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CASE REPORT

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Steroid-sparing effect of mepolizumab in children with severe eosinophilic nonallergic asthma

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Abstract
Background: Asthma is characterized by a chronic airway inflammation, usually sustained by type 2 immunity. Bronchial and peripheral eosinophilia are biomarkers for type 2 asthma. Biologicals are the most effective treatment for severe asthma at present. Mepolizumab is an antagonist of interleukin-5 (IL-5), the most relevant cytokine involved in eosinophilia.
Objective This case report evaluated the effectiveness of mepolizumab in two girls with severe eosinophilic non-allergic asthma.
Materials and methods Two female children with severe eosinophilic nonallergic asthma were treated with mepolizumab for two years. Clinical findings, lung function, peripheral eosinophils, asthma control, and bronchial endoscopy were performed.
Results Biologicals reduced the eosinophilia, asthma exacerbations, and improved lung function in both patients. The treatment was also safe and well-tolerated.
Conclusion: Mepolizumab represents an effective therapeutic option in the management of severe pediatric asthma.

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Introduction

Children with severe asthma (SA) may have overlapping clinical presentation and different pathophysiologic mechanisms. Patients with severe asthma usually experience poor disease control and frequent exacerbations despite the best standard of care. The recognition of different phenotypes and endotypes, identifying specific biomarkers, may guide management and predict response to treatment.[1] In this regard, blood eosinophil count is the most common biomarker used in clinical practice, as eosinophilia usually characterizes asthma in childhood. Consistently, peripheral eosinophils correlate with symptoms, lung function, asthma exacerbation rate, quality of life, and asthma control.[2] A UK cohort study, including 130,248 patients with asthma, identified 20,929 (16%) subjects with complete blood count (CBC) of >400 cells/μL.[3] The stated study evidenced that patients with eosinophils count of >400 cells/μL experienced more severe exacerbations and poor asthma control. Sputum eosinophils could be a further biomarker to reliably guide anti-inflammatory and biological therapies in children with continuous oral corticosteroids (OCS) treatment.[4] However, eosinophils recovered from bronchoalveolar lavage (BAL) are thorough representative of lung tissue eosinophilia.[5]

Type 2 inflammation signs eosinophilic asthma, sustained by a predominance of T helper 2 lymphocytes and/or innate lymphoid cells 2 that release a wide array of pro-inflammatory cytokines, including interleukin (IL)-5.[6] IL-5 plays a pivotal role in differentiation, growth, recruitment, activation, life span, and bronchial accumulation of eosinophils.[7,8] As a result, selective IL-5 antagonism may be an attractive therapeutic strategy in patients with severe asthma and airway eosinophilia resistant to daily inhaled corticosteroid (ICS).[9] Mepolizumab, a humanized monoclonal antibody, binds free IL-5 with high affinity and specificity and inhibits the interaction between IL-5 and IL-5 receptor complex on eosinophil.[10] In 2018, the European Medicine Agency approved mepolizumab as an add-on treatment for severe refractory eosinophilic asthma in patients aged 6–17 years. At present, only two trials have investigated mepolizumab in children. These studies mainly explored pharmacokinetic, pharmacodynamic, and safety aspects.[11,12] Both trials reported a relevant eosinophil reduction associated with improved asthma control.

On the other hand, type 2 inflammation commonly identifies the allergic phenotype, mainly in pediatric patients with severe asthma. However, nonallergic eosinophilic severe asthma may also occur in children. Based on this background, we present two female children suffering from severe asthma with nonallergic eosinophilia treated with mepolizumab. To our best knowledge, this is the first description concerning the use of mepolizumab in children with eosinophilic nonallergic severe asthma, evaluated with bronchoscopy and BAL, to detect eosinophils, as expression of lung tissue eosinophilia.

We evaluated two female children with eosinophilic nonallergic severe asthma. The diagnosis of asthma was performed according to validated criteria recommended by the Global Initiative for Asthma (GINA) guidelines.[13] It included history of respiratory symptoms compatible with asthma and documentation of bronchial airflow limitation reversible after bronchodilation testing. The asthma work-up aimed to exclude confounding diseases, including congenital malformations with recurrent infections, vascular rings with tracheobronchomalacia, vasculitis, autoimmune disorders, immunodeficiency, persistent bacterial bronchitis, bronchiectasis, cystic fibrosis, primary ciliary dyskinesia, aspergillosis, and eosinophilic pneumonia. Allergy was tested by skin prick test and serum allergen-specific IgE assay: both methods provided negative results, thus the diagnosis of nonallergic asthma was confirmed. Relevant comorbidities, including chronic rhinosinusitis, gastric reflux, obesity, and emotional disorders, were investigated but they had no comorbidity.

Both patients had experienced frequent asthma exacerbations in the year preceding the first observation and had received continuous oral prednisone to maintain partially controlled asthma (corticosteroid tapering induced rapid symptom worsening), fixed association containing inhaled fluticasone plus salmeterol. Based on this diagnostic pathway, we diagnosed severe eosinophilic nonallergic asthma in both children. Therefore, we decided to start biological therapy to taper OCS and improve asthma control.

Clinical examination, lung function evaluation, and blood eosinophil count were performed on monthly basis in the first semester. A complete assessment was established every 6 months during the 24-month follow-up. Bronchoscopy with BAL was planned at baseline and after 12 months of mepolizumab treatment. Standard dose of mepolizumab (40 mg or 100 mg, according to patient's age, every 4 weeks) was administered . Demographic and clinical data are provided in Table 1. The parents gave their signed informed consent, and the administration of therapy was approved by the Italian Agency for Drugs.

Case 1

The first patient was a 9-year-old female; she had asthma onset at the age of 5 years. She had 12 asthma exacerbations and four ward hospitalizations in the last 1 year prior to initiation of mepolizumab treatment. At baseline, she started mepolizumab and maintained prednisone (0.5 mg/kg body wt./day). Lung function parameters were normal at baseline; bronchial dilation (BD) testing showed reversibility. The endoscopy macroscopic findings revealed hyperemic mucosa.

The patient discontinued prednisone after 3 months, as she felt well. However, at 6-month follow-up visit, the asthma was uncontrollable as she had asthma exacerbation due to an acute viral infection. Spirometry revealed reversible bronchial obstruction. Consequently, relievers (short-acting B2-agonists) were used for more than twice a day but lung function worsened (overt bronchial obstruction without reversibility). Despite reduction of blood eosinophils, we decided to anticipate bronchoscopy to evaluate bronchial inflammation. Endoscopy revealed increased eosinophils in BAL; macroscopic findings showed hyperemic mucosa. Therefore, she was restarted with a short oral prednisone course (0.3 mg/kg body wt/day) for 4 weeks, including tapering. At the 12-month follow-up visit,

Table 1 Clinical and functional characteristics in two children with eosinophilic nonallergic severe asthma.

Parameters	Patient 1 Baseline	6 months	12 months	18 months	24 months	Patient 2 Baseline	6 months	12 months	18 months	24 months
Age at baseline (years)	9					13				
Age at onset of asthma (years)	5					5				
Asthma exacerbations	1	1	1	0	0	0	0	0	0	0
Hospitalization	1	0	0	0	0	0	0	0	0	0
Blood leukocytes (mm^3)	11040	7220	6180	6110	8,270	8720	8200	7350	8510	9510
Blood eosinophils (mm^3)	700	340	140	240	120	1060	230	110	120	180
Prednisone (mg/kg body weight/day)	0.5	0.3	0	0	0	0.3	0	0	0	0
Fluticasone (mcg/day)	500	500	200	200	200	500	500	200	200	50
Salmeterol	100	100	0	0	0	100	100	0	0	0
FEV_1 (% of predicted) pre-bronchodilation (BD)	81	78	74	92	85	85	82	79	92	96
FEV_1 (% of predicted) post-BD	105	91	94	99	90	84	85	82	99	96
FVC (% of predicted) pre-BD	97	110	96	105	79	106	96	106	105	100
FVC (% of predicted) post-BD	110	111	114	106	83	103	97	108	106	96
FEV_1/FVC pre-BD	79	67	73	75	90	76	81	71	87	90
FEV_1/FVC post-BD	79	78	79	80	91	77	83	72	93	94
FEF_{25-75} (% of predicted) pre-BD	67	43	55	65	67	72	68	58	59	81
FEF_{25-75} (% of predicted) post-BD	103	72	76	81	94	66	75	61	63	85
ACT	7	12	21	25	25	15	13	22	24	25
Relievers usage	2/week	2/week	1/month	0	0	2/month	1/week	0	0	0
BALF leukocytes (mL)	320000	150000				90000		210000		
BALF eosinophils (mL)	15680	20850				17460		7980		

FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; FEF_{25-75}: forced expiratory flow between 25 and 75% of vital capacity; BD: bronchodilation testing; ACT: asthma control test; BALF: bronchoalveolar lavage fluid.

reversible bronchial obstruction persisted, but asthma was controlled partially.

At the 18-month follow-up visit, asthma was well-controlled and lung function was normal and relievers were no more required. Long-acting B2-agonists, OCS, and inhaled fluticasone were tapered. At the 24-month follow-up visit, asthma was well-controlled according to the GINA control level and the asthma control test (ACT) score was 25.

Case 2

The second patient was a 3-year-old female; she had asthma onset at the age of 5 years. She had 10 asthma exacerbations and one ward hospitalization in the last 1 year prior to initiation of mepolizumab treatment. The baseline bronchial endoscopy revealed mild mucosal hyperemia and scattered mucous secretions. Lung function was normal, without bronchial reversibility, but the asthma was not controlled. She was started with mepolizumab treatment. She had a more favorable progress, as prednisolone was discontinued in the fourth month of mepolizumab treatment.

At the 6-month follow-up visit, lung function was normal, but asthma was not controlled. However, lung function improved progressively from the third visit, the number of both peripheral and bronchial eosinophils decreased over time, and asthma was well-controlled at the last visit (see Table 1). The second endoscopy revealed normal mucosa and a reduced number of eosinophils.

Discussion

These two cases demonstrated that mepolizumab is also useful in children with eosinophilic nonallergic severe asthma. Both pediatric patients achieved control over asthma and discontinued OCS within the first few months of the treatment. Lung function normalized, and relievers were no more used. Peripheral eosinophils also diminished. Reduction of bronchial eosinophils was consistent with clinical and functional improvement in the second patient. Remarkably, increase of bronchial eosinophils in the first patient was associated with clinical and functional worsening during a viral infection.

Some limitations were noticed in the study, including the assessment of blood eosinophils instead sputum eosinophils, although two BAL eosinophil counts were performed, and bronchoscopy improved diagnosis and well defined asthma phenotype. Another bias was the use of non-maximal inhaled corticosteroid dosage in the second patient, but the clinical outcomes improved quickly and systemic corticosteroid therapy was discontinued soon. Moreover, nasal lavage to investigate possible upper airway inflammation was not performed.

Finally, mepolizumab spared the use of both systemic and inhaled corticosteroids, reduced peripheral eosinophils, and improved clinical and functional features in both patients with eosinophilic nonallergic severe asthma. Bronchial eosinophils correlated with blood eosinophilia and the clinical features. Moreover, mepolizumab was safe

as no clinically relevant adverse events were observed in 2 years of treatment.

Conclusion

These two clinical cases showed that mepolizumab was effective and well-tolerated in eosinophilic nonallergic severe pediatric asthma. Bronchoscopy could be useful to characterize carefully asthma phenotype in refractory asthma (OCS-dependent) and to evaluate and monitor bronchial eosinophilia as expression of type 2 inflammation.[14]

Authors' Disclosure Statement

The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria. The authors had full access to all patient information provided in this paper and take responsibility for the integrity and accuracy of the same. The material has not been published or submitted elsewhere for publication.

Authors' contribution

All authors contributed equally to the study and writing of the paper. All authors reviewed the final manuscript, and agreed to the published version of the manuscript.

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