Italian Journal of Prevention, Diagnostic and Therapeutic Medicine.

CASE REPORT

OFF-LABEL TREATMENT WITH OMALIZUMAB: A CASE REPORT

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ABSTRACT

INTRODUCTION: Omalizumab is a monoclonal anti-IgEantibody,indicated as an add-on therapy in patients with severe uncontrolled asthma.
Therapy is guided by a nomogram based on total IgE and patients'weights.

AIM: Aim of this case is to describe off-label treatment with omalizumab and demonstrate effectiveness of this treatment despite high total IgE.

CASE PRESENTATION: We present a case of a patient followed in our Paediatric Allergology Centre since 2012 for allergic severe persistent asthma, treated with maximal dosage of fluticasone, montelukast, continuous salmeterol and steroid cycles, without clinical and spirometric changes. Despite high total IgE of the patient and with his consent , we decided to initiate treatment with omalizumab (600 mg every 15 days) with progressive improvement of spirometry and negative bronchodilation tests. At the end of treatment, we noticed a sudden worsening of spirometry and a significant asthma exacerbation over period of 6 months of treatment with omalizumab. Based on these data, he has renewed omalizumab.

CONCLUSIONS: We reported a case of an adolescent treated off-label with omalizumab. The case tests how patients with severe allergic asthma can benefit from therapy with omalizumab despite high total IgE.

Further studies will be necessary to evaluate the long-term beneficial effects of this therapeutic choice.

Parole chiave:
pediatria, anticorpi, terapia, off-label, allergia, asma

Keywords:
pediatrics, antobodies, off-label therapy, allergy, asthma

This article was published on September 20, 2018, at SIMEDET.EU.

doi.org/10.30459/2018-14

BACKGROUND

Asthma, a chronic heterogeneous airway inflammatory disease, is common in children with a reported prevalence ranging from 5 to 15% [(1) (2)].

About 70% of asthmatic patients have an allergic phenotype characterized by elevated serum levels of allergen-specific IgE [(3)].

Although most children respond well to safe and evidence-based stepwise pharmacological treatment, about <5% of children show a severe therapy-resistant asthma phenotype [(4)].

Here, we present a case of a 16years boy, followed in our Paediatric Allergology Centre since 2012 for allergic severe persistent asthma.

Since 2012, he was treated with maximal dosage of fluticasone, montelukast, continuous salmeterol and steroid cycles, without clinical and spirometric changes.

Before treatment with Omalizumab, spirometry revealed a Tiffenau index equal to 50%, severe mixed obstructive ventilatory defect and a positive bronchodilation test. He weighted 77 kg and has 1916 IU/mL of total IgE.

TAB.1

	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
PREFERRED CHOISE	-	Low dose ICS	Low dose ICS/LABA	Medium/High dose ICS/LABA	Add anti-IgE
ALTERNATIVE CHOISES	Low dose ICS	LTRA	Medium/High dose ICS	Add Tiotropium	Add Tiotropium
		Low dose theophylline	Low dose ICS+LTRA	High dose ICS+LTRA	Add low dose OCS
			Low dose ICS + theophylline	High dose ICS + theophylline	

theophylline is not recommended for children 6-11 years, while Tiotropium is not indicated in patients <18 years

ICS *inhaled corticosteroids,* **LTRA** *leukotriene receptor antagonist,* **LABA** *long-acting* β_2 *- agonist,* **anti-LgE** *anti-immunoglobulin E therapy,* **OCS** *oral corticosteroids*

Children with poor asthma control have an increased risk of severe exacerbations and progressive loss of lung function, which results in the relevant use of health resources and impaired quality of life (QoL) [(5)].

According to recent international guidelines, patients with uncontrolled asthma require a prolonged maintenance treatment with high-dose inhaled corticosteroids (ICS) in association with a long-acting beta2-agonist (LABA) plus oral leukotriene receptor antagonist (LTRA) [(6)].

Recommended options for initial controller treatment in children and adults according to GINA Guidelines [(6)]

Despite the fact that the level of total serum IgE was not within the recommended range, we opted to treat him with omalizumab.

Based on the nomogram, it was started a 6 months off-label therapy with omalizumab 600 mg every 15 days with progressive improvement of spirometry with Tiffenau index always higher than 70% and negative bronchodilation tests.

There were no serious adverse events and no exacerbations during the follow-up.

At the end of treatment, we noticed a sudden

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worsening of spirometry.
Furthermore, he was hospitalised for acute asthma attack with the need of oxygen for two days.

He presented again a Tiffenau index <70%, severe obstructive ventilatory defect and positive bronchodilation tests, despite the maximal background therapy.

Currently, he is treated with maximal dosage of fluticasone spray, montelukast, salmeterol and several steroid cycles per month.

At the last spirometry, Tiffenau index was equal to 66%. On February 2018, total IgE were 964.0 IU/mL. Based on these data, he has renewed omalizumab.

DISCUSSIONS AND CONCLUSIONS

Omalizumab is a recombinant DNA - derived humanized monoclonal antibody.
It is an immunoglobulin E (IgE)-specific, IgG1 κ antibody that targets circulating free IgEs [7].

It is an advanced humanized IgG1 monoclonal anti-IgE antibody specially designed to target circulating free IgE and prevent its interaction with the high-and low-affinity IgE receptors, thus interfering with cell activation and mediator release and comprehensively reducing allergic inflamation [7] [8].

In particular, omalizumab decreases levels of circulating IgE by binding to the constant region (Cε3) of the IgE molecule, which prevents free IgE from interacting with high-affinity and low-affinity IgE receptors (FcεRI and FcεRII)[9].

The reduction of free IgE levels following o malizumab administration leads to a downregulation of FcεRI expression on inflammatory cells [9].

In addition, it has been demonstrated that omalizumab also reduces FcεRI in vivo expression on dendritic cells, which may lead to a reduction in allergen presentation to T cells and attenuation in the Th2-mediated allergic pathway [10].

FIG. 1: MECHANISMOFACTIONOFOMALIZUMAB.MACMILLANETAL,NATREVIMMUNOL,2008.

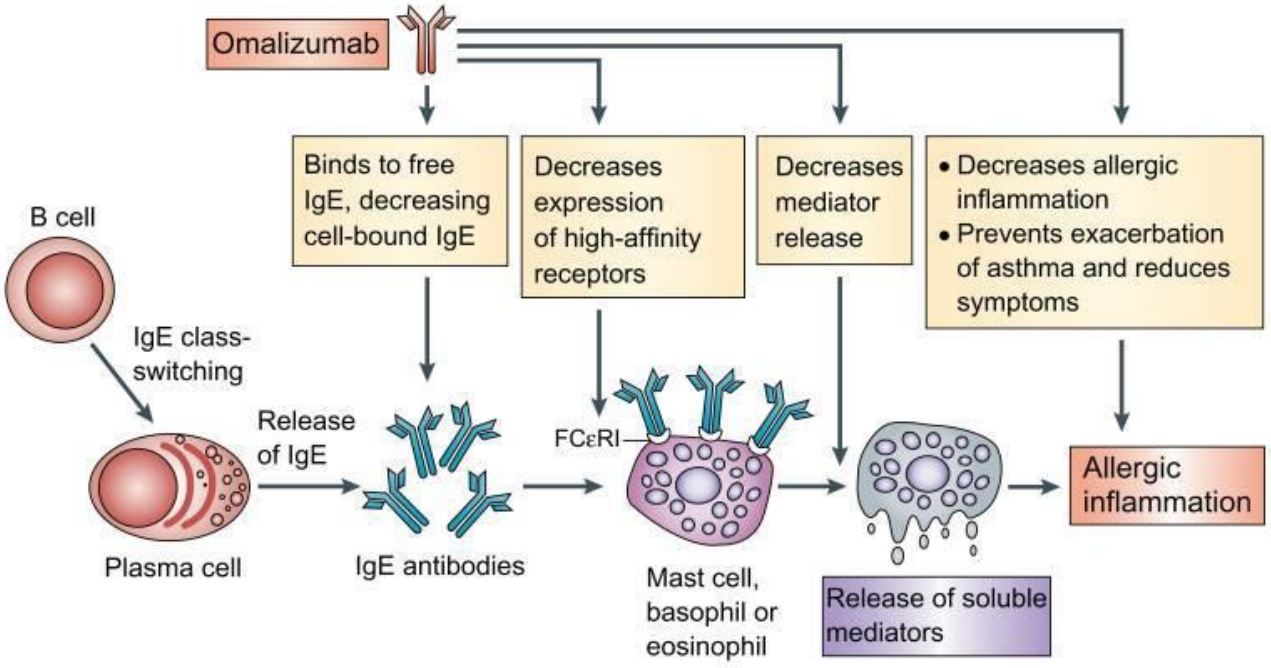
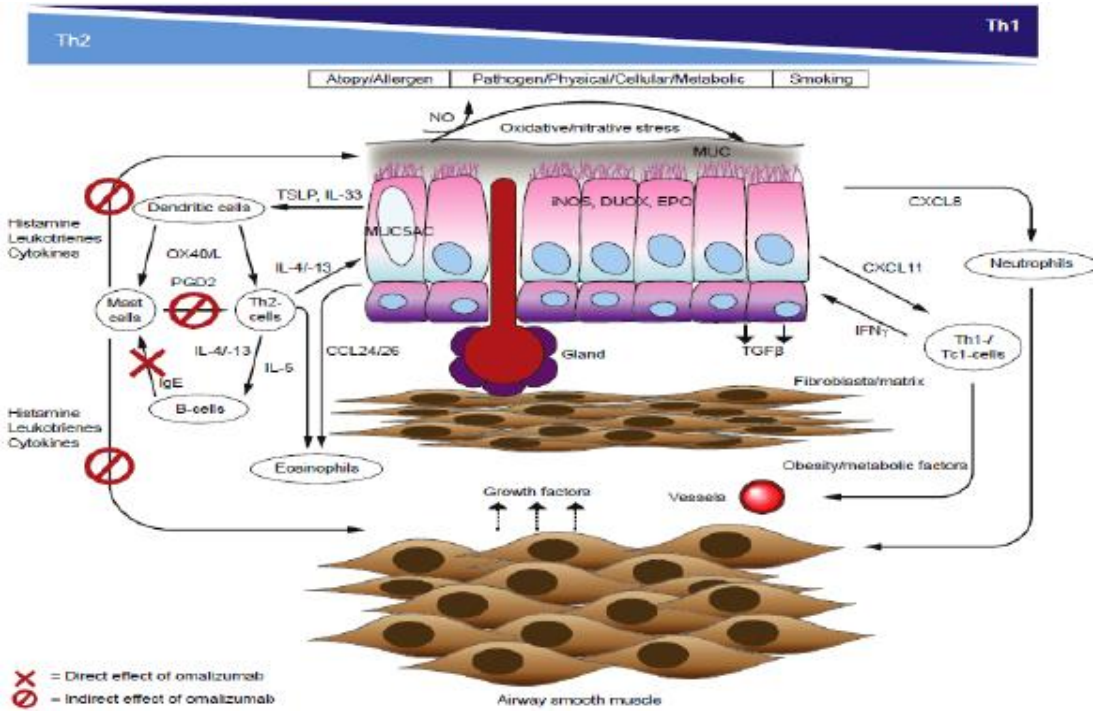


FIG. 2: IMMUNEANDANTI-INFLAMMATORYEFFECTSOFOMALIZUMAB.BRADLEYETAL,JALLERGYIMMUNOL,2017



To date omalizumab is the only biological drug currently licensed as add-on therapy in children >years with moderate-to-severe and severe allergic asthma uncontrolled after treatment with high dose of inhaled corticosteroids (ICS) plus-acting inhaled beta2-agonist (LABA) [(11)].

In Italy, omalizumab is indicated as add-on therapy to improve asthma control in adolescents (aged>12 years) and children (aged 6 to <12 years)with severe persistent allergic asthma who have a positive skin test or in vitro reactivity (blood test) to a perennial aeroallergen and who have frequent daytime syntoms or nighttime awakenings and who have a multiple documented severe asthma exacerbations despite daily high dose ICS plus LABA.

Patients aged >12 years must also have reduced lung function (forced expiratory volume in 1 s (FEV1) less than 80% of normal [(12)] .

In clinical practice, omalizumab is administered by subcu-taneous injection every 2 or 4 weeks. Dose and frequency of administration are guided by a nomogram that is derived from total serum IgE level at baseline (eligible between 30-1500 IU/ml) and patients' weight [(13)].

The results of the ICATA study, a multicenter RCT of 419 inner-city children, adolescents and young adults with persistent allergic asthma, showed that, compared to placebo, omalizumab reduces the number of days with asthma symptoms and the proportion of participants with at least one exacerbation by approximately 25% and 19%, respectively ($p < 0.001$) [(14)].

Another multicenter RCT of inner-city children and adolescents showed that the addition of omalizumab to ongoing guidelines-based care before patients return to school reduces fall asthma exacerbations (odds ratio, 0.48) [(15)].

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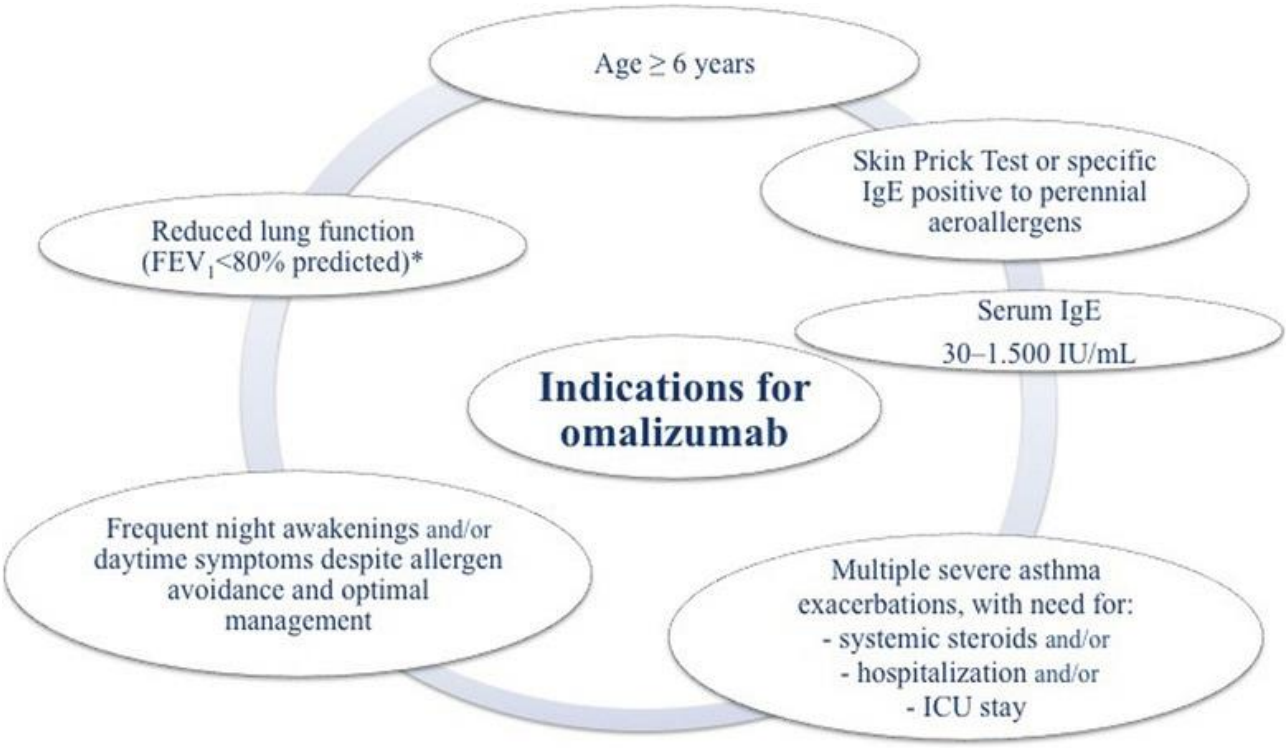
FIG. 3: INDICATIONSFOR OMALIZUMAB. MIRRA ET AL. BMC PEDIATRICS, 2018



** Not applicable in children less than 12 years*

Abbreviations: ***IgE (immunoglobulin E); FEV_1 (forced expiratory volume in 1 second); ICU intensive care unit.***

In the first Italian multicenter observational study conducted in 13 pediatric allergy and pulmonology tertiary centers in Italy, the lung function improved over the 12 months of treatment with omalizumab with FEV1increasing from 79% pred at baseline to 90% pred and 91% pred at 6 and 12 months, respectively [(16)].

Nevertheless, according to the literature, children with severe asthma often have a normal FEV1 that does not improve after bronchodilators, indicating that spirometry may be a poor predictor of asthma severity in childhood [(17) (18 (19)].

In a systematic review of pediatric RCTs of 1381 children and adolescents with moderate-to-severe allergic asthma, omalizumab decreased the number of patients with at least one exacerbation (risk ratio, 0.69; $p < 0.001$), the mean number of asthma exacerbations per patient (risk ratio, 0.35; $p < 0.001$), and the asthma symptom score (mean difference, 0.12; $p = 0.005$) when compared to placebo [(20)].

Also, the results presented in Sztafinska et al. study provided findings on how the improvement in quality of life in asthmatic children and adolescents observed after omalizumab correlates with the improvement of quality of life in caregivers and reduction in ICS use [(21)].

Several studies have assessed the long-term safety of omalizumab in children and adults. A pooled analysis of 67 RCTs conducted over 2 decades on 4254 children and adults treated with omalizumab showed no association between omalizumab treatment and risk of malignancy [(22)].

In an RCT evaluating 225 school-aged children, omalizumab was well tolerated, there were no serious adverse events, and the frequency and types of all adverse events were similar to the placebo group [(23)].

These results have been further confirmed by a recent systematic review of RCTs that concluded that treatment with omalizumab does not result in increased risk of malignancy or hypersensitivity reactions [(20)].

While the efficacy og omalizumab is supported by several studies, the duration of treatment is still under discussion.

Results from published studies suggest that omalizumab should be continued for > 1 year [(24) (25)].

In a retrospective study of adults and children with uncontrolled severe asthma treated with omalizumab, after the discontinuation of treatment, loss of asthma control was documented in 69.2% of the patients who had received omalizumab for < 1 year, 59.1% of the subjects treated for 1–2 years, and 46.1% of the cases treated for > 2 years [(24)].

Another study of Licari et al. the first Italian multicenter observational study, supports the existing evidence that omalizumab therapy reduces asthma exacerbations and healthcare utilization, has a steroid-sparing effect and improves lung function [(16)].

In conclusion omalizumab significantly improves the clinical management of severe and uncontrolled pediatric asthma; however, pre-treatment IgE levels limited the use of omalizumab in some patients [(26)].

However, in literature, a few studies showed the efficacy of omalizumab in the case the level of total serum IgE are not within the raccomended range.

Nobuhiro et al. demonstrated that omalizumab could be useful in patients with severe persistent asthma that remains uncontrolled despite multi-drug therapy, even when the total serum IgE level is higher or lower than the recommended range [(27)].

Further studies will be necessary to evaluate the long-term beneficial effects of this therapeutic choice.

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