exacerbations

People with asthma are more likely to develop lower respiratory tract symptoms because of a viral infection and consequently develop infection–induced asthma exacerbations. In a randomized trial, inhaled IFN-β treatment was administered in patients with a history of upper respiratory tract infection induced asthma exacerbations, and although failing to meet its primary endpoint, a positive effect on ACQ-6, it showed a positive effect in morning PEF, thus rendering IFN-β as a potential treatment for asthma complicated by virus-induced exacerbations.[61]

4.7. Agents acting against IL-33

IL33, an epithelial-derived "alarmin", is induced by respiratory viruses, environmental pollutants and allergens that trigger exacerbations in asthmatics, as a response to tissue injury. This pathway has been found to be linked with asthma susceptibility. In the ZENYATTA study, IL-33 receptor ST2 inhibitor Astegolimab reduced asthma exacerbation rate in both T2-high and T2-low patients, as IL-33 receptor ST2 is expressed in both groups.[62]

4.8. Agents acting against TNF-α

Various immunomodulatory agents were investigated for their ability to reduce airway inflammation in severe asthma, but no substantial clinical benefit was established. TNF-α was considered a promising target for severe asthma treatment due to its association with airway neutrophilia in severe asthmatic patients. The most common anti-TNFα agents are infliximab and golimumab, two monoclonal antibodies against TNFα and etanercept, a soluble TNFα receptor fusion protein with high affinity to TNF-α than the native receptor and has a longer half-life. All these molecules were administered in randomized trials and failed to show any clinical benefit in severe asthma patients. In addition, anti-TNFα treatment come with severe side effects, including increased risk for infections, malignancies, congestive heart failure and demyelinating disorders, that outweigh their limited benefit.[63-65]

4.9. Novel promising agents

An oral antagonist of the Prostaglandin D2 receptor 2 (DP2 receptor) GB001 was administered in a clinical trial with mild to moderate asthma and was compared to placebo in terms of ACQ score, symptoms free days and time to exacerbation and showed promising results, despite not improving morning PEF and FEV1.[66] In another study, another investigational DP2 receptor, Fevipiprant, showed an improvement in AQLQ score and postbronchodilator FEV1 compared to placebo in moderate to severe asthma patients.[67]

Despite initial favourable results, the effectiveness of fevipiprant in reducing exacerbations in patients with severe asthma was not proven in two recently published phase 3 randomised controlled trials (LUSTER-1 and LUSTER-2). Although both studies showed a reduction of 23% in the high eosinophil population and 22% in the overall population with the 450 mg dose of fevipiprant, these findings were not statistically significant when compared with placebo.[68]

Several clinical studies showed increased numbers of mast cells in asthmatic bronchial airways. Tyrosine kinase is a mediator for mast cells proliferation and the tyrosine kinase inhibitor imatinib was found to have a beneficial effect in airway hyperresponsiveness, measured by increasing PC20 in methacholine challenge test. [69]

GATA3 has a vital role in Th2 asthma pathogenesis, as it is essential for Th2 lymphocyte activation and differentiation. Inhaled SB010, a synthetic DNA molecule that binds to GATA3 messenger RNA, managed to attenuate late and early asthmatic responses after allergen provocation and more studies on targeting GATA3 need to be initiated to determine efficacy and safety.[70]

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4.11. Allergen Immunotherapy in asthma

Patients with allergic asthma phenotype could benefit by identifying the responsible allergens and take appropriate measures to avoid exposure to those specific allergens, or by using allergen immunotherapy (AIT) to de-sensitize the patient to the specific allergen responsible for their symptoms and exacerbations. Sublingual (SLIT) or subcutaneous immunotherapy (SCIT) involves administering increasing dosages of the relevant allergen in patients with allergic disease.[71] Numerous studies involving allergen immunotherapy for the house dust mite (HDM) allergen, one of the most prominent allergens identified in allergic asthma phenotype, showed promising results. In HDM-sensitized mild-to-moderate asthma, HDM-SCIT alleviates clinical symptoms of asthma, reduce asthma exacerbations rate, and decreases ICS dose. In addition, there is evidence that AIT can modify the natural course of asthma.[72,73] Despite the proven efficacy of allergen immunotherapy (AIT) in mild-moderate forms of the disease, its clinical value in severe asthma is limited. According to ARIA guidelines AIT should not be considered for severe asthma patients who are candidates for biologics.[74]

5. Conclusions

The need of moving from a disease-centric approach to a tailored therapy in severe asthma is already being established in the medical community and scientists are focusing on the identification of molecular targets in the pathogenetic pathway of severe asthma. A considerable number of targets have already been identified and various clinical trials showed promising results, especially in T2-high asthma, and several biological agents against Il-5/IL-5R, IL-4R and IgE have already been approved and incorporated in the management of Th2 severe, uncontrolled asthma.

This shift in pharmacological approach from the general concept of anti-inflammatory treatment with ICS and bronchodilatation with LABA, to targeting specific molecules in the pathway of disease process in severe asthma was not always without problems and mistakes. Initial clinical studies of anti-IL5 therapy in early 2000s were disappointing as mepolizumab failed to inhibit allergen-induced bronchoconstriction and airway hyperresponsiveness in human asthmatics[75] or to add significant clinical benefit in uncontrolled asthmatic patients on ICS therapy.[76] But when the research was focused on the targeted group of severe eosinophilic and OCS-depended asthma the role of anti-IL5 treatment was then clearly showed and the benefits of this treatment was well established in clinical trials.[21-34] Furthermore, the biomarkers used to identify eosinophilic asthma was evolved through time from sputum EOS – a method useful in research but cannot be used in clinical practice – to blood eosinophils and NO measures in order to bring this treatment in the daily clinical practice.

On the other hand, the molecular pathways of the pathogenesis of T2-low severe asthma remain unknown at a great extend and there is currently no available targeted therapy for the management of T2-low asthma. Various promising agents were studied with disappointing results and/or their safety profile was unacceptable. It is therefore essential to expand our knowledge in the molecular mechanisms of T2-low asthma, better describe its phenotypic and endotypic characteristics and discover new biomarkers and novel therapeutic agents for this group of asthmatic patients. [6,77-79]

The highway of targeted – personalized therapy in severe asthma has opened widely in front of us but we need to drive carefully on this, with opened minds and thoughts. We are still in the beginning, and we have a long way to travel in front, but we must be optimistic that the results will be in benefit of our patients.

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