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# Current and Future Asthma Treatments: Phenotypical Approach on the Path to Personalized Medicine in Asthma

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Additional information is available at the end of the chapter

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## Abstract

Despite widely available and effective treatments, achieving asthma control is still an unmet need for many patients. One of the explanations resides perhaps in the heterogeneity of the disease. Asthma is in fact, as we understand it today, a complex syndrome made up of numerous disease variants or asthma phenotypes; when the different underlying mechanisms are identified, the more ambitious term “endotype” is used, with consequent therapeutic implications. Remarkable efforts have been made to identify the features of difficult-to-control (usually severe) asthma, which are different from those described for mild-to-moderate asthma, setting the stage for the development of new and even individualized therapies. As different drugs target different pathways, it is necessary to determine the individual profile of pathophysiological abnormalities for each patient. The most fascinating options of the new asthma treatments are the monoclonal antibodies targeted against key inflammatory cytokines, and the most proximately available treatments within the next years are discussed here. Also, current evidence and understanding of somehow older therapeutic options, such as anticholinergics, thermoplasty, or omalizumab, are reviewed from a phenotypical approach.

**Keywords:** asthma, mepolizumab, monoclonal antibodies, omalizumab, phenotypes, thermoplasty, tiotropium

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## 1. Introduction

International [1] and national [2] guidelines for the management of asthma highlight the importance of finding the effective treatments for achieving and maintaining control. In spite

of the existence of uniform treatment guidelines, as well as of quite accessible and effective treatments, achieving asthma control often remains a constant challenge. Recent studies indicate that over 50% of patients with asthma are not controlled [3, 4], not even when receiving a combination of inhaled corticosteroids (ICSs) and a long-acting beta-2-agonist (LABA) [5] as controller treatment. These data suggest that the search for alternative treatments is required, particularly for patients with severe uncontrolled asthma.

When searching for new treatment options in asthma, it is important to remember that different drugs, particularly biological agents, act on different pathogenic pathways. So, the individual profile of physiopathological alterations of each patient should be determined to prescribe the most appropriate treatment in each case [6].

Asthma management, from both a current as well as a future risk perspective, must comprehend the stratification of patients into the recently defined phenotypes (such as clinical, inflammatory, and molecular) [7] and endotypes (such as allergic asthma, aspirin-sensitive asthma, late-onset hypereosinophilic asthma) [8], in the attempt to find a more personalized treatment for each patient. Moreover, in the last 10 years, significant efforts have been made to identify the characteristics that differentiate severe asthma from mild to moderate asthma, preparing the ground for the development of new selective treatments.

The main goal of the treatment is to achieve and maintain the control of the disease as soon as possible, to prevent chronic airflow obstruction, and to reduce mortality. The goals of the treatment, both in its current control domain and in preventing exacerbations and accelerated loss of lung function (future risk), could be achieved in most of the patients with appropriate treatment [9, 10].

## 2. New bronchodilators for asthma

### 2.1 Anticholinergics

Maintenance treatment to achieve asthma control currently includes inhaled or systemic glucocorticoids (ICS), leukotriene antagonists, LABAs, theophylline, monoclonal antibodies (mAbs) anti-IgE (omalizumab), and recently, newly included in the latest clinical practice guidelines, tiotropium bromide [1, 2]. The parasympathetic or cholinergic system is the most important bronchoconstrictor and hypersecretory neurological mechanism of the airways [11], and blocking specific muscarinic receptors is a therapeutic alternative to reduce the increase in parasympathetic activity that characterizes the main pulmonary obstructive diseases, such as asthma and chronic obstructive pulmonary disease (COPD). Therefore, the natural alkaloids from the Solanaceae family plants (*Atropa belladonna* and *Datura stramonium*) represent one of the traditional remedies against bronchospasm. Atropine, the prototype nonselective muscarinic receptor antagonist, with “tertiary ammonium” structure, was widely used from the late nineteenth century in oral, parenteral, and inhaled forms for the treatment of asthma; however, its use is constrained by the cardiovascular side effects. Following the introduction of ephedrine and adrenaline, in the early twentieth century, atropine fell into disuse. Later, anticho-

linergic therapy has returned to the forefront in the treatment of COPD, with the introduction of synthetic quaternary derivatives of atropine, short acting (ipratropium bromide) and long acting (tiotropium, aclidinium, umeclidinium, and glycopyrronium), the latter known under the acronym LAMA (long-acting muscarinic antagonists). The “quaternary ammonium” structure [12] makes them soluble in water and insoluble in lipids, therefore preventing the passage through biological barriers that are easily crossed by “tertiary ammonium” components, such as atropine, hence their lack of central nervous system effects; also they are poorly absorbed from the lung and gastrointestinal tract and do not inhibit the mucociliary clearance [13].

### 2.1.1 Tiotropium

Tiotropium bromide is the first long-acting anticholinergic agent (24 hours action), widely used for treatment of COPD. At the end of 2014, it was also approved by the FDA as an additional treatment of asthma in patients >12 years in the United States and in adult patients with asthma not controlled by the ICS in the European Union (Spiriva® Respimat). Such approval has been obtained based on sound scientific evidence on the effectiveness and safety of treatment with tiotropium in patients with mild-to-moderate and severe asthma. The major evidence is discussed below and is summarized in Table 1 [14].

Study	Patients' characteristics	Main results and Conclusions
Park et al. 2009 [15]	One hundred and thirty-eight patients with severe asthma on conventional medications and with decreased lung function.	<ul style="list-style-type: none"> <li>– Forty-six of the 138 (33.3%) of patients with severe asthma were found to respond to adjuvant tiotropium bromide.</li> <li>– The presence of Arg16Gly in ADRB2 (coding beta-2 adrenoreceptor) may predict response to tiotropium bromide.</li> </ul>
Peters et al. 2010 [17]	Two hundred and ten patients with poorly controlled asthma with an ICS alone.	<ul style="list-style-type: none"> <li>– Tiotropium bromide, added to an IC, improved symptoms and lung function in patients with inadequately controlled asthma.</li> <li>– Its effects appeared to be equivalent to those with the addition of salmeterol.</li> </ul>
Bateman et al. 2011 [16]	Three hundred and eighty-eight patients with asthma with the B16-Arg/Arg genotype whose symptoms were not controlled by ICS (moderate asthma).	<ul style="list-style-type: none"> <li>– Tiotropium bromide was more effective than placebo and as effective as salmeterol in maintaining improved lung function in B16-Arg/Arg patients with moderate persistent asthma.</li> <li>– Safety profiles were comparable.</li> </ul>
Kerstjens et al. 2011 [18]	One hundred patients with uncontrolled severe asthma, despite receiving treatment with high-dose ICS plus a LABA.	<ul style="list-style-type: none"> <li>– The addition of once-daily tiotropium to asthma treatment significantly improved lung function over 24 hours in patients with inadequately controlled, severe, persistent asthma.</li> </ul>

Study	Patients' characteristics	Main results and Conclusions
Kerstjens et al. 2012 [19]	Nine hundred and twelve patients (814 finished the study) with uncontrolled asthma in spite of ICS/LABA (studies PrimoTinAsthma 1 and 2).	– The addition of tiotropium (409 patients) compared with placebo (405 patients) significantly increased the time to the first severe exacerbation and provided a modest but sustained bronchodilation.

ICS = inhaled corticosteroids; LABA = long-acting beta-2-agonists.

**Table 1.** Summary of studies that demonstrate the efficiency of tiotropium bromide in asthma [14].

A study published in 2009 [15] showed additional improvement in lung function in patients with severe asthma when tiotropium was added to conventional treatment, according to the guidelines (LABA/ICS, theophylline, antagonists of leukotriene receptor, and oral steroids). A total of 138 severe asthmatics with decreased lung function were recruited. Tiotropium 18 µg (via HandiHaler) was added once a day, and lung function was assessed every 4 weeks. Responders were defined as those with an improvement of ≥15% (or 200 mL) in FEV1 that was maintained for at least 8 successive weeks. Of the 138 people with asthma, 46 (33.3%) responded to tiotropium.

Peters et al. [16] conducted an independent three-way, double-blind, crossover study in 210 patients with asthma to evaluate the effect of the addition of tiotropium to ICS, when compared with doubling the dose of ICS (primary superiority comparison) or adding salmeterol (secondary comparison of non-inferiority). Use of tiotropium was superior when compared with doubling the dose of ICS; it also demonstrated superiority in the secondary endpoints, including evening PEF, the proportion of asthma control days, prebronchodilator FEV1, and daily symptom scores. The addition of tiotropium was not inferior to the addition of salmeterol on all evaluated results and increased FEV1 prebronchodilator more than salmeterol. In summary, when added to an ICS, tiotropium improved symptoms and lung function in poorly controlled patients with asthma, and its effects appear to be equivalent to those obtained with the addition of salmeterol.

Bateman et al. [17] carried out a double-blind, double-dummy, placebo-controlled trial to compare the efficacy and safety profile of tiotropium (Respimat 5 µg, administered daily in the evening with the Respimat device) with that of salmeterol and placebo added to an ICS, in 16-Arg/Arg patients with asthma that was not controlled by ICS alone. The study population comprised patients aged 18–67 years, with reversibility to bronchodilators and symptoms that were not controlled by regular therapy with ICS (400–1000 µg of budesonide or equivalent maintained throughout the trial). Changes in weekly primary endpoint (PEF) from the last week of the run-in period to the last week of treatment showed that tiotropium was not inferior to salmeterol.

It has been also assessed whether tiotropium could be an effective bronchodilator in patients with severe asthma who remain symptomatic and obstructed despite maximum recommended treatment with the combination of ICS and LABA. Kerstjens et al. [18] compared the efficacy and safety profile of two doses of tiotropium (Respimat, 5 and 10 µg daily) with placebo as an

add-on therapy in 100 patients with uncontrolled severe asthma despite maintenance treatment with at least a high dose ICS combined with a LABA, in a randomized, double-blind, crossover study with three treatment periods of 8 weeks each. The PEF was peak FEV1 at the end of each treatment period. Peak FEV1 was significantly higher with 5 µg and 10 µg of tiotropium than placebo, whereas there was no significant difference between the two active doses. Domiciliary PEF values were higher with both tiotropium doses. Adverse events were balanced across groups, except for dry mouth, which was more common in patients taking tiotropium 10 µg. This study shows that the addition of once-daily tiotropium for asthma treatment, including a high-dose ICS combined with a LABA, significantly improves lung function over 24 hours in patients with uncontrolled severe asthma.

Subsequently, Kerstjens et al. [19] have evaluated the influence of add-on treatment with tiotropium on exacerbations, an important marker, as is well known, of asthma control. Two parallel, randomized, double-blind placebo-controlled trials (PrimoTinAsthma 1 and PrimoTinAsthma 2) were conducted between October 2008 and July 2011 in 15 countries, involving 912 patients with severe asthma and fixed airflow obstruction, who were randomized for tiotropium (Respimat, 5 µg) or placebo once daily for 48 weeks.

It was concluded that in patients with poorly controlled severe asthma despite the use of ICS and LABA, the addition of tiotropium significantly increased the time to the first severe exacerbation and provided a modest but sustained bronchodilation.

As mentioned in the introduction, we once more insist on the importance of determining the asthma phenotype: a small study (17 patients) showed that tiotropium is more effective in asthmatic smokers or non-smokers treated with medium-to-high doses of ICS if the inflammatory phenotype according to induced sputum is non-eosinophilic [20]. This suggests that perhaps early phenotyping poorly controlled asthmatic patients with high doses of ICS and even systemic corticosteroids (SC) could give tiotropium a corticosteroid-sparing effect in patients who turn out to have steroid-resistant asthma phenotypes. In fact, given its mechanism of action, the bronchodilator additive effect of tiotropium makes most sense in the following circumstances [21]: patients with asthma-COPD overlap syndrome (ACOS) [12], asthma of psychogenic origin, bronchospasm triggered by beta blockers, asthma with chronic airflow limitation, and severe asthmatics with Arg/Gly variation in codon 16 of the ADRB2 gene [15].

However, it seems that the effect of tiotropium goes beyond the bronchodilation because it has significant anti-inflammatory and antiproliferative capacities, such as reduction of hyperplasia of bronchial smooth muscle and inhibition of proliferation of fibroblasts and myofibroblasts [22]. Furthermore, *in vitro* studies using experimental models of asthma (ovalbumin-sensitized guinea pigs) have shown that tiotropium inhibits airway remodeling induced by allergens in a similar way to budesonide [23, 24], so its role in the management of allergic asthma may be more important than it seems at first glance.

Regarding adverse effects, tiotropium is a safe drug and is generally well tolerated, the most common side effect being dry mouth. The heart rhythm disturbances are rare (atrial fibrillation, atrial sinus, or supraventricular tachycardia). The TIOSPIR [25] study concluded that tiotropi-

um Respimat was safe in COPD patients with ischemic heart disease and/or stable arrhythmias. The study excluded patients with myocardial infarction in the past 6 months, class III–IV NYHA heart failure, potentially fatal arrhythmias, and chronic renal failure.

## 2.2. New combinations: ICS/LABA, LABA/LAMA, and triple therapy LABA/LAMA/ICS

Because combination therapy with ICS and LABA is the usual therapeutic option for the treatment of asthma, there is great interest in developing combinations of administration once a day, in an attempt to simplify treatment and improve treatment compliance [26], a currently achievable challenge with the new ICSs (such as ciclesonide, mometasone, and fluticasone furoate) and the emergence of new ultra-LABAs (such as indacaterol, vilanterol, and olodaterol), which can be administered in a single-daily dose. Currently, new combination therapies of ultra-LABA/ICS have been developed, are in clinical trial phases II–III, or have even recently marketed (vilanterol/fluticasone furoate), like several other LAMA–LABA combinations for the treatment of COPD: tiotropium/ olodaterol, aclidinium/ formoterol, umeclidinium / indacaterol, vilanterol / umeclidinium, and so on [27]. However, the use of some of these drugs in asthma is still being investigated (see also Table 2 ).

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### Long-acting muscarinic antagonists (LAMA):

- Acclidinium bromide (approved for treatment of COPD)

### Ultra-long-acting muscarinic antagonists (ultra-LAMA):

- Tiotropium bromide (approved for treatment of asthma and COPD)
- Glycopyrronium bromide (approved for treatment of COPD)

### Ultra-long-acting beta-2-agonists (ultra-LABA):

- Indacaterol maleate (approved for treatment of COPD)
- Carmoterol hydrochloride, milveterol hydrochloride, olodaterol hydrochloride

### New combinations of ultra-long-acting beta-2-agonists (ultra-LABA) and inhaled corticosteroids (ICS):

- Vilanterol trifenate / fluticasone furoate (approved for treatment of asthma and COPD)
- Indacaterol maleate / mometasone (MGC-149)
- Indacaterol maleate / QAE 397

### New combinations of LAMA or ultra-LAMA and LABA or ultra-LABA:

- Tiotropium bromide / olodaterol hydrochloride
- Indacaterol maleate / glycopyrronium bromide (QVA149)
- Umeclidinium bromide / vilanterol trifenate (approved for COPD)
- Formoterol/ aclidinium (approved for COPD)

**Triple therapy of ultra-long-acting beta-2-agonists (ultra-LABA), inhaled corticosteroids (ICS), and ultra-long-acting muscarinic antagonists (ultra-LAMA):**

- Vilanterol trifenate/fluticasone furoate/umeclidinium bromide

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*COPD = chronic obstructive pulmonary disease; ICS = inhaled corticosteroids; LABA = long-acting beta-2-agonists; LAMA = long-acting muscarinic antagonists.*

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**Table 2.** New bronchodilators, either available or under clinical development, with probable upcoming indication for asthma (monotherapy and combinations).

When talking about the triple combination, it refers to ICSs, such as beta-2-agonist and inhaled anticholinergics, but mainly to long-acting drugs (LAMA-LABA-ICS). The possibility of associating these three drugs can contribute to better compliance, better control of the symptoms, and improved quality of life, as well as to a decrease in exacerbations. There are several clinical studies in development: fluticasone/salmeterol/tiotropium and budesonide/formoterol/tiotropium [28]. The first triple combination formoterol/tiotropium/ciclesonide (Triohale®, Cipla) is now available in India [29], and its probable effectiveness in asthma is yet to be proven in future clinical trials.

### **3. Biological and other highly specialized therapies for uncontrolled asthma: Phenotype-oriented present and future options**

In the last decade, significant efforts have been made to identify the characteristics of severe asthma, which are different from those described in the mild-to-moderate asthma, setting the stage for the development of new personalized therapies [7, 30]. The most promising options are represented by biological therapies, including mAbs against selective targets [10]. Later, we summarize the evidence of the only mAb that is available today to treat patients with severe asthma (omalizumab) and review those biological treatments that are currently in clinical trials, but in a more advanced stage of development and will be available for the clinical practice in the upcoming years.

#### **3.1 Allergic asthma**

##### *3.1.1 Omalizumab: state of the art on long-term efficacy and safety in real life studies.*

Omalizumab is currently approved as an additional treatment in patients older than 6 years with severe allergic asthma [31]. The antibody is an IgG1 kappa that binds to IgE and prevents it binding to FC $\epsilon$ RI and FC $\epsilon$ RII (IgE receptors of, respectively, high and low affinity), expressed on mast cells, basophils, and dendritic cells [32]. Several post-marketing studies have been conducted in European countries [33–37] to assess the effectiveness of omalizumab: despite obvious differences between countries, all studies confirmed the usefulness and safety of omalizumab in real-life conditions. The discontinuation rate was variable, but the lack of efficacy was less than 20%, whereas in clinical trials, it was 30–40%. A probable explanation is



that the “real” patients are more serious and less selected than those included in clinical trials. In Spain, a multicenter study was conducted within the routine clinical practice, in Pulmonology and Allergology departments, to evaluate the efficacy and tolerability of omalizumab [38]. With the participation of 30 centers nationwide, 266 patients who had received at least one dose of omalizumab, with 2 years of follow-up at least, were analyzed. The global evaluation of therapeutic efficacy (GETE) was good or excellent in most treated patients: 74.6% at 4 months, reaching 81.6% of the patients after 2 years, with statistically significant differences from baseline. Significant improvements in asthma control test (ACT), lung function, and exacerbation frequency were also demonstrated. In terms of medication, the doses of ICSs were significantly decreased, and the maintenance treatment with oral corticosteroids was suspended in many patients [38].

### 3.1.2. Current evidence on omalizumab efficacy in off-label uses: Non-allergic asthma, nasal polyps, and allergic bronchopulmonary aspergillosis

The interaction between IgE and omalizumab prevents a fundamental step in the inflammatory cascade. The rapid decrease in the free circulating IgE leads to a progressive and significant decrease in the expression of IgE receptors on the inflammatory cells, so it is important to take into consideration certain entities in which IgE may also play a part even if the allergic etiology is not well established, such as nasal polyposis (NP) or non-allergic asthma.

While the inflammation in allergic or “extrinsic” asthma is clearly caused by outdoor allergens (such as dust mites and animal dander), in the intrinsic disease, there is no identifiable allergen, at least not by currently available methods. In this case, an unidentified exogenous antigen (without systemic sensitization), an infectious agent, or an endogenous “allergen” might be responsible for triggering the mechanism of atopy or in this case “entopy” [39]. The finding of specific IgEs against *Staphylococcus aureus* enterotoxins in patients with severe asthma, intolerance to NSAIDs and NP allowed to speculate that they were susceptible of having their airways colonized by *S. aureus*, which through the release of superantigens could trigger an inflammatory response with formation of local IgE [40]. NP may be present in asthma with or without concomitant atopy, but it is particularly associated with non-allergic aspirin-sensitive asthma and is one of the most common comorbid conditions in patients with severe asthma. NP is not a life-threatening condition, but the patients see their quality of life severely compromised and must undergo prolonged treatments with topical and systemic corticosteroids and multiple sinus surgeries in most cases. Over time, the lack of effective alternative treatments and the need to respond to these IgE-mediated diseases led professionals to use omalizumab off-label, with very promising results, as discussed later.

In 2010, a multicenter study performed in Spain described the evolution of nasal polyps in 19 patients with NP and severe asthma treated with omalizumab [41]. The average treatment time was 16 (15–28) months. Thirteen patients (68%) had undergone at least one endoscopic surgery. The size of the polyps (assessed by calculating a score of 0–8 points by means of nasal endoscopy and confirmed by CT scan) diminished significantly in both nasal cavities after the treatment. Later, Bachart et al assessed the usefulness of anti-IgE in severe or recurrent NP associated with asthma, in a prospective double-blind placebo-controlled study (24 patients)

[42]. There was a significant improvement at 16 weeks of treatment in clinical terms: nasal congestion, rhinorrhea, and loss of smell. An overall reduction in polyp size (primary endpoint, assessed using the same above-mentioned score) when compared to baseline was observed [41].

As to non-allergic asthma, in Spain it was first demonstrated, in a retrospective observational study [43], the efficacy of omalizumab in 29 patients with “non-atopic” asthma. GETE, ACT, the number of exacerbations and lung function improved significantly after treatment with omalizumab. There was no statistically significant difference in the response of the non-atopic asthmatics when compared with 266 patients with positive prick tests to usual inhalants. These results were subsequently confirmed in a prospective double-blind placebo-controlled trial [44].

Total IgE levels are a marker of immune activity in another severe lung disease, often without any effective therapeutic alternative to systemic corticosteroids: allergic bronchopulmonary aspergillosis (ABPA). The anti-IgE treatment was also evaluated in this pathology (also off-label). In 2011, a multicenter research conducted in Spain included 18 patients with ABPA from 11 hospitals [45]. Patients were followed for a median of 36 (28–42) weeks. In this series, the largest published so far, omalizumab was beneficial in reducing daytime symptoms (44%) and nighttime awakenings (22%), significantly reduced exacerbations and improved FEV1 ( $p = 0.03$ ), allowing a reduction or even discontinuance of systemic corticosteroids.

### 3.1.3. New anti-IgE agents: ligelizumab and quilizumab

The inverse correlation between free IgE levels and asthma control, found in several studies [46], suggests that a more profound suppression of free IgE could lead to an even more marked clinical improvement, so new, more potent anti-IgE mAbs are currently being assessed in clinical trials.

#### 3.1.3.1. Ligelizumab

QGE031B (ligelizumab) is a new anti-IgE mAb (Novartis). It is a humanized IgG1 that binds with higher affinity to the Ce3 region of IgE. QGE031 is designed for greater suppression of IgE, with a dissociation constant (Kd) of 139 pM, representing an increase in almost 50 times of the affinity for IgE when compared with omalizumab (Kd = 6–8 nM). This is hypothesized to overcome some of the limitations associated with the dosage of omalizumab and lead to better clinical outcomes in asthma.

Up to date, December 2015, we have only data from preclinical experiments, and the results of two phase I, randomized, double-blind placebo-controlled studies investigating the pharmacokinetics, pharmacodynamics, and safety of ligelizumab in atopic but otherwise healthy subjects [47]. Ligelizumab was superior to omalizumab in the suppression of free IgE and FcεRI expression on surface of basophils. These effects resulted in the almost complete suppression of skin response to allergens, which was higher in extent and duration when compared with omalizumab. In the 156 patients who completed the study, no serious adverse effects were reported, and only one patient developed urticaria accompanied by systemic

symptoms. QGE031B's effectiveness is currently being evaluated in patients with allergic asthma (GINA step 4/5) in a phase IIa clinical trial, with omalizumab as an active comparator.

## Quilizumab

Quilizumab (MEMP1972A, Genentech/Roche), another mAb anti-IgE, is being studied now in a phase IIb, randomized, double-blind, placebo-controlled clinical trial aimed to evaluate the efficacy and safety of three different doses (150, 300, and 450 mg, subcutaneously) in adults with allergic asthma not controlled with ICS and a second controller (NCT01582503). Quilizumab already has been proven effective in decreasing total and specific IgE in patients with allergic rhinitis (NCT01160861) and mild allergic asthma (NCT01196039), with a good safety profile [48].

### 3.2. Eosinophilic and Th2 high asthma

#### 3.2.1. Anti IL-5 monoclonal antibodies: mepolizumab, reslizumab, and benralizumab

Interleukin-5 (IL-5) is a hematopoietic cytokine produced by various cells such as Th2 lymphocytes, eosinophils, basophils, mast cells, and natural killer T-cells, and it is the main eosinophil modulator cytokine [49] because it enhances eosinophil chemotaxis, activation, and degranulation, while reducing apoptosis and prolonging eosinophils' survival. The IL-5 receptor (IL-5R), expressed on both basophils and eosinophils, is made up of two subunits: an  $\alpha$ -subunit (IL-5R $\alpha$ ) that is IL-5-specific and a  $\beta$ c-subunit (IL-5R $\beta$ c) that is responsible for signal transduction and is shared with the specific  $\alpha$ -receptor subunits of IL-3 receptors and granulocyte-macrophage colony-stimulating factor (GM-CSF).

Two mAbs (mepolizumab and relizumab) that neutralize IL-5 and another mAb (benralizumab) that blocks the IL-5R $\alpha$  have been developed and are currently being evaluated in clinical trials [50].

##### 3.2.1.1 Mepolizumab

Mepolizumab is a fully humanized anti-IL-5 IgG1 mAb that binds to the free IL-5 with high affinity and specificity, thus preventing its binding to the  $\alpha$  chain of the IL-5R on the eosinophil cell surface. It was the first IL-5 antagonist used in randomized, controlled trials in patients with mild asthma [51, 52] and with moderate uncontrolled persistent asthma [53]. A reduced eosinophil count was observed in both sputum and peripheral blood asthma in biopsies of bronchia and bone marrow, but with no effect on bronchial hyperresponsiveness (BHR), late asthmatic response, lung function, symptoms, or use of rescue medication whatsoever [51–53]. The reduction in the percentage of exacerbations [53] did not reach statistical significance though.

In these studies, patients were not selected according to the presence of eosinophilic airway inflammation, and the number of exacerbations, a parameter directly and causally related with

eosinophilic airway inflammation, was not evaluated as a principal variable of the response to treatment [49]. Two new trials were subsequently performed in patients with refractory severe persistent asthma with recurrent exacerbations, who had bronchial eosinophilic inflammation [54, 55]. Both trials reported a very significant reduction in the number of exacerbations and in the dose of oral corticosteroids in the active group when compared to those in the placebo group, as well as a major improvement in asthma control questionnaire (ACQ) scores. This response was accompanied by a significant reduction in eosinophil numbers in blood and sputum.

A phase IIb multicenter study (GlaxoSmithKline) has also been performed in order to determine the optimal dose of mepolizumab and to confirm its efficacy and safety in patients with severe eosinophilic asthma (the DREAM study) [56]. A total of 621 patients were randomized to placebo or one of three mepolizumab doses (75, 250, or 750 mg respectively) in parallel groups for 1 year. Mepolizumab reduced the number of severe exacerbations by 50% approximately in all the mepolizumab groups when compared with placebo, irrespective of the dose. Also, no dose–response effect was reported. The blood and sputum eosinophil counts were also reduced, and a dose–response effect was observed for eosinophil counts in sputum. On the other hand, no changes in asthma symptoms, quality of life, FeNO or lung function were observed. The drug was safe and effective. A multivariate analysis established that blood eosinophilia and the number of exacerbations in the 12 months prior to the study only were associated with a good response to mepolizumab. A meta-analysis performed on published clinical trials with mepolizumab, including a total of 1131 patients, confirmed that in cases of eosinophilic asthma, mepolizumab reduced the number of exacerbations and improved asthma-related quality of life [57].

### 3.2.1.2 Reslizumab

Reslizumab, a humanized IgG2, is another IL-5 inhibitor that is administered intravenously, although it has not been studied at such extent as mepolizumab. The only published clinical trial in patients with poorly controlled eosinophilic asthma proved that patients treated with reslizumab showed a significant improvement in FEV1 and, interestingly, patients with concomitant polyposis showed better asthma control compared to the placebo group [58].

### 3.2.1.3 Benralizumab

Benralizumab is a humanized IgG1 mAb targeting IL-5R $\alpha$ , which reduces eosinophilia by antibody-dependent cell-mediated cytotoxicity. Intravenous benralizumab has shown acceptable safety and tolerability in a phase I, dose-escalating study, with a marked reduction in circulating eosinophils [59].

In a phase I, multicenter, double-blind, placebo-controlled study, 13 patients were randomized to receive a single intravenous dose of placebo or 1 mg/kg benralizumab, and other 14 patients were randomized to receive a monthly subcutaneous dose of placebo, or either 100 or 200 mg benralizumab, for 3 months. The study concluded that both the single intravenous dose and the multiple subcutaneous doses of benralizumab reduced the percentage of eosinophils in

the bronchial biopsies and in induced sputum and suppressed eosinophil counts in the bone marrow and peripheral blood [60]. Additional studies are further required.

### 3.2.2. Anti IL-13 monoclonal antibodies: Lebrikizumab

IL-4 and IL-13 are key therapeutic targets in Th2 high asthma, due to their significant role in Th2 lymphocyte responses and in B lymphocyte isotype switching for IgE synthesis and also for their intervention in mast cell selection (see Figure 1). The strong evidence existing upon the involvement of this pathogenic pathway in asthma, initially ranging from genetic studies up to convincing data from animal studies, leads to the development of a wide range of biological agents aimed at these targets, including anti-IL-13, anti-IL-4R $\alpha$  and anti-IL-13R $\alpha$ 1 mAbs, IL-4R $\alpha$ /IL-13R $\alpha$ 1 fusion protein, IL-4/IL-13 vaccines, anti-IL-4R $\alpha$  antisense oligonucleotides, and double mutein IL-4 [61]. However, although many of these drugs are under development, to date only a few have been evaluated in patients with asthma [62] (see also Table 3).

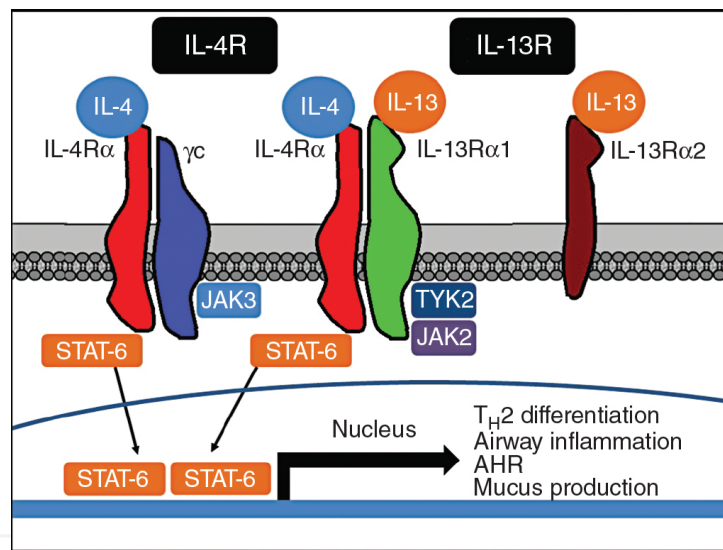


Figure 1. The IL-4/ IL-13 receptor.

		Drug	Pharmaceutical company
	mAb anti IgE	Quilizumab (MEMP1972A)	Genentech/Roche
		8D6	United BioPharma
		Ligelizumab (QGE031B)	Novartis
mAb anti IL-5	IgG1	Mepolizumab	GlaxoSmithKline
	IgG2	Reslizumab	TEVA
mAb anti IL-5	ASO anti-IL-5R $\beta$ c and anti-CCR3	TPI-ASM8	BioCentury

	Drug	Pharmaceutical company
mAb anti IL-5R $\alpha$ IgG1	Benralizumab	AstraZeneca
mAb anti IL-13	Lebrikizumab	Roche
	Anrukinzumab	AstraZeneca
	Tralokinumab	AstraZeneca
mAb anti IL-4 $\alpha$ /IL-13R $\alpha$ 1	Dupilumab	Sanofi
Other IL-4/IL-13 antagonists	mAb anti IL-4	Pascolizumab
	Recombinant soluble IL-4 receptor (sIL-4 R)	Altrakincept
	AcMo anti IL-4	Pascolizumab
	IL-4RI-selective mutein (IL-4/Q116E)	Pitrakinra
		Aerovance

ASO = "anti-sense" oligonucleotide; CCR3 = cysteine-cysteine chemokine receptor-3; IL = interleukin; mAb = monoclonal antibodies; sIL-4 R = recombinant soluble IL-4 receptor.

**Table 3.** Monoclonal antibodies for the treatment of asthma.

### 3.2.2.1 Lebrikizumab

Corren et al. [30] first studied the effects of lebrikizumab in 219 adults with moderate-to-severe persistent uncontrolled asthma. Lebrikizumab was administered subcutaneously every month for 6 months. A significant improvement in prebronchodilator FEV1 was recorded at 12 weeks in patients treated with lebrikizumab when compared to the placebo group. The study drug was significantly more effective in patients with pretreatment circulating periostin levels above the median and also in those with Th2-high phenotype (total IgE > 100 IU/ml and eosinophilia > 140/mm<sup>3</sup>), when compared to those with Th2-low phenotype. Exacerbations were not significantly reduced in the active group compared to placebo, but when sub analyzed in the Th2-high subgroup, the rate of exacerbations was 60% lower in patients receiving lebrikizumab compared to placebo. These data suggest that therapy with anti-IL-13 antibodies may be more effective when directed to a selected subgroup of patients (i.e. Th2-high –phenotype).

### 3.2.3. Anti IL4R monoclonal antibodies: Dupilumab

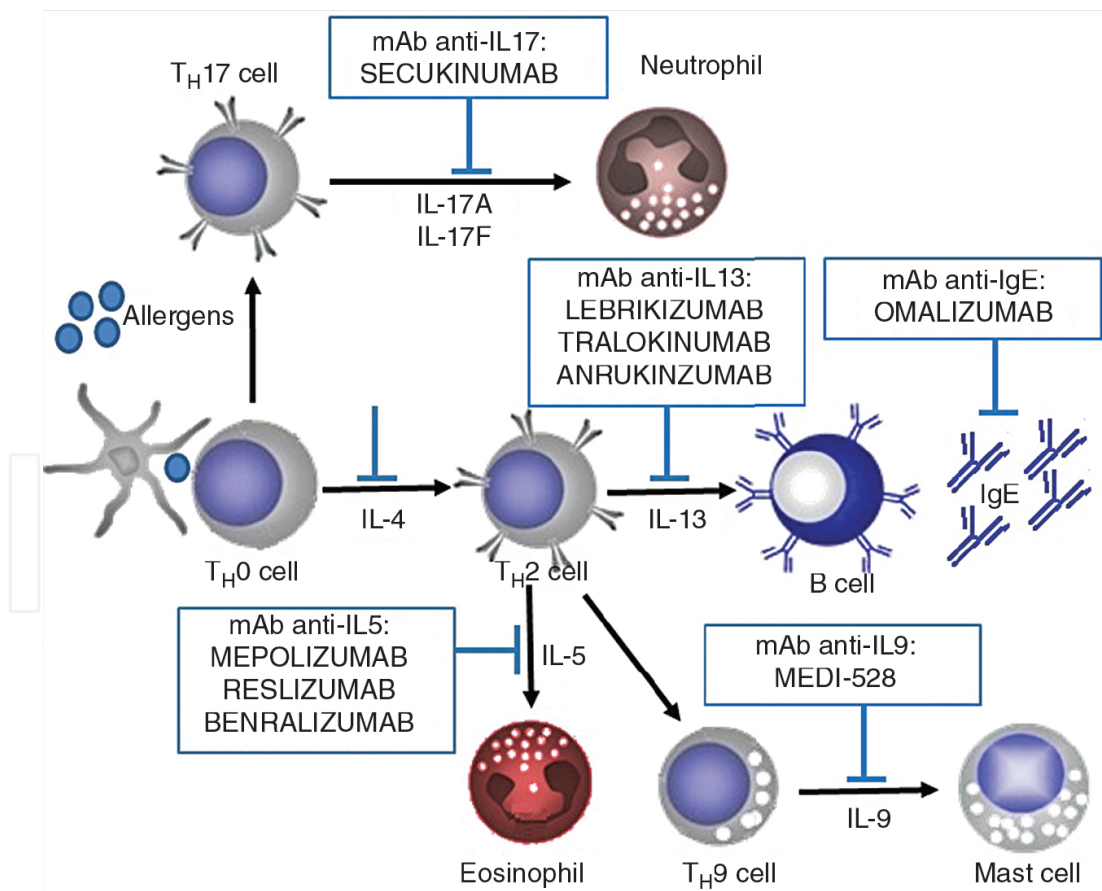
Dupilumab (Sanofi) is a humanized mAb that targets the  $\alpha$ -subunit of the IL-4–IL-13 shared receptor. The efficacy and safety of dupilumab in the treatment of patients with persistent eosinophilic asthma were evaluated in a phase IIa, randomized, double-blind, placebo-controlled study [63]. One hundred and five patients with moderate-to-severe persistent asthma and eosinophilia  $\geq 300/\text{mm}^3$  in blood or  $\geq 3\%$  in sputum were included. All patients were on moderate-to-high doses of ICS and LABA. They were randomized to receive either dupilumab 300 mg ( $n = 52$ ) or placebo ( $n = 52$ ), subcutaneously, once a week for 12 weeks, or until the development of a moderate or severe exacerbation (primary endpoint).

Asthma exacerbations were reduced by 87% in the active group (6% exacerbations in the patients receiving dupilumab versus 44% in the placebo group), being this difference statisti-

cally significant. Significant differences in favor of dupilumab in the time until the first exacerbation and in the risk of exacerbations were also recorded. In the dupilumab patient group, both the morning peak expiratory flow (PEF) and the asthma symptoms evaluated by the ACQ5 improved significantly. Nocturnal awakenings and the use of short-acting beta-2 agonists were also reduced.

Regarding adverse effects, more local reactions at the injection site, nasopharyngitis, nausea, and headache were reported in patients on active treatment, and there was one case of angioedema. The authors of this study emphasize the effect of dupilumab on the reduced frequency of exacerbations, even after withdrawal of ICS and LABA. Nevertheless, they admit that the definition of “exacerbation” used in their protocol does not coincide with that usually employed in clinical practice and, accordingly, recommend that larger studies should be further performed [63].

As we have seen, most new mAbs under development are directed against different targets of the Th2 pathway [62]. A summary of all these drugs is found in Table 3. Figure 2 briefly sketches the allergic inflammatory cascade, so that we might easily visualize these therapeutic targets.



**Figure 2.** Therapeutic targets within the allergic cascade.

### 3.3. Non-eosinophilic asthma: Neutrophilic, Th2-low asthma

#### 3.3.1. *Anti-tumor necrosis factor- $\alpha$ monoclonal antibodies*

Unfortunately, for patients belonging to severe asthma phenotypes other than eosinophilic asthma, current therapeutic options are scarce, and many of these patients are steroid-dependent and even steroid-resistant [2]. Clinical trials with anti-tumour necrosis factor (TNF)- $\alpha$  mAbs (such as infliximab, adalimumab, and golimumab) have been performed with discouraging results. A study including 309 patients with severe persistent asthma, randomized to receive placebo or three different doses of golimumab (50, 100, and 200 mg), showed no significant improvement in any of the efficacy variables [64]. More importantly, the trial had to be prematurely discontinued due to serious adverse events (SAEs), namely infections and malignancies, in the golimumab group. A post-hoc analysis suggested that patients with a prestudy history of sinusitis and FEV1 reversibility ( $\geq 12\%$ ) who received golimumab (100 and 200 mg) had fewer severe asthma exacerbations, apparently associated with a dose-response effect. Perhaps, if biomarkers were developed for predicting response to anti-TNF- $\alpha$  agents, then they could be used for selected subgroups of patients with severe asthma, but the contradictory efficacy results and especially the potential safety concerns have prevented the performance of any additional clinical trials so far.

#### 3.3.2. *Bronchial thermoplasty*

Thermoplasty is a bronchoscopic procedure that reduces the bronchial smooth muscle layer by applying heat by radiofrequency. The results of the studies showed, in patients with moderate and severe asthma, a significant improvement in their quality of life, increased disease control, and a reduction of exacerbations. These results persist for years after the procedure, without medium- to long-term secondary effects [65–67]. While new evidence is needed to identify the ideal candidate, it is currently considered to be preferably indicated in patients with severe uncontrolled asthma, with chronic airflow limitation (FEV1 > 50% and <80%), and without bronchial hypersecretion. Likewise, its application is recommended to be performed in centers with experienced and sufficiently trained endoscopists [2].

## 4. Conclusions and future perspectives

We are witnessing the rapid development of new molecules and also of promising new combinations in terms of efficacy, safety, and dosage for the treatment of asthma, except perhaps for treatment for a subgroup of patients with severe non-eosinophilic asthma, in which therapeutic options still remain limited. Given the heterogeneity of the disease, we consider it is important to establish the phenotype or endotype as a first step on the road to the “personalized” medicine in asthma.

From a practical point of view, in Table 4 we present the personal opinion of the authors of this chapter on the individualized utility of the new asthma treatments, already existing or proximally available.



Asthma phenotype/endotype and its major characteristics	Therapeutic options
<b>1. Extrinsic or allergic asthma</b>	– Allergen avoidance, montelukast, allergen-specific immunotherapy, omalizumab – Tiotropium bromide
<b>2. Intrinsic or non-allergic asthma</b>	
<b>Eosinophilic, may associate atopy or entopy</b>	<p><b>AERD (or NERD):</b> Th2-high and extensive eosinophilic infiltration, potentially severe or difficult-to-control asthma, glucocorticoid-dependent/glucocorticoid-resistant asthma</p> <p>– Montelukast, tiotropium bromide, aspirin desensitization – Omalizumab (anti-Th2 effect, off-label). – In the future: assess new treatments with anti-IL-5 and anti-IL-13</p> <p><b>Late-onset hypereosinophilic asthma:</b> similar to AERD, increased airway remodelling, fixed airflow limitation, usually glucocorticoid-dependent asthma</p> <p>– Tiotropium bromide – Omalizumab (off-label). – Future: anti-IL-5</p>
<b>Non-eosinophilic, non-atopic</b>	<p><b>Non-eosinophilic asthma:</b> obese females, neutrophilic or paucigranulocytic inflammation, Th2-low: worse prognosis, glucocorticoid-resistant asthma</p> <p>– Tiotropium bromide, ultra-LABA/LAMA – Bronchial thermoplasty. – Anti-TNF-<math>\alpha</math>???</p>

AERD = aspirin-exacerbated respiratory disease (or Samter's triad); ICS = inhaled corticosteroids; IL = interleukin; LABA = long-acting beta-2-agonists; LAMA = long-acting muscarinic antagonists; NERD = non-steroidal anti-inflammatory drugs-exacerbated respiratory disease; Th2 = helper type 2 lymphocyte; TNF = tumour necrosis factor

\* Clinical trials with anti-TNF agents (infliximab, adalimumab, and golimumab) had to be suspended prematurely due to the appearance of serious adverse events, especially severe infections and malignancies [64].

**Table 4.** The path to personalized treatment of asthma insufficiently controlled with ICS/LABA: Present and future.

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