CASE REPORT

Long term outcome of Omalizumab Therapy in childhood severe allergic asthma

Mariana Daud, MMed (USM)

Department of Pediatric, Hospital Raja Perempuan Zainab II, Kota Bharu, Kelantan

SUMMARY

Childhood severe asthma is different from adult asthma and little is known about the use of biologics in children in Malaysia. Uncontrolled severe asthma has significant morbidity and impact on the quality of life of the children and their families as well as increase healthcare burden. Anti-IgE therapy is known for its efficacy and safety for severe allergic asthma phenotype, both in adults and children. We describe our experience using omalizumab therapy in two pediatric cases of severe allergic asthma and the journey of these patients before and after omalizumab therapy.

INTRODUCTION

Severe asthma affects 5–7% of children worldwide[1] and it has significant morbidity and even mortality. Thus, children are at risk for asthma exacerbations, emergency visits, asthma related hospitalization, impairment in their quality of life, missing school and high economic burden.[2] There are limited therapeutic options in children with severe asthma, despite maximal guideline-based therapy and treatment of contributory factors. Omalizumab, a humanized recombinant monoclonal anti-IgE antibody, is the only approved biologic agent in Malaysia for children with severe allergic asthma. This therapy is approved for treatment of moderate to severe allergic asthma (SAA) and Chronic Idiopathic Urticaria (CSU) with good clinical efficacy and safety profile.[3] The experience of using omalizumab in pediatric patients has been very limited with almost no published report from Malaysia. Our aim is to share our experience of using omalizumab in two pediatric patients of severe allergic asthma (SAA) with multiple comorbidities, describing their profile, financial challenges and long term outcomes, including the dilemma faced during tapering/weaning off Omalizumab in our local setting.

Case 1

An 8-year-old Malay boy was referred from a district hospital for uncontrolled severe asthma to our center in 2010. He was the seventh of 11 siblings with family history of severe asthma where his father died due to an asthma exacerbation. The patient had daytime cough and chest tightness throughout the day, along with frequent nocturnal awakenings due to wheezing and breathlessness. His school performance had deteriorated as he was absent from his school most of the days. He was mainly confined to his house and his mother remained awake at night, worrying about his asthma. He was on Step 5 GINA {high dose Metered Dose Inhaler (MDI) Inhaled Corticosteroid and Long-Acting-Beta2-Agonist (ICS-LABA), oral anti-leukotriene, MDI salbutamol PRN and long course tapering to alternate low dose oral prednisolone (OCS)} and treatment for his allergic rhinitis (intranasal steroid, anti-histamine PRN). Through 2009 to 2011, the patient had in all 26 exacerbations, some that required hospitalizations but none required intubation, non-invasive ventilation support or intensive care (ICU) admission. He did not develop side effects for OCS but a decision to initiate Omalizumab was made in late 2012 at the age of 10 years old, as he still has frequent exacerbations that required hospitalizations despite good adherence, proper inhaler technique (via spacer) and avoidance of triggering factors. The baseline characteristics before and during Omalizumab therapy is shown in Table I.

In summary, this is a very severe case of childhood allergic asthma which showed a rather delayed, but a very good response to using omalizumab as an add on therapy for a period of 5 years. The low alternate dose of OCS was then possible to stopped by 16 months of Omalizumab therapy, a slower response than we predicted due to severe baseline asthma profile and multiple confounding factors, including irregular supply of Omalizumab especially during the initial 2-3 months of therapy. Despite no clear recommendation on how to taper Omalizumab, we initiated stepwise tapering as per Table I in view of good asthma control, budget constraint, and excellent quality of life achieved at 3.5 years of therapy. Omalizumab was then discontinued after 5 years of therapy. With a total of almost 20 months of symptoms and exacerbation free period after Omalizumab discontinuation, the onset of three exacerbations required the re-initiation of omalizumab therapy (Table I). His asthma remained well controlled after re-initiation of therapy.

Case 2:

An 8-year-old Malay girl was referred to us in early 2012 with a history of uncontrolled asthma of 2 years, chronic spontaneous urticaria (CSU), seafood allergies and persistent allergic rhinitis. Presenting complaints were persistent daytime and night time symptoms, frequent school absenteeism due to asthma exacerbations, exertional dyspnoea and frequent recurrent urticaria (skin redness and itchiness). She was on high dose Metered Dose Inhaler (MDI) Inhaled Corticosteroid and Long-Acting-Beta2-Agonist (ICS-LABA) via a spacer, oral anti-leukotriene, MDI salbutamol PRN, fluticasone nasal spray and anti-histamine, plus avoidance of triggering factors. Due to recurrent exacerbations, she was initiated with tapering dose of prednisolone until low alternate daily dose. Her childhood

This article was accepted: 17 February 2021
Corresponding Author: Mariana Daud
Email: marianamd1969@gmail.com

Table I: The clinical course of case 1 on Omalizumab through 9 years

Baseline	Initial Follow up	Tapering & Withdrawal	Discontinuation & Re-initiation
• FEV_1/FVC = 68%, FEV_1 = 77% predicted Positive reversibility ≥ 12% • Total IgE = 1091 IU/ml Specific IgE high for Shrimp • Baseline cACT = 5 • Asthma: uncontrolled (frequent exacerbations, school absenteeism, no sports) • Medications: o high dose ICS+LABA o anti-leukotriene o maintenance low dose OCS • Omalizumab initiated at 300mg every 2 weeks (27 August 2012) • Co-morbid: allergic rhinoconjunctivitis • HRCT Thorax; normal	• **3 months:** Partial response • **1 year:** 5 exacerbations • **16 months:** controlled asthma : o no exacerbations o FEV1: 106% of predicted o No daytime or nocturnal symptoms o No exercise-induced symptoms o Discontinued OCS. o Regular school and sports. o ACT = 25	• Omalizumab starting dose: 300 mg/2 weekly • tapered dose: o **3.5 years:** 300mg/4 weekly o **4.0 years:** 300mg/6 weekly o **4 years 8 months :** 300mg/8 weekly o **5 years:** Patient symptom free, no rescue medication use, no exacerbations thus Omalizumab discontinued (19 September 2017) • No asthma controller for 2 years (non-adherent) • Rhinoconjunctivitis controlled on antihistamine.	• **7 years:** asymptomatic for 23 months after discontinuation. o Not on controller ICS for 23 months • **7.5 years:** re-initiation of Omalizumab (6 August 2019) (3 mild exacerbations until July 2019, outpatient treatment with short course OCS) • Asthma controlled since then.

Table II: The clinical course of case 2 on Omalizumab through 8 years

Baseline	Initial Follow up & clinical course	Tapering & Withdrawal	Discontinuation
• FEV_1/FVC = 69% FEV_1 = 73% predicted Positive reversibility ≥ 12% • Total IgE = 1140 1U/ml • Specific IgE high for *Dermatophagoides pteronyssinus and Dermatophagoides farinae,* crab, shrimp and cockroach • Baseline cACT = 7-14 • Asthma : uncontrolled (School absenteeism, exercise induced, frequent exacerbations, nocturnal and daytime symptoms) • Medications: high dose ICS-LABA, anti-leukotriene , maintenance low dose OCS • Omalizumab initiated at 300mg /4 weekly (13.12.2012) • However, she developed pharyngitis within 24 hours thus subsequent dose was reduced to 150 mg/4 weekly • **Co-morbid:** o CSU o sea- food allergies o allergic rhinitis	• **1 months:** good response • OCS discontinued after second dose o FEV1: 103% predicted o Asthma: controlled (Regular school, sports, no daytime or nocturnal symptoms, no exacerbations) • cACT = 27 • 13 months; • Step down to ICS only • 2.5 years: • one mild exacerbation treated with prednisolone as outpatient. • CSU : full remission • Allergic rhinitis: controlled	• Omalizumab starting dose: 300 mg/4 weekly • tapered dose: o **1 month:** 150mg/4 weekly o **2.5 years:** 150mg/6 weekly o **4.0 years:** 150mg/8 weekly o **4 years 8 months:** step up 150 mg/6 weekly* o (*due to recurrence of CSU although asthma was controlled) o **5 years:** step up 150mg/ 4 weekly- for CSU	• **5 years 10 months:** Discontinuation of Omalizumab (15 Oct 2018) • **28 months post discontinuation:** o Asthma remained controlled o Recurrence of her CSU, but milder and controlled with high dose anti-histamine.

asthma control test (cACT) improved from 7 to 14 but her asthma was still uncontrolled with very poor quality of life. Baseline spirometry showed mild obstructive lung disease with significant reversibility post-bronchodilator. Her total IgE was remarkably high of 1140 IU/ml with raised specific IgE for house dust mites, seafood and cockroach (Table II). We initiated omalizumab 300 mg every 4 weeks based on weight and IgE level at the age of almost 9 years old. After the first injection, an episode of pharyngitis was reported within 24 hours, which required observation in hospital for one day. Omalizumab was adjusted at 150mg/4 weekly. Remarkably her asthma and CSU became completely controlled after first dose and oral prednisolone was discontinued after the second dose. Her cACT was 27 and her spirometry normalized. She was a very fast responder to Omalizumab. We were able to discontinue OCS after the second dose of Omalizumab and subsequently reduce ICS-LABA combination to ICS only after 13 months of therapy. She had one mild asthma exacerbation 2.5 years later that required prednisolone as outpatient basis. The clinical course of the patient is summarized in Table II.

For both patients, the funding for Omalizumab was from limited hospital's budget. Omalizumab were supplied by the company for the initial 2 months while waiting for approval from the Malaysian Director-General of Health.

DISCUSSION

Omalizumab is one of the recommended options in GINA Step-5 severe allergic (IgE-mediated) asthma phenotype for patients aged ≥ 6 years.[3,4] It is indicated in patients with following characteristics:

i. High IgE (≥30-1500 IU/ml)
ii. Positive skin test or in vitro reactivity (radioallergosorbent test [RAST]) to a perennial aeroallergen.
iii. Reduced lung function (FEV1 < 80%).
iv. Frequent daytime symptoms or night-time awakenings.
v. Multiple documented severe asthma exacerbations.
vi. Receiving daily high-dose ICS-LABA and other controller (GINA Step 4/5)

The other indication is uncontrolled Chronic idiopathic urticaria (CSU) despite standard therapy in patients ≥ 12 years old.

Omalizumab inhibits the binding of IgE to Fc3RI receptors on mast cells, basophils and dendritic cells, thus preventing release of cytokines and subsequent eosinophilic airway inflammation. It reduces free-IgE and downregulates high-affinity IgE receptors on multiple cells in the airway mucosa, thereby reduce early and late phase inflammatory cell recruitment, tissue remodelling and functional changes in the airways.[3]

Omalizumab has been shown to reduce asthma exacerbation, emergency visits, provide control of symptoms, reduce oral corticosteroid (OCS) burden and improve patient's quality of life.[3] An excellent clinical response was observed in our patients with good asthma control, cACT score, reduction in exacerbation rate, reliever use, atopic symptoms, ICS doses, OCS usage, and normalization of lung functions. Studies have shown that IgE levels correlate with disease severity[3] and clinical data suggests that the patients who are the best 'responders' to anti-IgE treatment are those with more severe asthma, like our two patients.[5]

We also report a period up to almost two years of preservation of good clinical response post-cessation of Omalizumab in the first patient, despite ICS-free for almost 4 years duration (Table I). This is consistent with findings that ICS use was withdrawn completely in a greater percentage of omalizumab-treated patients versus placebo without compromising asthma control.[6] He developed mild exacerbations requiring outpatient treatment only after 20 months later. The second patient had recurrence of non-asthma atopic symptoms (i.e. CSU) earlier than symptoms of asthma, post discontinuation of omalizumab. The two cases illustrate the clinical efficacy of omalizumab used for a long term, the first of its kind in childhood severe asthma in Malaysia. From the safety perspective, we did not identify any severe adverse events, although upper respiratory tract infection was noted in the second patient. None of them developed anaphylaxis.

These two patients had a significant duration of uncontrolled symptoms and OCS use burden before we initiated omalizumab, showed delayed initiation of biologic in eligible patients. Many factors including lack of early access of drug, affordability by poor patients, issues with availability, delay in referral, low awareness level among patients/caregivers could result in this delay of initiating right treatment for these eligible patients for omalizumab in our healthcare scenario. We identified that lack of centers with adequate experience and availability of omalizumab, will pose additional challenge for the patients to get the best quality of care. The frequent visits for the injections and the need to travel to limited number of referral centers (in this case, our hospital) may pose an additional hurdle towards compliance of patients.

The cost and duration of Omalizumab treatment significantly affects the selection of patients for this therapy. Although with initial success in our cases, we needed to taper down and subsequently stop omalizumab once their treatment reached 5-6 years duration. The recurrence of symptoms post cessation of omalizumab would also require us to evaluate the need for omalizumab re-initiation. Financial access determines initiation as well as re-initiation of omalizumab in our setting. Although there is lack of evidence on re-initiation and tapering regimen, affordability of the drug requires us to consider tapering while monitoring clinical parameters. We describe the tapering regimen in the Malaysian context based on symptoms control and spirometry, and adjusting the dosages and interval based on its impact on asthma control in patients. Our experience with the use of omalizumab has demonstrated a life changing situation in our patients.

We recommend a holistic approach to improving childhood asthma care in Malaysia which includes:

i. Early referral from peripheral centers to specialized/experienced center,
ii. Facilities for phenotyping related investigations,
iii. Increased awareness among population and physicians,
iv. Dedicated fund for biologic access,
v. Financial support for patients to enable long term therapy,
vi. Severe childhood asthma registry to understand the problem statement, and
vii. Consideration of biologic in selected patients earlier than current practice,
viii. Multidisciplinary approach to severe asthma care.

We recommend early phenotyping of the patients uncontrolled on GINA step 4/5 treatment (blood eosinophils, allergy profile by skin prick or specific IgE or equivalent tests, total IgE, FENO (fractional exhaled nitric oxide) in childhood asthma to identify patients eligible for biologic therapy, enabling them to live life to the best.

CONCLUSION

Anti Ig-E therapy is a safe and efficacious in pediatric patients with severe allergic (IgE-mediated) asthma and atopic comorbidities. To improve the access of anti IgE therapy, we recommend a holistic approach in Malaysia to overcome the existing challenges of the delay in treatment. More data is needed to guide tapering, cessation and re-initiation of anti-IgE therapy.

REFERENCES

1. Lai CK, Beasley R, Crane J, Foliaki S, Shah J, Weiland S. International Study of Asthma and Allergies in Childhood Phase Three Study Group. Global variation in the prevalence and severity of asthma symptoms: phase three of the International Study of Asthma and Allergies in Childhood (ISAAC). Thorax 2009; 64(6): 476-83.
2. Sullivan SD, Wenzel SE, Bresnahan BW, Zheng B, Lee JH, Pritchard M, et al. TENOR Study Group. Association of control and risk of severe asthma-related events in severe or difficult-to-treat asthma patients. Allergy 2007; 62(6): 655–60.
3. Chipps BE, Lanier B, Milgrom H, Deschildre A, Hedlin G, Szefler SJ, et al.. Omalizumab in children with uncontrolled allergic asthma: Review of clinical trial and real-world experience. JAllergy Clinl Immunol 2017; 139(5): 1431-44.
4. Global Initiative for Asthma (GINA) 2020. Global Strategy for Asthma Management and Prevention, Available at: http://www.ginasthma.org/. Date accessed: June 2020.
5. Holgate S T, Djukanović R, Casale T, Bousquet J. Anti-immunoglobulin E treatment with omalizumab in allergic diseases: an update on anti-inflammatory activity and clinical efficacy. Clin Exp Allergy 2005; 35(4): 408-16.
6. Milgrom H, Berger W, Nayak A, Gupta N, Pollard S, McAlary M, et al. Treatment of childhood asthma with anti-immunoglobulin E antibody (omalizumab). Pediatrics 2001; 108(2): E36