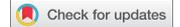


PRODUCT REVIEW



Mabs for treating asthma: omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab

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ABSTRACT

The introduction of biologics for the treatment of patients with refractory asthma represented a marked therapeutic advance. For more than 10 y, the only biologic available has been the monoclonal anti-IgE antibody omalizumab, reserved for patients with asthma caused by perennial allergen. In recent years, other biologics have been licensed for the treatment of severe eosinophilic asthma. They include monoclonal antibodies that target the Th2-pathway cytokines, such as IL-5 (mepolizumab and reslizumab) or its receptor (benralizumab) and the IL-4 and IL-13 receptor (dupilumab). The effectiveness of these biologics was demonstrated in several placebo controlled trials, the main outcomes being the significant reduction of the rate of asthma exacerbation and the improvement of respiratory function in actively treated patients. Based on the further understanding of the pathogenesis of asthma, new cytokines network and new targets are emerging, such as thymic stromal lymphopoietin, which can activate Th2 cells, innate lymphoid cells, or both, or prostaglandin D2 (PGD2), to develop additional biologics.

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Introduction

Asthma is one of the most common airway diseases, affecting more than 300 million people worldwide, with a prevalence in the general population of 4.2–4.4%.¹ Asthma's incidence is higher in childhood, boys being more interested than girls, but the figures change after puberty, when asthma affects females with a 20% higher percentage than boys.² The main risk factors for the development of asthma are smoke and obesity, while the role of sexual hormones is still being discussed.² As many other immune-mediated diseases, the development of asthma is the result of the interaction between genetic predisposition, exposition to external risk factors and the alteration of specific pathways of the immune network. Most genes causing predisposition to asthma are those regulating the epithelial barrier function and the innate and adaptive immune responses, such as polymorphisms for IL1RL1/IL18R1, IL2RB, IL33, HLA-DQ and SMAD3,³ and the locus on chromosome 17q21.⁴ Presently, two types of asthma are defined, characterized by different cellular and molecular phenotypes: “high type 2 immunity asthma” and “low type 2 immunity asthma”. The first subset, also known as “eosinophilic asthma”, concerns almost 50% of asthmatic patients and is defined by the presence of eosinophilic airway inflammation, often associated with peripheral eosinophilia (blood eosinophils over 150 or 300/mm³, depending on the cutoffs). The latter one, also known as “non-eosinophilic asthma”, shows a low Th2 response and its cause is still unknown, with ranks of possible causes ranging from neutrophilic or IL-17 driven inflammation, intrinsic defects in barrier function and chronic subclinical infection by viruses or atypical intracellular bacteria.⁵ Atopy is

present in more than 50% of the asthmatic patients but is more common in children with severe asthma and adults with childhood-onset disease.⁶ In allergic patients, T helper 2 cells release IL-4, which induces IgE switch in B-cells. The cross-link between allergens and mast-cells in the presence of specific IgE causes degranulation and release of pre-formed mediators such as histamine, which cause bronchospasm, and leukotriene C4 which cause bronchospasm and mucus production. Patients with chronic non-responsive disease, but also children with a recent diagnosis of disease, can present epithelial damage, goblet cell hyperplasia, increased thickness of lamina reticularis and basement membrane and rise in the number and mass of fibrocytes and myofibroblasts, resulting in airway remodeling and secondary airflow limitation.⁷

Asthma treatment

The treatment for asthma consists of nonpharmacological treatment (weight loss, avoidance of tobacco or occupational exposure, allergen immunotherapy in allergic patients, remediation of mold and avoidance of aspirin in patients with aspirin-exacerbated asthma) and pharmacological treatment. The latter is based, both in children and adults, on a stepwise approach, consisting a cycle of assessment of risk factors and symptoms, adjustment of pharmacological therapy and subsequent review of the response.⁸ In the first of the five steps is recommended the use of an association of a low-dose inhaled corticosteroid (ICS) and a bronchodilator (formoterol), as needed for quick relief of symptoms. The second step suggests regular use of low doses of ICS, low-dose ICS-formoterol as

needed or leukotriene receptor antagonist (LTRA). Steps three and four introduce the use of ICS and long-acting- β -agonists (LABAs) association, in low and medium dose, respectively. The fifth step, comprising patients with so-called “severe asthma”, recommends the use of a high dose of ICS-LABA formulation, in association with add-on therapy such as tiotropium, LTRA, theophylline and biologic therapy.

Role of biologic therapy in asthma

Biologic therapy is a staple for the treatment of rheumatological, dermatological and gastroenteric diseases, and has an important role in the treatment of moderate to severe asthma as well. Biologic drugs used in asthma are monoclonal antibodies, which target IgEs (omalizumab) and the Th2-pathway cytokines, such as IL-5 (mepolizumab and reslizumab) or its receptor (benralizumab) and the IL-4 and IL-13 receptor (dupilumab). As the studies on asthma and its pathogenesis discover a new and different cytokines network, new targets are emerging, such as thymic stromal lymphopoietin (TSLP) and prostaglandin D2 (PGD2).

Omalizumab

Omalizumab (Xolair[®], Novartis Pharmaceuticals Corp, Basel, Switzerland) is an anti-IgE humanized monoclonal antibody which is licensed for use in moderate-to-severe persistent asthma in allergic adults and children over 6 y old, with serum IgE between 30 and 700 IU/mL and displaying specific allergens year-round (demonstrated by positive skin test or specific serum IgE). Dosing is based on total serum IgE and body weight, with adjustment for significant changes in weight, not for IgE levels taken during the treatment. No dosage adjustment is required for hepatic or renal dysfunction.⁹ Omalizumab was the first biologic therapy to be licensed for asthma, and to this day is the only biologic therapy targeting IgE. In allergic asthma, the cross-link between the allergen, IgE and Fc ϵ -RI on the mast cells causes the release of preformed mediators and concurrent synthesis of inflammatory lipid mediators from arachidonic acid, initiating the early and late-phase of the allergic response. Omalizumab prevents the genesis of this response not only by its binding to free IgEs but also by down-regulating the expression of Fc ϵ -RI on basophils and mast cells,^{10,11} and detaching IgEs from Fc ϵ -RI. A recent study also showed that omalizumab treatment can reduce the expression of CD154, a protein generated by activated T cells which induce Ig production,¹² thus supporting the finding that omalizumab can decrease IgE production.¹³ Another study reported that in patients under omalizumab therapy the number of plasmacytoid dendritic cells (pDCs), a subtype of dendritic cells increased during asthma exacerbations, was significantly reduced.¹⁴ In the FDA clinical trials, omalizumab therapy has proven to reduce exacerbations and hospital admissions,¹⁵ as well as it decreases overall corticosteroid use. A number of randomized, placebo-controlled trials explored omalizumab efficacy and safety as an add-on therapy in children and adults with moderate to severe allergic asthma. The efficacy of omalizumab in reducing asthma exacerbations and steroid dependency was proved in a 28-week trial: over the course of the study, only 14.6% of the

patients under omalizumab therapy experienced one or more exacerbations, compared to 23.3% of the placebo group ($p = .0009$). The omalizumab group also showed lower mean number of per-subject exacerbations (0.28 vs 0.54, $p = .006$) and mean duration of the episodes (7.8 vs 12.7 d, $p < .001$). Regarding the steroid-sparing therapy effect, 72.4% of the omalizumab patients achieved at least a 50% reduction in the initial ICS dose, compared to only 54.9% of the placebo patients ($p < .001$). The study also proved omalizumab effect in improving respiratory function, as both FEV1 and FEF showed significant improvement under omalizumab therapy ($p < .001$). The rate of adverse effects was 89.2% in omalizumab patients and 89.1% in placebo patients, showing a non-significant difference.¹⁶ A subsequent trial confirmed the efficacy of omalizumab not only in reducing the exacerbation rate but also in improving the overall quality of life in asthmatic patients. Asthmatic patients were enrolled based on the use of high-dose of ICS and LABAs, with or without additional therapy, then stratified in three groups: the first (M1) using ICS and LABA alone, the second (M2) using ICS, LABA and one or more additional controller therapy (but not oral corticosteroids, OCS), and the third (M3), using ICS, LABA and OCS. The primary endpoint of the study was the exacerbation rate, which was significantly lower in the omalizumab group, with a 25% reduction in relative exacerbation rates (0.66 vs 0.88, $p = .006$); analysis of the subgroup results suggested larger treatment effects in patients using ICS and LABAs alone (M1: IRR, 0.66 [CI, 0.44 to 0.97]) or with one additional controller (M2: IRR, 0.72 [CI, 0.53 to 0.98]) than with ICS plus LABAs and maintenance therapy with OCS (M3: IRR, 0.95 [CI, 0.63 to 1.43]). Quality of life was evaluated in the study's secondary endpoints, which were the mean overall score for the Asthma Quality of Life Questionnaire (AQLQ), the changes from the baseline score in the asthma symptom severity score (TASS) and the use of relieve therapy. The omalizumab patients showed a greater increase in their mean AQLQ scores (0.29 point [CI, 0.15 to 0.43]), a significant decrease in mean asthma symptom score (0.26 [CI, 0.42 to 0.10]) and a decrease in their need for albuterol as a relieve therapy (0.27 puff/d [CI, 0.49 to 0.04 puff/d]). As for the previous study, the incidence of adverse events (80.4% vs. 79.5%) and serious adverse events (9.3% vs. 10.5%) was similar in the omalizumab and placebo groups.¹⁷ Omalizumab safety in pregnant women was evaluated via a prospective observational study, the EXPECT pregnancy registry, established to evaluate perinatal outcomes in women treated with omalizumab during their pregnancy (EXPECT cohort). This cohort was compared to women with moderate-to-severe asthma not treated with omalizumab (Quebec External Comparator Cohort – QECC), and perinatal outcomes were collected up to 18 months after delivery. The results proved that the prevalence of major congenital anomalies was 8.1% (18/223) in infants of women treated with omalizumab during pregnancy, similar to that in untreated ones (8.9%). In the EXPECT cohort, 99.1% of the pregnancies led to a live birth and 0.9% ended in at least one fetal death/stillbirth, similar to the 99.3% and 0.9%, respectively, found in QECC. Premature birth happened in 15% of EXPECT infants and 11.3% of QECC ones, while small for gestational age (SGA) were identified in 9.7% of EXPECT infants and 15.8% of the ones in the QECC cohort.¹⁸

Mepolizumab

Mepolizumab (Nucala®, GlaxoSmithKline, Brentford, UK) is a humanized monoclonal antibody targeting Interleukin 5 (IL-5). It is licensed for use as add-on therapy in patients over 12 y of age, with uncontrolled asthma despite the use of medium or high dose of inhalation steroids, with or without the addition of oral corticosteroids, and showing peripheral eosinophilia (current eosinophils >150/mmc or eosinophils >300/mmc once in the previous year).¹⁹ Dosing for mepolizumab is 100 mg subcutaneous injection every 4 weeks, with no dose adjustment required for geriatric patients, or in case of hepatic or renal dysfunction. Common adverse reactions reported during the treatment are headaches, back pain, fatigue, reaction in the injection site; some hypersensitivity reactions have also been reported, consisting of rash, urticaria, angioedema and hypotension, often the cause of discontinuation of therapy. Vaccination against chickenpox is recommended prior to the beginning of the treatment,²⁰ as one of the first trials on mepolizumab found that in the group of patients using mepolizumab, 1 out of 29 patients reported the development of shingles, compared to none in the control arm.²¹ Also, patients with preexisting helminth infections must complete anti-parasite therapy before starting mepolizumab treatment.²² Eosinophils normally make up about 1–3% of total white blood cell count, on the whole residing in tissues: they can be found in the thymus and in secondary lymphoid organs such as the spleen and lymph nodes, and in the lower gastrointestinal tract, in the uterus and ovaries, but not in the lungs, skin, esophagus, under normal conditions. Eosinophilia is defined by a count of 500 eosinophils/mmc or more, and it could be detected in patients with helminth infections of the GI tract, malignancies (leukemia and Hodgkin's disease), reflux esophagitis (secondary eosinophilia) or in asthma and eosinophil esophagitis (primary eosinophilia). Interleukin 5 (IL-5) is a cytokine released by Th2 cells which binds to IL-5 R α on eosinophils, promoting their production, activation and survival; IL-5 also up-regulates the expression of adhesion molecules on endothelial cells, facilitating the adhesion of eosinophils.²³ After their activation by IL-5, eosinophils release the major basic protein (MBP) and other proteins and enzymes which cause toxic damage on cells, directly or through the production of cytotoxic reactive oxidant species; the subsequent release of TGF- β and the activation of repair pathways results in structural changes of the tissue, which in asthmatic patients causes hyperplasia of fibroblasts, airway smooth muscle (ASM) and goblet cells, deposition of ECM proteins, and angiogenesis,²⁴ a process called airway remodeling and associated with asthma severity. By blocking IL-5 activity, mepolizumab causes a significant depletion of circulating eosinophils, while its effect on bronchial tissue eosinophilia is less marked, with a median reduction of 55%.²⁵ This residual tissue eosinophilia may reflect ongoing effects mediated by IL-3 and GM-CSF, which are closely linked and share a common β -subunit in their receptors.²⁶ Mepolizumab was approved in 2015 by FDA as an add-on therapy in the maintenance treatment of asthma, after a number of trials showed that it reduces the number of annual exacerbations²⁷ and also the

need for oral corticosteroids in steroid-dependent patients, while also improving the overall quality of life.²⁸ The three main clinical trials which proved the efficacy and safety of mepolizumab are the DREAM trial (Dose Ranging Efficacy and Safety with Mepolizumab in Severe Asthma), the MENSA trial (Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma) and the SIRIUS trial (Mepolizumab Steroid-sparing Study in Subjects with Severe Refractory Asthma). One other study, the COSMOS trial, evaluated the long-term efficacy and safety of mepolizumab using patients from the MENSA and SIRIUS trials. The DREAM trial was designed to define the better dosing for mepolizumab therapy. Patients were randomized in four groups, three of which received intravenous mepolizumab at three different doses: 75, 250 and 750 mg, and the latter receiving placebo (100 mL of saline solution). All patients treated with mepolizumab experienced a reduction in their asthma exacerbation rate (respectively 1.24 rate, 48% reduction, $p < .0001$ in the 75 mg group, 1.46 rate, 39% reduction, $p = .0005$ in the 250 mg group and 1.15 rate, 52% reduction, $p < .0001$). Mepolizumab at any dose gave reduced mean blood eosinophil count and also eosinophil sputum count. According to the authors, the model and the separate subgroup analyses suggested that the drug's efficacy increases with baseline eosinophil counts and number of exacerbations in the previous year, but not with atopic status.²⁹ The MENSA trial evaluated the treatment's impact on asthma exacerbations, respiratory function and quality of life. It enrolled patients showing peripheral eosinophilia (eosinophil count of at least 150/mmc at screening or at least 300/mmc at some time during the previous year), with recurrent asthma exacerbations despite the use of high dose ICS. Patients were randomly assigned to receive mepolizumab as either a 75-mg intravenous dose or a 100-mg subcutaneous dose, or placebo every 4 weeks. The annualized frequency of clinically significant exacerbations showed a reduction rate of 47% in patients receiving mepolizumab IV (95% CI, 28–60% $p < .001$) and 53% in those who got the subcutaneous administration (95% CI, 36–65% $p < .001$). Secondary outcomes included improvement of lung function and in the quality of life. As for the respiratory function, FEV1 showed an increase of average of 100 mL and 198 mL in the IV and SC groups, respectively ($p = .02$ and 0.03). The evaluation of quality of life via the St. George's Respiratory Questionnaire (SGRQ) and the symptom's control via the 5-item Asthma Control Questionnaire (ACQ-5) showed that patients in the two mepolizumab groups had a significant improvement in SGRQ total scores than in the placebo group (respectively, 6.4 points greater for IV administration and 7.0 points for SC administration), while ACQ-5 score showed an improvement of 0.42 points in IV mepolizumab and 0.44 in SC mepolizumab ($P < .001$ for all comparisons). The safety profile of mepolizumab was similar to that of placebo.²² The SIRIUS trial evaluated the steroid-sparing effect of mepolizumab. It compared mepolizumab at a dose of 100 mg with a placebo administered subcutaneously every 4 weeks in patients with eosinophilic asthma. The mepolizumab group showed a likelihood of reduction in the glucocorticoid-dose stratum 2.39 times greater than the placebo group (95% CI, 1.25 to 4.56, $p = .008$); the median percentage reduction from

baseline in the glucocorticoid dose was 50% in the mepolizumab group, with no reduction in the placebo patients ($p = .007$). Patients in the mepolizumab group had also a relative reduction of 32% in the annualized rate of exacerbations (1.44 vs. 2.12, $p = .04$) in comparison to those in the placebo group. In regard to quality of life, patients treated with mepolizumab had a reduction of 0.52 points in asthma symptoms ($P = .004$), as measured on the 5-item ACQ-5.³⁰ The efficacy and safety of mepolizumab in the long term was studied by the COSMOS trial, a 1-y open-label extension of the previous SIRIUS and MENSA studies. Of all the 651 patients in the study, 558 (86%) of them experienced adverse effects, 358 (86%) in the mepolizumab group and 200 (84%) from the placebo group; serious adverse events were reported by 94 (14%) patients, 58 (14%) on mepolizumab, 36 (15%) on placebo. Only 2% of the patients experienced systemic reactions (6 of them, 1%, under mepolizumab therapy) and 4% reported localized site reactions. No anaphylaxis or fatal adverse reaction was reported in the mepolizumab group of patients. As in the previous studies, mepolizumab patients experienced less asthma exacerbation in numbers and severity and showed a greater improvement in quality of life compared to the placebo group.³¹

Reslizumab

Reslizumab (Cinqair® and Cinqaero®, Teva Pharmaceuticals, Petah Tiqwa, Israel) is a humanized monoclonal antibody which targets IL-5, licensed for use as add-on therapy in adult patients (over 18 y of age) with uncontrolled asthma despite the use of medium or high dose of inhalation steroids with or without the addition of oral corticosteroids, and peripheral eosinophilia (eosinophils >400/mm³). As for mepolizumab, reslizumab prevents the bound of IL-5 to its receptor, IL-5R, thus blocking IL-5 signaling on eosinophils, reducing their production, activation and survival rate.^{32,33} Unlike other common biologics used in asthma treatment, reslizumab is administered only via intravenous infusion: the recommended dosage is 3 mg/kg, infused over a 20–50-min period, once every 4 weeks. No dosage adjustment is required in case of renal or hepatic failure or in elderly people. To this day, reslizumab is not licensed for use in pediatric population. The most common reported side effects during the course of the treatment are elevation of CPK, myalgias and anaphylactic reactions. As for mepolizumab, patients with helminthic infections have to complete antiparasitic therapy before starting the treatment. In patients with uncontrolled eosinophilic asthma, reslizumab has an impact on the time and rate of asthma exacerbations, and it also reduces blood and sputum eosinophils count.^{34,35} Two simultaneous studies evaluated the efficacy of reslizumab in eosinophilic asthma, enrolling patients with eosinophil count >400/mm³, uncontrolled (ACQ ≥ 1.5) despite medium to high-dose ICS therapy. Patients were treated with IV infusion of reslizumab (3 mg/kg) or placebo once every 4 weeks for a total of 13 doses and, if needed, OCS maintenance therapy. Compared to the placebo group, the group treated with reslizumab showed a lower rate of asthma exacerbations, with a significantly longer time to first exacerbation and a relative reduction of 50% in Study I and 41% in Study II. Also, the reslizumab group showed a reduction in the number of

exacerbations requiring hospitalization (66% and 69% in Studies I and II compared to placebo).³⁴ A subsequent study evaluated the effects of reslizumab on respiratory functions. In this trial, reslizumab was administered at the dose of 0.3 and 3.0 mg/kg as treatment for patients with eosinophilic asthma (eosinophil count >400/mm³). FEV₁ improved significantly both with reslizumab 0.3 mg/kg (115 mL; $P = .0237$) and 3.0 mg/kg (160 mL; $P = .0018$) compared to placebo, while only reslizumab 3 mg/kg produced substantial improvements in FVC (treatment difference, 130 mL) and FEF_{25%-75%} (treatment difference, 233 mL/s). Both reslizumab doses caused decreases in blood eosinophil, greatest for the higher dose (LSE mean of -358 ± 27.7 for the 0.3 mg/kg dose -529 ± 27.0 for the higher dose, both $p < .001$).³⁶ Reslizumab impact on respiratory function and on quality of life of asthmatic patients was evaluated in another study, which enrolled patients with asthma inadequately controlled (ACQ ≥ 1.5) by at least a medium-dose ICS, with or without the addition of LABA or LTRAs. Eosinophilia was not required, as almost four-fifths of the patients had less than 400 eosinophils/mm³. In the overall population and in the subgroup of patients with baseline eosinophils <400 cells/mm³, mean FEV₁ change from baseline was not significantly different between reslizumab and placebo, while with eosinophils >400 cells/mm³, treatment with reslizumab was associated with larger improvements in FEV₁, ACQ-7, rescue SABA use, and FVC. Reslizumab was well tolerated, with fewer overall adverse events compared with placebo (55% vs 73%).³⁷

Benralizumab

Benralizumab (Faserna®, AstraZeneca, London, UK) is a humanized, afucosylated monoclonal antibody that targets the α chain of IL-5 receptors, expressed by eosinophils and basophils. It is licensed as an add-on therapy in patients over 12 y of age, with asthma uncontrolled by high dose of ICS and peripheral eosinophilia (eosinophils >300/mm³). Dosing for benralizumab is 30 mg subcutaneous injection every 4 weeks for the first three doses of therapy, then once every 8 weeks. The most commonly reported adverse reactions are headache and pyrexia.³⁸ Unlike mepolizumab and reslizumab, which block the IL-5 pathway binding to the cytokine, benralizumab targets directly the cytokine receptor, inhibiting the heterodimerization of α and β subunits, thereby preventing the activation of the signal transduction and so inhibiting the growth, maturation, activation and survival of eosinophils. By the binding to the Fc γ III_Ra receptor, which is expressed by neutrophils, macrophages and NK cells, benralizumab also produces an antibody-directed cell-mediated cytotoxicity (ADCC) against eosinophils and basophils, promoting their apoptosis through the release of pro-apoptotic factors. The affinity to the Fc γ III_Ra receptor is enhanced by the removal of the fucose sugar residue in the CH₂ region of the monoclonal antibody, resulting in a 1000-fold amplified eosinophils apoptosis *in vitro* over the parental antibody.³⁹ Prior to its release, benralizumab efficacy and safety was evaluated in three double-blind, placebo-controlled trials: the SIROCCO trial (Efficacy and Safety Study of Benralizumab Added to High-dose ICS, plus LABA in Patients with Uncontrolled Asthma), the CALIMA trial (Efficacy and Safety Study of Benralizumab in Adults and Adolescents Inadequately Controlled on Inhaled Corticosteroid, Plus Long-

acting β_2 Agonist) and the ZONDA trial (Efficacy and Safety Study of Benralizumab to Reduce OCS Use in Patients with Uncontrolled Asthma on High-dose Inhaled Corticosteroid, Plus LABA and Chronic OCS Therapy). The SIROCCO trial evaluated changes in asthma exacerbation rates and in FEV1 in different therapy regimens: 30 mg either every 4 or 8 weeks. Asthma annual exacerbation rates showed a significant reduction in both the groups of patients under reslizumab treatment ($p < .0001$ for both the scheme of treatment); similar improvements were seen in pre-bronchodilator FEV1, while only the 8-weeks regimen group reported a significant improvement in overall asthma symptoms.⁴⁰ The CALIMA trial had a design similar to the SIROCCO trial, evaluating benralizumab efficacy and safety on patients with uncontrolled eosinophilic asthma despite the use of high-dose ICS and LABA. Patients were divided into a control arm and two experimental arms, which received 30 mg of benralizumab as add-on therapy every 4 or every 8 weeks. Benralizumab treatment resulted in significantly lower annual exacerbation rates with both the 4-weeks regimen (rate 0.60 [95% CI 0.48–0.74], rate ratio 0.64 [95% CI 0.49–0.85], $p = 0.0018$) and the 8-weeks regimen (rate 0.66 [95% CI 0.54–0.82], rate ratio 0.72 [95% CI 0.54–0.95], $p = 0.0188$, $n = 239$) compared with placebo. In both the experimental arms, patients had significantly improved pre-bronchodilator FEV1, while only the 8week regimen group of patients showed significant improvement in total asthma symptom score.⁴¹ The BORA trial was an extension study of patients who completed the SIROCCO or CALIMA trials and remained on subcutaneous benralizumab 30 mg every 4 weeks or every 8 weeks. The aim of the study was to evaluate the safety and tolerability of the two dosing schemes of benralizumab in the long term. The most common adverse events in all groups were viral upper respiratory tract infection (14–16%) and worsening asthma (7–10%); the most common serious ones were worsening asthma (3–4%) or occurrence of pneumonia (1%). No new consequences of long-term eosinophil depletion were noted, and the incidence of other adverse events was similar during the second year of treatment with benralizumab to the incidence during the first one.⁴² The efficacy of benralizumab as an oral-glucocorticoid sparing therapy was studied in the ZONDA trial. After 28 weeks of therapy, patients under benralizumab treatment (both the 4 weeks regimen and 8 weeks regimen) showed a significant reduction in oral steroid use (75% from basal line, $p < .001$ for both groups), proving that benralizumab not only improves the control of asthma exacerbations but is also an effective steroid-sparing therapy.⁴³

Dupilumab

Dupilumab (Dupixent®, Sanofi Biotechnology, Paris, France) is a humanized monoclonal antibody, which binds to the α subunit of IL-4 receptors, licensed for use as add-on therapy in patients over 12 y of age already with asthma receiving ICS and LABAs. Dupilumab is administered by subcutaneous injections once every 2 weeks; dosing consists of a loading dose of 600 or 400 mg (for patients aged 12–17 y or of weight less than 60 kg), followed by a maintenance dose of 300 or 200 mg (for patients age 12–17 y or of weight less than 60 kg). There are no recommendations for dose reductions in case of hepatic or renal

failure. Dupilumab is also licensed for the treatment of eczema in adults, for moderate-to-severe atopic dermatitis in adolescents and for chronic rhinosinusitis with nasal polyposis. Most common reported adverse reactions during dupilumab treatment are injection site reactions, upper respiratory tract infections and headaches. IL-4 α subunit is a transmembrane protein, which can bind interleukin 4 (IL-4) and interleukin 13 (IL-13), two types of structurally similar cytokines produced and released by Th2 cells. Alteration and hyperactivation of the IL-4/IL-13 pathway is associated with allergic rhinosinusitis, atopic dermatitis and asthma. IL-4 and IL-13 both act on B cells, causing IgM to IgE switch thus activating inflammation cascade,⁴⁴ while only IL-13 has proven to have a specific effect on airways' cells, augmenting mucus production and causing goblet cell hyperplasia and causing airway remodeling through collagen accumulation and fibroblasts' conversion to myofibroblasts.⁴⁵ By its targeting of IL-4 R α , dupilumab acts as a dual inhibitor, blocking IL-4 and IL-13 signaling, thus reducing inflammation and airway remodeling in Th2 high asthma phenotypes. The first dupilumab trial enrolled patients with persistent, moderate-to-severe asthma, an elevated blood eosinophil count (≥ 300 cells per microliter) or an elevated sputum eosinophil level ($\geq 3\%$). During the course of the study 26 exacerbations occurred, 3 in the group receiving dupilumab 300 mg (6%) and 23 in the placebo group (44%) (odds ratio with dupilumab, 0.08; 95% confidence interval [CI], 0.02 to 0.28; $P < .001$). Dupilumab also proved its impact on respiratory function, as FEV1 showed significant improvement in the dupilumab group vs placebo (0.05 ± 0.06 vs -0.22 ± 0.06 $p < .001$). Inflammatory markers of Th2 inflammation, such as plasma eotaxin-3 and TARC, decreased, and also FeNO and IgE has shown significant reduction. Conversely, eosinophils blood count has shown no significant reduction in neither groups.⁴⁶ The second dupilumab trial was designed to study the best therapeutic scheme. Four therapy regimens were evaluated: 200 mg or 300 mg of dupilumab, every 2 or 4 weeks. Patients were also stratified by their eosinophilic blood count: under or over 300/mm³. FEV1 showed the highest increase, despite eosinophilic count and dosing, in both the biweekly regimen, 300 mg (mean change 0.39 L [SE 0.05]; mean difference 0.21 [95% CI 0.06–0.36; $p = 0.0063$]) and 200 mg (mean change 0.43 L [SE 0.05]; mean difference 0.26 [0.11–0.40; $p = 0.0008$]). Exacerbation rates, time of exacerbation's occurrence and asthma symptoms were significantly reduced in all the dupilumab groups, with greatest reduction in the two biweekly regimes. Most common reported adverse events with dupilumab were upper respiratory tract infections (33–41% dupilumab vs 35% placebo) and injection-site reactions (13–26% dupilumab vs 13% placebo).⁴⁷

The future of biologics: the IL33-TSLP/PDG2 pathway

Emerging biologic therapies consist of antibodies targeting Th2-mediated immunity, which comprises a number of cytokines and their receptors (Table 1). A lot of new monoclonal antibodies are now being studied, and everyday new cells, new cytokines and new pathways in the pathogenesis of asthma are discovered, unveiling new targets for possible treatment. To date, one of the main focus of the researchers is a specific pathway involving inflammatory mediators such as prostaglandins,

Table 1. Main characteristics of biologics for asthma.

Cytokine or receptor	Production	Receptor	Effect on T-cells	Effect on B-cells	Other effects
Interleukin 4 (IL-4)	Th2 cells	IL-4 R type 1 IL-4 R type 2	Promotes differentiation of Th2	IgE switch	Differentiation of macrophages into M2 cells which produce IL-10 and TGF- β
Interleukin 5 (IL-5)	Th2, CD8 + T cells and mast cells	Heterodimeric (specific IL-5Ra subunit and β subunit, found also in GM-CSF and IL-3R)		Promotes B cell growth and IgA secretion	Eosinophil-colony stimulating factor, it also promotes eosinophil activation and survival
Interleukin 9 (IL-9)	Mostly Th9 cells mast cells, but also NK cells, Th2, Th17, Treg and ILC2	Complex receptor (IL9-R and IL-2R γ subunit)	Promotes growth and proliferation of T cells	In the presence of IL-4 promotes IgE switch and IgE and IgG1 release	Proliferative effect on goblet cells and other mucin producing cells in the airways; enhances airway hyper responsiveness
Interleukin 13 (IL-13)	Th2, CD8 + T cells and mast cells	IL-4R type 2 IL-13Ra2		IgE switch (minor effect than IL-4)	Goblet cell differentiation, production of inducible nitric oxide, activation of macrophages, increase in permeability of epithelial cells, transformation of airway fibroblasts in myofibroblasts
Interleukin 17 family	Th17 cells, mast cells, basophils	IL-17 R, an heteromeric complex consisting of at least IL17RA and IL17RC. Depending on the third subunit, it binds with different affinity various members of the IL-17 family.			Induces production of cytokines, chemokines and prostaglandins from epithelial and endothelial cells, keratinocytes, fibroblast and macrophages
Interleukin 25 (IL-25)	T cells, dendritic cell, macrophages	Heterodimeric (IL-17RA and IL-17RB)	Induces production of IL-4, IL-5 and IL-13 and decreases the production of IFN γ on Th cells		Activation of ILC2
Interleukin 33 (IL-33)	Fibroblasts, mast cells, dendritic cells	IL-1RL1	Induces production of IL-4, IL-5 and IL-13 on Th2 cells	Promotes survival and IL-5 production	
Thymic stromal lymphopoietin (TSLP)	Fibroblasts, epithelial and stromal-like cells	Heterodimeric (CRLF2 and IL-7Ra)			Activates Langerhans cells in the epidermis and induce the production of TNF- α , induces the production of Th2 cytokines in APCs

PGD2 in particular, and alarmins, such as TSLP and IL-33, which are constitutively expressed chemotactic and immune-activating proteins and peptides released after cell injury or death that can induce mast cells, ILC2 and Th2.⁴⁸ Tezepelumab is a humanized monoclonal antibody, targeting the epithelial-cell-derived cytokine thymic stromal lymphopoietin (TSLP). TSLP is produced and released by keratinocytes, lung and intestinal epithelial cells, and fibroblasts,⁴⁹ and it binds to a high-affinity heteromeric complex, composed of thymic stromal lymphopoietin receptor chain and IL-7Ra. TSLP activates ILC2 and promotes the differentiation of CD4+ in Th2 cells in two ways: by the activation of DCs and basophils,⁵⁰ or through direct induction of Th2 differentiation in naive T cells.⁵¹ A phase II study evaluated the use of three different regimens of tezepelumab (70 or 210 mg every 4 weeks and 280 mg every 2 weeks) in patients with uncontrolled asthma despite the use of medium-to-high ICS and LABAs. Exacerbation rates were lower by 61%, 71%, and 66% in the three tezepelumab groups, respectively, than in the placebo group ($p < .0001$ for all the groups), while FEV1 improved by 0.12 L in the first group (95% CI, 0.02 to 0.21; $P = .01$), by 0.11 L (95% CI, 0.02 to 0.20; $P = .02$) in the second and by 0.15 L (95% CI, 0.06 to 0.25; $P = .002$) in the third group. The results of the phase III study (NCT03347279 – NAVIGATOR) aimed to evaluate the efficacy and safety of tezepelumab in adults and adolescents with severe uncontrolled asthma will be published in 2020.⁵² Anti-IL-33 and anti-IL-33 R

blockers. Interleukin 33, a member of the so-called IL-1 superfamily, is produced and released by dendritic cells, mast cells and fibroblasts; it binds to IL-1RL1 (Interleukin 1 receptor-like 1), inducing production of Th2 cytokines such IL-4, IL-5 and IL-13 from Th2 cells and promoting survival and IL-5 production on B cells. It also causes activation of mast cells and release of inflammatory mediators. Phase I and phase II studies of antibodies targeting the cytokine and its receptor are in progress.⁵³ Fevipiprant. Prostaglandin D2 (PGD2) is one of the products of arachidonic acid metabolism in the cyclooxygenase (COX) pathway; it is produced and released by mast cells after their activation by cytokines (IL-25 and IL-33) and alarmins (in particular, TSLP). Upon its release, PGD2 binds to the chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2), promoting Th2 cell migration and up-regulating the production of Th2 cytokines.^{54,55} Fevipiprant is a selective antagonist of CRTH2, which can be administered daily and suitable for oral administration. Phase II studies have shown significant improvement in FEV1 in patients with moderate-to-severe asthma⁵⁶ and several phase III studies are currently ongoing.⁵⁷ IL-13 blockers. IL-13 is a Th2 cytokine which binds to two different receptors: IL-4 R type 2 (which also binds IL-4) or IL-13 Ra2 (specific for IL-13), inducing airway hyper-responsiveness, goblet cell metaplasia and lung eosinophilia.⁵⁸ IL-13 has proven to contribute to airway remodeling via collagen deposition, mediated by the release of TGF- β .⁵⁹ This cytokine is

one of the two targets of dupilumab therapy (which targets IL-4 R α subunit), so there have been a lot of studies focusing on its specific blocking. Unfortunately, clinical trials on the two monoclonal antibodies targeting specifically IL-13, lebrikizumab and tralokinumab, did not prove significant therapy efficacy, as lebrikizumab has shown no significant impact on respiratory function⁶⁰ while tralokinumab did not improve the rate of annual exacerbations in patients with moderate-to-severe asthma.⁶¹

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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