

CASE REPORT

Omalizumab for the treatment of severe allergic asthma in children: A tale of two

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Abstract

Omalizumab is a monoclonal antibody which targets immunoglobulin E. It is approved as an add-on therapy for children with severe allergic asthma. Assessment of endotype and phenotype is necessary in order to correctly identify those patients who are most likely to respond to omalizumab. Children with severe asthma represent a complex heterogeneous group. This report outlines the background, management, and outcomes for two children initiated on omalizumab for severe allergic asthma in Children's Health Ireland at Tallaght. It demonstrates the difficulties faced by this cohort and the positive impact targeted biological therapy can have. Given the substantial cohort of children with asthma attending our tertiary center, it also indicates that comprehensive stepwise care can achieve adequate control in the vast majority of cases without the requirement for additional therapies.

KEYWORDS

allergy and immunology, asthma, biologic therapies, pediatrics and adolescent medicine, respiratory medicine

1 | BACKGROUND

Asthma is the most common chronic disease of childhood and the most common respiratory condition in Ireland.¹ An allergic component is observed in approximately 80 percent of children with asthma,² demonstrated by raised total serum immunoglobulin E (IgE) levels and evidence of raised specific IgE antibodies to a relevant aeroallergen (in particular, house dust mite; HDM). The Global Initiative for Asthma (GINA) reports that approximately three to ten percent of people with asthma have severe asthma.³ Severe asthma is a heterogeneous disorder; it represents uncontrolled asthma with poor symptom

control despite adherence with optimized Step 4 or Step 5 therapies along with treatment of contributory factors (e.g., allergic rhinitis) and enhancement of inhaler technique, or asthma that worsens with weaning of high-dose treatment.^{3,4} It poses a significant burden for individuals and society. Children with severe asthma experience persistent symptoms, multiple unplanned interactions with healthcare settings including life-threatening acute exacerbations, significant impact on activities of daily living, associated neuropsychological impacts, and side effects from high-dose corticosteroids.^{5,6}

Targeted biologic therapies for asthma have emerged as effective add-on options. For patients with persistent

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symptoms and/or exacerbations despite high-dose inhaled corticosteroids, the clinical or inflammatory phenotype should be assessed in order to guide further management.³ Biologics are increasingly targeting both phenotype and endotype using biomarkers as indicators for disease type. Phenotype represents the observable characteristics of a disorder with no direct relationship to the disease process, while the endotype is an identified specific biological pathway that explains the observable properties of a phenotype.⁷ Stratification according to inflammatory endotype is now deemed a central component in the algorithm for management of severe asthma.⁷ There are two major endotypes defined for asthma: type 2 (T2)-high asthma and T2-low asthma, based on the type of underlying airway immune-mediated inflammation.⁸ T2-high asthma is typically characterized by eosinophilic inflammation, with type 2 cytokines actively recruiting eosinophils, mast cells, and basophils in the airways, and directly mediating IgE synthesis. The T2-high asthma endotype encompasses the atopic phenotype. It generally displays a good response to corticosteroid therapy and has become the target of biological therapies (for example, anti-IgE and anti-interleukin-5 therapies).⁹

Omalizumab represents the first available humanized monoclonal anti-IgE for use in pediatric severe allergic asthma (approved for use in children ≥ 6 years of age), with an established efficacy and safety profile.¹⁰ As per the GINA 2020 guideline (section 6B ‘consider add-on biologic Type 2 targeted treatments’),³ omalizumab is suitable for patients with severe T2-high asthma with aeroallergen sensitisation demonstrated by skin prick testing or specific IgE, raised total IgE, and frequent exacerbations. Biologic treatment is also guided by local availability and access to these treatments can be very limited. Two children have been commenced on omalizumab for severe allergic asthma by the respiratory department in Children’s Health Ireland (CHI) at Tallaght. We performed a literature review on biological therapies in pediatric asthma. We present the presentation, management, and outcomes of the two children commenced on omalizumab in CHI at Tallaght.

2 | CASE PRESENTATION

2.1 | Case 1

A 16-year-old male patient was initiated on omalizumab at 11 years of age. He has a background of severe asthma, allergic rhinitis, eczema, and food allergies. Prior to commencement of omalizumab, he was on high-dose inhaled corticosteroid in combination with a long-acting $\beta 2$ -agonist (fluticasone propionate 1000 micrograms/

salmeterol 100 micrograms per day) via Volumatic device. He was on a maintenance oral corticosteroid (OCS; prednisolone 5 mg on alternate days; commenced 3 months prior to omalizumab induction). He was requiring frequent inhaled and nebulized salbutamol. His therapy was optimized with control of his allergic rhinitis using daily intranasal fluticasone, saline rinse, antihistamine, and aeroallergen avoidance. He had previously been trialed on montelukast with no observed benefit. Though theophylline is no longer a recommended therapy, it was trialed as an adjunct in Step 4 management as per the GINA 2015 guideline in use at the time.¹¹ It should be noted that this guideline did not recommend theophylline for children aged 6 to 11. However, he was experiencing ongoing severe symptoms with limited regional access to other add-on therapies, including biologics. This was a tertiary individualized therapy decision and not generalized to other children with asthma in the center. There was no observed benefit and it was discontinued following 3 months. Enhancement of adherence, inhaler technique, asthma action plan, and self-management skills was achieved following input from the center’s advanced nurse practitioner in asthma. Despite this, he was reporting daily cough, wheeze, dyspnea, fatigue, and sleep disturbance. His control significantly deteriorated from 1 year prior to commencement of omalizumab, including an admission to the pediatric intensive care unit. His management was at Step 5 with ongoing inadequate control; therefore, he underwent phenotypic assessment (see “Investigations”).

2.2 | Case 2

An 8-year-old male patient was initiated on omalizumab at 5 years of age. He has a background of severe asthma, eczema, allergic rhinitis, and recurrent spontaneous urticaria. He was delivered at 29 weeks gestation and developed bronchopulmonary dysplasia. Prior to commencement of omalizumab, he was on high-dose inhaled corticosteroid in combination with a long-acting $\beta 2$ -agonist (fluticasone propionate 500 micrograms/salmeterol 100 micrograms per day). At the time, GINA 2016 guidance was in use which specified that the best treatment for the population below the age of 5 had not been established and theophylline could be considered as a Step 4 option (it has been removed as an option in later guidelines).^{3,12} Due to the high burden of symptoms, theophylline 250 mg per day was commenced as a trial via primary care while awaiting specialist input. It was subsequently continued for a prolonged period due to perceived benefit and reluctance to discontinue it. However, he continued to require frequent inhaled and nebulized salbutamol despite this escalation

of therapy. He had undergone previous trials of montelukast, prophylaxis with azithromycin, and maintenance daily oral corticosteroid with no significant benefit. His treatment was optimized with control of his allergic rhinitis using a daily antihistamine, intranasal fluticasone, and aeroallergen avoidance. Enhancement of adherence, inhaler technique, asthma action plan, and self-management skills was achieved following input from the center's advanced nurse practitioner in asthma. Despite these measures, daily symptoms of wheeze, cough, and poor sleep were reported. He required frequent hospital admissions for exacerbations, including management in the high dependency unit. Prior to omalizumab, he was completing more than ten courses of oral corticosteroids per year. His management was at Step 4 with ongoing inadequate control.

3 | INVESTIGATIONS

Both patients underwent comprehensive assessment prior to the initiation of omalizumab. Table 1 outlines the patient profiles. Patient 1 had a raised total IgE level with a positive skin prick test to house dust mite (6 mm). Serum eosinophils were raised. He underwent ophthalmology review which demonstrated early posterior subcapsular cataracts (PSCC) likely secondary to corticosteroid use. A bone density scan was normal. Pulmonary function tests

prior to initiation of omalizumab showed an FEV₁ of 78%, FEF_{25–75%} of 46%, and a PEF of 90% predicted. Assessment of endotype was consistent with T2-high asthma with an atopic phenotype.

Total IgE level was raised in Case 2 with a positive specific IgE to house dust mite of 64.4 IU/ml. Of note, his serum eosinophils were normal, possibly due to frequent OCS use. Ophthalmological review to assess for adverse effects of corticosteroid use demonstrated no abnormalities. High-resolution CT thorax and bronchoscopy were normal. This patient represented diagnostic and management difficulties; his pulmonary function tests prior to initiation of omalizumab showed an FEV₁ of 155%, FEF_{25–75%} of 137%, and a PEF of 132% predicted with a 14% reversibility (supernormal values may be due to extrapolation of normal parameters in children less than 6 years of age). Though serum eosinophils were normal, assessment of endotype based on IgE was consistent with T2-high asthma with an atopic phenotype.

4 | TREATMENT

Both patients met the criteria for initiation of omalizumab based on severity of asthma and phenotype profile. Patient 1 was commenced on omalizumab 375 mg alternate weeks via subcutaneous injection (dose guided by weight) which was subsequently decreased

TABLE 1 Pre-omalizumab demographics and parameters

	Case 1	Case 2
Age (years)	11	5
Gender	Male	Male
FEV ₁ (% of predicted)	78% (12% reversibility)	155% (14% reversibility)
Total IgE (IU/ml)	733	863
Aeroallergen sensitivity	HDM	HDM
Serum eosinophils (×10 ⁹ /L; reference range: 0.06–0.84)	1.7	0.0
Exacerbations/year	>10	>10
Courses of OCS/year	>10	>10
Maintenance OCS	Yes	No
Frequency of interval symptoms	Daily	Daily
Triggers	HDM Exercise Viral illness	HDM Viral illness
Comorbidities	Allergic rhinitis Eczema Food allergies	Allergic rhinitis Eczema Spontaneous urticaria
Corticosteroid adverse effects	PSCC	Weight gain
Advanced nurse practitioner input	Yes	Yes
GINA step	5	4

to monthly. Patient 2 commenced omalizumab 225 mg administered subcutaneously on alternate weeks (dose guided by weight).

5 | OUTCOME AND FOLLOW-UP

5.1 | Case 1

The patient had a significant improvement in his asthma control within 6 weeks of commencing omalizumab. To date, he reports no oral steroid use since the commencement of omalizumab 5 years ago, along with no exacerbations or interval symptoms, and extremely rare use of short-acting β 2-agonist. His quality of life improved dramatically. Of note, his pulmonary function tests showed an initial improvement but quickly returned to his pre-omalizumab baseline. This may indicate that the use of pulmonary function tests as an outcome endpoint is inappropriate. The patient remains on high-dose inhaled corticosteroid in combination with a long-acting β 2-agonist. Omalizumab was discontinued recently due to his high level of control and, though he reports occasional interval symptoms and increased use of short-acting β 2-agonist, his asthma remains adequately controlled. His current Asthma Control Test score is 21/25. He will undergo interval respiratory and ophthalmology review for follow-up.

5.2 | Case 2

Asthma control improved but not as dramatically or immediately as in the first case. He completed four courses of oral steroids in the last year and required one acute admission. His exacerbations are now primarily managed at home with an asthma action plan. He denies any interval symptoms or use of salbutamol. There has been a notable reduction in symptoms and severity of exacerbations and his quality of life has increased significantly. His allergic rhinitis and eczema have improved, and his urticaria has resolved (omalizumab is indicated as an add-on therapy for the treatment of chronic spontaneous urticaria¹³). His weight is now tracking the 75th centile, while it had previously increased above the 91st centile perhaps secondary to corticosteroid use. His pulmonary function tests post-omalizumab initiation showed an FEV₁ of 131%, FEF_{25–75%} of 133%, and a PEF of 115%, with ongoing reversibility demonstrated. Fractional excretion of nitrous oxide (FeNO) remains stable below 20 ppb. Theophylline has recently been weaned and discontinued; and his omalizumab dose is now administered every 6 weeks. His inhaled corticosteroid has been decreased to medium total daily dose (budesonide 300 micrograms/formoterol 18

micrograms per day). He is now managed in a peripheral center. His current Asthma Control Test score is 26/27.

6 | DISCUSSION

Omalizumab is recommended as an add-on treatment for children with severe allergic asthma with elevated serum IgE and positive-specific IgE to at least one aeroallergen.³ By binding to free IgE, omalizumab reduces cell-bound IgE, down-regulates IgE receptors, and prevents the release of pro-inflammatory mediators.¹⁴ Both patients discussed in this report showed either complete control or marked improvement in their symptoms. They demonstrated a significant reduction in the number of asthma exacerbations, use of systemic corticosteroids, unscheduled healthcare interactions, and hospitalizations. FEV₁ has been proposed as an outcome endpoint in the literature¹⁵; however, neither of these patients demonstrated a sustained improvement in FEV₁ despite ongoing good subjective control. Though we do not have documented pre-omalizumab Asthma Control Test scores, these are likely to have vastly improved. This case series indicates that a combination of both subjective and objective measures is needed in order to assess response and efficacy.

The phenotype most likely to respond to omalizumab has been identified in the literature as severe asthma with clinically relevant allergic sensitization(s), multiple atopic comorbidities, high serum eosinophils, total IgE, and FeNO.^{10,16} Perhaps the reason the patient in *Case 1* had a more pronounced response was due to the presence of eosinophilia, although biomarkers can fluctuate over time and eosinophils may also be repressed due to concurrent OCS use.³ *Case 2* was more complex in nature, given the very young age of the patient, along with a history of prematurity and bronchopulmonary dysplasia. His response to omalizumab was not as extensive as in *Case 1*, and this may be due to an element of chronic obstructive pulmonary disease secondary to bronchopulmonary dysplasia. However, he had many hallmarks of atopic disease and responded favorably to omalizumab both objectively and subjectively (see “Patient’s Perspective”). Evidence supports the role of omalizumab in treatment-resistant allergic asthma in the pediatric population.¹⁷ The steroid-sparing effects are especially important in this cohort. The optimal duration of omalizumab therapy, along with its long-lasting effects following discontinuation, is not yet clearly defined and further real-world longitudinal studies are needed.^{10,17}

Biologics represent an evolving domain of asthma management. More recently, the anti-interleukin-5 humanized monoclonal antibody mepolizumab has been approved for the treatment of severe eosinophilic asthma

in children. Dupilumab (targeted agent against the interleukin-4 receptor α -chain) has been approved for use in pediatric severe allergic asthma. However, though these more recent agents are approved for children ≥ 6 years of age, there is a concern regarding absence of efficacy data in children aged 6–11 years.^{10,18} The ongoing TREAT trial (treating severe pediatric asthma; a randomized trial of mepolizumab and omalizumab) in the UK hopes to address the lack of tailored pediatric evidence for biological therapies in asthma.¹⁸ It is a non-inferiority trial with asthma exacerbations as the primary outcome. It will also investigate biomarkers of response in children. This may prove useful in determining protocols for monitoring children on biological therapies and also for further defining the responsive phenotypes and endotypes. It may also provide a gateway for new alternatives for asthma therapy in the pediatric and adolescent population. Currently, omalizumab remains the only biologic with robust efficacy and safety evidence for use in children.

7 | LEARNING POINTS/TAKE-HOME MESSAGES

- The impact severe asthma has on a child and their family cannot be underestimated—omalizumab can have a significant positive effect on quality of life and burden of disease in selected individuals.
- Assessment of endotype and phenotype is essential when considering targeted biological therapy.
- A combination of both subjective and objective measures is needed in order to assess response and efficacy to omalizumab.
- Further exploration of biologics in pediatric asthma is needed in order to develop appropriate protocols.
- There is a significant number of children with asthma attending CHI at Tallaght. Two children have been commenced on biological therapy in this cohort—an indication of the control that can be achieved with standard therapies. Comprehensive stepwise care and education remain the bedrock of asthma management.

8 | PATIENT'S PERSPECTIVE

8.1 | Case 1

My name is [-] and I am the recipient of omalizumab since January 2015. From a very young age, I was unable to take part in most activities that kids my age were doing. The change of season would most definitely mean a hospital stay, and my asthma was rarely under control. Since omalizumab, I noticed an immediate improvement in my

condition and began to attend school on a regular basis, and take up sports and music, which requires regular attendance which isn't a problem nowadays. Whilst I finished omalizumab in August 2020, I remain on Seretide and occasionally Ventolin. To date, my asthma is under control.

8.2 | Case 2

As parents of a medically complex child, who outwardly always appeared 'well', we have found this journey very challenging at times. From numerous inpatient stays, to the worry of excessive medication usage and time off school due to flare ups. What we found with [-] is that through Xolair he has 70% less inpatient stays, he is now a 'normal' socially active child (i.e. going to parties, play centres etc.) He also does not miss as much school either. While it took him longer than predicted to react to Xolair, it has been nothing short of life changing for us as a family. As his condition has stabilised, he is now on the least amount of medication since he was born. Our hope for [-] and others like him is that the threshold to get it is lowered to give everyone a fair chance at a relatively normal childhood.

AUTHOR CONTRIBUTIONS

OA and BE conceived of the presented idea. MM, OA, and PG identified the appropriate patients. SB and MM collected the data from the chart reviews. SB collated the information and compiled the manuscript under the supervision of OA. All authors reviewed and edited the final manuscript.

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CONFLICT OF INTEREST

There are no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

CONSENT

Written informed consent was obtained from the patients (and/or their parent/guardian) to publish this report in accordance with the journal's patient consent policy.

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