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## **New perspectives of childhood asthma treatment with biologics**

### **Short Title**

Biologics and childhood asthma

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## **Abstract**

Asthma is no longer considered as a single disease but rather as a syndrome corresponding to different entities and pathophysiological pathways. A targeted strategy is part of personalized medicine which aims to better define each patient's phenotype and endotype so as to prescribe

the most suitable treatment at an individual level. Omalizumab, and more recently mepolizumab, are the first biologics approved for children (6-18 years). Omalizumab is now widely used to treat severe allergic asthma in children and is highly effective for asthma exacerbations and asthma control with a good safety profile. Moreover, several other drugs – lebrikizumab, dupimumab, tezepelumab, mepolizumab, reslizumab, benralizumab– are used or are being studied in both teenagers and adults, and could benefit younger children in the near future. We hypothesize that defining the asthma phenotype/endotype regarding the type and intensity of inflammation, association with allergic or non-allergic comorbidities, and airway remodeling should contribute to the choice of a specific biologic. Pediatric specificities have to be addressed and validated by studies in children. Long-term effectiveness and particularly the impact on the natural history of asthma should also be investigated. Severe asthma in children is a complex disease and patients have to be referred to a specialized pediatric asthma center to confirm diagnosis and initiate the best treatment strategy which could include biologics whilst taking into account their high cost.

### ***Introduction***

Severe asthma that is poorly responsive to current treatments has been reported in approximately 4.5% of children with asthma [1, 2]. Severe asthma is no longer considered as a single disease but rather as a syndrome corresponding to different entities and pathophysiological pathways. This understanding has given rise to the concept of clinical phenotypes –a combination of clinical characteristics and prognoses shared by similar individuals– and endotypes –subtypes of the disease with similar pathophysiological mechanisms linked to specific biomarkers. Biomarkers can constitute either therapeutic targets or prognostic factors. Targeted therapy is part of personalized medicine which aims to

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better define each patient's phenotype and endotype to prescribe the most suitable treatment at an individual level [3]. The pathophysiology of severe pediatric asthma involves the Th2 inflammatory pathway of both the adaptive and the innate immune systems: adaptive immunity associated with cytokines IL-4 or IL-13 linked to IgE production and with IL-5 linked to activation and survival of eosinophils, and innate immunity associated with the type-2 innate lymphoid cells activated by the epithelial alarmins TLSP, IL-33 or IL-25 (Figure 1) [4]. More rarely a Th1 and/or Th17 inflammatory process is involved. These different pathways can be involved alone or in association, depending on genetics and disease control, but also on environmental exposure and aging.

Personalized medicine for a patient with severe asthma first requires a step-by-step assessment in a specialized pediatric asthma center including a full diagnostic work-up and management optimization. This includes: exclusion of a differential diagnosis; improvement in the patient's environment; evaluation of the inhaler technique and adherence to long-term treatment; and finally assessment of the inflammatory pathways using blood biomarkers (mainly eosinophil counts in current clinical practice), respiratory biomarkers (fractional exhaled nitric oxide: FeNO) and/or measurement of deep lung biomarkers using induced sputum, broncho-alveolar lavage or bronchial biopsy. Once completed, severe asthma refractory to treatment can be diagnosed and a targeted therapy initiated if appropriate [5].

The only biologics currently approved for children (6-18 years) are omalizumab and, more recently, mepolizumab. Others –lebrikizumab, dupilumab, tezepelumab, reslizumab and benralizumab– are available for adult patients and some of them for teenagers ( $\geq 12$  years).

### ***Defining asthma phenotypes with the best predictable response to omalizumab***

Omalizumab was approved by the FDA in 2003 for adults and adolescents  $\geq 12$  years with moderate-to-severe persistent allergic asthma (perennial allergen sensitization) uncontrolled by inhaled corticosteroids (ICS). The European Medicines Agency (EMA) gave approval in 2005 as an add-on therapy for patients aged  $\geq 12$  years with severe persistent allergic asthma despite daily high-dose ICS plus inhaled long-acting  $\beta$ -2 agonist (LABA). The pediatric indication for omalizumab (children aged  $\geq 6$  years) was then approved by the EMA (2009) and FDA (2016). Omalizumab is now recommended as a first-line add-on treatment option in severe allergic asthma in children resistant to Global Initiative for Asthma (GINA) Step 4 treatment [6]. It is an advanced subcutaneous humanized IgG1 monoclonal anti-IgE that binds to the free IgEs thus preventing contact between IgE and major IgE receptors on the surface of immune cells [7] (Figure 2). Improvement of antiviral innate immunity by the restoration of interferon production has also been reported [8].

#### ***Clinical trial data***

The clinical trials that have been conducted in children have not all been restricted to severe or uncontrolled asthma (Table I). The initial double-blind, placebo-controlled (DBPC) study included 334 allergic asthmatic children aged 6 to 12 years, controlled by a low to medium dose of beclomethasone [9]. After 24 weeks, ICS dose was significantly reduced in patients treated with omalizumab and ICS were withdrawn completely in 55% of them compared to 39% in the placebo arm. Exacerbations also decreased and physicians reported a significant improvement in the patients' condition. A complementary study by Lemanske *et al* [10] found a significant improvement in quality of life. An open-label 24-week extension confirmed the ICS-sparing effect and the benefit on the exacerbation rate [11]. In addition, Silkoff *et al*

reported a significant decrease in FeNO along with a decrease in ICS dose, highlighting the anti-inflammatory effect of omalizumab [12].

In 2009, Lanier *et al* reported the results of a DBPC clinical trial conducted in 627 children with moderate-to-severe asthma, not controlled despite medium-to-high dose ICS +/- another controller treatment, and with a history of severe exacerbations [13]. In this 52-week, two-phase study, children in the active group were administered omalizumab treatment and a constant dose of ICS for the first 24 weeks (phase 1) before reducing the ICS dose according to predefined criteria (phase 2). Overall, compared to placebo, there was a significant reduction in severe exacerbations requiring a corticosteroids burst (-43%) and in the rate of hospitalization (-50%). Physicians also reported a significantly higher frequency of global improvement in the omalizumab group. Similar results were found in the subgroup of 235 patients with severe asthma ( $\geq 500$   $\mu\text{g/day}$  of fluticasone equivalent plus LABA) [14].

In the Inner-City Anti-IgE Therapy for Asthma (ICATA) Study, 419 patients, aged 6 to 20 years (60% 6 to 11 years), with uncontrolled persistent asthma or a history of exacerbations within the previous 6 to 12 months, received additional treatment with omalizumab or placebo for 60 weeks [15]. The authors reported a significant decrease in the number of days with asthma symptoms (-24.5% compared to placebo). The percentage of patients with at least one exacerbation was also significantly lower (30% versus 48.8%). Finally, a significant decrease of daily dose of ICS (109  $\mu\text{g}$  fluticasone equivalent) was reported. In a post-hoc analysis, the authors showed that the benefit on exacerbations was observed during the spring and fall, i.e. not only during the pollinic season but also, and mainly, during the period when viral infections are most frequent. This suggests some interaction between allergic background, viral infection and exacerbation risk, also reported in translational studies evaluating innate immunity responses in asthmatic patients [16-18].

Taking into account the latter findings, Teach *et al* conducted a seasonal back-to-school treatment (PROSE study) in children aged 6 to 17 years with persistent asthma, not controlled by an ICS dose  $\geq 200$   $\mu$ g fluticasone equivalent/day and who had at least one exacerbation treated with a systemic corticosteroid burst in the previous 19 months [8]. Three treatment arms were defined: treatment according to the US recommendations, doubling the dose of ICS, or adding omalizumab. The duration of the study was 90 days, starting 4 to 6 weeks before returning to school. The authors showed that the benefit of omalizumab treatment was more pronounced in patients who met the definition of severe asthma (Step 5 treatment, US guidelines), and in those who had a severe exacerbation during the run-in phase, even when compared with the doubling of ICS dose arm for the latter. Finally, the authors reported that response to omalizumab was associated with the restoration of antiviral defenses evaluated through type I interferon production (*ex vivo* interferon- $\alpha$  production by peripheral blood mononuclear cells). The study thus highlights the links between allergic background and alteration of innate antiviral immunity, and consequently the benefit of an anti-IgE treatment on events triggered by viral infections, mainly rhinoviruses. Esquivel *et al* reported on the viral infections, mainly rhinovirus, recorded in the asthmatic patients of the PROSE study: significantly fewer infections and viral symptoms, and less peak viral shedding were observed in children under omalizumab compared to placebo [19].

#### *Real-life studies*

A survey conducted in France in 104 children, aged 6 to 18 years, all with severe allergic asthma resistant to high-dose treatment, found a highly significant improvement in control, observed from the first weeks, as well as a huge decrease in the number of severe exacerbations and hospitalizations. [20] (Table 1). After 1 year, only 8% of the children

remained uncontrolled compared to 82% initially. The number of severe exacerbations had fallen by 72%, and hospitalizations by 88.5% (none in intensive care units). The impact was also observed on the decrease in ICS dose (-30% of the initial dose after 1 year; >50% in 47% of cases). Daily oral corticosteroids (OCS) were discontinued in the six children receiving this maintenance treatment at omalizumab initiation. An improvement in respiratory function was also shown (+4.9% for FEV<sub>1</sub>). The benefits continued or even increased in the 78 patients reviewed after 2 years of treatment (Table I) [21]. Of particular note, severe exacerbations almost disappeared and none of the children under treatment had been hospitalized.

Another study involved 34 children with severe allergic asthma (15 of whom were under 12 years) treated with long-term OCS. After 16 weeks, the authors reported a decrease in the median daily dose of prednisolone from 20 mg to 5 mg (7 discontinuations) and a significant improvement in quality of life [22]. Pitrez *et al* also reported an improvement in 14 severely allergic children (mean age: 11.9 years), with nine having been on daily OCS treatment for 27+/-16 months. Hospitalization for exacerbations was reduced by 70% and OCS could be stopped in eight children [23].

*Severe asthma with multiple allergic comorbidities could be the best responding phenotype to omalizumab (Figure 3)*

In children with severe allergic asthma, our team recently showed that early and total response to omalizumab was associated with a normal FEV<sub>1</sub> at baseline and multiple allergic comorbidities such as multiple sensitizations, active atopic dermatitis (72%) and food allergy (50%), and higher levels of blood eosinophilia, total IgE and FeNO (manuscript submitted). Allergic rhinitis was not a discriminating factor. This phenotype could correspond to a higher allergic phenotype, best responder to omalizumab. The results reported in children may differ

from those observed in adults. In a recent study of mainly adult patients, Casale *et al* failed to identify any significant differences in odds of successful treatment according to eosinophilia, total IgE and FeNO [24]. In the same way, Humbert *et al* in the STELLAIR study showed that omalizumab effectiveness was similar in "high" and "low" eosinophil subgroups in a large population of 872 severe allergic asthmatic patients (adults: 83%) [25].

*Is there an indication for omalizumab in severe eosinophilic asthma without allergic sensitization?*

In a small series of seven children with severe eosinophilic non-allergic asthma, we previously showed that elevated serum total IgE could be associated with a better response to omalizumab in the responder group, median total IgE was 210 kU/L (IQR 192-269) versus 38.5 (IQR 36-41) in the non-responder group ( $p=0.05$ ) [26]. This result is in accordance with the study by Garcia *et al* who found that omalizumab was effective in a cohort of adults with severe eosinophilic non-allergic asthma with elevated total IgE [27].

#### *Side effects*

Overall, the safety data from clinical trials conducted in patients with moderate-to-severe allergic asthma show that omalizumab is generally well-tolerated (Table III) [7]. The risk of anaphylaxis reported in adolescents and adults [28] has not been observed in studies conducted in children. In the meta-analysis of three clinical trials by Rodrigo *et al* involving 1,380 children aged 6 to 11 years, cases of anaphylaxis were not more frequent in the placebo than in the omalizumab arm [1.04% versus 0.58%; RR=0.51 (0.09, 2.82);  $p=0.44$ ] [29]. Milgrom *et al* pooled safety data from two trials [7, 11] and reported serious side effects in

3.4% of the children treated with omalizumab vs 6.6% in the placebo arm; neither of the two cases of anaphylaxis were related to omalizumab [30]. In the IA010 52-week extension, Berger *et al* reported no cases of anaphylaxis [11]. In the ICATA study, Busse *et al* found seven cases of anaphylaxis, including six in the placebo arm [15]. The PROSE Study confirmed the good safety profile of omalizumab [8]. In the French real-life survey, the main side effects during the first year were local (pain at the injection site, skin reaction), probably partly linked to the conditions of reconstitution which was required when omalizumab was first released [20]. Six patients experienced a serious treatment-related side effect resulting in discontinuation. The patient who experienced anaphylaxis initially described pruritus and urticaria at the injection site for the three first injections, bronchospasm and generalized urticaria then occurred at the time of the 4<sup>th</sup> injection, requiring epinephrine. Omalizumab could be reinitiated by subcutaneous infusion and premedication by corticosteroids and antihistamines. No cases of anaphylaxis occurred during the 2nd year of treatment [21]. Six patients experienced significant fatigue within 24 hours of the injection. Two serious side effects were observed –a combination of fever, abdominal pain and headache in one case, hematuria, hemoptysis and arthralgia in the other– both of which resolved after stopping treatment [21]. To date, there is no evidence to support an increased risk of malignancy in patients treated with omalizumab [31-33]. Nevertheless, long-term monitoring of exposure to treatment is needed to confirm the good safety profile.

***Other biologics which could be of interest in children with severe asthma in the near future***  
***(Figure 3)***

Results from recent clinical trials with other biologics, mainly conducted in adults but also in teenagers, are now available (Table II).

***Monoclonal antibodies directed against IL-4 and IL-13***

IL-4 and IL-13 have been investigated as possible targets as they are both involved in the switch towards IgE production. IL-13 is also involved in bronchial remodeling.

Lebrikizumab is a humanised monoclonal antibody that binds to soluble IL-13 with high affinity and blocks signalling through the active IL-4R $\alpha$ /IL-13R $\alpha$ 1 heterodimer [34]. Two studies –LUTE and VERSE– evaluated the efficacy and safety of different doses of lebrikizumab in 463 adult patients with moderate-to-severe asthma. Patients aged 18–75 years with uncontrolled asthma despite daily use of 500–2000  $\mu$ g/day of equivalent fluticasone propionate and a second asthma controller medication were included in the studies. Lower exacerbation rates were observed in the lebrikizumab treatment groups compared with placebo, especially in patients with a high level of blood periostin (~60% reduction in the rate of exacerbations compared with placebo) [35]. However, these encouraging results remain to be confirmed. Although a pharmacological effect seems to be observed with a decrease of IL-13-related biomarkers during treatment, no significant reduction in asthma exacerbations was shown in patients with Th2-high biomarkers (i.e. periostin  $\geq$ 50 ng/mL or eosinophil count  $\geq$ 300/mm<sup>3</sup>) in the LAVOLTA I and II studies [36]. Phase 3 studies of biologics targeting IL-4 and IL-13 have shown variable results on severe asthma [37] and their development has been interrupted.

In contrast to the anti-IL-13 drugs, the development of dupilumab (a monoclonal antibody directed against the common  $\alpha$ sub-unit of IL-4 and IL-13 receptors) is ongoing in severe asthma [38] and other allergic diseases. Dupilumab has recently been approved by the FDA and EMA for the treatment of adult patients with moderate-to-severe atopic dermatitis. Results from some phase 2 and 3 DBPC trials including adults with persistent moderate-to-severe atopic dermatitis despite treatment with topical corticosteroids and calcineurin inhibitors, have shown considerable efficacy [39].

In a phase 2 study conducted by Wenzel *et al* in a population of adults with severe eosinophilic asthma (blood eosinophilia  $>300/\text{mm}^3$  and sputum eosinophil count  $>3\%$ ), dupilumab was associated with a reduction in asthma exacerbations during a phase of ICS discontinuation [40]. Wenzel *et al* also performed a phase 2b DBPC clinical trial in adults receiving medium-to-high-dose ICS plus a LABA and an add-on subcutaneous (SC) treatment with dupilumab (200 mg or 300 mg, every 2 weeks or every 4 weeks) or placebo, over a 24-week period. Overall, the greatest decrease in the annualized rate of exacerbations was observed with the 2-week administration regimen (-70% and -70.5% in the 200 mg and 300 mg arms, respectively), in both the subgroup with at least 300 blood eosinophils/ $\text{mm}^3$  (-71.2% and -80.7% in the 200 mg and the 300 mg arms, respectively) and in the subgroup with fewer than 300 eosinophils/ $\text{mm}^3$  (-59.9% and -67.6%, respectively). The most common adverse events were injection-site reactions (13 and 26% in the 200 and 300 mg arms, respectively, versus 13% in the placebo group) [41].

More recently, the phase 3 DBPC QUEST trial [42] included more than 1900 patients aged  $\geq 12$  years with moderate-to-severe asthma. Patients who received dupilumab had significantly lower rates of severe asthma exacerbations than those who received placebo, as well as better lung function and asthma control. Greater benefits were seen in patients with higher baseline

levels of eosinophils. However, an increase in eosinophilia was also reported as a side effect. Finally, no difference in the frequency of antidrug antibodies was found between the groups.

In the last phase 3 VENTURE study [43], 210 teenagers (aged  $\geq 12$  years) and adults with oral glucocorticoid-treated asthma received 300 mg of add-on dupilumab treatment every 2 weeks for 24 weeks. This study showed the efficacy of dupilumab on the reduction of OCS treatment (-70.1% in the dupilumab group versus -41.9% in the placebo group), with 48% of the patients completely discontinuing OCS in the dupilumab group. Furthermore, the rate of severe exacerbations was lower despite the reduction of OCS (-59% compared to the placebo group), and the FEV<sub>1</sub> higher.

Transient blood eosinophilia was also more frequently observed in the dupilumab group than in the placebo group (14% versus 1%). Serious adverse events were reported in 9% of patients in the dupilumab group and 6% in the placebo group. Antidrug-antibodies were detected in five patients in each group but had a non-meaningful effect on safety and efficacy. No conjunctivitis was observed in contrast with some studies of dupilumab in patients with atopic dermatitis.

Finally, Weinstein *et al* recently showed that dupilumab 300 mg every 2 weeks significantly improved allergic rhinitis associated nasal symptoms in patients with uncontrolled persistent asthma and comorbid perennial allergic rhinitis [44].

Considering all these results, we hypothesize that dupilumab could be interesting in children with severe eosinophilic asthma with allergic comorbidities, especially severe atopic dermatitis and allergic rhinitis, and with lung function impairment.

Thymic stromal lymphopoietin (TSLP) is an epithelial alarmin protein that may induce a Th2 response. Its expression increases very early in the inflammatory cascade on Th2 pathway and enhances both adaptive and innate immunities. A phase 2 DBPC trial included adults with moderate-to-severe asthma, partly controlled with medium-to-high doses of ICS and an eosinophilic component attested by elevated blood eosinophilia and FeNO [45]. Tezepelumab, a biologic targeting TSLP, was used at different doses and frequency of administration (70 mg every 4 weeks, 210 mg every 4 weeks, and 280 mg every 2 weeks). Exacerbation rates were significantly reduced in the treatment groups (by 61%, 71%, and 66%, respectively,  $p < 0.001$  for all). Similar results were observed in patients regardless of blood eosinophil counts at enrollment. The prebronchodilator FEV<sub>1</sub> at week 52 was higher in the three dose groups compared to the placebo group (+0.12 liters/sec with the low dose [ $p = 0.01$ ], +0.11 liters/sec with the medium dose [ $p = 0.02$ ], and +0.15 liters/sec with the high dose [ $p = 0.002$ ]). Five patients had to discontinue treatment because of adverse events (two in the medium-dose and three in the high-dose group) versus one in the placebo group. Reasons for each discontinuation were not specified but one patient died in the low-dose group after pneumonia and stroke 2 months after the last dose of tezepelumab, and one Guillain-Barré syndrome was reported in the medium-dose group.

Gauvreau *et al* performed a DBPC study including 31 adults with mild allergic asthma and sensitization to pollens (3-monthly intravenous doses of 700 mg of tezepelumab or placebo). Bronchial allergen challenges were then conducted on days 42 and 84. Attenuation of allergen-induced early and late asthmatic responses was confirmed by a significant reduction in the decrease of FEV<sub>1</sub> after challenge (–34% in the tezepelumab arm versus –45.9% in the

placebo arm,  $p < 0.02$ ). Blood and sputum eosinophils were also significantly reduced after challenge in the tezepelumab arm. No serious adverse event was recorded [46]. These results suggest that the indications of tezepelumab could be similar to those of omalizumab (Figure 3).

*Mepolizumab and reslizumab: monoclonal antibodies targeting IL-5 (Figure 3)*

Gupta *et al* recently reported on mepolizumab effectiveness observed during a 12-week pharmacokinetic/pharmacodynamics study in 36 children (6-12 years). The exacerbation rate was consistent with that observed in adolescents and adults (27.8%) [47]. Based on these data and those from teenagers in the mepolizumab severe asthma pivotal programme, the EMA has recently recommended its approval as an adjunctive treatment for severe refractory eosinophilic asthma in children aged 6 to 17 years.

Severe eosinophilic asthma phenotypes without specific allergy often require not only high doses of ICS but also daily OCS to ensure asthma control. In this context, eosinophilia is the cornerstone of asthma severity [48]. This phenotype is very rare in children, but some cases have been described in teenagers. IL-5 is a cytokine that causes chemo-attraction, activation and decrease of apoptosis of eosinophil cells. In this context, monoclonal IL-5 antibodies and biologics directed against the receptor of IL-5 could be a targeted therapy for the eosinophilic severe asthma phenotype [49-51].

In a DBPC phase 2 study (MENSA trial), 576 teenager or adult patients with recurrent asthma exacerbations despite high doses of ICS and evidence of eosinophilic inflammation (at least  $300/\text{mm}^3$  in the year prior to inclusion or  $150/\text{mm}^3$  at the time of inclusion) were recruited. Patients were assigned to receive mepolizumab -75-mg intravenous dose or a 100-mg SC dose- or placebo every 4 weeks for 32 weeks. A 100 mg SC dose every 4 weeks was

effective on asthma exacerbations, with an enhanced response in the subgroup of patients with more than 500 eosinophils/mm<sup>3</sup> at baseline [52]. Mepolizumab was also effective in the SIRIUS trial including patients with refractory asthma, uncontrolled despite long-term treatment by oral corticosteroids, treated by a 100 mg SC dose of mepolizumab every 4 weeks for 24 weeks [53]. An OCS-sparing effect was also reported. A recent meta-analysis showed that mepolizumab was effective in reducing severe exacerbations requiring hospitalization (RR, 0.55; 95% CI, 0.36-0.83; p=0.004) [54]. Furthermore, recent results from the MUSCA Study (randomized DBPC trial studying the effects of a 100 mg SC dose of mepolizumab every 4 weeks for 24 weeks) showed a significant improvement in quality of life [55] and supported the use of mepolizumab as an effective add-on treatment option for patients with severe eosinophilic asthma. Overall, safety results are reassuring. Most of the studies suggest that the more severe phenotype was the best responder. Finally, blood eosinophilia appeared to be a good biomarker for identifying good-responder patients, since exacerbations in the mepolizumab group were reduced by 52% compared to placebo when the initial eosinophil blood count was 150/mm<sup>3</sup>, and by more than 70% when the initial eosinophil blood count was  $\geq 500/\text{mm}^3$ . Nevertheless, concerns about auto-antibodies have been reported and could be associated with a loss of treatment efficacy.

Reslizumab has been evaluated in two phase 3, multicentric, DBPC studies. More than 6000 teenagers (aged 12 years and older) and adults with asthma inadequately controlled by medium-to-high doses of ICS, a blood eosinophil count  $\geq 400/\text{mm}^3$  and one or more exacerbations in the previous year were recruited and received either a dose of 3 mg/kg of reslizumab administered intravenously every 4 weeks for 52 weeks, or a placebo. In both studies, a significant reduction in the frequency of asthma exacerbations was observed in the patients in the reslizumab group (study 1: RR 0.50; 95% CI 0.37-0.67; study 2: RR 0.41 [0.28-0.59]; both p<0.0001) compared with those receiving placebo [56].

Post-hoc analysis performed on the most severe patients receiving baseline treatment per GINA Step 4 and Step 5 guidelines showed that compared with placebo, a reslizumab add-on therapy reduced the exacerbation rate in the Step 4 population by 53% (RR 0.47; 95% CI 0.36–0.62) and the Step 5 population by 72% (RR 0.28; 95% CI 0.15–0.52) [57]. Corren *et al*, in a recent study including only adults, found reslizumab to be effective on Asthma Control Questionnaire-7, use of rescue  $\beta_2$  mimetics and Forced Vital Capacity, but only in patients with an eosinophil count  $\geq 400/\text{mm}^3$  [58]. Bjermer *et al* confirmed the results on quality of life and pulmonary function after 16 weeks of treatment in a study including adults and a few teenagers (aged 12 years and older, representing only 5% of the whole cohort) with asthma inadequately controlled by at least a medium-dose ICS and with a blood eosinophil count  $\geq 400/\text{mm}^3$ , with the usual dose of 3 mg/kg of reslizumab every 4 weeks [59].

Adverse events were similar in both reslizumab and placebo arms in the studies by Castro *et al* [56] with the most common being: worsening asthma symptoms (52% for placebo and 40% for reslizumab in study 1; 51% for placebo and 29% for reslizumab in study 2), upper respiratory tract infections (13% and 16%, respectively, in study 1; 7% and 3%, respectively, in study 2), and nasopharyngitis (14% and 11%, respectively, in study 1; 24% and 19%, respectively, in study 2). Two patients in the reslizumab group had anaphylactic reactions (time of occurrence not reported) with both responding to standard treatment at the study center. In the trial reported by Corren *et al*, one case of reslizumab-related anaphylaxis treated with epinephrine was also recorded [58].

### *The anti-IL5 receptor antibody, benralizumab*

A pooled analysis of the results from the randomized DBPC SIROCCO [60] and CALIMA [61] phase 3 studies was performed to assess the efficacy of benralizumab according to different baseline blood eosinophil thresholds and exacerbation histories in adult patients with severe, uncontrolled asthma, randomly assigned to receive subcutaneous benralizumab 30 mg, either every 4 or 8 weeks (with the first three doses given every 4 weeks), or placebo every 4 weeks. Greater improvements in asthma exacerbation rates were seen with benralizumab compared with placebo for patients with a combination of high blood eosinophil thresholds and a history of more frequent exacerbations [62].

The effectiveness of benralizumab as an OCS-sparing therapy in patients on daily OCS has also been demonstrated in a recent randomized controlled trial (ZONDA). The two benralizumab dosing regimens (30 mg administered subcutaneously either every 4 or 8 weeks) significantly reduced the median final OCS doses from baseline by 75%, as compared with a reduction of 25% in the placebo group ( $p < 0.001$  for both comparisons). The odds of reducing the OCS dose were more than 4 times higher with benralizumab than with placebo [63]. The rate of adverse events was similar in both benralizumab groups and the placebo group.

*Research on biologics targeting poorly controlled noneosinophilic asthma remains a challenge (Figure 3)*

“Off-label” studies have shown that azithromycin could have an ICS-sparing effect in adults with neutrophilic severe asthma [64]. Currently, no other drug, especially no biologic, is

known to target this asthma phenotype. The results of clinical trials of biologics targeting mediators associated with noneosinophilic inflammation, such as IL-17 and tumor necrosis factor (TNF)- $\alpha$ , are disappointing [65].

### **Conclusion**

New biologic therapies may provide relief for severe asthma patients not controlled by inhaled treatment or requiring frequent or daily OCS. Omalizumab is the most-studied drug and is now widely used in severe allergic asthma in children with a good efficacy and safety profile. Several other drugs, including lebrikizumab, dupilumab, tezepelumab, mepolizumab, reslizumab, benralizumab, are being used or studied in teenagers and adults and could be of benefit to younger children in the near future.

Biologics represent a new and promising approach in the treatment of asthma, based on the physiopathological mechanisms of the disease. We hypothesize that they will be developed to target specific asthma phenotypes/endotypes considering both type and intensity of inflammation and association with allergic or non-allergic comorbidities (Figure 3).

Prolonged effectiveness and particularly the impact of such treatments on the natural history of the disease should also be studied. It is crucial to take into account the specificities of pediatric asthma, and design trials for children: the latest treatments have not been investigated in younger patients (<6 years) with severe refractory asthma which remains an issue. Finally, prevention of asthma, especially severe asthma, is another challenge. Biologics may play a role in this strategy, as illustrated by the Preventing Asthma in High Risk Kids (PARK) trial with omalizumab in preschool children (24-47 months) at high risk of developing atopic persistent asthma (NCT02570984). The aims and target populations for such a program will need, of course, to be carefully defined.

Although the prevalence of severe asthma in childhood is low, it is characterized by high morbidity, even mortality, and associated with increased healthcare utilization and a disproportionate amount of healthcare resources. These children have to be early identified and referred to a specialized pediatric asthma center where the diagnosis will be confirmed, and the best treatment initiated. Biologics, when appropriate, play an important role in the management strategy though the high cost of these new treatments must be taken into account.

Figure 1 – Main pathways involved in pathophysiology of severe pediatric asthma. IL interleukine, TSLP thymic stromal lymphopoietin, L lymphocytes, FcεRI Fcε receptor I, NK natural killer, ILC2 innate lymphoid cell 2, IL17Rβ interleukine 17 receptor β, IgE immunoglobulin E

Figure 2 – Mechanisms of action of omalizumab in severe allergic asthma

Figure 3 – Biologic treatments according to the different phenotypes

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**Table I: Studies on omalizumab in childhood asthma: main results**

| Study Design                                                                 | No of patients, Age, IgE level                                     | Severity scoring                                                                                                   | Treatment dose frequency                        | Outcomes (significant difference)                                                                                                                                                                                                                                                                                                                                                                                 |
|------------------------------------------------------------------------------|--------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------|-------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Randomized Double-blind Placebo-controlled Trials</b>                     |                                                                    |                                                                                                                    |                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Milgrom 2001 [9]<br>28 weeks                                                 | 334 children<br>5-12y<br>IgE: 30-1300 kU/l<br>Mean: 335 kU/l       | Moderate-to-severe allergic asthma                                                                                 | 0.016 mg/kg/IgE every 2-4 weeks                 | - Median reduction of ICS <sup>†</sup> dose:<br>Omalizumab: 100% vs Placebo: 66.7%<br>- Exacerbation rate:<br>Omalizumab vs placebo: -36%<br>- Physician/patient evaluation (GETE <sup>‡</sup> ) excellent/good:<br>Omalizumab: 31.5/56% vs Placebo: 16/33%                                                                                                                                                       |
| Lemanske 2002 [10]<br>28 weeks (part of Milgrom study)                       | <i>idem</i>                                                        | <i>Idem</i>                                                                                                        | <i>Idem</i>                                     | - Significant improvement compared to baseline in overall AQLQ <sup>§</sup> , and especially in activities and symptoms domains in the omalizumab group compared to placebo group                                                                                                                                                                                                                                 |
| Berger 2003 [11]<br>52 weeks<br>(open-label extension of study from Milgrom) | <i>idem</i>                                                        | <i>Idem</i>                                                                                                        | <i>Idem</i>                                     | Safety:<br>- 15 patients (6.7%) experienced an adverse event suspected to be omalizumab-related<br>-1 severe adverse event (generalized urticaria)<br>- Most frequently reported: upper respiratory tract infection (106/41%), headache (96/43%), pharyngitis (78/35%), viral infection (71/32%).<br>Efficacy: Similar results to the core study by Milgrom et al                                                 |
| Silkoff 2004 [12]<br>52 weeks                                                | 29 patients<br>6-12y<br>IgE: 316- 280 kU/L in the omalizumab group | Allergic asthma well controlled with ICS <sup>†</sup> (budesonide dipropionate equivalent dose 168 to 420 µg/day). | 0.016 mg/kg/IgE every 2-4 weeks                 | Significant reduction of FeNO <sup>††</sup> from baseline to the end of the open-label period (41.9± 29.0 to 18.0 ±21.8 ppb) despite a high degree of steroid reduction in the omalizumab group<br>Omalizumab vs placebo: FeNO <sup>††</sup> fell from 82.1±55.6 ppm at the end of the steroid-reduction phase to 33.3 ±21.6 ppb at the end of the open-label period (placebo group placed on active omalizumab). |
| Lanier 2009 [13]<br>52 weeks                                                 | 627 children,<br>6 to <12y<br>IgE: 30-1300 kU/l<br>Mean: 470 kU/l  | Moderate-to-severe uncontrolled allergic asthma (Severe: 37.5%), history of severe exacerbations                   | 75 to 375 mg according to table every 2-4 weeks | Omalizumab vs placebo:<br>exacerbation rate: -43%, severe exacerbation: -50%<br>-physician/patient evaluation (GETE <sup>‡</sup> ) excellent/good:<br>omalizumab: 79%/80% vs placebo: 56/72%                                                                                                                                                                                                                      |
| Kulus 2010 [14]<br>¶<br>52 weeks                                             | 246 children<br>Sub-analysis restricted to severe asthmatic        | Severe allergic asthma with exacerbations and symptoms despite treatment with high                                 | 75 to 375 mg according to table every 2-4       | Omalizumab vs placebo:<br>exacerbations: -50%                                                                                                                                                                                                                                                                                                                                                                     |

|                                                      |                                                                                         |                                                                                                                                                                                                                                                                               |                                                                                           |                                                                                                                                                                                                                                                                                                                                           |
|------------------------------------------------------|-----------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                      | children of Lanier                                                                      | ICS† dose plus a LABA††.                                                                                                                                                                                                                                                      | weeks                                                                                     |                                                                                                                                                                                                                                                                                                                                           |
| Busse 2011 [15]<br>60 weeks                          | 419 patients<br>6-20y<br>IgE: 30-1300 kU/l                                              | Moderate-to-severe allergic<br>asthma: 73%                                                                                                                                                                                                                                    | 0.016<br>mg/kg/IgE<br>every 2-4 weeks                                                     | Omalizumab vs placebo:<br>- Number of days with asthma symptoms: -25.5%<br>- % of patients with ≥1 exacerbation: -38%                                                                                                                                                                                                                     |
| Teach 2015 [8]<br>PROSE study<br>(3-arms)<br>90 days | 478 children<br>(6-17y)                                                                 | Allergic asthma with various<br>levels of severity (minimal<br>inhaled daily treatment 200<br>µg/d of fluticasone<br>propionate)<br>184/35% receiving a step-5<br>treatment according to report<br>3 of the National Asthma<br>Education and Prevention<br>Program guidelines | 75 to 375 mg<br>according to<br>table every 2-4<br>weeks                                  | -Odds of participants at all step care levels (2-5) having at least one<br>exacerbation during the 90-day outcome period significantly lower in<br>the omalizumab versus placebo arms (11.3% vs 21.0%; OR, 0.48;<br>95% CI, 0.25-0.92).<br>Persistent effect after stratifying by treatment step in those receiving<br>a step-5 treatment |
| <b>Real-life studies</b>                             |                                                                                         |                                                                                                                                                                                                                                                                               |                                                                                           |                                                                                                                                                                                                                                                                                                                                           |
| Brodie 2012 [22]<br>observational<br>16 weeks        | 34 children<br>(5-16y, 15 children<br><12y)<br>IgE: 30-1300kU/l<br>Median IgE: 411 kU/l | Severe asthma maintained<br>on oral prednisolone                                                                                                                                                                                                                              | 75 to 375 mg<br>according to<br>table every 2-4<br>weeks                                  | - Median daily prednisolone dose reduced from 20 mg to 5 mg<br>including seven children who stopped prednisolone completely.<br>-Mini-AQLQ§ score increased from 3.5 to 5.9.                                                                                                                                                              |
| Deschildre 2013 [20]                                 | 104 children (6-18<br>years, 47 children<br><12y)<br>Median IgE: 1125 kU/l              | Severe resistant to treatment<br>allergic asthma                                                                                                                                                                                                                              | 75 to 375 mg<br>according to<br>table every 2-4<br>weeks<br>(max=375 mg<br>every 2 weeks) | - Control improvement: good control: 0% at initiation, 67% at week<br>52<br>- Exacerbation rate: -72%<br>- FEV1: + 4.9%<br>- ICS† daily dose: - 30%                                                                                                                                                                                       |
| Deschildre 2015 [21]                                 | 78 children of the<br>initial cohort still under<br>treatment after one year            | <i>idem</i>                                                                                                                                                                                                                                                                   | <i>idem</i>                                                                               | - Control improvement: good control: 80% at week 104<br>- Exacerbation rate: -83%<br>- No additional gain in FEV1 or mean ICS daily dose.                                                                                                                                                                                                 |
| Pitrez 2017 [23]                                     | 14 children (mean age:<br>9.2y +/-1)                                                    | Severe resistant to treatment<br>allergic asthma, maintained<br>on oral prednisolone                                                                                                                                                                                          |                                                                                           | - Reduced hospitalization rate by 70%<br>- Stop of oral corticosteroids course: 8 children/14                                                                                                                                                                                                                                             |

† ICS: inhaled corticosteroids; ‡ GETE: global evaluation of treatment effectiveness; § AQLQ: Asthma Quality of Life Questionnaire; ; †† FeNO: Fractional exhaled nitric oxide; †† LABA: long acting β2 agonists ; ‡‡ FEV1: Forced expiratory volume in one second.

**Table II: Studies and efficacy outcomes in phase III clinical trials of the newer biologics involving teenagers and/or adult patients**

| Biologic                                | Study and duration-route                                                                                                                                                                        | Age of the patients                                                                                                                                                       | Efficacy outcomes                                                                                                                 | Main results versus placebo                                                                                                                               |
|-----------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Anti IL13</b><br><b>Lebrikizumab</b> | LAVOLTA I and II (2 pooled studies)<br>Hanania 2016 [36]<br>52 weeks, SC†<br>Every 4 weeks (37.5 or 125 mg)                                                                                     | 2148 adults<br>Severe uncontrolled asthma<br>FEV1‡: 40-80%<br>Biomarker-high patients defined with screening periostin ≥50 ng/mL or screening blood Eo >300 cells per µL. | Exacerbations rate                                                                                                                | ↘ 26 to 51%, non-significant difference<br><br>Discordant results between LAVOLTA I and II                                                                |
| <b>Anti-IL4 Rα</b><br><b>Dupilumab</b>  | QUEST<br>Castro 2018 [42]<br>52 weeks, SC†<br>200/300 every 2 weeks<br><br>VENTURE<br>Rabe 2018 [43]<br>24 weeks<br>SC†<br>300 mg every 2 weeks                                                 | 1902 Adults and children ≥12 y<br>Moderate-to-severe, uncontrolled asthma<br><br>210 patients<br>≥12y<br>Severe asthma with daily OGC§ therapy for ≥6 months              | Exacerbations<br><br>FEV1‡ (12 weeks)<br><br>% change in the OGC§ dose from baseline to week 28.<br>Annual exacerbations<br>FEV1‡ | ↘ 46% (300)<br>-48% (200)<br>Better response if Eo>300/mm <sup>3</sup> :<br>↗ 130ml/300 mg<br><br>-70.1% (versus -41.9% (p<0.001)<br><br>-59%<br>+ 0.22 l |
| <b>Anti IL5</b><br><b>Mepolizumab</b>   | MUSCA<br>Chupp 2017 [55]<br>24 weeks, SC†<br>Every 4 weeks<br><br>SIRIUS<br>Bel 2014 [53]<br>20 weeks, SC† every 4 weeks<br><br>MENSA<br>Ortega 2014 [52]<br>32 weeks SC†/IV‡‡<br>Every 4 weeks | 56 Adults and children > 12y<br><br>135 Adults and children, 16-74y<br><br>576 Adults and children ≥12y                                                                   | SGRQ¶<br>Exacerbations<br>FEV1‡<br><br>Daily OGC§<br>Exacerbations<br>ACQ††<br><br>Exacerbations<br>ACQ††<br>SGRQ¶<br>FEV1‡       | ↘7.7<br>↘ 42 %<br>↗ 120 ml<br><br>↘ ~ 50%<br>↘ 32%<br>↘ ~ 0.52<br><br>↘ 50%<br>↘ ~ 0.43<br>↘ ~ 7<br>↗ 100 ml                                              |

|                                   |                                                                                |                                                                                                        |                                                                                 |                                                                                           |
|-----------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|
| <b>Reslizumab</b>                 | Corren 2016 [58]<br>16 weeks IV‡‡<br>Every 4 weeks                             | 492 adults (18-65y)                                                                                    | FEV1‡ (Eo high)<br>ACQ†† (Eo high)                                              | ↗ 270 ml<br>↘ 0.49                                                                        |
|                                   | Part of BREATHE program<br>Bjerner 2016 [59]<br>16 weeks IV‡‡<br>Every 4 weeks | 315 patients (12-75y), 5%: 12-17y                                                                      | FEV1‡ (Eo high)<br>ACQ††<br>AQLQ§§                                              | ↗ 140 ml<br>↘ ~ 0.3<br>↗ ~ 0.3                                                            |
|                                   | Castro 2015 [56]<br>52 weeks IV‡‡<br>Every 4 weeks                             | 953 adults and children (12-75 y)                                                                      | Exacerbations<br>FEV1‡ACQ††<br>AQLQ§§                                           | ↘ 60-80%<br>↗ 100 ml<br>↘ ~ 0.25<br>↗ ~ 0.23                                              |
| <b>ANTI-IL5R<br/>Benralizumab</b> | SIROCCO<br>Bleecker 2016 [60]<br>48 weeks SC†<br>Every 4/8 weeks               | 1205 adults and children (12-75 y)<br>Severe, uncontrolled<br>asthma                                   | Exacerbations<br>FEV1‡<br>ACQ††<br>AQLQ§§                                       | ↘ 50% (Eo high)<br>↗ 1100 ml<br>↘ ~ 0.25<br>↗ ~ 0.25                                      |
|                                   | CALIMA<br>Fitzgerald 2016 [61]<br>56 weeks SC†<br>Every 4/8 weeks              | 306 adults and children (12-75 y)<br>Severe, uncontrolled asthma                                       | Exacerbations<br>FEV1‡<br>ACQ††<br>AQLQ§§                                       | ↘ 30% (Eo high)<br>↗ 120 ml<br>↘ ~ 0.2<br>↗ ~ 0.2                                         |
|                                   | ZONDA<br>Nair 2017 [63]<br>28 weeks, SC†<br>Every 4/8 weeks                    | 220 adults<br>Severe asthma with daily oral<br>glucocorticoid for ≥6 months<br>Eo >150/mm <sup>3</sup> | % change in the<br>OGC§ dose from<br>baseline to week 28.<br>FEV1‡,<br>Symptoms | ↘ 75% versus 25%<br>↘ 55% (4 weeks) or 70% (8<br>weeks)<br>FEV1: NSD<br>Some improvements |

† SC: subcutaneous; ‡ FEV1: Forced expiratory volume in one second; § OGC: Oral glucocorticoid course; ¶ SGRQ: Saint George Respiratory Questionnaire; †† ACQ: Asthma Control Questionnaire; ‡‡ IV: intravenous; §§ AQLQ: Asthma Quality of Life Questionnaire.

**Table III: Studies on omalizumab in childhood asthma: safety outcomes**

| Study                                                                | Safety outcomes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|----------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Milgrom 2001 [9]<br>28 weeks                                         | <ul style="list-style-type: none"> <li>- Any study related adverse events: 6.2% (omalizumab) versus 0.9% (placebo). <ul style="list-style-type: none"> <li>- Omalizumab arm: urticaria (1.3%), maculopapular rash (0.4%), flushing (0.4%), pruritus (0.4%), pain arm (0.4%)</li> <li>- Injection site pain or other skin reactions: 37.5% (omalizumab) versus 36.6% (placebo)</li> </ul> </li> <li>- No serious treatment related adverse event</li> </ul>                                                                                                                                                                                       |
| Berger 2003 [11]<br>52 weeks (open-label extension of Milgrom study) | <ul style="list-style-type: none"> <li>- Similar adverse events in the open label extension.</li> <li>- One patient discontinued participation in the study because of generalized urticaria (mild or moderate hives after the seventh and eighth injections of omalizumab, which resolved completely after administration of antihistamine)</li> </ul>                                                                                                                                                                                                                                                                                          |
| Lanier 2009 [13]<br>52 weeks                                         | <ul style="list-style-type: none"> <li>- <math>\geq 1</math> adverse event: 93.7% (placebo), 90.3% (omalizumab). Serious adverse event: <math>\geq 1</math>; 8.2% (placebo) versus 4% (omalizumab), (<math>p &lt; 0.05</math>).</li> <li>- Asthma exacerbation: 4 % (omalizumab) versus 8.7% (placebo). Discontinuation: 0.2% (omalizumab) versus 0.5% (placebo)</li> </ul>                                                                                                                                                                                                                                                                      |
| Busse 2011 [15]<br>60 weeks                                          | <ul style="list-style-type: none"> <li>- <math>\geq 1</math> adverse event: 47.4% (placebo), 39.4% (omalizumab), (<math>p = 0.06</math>).</li> <li>- <math>\geq 1</math> serious adverse event: 13.7% (placebo) versus 6.3% (omalizumab), (<math>p = 0.02</math>)</li> <li>- Majority of serious adverse events: asthma-related hospitalizations</li> <li>- Anaphylaxis: 6 (placebo arm), 1 (omalizumab arm): mild cough and throat pruritus after receiving the final injection during the study</li> </ul>                                                                                                                                     |
| Brodie 2012 [22]                                                     | No major adverse effect (no details)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Deschildre 2013 and 2015 [20, 21]                                    | <ul style="list-style-type: none"> <li>- During the first year of treatment <ul style="list-style-type: none"> <li>- <math>\geq 1</math> adverse events: 47 patients (46%), mostly pain at injection site (26%)</li> <li>- 6 Serious adverse events leading to discontinuation: 4 multi-systemic reaction, 1 extended urticarial, 1 anaphylaxis, 1 anaphylaxis outside the treatment (kiwi allergy)</li> </ul> </li> <li>- During the second year of treatment: <ul style="list-style-type: none"> <li>- 8 patients with adverse events leading to treatment discontinuation: fatigue (6) and multi-systemic reaction (2)</li> </ul> </li> </ul> |
| Teach 2015 [8]<br>PROSE study<br>(3-arms)<br>90 days                 | <ul style="list-style-type: none"> <li>- <math>\geq 1</math> adverse events: Step 2-5: 54.5% (omalizumab) versus 54.8% (placebo), (<math>p &gt; 0.99</math>), steps 2-4: 43.5% (ICS boost) versus 53.3% (placebo) (<math>p = 0.3</math>)</li> <li>- Grade 1 anaphylaxis: 3 in ICS boost arm, 2 in the placebo arm, and 3 in the omalizumab arm</li> <li>- Serious adverse event: Placebo arm: 1 seventh nerve palsy, ICS boost arm: 1 anaphylaxis</li> <li>- No deaths, no non-asthma-related hospitalizations during the intervention phase</li> </ul>                                                                                          |

† ICS: inhaled corticosteroids



