LETTER TO THE EDITOR

SEASONAL MONITORING OF SERUM IgE AND BLOOD EOSINOPHIL VARIABILITY MAY LEAD TO A BETTER SEVERE ASTHMA PHENOTYPING AND TO A CORRECT BIOLOGIC PRESCRIPTION

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To the Editor,

According to Global Initiative for Asthma Guidelines (GINA) (1), we should consider adding on type 2-targeted biologic drug [anti-immunoglobulin E (IgE), anti-IL5/anti-IL5R, anti-IL-4R] for patients who have eosinophilic/allergic biomarkers with frequent exacerbations or poor symptom control, although treated with high doses of inhaled corticosteroid/long-acting ß-agonist (ICS/LABA) and/or who need oral corticosteroid maintenance. Guidelines (1) suggest choosing one of the above-mentioned biologic medications on the basis of allergic sensitization and/or blood eosinophil counts, considering also some factors that may predict a good response [higher number of blood eosinophils, fractional exhaled nitric oxide (FENO), exacerbations, childhood/adult asthma onset and nasal polyps].

However, the different pathways of allergic or eosinophilic asthma indicating anti-IgE or anti-IL5/anti-IL5R may overlap in some patients, and it may therefore be difficult to choose the right treatment with a possible consequent lack of improvements or reduced outcomes in asthma. In this case, it is not always easy to understand whether eosinophilic asthma is a pathway independent of IgE-induced allergic activation, consequent to allergen exposure. In fact, the latter leads to the activation of Th2 cells and the production of cytokines, interleukin IL-4, IL-5, IL-9, and IL-13, resulting in IgE production (2), eosinophilia and mast cell activation, whereas ILC2 cells (type 2 innate lymphoid cells) are involved in the innate immune response, that is independent of allergen sensitization, producing IL-5 and IL-13 (2, 3) with consequent eosinophilia.

Allergic asthmatics may have a serum IgE level increase during pollen seasons and a reduction in all other periods (4). These seasonal IgE variations may also influence the number of blood eosinophils in the severe allergic asthma phenotype. In fact, other authors have demonstrated a seasonal variability of eosinophil counts in asthmatics (5). One out of 6 patients**,** whose average count was above the 150 cells/mm3 cut-off value, had initial counts below such value (5). Therefore, a monitoring of IgE and eosinophil levels in the different seasons may lead to divergent results and therefore to a different indication on the choice of biologic treatment in severe asthmatics showing an overlapping phenotype.

Key words: biologic treatment; severe asthma; blood eosinophils; IgE, season; prescription

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DISCLOSURE: ALL AUTHORS REPORT NO CONFLICTS OF INTEREST RELEVANT TO THIS ARTICLE.

We report a case of a severe asthmatic studied in two different seasons (winter and summer) for a biologic treatment prescription. The subject was a 66-year-old man with uncontrolled severe allergic asthma (sensitized to Dermatophagoides, Parietaria, Cypress). His clinical history was remarkable for the following: he was a non-smoker with allergic asthma from the age of 12; his severe asthma was diagnosed in 2014 associated to nasal polyps that had been surgically treated but with no other significant comorbidities; he had no suggestive history of occupational respiratory disease. Even though he was being treated with high doses of ICS/LABA, Tiotropium and leukotriene inhibitors, he had experienced 7/8 asthma exacerbations per year during the previous 4 years with several admissions to the emergency room and some hospitalizations. He had frequently used oral corticosteroids (almost every month), even for long periods of time. In early March 2019, he showed a serum IgE level of 1,300 U.I./ml and blood eosinophil counts of 950 cells/mm^3 that indicated the prescription of a biologic therapy. Since he had a high number of eosinophils and a high IgE level associated with an elevated body weight, an omalizumab treatment was not suggested, while an indication for anti-IL-5/IL5R was given. For some reasons, the beginning of treatment was delayed and when the patient was retested at the end of June his total serum IgE and blood eosinophil counts were 904 U.I./ml and 100 cells/mm^3, respectively. His last treatment with oral corticosteroid had been in early April for ten days. The pollen exposure reduction had probably led to a decrease in IgE and a consequent normalization of the blood eosinophil number. This result led to reconsider the type of biologic drug to be prescribed, thus correctly orientating towards the use of omalizumab (Fig. 1). After 4 months of Omalizumab treatment (early September 2019 to the end of January 2020), the patient was revalued. He did not show any asthma exacerbations ,and oral corticosteroids had been used only once for a few days during the that period. The asthma control test (ACT) increased from 12 to 20. Pre-treatment FEV_1 was 1.81 L - 55% (July 2019), whereas post-treatment FEV_1 was 2.2 L – 66.2% (end of January 2020).

DISCUSSION

This case shows a serum IgE reduction during summer, when allergen exposure is low, with a consensual normalization of blood eosinophils, which allows us to consider the patient was affected by an allergic asthma rather than by an eosinophilic asthma phenotype. This normalization should not occur in innate-immune-induced eosinophilic asthma. In fact, eosinophilic asthmatics, who are poorly responsive to a trial of systemic corticosteroids, showed baseline high blood eosinophil counts associated to IgE low levels (6), suggesting that eosinophils and IgE may be unrelated as the former may be innate-immune induced. Consequently, Omalizumab becomes the best therapeutic choice for such subjects affected by a severe allergic asthma phenotype.

We know that serum IgE concentrations show variability over time in subjects with moderate to severe allergic asthma (4). IgE levels in allergic patients are influenced by different seasonal allergenic exposure. In fact, some authors have found that Japanese cedar pollen-IgE production is mainly associated with the degree of allergen exposure (7). Furthermore, a recent study on pediatric patients observed that serum allergen specific IgE levels measured during asthma exacerbations were elevated compared with the values observed when asthma was under control (8), confirming that allergen exposure, increasing IgE production, can be a trigger of exacerbations. In our case, in early March, when IgE was measured for the first time, allergen exposures were higher but decreased in summer, as demonstrated by lower IgE values measured at the end of June. In the patient's area, the cypress pollen concentration peak (which disappears in May) is usually observed in February-March (9). Dust mite exposure, instead, can be constant during autumn/winter/spring but is lower in summer. Indoor *Dermatophagoides pteronyssinus* 1 (Der p 1) antigen concentrations in homes can be higher in cold months in comparison to hot months (10). Furthermore, in summer, there is a significant reduction of allergic symptoms in dust-mite-induced respiratory allergy (11). Even though the Parietaria pollen is a perennial allergen during the whole year, it shows lower concentrations in summer in Italy and

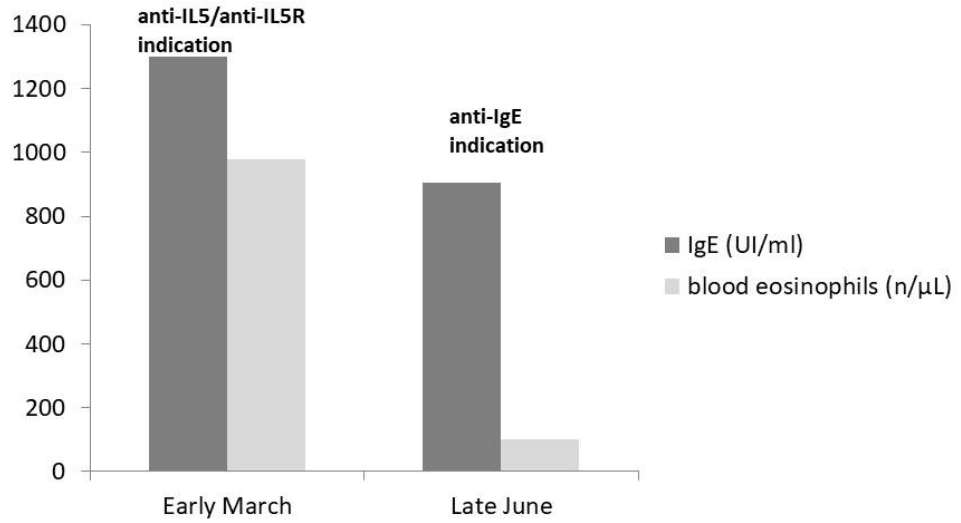

Fig. 1. *Severe asthmatic patient with a seasonal variability in serum IgE and blood eosinophils that led to a different indication for biologic prescriptions*

especially in the patient's area (9, 12).

Variability in IgE levels seems to have influenced clinical decisions for anti-IgE therapy (dosing and/or treatment choice) in approximately 40% of patients (4). As already stated, blood eosinophils can also show a significant variability in different measurements (5). In 17% and 22% of asthmatics, whose average counts were above the 150 or 300 cells/mm^3 cut-off values respectively, had initial counts below these cut-off values (5). These data suggesting the use of a single eosinophil or IgE count as a criterion for eligibility for specific therapeutics may be inadequate to identify all patients with potential benefit**s**.

After 4 months of omalizumab treatment, the patient did not show any significant asthma exacerbations, he used oral steroids only once for few days and showed a significant improvement in symptoms and lung function, demonstrating that the choice of the anti-IgE therapy was the right one.

Our case not only confirms that there is a seasonal variability of eosinophil counts and IgE levels, but also highlights that the variability of measurements may allow to properly differentiate allergic from eosinophilic asthma phenotypes in overlapping subjects, enabling to choose the most suitable biologic drug (anti-IgE *vs* anti-IL5/anti-IL5R).

In conclusion, on the basis of our case, we observed that blood eosinophil measurements in overlapping subjects in the different seasons (with high/low allergen exposure), may lead us to change the diagnosis of presumed eosinophilic asthma to allergic asthma and therefore indicate the right biologic treatment in cases of overlapping severe asthmatics. Therefore, in patients with overlapping eosinophilic and allergic phenotypes, according to the biomarkers measured in winter, it is advisable to monitor such biomarkers in the other seasons before deciding which biologic drug to prescribe.

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