THERAPEUTIC DILEMMA IN A PATIENT WITH LONGSTANDING SEVERE ASTHMA AND HIGH LEVELS OF TOTAL IGE

Vladislava Ada Grueva Karanfilova
University Clinic of Pulmonology and Allergology – Skopje, N. Macedonia, adagrueva@gmail.com
Elena Grueva Nastevska
University Clinic of Cardiology – Skopje, N. Macedonia

Abstract: Asthma is a heterogeneous chronic inflammatory disease of the airways characterized by chronic airway inflammation bronchoconstriction, airway hyperresponsiveness, and mucus hypersecretion. Typical symptoms are wheezing, shortness of breath, chest tightness, and cough with variable expiratory flow limitation. Asthma affects approximately 300 million people worldwide. About 5–10% of all asthmatics suffer from severe or uncontrolled asthma, associated with increased mortality and hospitalization, reduced quality of life, and increased health care costs[11]. Endotypes were recently described, aiming at defining asthma entities according to identified or suspected mechanisms associated with and putatively leading to the disease with variable clinical presentation (phenotypes)[12]. They include parameters such as clinical characteristics, biomarkers, genetics, histopathology, lung physiology and response to therapy[13]. Asthma endotypes may be broadly regarded as type 2 (T2) high or T2-low according to Severe Asthma Research Program (SARP), the Unbiased Biomarkers for the Prediction of Respiratory Disease Outcome (U-BIOPRED), and Airways Disease endotyping for Personalized Therapeutics (ADEPT)[14]. Th2-high-related inflammation is the main characteristic of Th2-high phenotypes, together with early-onset allergic asthma and late-onset eosinophilic asthma. Neutrophilic asthma and obesity-related asthma are considered Th2-low phenotypes. In allergic asthma, the allergens presented to naive $CD4^+$ T cells by dendritic cells (DCs) induce differentiation into Th2 cells[15]. In nonallergic eosinophilic asthma, respiratory epithelium-derived cytokines and chemokines, also called alarmins, are released in response to various harmful triggers (air pollutants, microbes, or glycolipids), which then bind to the receptors on type-2 innate lymphoid cells (ILC2s). Both of these types of activated cells (Th2 cells and ILC2s) produce cytokines such as IL-4, IL-5, and IL-13, which are the principal effectors of type 2 inflammation. IL-5 is the most specific trigger for eosinophils, IL-4 and IL-13, which share a common receptor subchain (IL-4Rα), induce allergen-specific immunoglobulin (Ig) E synthesis. IgE, through its interaction with the specific receptor FcεRI (expressed in different immune cells), promotes the release of mediators that are responsible for functional and structural modifications of the bronchial wall[16]. Biological therapy has been demonstrated to be effective at reducing asthma exacerbations, maintaining control over asthma symptoms, and reducing the need for steroid bursts while preventing the well-known adverse events associated with steroid use.[17][18][19]. GINA final report 2019 on severe asthma, define difficult to treat and severe asthma as a concept of an

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uncontrolled asthma, which includes one or more of: poor symptom control (frequent symptoms or reliever use, limited activity or night waking) or frequent exacerbation (>2 /year requiring oral corticosteroids, or serious exacerbation >1/year requiring hospitalization. Taking into account the heavy burden of symptoms, exacerbations and most serious medication side-effects, timely and prompt assessment and evaluation of the patients with uncontrolled asthma is of great importance[2021].

In this paper we will review treatment options and dilemmas of a 63 years old woman, with long standing severe asthma (> 15 years), chronic allergic rhinosinusitis and nasal polyposis. The patient was receiving regular asthma treatment, according to GINA step 4 and step 5 plus additional anti-allergy medications. She was experiencing frequent symptoms and she was using Salbutamol as a reliever >2 times per week, and had serious exacerbation which required hospitalization 2-3 times per year and treatment with i.v corticosteroids and on OSC on discharge.

Keywords: Th2-high-related inflammation, severe asthma, nasal polyposis, positive SPT and High Levels of IgE.

1. CASE REPORT

63 years old woman with long history of allergic asthma (>15years) and comorbid nasal polyposis (diagnosed 8 years) and chronic allergic rhinosinusitis (>20 years) was frequently admitted to our hospital due to poor symptoms control and frequent exacerbation peculiarly in the spring allergy season. The initial diagnosis for asthma in our clinic was made 8 years ago, and she was treated with ICS, antihistamines, antileukotrienes, and nasal corticosteroid spray. Although the patient disclose that she had atopic dermatitis and allergic rhinitis long before she was diagnosed with asthma. Due to the persistent disease symptoms it was indicated, according to GINA Severe Asthma assessment, reassessment and reevaluation of the patient diagnosis.

- 63 years old woman, non-smoker (never smoked) and had no second hand tobacco exposure, worked as accountant. Known drug allergy to Paracetamol and Penicillin, and grass pollen allergy (first diagnosed 10 years ago). Has no pets.
- Comorbid diseases: Chronic allergic rhinosinusitis, Nasal polyposis and Atrial fibrillation (first diagnosed 4 years ago)
- BMI: 21,7 (height:175cm; Weight: 65) Normal
- Her complaint wheezing and dry coughing accompanied with chest tightness, which become severe during the night or early in the morning
- On physical exam she had high pitched wheezes more pronounced on exhalation diffusely distributed.
- ECG: AF, hr ~ 75/min, normal axis and QRS complex with normal morphology and conductivity.
- Her initial, on admission lung function test was as following : FEV1=57% FVC=53% and FEV1/FVC=81%
- Pulsoxymetry = 98% and ear lobe blood gas analysis= pH 7,37 PaCO2=4,56 kPa, PaO2=10,9 kPa, OSat=97,4% , HCO3-=25mmol/L
- Complete Blood analysis : Sedimetation= 22/mm/h ; Hb=130 g/L; Hct=40% Erythrocytes =4,20x10^{12}/ L Leucocytes= 12,4 x 10^9 /L Thrombocytes- 236x 10^9/ L ; Glucose= 5mmol/L, CRP=0,5 mg/ L; Electrolytes: 140mmol/ k=4,54mmol/l Ca=2,53mmol/L; Urea=8,1 mmol/L Creatinine= 89 umol/L
- Sputum for microbiological examination was performed and was microscopic positive for leucocytes with normal oropharyngeal flora. Pneumoslide was positive for RSV IgG.
- Chest x-ray was performed and reviled only hyperinflation without signs for parenchymal opacities, and free f-c sinuses.

Before initiating treatment she was reassessed for asthma diagnosis using a simple bronchodilator responsiveness test : Before the test initial spirometry was performed, then the patient was asked fully and slowly to exhale , and then to inhale slowly and deeply, until reaching TLC, a short-acting β_2-bronchodilator, salbutamol, holding the breath for 5-10 seconds, and then exhale. The dose of salbutamol was of 100 μg (1 puff) using a valved chamber.

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The procedure was performed twice, total 200 μg of salbutamol, because the positive AFF diagnosis. After 15-20 minutes another spirometry test was performed, giving positive response to a bronchodilator with an increase of 21% and an absolute value of 400mL compared to baseline FEV1[22] confirming the diagnosis of asthma. FEV1=57% FVC=53% and FEV1/FVC=81% (baseline) and after bronchodilator FEV1=71% and FVC=74%.
Assessment of the inhaler technique was made, and she had excellent systemic approach of exhaling, holding breath and inhaling again.[23]
She was treated with systemic corticosteroids starting dosage 60 mg, and gradually lowering dose until oral CS was given , short course of antibiotic therapy (macrolide- Azithromycin) intravenous for 3 days, and 3 days with oral Azithromycin, nasal ICS therapy . On discharge was prescribed asthma treatment therapy according to GINA step 4 and 5: Budesonide/ formotetrol 320 /9mcg (2 actuations of 160 mcg/4.5 mcg, q12hr; not to exceed 320 mcg/9 mcg q12hr, Oral CS, with gradually lowering dose (In the morning , after breakfast : 3 days 20mg once daily ,then 3 days 10mg once daily and 3 days 5mg once daily), Tiotropium bromide 2,5mcg Anti-leukotriene agent (Montelucast 10mg) once daily, and Tiotropium bromide 2,5mcg two puffs, as add-on therapy for uncontrolled asthma. The patient was rescheduled for control visit in 3 months.

2. FOLLOW UP

On follow up the patient complained again for poor symptom control such as wheezes 2-3 times per week, night waking and in one occasion requiring short course of oral corticosteroids and additional salbutamol once-twice per week . The patients was scheduled for phenotypic assessment : Sensitization on skin prick testing and specific IgE, Total Serum IgE, blood eosinophils, FeNo and sputum eosinophils was not done.

- Skin prick testing for inhalant allergen was performed using positive and negative controls, asking the patient about medication that could interfere with the skin test and taking a 3mm diameter cut of as a definition as positive test. All solutions and positive and negative controls were manufactured by Allergopharma GmBH & Co. KG, Reinbek, Germany[24]: The test revealed : positive for Dermatophoides. Pteronysimus et farinae, and grass pollen (Phleum pratense-Timothy grass) Birch pollen, and weeds (Ragweed)

In current medical practice, analysis for circulating specific and total IgE antibodies in serum, as well as the clinical history and SPT are considered to be standard methods to differentiate sensitized from non-sensitized patients and as confirmation for allergen in question.[25]

- ImmunoCAP quantitative test revealed very high total IgE levels as well specific IgE levels in serum:
  - d1 – Dermatophagoides pteronyssinus – House dust mite and
  - d2 – Dermatophagoides farinae – House dust mite
  - g5 – Rye-Grass Lolium perenne
  - t3 - Birch tree
  - And Total IgE of 1001 IE
  - m3 – Aspergillus fumigatus was negative(not detected)
- Blood eosinophils were 230μl

The patient was not eligible for trial of biologic therapy with anti-IgE monoclonal antibody, Omalizumab.[26]

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Table 1. Subcutaneous XOLAIR Doses Every 2 or 4 Weeks* for Patients 12 Years of Age and Older with Asthma

Pretreatment Serum IgE (IU/mL)	Dosing Freq.	Body Weight			
		30–60 kg	>60–70 kg	>70–90 kg	>90–150 kg
		Dose (mg)			
≥30–100	Every	150	150	150	300
>100–200	4	300	300	300	225
>200–300	weeks	300	225	225	300
>300–400	Every	225	225	300	
>400–500	2	300	300	375	
>500–600	weeks	300	375	Insufficient Data to Recommend a Dose	
>600–700		375			

*Dosing frequency:
- Subcutaneous doses to be administered every 4 weeks
- Subcutaneous doses to be administered every 2 weeks

[27]

Table 3. Subcutaneous XOLAIR Doses Every 2 or 4 Weeks* for Adult Patients with Nasal Polyps

Pretreatment Serum IgE (IU/mL)	Dosing Freq.	Bodyweight							
		>30-40 kg	>40-50 kg	>50-60 kg	>60-70 kg	>70-80 kg	>80-90 kg	>90-125 kg	> 125-150 kg
		Dose (mg)							
30 - 100	Every 4 Weeks	75	150	150	150	150	150	300	300
>100 - 200		150	300	300	300	300	300	450	600
>200 - 300		225	300	300	450	450	450	600	375
>300 - 400		300	450	450	450	600	600	450	525
>400 - 500		450	450	600	600	375	375	525	600
>500 - 600		450	600	600	375	450	450	600	
>600 - 700		450	600	375	450	450	525		
>700 - 800	Every 2 Weeks	300	375	450	450	525	600		
>800 - 900		300	375	450	525	600			
>900 - 1000		375	450	525	600				
>1000 - 1100		375	450	600					
>1100 - 1200		450	525	600	Insufficient Data to Recommend a Dose				
>1200 - 1300		450	525						
>1300 - 1500		525	600						

*Dosing frequency:
- Subcutaneous doses to be administered every 4 weeks
- Subcutaneous doses to be administered every 2 weeks

Duration of Therapy

Periodically reassess the need for continued therapy based upon the patient's disease severity and level of symptom control.

[28]

Taking into account the patient history of severe allergy as well as the contraindications for a trial with Omalizumab because of the very high level of total IgE and body weight of 65kg the patient was treated with standard asthma treatment for another 5 months when another reevaluation was scheduled. Additional therapy of antihistamines was given for 4 months (allergy season).

After 5 months the patients had two hospitalization and was still with poor symptom control, and taking salbutamol as a reliever, despite the given high dose ICS/LABA and add-on tiotropium bromide therapy. Patient's total IgE was reevaluated, due to the fact that the first test was made at the beginning of allergy season. The Patient's Total IgE was still high (860 IU/L) but only in the group for administration of subcutaneous Omalisumab in asthma patients, but not for treatment of nasal polyposis.[29]

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The treatment was started with initiate dose of 300mg subcutaneous injection every 2 weeks. After 4 weeks total serum IgE (IU/mL) was measured and the weight of the patient before the start of the treatment. The patient had no complaints for night waking, wheezes and dry cough, the total IgE levels were lowered to 640IU/L. Pulmonary lung function test were performed , spirometry and BODYplethismography , giving very much improved results: FEV1=90% FVC=91% FEV1/FVC=78%. The previous asthma treatment was replaced, step down, with lowered doses of ICS (Budesonide/formoterol 160mcg/4,5 mcg , 2 actuations of 160 mcg/4.5 mcg, q12hr) and Tiotropium bromide 2,5 mcg 2puffs once daily, and she was scheduled for another visit in one month.

When treating patient with long established chronic disease, poor symptom control and high exacerbation rate is very challenging as for the physician as well for the patient. Reevaluation and reassessment of the patient's symptoms and signs of disease is crucial for successful treatment.

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