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Biomarkers for severe allergic asthma in children: could they be useful to guide disease control and use of omalizumab?

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ABSTRACT

Introduction: Although symptom controls in asthmatic children can be achieved through compliant use of conventional medication, some children have uncontrolled severe persistent asthma, especially if they are allergic. For these children, omalizumab (approved by the EMA and FDA in children aged > 6 years) could be a therapeutic option. However, response to omalizumab varies from one child to another. Predictive biomarkers of omalizumab effectiveness could be useful to monitor response to treatment.

Area covered: The authors searched in the PubMed database for publications related to the use of biomarkers in allergic asthma. Supported by their own experience in phenotyping asthma in children, they analyzed whether these biomarkers could be useful in assessing response to omalizumab.

Expert commentary: Th2 inflammation in children with allergic asthma can be assessed by measuring several biomarkers (blood eosinophil, serum ECP or periostin, FeNO). While a single measurement may be insufficient, a combination of biomarkers assessments may improve the follow-up of children treated by omalizumab.

1. Introduction

The reasons why some patients develop severe persistent asthma and difficult-to-treat asthma that does not completely respond to inhaled corticosteroids (ICSs) are not yet fully understood [1]. Typical aggravating factors include poor treatment compliance, an unfavorable environment, exposure to allergens or irritants, psychological problems, and aggravating comorbidities, such as obesity, allergic rhinitis, and gastroesophageal reflux disease [2,3]. Once these typical causes have been ruled out or successfully managed, some patients remain uncontrolled despite high dose ICSs.

This has prompted the notion of a specific asthma phenotype rather than the progression of a few symptoms developing into uncontrolled disease. Targeted therapy is therefore of critical importance since response to treatment depends on both the initial asthma phenotype and the mechanism of action of the drug. Phenotyping and pathophysiological markers are useful not only in characterizing different patient populations but also in providing information to guide the therapeutic choice [4].

Much progress has been made over the last 15 years in the noninvasive assessment of bronchial inflammation [5]. Some candidate biomarkers have been developed and validated [6–8] and there is evidence that they can help monitor treatments in clinical practice [9–13].

In this review, we describe some biomarkers that could help the clinician manage a child with severe allergic asthma receiving omalizumab.

2. Eosinophilic inflammation

Eosinophils are circulating cells that belong to the granulocyte lineage and are involved in the pathophysiology of allergic asthma. An inflammatory cascade mediated by cytokines produced by Th2 lymphocytes leads to the recruitment of eosinophils to the lung. The cytokines IL-5, IL-13, eotaxin, Clara cells, and the chemokine CC3 receptor are particularly involved. Chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTh2) is a glycoprotein coupled receptor that binds to the ligand prostaglandin D2. There is evidence from both in vitro and in vivo studies that the CRTh2 is involved in allergic and eosinophilic inflammation [14].

Once they are recruited, the eosinophils take part in the modulation of immune response [15], and, more specifically, in bronchial remodeling [15,16].

In children, severe uncontrolled allergic asthma treated by high doses of ICSs is sometimes considered to be closely related to eosinophil-type bronchial inflammation, as observed by Bossley et al. in a cohort of predominantly allergic asthmatic children [17].

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Because of their important role in the pathophysiology of allergic asthma, eosinophils have become a subject of increasing research in recent years.

2.1. Blood eosinophil counts

Indirect assessment of bronchial inflammation in allergic asthma by blood eosinophil counts has been long used in clinical practice [18,19], as it is fast and easy to perform.

Blood eosinophilia seems to be fairly well correlated with adult lung eosinophilia, as recently reported by Simpson et al. (area under the curve 0.82, \(p = 0.08\)) [20] and in line with previous findings [21,22]. However, thresholds vary according to the study population and to the clinical objective: various ranges of asthma severity [22], detection of eosinophilic asthma, prediction, or assessment of treatment response [21].

In adults, blood eosinophilia is correlated in adults with asthma control. A recent study involving a cohort of 2392 asthmatic patients found that a blood eosinophil count of at least 400/mm\(^3\) was associated with a higher annual risk of exacerbation and use of bronchodilators [23]. The authors obtained similar results in children [24]. Concordant results were also found in a large historical cohort of patients from the United Kingdom. In this study, the authors investigated the relation between blood eosinophil count and asthma-associated events over a period of 1 year. In a cohort of 130,248 adolescents and adults receiving primary care for asthma, 20,929 (16%) had a blood eosinophil count greater than 400/mm\(^3\). During the 1-year follow-up, these patients had significantly more severe asthma exacerbations and a poorer chance of achieving control of their symptoms (OR 0.74; confidence interval 0.72–0.77). Furthermore, a relation between the increase in blood eosinophil count and the frequency of exacerbations was observed [25].

However, several studies have shown the limits of the use of blood eosinophil count to assess the intensity of bronchial inflammation and therefore of asthma control. In a European cohort of 88 children suffering from uncontrolled severe persistent asthma, 84% of those with a blood eosinophil count lower than 100/mm\(^3\) had significant airway eosinophilia as determined by bronchoalveolar lavage or bronchial biopsy [26]. Used alone, blood eosinophil count is not therefore a sufficiently reliable biomarker of bronchial inflammatory activity.

In the future, it may be possible to routinely determine blood eosinophilia in primary care, as tested in a pilot study using a peripheral blood counter that yielded results perfectly correlated with those of standard blood sampling techniques [27].

2.2. Induced sputum eosinophilia

Between 66% and 100% of adult asthmatic patients in various cohorts have abnormal sputum eosinophils counts [28]. A proportion of sputum eosinophils counts greater than 2% is correlated with bronchial inflammation [4]. Monitoring eosinophil counts in induced-sputum from adults using a validated technique [29] has proved to be useful in predicting the risk of exacerbation after discontinuation of ICSs [30]. One study including adult patients with severe uncontrolled asthma showed that normalizing eosinophil counts in induced-sputum can contribute to therapeutic management, since it is associated with a reduced risk of severe exacerbations and of hospital admissions [10]. These findings were confirmed in another cohort of adult patients with mild-to-severe asthma suggesting that this therapeutic target may be useful in therapeutic adjustment [12].

However, sputum induction requires a certain technical expertise that makes it difficult to perform on a routine basis [4]. In addition, the technique cannot be carried out in children under 8 years [4] and can be difficult to perform even beyond this age [31]. Covar et al. in the Childhood Asthma Management Program were able to analyze 76% of samples taken from children aged 11–15 years. Of the 117 children recruited, 9 experienced a bronchospasm related to sputum induction. All nine were suffering from more severe asthma, which raises the question of the feasibility and tolerance of this type of examination in children with uncontrolled severe asthma [32]. Furthermore, a more recent study by Fleming et al. raised doubts about the stability of the phenotypes related to sputum eosinophilia in asthmatic children: the authors did not find any correlation between asthma severity and control, ICS dose, atopic comorbidity, and the level of eosinophils in induced sputum [33]. Nevertheless, a number of potential confounding factors, which need to be considered, are dealt with in the latter part of this study. For example, during the follow-up period, the children experienced variations in clinical control and ICS dose, which could have accounted for some of the observed changes.

2.3. Fractional exhaled nitric oxide (FeNO)

Nitric oxide (NO) is produced in the airways by the conversion of L-arginine to L-citrulline, which is catalyzed by the enzyme known as NO synthase (NOS). Four main isoforms of NOS have been identified. NOS2 is the predominant NOS isoform in the epithelium of the airways and is the main determinant of NO levels in exhaled breath [34]. Fractional exhaled NO (FeNO) is increased in asthmatic patients [35–37] due to the overexpression of the NOS [37,38]. NO can be produced by endo- and epithelial cells of the airways and by the inflammatory cells. Although the exact function of NO in respiratory disease is not yet fully understood, it is now established that FeNO is correlated with eosinophilic inflammation of the airways in allergic asthma [38,39,40–42]. FeNO levels are decreased by ICSs [43,44]. In a study of adults with various levels of asthma severity conducted in New Zealand, an increase in FeNO was associated with loss of symptom control after discontinuation of long-term treatment [45]. The same trend has been observed in pediatric populations [46,47]. Higher levels are sometimes observed in patients with severe uncontrolled asthma compared to patients with milder controlled asthma. Consequently, the measurement of FeNO has been suggested as a noninvasive method for monitoring bronchial inflammation [48]. Likewise, FeNO levels were found to be higher in children with uncontrolled asthma than in a control group with controlled disease [49]. A recent study performed as part of the Trousseau Asthma Program (TAP) confirmed these results, suggesting that FeNO levels in
asthmatic infants are strongly influenced by the control and the severity of the disease [50]. Finally, higher levels of FeNO were consistently found in a cohort of 46 older children with severe persistent asthma who were predominantly atopic (89%) and whose symptoms were uncontrolled despite regular intake of ICSs [51].

Other works, however, have yielded less convincing results [30,52–55], probably because of the numerous factors that can influence the measurement of FeNO: the intensity of the ICS treatment, passive smoking, epithelial airway surface, and gender [56]. In a recent Swedish study, high FeNO levels were associated with failure to control asthma and greater bronchial hyperreactivity when co-occurring with blood eosinophilia [57].

Exhaled NO may have a role in assessing compliance to ICSs. Koster et al. [58] reported that high FeNO levels in children treated by ICSs were associated with low treatment compliance. The authors suggested that communicating FeNO results to parents or caregivers could positively influence compliance and improve asthma control.

Finally, assessment of FeNO and blood eosinophilia during patient’s follow-up should be complementary: both adults and children with high levels of the two have a more severe form of the disease that is more systemic and probably more difficult to control [55,57–61]. Measuring FeNO levels to assess asthma control should not therefore be performed alone to assess Th2 inflammation, but rather in combination with other methods of evaluation [62].

2.4. Analysis of exhaled breath condensate

Endogenous acidification of the airways can be measured in exhaled breath condensate (EBC). A low pH in the EBC is closely related to underlying inflammatory activity and is influenced by oxidative stress and the products of NO metabolism [63]. Impaired oxidant–antioxidant balance is associated with bronchial obstruction [64]. Uric acid seems to be the predominant antioxidant in nasal secretions [65] and can also be measured in EBC. A recent study in a cohort of asthmatic children reported a significantly lower level of uric acid in EBC in children when asthma was controlled than for controlled disease [65], suggesting that it could be an interesting biomarker in the assessment of control. However, although most patients in the study were sensitized, the authors did not specify the relation of the marker with atopy.

Several volatile organic compounds and biomarkers in EBC may possibly help to distinguish patients from healthy control and to monitor treatment responses. However, a lack of standardization in collection methods and in analysis techniques make it difficult to introduce in clinical practice. There is also a lack of longitudinal studies to confirm the added value of EB and EBC analysis in the follow-up of children with respiratory diseases [66].

2.5. Eosinophil cationic protein

Eosinophil cationic protein (ECP) is secreted by eosinophils and seems to play a key role in the allergic response [67]. Several studies have correlated blood levels of ECP to the extent of eosinophilic inflammation, which could make it an indirect marker of eosinophilic activity [65–67,68]. Prehn et al. showed that blood levels of ECP in children were higher in asthmatic children and correlated it with blood eosinophil count the severity of clinical symptoms and the patterns of allergic sensitization [69]. Niimi et al. showed that the ECP blood level was also related to eosinophil infiltration in lung tissues [70]. Blood levels of ECP increase during asthma exacerbations and are sensitive to the action of oral corticosteroids [71]. In a recent study of 339 asthmatic adults, concomitantly high levels of blood ECP and of FeNO were associated with a greater risk of exacerbations [72]. Finally, measurement of ECP blood levels could replace that of blood eosinophil counts and serve as a similar marker of systemic inflammation [55].

However, standardized conditions of collection are necessary to ensure the correct interpretation of serum ECP concentration, temperature, duration of blood clotting, centrifugation, hemolysis may cause false positives in serum ECP results [73].

2.6. Eosinophil-derived neurotoxin

Eosinophil-derived neurotoxin (EDN) is a protein derived from the degranulation of eosinophils. Its biochemical properties are close to those of ECP, especially as it also induces the release of histamine and stimulates the expression of some epithelial cells receptors, but without any apparent cytotoxic effects [74]. Blood levels of EDN seem to be correlated with atopy but also with asthma severity [75,76], perhaps to a more discriminative degree than those of ECP [76]. We showed the interest of urine assay in a population of children with asthma and chronic cough, especially for monitoring ICS treatment [77]. However, EDN has not been widely studied and further studies are needed to validate its usefulness in clinical practice.

2.7. Periostin

Periostin, a protein of the extracellular matrix induced by IL-4 and IL-13 in the lung epithelial cells and in fibroblasts, plays a role in epithelial fibrosis and infiltration of the tissues by the eosinophils [78,79]. Serum periostin has been proposed as a biomarker of allergic asthma: high serum periostin levels are correlated with lung eosinophilia [80] and respiratory function [81] and are predictive of the response to ICSs [82,83], omalizumab [84], and lebrikizumab (anti-IL13 antibody). Furthermore, a faster decline in respiratory function has been seen observed when serum periostin levels are high [85]. Although periostin is easy to measure in the blood, it can also be produced by tissues other than the lung [78,86] and influenced by environmental factors [87]. Therefore, its measurement lacks specificity and is of limited application [86]. In addition, there are issues about the predictive value of periostin levels to assess asthma severity in young children. For example, Konradsen et al. did not find any no difference between serum periostin levels and asthma severity, or between serum periostin levels and the other markers of local (FeNO) or systemic (e.g. total IgE and blood eosinophilia)
Th2 inflammation [59]. This could be explained by the slight difference observed in levels observed between healthy children patients [88], due to high bone production in children [83]. Consequently, sputum periostin levels could be a better biomarker in combination with others, because it is more organ-specific [6]. Patients with increased FeNO and high sputum periostin levels are likely to be at risk of a fast decline in respiratory function and of more frequent exacerbations despite high doses of ICSs [89].

3. Value of these biomarkers in the assessment of response to omalizumab

3.1. Mechanism of action of omalizumab

Omalizumab is an advanced humanized IgG1 monoclonal anti-IgE antibody specifically designed to bind circulating free IgE and to prevent interaction with the high- and low-affinity IgE receptors. Omalizumab blocks IgE-receptor binding on the surfaces of antigen-presenting cells, mast cells, and basophils. This prevents subsequent inflammatory cell activation and causes IgE-receptor downregulation. Omalizumab could prevent inflammatory responses or the long-term consequences of allergen exposure, including tissue remodeling, inflammatory cell recruitment and Th2 inflammation. In France, omalizumab is indicated as an add-on therapy to improve asthma control in children from the age of 6 with severe persistent uncontrolled allergic asthma despite high daily dose of ICSs plus long-acting β2 agonists, and who have a positive skin test or an in vitro reactivity to a perennial aeroallergen. Adolescents aged > 12 years must also have a reduced forced expiratory volume in 1 s (FEV1) under 80% of the theoretical value. It is also possible that omalizumab is effective in children with severe eosinophil nonallergic asthma with an abnormal total serum IgE and nasal polyposis, as reported recently [90]. It has been shown that IgEs are able to trigger the intracellular signaling pathways, leading to the production of pro-inflammatory cytokines even in the absence of an allergen [91]. In this context, omalizumab could nonspecifically modulate the number of high-affinity IgE receptors in plasmacytoid dendritic cells that may be expressed independently from any sensitization.

One aspect that should not be forgotten when assessing the effectiveness of omalizumab is that it is an injectable drug which undeniably improves compliance and consequently asthma control. Another aspect, however, is the cost of the treatment, which can be as much as 37,600 € per year per patient in France for the maximal dose.

3.2. Clinical efficacy of omalizumab

The clinical efficacy of omalizumab in moderate to severe allergic asthma is now well-proven. Omalizumab has been shown to significantly reduce the rate of exacerbations in many placebo-controlled studies in large patient cohorts. It also results in a 75–100% decrease in the dose of ICS necessary to control asthma, versus a 43–66% in control groups [92–94] Evidence is particularly strong for severe uncontrolled asthma despite high doses of ICSs [95–97]. Omalizumab not only reduces the rate of exacerbations, but also other symptoms of asthma. In a meta-analysis, Holgate et al. [96] have shown that omalizumab was effective for nocturnal symptoms. A multicenter study [98] showed that omalizumab can reduce the severity of exacerbations and the number of unplanned medical visits due to asthma (21.3/100 patient-years vs. 35.5/100 patient-years in the placebo arm, \( p = 0.001 \)), emergency visits (1.8/100 patient-years vs. 3.8 patient-years in the placebo arm, \( p = 0.05 \)), and hospitalizations for severe exacerbation (0.26 patient-years vs. 3.42 patient-years in the placebo arm, \( p = 0.01 \)). Humbert et al. [99] showed similar results in another international study including adults and children.

3.3. Medico-economic studies: cost/effectiveness ratio

Due to the cost of the treatment, cost/effectiveness ratio is a primordial question. Most of the health expenditure for asthma is from managing patients with severe uncontrolled asthma. Costello et al. [100] showed that omalizumab could lead to a saving of 834 € per patient within 6 months. A Quality-Adjusted Life Year (QALY) index has been calculated in the United States [101]. This index takes health costs, treatment duration, and quality of life in account. QALY was positively influenced by omalizumab prescription but led to an increase in health costs (+91,000 $/QALY). Some of the discrepancies in the economic evaluation of omalizumab from one country to another may be due to different guidelines and specific health systems. It is worth noting that omalizumab can reduce the rate of exacerbations, emergency visits, and hospitalizations, which constitute the main part of health expenditure [102,103].

3.4. Growing evidence for biomarkers in phenotyping asthma for the choice of omalizumab

Bronchial inflammation is one of the main therapeutic targets of asthma treatment. The pathophysiology of the inflammation can differ according to the asthma phenotype and as can the effects of any treatment [92,93]. A better understanding of the mechanisms that govern the variability in response to treatment is essential to develop personalized health care. This personalized approach tailored to the patient’s condition is based on the identification and use of biomarkers that are either predictive of response before the start of therapeutic management or associated with the response to treatment during the course of management [94].

It has already been stated that IgEs play a key role in the pathophysiology of allergic asthma. Bronchial inflammation in allergic asthma is characterized by the production of specific cytokines by the Th2 lymphocytes, in particular IL-4, IL-5, and IL-13 [95,96], which contribute to the production of IgEs [97]. However, it is generally difficult to measure the serum levels of these cytokines. Total IgE assay, which is easier to perform, is not particularly predictive of response to omalizumab among allergic asthma phenotypes [98,99] and neither is specific IgE assay [100].
Although omalizumab is of particular benefit to patients with uncontrolled severe persistent asthma [100–107], not all patients with this phenotype will respond to treatment and the biomarkers predictive of response are as yet largely unknown [108].

Busse et al. suggest that the best responders among patients with moderate-to-severe allergic asthma would be those with the highest blood eosinophil counts at baseline [101]. They conducted a 60-week, randomized, double-blind, placebo-controlled, multicenter study of 419 inner-city children, adolescents, and young adults with persistent asthma to assess the effectiveness of omalizumab, when added to the guideline-based therapy. Omalizumab significantly reduced the number of days with asthma symptoms and reduced the proportion of patients who had one or more exacerbation. Sensitized patients who were exposed to cockroaches were the best responders.

The results of a retrospective analysis of a cohort of 850 adolescent and adults in the United States receiving omalizumab for uncontrolled severe persistent asthma showed that patients with the highest levels of FeNO, blood eosinophilia, and serum periostin before treatment had the best response to omalizumab at week 48, with a significantly greater reduction in the number of exacerbations [104]. These findings add weight to the hypothesis that omalizumab has a systemic anti-inflammatory role: patients with the most severe clinical symptoms [98] and eosinophilic inflammation are those who benefit most from the treatment [109–119]. Eosinophilic inflammation biomarkers seem to be useful for the prediction of response to treatment.

4. Conclusion

Allergic asthma requires regular clinical assessment to decide on suitable personalized therapeutic management. Studies of the different biomarkers correlated a lack of asthma control with an underlying inflammatory activity. Eosinophilic airway inflammation assessed by FeNO, blood eosinophil count, and ECP serum level, particularly when they are concomitantly high, seem to indicate a systemic inflammation that is more difficult to control but potentially sensitive to the overall anti-inflammatory action of omalizumab.

5. Expert commentary

Severe pediatric asthma represents a small proportion of asthmatic children, only 2–4.5%. However, severe asthma leads to an altered quality of life and to substantial public health costs due to the burden of treatment. Severe uncontrolled asthma in children is more likely linked with eosinophilic bronchial inflammation. Indirect assessment of bronchial inflammation through blood eosinophil count is already done in clinical practice, in particular to monitor omalizumab efficiency. However, blood eosinophil count is not always linked with bronchial eosinophilia. Discrepancies between blood and airway eosinophilia have been described, and blood eosinophil count used alone is not sufficient to properly assess bronchial inflammation activity. The specific mode of action of omalizumab is not yet fully known. Furthermore, different courses of severe allergic asthma treated by omalizumab have been described. Combination of various biomarkers linked with Th2 pathway may help to define the best responders to omalizumab.

6. Five-year review

Biomarkers are objective and quantifiable characteristics of the biological process. Most of the characteristics that define the phenotypes of severe asthma are either nonspecific clinical factors or inflammatory factors that give an insight into the underlying pathobiology of the disease.

The current challenge is to advance in the assessment of these biomarkers with the aim of tailoring therapeutic approaches to the individual.

Currently, biomarkers are mainly used in severe allergic asthma to support the use of anti-IgE or anti-IL5 antibody biotherapy. Their use would also be of interest in moderate or incipient asthma to guide the decision to initiate specific treatment or to discontinue treatment if symptoms are fully controlled.

The development of metabolomics could provide answers to these issues in the near future.

Key issues

- In children, severe uncontrolled asthma treated by high doses of inhaled corticosteroids (ICS) is sometimes considered to be more closely related to eosinophil-type bronchial inflammation.
- Sputum induction requires a certain technical expertise that makes it difficult to perform on a routine basis and in children.
- Assessment of FeNO and blood eosinophil count during patient management should be complementary: patients with high levels of both, including children, have a more severe form of the disease that is more systemic and probably more difficult to control.
- Several volatile organic compounds (VOC) in exhaled breath (EB) and biomarkers in exhaled breath condensate (EBC) have the potential to distinguish patients from healthy controls and to monitor treatment responses. Lack of standardization of collection methods and analysis techniques hampers their introduction in clinical practice.
- Patients with increased FeNO and high periostin levels are likely to be at risk of rapid decline in respiratory function and of more frequent exacerbations despite chronic treatment by strong doses of inhaled corticosteroids.
- Omalizumab has a systemic anti-inflammatory role: patients with the most severe clinical symptoms and eosinophilic inflammation are those who benefit most from the treatment.

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Papers of special note have been highlighted as either of interest (•) or of considerable interest (☆) to readers.


• One of the first study on induced sputum and airflow inflammation.

☆ General recommendations for sample collection of exhaled breath condensate.
• A rare study on FeNO in recurrent infantile wheezing.
• Increased airway inflammation was associated with lower ICS adherence.
• The use of VOCs in EB and biomarkers in EBC as markers of inflammatory airway diseases in children.
• One of the rare study of the utility of urinary protein X in asthma children.
• Position paper on biomarkers and severe asthma.


Asthma phenotypes and personalized medicine in children.


Position paper on cytokine network and airway inflammation.


A randomized, double-blind, placebo-controlled, parallel-group trial at multiple centers to assess the effectiveness of omalizumab, as compared with placebo in children.


