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Review

Diagnosis and Treatment in Asthma and Allergic Rhinitis: Past, Present, and Future

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Abstract: Respiratory diseases are pathological conditions that affect airways, hampering breathing and causing high mortality. In particular, asthma and allergic rhinitis (AR) are two of the most common airway diseases that affect millions of people and have a high prevalence in childhood and adulthood. Asthma is a heterogeneous chronic inflammatory disease characterized by wheezing, chest tightness, shortness of breath, and cough. AR occurs with rhinorrhea, nasal congestion, and sneezing. Indeed, these pathologies share common physiopathological mechanisms such as airway hyperresponsiveness and similar immunopathology such as tissue eosinophilia and T-helper type 2 inflammation. Moreover, AR can be an important risk factor for suffering asthma. Thus, early diagnosis and effective treatment are crucial to improving the health and quality of life of these patients. Classical drugs such as corticosteroids have been used; however, in the last decades, efforts to improve treatments have increased, focusing on biological agents and specific allergen immunotherapy development. Moreover, more precise diagnostic tools have been elaborated, besides classical methods (medical history, physical examination, and pulmonary function tests), such as basophil activation test, and specific cellular and molecular biomarkers (microRNAs, sputum/blood eosinophils, IgE serum, and periostin levels). Therefore, in this review, we compile all these important issues for managing asthma and AR.

Keywords: asthma; allergic rhinitis; eosinophils; diagnosis; treatment; biologicals; microRNAs

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1. Introduction

Respiratory diseases are pathological disorders of the airways and other parts of the lungs that represent a major health and economic burden, with high prevalence, and one of the leading causes of mortality and morbidity worldwide [1]. They are caused by multiple triggers, with air pollutants (nitrogen dioxide, carbon monoxide, or some volatile organic compounds), allergens (pollen, dust mite, pet dander, mold), biological agents (viruses, bacteria, fungi), and smoking tobacco being the most common ones [2]. Respiratory diseases comprise a wide spectrum of pathologies, with asthma, chronic obstructive pulmonary disease (COPD), lung cancer, and rhinitis being the most frequent ones [3]. Additionally, COVID-19 has become a common respiratory pathology in the last few years [4].

The management and treatment of respiratory diseases have always been a challenge for clinicians, especially due to the pathological heterogeneity of these diseases. Thus, the correct diagnosis and choice of effective treatment are crucial to improving the health of patients suffering from these diseases. In the present review, we focus on the diagnosis and therapeutic tools for asthma and allergic rhinitis (AR), recapitulating the advances and research performed in the last years.

2. Materials and Methods

The search of literature was performed between November and December 2022 in the PubMed database, using the following terms for asthma: "asthma" AND "clinical diagnosis" OR "miRNAs" OR "metabolomics" OR "proteomics" OR "transcriptomic" OR "inhaled drugs" OR "monoclonal antibody therapy" OR "allergen immunotherapy". In the same line, for AR we used the following terms: "allergic rhinitis" AND "clinical diagnosis" OR "molecular diagnosis" OR "inhaled therapy" OR "monoclonal antibody therapy" OR "allergen immunotherapy". We tried to omit general terms as "treatment" to prevent the ambiguity of irrelevant articles.

Original articles, reviews, clinical trials, randomized clinical trials, systematic reviews, and meta-analyses indexed from January 2000 to November 2021 using the search terms described above were searched. Mainly, we focused on eligible studies published since 2015, although earlier studies were also included if they were considered relevant to the topic. The inclusion criteria for the articles were the following: (i) written in English; (ii) performed on human subjects, in both adults and children; and (iii) articles or clinical guidelines for the management of asthma and allergic rhinitis. The exclusion criteria were the following: (i) animal and in silico studies; (ii) articles not written in English; (iii) articles mainly focused on other diseases that only mentioned asthma and AR; (iv) abstracts (not full text); and (v) studies lacking controls such as control case studies. A flowchart of the literature and article search can be observed in Figure 1.

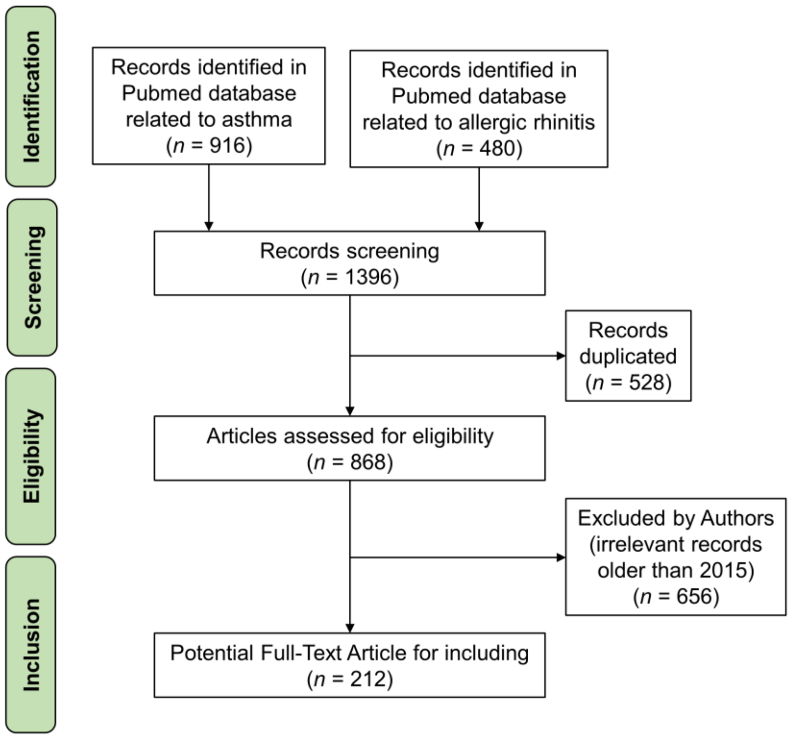

Figure 1. Overview of literature search and the steps performed.

3. Results

3.1. Asthma

Asthma is a chronic and heterogeneous respiratory disease characterized by airway inflammation and hyperresponsiveness, wheezing, shortness of breath, chest tightness, and cough [5]. It affects 300 million people around the world. Although its prevalence, morbidity, and mortality vary globally, asthma produced almost 500,000 deaths in 2019 [6].

Therefore, this respiratory pathology has become an important social and economic problem for multiple countries (high consumption of healthcare resources), making early diagnosis and effective treatment crucial. Despite its heterogeneity, asthma is presented with several phenotypes and endotypes, which makes, in most cases, its diagnosis difficult [7]. Traditionally, asthma has been divided endotypically into type 2 (T2) asthma and non-T2 asthma, and phenotypically into atopic, late-onset, obesity-related, or non-inflammatory phenotypes [7,8]. T2 asthma is triggered by allergic contaminants producing a typical T2 immune response, with cellular components as eosinophils, basophils, dendritic cells (DCs), immunoglobulin E (IgE)-producing cells, T-helper type 2 (Th2) cells, and pro-inflammatory cytokines being key players [9,10]. On the other hand, non-T2 asthma usually manifests itself in more severe states, where Th1 and Th17 cells, neutrophils, and non-Th2 cytokines are commonly present [11,12].

Taking this into account, effective treatments and diagnoses are needed. Hence, in this part of review, we focus on the different methods to diagnose this respiratory pathology and on how it can be treated.

3.1.1. Asthma Diagnosis

Clinical Diagnosis of Asthma

Over many years, the diagnosis of asthmatic pathology has been made by assessing the evaluating airflow limitation, bronchodilator responses, and by bronchial provocation challenges [13]. Additionally, the use of several biomarkers, such as fractional exhaled nitric oxide (FeNO), forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), and peripheral blood eosinophils, are of great utility (Figure 2). However, due to the heterogeneity in the pathomechanisms involved in this disease, currently, there are many challenges related to the development of more personalized and precise diagnostic tools [14].

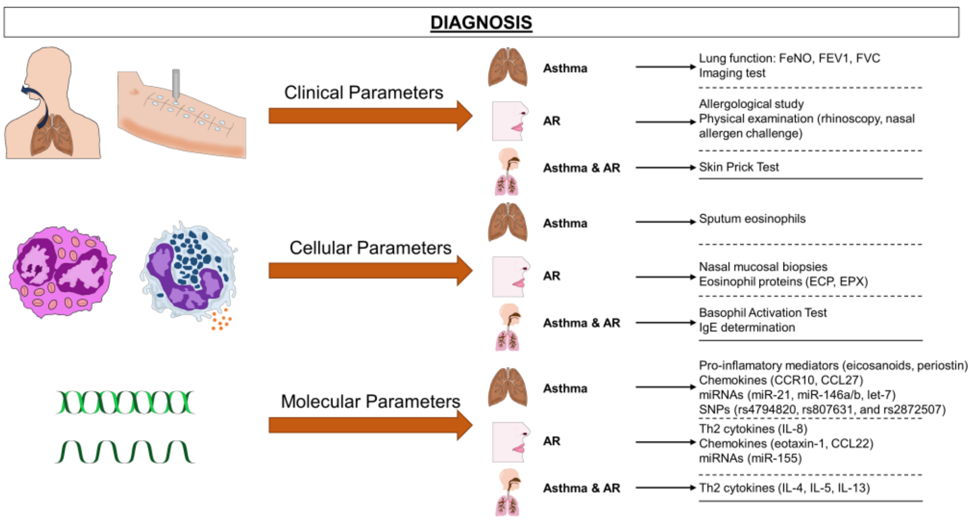

Figure 2. Diagnostic tools in asthma and AR. Different diagnostic methods can be used in asthma diagnosis, from classical methods (lung function, medical history, skin prick test) to cellular (eosinophil counts, basophil activation test) and molecular (measurements of cytokines and chemokines, and other biomarkers such as miRNAs) novel methods.

The development in recent years of drawing up guidelines updated by societies and working groups has led to an improved approach and clinical management of asthma [15]. An anamnesis should always be carried out to search for possible triggers and a complete allergological study should also be performed: with skin prick tests (SPT), detection of total and specific IgE (sIgE), and an allergen-specific nasal or bronchial challenge test to indicate an atopic state (Figure 2) [16]. Although there is no *gold standard* test, spirometry is essential, despite it maybe not being sufficient to confirm the diagnosis. Then, the spirometry parameters include FEV1 and FVC, which are variable according to age, height, weight, sex, and ethnic group. The main alterations in asthma are airflow obstruction, reversibility, variability, and bronchial hyperresponsiveness, so a reversible obstruction that improves after short-acting beta-agonists (SABA) administration confirms the diagnosis, although a normal result does not exclude it. Variations in peak expiratory flow (PEF) and FEV1 between exacerbations and stable periods in the same patient are also common. Spirometry with bronchodilator test and PEF measurement should be performed prior to the initiation of treatment, since as lung function improves, variability decreases. In cases where spirometry values comprised the normal range (FEV1/FVC > 0.7, FEV1 increase < 12%), it is possible to confirm the diagnosis by bronchial challenge with direct (methacholine) [17], indirect (mannitol, physical exercise) [18] or allergen-specific (decreasing FEV1 $\geq$ 20%) bronchoconstrictor agents, measurement of nitric oxide in exhaled air (FeNO > 40ppb) [19], diurnal variability of peak expiratory flow (PEF $\geq$ 20%) [20], or analysis of induced sputum (levels of sputum eosinophils, elevated values of eosinophil cationic proteins and Creola bodies) [21]. In addition, when a diagnosis cannot be reached, normalization of the pattern after treatment with oral glucocorticoids (GCs) for 14–21 days confirms it [22].

In any case, a correct differential diagnosis should be always reached, especially in treatment-refractory cases and if the evolution is not favorable. Imaging tests such as thorax radiography can rule out other respiratory diseases (signs of air trapping, atelectasis, or bronchial thickening) [15]. Establishing the phenotype (total and specific IgE determination, peripheral eosinophilia, FeNO measurement, and induced sputum), mainly in patients with severe asthma, allows for improvement in the clinical management of these patients and to offer them the most appropriate treatment.

Cellular Diagnostic Parameters and Biomarkers in Asthma

As support to clinical diagnosis, biomarkers and cellular and molecular parameters have been developed to diagnose asthma pathology (Figure 2). Asthma classification (T2 and non-T2) enables the establishment of an effective treatment strategy [23–25]. Th2 cells, type 2 innate lymphoid cells (ILC2), eosinophils, mast cells, and M2 macrophages are involved in T2 inflammation, characteristic of T2 asthma, which is primarily caused by the activation of the Th2 cells and ILC2, producing Th2 cytokines (IL-4, IL-5, IL-9, IL-13, and IL-31) [26,27]. At the cellular level, several immune cells (eosinophils, Th2 cells, ILC2, B cells, and mast cells) are present in T2 asthma. On the other hand, it is also known that neutrophils, Th1, and Th17 cells are the main mediators in non-T2 asthma [26]. Although the phenotypes of non-T2 asthma are still poorly known (some associated symptoms include obesity, smoking, and psychological factors), the innate immunological, metabolic, and epigenetic indicators must be considered [8]. Therefore, searching for new biomarkers and cellular diagnostic tools for allergy disorders, including asthma, has been the focus of a plethora of studies in recent years [28,29].

The basophil activation test (BAT) is a functional assay that evaluates the percentage of degranulation of the basophils after allergen incubation by flow cytometry. In the last few years, BAT has become a novel promise diagnostic tool for allergic asthma [30]. Basophil sensitivity, measured by CD-sens, has been demonstrated as a useful parameter in the diagnosis of allergic asthma, correlating with the dose of allergen used in the bronchial challenge that causes a 20% drop in FEV1 [31].

On the other hand, biomarkers are important parameters for precision medicine as they provide information on disease endotypes, clusters, precise diagnoses, identification of therapeutic targets, and tracking of therapy efficacies. Several studies have shown some clinically applicable cell point-of-care biomarkers [11,32–35], including sputum and blood eosinophils [36,37], circulating ILC2s expressing chemokine receptor (CCR) 10, plasmatic CCL27 levels, and an increase in serum IgE (Figure 2). Moreover, innate epithelial cytokines (IL-25, IL-33, and thymic stromal lymphopoietin [TSLP]), Th2 cytokines (IL-4 and IL-13), and receptor for advanced glycation end products (RAGE) are also important biomarkers in asthma [32,38–43]. In contrast, non-T2 asthma typically relies on neutrophilic or paucigranulocytic patterns [11,44,45], so calprotectin and HMGB1 levels are also useful biomarkers for this type of asthma. Although these biomarkers could provide limited information [37], they are used for multiple approaches: disease diagnosis, selection of targeted therapy, disease monitoring, and prediction of prognosis [46].

Molecular Diagnostic Parameters in Asthma: Proteomics, Metabolomics, and Transcriptomics Analysis

Several novel diagnostic tools are under current investigation, such as other biomarkers that may be measured in serum, bodily fluids, and exhaled air, such as pro-inflammatory mediators, micro RNAs (miRNAs), eicosanoid molecules, epithelial barrier integrity, and microbiota alterations [24,47,48] (Figure 2). They are helpful in the diagnosis and monitoring of allergic disorders [24,26,49,50].

New technologies such as imaging, artificial intelligence, and omics models further enable a precision treatment strategy for asthma [8]. Specifically, omics studies [51], such as proteomics [52,53], metabolomics [54], and transcriptomic (real-time PCR, microarrays, and RNA sequencing), have been recently used as tools for the identification of novel biomarkers as diagnostic tools. These are becoming even more necessary because of the use of biologicals in clinical practice for patient selection, outcome prediction, and monitoring, allowing for a suitable choice of how long to administer these expensive and long treatments [24].

On the other hand, the function of metabolites in allergic disorders has recently attracted scientific interest. Several pathophysiological processes in allergic diseases are influenced by eicosanoids, which include thromboxanes, leukotrienes, prostaglandins, and lipoxins [55]. In addition, periostin is an extracellular matrix protein that exhibits surrogate indicators for T2 immunity and tissue remodeling, making it a useful diagnostic marker for the early identification of asthma [56–58].

According to transcriptomic analysis, chromosome 17q21 is of interest in genetic epidemiological studies of asthma because it contains important genes (*ORMDL3*, *GSDMB*, *LRRC3C*, *GSDMA*, *ZPBP2*, *IKZF3*, *GRB7*, *ERBB2*, and *PGAP3*) and three single nucleotide polymorphisms (SNPs) (rs4794820, rs807631, and rs2872507) that are strongly associated with the pathogenesis and severity of asthma [26,59]. However, a multitude of factors (innate and adaptive immune response, metabolic pathways, microbiome infections, epithelial barrier, genetic and epigenetic factors, remodeled resident cells, anatomical factors, exposome allergens, irritants, pollutant- and psychosocial factors) can induce or suppress certain genes or pathways and may play a role in the development of certain phenotypes and endotypes as well as in the control of asthma [25]. In addition, differential gene expression related to cytokines and transcription factors, as well as immunological response and elevation of numerous cellular processes, are influenced by DNA methylation [60] and histone modifications [61–63]. Therefore, searching for epigenetic markers is also essential to finding out asthma endotypes, phenotypes, individualized treatments, and prevention.

Finally, over the past ten years, the interest in miRNAs has increased [26,38,64]. MiRNAs are short noncoding RNAs that behave as post-transcriptional negative regulators by inhibiting the translation of mRNA or initiating its degradation [65]. MiRNA levels in asthma have been correlated to the expression of the Th2 cytokines [66,67] IL-5 [68], IL-13 [69], as well as the tissue remodeling factor VEGF [70], which are key molecules in asthma pathogenesis [38]. Recent research has revealed that most miRNAs are involved in Th1 and Th2 cytokine secretion, anti-inflammatory responses, macrophage polarization, T cell differentiation towards T2 response, and bronchial smooth muscle cell hyperplasia and hypertrophy [71]. miRNA profiles can be correlated to clinical traits, such as lung function, phenotype, and asthma severity [72]. Moreover, miRNAs have been shown to be signaling molecules released by cells and transported in extracellular vesicles such as exosomes [73–75]. According to previous studies [76], asthma is primarily characterized by the upregulation of miR-21 [77–79], miR-223 [80], miR-146a [78], miR-142-5p [81], miR-142-3p [82], miR-146b [83], and miR-155 [84], and downregulation of the let-7 family [85], miR-193b [86], and miR-375 [87,88]. It has been shown that miR-155, miR-146a, miR-21, miR-1248, and miR-210 play key roles in controlling eosinophil and T cell activities as well as the release of Th2 cytokines (IL-4, IL-5, IL-13) [76]. However, for the use of miRNAs as biomarkers, they must be specific to each pathology, able to predict asthma phenotypes, and easy to detect in bodily fluids [38]. Therefore, clinical investigations may benefit from the expression of circulating miRNAs [36], because several of these miRNAs were found to distinguish asthmatic from non-asthmatic children [89] and adults [66,67,84,90–93], and rank asthma severity [94].

3.1.2. Asthma Treatment

Due to asthma heterogeneity, symptoms, and severity, the goal of asthma treatment is to ameliorate this pathology's symptoms, avoiding future risks. Historically, asthma has been treated with anti-inflammatory drugs and bronchodilators [95]. The reliever treatment with inhaled corticosteroids (ICs)-formoterol reduces the risk of exacerbations as compared to the use of SABA. However, nowadays, new techniques have been developed, comprising immunotherapy and biologics [95,96] (Figure 3). In most cases, personalized asthma treatment is necessary, because each patient develops symptoms in a different way [97]. Therefore, there are two critical factors in the treatment of asthma: the patient's symptoms and the way that the patient reacts to medication [98].

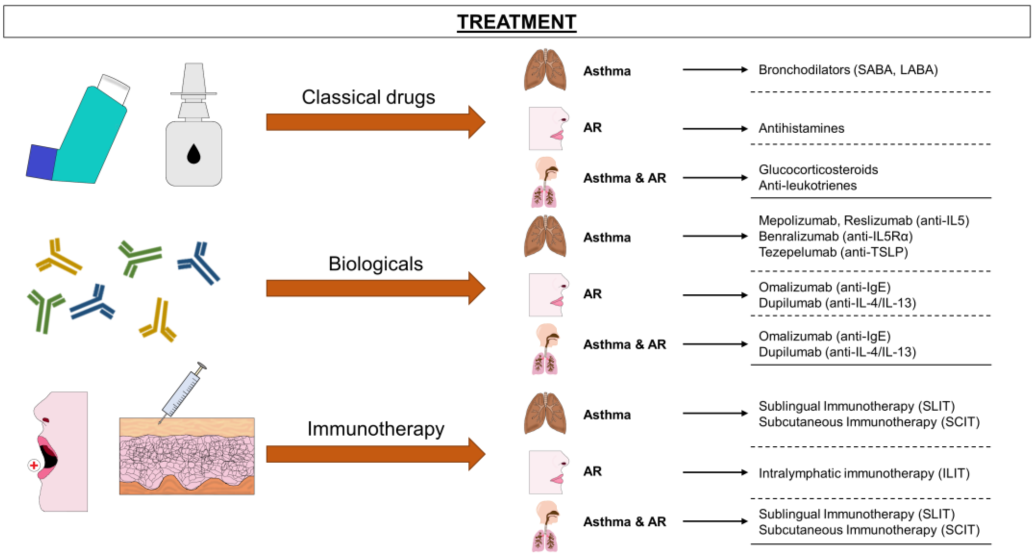

Figure 3. Therapeutic tools in asthma and AR. Traditionally, asthma and AR have been treated with classical drugs, such as bronchodilators, antihistamines, and corticosteroids. The form of administration of glucocorticoids is inhaled in asthmatic patients, while in patients with AR it is intranasal. However, in the last decades, the development of novel and more specific therapeutic tools such as biologicals and immunotherapy have permitted a more personalized medicine for asthma and AR.

Currently, two categories of drugs are used for the treatment of asthma: rescue and controller drugs [15] (Figure 3). Rescue drugs are used to alleviate symptoms quickly (within minutes), whereas controller medicines are used daily to treat all asthma symptoms and to achieve asthma remission [15,99].

The main rescue drugs are inhaled, rapid-acting β2 adrenergic agonists (SABAs), such as albuterol and levalbuterol [100]. They are recommended for patients with mild or intermittent asthma [15]. SABAs bind to β-adrenergic receptors from the smooth muscle cells of the lung, causing the release of $Ca2^{+}$ and, subsequently, muscle relaxation, mitigating asthma symptoms in a few minutes [101]. The use of these medicines is still limited because of their adverse effects: tremors, tachycardia, and hypocalcemia [100].

Severe asthma is defined as uncontrolled asthma despite optimized treatment with high-dose of ICs and long-acting β2 adrenergic agonists (LABAs), or requires this treatment to prevent exacerbations [15]. So, ICs are the first option as controller drugs, such as mometasone, budesonide, and ciclesonide [100]. These medications act as anti-inflammatory molecules, producing a long-term reduction in asthma symptoms [100,102]. However, ICs have negative side effects such as oral infections, hoarseness, reduction in growth velocity, osteoporosis, or hypothalamic–pituitary–adrenal axis suppression [103].

In addition to ICs, oral corticosteroids (OC) can be also used in asthma management [15]. They have more anti-inflammatory power than ICs, but also more adverse effects (loss of bone density, hyperglycemia, weight gain, cataracts, hypothalamic–pituitary–adrenal axis suppression, diabetes, sleep apnea, etc.) [104,105]. Nevertheless, an optimal concentration of OCs can be helpful in relieving symptoms of moderate–severe asthma [100].

Another type of drug employed in asthma control treatment is an LABA, such as salmeterol, formoterol, and vilanterol, having a similar mechanism of action to SABAs, blocking β-adrenergic receptors on the smooth muscle of the lung, and relaxing smooth muscle [100]. Although LABAs have a longer half-life than SABAs, they are considered controller drugs. LABAs are recommended to be used in combination with other corticosteroids [15].

On the other hand, other drugs used in the treatment of asthma are antileukotrienes, such as montelukast and zafirlukast. Leukotrienes are inflammatory molecules produced during the Th2 response by the degranulation of basophils, mast cells, and eosinophils. These molecules are responsible for airway inflammation and subsequent asthma symptoms [106,107]. Anti-leukotrienes are anti-inflammatory drugs that interfere with leukotrienes synthesis by inhibiting the 5-lipoxygenase activity, and they also act as cysteinyl leukotriene receptor 1 (CysLT1) inhibitors [108,109], blocking leukotrienes inflammatory activity. Several studies have found that these drugs have less anti-inflammatory capacity than the others mentioned above. Bleecker et al. demonstrated that inhaled fluticasone propionate was more effective than montelukast in improving some asthma exacerbations: FEV1 (0.42 L vs. 0.20 L over baseline, $p < 0.001$), morning PEF (49.94 L/min vs. 11.68 L/min over baseline, $p < 0.001$), and evening PEF (38.91 L/min vs. 10.50 L/min over baseline, $p < 0.001$) [110]. Thus, antileukotrienes are only used in the treatment of mild asthma [15]. However, anti-leukotrienes have several side effects such as elevated levels of transaminases, which indicates hepatocellular injury [109].

Finally, long-acting muscarinic antagonists (LAMAs) are used in the treatment of severe asthma, such as tiotropium, which is among the most used ones [15]. They are suppressors of acetylcholine, which acts as a bronchoconstrictor during asthmatic responses [111]. LAMAs inhibit the muscarinic receptors of the bronchioles (there are five muscarinic receptors, but only M1, M2, and M3 are enrolled in asthma exacerbations); thus, acetylcholine cannot bind to these receptors and muscle relaxation occurs [112].

3.2. Allergic Rhinitis

One of the most common comorbidities associated with asthma is AR, which also contributes to asthma severity [113]. AR is a heterogeneous disease that affects the upper airway and nose, and it is characterized by itching, sneezing, watery rhinorrhea, and nasal congestion [114]. AR also contains an allergic component characterized by an IgE-mediated response against specific allergens, producing inflammation by several mediators released by Th2 cells, eosinophils, and mast cells [115]. Although nasal allergen challenge (NAC) is the gold standard method to diagnose AR (with optimal sensitivity, specificity, and safety) [116], the development of novel diagnostic methods is needed, such as BAT [117] (Figure 2). Treatment options comprise ICs, antihistamines (AHs), allergen immunotherapy [114], and, during the last years, the study of treatment using biologic therapies in severe AR have increased exponentially [118–121] (Figure 3).

Symptoms begin after exposure to the sensitized allergen, which triggers within minutes rhinorrhea, sneezing, nasal itching, and nasal obstruction, which can also occur at a later time. AR can present ocular symptoms in up to 60–80% of cases, bronchial symptoms (75–80%) [122], and nasal polyposis (1.5%) [123].

AR is commonly classified based on the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines, which has a good clinical correlation with the visual analogue scale (VAS) [124]. According to its duration, it can be classified into intermittent/persistent (taking 4 days/week and/or 4 consecutive weeks as the cutoff point) and according to the impact on quality of life (impairment of activities of daily living, disturbance of night-time rest, disturbance of work/study, bothersome symptoms) into mild and moderate/severe.

3.2.1. Diagnosis of Allergic Rhinitis

Clinical Tools to Diagnose Allergic Rhinitis

The allergological study begins with a detailed clinical history [125] (symptoms, seasonality, relationship with triggers, associated symptoms, need for treatment, and response) as the diagnosis is fundamentally clinical. Complementary tests are necessary to study its etiology and phenotype, as well as a correct physical examination [126]. Physical examination by anterior rhinoscopy or nasal endoscopy provides information (mucosal coloration, turbinate morphology, or the presence of polyps) that may indicate the presence of other associated pathologies, although there are no pathognomonic signs.

To confirm the presence of allergen-specific IgE, intraepidermal SPT and/or detection of specific IgE in serum against allergens that are considered clinically relevant for the patient can be performed. Skin tests can diagnose two out of three allergic diseases and up to 90% of respiratory allergies [127]. Skin prick tests are considered to be more sensitive, fast, and cost-effective than serum IgE tests [128].

Circulating sIgE against whole allergens or components allows us to differentiate between genuine sensitization or cross-reactivity, which is essential information for the indication of treatments such as immunotherapy [129,130].

NAC can be performed by acoustic rhinometry, anterior or posterior rhinomanometry, or measurement of nasal peak inspiratory flow (NPIF). Although its use is becoming increasingly widespread, NAC is not routinely performed. NAC can be used to assess the clinical relevance in polysensitized patients [126] or when it is not possible to determine sIgE (serum and/or skin tests) [131]. In addition, NAC is currently the gold standard for the diagnosis of local allergic rhinitis (LAR), as it is a safe and reproducible technique [116].

The diagnosis is, therefore, clinical; therefore, it is important to differentiate between sensitization and allergy [132]. In addition, the infiltration of cells and inflammatory mediators can be studied by the detection of sIgE in nasal secretions, which is common in research, as well as BAT [133]. Once a diagnosis is reached, we will use methods to assess control: the VAS, considering uncontrolled rhinitis $\geq$5, and specific validated questionnaires, commonly used in research, such as the Rhinitis Control Assessment Test (RCAT) and Allergic Rhinitis Control Test (ARCT), or the more recently published ARIA-c, with the same parameters used for the staging of severity.

Cellular Diagnostic of Allergic Rhinitis

Similar to asthma, AR is characterized by an inflammation produced by the T2 immune response, which involves: Th2 cells, IgE-producing B cells, basophils, mast cells, eosinophils, and a plethora of Th2 cytokines (IL-4, IL-5, IL-9, IL-13, IL-25, IL-31, IL-33, and TSLP) [134–140]. Patients with AR are characterized by a pattern with a cellular infiltrate that induces a nasal production of mediators such as tryptase, eosinophilic cationic protein (ECP) [141,142], and sIgE [143]. In this context, a study performed by Chen and colleagues concluded that the levels of activated and pathogenic eosinophils, which are associated with higher production of ECP, eosinophil peroxidase (EPX), and IL-4 in the peripheral blood were elevated in patients with moderate–severe AR in comparison with mild patients and healthy controls [144]. In addition, several chemokines, such as the eotaxin family, which recruit and activate Th2 lymphocytes, mast cells, and eosinophils, seem important in allergic diseases as well [145]. In this regard, for example, high levels of eotaxin-1 (CCL11) were obtained after NAC in patients with AR in comparison with controls [146].

On the other hand, ILC2 residing at mucosal and barrier surfaces can act as effector immune cells. ILC2 are associated with allergic disorders, including AR [147,148], and they are functionally like T cells (but lack antigen receptors). Allergic phenotypes of rhinitis are determined by measuring allergen-sIgE in serum and BAT [149]. BAT reproduces in vitro, after allergen exposure, the type I hypersensitivity reaction [150]; an immediate reaction that involves IgE-mediated release of antibodies against the soluble antigen [151]. For LAR diagnosis, BAT exhibits a high specificity (100%), in contrast to its sensibility (ranging from 50% to 66.6%) depending on the allergen evaluated [117,152,153]. In this regard, 37.5% of LAR individuals (all of them with NAC positive to *Dermatophagoides pteronyssinus*) and 60% of dual allergic rhinitis (DAR) patients showed positive BAT responses with perennial allergens, as opposed to NAR and healthy subjects (negative for all of them) [154].

Molecular Diagnostic Parameters in Allergic Rhinitis

In the last few decades, several studies have focused on molecular parameters associated with inflammation in AR, such as chemokines associated with Th2 function [8]. In this context, high levels of CCL22 (monocyte-derived chemokine (MDC)), which promote selective migration of Th2 cells, were found in the serum of patients with AR sensitized to birch pollen [155] and ragweed pollen [156], suggesting a possible role in the pathogenesis of AR. Another chemokine that has been associated with AR is CCL13, whose expression is stimulated by IL-4 and was found to be increased in the serum of AR patients after NAC [157].

On the other hand, miRNAs are thought to be involved in the pathogenesis of AR [40,158,159]. MiR-155 levels in serum of children with pollen-induced AR were higher in comparison with healthy controls, and miR-155 in the serum correlated significantly with nasal symptoms in children with AR (r = 0.494, $p < 0.001$) [160]. Moreover, Luo and colleagues found serum TSLP, expression of miR-375 from whole blood, and frequencies of ILC2 in peripheral blood levels significantly higher in AR children compared with controls [140]. Moreover, another study showed that the level expression of miR-487b was repressed in AR in comparison to control cases [161]. Finally, Teng et al. found that the expression of miR-143 was significantly decreased in nasal mucosal tissues from AR patients compared with tissues from NAR subjects [162].

Additionally, Th1/Th17 were also proposed to be involved in allergic diseases, such as AR [163]. In this context, Erkan et al. [143] showed that serum and nasal IL-17 were higher in AR in comparison with control individuals. Moreover, Lee and collaborators showed that serum levels of IL-8 were significantly higher in patients with allergic asthma in comparison with AR and controls, suggesting that IL-8 is associated with a more severe inflammatory response [164]. However, other studies showed that elevated levels of IL-8 can also be related to pollution and not only allergic sensitization, suggesting that air pollution might induce or aggravate AR through this cytokine [165]. Other studies, such as Yu et al., showed a decreased surface CXC motif chemokine receptor 3 (CXCR3) expression in $CD4^+$ T cells of AR patients [166].

In the case of the innate immune response, a study performed by Kant (which excluded individuals with an active infection), with 205 AR patients and 49 healthy controls, found that the neutrophil/lymphocyte ratio was significantly lower in patients with AR than in healthy controls [167]. In relation to ILC2, several studies showed that these cells in peripheral blood and nasal samples are increased after NAC, and there was also a positive correlation between eosinophils and IL-5 concentrations in patients with AR [168,169]. In this context, several studies showed evidence of increased epithelial proinflammatory cytokines, such as IL-25, IL-33, and TSLP in the nasal lavage from patients with house dust mite (HDM) sensitivity [170,171]. Other studies have shown that patients with AR displayed high levels of IL-33 and TSLP mRNA in the nasal epithelium [172–174].

3.2.2. Treatment of Allergic Rhinitis

AR management includes patient education, allergen avoidance, pharmacotherapy, immunotherapy, and biologics. It is essential to explain to the patient about their disease and how to take their treatments. The first step is to avoid exposure to the allergen. However, if the symptoms persist, the first line of treatment is drug therapy. Immunotherapy is recommended when the disease is not controlled with the usual drugs. In addition, in recent years, biologics have emerged as a novel therapeutic option with promising results [175–178] (Figure 3).

Typical AR drugs include AHs, GCs, and leukotriene receptor antagonists. Second-generation oral antihistamines are the first line of pharmacological treatment, as well as intranasal corticosteroids (INCs), which have demonstrated even greater efficacy than AHs. [179]. Intranasal combination therapies with AHs and GCs, such as azelastine hydrochloride/fluticasone propionate (AZE/FP), are also recommended [180].

Antihistamines bind to the histamine H1 receptor and block its action. First-generation of oral antihistamines (OAHs), such as diphenhydramine or chlorpheniramine, have been widely used in the clinic. However, due to their adverse effects, they are no longer supported for AR [181]. Their main secondary effect is sedation as they cross the blood-brain barrier causing drowsiness and fatigue, among other symptoms [182]. Therefore, the use of new-generation AHs (such as desloratadine, loratadine, cetirizine, levocetirizine and rupatadine, fexofenadine, and bilastine) is strongly recommended. These have been shown to be safer than the previous ones, maintaining the same efficacy without the sedative effect [181,183].

Intranasal antihistamines (INAHs) improve the effect of oral antihistamines at the nasal mucosa [184,185]. Moreover, they are more effective in controlling local symptoms, such as nasal congestion [186,187]. In addition, they act faster than OAHs and reduce potentially systemic effects [187]. They are recommended as first-line treatment for seasonal AR (SAR) [122]. The two INAHs approved for the management of SAR are azelastine and olopatadine. Both have demonstrated similar efficacy [188]. They differ in that azelastine inhibits both H1 and H2 receptors, while olopatadine only inhibits H1.

INCs (beclomethasone, budesonide, ciclesonide, fluticasone propionate, fluticasone furoate, mometasone furoate, and triamcinolone acetonide) have a local anti-inflammatory effect by preventing the recruitment of immune cells into the nasal mucosa. They are indicated as first-line treatment in patients with moderate or persistent symptoms [180]. In addition, they have the advantage of having no systemic adverse effects [189,190]. INCs have demonstrated efficacy in controlling the main symptoms of AR: nasal congestion, itching, rhinorrhea, and sneezing [191,192]. INCs have been described to be more effective than AHs for nasal congestion [179].

OCs are not used as a routine treatment for rhinitis, because their adverse effects exceed the potential benefits [193]. A short course, only for a few days, with oral corticosteroids, can be indicated in patients with severe symptoms that do not respond to other drugs [194]

A novel formulation combines azelastine hydrochloride (AZE) and fluticasone propionate (FP) in a single nasal spray. This combined therapy has proved to be faster [195] and more effective than both drugs taken individually. [196,197]. One of the advantages is that it increases adherence to treatment by administering both drugs at the same time. In addition, the drugs are more homogeneously distributed in the nasal mucosa than if AZE and FP sprays were used sequentially [198]. It is recommended for the initial treatment of moderate to severe nasal symptoms of SAR [180], as well as for patients with both seasonal and perennial AR who do not respond to monotherapy [122].

LTRAs act by blocking the activity of cysteinyl leukotrienes, an inflammatory mediator associated with the main symptoms of AR, such as nasal congestion and mucus production [199]. The main LTRAs are montelukast and zafirlukast. They should only be used when the patient does not respond to any other drug. This is because they are equally or less effective than INAH, INCs, or OAH, [200,201] and have also been associated with serious neuropsychiatric adverse effects. In fact, in Europe, they are only approved for the treatment of patients with asthma and rhinitis comorbidity [202].

3.3. Biologicals in Asthma and Allergic Rhinitis

Due to the diversity of adverse effects induced by classical drugs, new approaches for the treatment of asthma have been sought. Among these new therapies for asthma and rhinitis are biologicals (Figure 4). Biologicals are humanized monoclonal antibodies that target several molecules responsible for the T2 response, inhibiting it and ameliorating asthma symptoms. The main targets of biologics for asthma treatment are IgE (omalizumab), IL-5 (mepolizumab and reslizumab), the IL-5 receptor (benralizumab), the IL-4/IL-13 receptor (dupilumab), and TSLP (tezepelumab) [203] (Figure 4), although novel biologicals against other targets are being developed. Although these drugs have been studied and approved for asthma treatment, only the use of omalizumab and dupilumab in rhinitis have also been extensively studied [204,205]; however, to date, none have been approved by drug agencies for the treatment of AR.

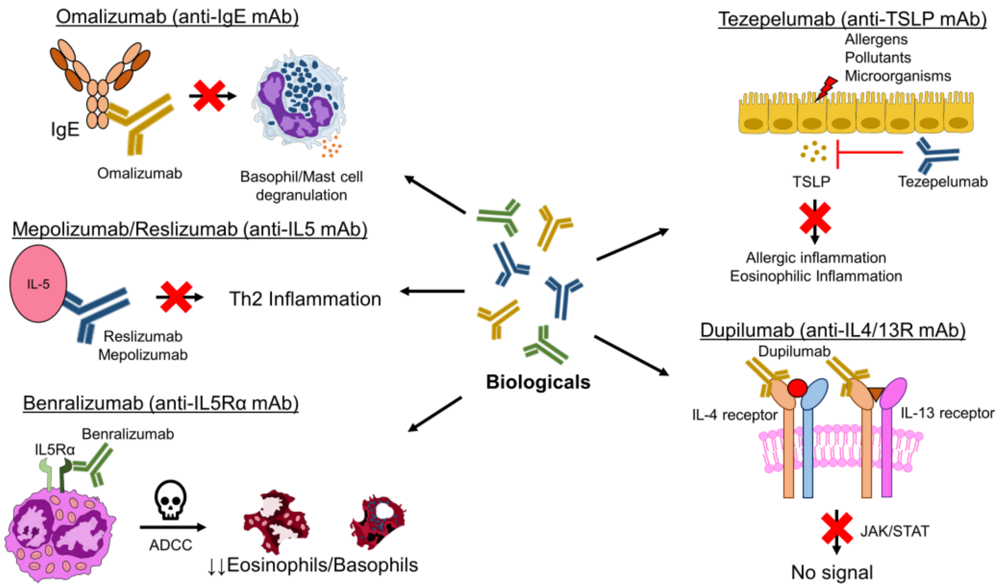

Figure 4. Biologicals used in asthma and AR. Mechanisms of action of different biologics are schematized (omalizumab, mepolizumab, reslizumab, benralizumab, tezepelumab, and dupilumab). Biologicals usually target inflammatory molecules, cytokines, or their receptors, blocking downstream inflammatory pathways or triggering-induced cell death. ADCC: antibody-dependent cell-mediated cytotoxicity; mAb: monoclonal antibody.

3.3.1. Omalizumab (Anti-IgE)

It was the first biological approved for the treatment of asthma by the Food and Drug Administration (FDA) in 2003 [206]. Nowadays, it is used in patients aged 6 years and older with moderate–severe asthma, and it is recommended its subcutaneous administration every 2 or 4 weeks depending on IgE serum levels and body weight [15].

Several studies have demonstrated the efficacy of omalizumab in the treatment of severe asthma [207]. The EXTRA study (NCT00314574) enrolled 850 patients with uncontrolled severe allergic asthma [208]. Asthma biomarkers: FeNO, blood eosinophils, and serum periostin showed a normalization in the patients that received omalizumab in comparison to the placebo group. The PROSPERO study (NCT01922037) demonstrated an improvement in asthma symptoms in 87% of the patients after receiving omalizumab for 48 weeks [209].

Recently, two meta-analyses have been performed, evaluating several trials testing the use of omalizumab in AR [176,177]. In one meta-analysis, Yu et al. included 16 randomized clinical trials, while Tsabouri et al. developed a systematic review of 12 trials. Both studies reached almost the same conclusions: treatment with omalizumab significantly improves both ocular and nasal symptoms, reduces the use of rescue medication, improves the quality of life, and, in addition, no increase in adverse effects was observed compared to the placebo group.

3.3.2. Mepolizumab and Reslizumab (Anti-IL-5)

In 2015 the FDA authorized mepolizumab [210] for patients aged 6 years and older with severe eosinophilic asthma. The recommended dose by subcutaneous injection every 4 weeks depends on the patient's age [15].

Mepolizumab effectiveness was evaluated for the treatment of severe eosinophilic asthma in the MENSA study (NCT01691521) [211]. Mepolizumab reduced asthma exacerbations by 47% in patients who received intravenous doses and by 53% in those receiving subcutaneous doses as compared with the group receiving placebo. Recently, the COSMEX study (NCT02135692) showed the long-term efficacy of mepolizumab [212]. This Phase IIIb clinical trial involved 340 patients with eosinophilic asthma who had previously participated in the SIRIUS (NCT01691508), MENSA (NCT01691521), and COSMOS (NCT01842607) [211,213,214]. In the COSMEX study, patients received mepolizumab subcutaneously every 4 weeks for at least 188 weeks, showing a fivefold reduction in the rate of exacerbations per year [212].

On the other hand, reslizumab was approved by FDA one year after mepolizumab [215]. Its mechanism of action is the same as mepolizumab, but reslizumab has weight-based dosing, so it is useful for patients with high body mass index [216]. It is authorized for patients aged 18 years and older with severe eosinophilic asthma, recommended to administer 3 mg/kg by intravenous infusion every 4 weeks [15]. In 2016, Corren et al. showed the efficacy of reslizumab in a randomized, double-blind Phase III trial (NCT01508936) [217]. In this study, the administration of reslizumab once a month for 16 weeks in 492 patients with asthma exacerbations demonstrated an improvement in exacerbations, especially in those patients with baseline eosinophils $\geq$ 400 cells/μL.

3.3.3. Benralizumab (Anti-IL-5 Receptor)

At the end of 2017, benralizumab was approved [218]. It is administered to patients over 12 years with severe eosinophilic asthma by subcutaneous injection every 4 weeks for the first three doses and then every 8 weeks [15]. The CALIMA study (NCT01914757) showed the efficacy of benralizumab in the treatment of severe eosinophilic asthma [219]. This randomized Phase III clinical trial performed by FitzGerald et al. enrolled 1306 patients with asthma symptoms. In this study, the annual exacerbation rate in the patients who received benralizumab was diminished by 36% in those patients who received the treatment every 4 weeks and by 28% in those who did it every 8 weeks. Similar results were found in SIROCCO study [220], corroborating the efficacy of benralizumab in the treatment of severe eosinophilic asthma.

3.3.4. Dupilumab (Anti-IL-4/13 Receptor)

Dupilumab was approved by the FDA in 2017 [221]. It is recommended for patients aged 6 years and older who present severe eosinophilic asthma, but also for the treatment of moderate to severe atopic dermatitis, moderate to severe asthma, and chronic rhinosinusitis with nasal polyps (CRSwNP) [222]. It is administered by subcutaneous injection every 2 weeks in patients older than 12 years. For children between 6–11 years of age, the dose depends on weight [15].

Several studies have demonstrated the efficacy of dupilumab in the treatment of asthma and chronic rhinosinusitis [223]. In 2018, Castro et al. carried out a randomized, double-blind trial (NCT02414854) involving 1902 patients aged 12 years and older with uncontrolled asthma [224]. Participants received dupilumab 200 or 300 mg or placebo every 2 weeks for 52 weeks. Results showed that severe asthma exacerbations were reduced by 47.7% among patients receiving dupilumab as compared with individuals that received a placebo. Moreover, dupilumab has been shown to be more effective than OCs in the treatment of severe asthma [225]. Rabe and collaborators carried out a randomized phase III clinical trial (NCT02528214) in which 210 patients with OC-treated asthma were recruited [225]. They received dupilumab (300 mg) or a placebo every 2 weeks for 24 weeks. During the study, the glucocorticoid doses were reduced each week, and at the end of the study, the decrease in the dose was 70.1% for the dupilumab group and 41.9% for the placebo group. Despite dose reduction, dupilumab treatment showed a 59% lower exacerbation rate as compared with the placebo group. Nevertheless, this biological presents important adverse effects like blood eosinophilia, dry eyes, keratitis, conjunctivitis, head and neck dermatitis, and arthritis [226].

Regarding the use of dupilumab in AR, Weinstein et al. recently reviewed a randomized, double-blind Phase IIb clinical trial (NCT01854047) in patients with asthma and perennial AR (PAR) [227]. This trial evaluates the efficacy of dupilumab at different doses: 200 mg or 300 mg subcutaneously every 2 or 4 weeks; versus placebo. There was evidence that 300 mg of dupilumab every 2 weeks in combination with intranasal corticosteroids and β2 agonists, significantly reduced nasal symptoms in patients with asthma and comorbidity with PAR [178]. Although dupilumab has demonstrated several benefits in the treatment of AR, as well as omalizumab, further studies are needed to corroborate their cost-effectiveness against current therapies.

3.3.5. Novel Biologic Therapies

Nowadays, other biologicals are being studied with the aim of treating non-allergic asthma.

Tezepelumab is an IgG_2 monoclonal antibody that targets TSLP, which is a protein produced by epithelial cells in response to both allergens, viruses and other toxins involved in the triggering of asthma. This biological has recently been approved to treat severe asthma in patients aged 12 years and older [228], supported by previous clinical trials that have shown promising results in the treatment of allergic and non-allergic asthma with this biological [229]. In this randomized, double-blind, placebo-controlled trial, 1061 patients were randomized to receive tezepelumab or placebo subcutaneously for 52 weeks, once a month. Results showed that patients that received tezepelumab had lower rates of asthma exacerbations, lower blood eosinophil count, and an improvement in lung function parameters.

On the other hand, another biological still under development is astegolimab, a monoclonal IgG_2 antibody that binds to the IL-33 receptor (anti-ST2) [230]. The ZENYATTA study comprised 502 severe asthmatic individuals distributed into several groups: patients that received placebo or 70 mg, 210 mg, or 490 mg doses of astegolimab subcutaneously every 4 weeks [230]. Patients that received the highest and the lowest dose of astegolimab showed higher rates of reduction of asthma exacerbations in both types of patients with uncontrolled asthma: eosinophil—high (≥300 cells/μL) and eosinophil—low (<300 cells/μL).

3.4. Allergen-Specific Immunotherapy

Classical treatments for asthma have been used to relieve the symptoms caused by the inflammatory process. Nevertheless, these do not solve the underlying problem: the disproportionate response of the immune system. In addition, classical therapies have various long-term side effects, and it is difficult to find an optimal treatment for each patient, because of asthma heterogeneity. Therefore, immunotherapy has been postulated as an effective strategy offering long-term tolerance [231]; additionally, it is less expensive than other treatments commented on previously, like biologicals [96,232,233].

Immunotherapy involves the administration of increasing amounts of the allergen until an adequate dose to produce immunological tolerance is achieved [128]. Repeated exposure to the allergen causes the DCs to produce IL-10, IL-12, and IL-27, which are regulatory cytokines. They stimulate Th1 response, thus restoring the balance between the T1 and T2 response. In addition, IL-10, IL-12, and IL-27 also activate Treg and B cells, favoring the production of antibodies that will block future T2 responses, such as IgG_4 [234]. There is also a modification of the activation threshold of mast cells and basophils [202].

It has been proven that AIT has long-term benefits for asthma and AR [235–238]. Its effect persists even years after ending the treatment, with a consequent reduction in medication use as well as a decrease in the risk of developing asthma [88]. Despite its more than proven efficacy, immunotherapy is mainly recommended when patients do not control their symptoms with conventional pharmacotherapy or if they do not tolerate these drugs [142,239]. Different types of allergens can be used in immunotherapy: crude allergen extracts, purified or recombinant allergens, modified allergens (allergoids), and purified peptides [240]. Allergen administration is usually subcutaneous, but sublingual immunotherapy (SLIT) is also available, in addition to a less common route of intralymphatic immunotherapy (ILIT). The main adverse effect of immunotherapy is the development of uncontrolled allergic responses [234].

On the one hand, SCIT is based on the periodical administration of increasing amounts of the allergen until immunological tolerance is achieved. SCIT is effective against several allergens, such as HDM, birch pollen, timothy grass, and ryegrass [241–243]. However, SCIT has some drawbacks, such as the need for frequent injections; moreover, these must be administered in a hospital [239], in addition to the potential risk of anaphylaxis [244]. In several studies, AIT has been demonstrated to be more effective than conventional drugs in controlling AR symptoms. A recent randomized clinical trial compared a group of patients receiving AIT plus pharmacotherapy versus a control group receiving only drug treatment. The results showed a significant decrease in symptoms in the immunotherapy-treated group, as well as an improvement in quality of life, compared to the control group [245]. Rondon and collaborators developed another randomized, double-blind placebo-controlled trial with *Phleum pratense* SCIT performed in 56 patients with moderate–severe LAR to grass pollen demonstrating that SCIT increased allergen tolerance [246]. Most patients treated with SCIT for more than 6 months showed an allergen tolerance over 50 times higher than baseline, and 56% showed a negative nasal allergen provocation test. Moreover, these authors demonstrated that SCIT was safe for patients not having serious adverse events related to the medication.

On the other hand, SLIT offers multiple benefits over the subcutaneous route as it does not require injections, can be administered at home, and has a lower risk of systemic adverse effects [247]. However, it must be administered daily, which may be a problem for adherence to treatment [248]. Previous studies have demonstrated the efficacy of SLIT in asthma treatment, although it has not been officially approved [15]. In a randomized trial, Virchow et al. showed that SLIT may reduce the dose of ICs needed in HDM allergic asthma [249]. The study enrolled 693 patients with no controlled asthma related to HDM who received placebo or HDM-SLIT tablets in addition to ICs and salbutamol. Results showed that HDM immunotherapy decreased asthma exacerbations during ICs reduction as compared with the placebo. Moreover, immunotherapy may also reduce the risk of suffering from asthma in patients with other allergic symptoms. In this context, Valovirta et al. carried out a randomized clinical trial involving 812 children with grass pollen allergies who had no signs of asthma [250]. Results showed that the treatment with grass pollen SLIT decreased the risk of suffering asthma symptoms at the end of the study (3 years) and in the following 2 years. Regarding AR treatment, both SLIT and SCIT have similar efficacy. A systematic review compared both immunotherapies against placebo, and the two were more effective, with a similar quality of life score [251]. A recent meta-analysis evaluated multiple clinical trials also comparing SCIT versus SLIT. It concluded that SCIT was slightly superior in improving AR symptoms, however, the differences between the two groups were not significant [252].

Finally, ILIT consists of injecting the allergen directly into the lymph nodes. The main advantage of this treatment is that it considerably reduces immunotherapy time, lasting only a few months, and reduces the amount of allergen used [87], but this AIT has been poorly studied in asthma [253]. A recent meta-analysis evaluated 17 clinical trials comparing ILIT against placebo. ILIT requires only three injections, spaced one month apart. This meta-analysis concluded that ILIT is safe and reduces both symptoms and medication use in patients with AR [254]. Another randomized, double-blind clinical trial evaluated the use of ILIT in patients with grass pollen rhinoconjunctivitis. Patients were also treated with 3 ILIT injections and the results show a significant reduction in allergy symptoms [255]. Although ILIT appears to be a promising new therapy for AR, further clinical trials are needed to demonstrate its efficacy against standard immunotherapies.

4. Conclusions

Asthma and AR are two common respiratory diseases that produce high socioeconomic and health problems; however, because of the heterogeneity of these pathologies, a search for precise and personalized medicine in these patients is mandatory. Moreover, the evolution of research on these pathologies has changed our understanding of cellular and molecular mechanisms; thus, treatments need to evolve. Although classic and emerging therapies for asthma and AR have improved the quality of life of patients, more efforts need to be performed to improve diagnosis and treatment. In this sense, a search of biomarkers for each phenotype and endotype is needed to choose the optimal treatment for each patient. However, currently, a lack of specific biomarkers of diagnosis often means that the administered treatment is not the right one. Moreover, a lack of biomarkers to predict immunotherapy efficacy courses with long and costly ineffective treatments for patients. In addition, the efficacy of immunotherapy is not clear yet, so the search for these biomarkers is crucial. However, promising drugs such as biologicals have been developed to improve the quality of treatments and the quality of life of patients. In conclusion, although nowadays there are several therapeutic and diagnostic tools for asthma and AR, further studies are needed to develop more precise and effective methods towards a more specific and personalized medicine.

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