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Clinical Efficacy of Mepolizumab in An Adolescent with Airway Eosinophilia

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Abstract

Pediatric asthma is a chronic inflammatory disease affecting the airways. It is a significant problem in the United States affecting 6.3 million children. Inhaled bronchodilators and corticosteroids are common treatments for asthmatics. However, some patients with severe asthma do not respond well to such treatments. These patients are hospitalized more often and require systemic steroids. Mepolizumab is an interleukin 5 antagonist, a monoclonal antibody approved as an add-on therapy for patients 12 years and above with refractory and severe asthma. We present an atopic 13-year-old patient with a history of severe persistent asthma with severe airway obstruction and bronchiectasis**.** Standard asthma treatment was unsuccessful in controlling asthma symptoms and exacerbations. There was marked improvement in patient's lung function and symptoms after starting mepolizumab.

Keywords: Asthma; Children; Mepolizumab

Introduction

Pediatric asthma, a chronic inflammatory disease, is a significant health problem in the United States affecting about 6.3 million children. In 2010, 1 in 11 children were diagnosed with asthma and 1 in 5 of those children were hospitalized [1]. Asthma is defined as a chronic, life-threatening lung disease that involves the narrowing and inflammation of the airways and is classified as mild, moderate and severe persistent. Patients with moderate to severe persistent asthma experience increased morbidity including emergency department visits and hospitalizations [2]. Bronchial asthma patients present with various phenotypes and are often treated with inhaled corticosteroids [3-13]. However, there are some patients with severe asthma that do not respond well to such treatment. These patients are at increased risk for inpatient hospitalizations and requiring systemic steroids for treatment. Mepolizumab is an

interleukin 5 antagonist, a monoclonal antibody approved as an add-on therapy for patients 12 years and above with refractory and severe asthma [8].

Case Report

A 13-year-old African American atopic male, with a history of severe persistent asthma and recurrent pneumonia presented to our multidisciplinary life-threatening asthma clinic on June 16th, 2015. The patient's symptoms began at 6 months of age including: productive cough, wheezing, dyspnea. Additional symptoms included nasal congestion, postnasal drip, rhinorrhea, and sneezing. He had multiple emergency room visits and hospitalizations due to respiratory distress. On an average, he was hospitalized three times a year for asthma but was never intubated nor admitted to the intensive care unit. His treatment regimen included salmeterol/fluticasone propionate 230/21 two puffs twice a day, tiotropium 18 mcg, one puff once daily, albuterol prior to exercise and as needed, montelukast 4 mg, cetirizine 10 mg, fluticasone nasal spray 2 puffs daily, vest therapy 2 times daily with nebulized albuterol 2.5mg and sodium chloride 3%. He was also on 20 mg prednisone on alternate days.

Assessment of patient's pulmonary function is depicted in Table 1. Allergic skin testing resulted in a positive skin test for cedar. Serum IgE levels were between 50-105 IU/ml. Spirometry testing resulted in forced expiratory volume (FEV1) of 52%, forced vital capacity (FVC) of 91%, and–FEV1/FVC of 50% and forced expiratory flow (FEF25-75) of 19%. Exhaled nitric oxide value was 19 ppb. Eosinophils in the blood were 0-5%. Aspergillus epicutaneous test was negative. Flexible fiberoptic bronchoscopy conducted in March 2016 revealed thick, white secretions bilaterally in lower airways and lingula. Bronchoalveolar lavage showed significant eosinophilia (89% eosinophils), 5% macrophages, 5% lymphocytes and 1% neutrophils. Incidentally, viral panel was positive for influenza A. There was no history of a parasitic infection or foreign travel to contribute to the high eosinophil count. A computerized tomography of the chest showed diffuse bronchiectasis with cystic changes in left upper lobe and apical segment of the left lower lobe. Atelectasis was noted in the right middle lobe. Tree in bud appearance was noted following the distribution of atelectasis. The patient was started on mepolizumab, via monthly subcutaneous injections, in June 2016 due to persistent symptoms and the presence of eosinophilia in the airways. Significant clinical improvement was noted following implementation of this medication.

Pulmonary Function Testing (Spirometry)	5/17/2016		9/5/2017		
	Measured	%Predicted	Measured	%Predicted	%Change
FEV1 Liters	1.05	52	2.06	83	Improved by 96
FVC Liters	2.11	91	3.03	107	Improved by 44
FEV1/FVC (Ratio)	50		68		
FEF 25-75% L/Sec	0.46	19	1.43	48	Improved by 210

Table 1: Case patient pulmonary assessment pre- and post- mepolizumab treatment.

Fourteen months after starting mepolizumab, continued improvement in symptoms was noted, and the patient reduced albuterol inhaler usage to three times per month. Spirometry also indicated significant improvement (Table 2). Tiotropium was discontinued and no emergency

department visits or hospitalizations for asthma symptoms occurred in the 18 months of treatment through December 2017.

LABS	DATE	VALUE	REFERENCE RANGE
WBC	5/5/2015	18.0 (HIGH)	4.8 - 10.8 10*9/L
RBC	5/5/2015	6.1	4.70 - 6.10 10*12/L
HEMOGLOBIN	5/5/2015	14.1	11.0 - 16.0 g/dL
HEMATOCRIT	5/5/2015	41.3	30.0 - 48.0 %
MCV	5/5/2015	67.7 (LOW)	80.0 - 94.0 fL
MCH	5/5/2015	23.2 (LOW)	27.0 - 34.5 pg
PLATELET COUNT	5/5/2015	401	150 - 450 10*9/L
GRAN #	5/5/2015	9.90 (HIGH)	1.92 - 8.64 10*9/L
LYMPH #	5/5/2015	5.76 (HIGH)	0.72 - 4.32 10*9/L
EOS#	5/5/2015	0.90 (HIGH)	0.00 - 0.76 10*9/L
IgE	5/5/2015	105	0-260 [IU]/mL
IgE	4/8/2016	50	0 - 260 [IU]/mL
IgA	2/3/2016	76 (LOW)	79-347 mg/dL
IgM	2/3/2016	186	40-244 mg/dL

Table 2: Case patient laboratory results

It is of note that the patient experienced an increase in allergy and sinus symptoms when two sequential injections were missed, however, symptoms were alleviated when treatment resumed. Mepolizumab injections were well tolerated without significant local or systemic reactions. At his most recent follow-up, 20 months after starting Mepolizumab, the patient was overall doing well but was experiencing chest tightness for which he was prescribed oral prednisone. Patient was positive for scant productive cough and fever at the most recent follow-up. Due to overall improvement, the patient continued treatment with mepolizumab, and salmeterol/fluticasone dose was reduced to Advair 115/21, 2 puffs bid.

Discussion

Patients with uncontrolled asthma, despite an add-on therapy, are diagnosed with severe refractory asthma [3]. Different asthma phenotypes have been described. One phenotype is characterized by a high degree of allergic inflammation and obstructive pulmonary physiology with severe persistent asthma and allergic rhinitis symptoms despite maximal asthma therapy [13]. In patients with unresponsive asthma, treatment choices include oral corticosteroids and biological treatment targeting the Th2 biological pathways. Oral corticosteroids are associated with significant adverse effects, especially when used long-term [9]. Th2-targeted therapies either approved or in clinical trials target IgE, IL-5, IL-13, 1l-4. There are four biologics which target T2 inflammation that are approved for asthma including omalizumab (anti-IgE), mepolizumab (anti-IL-5), reslizumab (anti-IL-5) and benralizumab (anti-IL-5 receptor). Studies have shown these biologics reduce asthma exacerbations [14]. When comparing the common biologicals, omalizumab is approved for children 6 years and older (15, 16). Mepolizumab and benralizumab are approved for children 12 years and older and reslizumab is not approved for use in children [17,18]. All these medications have a subcutaneous route of administration, with the exception of reslizumab which is intravenous [17]. Dosing for

Omalizumab is based on weight and IgE levels [15,16]. The dose of mepolizumab is 100 mg, reslizumab dosing is 3 mg/kg and usual dose of benralizumab is 30 mg, and all are administered every 4 weeks [17,18]. Targets of IL-4, IL-13 such as Pitrakinra, dupilumab have proven efficacy, but are not FDA approved [19,20].

The patient reported in this case was started on mepolizumab. Mepolizumab is indicated for patients with severe, refractory eosinophilic asthma [8]. Apart from severe atopic asthma, other causes of pulmonary eosinophilia include helminthic infections, coccidiodes infection, eosinophilic pneumonia, eosinophilic granulomatosis with polyangitis and allergic bronchopulmonary aspergillosis [12]. Many of these conditions could manifest with pulmonary eosinophilia and normal peripheral eosinophils.

Mepolizumab decreases exacerbation and chronic use of oral steroids (4). Mepolizumab prevents interleukin 5 (IL-5) from binding to the IL-5 receptor complex alpha chain that is present on the surface of eosinophils and stops IL-5 from properly sending out signals (4). Mepolizumab is given every four weeks in a dose of 100 mg subcutaneously and has minimal side effects, the most common being headache, injection site reaction, back pain and fatigue [7].

In recent clinical trials, patients (aged 12-74 years) receiving mepolizumab had fewer exacerbations, lower rate of hospitalizations and fewer emergency room visits for asthma compared to those patients who received the placebo [5]. Furthermore, the use of mepolizumab reduced the doses of glucocorticoid for maintaining asthma control [5,6]. In the "DREAM" study, patients receiving mepolizumab experienced improvement in the FEV_1 [10]. The duration of desired drug therapy is still not clear. In recent studies, the discontinuation of mepolizumab after 12 months of therapy resulted in the return of symptoms, a rise in eosinophils in the blood, and an increased occurrence of exacerbations [9]. Research on use of mepolizumab in pediatric patients is limited. In patients with severe uncontrolled asthma, mepolizumab is an effective at improving lung function and morbidity.

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