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IgE, blood eosinophils and FeNO are not enough for choosing a monoclonal therapy among the approved options in patients with type 2 severe asthma

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ABSTRACT

Type-2 inflammation is the most frequent endophenotype of asthma. Different biomarkers have been proposed to identify this inflammation because highly effective therapies have improved type-2 severe asthma control. We investigated the frequency of some biomarkers of type-2 inflammation (total IgE, sIgE, blood eosinophil, and FeNO) in the framework of severe asthma and assessed its ability to help us to choose the best biological therapy for each patient. Different scenarios (sensitivity analysis) were evaluated according to the biomarkers proposed for each biological therapy in 72 patients with type-2 severe asthma. Between 54.1% and 68% of patients could receive at least 2 different biological therapies and 34.7%–40.2% could receive any of the 3 types of therapies (anti-IgE, anti-eosinophil, anti-IL4). Biomarkers help to identify type-2 severe asthma but total IgE, sIgE, blood eosinophil, and FeNO are not enough to select 1 specific therapy. With the increasing arrival of new biological therapies, it is necessary to identify new biomarkers that allow us to improve our selection criteria for the best therapy for each patient or to construct a prediction rule.

Keywords: Asthma, Biomarkers, Eosinophils, FeNO, Immunoglobulin E

Different endophenotypes of asthma with distinct clinical and molecular features are well recognized.[1] Type-2 inflammation is driven by various cytokines (IL-4, IL-5, and IL-13) and is generally associated with the diagnosis of "allergic asthma" or "eosinophilic asthma".[1] Different biomarkers have been proposed to identify this inflammation: blood and airway eosinophil counts has evolved as a marker of "eosinophilic" endotype and total and specific IgE (sIgE) are usually used to identify the "allergic" endotype.

The greater knowledge of the pathogenesis of asthma allowed the rise of new biological therapies, which generates hope for the clinical control of patients in whom traditional options do not work. These highly effective therapies have improved asthma control in type-2 severe asthma.[2]

Different international guidelines[3,4] have proposed recommendations for choosing a monoclonal among the approved options and to predict clinical response with each therapy. These

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Is the patient eligible?	GINA recommendations	n 72 (100%)
Anti-IgE	At least one sIgE[a] $\geq$ 0.35 KU_A/l	57 (79.1%)
	Total IgE $\geq$ 100UI/ml	45 (62.5%)
Anti-IL5/anti-IL5R	Blood eosinophils >300/cells	39 (54.1%)
Anti-IL4R	Blood eosinophils >150/cells	56 (77.7%)
	FeNO >25 ppb	34 (47.2%)
	Exacerbations in last year[+]	72 (100%)
What factors may predict response?	**GINA predict factors**	**n 72 (100%)**
Anti-IgE	Blood eosinophils >260/cells	42 (58.3%)
	FeNO >20 ppb	53 (73.6%)
Anti-IL5/anti-IL5R	Higher blood eosinophils[b]	10 (13.8%)
	Nasal polyposis	12 (16.6%)
Anti-IL4R	Higher blood eosinophils[b]	10 (13.8%)
	Higher FeNO[c]	18 (25%)
	Nasal Polyposis	12 (16.6%)
	Moderate/severe atopic dermatitis	6 (8.3%)

Table 1. Selection of type-2 monoclonal according GINA recommendations. [5]*Exacerbations in the last year is a recommendation for any of the three therapies. a.* sIgE: specific IgE against aeroallergens. The minimum weight for anti-IgE is 20–30kg, all included patients are adults and exceed this weight. As adult patients, they all exceeded this weight. b. Higher blood eosinophils: With 500/cells were 10 patients and with 400/cells were 24. Eosinophil levels for selection could change among the different anti-IL5. c. FeNO: >35 ppb.

recommendations are based on clinical characteristics (FVC, BMI, comorbidities like nasal polyposis, atopic dermatitis, and chronic urticaria) and biomarkers (FeNO, eosinophils count, total IgE, and sIgE). Since there are no studies evaluating all therapies in the same conditions at the same time, it has not been properly explored how effective and specific these recommendations really are in choosing one therapy over another.

In this study, we investigated the frequency of some biomarkers of type-2 inflammation in the framework of severe asthma and assessed its ability to help us to choose the best biological therapy in each patient. We use GINA 2020 recommendations[5] (Table 1) as reference criteria for the selection of biological therapy according to results of these biomarkers. In 2 medical centers, we collected patients diagnosed with severe and difficult-to-treat asthma according to clinical and spirometry criteria.

Eighty-four patients were evaluated (Table 1); 72 patients had type-2 inflammation[1] (total IgE >100 UI/ml or sIgE >0.35 kU_A/l or blood Eosinophil >150/cells or FeNO >25 ppb), 42 (58.3%) were men, average age was 47 years (range 28–64). Twelve (14.2%) patients had severe asthma but not type-2 inflammation, therefore, they were not included in subsequent analyzes (Table 2).

Fifty-seven (79.1%) patients had sIgE and 45 (62.1%) high total IgE. All patients with high total IgE had at least one sIgE, most of them to house dust mites (HDM) (n = 55; 76.3%); blood eosinophils over 150/cells was presented in 56 (77.7%) patients and 39 (54.1%) of them had eosinophils over 300/cells respectively; FeNO >25 ppb was presented in 34 (47.2%) patients (Table 1). According to these results, 79.2% of patients could receive an anti-IgE; 54.1%, anti-IL5/anti-IL5R, and 77.7% an anti-IL4Rα (Fig. 1a).

We evaluated different scenarios according to the high or low cutpoint proposed for the different

Baseline data	Asthma patients included (n 72)	Asthma patients no included (in 12)
Age, Median (Range)	53 (32)	53 (28)
Asthma onset, Median (Range)	32 (12)	31 (11)
Sex: Male (%)	40 (55.5%)	8 (66.6%)
Atopy (%)	57 (79.1%)	0
Total IgE (IU/ml), Mean +SD	488 ± 244*	63 ± 34
Eosinophil serum (cells/count) mean ± SD	325 ± 211*	90 ± 43
Atopic dermatitis (%)	6 (8.3%)	0
Nasal polyps (%)	12 (16.6%)	1 (8.3%)
Smoker (%)	0	0
Ex-smoker or passive smoker (%)	6 (8.3%)	2 (16.6%)
FEV1 Mean +SD	59.5 ± 20	60.5 ± 22
FEV1/FVC ratio Mean +SD	0.6 ± 11	0.6 ± 12
FeNO (%)	27,5 ± 16.5	20 ± 8

Table 2. Baseline data. *General characteristics patients included and not included in the study. Some difference (*p < 0.05) were observed in variables related with selection criteria (Total IgE and Eosinophils). SD: Standard deviation.*

biomarkers according each biological therapy (eg, eosinophils <150/cells or <300/cells) (Fig. 1b). Depending on the scenario, between 39 and 49 (54.1%–68%) of patients could receive at least 2 different biological therapies and 25 to 29 (34.7%–40.2%) could receive any of the 3 types of therapies.

All patients with an indication for anti-IL5/anti-IL5R could receive anti-IL4R because they share eosinophils as a selection biomarker but with a different cutpoint, being lower for anti-IL4R. Most patients with eosinophils >300/cells also had sIgE (37/39, 94.8%) or high total IgE (30/39, 76.8%). All the patients with FeNO >25 ppb (n = 34) had

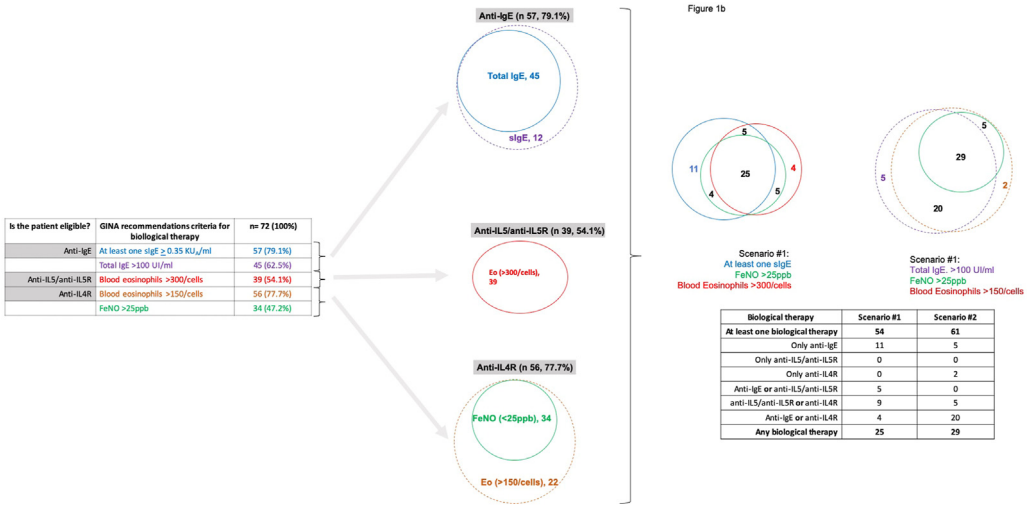

Fig. 1 a: Biomarkers for each biological therapy. **b:** Interaction of biomarkers in two scenarios according to GINA recommendations criteria using sIgE or total IgE, and blood eosinophil levels of 150/cells or 300/cells.[5] The minimum weight for omalizumab is 20–30kg. As adult patients, they all exceeded this weight.

eosinophils > 150/cells, but some patients with eosinophils > 150/cells (n = 56) did not have FeNO > 25 ppb (n = 22).

Different biomarkers are used as a surrogate of airway Type-2 inflammation among asthma patients since the high efficacy of biologics depends on their appropriate selection in each patient. According to GINA recommendations, the use of anti-IgE is indicated for "allergic asthma", anti-IL5/anti-IL5R for "eosinophilic asthma" and anti-IL4R "eosinophilic or type 2 asthma".[5] However, a high production of IgE and eosinophils is promoted for the same cytokines (IL4, IL5, IL13) and similar triggers. In tropical regions, patients have a high production of total IgE and sIgE to different allergens and there is a strong correlation between IgE levels and eosinophils.[6] It is also frequent to find high levels of total IgE secondary to the fact that parasitic infections are endemic. Additionally, FeNO is considered a surrogate of eosinophilic airway inflammation and albeit to a lesser extent, of blood eosinophilia. Therefore, these markers alone or together are useful to identify the type-2 inflammatory response in asthma, but they can be unspecific to differentiate some endophenotypes as our results confirm.

Since all monoclonal drugs currently available are focused on type 2 inflammation, it is anticipated that many patients will be able to receive several of these therapies. Nevertheless, the concept of type-2 inflammation involves mechanisms with common points in the pathogenesis but each mechanism also has particularities, and patients could have a better clinical response with one alternative than with another. In our study, the presence of nasal polyposis and atopic dermatitis was low n = 12 (16.6%) and, n = 6 (8.3%) respectively, but these are clinical characteristics that should be studied in the future for the selection of a monoclonal antibody.

From these results, it is clear that recommendations to select "the best option"[7] of monoclonal agent for each patient should be reevaluated since, given the high correlation of the available biomarkers (at least in tropical population), it is useless to select 1 therapy over the others in each patient. Other proposed biomarkers (eg, TSLP, IL4, periostin), despite being promising, are limited in clinical practice due to difficulties in access. We must emphasize that in our study we did not evaluate the clinical response to biological therapies. We focused on selection criteria.

In conclusion, single or composite biomarkers help to identify in severe asthma type-2 inflammation. Nevertheless, total IgE, sIgE, blood eosinophil count and FeNO are not enough to select one therapy over another. With the increasing arrival of new biological therapies, it is necessary to identify new biomarkers that allow us to improve our selection criteria for the best therapy for each patient or to construct a prediction rule that includes, among other variables, old and new biomarkers.

ABBREVIATIONS

IgE, Immunoglobulin E; sIgE, specific immunoglobulin E; FeNO, Exhaled nitric oxide test; IL, interleukin; GINA, Global Initiative for Asthma; Ppb, part per billion; TSLP, Thymic Stromal Lymphopoietin

Ethics statement
This project was approved for ethics committee of the university of Antioquia.

Author contribution
All authors make substantial contribution in the conception and design of the study.

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Consent for publication
All authors accept the publication of this article.

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