ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Severe mixed-endotype asthma responsive to tezepelumab: a case report of an adolescent

Asma grave de endótipo misto com resposta a tezepelumabe: relato de caso de um adolescente

Gabriela Spessatto[1], Aline Didoni Fajardo[2], Juliana Gonçalves Primon[2], Thalita Gonçalves Picciani[2], Guilherme da Silva Martins[1], Bruno Hernandes David João[1], Larissa Machado Carvalho[2], Angelica Fonseca Noriega[2], Maitê Milagres Saab[1], Tayna Padilha Miranda[1], Cristine Secco Rosário[3], Laura Maria Lacerda Araujo[4], Carlos Antônio Riedi[7], Roberta Corrêa da Cunha[5], Denise Eli[6], Débora Carla Chong Silva[7], Herberto J. Chong-Neto[7], Nelson Augusto Rosário Filho[8]

ABSTRACT

Most children and adolescents with severe asthma have an eosinophilic inflammatory phenotype and are at risk of exacerbations, systemic corticosteroid use, and reduced quality of life. Children with type 2 inflammation respond well to conventional treatment; however, there is a small group that is unresponsive to conventional therapy and requires additional medication for disease control, such as immunobiologic agents. Knowledge of the pathophysiology of bronchial inflammation and biomarker assessment are essential for the appropriate choice of an immunobiologic agent. We report the case of a 13-year-old patient with severe type 2 allergic asthma, with no indication for omalizumab, who did not respond to mepolizumab after 12 months of treatment. The sputum cytology identified a mixed inflammatory endotype that led to replacement with another immunobiologic agent, tezepelumab, achieving control of exacerbations by probable reduction in bronchial hyperresponsiveness. Assessment of asthma endotype with the available biomarkers allowed precise and personalized treatment for this patient.

Keywords: Severe asthma, bronchial hyperresponsiveness, type 2 inflammation, thymic stromal lymphopoietin.

RESUMO

A maioria das crianças e adolescentes com asma grave apresenta fenótipo de inflamação eosinofílica, com risco de exacerbações, uso de corticosteroides sistêmicos e redução na qualidade de vida. Crianças com inflamação tipo 2 respondem bem aos tratamentos convencionais, no entanto, há um grupo pequeno que falha na resposta terapêutica habitual e necessita medicamentos adicionais, como imunobiológicos, para o controle da doença. O conhecimento da fisiopatologia da inflamação brônquica e a avaliação de seus biomarcadores é fundamental para escolha adequada do imunobiológico. Relatamos o caso de um paciente de 13 anos, com asma grave do tipo 2 alérgico, sem indicação de omalizumabe, e que em uso de mepolizumabe não apresentou controle da doença depois de 12 meses de tratamento. A avaliação do endótipo com citologia de escarro identificou fenótipo inflamatório misto, direcionando a substituição por outro imunobiológico, o tezepelumabe, atingindo o controle das exacerbações, por provável redução da hiper-responsividade brônquica. A avaliação do endótipo da asma com os biomaracadores disponíveis permitiu um tratamento preciso e individualizado para o paciente.

Descritores: Asma grave, hiper-responsividade brônquica, Inflamação tipo 2, linfopoietina do estroma tímico.

1. Residente de Pneumologia Pediátrica do Complexo Hospital de Clínicas da Universidade Federal do Paraná (UFPR) - Curitiba, PR, Brazil.
2. Residente de Alergia e Imunologia Pediátrica do Complexo Hospital de Clínicas da Universidade Federal do Paraná (UFPR) - Curitiba, PR, Brazil.
3. Doutora em Saúde da Criança e do Adolescente - Curitiba, PR, Brazil.
4. Professor Adjunto de Pediatria, UFPR - Curitiba, PR, Brazil.
5. Fisioterapeuta, Mestranda em Saúde da Criança e do Adolescente - Curitiba, PR, Brazil.
6. Farmacêutica e bioquímica, Mestre em Saúde da Criança e do Adolescente - Curitiba, PR, Brazil.
7. Professor Associado de Pediatria, UFPR - Curitiba, PR, Brazil.
8. Professor Titular de Pediatria, UFPR - Curitiba, PR, Brazil.

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Introduction

Severe asthma requires treatment with high doses of an inhaled corticosteroid plus a second controller medication (and/or systemic corticosteroid) to prevent it from becoming "uncontrolled" or remaining "uncontrolled" despite treatment.[1] Although most children with asthma achieve symptom control with low or medium doses of inhaled corticosteroids, there is a small but significant group with severe asthma who either require higher doses of inhaled corticosteroids plus controller medication to control their symptoms or who remain uncontrolled despite such therapy.[2]

According to the International Study of Asthma and Allergies in Childhood, the global prevalence of severe asthma among adolescents is 6.9%, ranging from 3.8% in the Asia Pacific region and in Northern and Eastern Europe to 11.3% in North America.[3]

Children with severe asthma are at increased risk of adverse outcomes, including medication-related side effects, life-threatening exacerbations, and impaired quality of life.[4] The economic impact of severe asthma in the United States is significant, costing $56 billion in 2007, with 50% of these costs being indirect, such as doctor visits, hospitalizations, medications, and missed days of school and work.[5] Among children aged 5 to 17 years, asthma is one of the most common causes of school absence, impaired academic performance, and low participation in school-related activities.[6]

In the last decade, as knowledge of the pathophysiology of asthma has increased, biomarkers have been used to determine the endotype of asthma according to the inflammation profile. Elevated total serum immunoglobulin E (IgE), specific serum IgE, immediate skin-test reactivity, elevated exhaled nitric oxide (FeNO), eosinophilia in peripheral blood, and sputum are biomarkers of type 2 inflammation, the phenotype of most children with asthma. These biomarkers are increased in type 2 inflammation, since it is dependent on inflammatory cytokines such as IL-4, IL-5, and IL-13, which are produced by innate immune cells, as well as type 2 lymphoid cells and adaptive immune cells, such as Th2 lymphocytes, which are activated shortly after the release of alarmins such as thymic stromal lymphopoietin (TSLP).[1,7] However, non-type 2 inflammation with a mixed granulocytic profile can also occur, involving Th1, Th17 lymphocytes, and neutrophils, in addition to eosinophils.[7]

A randomized, double-blind, placebo-controlled study of adolescents and adults found that 52 weeks of tezepelumab reduced the annual rate of exacerbations by 39% in patients with non-type 2 inflammation with < 150 eosinophils/μL.[8]

Case report

The patient was a 13-year-old boy born and raised in Curitiba, Brazil. Episodes of wheezing began at six months of age and he was diagnosed with persistent severe allergic asthma at 8 years of age, having 2 to 3 exacerbations per year that required emergency room visits and oral corticosteroids. He was admitted to the intensive care unit for asthma at 10, 11, and 12 years of age, requiring orotracheal intubation. He had been taking budesonide 800 μg + formoterol 24 μg since 8 years of age, without improvement. He was given montelukast 5 mg daily at 9 years of age and tiotropium 5 μg daily at 10 years of age, with continued exacerbations requiring emergency room visits, oral corticosteroids, and hospitalization. He was also diagnosed with allergic rhinitis, for which he was treated with budesonide 32 μg twice daily. He had no history of smoking, no pets, and a positive family history of asthma (mother).

Differential diagnosis was based on sweat chloride, serum immunoglobulin, and chest tomography, which were normal. Spirometry showed mild obstructive lung disease, and the bronchodilator test was positive. The patient's forced vital capacity (FVC) = 2.54 L (91%), forced expiratory volume in 1 second (FEV_1) = 1.64 L (65%), FEV_1/FVC ratio = 0.65, and mean forced expiratory flow 25-75 = 0.78 L (39%). Other tests showed an allergic phenotype: total IgE = 1726 kU/L, eosinophils 663 cells/μL, *Dermatophagoides pteronyssinus* skin test = 7x5 mm in diameter.

At 12 years of age, mepolizumab 100 mg was administered every 4 weeks, but poor disease control persisted: Asthma Control Test = 13 points, 2 exacerbations with systemic corticosteroids administered at home, and 1 ICU admission with noninvasive ventilation within 1 year. After 12 months of treatment with mepolizumab, the disease persisted uncontrolled: FeNO = 46 ppb and sputum cytology analysis showed a mixed pattern (neutrophils = 58%; eosinophils = 3%) (Figure 1).

At the age of 13, anti-TSLP (tezepelumab) 210 mg was administered subcutaneously every 4 weeks, with

a good response, no new exacerbations, and no need for oral corticosteroids. In follow-up consultations, after 2 months of medication use, the disease was under control (Asthma Control Test = 25 points), and spirometry revealed improved lung function: FVC = 2.80 L (100%); FEV_1 = 1.88 L (75%); FEV_1/FVC ratio = 0.68; FEF 25%-75% = 0.94 L (47%), and FeNO = 116 ppb.

After 3 months of tezepelumab use, the disease remained under control and lung function was stable. A new analysis of biomarkers indicated increased peripheral and sputum eosinophils, reduced FeNO, and total serum IgE stability.

In the 6-month evaluation after starting tezepelumab, a mild exacerbation occurred between consultations, which was resolved with salbutamol and no oral corticosteroids. Approximately 2 weeks later, the patient was infected with influenza, which was resolved through symptomatic medications, with no new exacerbations. The markers showed increased FeNO, continued high levels of total IgE and eosinophils in peripheral blood. A new spirometry test was performed, showing stable pulmonary function (Table 1).

Discussion

Ten percent of asthma cases are severe, significantly impacting the lives of children/adolescents and their families and resulting in increased morbidity.[1] This adolescent, who had suffered asthma symptoms

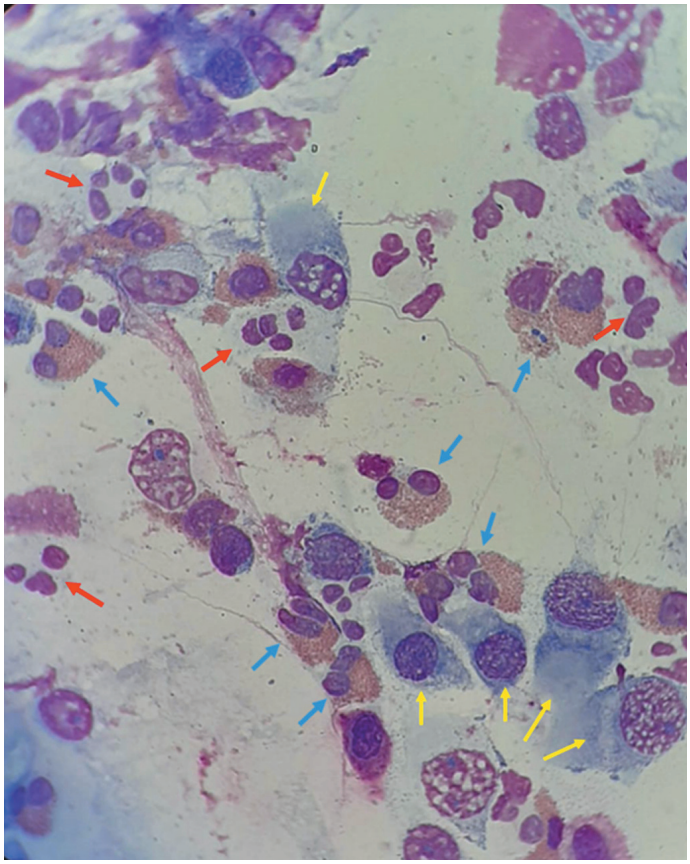

Figure 1
Sputum cytology with mixed inflammatory pattern (May-Grunwald-Giemsa staining). Blue arrows: eosinophils; red arrows: neutrophils; yellow arrows: macrophages

Table 1
Clinical, functional, and biomarker response to treatment with mepolizumab and tezepelumab

	Before mepolizumab	12 months after mepolizumab	2 months after tezepelumab	3 months after tezepelumab	6 months after tezepelumab
Clinical control					
ACT score	13 points	13 points	25 points	25 points	25 points
Number of exacerbations	3	2	0	0	1
Biomarker					
Peripheral blood eosinophil count (cells/μL)	663	32	–	744	520
Fraction of exhaled nitric oxide (ppb)	–	46	116	38	102
Sputum cytology (% cells)	–	Neutrophils = 58 Eosinophils = 3	–	Neutrophils = 4 Eosinophils = 80	Neutrophils = 44 Eosinophils = 48
Total IgE (kU/L)	1946	–	–	1781	1469
Lung function					
FEV_1 (%)	–	65%	75%	73%	76%
FVC (%)	–	91%	100%	99%	105%
FEV_1/FVC	–	0.65	0.68	0.67	0.65
FEF 25-75 (%)	–	39%	47%	48%	39%

ACT: Asthma Control Test; FEF: forced expiratory flow; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity.

since early childhood, had been using high doses of inhaled corticosteroids associated with two other controller medications (a LABA and a LAMA), but without success. Given his type 2 inflammation profile and lack of response to treatment in step 4 of the Global Initiative on Asthma guidelines, it was decided to associate a biological agent.[2]

Due to the patient's type 2 allergic inflammatory profile, the recommended biological agent was omalizumab, but his serum IgE levels were too high for it[2] and mepolizumab was used instead, which failed to control the disease. Exacerbations ensued, requiring oral corticosteroids and ICU admission.

After 12 months of mepolizumab treatment, the eosinophil count in peripheral blood dropped significantly, which suggested anti-IL5 action, although it was not correlated with clinical manifestations due to continued exacerbations and poorly controlled disease.

In further evaluation of the patient's endotype, a mixed inflammatory pattern was identified in sputum cytology when mepolizumab was replaced with tezepelumab. This indicated a favorable response to treatment, with a high and low type-2 endotype,[8] and the patient showed clinical improvement, despite the short observation time. Only a mild exacerbation

occurred, but there were no emergency room visits or need for oral corticosteroids.

Tezepelumab is an antibody that blocks TSLP, an alarmin derived from epithelial cells that is involved in airway inflammation. TSLP is released after epithelial injury, promoting activation of type 2 inflammatory cells and cytokines (dendritic cells, group 2 innate lymphoid cells, Th2 lymphocytes, mast cells, IL-4, IL-5, and IL-13), in addition to affecting the regulation of factors related to neutrophilic inflammation, which results from the activation of Th1 and/or Th17 cells and the release of their cytokines, such as IFNγ and IL-17. It also exerts a direct action on smooth muscle, contributing to airway remodeling by increasing collagen production through fibroblast and myocyte proliferation.[9]

In phase 2 and 3 studies of patients with severe uncontrolled asthma, tezepelumab significantly reduced exacerbations compared to placebo, regardless of type 2 inflammation biomarkers. In the present case, after 6 months of medication use and clinical improvement, type-2 inflammation biomarkers had not reduced, but blood eosinophils increased and the mixed sputum pattern changed to an eosinophilic pattern. The FeNO results were variable, increasing in the first assessment (after 2 months of tezepelumab), decreasing at 3 months of treatment, and increasing again at 6 months of treatment. Lung function improved significantly after 2 months and remained stable at 3 and 6 months of treatment.

The small effect on type-2 inflammation biomarkers associated with improved clinical and pulmonary function suggests that the most important inflammatory profile in this patient was neutrophilic, although this does not explain the inefficiency of anti-TSLP for eosinophilic inflammation, as observed in pivotal studies.[8] TSLP can act on other cells, such as bronchial smooth muscle, mast cells, etc., which may be related to bronchial hyperresponsiveness (BHR).[10]

BHR, a pathophysiological process of asthma, is defined as airway predisposition to narrowing (bronchoconstriction) in response to stimuli that have little or no effect on healthy individuals.[11] It is a marker of symptomatic asthma, independent of the eosinophilic pattern, leading to exacerbations and reduced disease control.[10]

The clinical improvement confirms that tezepelumab reduces exacerbations independently of type-2 inflammation biomarkers and reduces BHR.[8,9] Andreasson et al. described the effects of TSLP on BHR, investigating the association between BHR (by bronchoprovocation with mannitol) and TSLP levels in serum, sputum, and bronchoalveolar lavage in patients with asthma with and without type 2 inflammation. They found that sputum TSLP levels were associated with the degree of BHR in patients with eosinophilic and non-eosinophilic asthma, corroborating the role of TSLP and BHR beyond type 2 inflammation.[12]

Similarly, a phase 2 study by Diver et al. found significantly lower BHR in the tezepelumab group than the placebo group in the mannitol test ($p = 0.03$). At the end of treatment, more patients who used tezepelumab had a negative bronchoprovocation test than the placebo group (43% vs. 25%). These results were independent of the peripheral eosinophil count or type 2 inflammation markers.[9]

The exact mechanism by which tezepelumab reduces exacerbations in patients with non- type-2 inflammation is not yet fully understood. Studies have shown that a wide range of cells express TSLP receptors, such as ILC-3 and IL-17, which are involved in the non-type 2 inflammation pathway, in addition to having a direct effect on mast cell activation and mediation between structural muscle cells and immune cells, which are directly involved in BHR.[13,14] Mast cell activation by TSLP leads to bronchoconstriction, mucus secretion, and collagen release by fibroblasts, factors that may be related to structural changes in the disease and lung function decline.[11,15]

Unfortunately, bronchoprovocation was not performed in this case but, due to the relationship between BHR and TSLP, it is likely that a reduction in our patient's BHR was the main factor in controlling the disease, regardless of type 2 inflammatory marker reduction.

Conclusion

Tezepelumab, a human monoclonal antibody that specifically binds to TSLP, may be the first-choice biological agent for patients with severe asthma who are at least 12 years of age. The response is greater in patients with a type 2 inflammation profile and it is the only agent that can also improve asthma in patients with non-type 2 inflammation. Although type-2 inflammation biomarkers were not reduced, our patient achieved disease control. In this case, the role of non- type-2 inflammation was predominant,

and the action of anti-TSLP on inflammatory cells other than eosinophils was predominant, probably reducing BHR.

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Corresponding author:
Herberto Jose Chong Neto
E-mail: hchong@ufpr.br