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Is the allergic reaction to Aspergillus a contraindication for biological therapy in severe asthma?

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Abstract

English:

Introduction: *According to the available speciality data, a study from the Netherlands has proven that 24% of patients are in Stage 4–5 of the Global Initiative for Asthma guide (GINA) treatment. Among them, 17% have difficult-to-treat asthma and only 3.7% have severe asthma. Patients with severe asthma have a poor prognosis, with numerous exacerbations that are usually severe. Therefore, add-on biological treatments used for eligible patients may change the outcome.*

Case report: *A 56-year-old female patient, diagnosed 10 years ago with asthma, without professional exposure, treated at home with maximal inhalation treatment, with multiple exacerbations and therefore multiple admissions to the hospital, one of which in the intensive care unit where she received endotracheal intubation and mechanical ventilation, is admitted to the hospital for persistent dyspnoea at rest, wheezing and chest tightness. Investigations revealed obstructive ventilatory dysfunction with a decreased value of forced expiratory volume (FEV1) by 37.57% and a reversibility ratio of 156%. Radiography results indicated absence of acute pleuropulmonary lesions; white blood cells (WBC) at 13,550 and eosinophils at 5566/μL; and 4.107% confirmed immunoglobulin E (IgE)-mediated allergy. The score for asthma control test (ACT) taken on 26 April 2018 was −8 and total IgE was 513 UI/L. Allergology evaluation results did not indicate allergies at prick test. Specific IgE was done for allergy for cat epithelium, guinea pig, rabbit, Penicillium notatum, Cladosporium herbarum and Aspergillus fumigates. Negative fungal test after bronchoscopy was performed to exclude pulmonary Aspergillosis. Omalizumab at 900 mg/month treatment was started. The outcome after 1 year showed no exacerbations, no admissions and no systemic corticotherapy usage.*

Discussion: *Allergic reaction to Aspergillus does not overlap with the diagnosis of pulmonary Aspergillosis; the condition is rather associated with immunosuppression and with a poor outcome. Severe asthma with prolonged progression and multiple risk factors must be treated with maximal therapy.*

Keywords

severe asthma • Aspergillus • biologic therapy

Este alergia la Aspergilus contraindicație pentru terapia biologică în astmul sever?

Rezumat

Romanian:

Introducere: *Conform datelor din literatura de specialitate, un studiu din Olanda a demonstrat că 24% dintre pacienți sunt în treapta 4-5 de tratament Global Initiative for Asthma guide (GINA). Dintre aceștia, 17% prezintă astm greu de tratat și 3.7% astm sever. Pacienții cu astm sever au prognostic infaust, cu numeroase exacerbări, de regulă grave. De aceea, terapia biologică de tip add on la pacienții eligibili poate modifica prognosticul.*

Descrierea cazului: *Pacientă de 56 ani, diagnosticată de peste 10 ani cu astm bronșic, fără expunere profesională, cu tratament ambulator inhalator maximal, cu repetate internări în Serviciul Pneumologie pentru exacerbări severe, una dintre exacerbări cu spitalizare în serviciul anestezie si terapie intensivă (ATI), intubație orotraheală (IOT), ventilație mecanică (VM), se prezintă pentru persistența dispneei de repaus, wheezing și senzație de constricție toracică. Investigații: Disfuncție ventilatorie obstructivă cu scăderea volumul expirator maxim pe secundă (VEMS) cu 37.57% și reversibilitate de 156%. Radiografie- fără leziuni acute pleuro-pulmonare: Leucocite: 13,550, Eozinofile 5566/μL, 4107%. Alergie Imunoglubulina E (IgE) mediată confirmată. Scor asthma control test (ACT) 26.04.2018: 8. IgE TOTAL: 513 UI/L. Consult alergologic- fără alergii la prick teste. Ig E specifice: alergie la epiteliu de pisică, porc de Guineea, iepure, Pennicilium notatum, Cladosporium herbatum, Aspergilus fumigates. S-a efectuat bronhoscopie- pentru excluderea unei Aspergiloze pulmonare. Examen micologic negativ.*

S-a inițiat tratament cu omalizumab 900 mg/luna. La 1 an: fără exacerbări, fără spitalizări, fără administrare de corticoterapie sistemică.

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Discuții: *Alergia la Aspergillus nu se suprapune peste diagnosticul de Aspergiloză pulmonară, acesta fiind de regulă asociat imunosupresiei și având un prognostic nefavorabil. Astmul sever cu evoluție îndelungată și multiplii factori de gravitate trebuie să beneficieze de tratament maximal.*

Cuvintele-cheie

astm sever • terapie biologica • Aspergilus

Introduction

Severe asthma is a subcategory of difficult-to-treat asthma; it is asthma that remains uncontrolled despite the patient's proper adherence to maximal therapy and after the avoidance of risk factors and control of comorbidities. According to data from the literature, a study in the Netherlands showed that 24% of patients are in Stage 4–5 of the Global Initiative for Asthma guide (GINA) treatment. Of these, 17% have asthma that is difficult to treat and 3.7% have severe asthma. Patients with severe asthma have a poor prognosis, with many exacerbations that are usually severe. Therefore, add-on biologic therapy in eligible patients may alter the prognosis (1,2).

The use of biomarkers in the determination of severe asthma endotypes ultimately leads to the establishment of a targeted therapeutic response (1,3). The biomarkers used to determine the severe asthma endotype are the blood eosinophils value, the serum Ig E value, the FeNo value and serum periostea (3).

Omalizumab reduces exacerbations in severe asthma regardless of eosinophil levels, and biologic anti-interleukin 5 receptor (IL-5R) medication is indicated in severe asthma regardless of allergies (4).

Allergic bronchopulmonary aspergillosis is known to be a fungal complication of asthma, while severe asthma with fungal sensitisation is a separate entity (5). In allergic pulmonary aspergillosis, the value of immunoglobulins E (IgE) frequently exceeds 1000 IU/mL. Allergy identified by prick tests or a panel of respiratory allergens has no correspondent in the identification of fungi in spontaneous sputum or bronchial aspiration (5,6).

Case presentation

We present the case of a 56-year-old female patient, diagnosed >10 years ago with asthma and arterial hypertension (AH) stage II, on outpatient treatment with long-acting B_2 agonist-inhalation corticosteroid (LABA-ICS) combination in high dose for respiratory pathology. The patient has no occupational exposure to respiratory toxins and presented to our clinic with the persistence of resting dyspnoea, wheezing and chest tightness. During hospitalisation, she received treatment with antibiotic therapy, systemic corticosteroid therapy, inhalation treatment and aerosolisation with salbutamol and fluticasone, with a slightly favourable evolution. No acute pleuropulmonary lesions were observed on chest radiography.

Upon discharge, tiotropium inhalator was also associated with LABA-ICS inhalation treatment. However, the patient subsequently presented numerous moderate exacerbations at home and severe exacerbations with hospitalisation. Inhaled corticosteroid treatment was supplemented with beclomethasone 2 $\times$ 250 μg (combined with salmeterol/fluticasone 50/500 μg, tiotropium 18 μg), but the patient's evolution remained unfavourable, presenting after 3 months a severe exacerbation with hospitalisation that required admittance to the intensive care unit, mechanical ventilation and orotracheal intubation.

Maintaining the same maximum recommendations for inhalation treatment at home, the patient required repeated courses of oral corticosteroids (OCS) for episodes of respiratory failure in the context of exacerbations, which is why the decision was made to re-evaluate the case.

During this interval, the patient presented with spontaneous fracture of the femur, while walking, for which surgery was performed in the Orthopaedic Service and which was interpreted as a complication of the use of OCS.

Thus, the pulmonary reassessment reveals, from the point of view of functional explorations, average obstructive ventilatory dysfunction with the decrease of forced expiratory volume (FEV1) by 37.57% and significant response to bronchodilator (reversibility of 156%).

The complete blood count shows leukocytosis (13,550/μL) and eosinophilia (5566/μL–4.107%), which is why the total immunoglobulin E (IgE) value was determined, and the result was 513 IU/L.

After the allergology consultation, there were no allergies to prick tests, but the panel of respiratory allergens revealed specific IgE to cat epithelium, guinea pig, rabbit, Penicillium notatum, Cladosporium herbarum and Aspergillus fumigates.

This allergy to Aspergillus raised the suspicion of pulmonary aspergillosis to the allergist, due to which bronchoscopy

was performed in order to exclude a diagnosis of Pulmonary Aspergillosis – with a negative mycological examination from bronchial aspirate and without suggestive endobronchial lesions. ACT score calculated on 26 April 2018 was 8.

In order to establish biologic therapy, the inclusion and exclusion criteria must be analysed. As the patient meets all inclusion criteria (7) (age >12 years, documented asthma diagnosis of at least 1 year, IgE-mediated allergy confirmed by specific IgE, optimised asthma management with a follow-up of at least 6 months and uncontrolled asthma) and no exclusion criteria (intolerant to omalizumab, active smoker or weaned <3 months, recent respiratory infection in the last month, pregnancy or lactation and non-compliance), treatment with omalizumab was initiated. The appropriate dose and frequency of administration are decided based on the initial amount of IgE as determined before starting treatment and body weight. Thus, at a weight of 80 kg and a total IgE value of 513 IU/L, 450 mg (three ampoules of 150 mg every 14 d) was administered with good evolution, no reactions at the site of administration and no systemic reactions. The patient presented to the Pulmonology Service for administration once every 2 weeks.

The evolution at 2 months was clearly favourable, with the improvement of symptoms and a considerable reduction of systemic corticosteroid doses, increase of respiratory volumes (an increase of FEV1 by 21.17% was observed compared with the initial value) (Table 1), ACT score of 14 and absence of severe exacerbations.

The evolution at 1 year was also favourable, with the improvement of respiratory symptoms and exclusion of systemic corticosteroid therapy from treatment, without the use of long-term oxygen therapy (LTOT) at home, without exacerbations and without hospitalisations.

At present, 27 months have passed after starting the biological treatment, the patient is on inhalation treatment with salmeterol/fluticasone 50/500 μg administered 2 times/d, tiotropium 5 μg/d, add-on treatment with omalizumab 2 × 450 mg/month, did not use OCS for 6 months and did not require hospitalisation for respiratory pathology.

Table 1. Spirometry values between 17 September 2017 and 05 April 2018.

	17.09.2017		29.09.2017		05.04.2018	
	Pre	**Post**	**Pre**	**Post**	**Pre**	**Post**
FVC (%)	91.2	101.2	92.7	107.5	84.7	105
FEV1 (%)	51.4	69.1	56.6	72.8	65.2	81.9
FEV1/FVC	52.56	50.74	61.5	73.8	62.43	78.4
FEF25 (%)	19.7	33.8	13.9	29.6	42.1	60.1
FEF50 (%)	20.2	31.4	15.8	37.6	30.4	35.1

FVC, forced vital capacity; FEV1, forced expiratory volume 1; FEF 25–50, forced expiratory flow 25–50.

Discussion

In recent years, clinical trials have focused on classifying severe asthma into phenotypes and endotypes according to epidemiology, immunology, biomarkers, response to pharmacological interventions and long-term prognosis (3). Based on these premises, the patient in the case described falls into the phenotype of severe eosinophilic persistent asthma (3,8). However, in the age of personalised medicine, many subdivisions of phenotypes can be distinguished according to the clinical profile and biomarkers (9).

The endotype of severe asthma in this case is characterised by much higher values of both blood eosinophils and IgE (3). The EXTRA study, published in 2013, showed that in patients with severe asthma with a Th2 endotype with combined increases in biomarkers, as in our case, the response to omalizumab therapy is better than with other biologic therapies (10).

On the other hand, a peculiarity of the case was the presence of allergy to Aspergillus, interpreted from the point of view of the allergist as pulmonary aspergillosis, and therefore a contraindication to biological therapy.

Fungal sensitisation is an additional severity factor in allergic asthma. Aspergillus was isolated from sputum examination in many patients with allergic asthma, demonstrating a link between fungal sensitisation and fungal colonisation in these patients (6). In our case, isolated sensitisation to Aspergillus was demonstrated, but not endobronchial colonisation.

Systemic corticosteroid therapies, parenteral or oral, are fraught with many complications and side effects; so, the decision to administer these preparations should balance the risk–benefit balance (4). Due to repeated courses of oral corticosteroid therapy, the patient had many complications, culminating in spontaneous femoral fracture while walking, without trauma: a complication that required emergency surgery.

The use of biological therapy, both in order to control the severity of asthma and to reduce the use of oral corticosteroid therapy, has been a real benefit for the quality of life and prognosis of this patient. Aspergillus allergy should not be a contraindication to biological therapy, but only a starting point for further investigations.

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Not applicable.

Conflict of Interest

Not applicable.

References

1. Global Initiative for Asthma - Global Initiative for Asthma - GINA [Internet]. [cited 2020 Dec 14],2020. Available from: https://ginasthma.org/wp-content/uploads/2020/04/GINA-2020-full-report_-final-_wms.pdf
2. Menzella F, Galeone C, Formisano D, Castagnetti C, Ruggiero P, Simonazzi A, et al. Real-life efficacy of omalizumab after 9 years of follow-up. *Allergy, Asthma & Immunology Research*. 2017;9(4): 368–372.
3. Loureiro CC, Amaral L, Ferreira JA, Lima R, Pardal C, Fernandes I, et al. Omalizumab for severe asthma beyond allergic asthma. *BioMed Research International*. 2018. Available from: https://downloads.hindawi.com/journals/bmri/2018/3254094.pdf
4. Katsaounou P, Buhl R, Brusselle G, Pfister P, Martinez R, Wahn U, et al. Omalizumab as alternative to chronic use of oral corticosteroids in severe asthma. *Respiratory Medicine*. 2019;150: 51–62. Available from: https://www.resmedjournal.com/article/S0954-6111(19)30039-3/fulltext
5. Hogan C, Denning DW. Allergic bronchopulmonary aspergillosis and related allergic syndromes. *Seminars in Respiratory and Critical Care Medicine*. 2011;32(6): 682–692.
6. Farrant J, Brice H, Fowler S, Niven R. Fungal sensitisation in severe asthma is associated with the identification of *Aspergillus fumigatus* in sputum. *Journal of Asthma*. 2016;53(7): 732–735.
7. protocoale-2018-MOf-754Bis_18.pdf [Internet]. [cited 2020 Dec 20]. Available from: http://www.inmas.ro/wp-content/uploads/2018/09/protocoale-2018-MOf-754Bis_18.pdf
8. Lin CH, Cheng SL. A review of omalizumab for the management of severe asthma. *Drug Design, Development and Therapy*. 2016;10: 2369–2378.
9. Froidure A, Mouthuy J, Durham SR, Chanez P, Sibille Y, Pilette C. Asthma phenotypes and IgE responses. *European Respiratory Journal*. 2016;47(1): 304–319.
10. Gauthier M, Ray A, Wenzel SE. Evolving concepts of asthma. *American Journal of Respiratory and Critical Care Medicine*. 2015;192(6): 660–668.