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Omalizumab could be effective in children with severe eosinophilic non-allergic asthma

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Capsule summary (26 words)

Severe eosinophilic non-allergic asthma is a rare phenotype that could be effectively treated by omalizumab, especially when associated with elevated total serum IgE and nasal polyposis.

Manuscript (1036 words)

Introduction

Severe eosinophilic non-allergic asthma is a specific phenotype, rarely described in children, sometimes associated with nasal polyposis and aspirin intolerance (i.e., Widal's syndrome). This asthma phenotype is known to be particularly severe and steroid resistant (1).

Monoclonal antibodies are currently used to treat severe asthma. The first of these to be developed was omalizumab, which is reserved for allergic asthma. A growing body of research in adults suggests that omalizumab could also be effective in patients with non-allergic asthma (2–6). However, to our knowledge, no studies have reported on the use of omalizumab in this asthma phenotype in children. Other monoclonal antibodies are also being developed (such as anti-IL-5 or anti IL-13) for cases of severe asthma with elevated blood eosinophilia but there is no data about the use of these molecules in children either.

Case reports

We report here a short series of seven children from Department of Allergology—Centre de l'Asthme et des Allergies, Hôpital d'Enfants Armand Trousseau, average age 11.5 years (range 6 to 13.5) at treatment initiation, with severe eosinophilic non-allergic asthma treated by omalizumab. Comorbidities included nasal polyposis (n=4), atopic dermatitis (n=1), and vernal kerato-conjunctivitis (n=1). None of the children included had known associated vasculitis disease. Six of the children had never received aspirin or non-steroid anti-inflammatory drugs (NSAIDs), and the one who had received NSAIDs regularly had never experienced any complications.

Asthma severity was attested by (1) severe exacerbations (hospitalizations for five children and intensive care unit for two), (2) frequent use of oral corticosteroid (weekly to bimonthly) for four children, lasting several weeks for three, and (3) altered lung function with an average FEV1/FCV of 79% (IQR 62-83%). None of them had allergic sensitization, explored by skin-prick tests, Phadiatop® and specific IgEs for a panel of the most frequent inhaled allergens (house dust mites, molds, pollens, cat and dog dander). ISAC micro-array

was performed for three patients and were all negative. Elevated eosinophilic-derived inflammation was attested by high blood eosinophilia (average 1115/mm³ (IQR 700-1400)) and high FeNO (average 30 ppb (IQR 73-140)). Bronchoalveolar lavage was performed in four children and all of them had elevated pulmonary eosinophilia (range 7 to 45%). Average total serum IgE was 192 IU/mL (IQR 41-269) (Table 1).

All the children were treated by omalizumab according to their weight and initial total serum IgE. Doses ranged from 75 mg a month to 600 mg every two weeks and the follow-up was 18 months (IQR 6-36).

Five of the seven patients responded to omalizumab as attested by a significant decrease of severe exacerbations (n=5), improvement of lung function (n=3), reduced usage of oral (n=5) and/or inhaled steroids (n=3). There was no difference between responders and non-responders in terms of sex, age, lung function parameters or blood eosinophilia before the initiation of treatment by omalizumab. However, total serum IgE was higher in responders compared to non-responders: respectively, 210 (IQR 192-269) vs. 38.5 (IQR 36-41) (Kruskal-Wallis test, p=0.05). Four of the five responders had nasal polyposis compared to none of the non-responders (p=0.14, NS).

Eosinophilia significantly decreased under treatment in the group of responders from 1180/mm³ (IQR 1115-1400/mm³) to 422/mm³ (IQR 400-560/mm³) (Wilcoxon rank test, p=0.04) (Figure 2). A non-significant change in eosinophilia was observed in the group of non-responders: from 750/mm³ (IQR 400-1100) to 1085/mm³ (IQR 1070-1100) (Wilcoxon rank test, p=0.32). No significant changes were observed in lung function parameters (assessed for all patients) or FeNO values (assessed in five patients).

Discussion

Several publications of case reports or short series describe the use of omalizumab in mainly adult patients suffering from severe non-allergic asthma, sometimes reporting the successful withdrawal of systemic corticosteroids under treatment (2–5). One randomized controlled trial in a cohort of 41 nonatopic asthmatic adults showed that omalizumab could be effective in this setting and significantly improved lung function and reduced the expression of high affinity IgE receptors on basophils and plasmacytoid dendritic cells (6). Another randomized trial was carried out in 18 non-atopic asthmatics who underwent bronchial biopsies before

and after 12-14 weeks treatment, which also showed that Omalizumab improves lung function, despite withdrawal of conventional therapy; biopsies highlighted reduced bronchial mucosal IgE mast cells after treatment (7). Of note, there was no significant decrease in median total eosinophils (7).

Our results suggest that children with severe eosinophilic non-allergic asthma with an associated elevated total serum IgE and, probably, nasal polyposis could be better responders to omalizumab than children without these features. This is in accordance with previous reports (8) where omalizumab was shown to be effective in nasal polyposis, regardless of the atopic status. Furthermore, this highlights that severe eosinophilic non-allergic asthma associated with nasal polyposis is probably a particular rare phenotype of asthma in children with a specific underlying pathophysiology.

Study limitations

Some limitations to this report deserve to be mentioned. We describe here a small population representing a rare asthma phenotype in children. However, despite this small sample size, we obtained statistically significant differences. Furthermore, the duration of treatment at assessment was different from child to child, ranging from 6 to 24 months, but the response to omalizumab remained stable during follow-up. Finally, this is a descriptive report without a control group and the results should be confirmed by a larger randomized controlled trial.

Potential mechanisms for the effectiveness of omalizumab in non-allergic asthma

The pathophysiology of allergic and non-allergic asthma highlights many similarities. The inflammatory cascade observed in the airway is very similar for both phenotypes, with a type 2 profile of T-helper cells, mast cell activation and infiltration of the mucosa by eosinophils. The same inflammatory mediators, particularly Th-2 cytokines and eosinophil chemoattractant chemokines, are expressed. In addition, patients with non-atopic asthma can also have elevated total serum IgE. In our series, the group of responders had significantly higher total serum IgE than the group of non-responders. Recently, Song *et al.* described an association between enterotoxin-IgE sensitization and severe eosinophilic asthma with chronic rhinosinusitis (9). This phenotype of asthma is very similar to our cohort and this might explain the effectiveness of omalizumab with respect to enterotoxin-IgE sensitization. Further studies are required to confirm this hypothesis.

Moreover, it is known that total serum IgE is correlated with the severity of asthma, including non-atopic asthma (10), and it has been demonstrated that IgEs are able to trigger the

intracellular signaling pathways leading to the production of pro-inflammatory cytokines even in the absence of allergen (11). 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 (6,11). In addition, IgE can directly activate receptors present on eosinophils, neutrophils and monocytes (4). Finally, some studies have highlighted additional anti-inflammatory effects of omalizumab by limiting recruitment and activation of eosinophils (12).

In conclusion, omalizumab may be effective in children with severe non-allergic eosinophilic asthma. Children with elevated total serum IgE and nasal polyposis seem to be better responders. This severe non-allergic eosinophilic asthma phenotype corresponds to a rare disease that should be further explored in order to understand the mechanisms of action of omalizumab as a global anti-inflammatory drug. More widely, the effectiveness of omalizumab in this rare severe pediatric asthma phenotype supports the need for designing larger double-blind placebo controlled studies in pediatric populations. Furthermore, other biotherapies currently under development such as anti-IL15 and anti-IL13 are emerging as promising options for a more targeted management of eosinophilic asthma in children.

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Figure legend

Figure 1: Kinetics of blood eosinophilia in responders group

Tables

Table 1: Baseline characteristics of the patients before treatment by omalizumab and outcomes after 6-24 months of treatment

Patients n° 1 and 5 were considered non-responders

Patient	Demographic data			Co-morbidities	Time to assessment (months)	Asthma control						Lung function tests				Serum level		
	Gender	Age	Ethnic background			ICS µg/d before	ICS µg/d after	Hospital admissions		Use of oral steroids		FEV1/ FVC pre	FEV1 /FVC post	FeNO (ppb)		Total IgE	Blood eosinophils	
								pre	post	pre	post			pre	post		pre	post
1	M	7	Caucasian	VKC	6	2000	2000	2	0	Weekly (considered continuous)	Monthly	80	71	73	70	36	400	1070
2	M	12	Caucasian	Polyposis	24	2000	2000	Multiple	0	6/year	0	83	74	37	-	42	1180	400
3	M	7	African	No	6	2000	2000	3	0	Continuous (0.7mg/kg/d)	0	71	77	-	16	192	1115	560
4	F	11	Haitian	Polyposis, AD	12	2000	600	2	0	Monthly	0	58	63	141	169	210	700	300
5	M	6	Caucasian	No	36	2000	2000	3	1	10/year	4/year Then continuous	79	83	-	13	41	1100	1100
6	F	13	Caucasian	Polyposis	18	2000	600	Multiple	0	Continuous	0	84	84	130	48	637	1400	422
7	F	11	Caucasian	Polyposis	36	2000	1000	Multiple	0	1 month	0	62	56	140	38	269	2380	715

VKC : vernal keratoconjunctivitis; AD : Atopic Dermatitis; ICS : Inhaled Corticosteroid

Non-responders are **highlighted**.

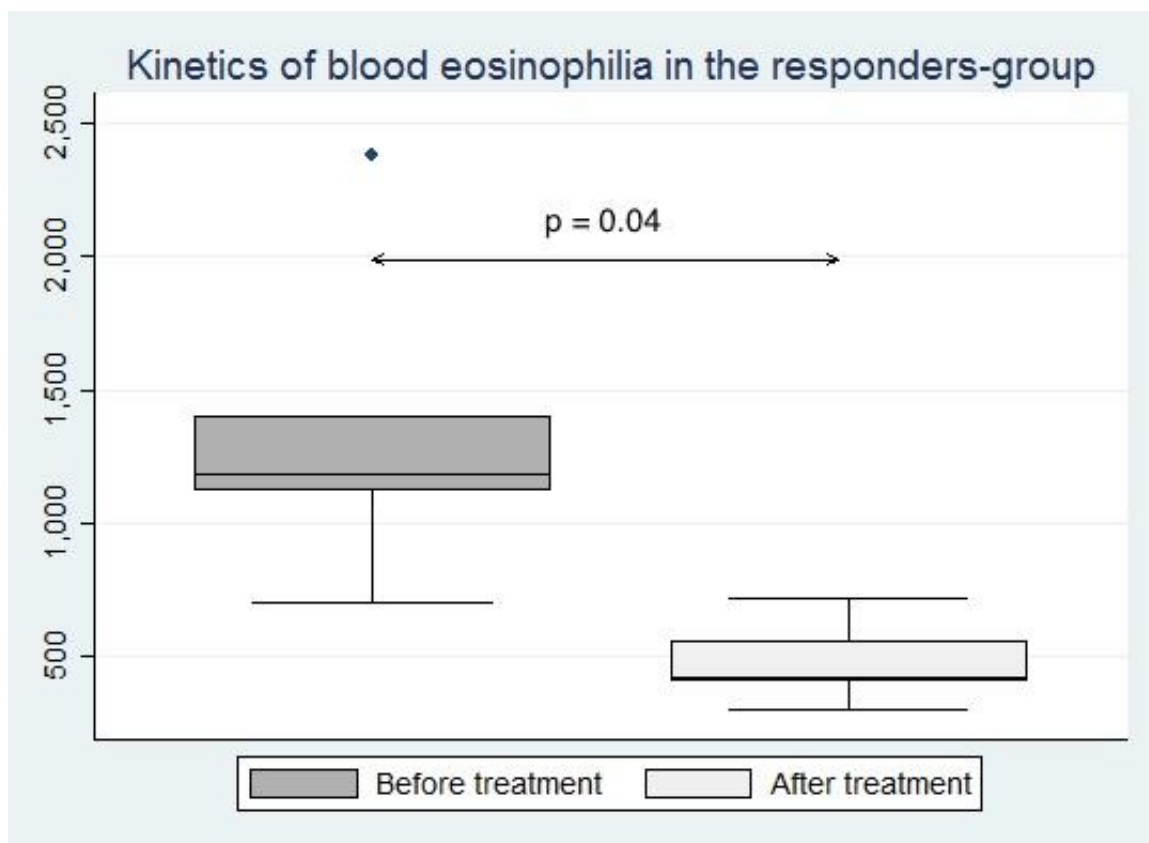


Figure 2.JPEG

Author contributions

All the authors approved the submission of this version of the manuscript and takes full responsibility for the manuscript

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J Just: involvement in the conception, hypotheses delineation, and design of the study, writing the article and substantial involvement in its revision prior to submission