CONTROLLING SEVERE ALLERGIC ASTHMA 
WITH OMALIZUMAB (MONOCLONAL ANTI-IgE ANTIBODIES) IN CHILDREN

M. Craiu 2,3, I.V. Stan 1, V. Comanici 2, C. Popescu 3, D. Valceanu 3, R. Bumbacea 4

1. First Pediatric Clinic IOMC, Alfred Rusescu, Bucharest
2. Second Pediatric Clinic IOMC, Alfred Rusescu, Bucharest
3. Emergency Department IOMC Alfred Rusescu, Bucharest
4. Alergology Department, Elias Hospital, Bucharest

Abstract
Allergic severe asthma is rare disease among young children. Most of these patients should be evaluated by an expert and treatment has to be tailored according to evolutive phenotype. One option for adult patients with such a condition is adding omalizumab [anti-IgE antibodies] to step IV GINA medication.

Authors present a small pediatric series of severe uncontrolled asthmatic patients treated with an average 12 months course of omalizumab. Demographics, clinical features and comorbid conditions are documented. Due to safety issues all patients were monitored during and after omalizumab injection in the resuscitation module of the Emergency Department from a tertiary referral pediatric hospital. Monitoring and protocol are presented. All children had a positive outcome, three with partial control and one with complete control. No serious side effects were observed. Low grade fever was easily controlled with trivial antipyretics.

Conclusion: anti-IgE monoclonal antibodies in severe allergic asthma patients are efficacious also in children and represent a safe and solid alternative for long-term oral corticosteroid treatment.

Keywords: allergic asthma, anti IgE antibodies, child

Background and aim
Asthma is a respiratory disease that affects approx. 300 million people worldwide and is associated with significant morbidity and mortality. Severe asthma (SA) in children is a rare and heterogeneous condition, representing 2-10% of various asthma cohorts. 1, 2, 3 also in Romania. 4 In spite of being a rare condition it accounts for more than 1/3 of total costs of asthma patients. 5 Clinically, children with SA are different from other asthmatics by greater allergic sensitization, increased exhaled nitric oxide and significant bronchospasm that worsens as child grows older. These findings are generated by structural airway changes, abnormal and excessive airway inflammation which may explain the heterogeneity of treatment responsiveness of SA patients. 5, 6

Guideline-based therapy of SA in childhood is based on extrapolated adult studies data. They should be treated with a similar step-wise tailored strategy: higher-dose inhaled or oral corticosteroids combined with long-acting β-agonists and other add-on therapies, such as antileukotrienes and methylxanthines. Crucial is to identify and approach influences that make asthma difficult to control: revisiting diagnosis, removing causal or aggravating factors, improving treatment compliance.

Progress in immunological methods used to evaluate human allergic diseases has led to identification of immunoglobulin E (IgE) as a diagnostic biomarker and a potential therapeutic target. Omalizumab (OZ) is the most advanced humanized anti-IgE monoclonal antibody that specifically binds serum-free IgE. OZ interrupts allergic cascade by preventing binding of IgE with FcεRI receptors on mast cells, basophils, antigen-presenting cells and other inflammatory cells. A 2013 update of National Institute for Health and Care Excellence (NICE) guidelines 7 recommends OZ for use as add-on therapy in adults and children over six years of age with non-controlled severe persistent allergic IgE-mediated asthma who require continuous or frequent treatment with oral corticosteroids. Because most children with SA have an inflammatory pattern OZ plays a central role in disease control 8, 9 or even can change natural course of disease - suggested by a one year course of OZ followed by 4 years of prospective survey. 10 OZ can decrease exacerbation rate in patients with moderate to severe asthma and is an efficient corticoid-sparing drug. 11 In special patients in whom treatment adherence does not improve in spite of strenuous efforts, OZ is an alternative, because it is provided in-office on a monthly [or bimonthly] basis. 12 OZ is the first of its class and many other biological agents and humanized monoclonal antibodies will be soon available. One such agent is nopolizumab that significantly reduces asthma exacerbations and improves markers of asthma control. 13

The authors aim to describe a small group of children younger than 12 years treated with omalizumab for a relative long time.
Material and method

Retrospective analysis of a small group of severe asthma patients.
Inclusion criteria were age (6-12 years old), allergic asthma (ICD code J 45.0), uncontrolled disease (Asthma Control Test below 19), severe disease in spite of optimal treatment and rigorous compliance.
Exclusion criteria were non allergic asthma (ICD code J 45.1), moderate, mild-persistent or intermittent disease, controlled disease and uncompliant patient or family.

Results

From a group of 8 children with severe asthma previously published \(^4\) we selected only allergic asthma patients with documented mechanism of disease: 3 boys and one girl. Increased eosinophilia, high IgE levels were present in all patients plus skin prick test in two children and elevated specific IgE titers in the other two [mould and house dust mite respectively. 

Average age at onset 7.81 years [extremes 6 – 9.75y]. All were previously treated with inhaled corticosteroids (ICS), medium or high dose, and intermittent systemic steroids. Three children were on combination therapy (ICS + LABA) and one child also with LTRA. Compliance was evaluated pre-treatment and was excellent. Inhalation technique was retrained with video and hands-on, both in children and parents, before treatment with omalizumab was started. Written action plan was provided and end extensive communication and adverse reaction reporting was explained.

Omalizumab has a relative large list of side-effects and most parents are reluctant in accepting anti-IgE treatment initially. In severe cases with a very low quality of life and a significant number of exacerbations in a given child, parental concern is shifted toward disease control than on potential side-effects of controller medication. In order to increase acceptance and to decrease parental anxiety all Omalizumab injections were performed according to a pre-specified protocol in the Resuscitation room of the Emergency Department (ED) of IOMC.

After patient file was recorded in hospital electronic file and informed-consent was signed, all patients had a complete evaluation and vital signs measurement. ECG, body temperature, pulse-oximetry, heart rate, respiratory rate and blood-pressure were continuously monitored with a Phillips triage monitor. Vacuum aspiration, advanced airway tools and devices, defibrillator and adequate amount of medication for the given weight were prepared. Omalizumab vial was slowly rewarmed at room temperature and homogenized according to in-file specifications. Only when child provided assent injection was performed in the deltoid area according to child preference. 75% of procedures were performed with topical analgesia (EMLA cream). All injections were administered by same physician. After continuous monitoring of at least one hour, each child had a complete clinical check-up and pulmonary function testing [PEF-spirometry]. In some cases exhaled nitric oxide levels were measured. Children were discharged from ED in the same day after an average of 100 minutes monitoring. Longest stay were noted for first visit in all patients: 160-180 minutes.

A total of 51 sessions of omalizumab treatment were delivered. Average doze was 156 mg [extremes 75 – 300 mg] – fig. 1 Omalizumab time line and doses in IOMC patients.

No significant adverse events were documented. Fever was present in 3 children, never above 39°C, lasting one up to three days. One child had intermittent fever post-injection for several months after onset and other two only 3 months. Fever was not associated with severe discomfort or pain and was easily controlled with regular fever-reducing agents [paracetamol or ibuprofen]. No severe allergic reactions were encountered, not local nor systemic. Only significant disease episode was varicella in patient number 4.

All patients had an improvement in ACT score and were able to perform after a while normal school activities – fig.2. Asthma Control Test during treatment. During this interval of 51 patient-months only 3 exacerbations were noted compared with a total or 11 episodes in the previous year before treatment [48 patient-months] (23% reduction in exacerbation rate, p=0.0061). – fig. 3. Exacerbation rate

Eosinophil count decreased and presented a rebound after stopping treatment [only one’s child family decided to stop medication because of excellent control and fear of potential adverse events] - fig. 4. Eosinophil count in IOMC patients.
Discussion

Limited options are available for severe, treatment-resistant asthma pediatric patients. Because of parental corticophobia and because of severe limitations in quality of life in these patients alternative treatment approaches should be identified before significant airflow limitation occurs. One such option is add-on anti-IgE antibodies to step IV GINA treatment. Current indications for treatment with omalizumab in pediatric patients are clearly defined and are confined to moderate-to-severe uncontrolled allergic asthma and chronic spontaneous urticarial. According to European Medical Agency omalizumab can be also used in selected asthma patients of 6 to 12 years old.

Fig. 2. Asthma Control Test during treatment [note – time intervals are not similar for all 4 patients and are not repetitive]

Fig. 3. Exacerbation rate in pre/post onset of omalizumab treatment

Fig. 4. Eosinophil count in IOMC patients
Authors present a limited experience of Omalizumab treatment in young children. To our knowledge this is the first such a paper regarding Romanian children with severe asthma treated with OZ. More patients should be included for a more robust result.

Conclusions

Omalizumab is an efficient and safe add-on treatment option in children with uncontrolled asthma. Significant reduction of exacerbation rate and sustained increase of quality of life are solid arguments to use anti-IgE medication in selected severe asthma children, even in the young age group (6-12 years).

References


Correspondence to:
Mihai Craiu MD, PhD
Associate Clinical Professor of Pediatrics,
Second Pediatric Clinic IOMC, Emergency Department IOMC “Alfred Rusescu”, Bucharest
120, Lacul Tei avenue, 020395 Bucureşti
E-mail: mcraiu@yahoo.com