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Eosinophils as a Biomarker in Asthma and COPD

Jose Carlos Herrera Garcia

Abstract

Asthma and COPD are two diseases related to eosinophils. But at present, we do not know with certainty how much these cells participate in these diseases, beyond that the treatment of the underlying cause produces the resolution of eosinophilia in a “reactive” way. Eosinophil-related diseases are a spectrum of systemic diseases such as Asthma and COPD in pneumology area. Under inflammatory conditions, the number of circulating eosinophils or tissues can increase dramatically, with rapid development of eosinophilia and we can obtain in a simple laboratory test. In general, the number of eosinophils in the blood can provide useful information and considering the differential diagnosis and for the subsequent test of patients presenting with eosinophilia. The treatment of eosinophilia currently in number of 300 cells in which is the criteria and the target to be treat. The best known and most used of all treatments for diseases related to eosinophils are corticosteroids, which decrease circulating and tissue eosinophils in a few hours, through mechanisms that include the direct activation of eosinophil program death. Targeted treatment against eosinophils could improve airway remodeling through mechanisms that are not fully known, and their effects on lung function are variable and decreasing symptoms in patients.

Keywords: eosinophil, asthma, COPD

1. Introduction

Asthma and COPD are two diseases related to eosinophils in which eosinophils are the main cause and journals have evidence an increase in their number in the blood with or without evidence of their activation. But at present, we do not know with certainty how much these cells participate in these diseases, beyond that the treatment of the underlying cause produces the resolution of eosinophilia in a “reactive” way. Eosinophil-related diseases are a spectrum of systemic diseases such as Asthma and COPD in pneumology area. Even within the principal diseases related to eosinophils, the location, type of tissue involved, and magnitude of eosinophilia vary greatly. Under inflammatory conditions, the number of circulating eosinophils or tissues can increase dramatically, with rapid development of eosinophilia and we can obtain in a simple laboratory test. In general, the number of eosinophils in the blood can provide useful information and considering the differential diagnosis and for the subsequent test of patients presenting

with eosinophilia. Currently eosinophils has taken a very important role in the treatment of severe diseases, we know are so prevalent and increased morbidity and mortality in serious phases which produce a lower quality of life in patients, the treatment of eosinophilia currently in number of 300 cells in which is the criteria and the target to be treat. The best known and most used of all treatments for diseases related to eosinophils are corticosteroids, which decrease circulating and tissue eosinophils in a few hours, through mechanisms that include the direct activation of eosinophil program death. But, under certain circumstances, eosinophils can become resistant to these drugs or in the presence of high levels of eosinophil survival cytokines, such as IL-5 by example. With the administration of anti-IL-5 antibodies, such as mepolizumab or reslizumab the blood eosinophils typically decrease by at least 80% within a few days, without decreasing them much in the tissues, such as in the lower airways. Asthma, presumably due to the action of other eosinophil cytokines, such as GM-CSF, present in tissues. Comparatively, the administration of benralizumab, an anti-IL-5 antibody that acts on the IL-5 receptor, causes a much deeper and longer decrease in eosinophils, by activating antibody-dependent cellular cytotoxicity. Targeted treatment against eosinophils in eosinophilic asthma and eosinophilic COPD decreases exacerbations and could improve airway remodeling through mechanisms that are not fully known, and their effects on lung function are variable and decreasing symptoms in patients.

Data from multiple studies in asthma and eosinophilic COPD suggest that they are safe long-term drugs despite the decrease in eosinophils over time, as well as being well tolerated. Eosinophils exist in virtually all vertebrates as part of the innate immune system, which underscores the important benefits they must provide to their guests. In humans, they are in normal ranges when their blood levels are $<500 / \mu\text{L}$, although this number can vary between 350 to 600 depending on the laboratory. Eosinophilia is defined when its number is $>300/\mu\text{L}$ in the recent studies and guidelines [1, 2].

2. Eosinophil hematopoiesis

For eosinophils to develop, a unique set of transcription factors is required, which if not present, do not develop (**Figure 1**). Similarly, the eosinophil lineage

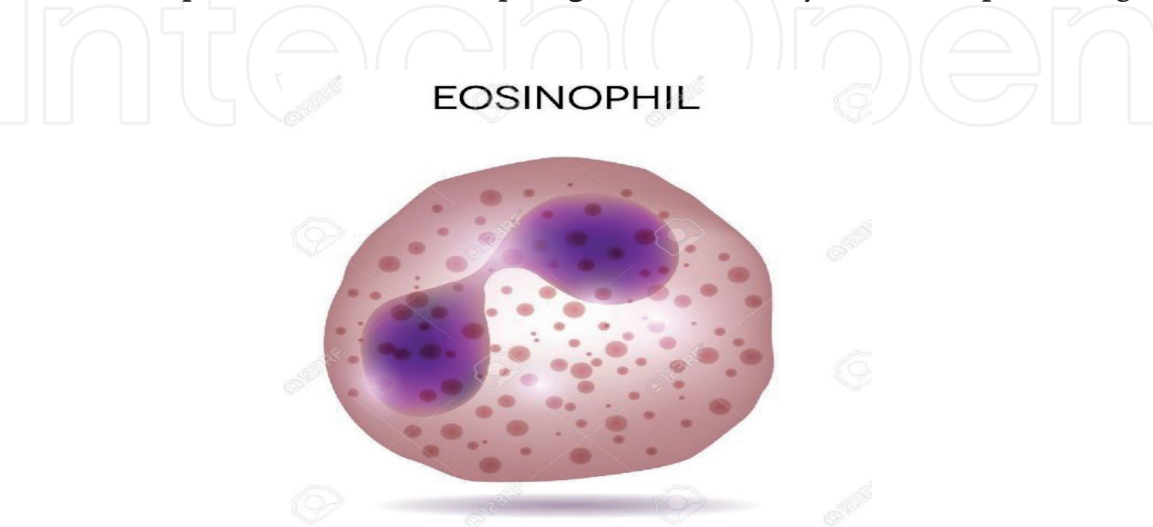


Figure 1.
The eosinophil.

depends on the appearance of a specific receptor on its surface for IL-5. The expression on the cell surface of the IL-5 receptor is one of the first events for the development of the specific eosinophil lineage that occurs in the bone marrow, although recent data in rats suggest that another cytokine, the IL-13, has a role in increasing the differentiation of eosinophils at a point “upstream” to that of IL-5. Although the source of IL-5 and IL-33 within the bone marrow necessary for the development of eosinophils is not known exactly, it is likely that T cells and certain innate lymphoid cells (CLI2) are the important sources, at least for IL-5 [2].

3. Beneficial functions of eosinophils in homeostasis and host defense

Most of what is known about eosinophils in terms of their roles in health and homeostasis, comes from data obtained from animal studies. It is believed that eosinophils contribute a large amount of beneficial substances that help in the development, remodeling, and tissue repair. Their roles in innate and adaptive immune responses include the favorable influence on the development of immune cells, provide antibacterial, antifungal, and antiviral responses and help control glucose metabolism, myocyte regeneration, lean fat development and adiposity. Most of these functions have been demonstrated in animal models, so their reality in humans is uncertain. In addition, although the very important role of eosinophils during type 2 immune responses against helminths and other parasitic infections is considered almost dogmatic, their total certainty in humans is controversial because in many patients in pandemic parasitic infections we know have increase eosinophils and we do not the normal range in laboratory test and the main changes that decreasing of increasing (**Figure 2**). Therefore, despite the growing interest in knowing what eosinophils actually in the immune system and in disease circumstance, in the nest days we need to know and much remains to be investigated [3].

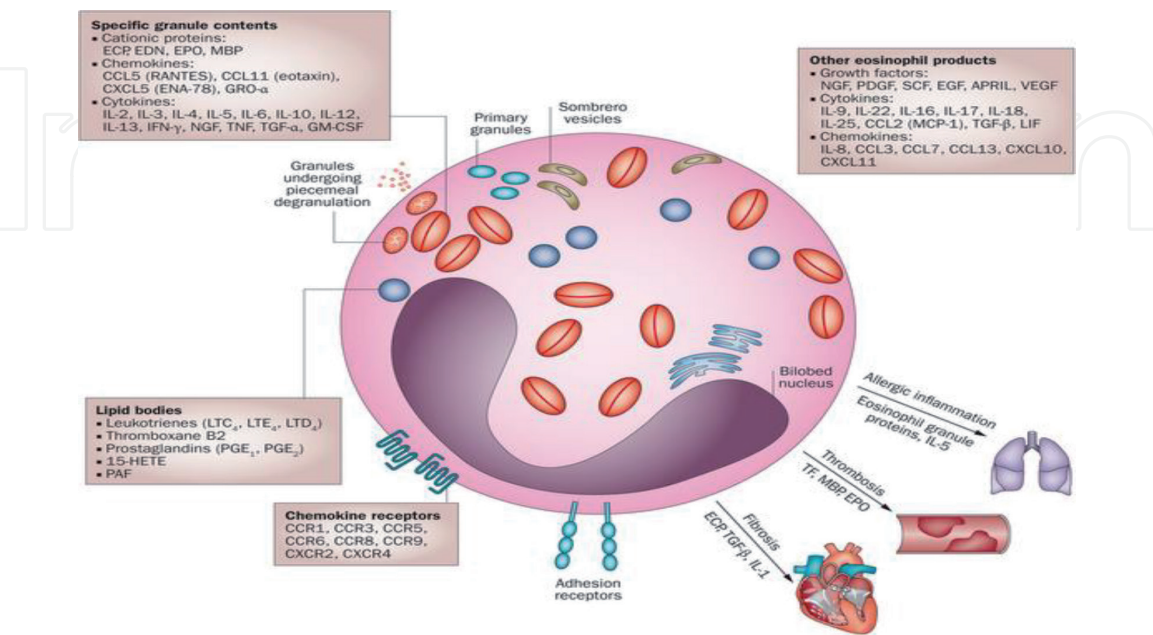


Figure 2.
The eosinophil cycle and function.

4. Asthma and COPD

COPD and asthma have a pathogenic and pathophysiological basis easily differentiable in most cases. They also share a series of clinical similarities that often make their differentiation complex, especially in-patient smokers with a history of atopy and eosinophilia. But we have patients with combined symptoms and different phenotypic. The characteristics clinics shared by both diseases are based on inflammation and airway obstruction, now we know in certain papers that COPD is a fibrotic disease but when the patient have some allergic characteristics the disease is like an inflammatory problem and the eosinophils have a role in both. The incomplete reversible and progressive in COPD and variable and reversible in asthma. Also, the location of the inflammatory response in these pathologies also have differences, allowing to locate the predominant involvement of COPD in the peripheral airway and in the pulmonary parenchyma, in contrast to the respect of pulmonary parenchyma and panfocal airway involvement in asthma. The cell count obtained from bronchioalveolar lavage (BAL), induced sputum and bronchial biopsies in patients with COPD demonstrate the predominant presence of neutrophils, CD8 + T lymphocytes and abundant macrophages. In asthma, eosinophils, mast cells, CD4 + T cells and fewer macrophages meet in samples representative of the tracheobronchial tree, but there are some patients with paucigranulocytic phenotypic. Inflammatory mediators also differ, playing a predominant role leukotriene-B4 (LTB4), interleukin 8 (IL-8) and tumor necrosis factor alpha (TNF- α), among others, in the case of COPD, while in asthma have found multiple inflammatory variables, represented for histamine, leukotrienes and interleukins 4 and 5.

The fraction of exhaled nitric oxide in patients with asthma is found increased, reflecting the greater eosinophilic inflammation. Thus, it seems reasonable to define a high Th2 patient profile in a non-invasive way by using indirect markers such as IgE > 100 IU and blood eosinophils > 300 cells/microliter, or eosinophils in sputum > 3%. Along these lines, a recent study has shown that eosinophilia together with elevated levels of periostin was the best predictor of improvement in lung function in COPD patients treated for three months with inhaled corticosteroids and LABA. However, it seems that a more integrative approach, which unites clinical features and molecular mechanisms, is the best way to identify disease sub phenotypes and individualized treatments. The fraction of exhaled nitric oxide is poor studied in COPD, and we know there is not a confinable test to follow a patient we do not have inflammation or have both [3].

5. Eosinophils and COPD

In December 2017, we published in the journal Respirar de ALAT, a manuscript of the study findings of 50 Mexican patients in the outpatient pulmonology clinic at the University Hospital of Puebla, Mexico, the results were prevalence of eosinophilia (74% women and 26% men). 50% associated with smoking and 50% with exposure to biomass. 36% presented representative eosinophilia which indicated the relevance of this marker taking into account that 50% of all the patients studied were in GOLD IVD stage. Tine and colleagues pointed out that blood eosinophils may have a paradoxical benefit for COPD patients; In patients with blood eosinophil counts of 2% or more versus patients with counts of less than 2%, better lung function, better quality of life, fewer symptoms and less comorbidities have been reported. It has also been shown that the risk of

pneumonia, regardless of the use of inhaled steroids, is lower in patients with eosinophil blood counts of 2% or more. These facts suggest, the authors wrote, that the use of eosinophil-targeted therapies can actually be detrimental to COPD patients [4, 5].

6. Eosinophilic pathways in asthma

The Eosinophils nowadays are the most inflammatory status seen in asthma, in patients that have persistent eosinophilic airway inflammation is a severe status in some cases. Because these patients have neutrophilic or paucigranulocytic count and separate in allergic and nonallergic patients with severe symptoms. The pathways for eosinophil recruitment are quite distinct. Allergic eosinophilic asthma is driven by Th2 lymphocytes. Allergens, presented to naive CD4+ T cells by dendritic cells, induce differentiation toward Th2 cells, which produce IL4, IL5 and leading to IgE class to airway eosinophilia and mucous hypersecretion. In nonallergic eosinophilic asthma, epithelium-derived cytokines (IL25, IL33, TSLP) are released in response to air pollutants, microbes or glycolipids (**Figure 3**). These bind to receptors on type-2 innate lymphoid cells (ILC2s), activating them to produce the Th2-associated cytokines IL5 and IL13, which lead to eosinophilia, mucous hypersecretion and airway hyper-reactivity, in the majority of allergic asthma cases, the presence of eosinophils may be a secondary consequence of the allergic cascade that recruits them to the site of inflammation in the evolution of the disease. In some patients, however, particularly those with severe, non-allergic asthma the eosinophil may play a more central role, possibly initiating the disease or persistent disease or persistent symptoms, these patients are typically older women with comorbid nasal polyps, aspirin sensitivity and late-onset asthma concluded in a different phenotypic [5].

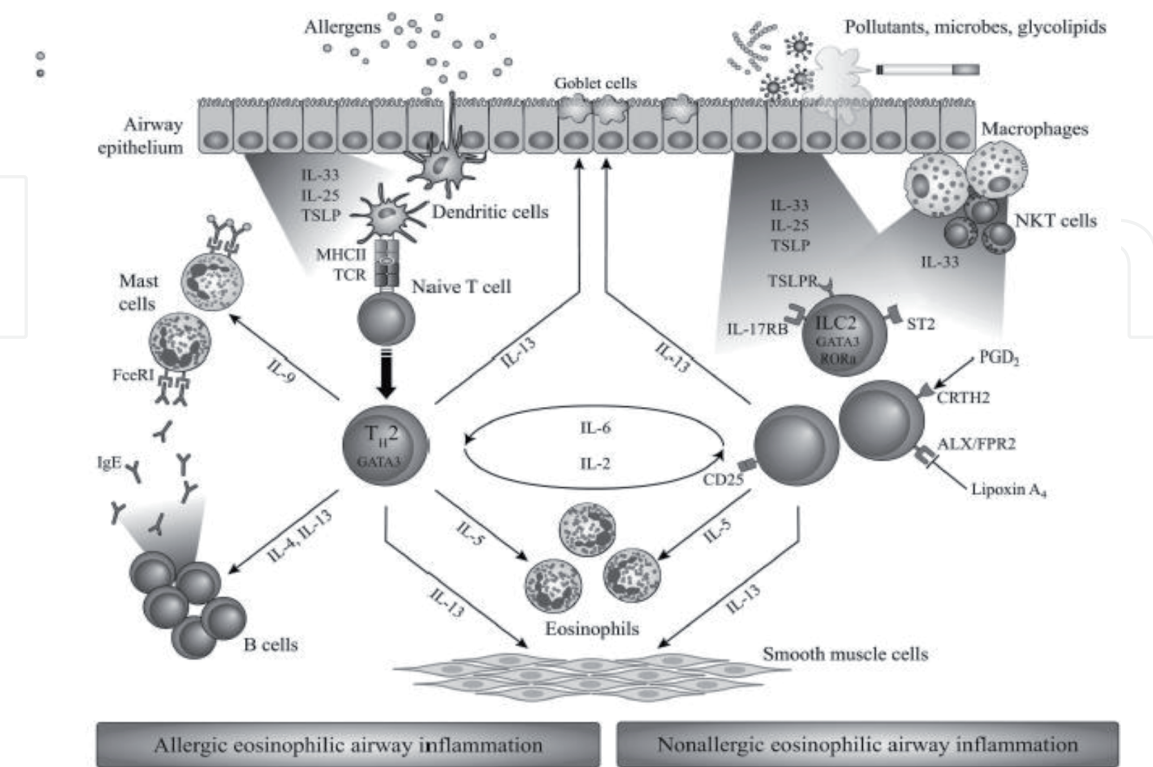


Figure 3.
Allergic and non-allergic eosinophilic pathways in asthma.

7. Eosinophilic inflammation in COPD

In COPD, inflammation is more commonly associated with T helper 1 lymphocyte (Th1)-mediated immunity driven by neutrophils, often in response to bacterial colonization. However, as with asthma, COPD presents as a number of different clinical phenotypes and, in around 10–40% of patients, a degree of eosinophilic inflammation is present during stable state. We published some cases with severe COPD versus health patients in a asthma clinic in Puebla, and we describe that we do not know when is the time to take a eosinophils sample and make a different diagnosis in the clinic, the patients came to take a sample in stable state and have minor eosinophils cells like health people, and concluded like we need to know when is the better time to take a eosinophils sample. The cell senescence likely plays a pathophysiological role in COPD (**Figure 4**) particularly in relation to the release of cytokines other factors from senescent cells, many of which are also implicated in the pathogenesis of COPD [5].

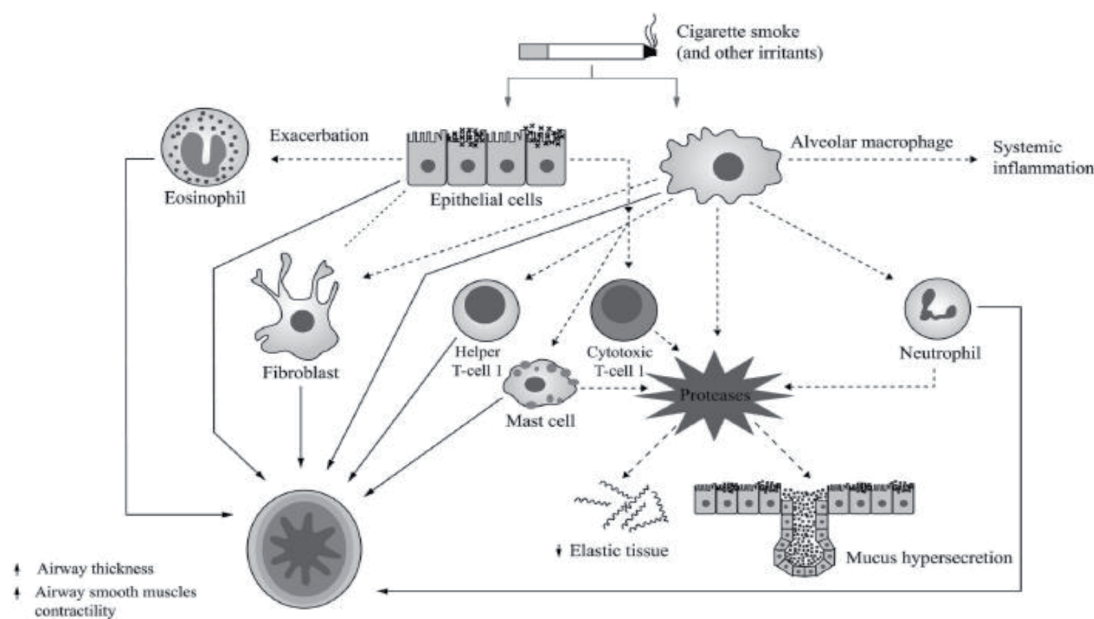


Figure 4.
Relationship between airway inflammation and bronchial abnormalities in COPD.

8. The utility of measuring blood eosinophil levels in asthma and COPD

The most important point in this chapter is the utility of measuring blood eosinophils as a biomarker to treatment in stable or exacerbating COPD. Blood eosinophil levels can either be expressed as an absolute count (150 cells) or as a percentage, actually there are many groups that define them, like $<2\%$, ≥ 2 – $<3\%$, ≥ 3 – $<4\%$, <150 cells· μL^{-1} , 150 – <300 cells· μL^{-1} , ≥ 300 – <400 cells and ≥ 400 cells were used in the post hoc analysis of WISDOM. 2020 guidelines from the Global Initiative for Chronic Obstructive Lung Disease (GOLD) have recommended blood eosinophil counts ≥ 300 cells in stable COPD as the diagnostic criterion for initiating therapy with ICS/long-acting β -agonist (LABA). However, eosinophilia is defined, the utility of the measurement is limited by the stability of the measurement. People with COPD often start treatment with Dual Therapy (LABA/LAMA) some people use monotherapy in some patients, but in some group of patients continue use inhaled corticosteroids like added, sure measuring the number of

eosinophils and concluded the people who will benefit with this kind of therapy. Some patients experience a worsening of their symptoms known as an exacerbation and the eosinophils maybe predict the risk of exacerbations that is so important for clinicians treating this patients, but there is a pooled analysis in 2020 with Singh et al. concluded that in a pooled analysis of 22,125 patients with COPD, do not find a clinically important relationship between baseline blood eosinophils count and exacerbation rate and is not a clinically useful predictor of future exacerbation risk, I think maybe we can use in worsening symptoms in a single time of the life of the patient, COPD is dynamic and heterogenic disease, maybe we can use in some cases in which the patient worsening symptoms [6].

The utility of measuring blood eosinophils to guide therapy is likely to vary depending upon the clinical status of the patient, i.e. whether their COPD is stable, or they are experiencing an exacerbation. Now in press we have a manuscript that we can show in a cohort with severe COPD patients and healthy controls the blood eosinophils count do not change in a single sample and the count was similar in the same group in the same time. The evidence suggests that measuring, eosinophil levels to help guide therapy is useful with measuring eosinophils count to use ICS/LABA, and reduction the use of inhaled corticosteroids y some patients that do not need this treatment. In COPD we need to consider the eosinophil count to choose treatment [6].

9. We can use eosinophils like a target and biomarker in the biologics era

Anti-IL5 therapies are a great promise in patients with eosinophilic asthma, and we do not know if is the same to COPD, suggesting that depletion of eosinophils may not be a valid target in COPD. An initial study using the anti-IL5R antibody, benralizumab, in COPD patients with elevated baseline sputum eosinophils ($\geq 3\%$) demonstrated numerical improvements in exacerbation rates, SGRQ-C and the self-administered Chronic Respiratory Questionnaire (CRQ-SAS) scores, and FEV1 (fraction exhalation volume in 1 second) however, these improvements were not statistically significant. Mepolizumab significantly reduced sputum and blood eosinophil counts compared with placebo in COPD patients with raised baseline eosinophils but, again, these differences did not translate into significant between-group differences in lung function parameters, exacerbation rates, and health-related quality of life. The role of eosinophils in COPD is complex and the benefits observed with ICS (inhaled Corticosteroids) are likely related to their effects on cells or pathways that do not involve eosinophils. These results suggest a potential role for eosinophilic airway inflammation on COPD exacerbations, but also clearly underline the fact that further studies are needed to refine the patients who may benefit from eosinophil-targeted treatments in COPD. The Benefit-risk ratio of ICS in patients with COPD based on blood eosinophil level in stable disease with increasing eosinophils counts, the use of ICS may offer increased benefit by reducing COPD exacerbations and always have precaution for development a pneumonia. ICS use in patients with lower eosinophils counts is potentially associated with decreased benefit and increased risk of pneumonia. Celli comment that the possibility that an easily obtained biomarker such as peripheral blood eosinophil count may help determine a patient's risk for certain outcomes and likelihood of responding to specific therapy is very appealing. However, as in many areas in life, "the devil is in the details", and more data is needed before blood eosinophil levels can be used to identify a COPD phenotype amenable to specific immunomodulatory therapy [7].

10. Variability of blood eosinophils as a biomarker in asthma and COPD

Peter G. Gibson et al. described to consider are those that lower the count and could lead to a false-negative test for diagnosis of the eosinophilic phenotype. These include eating, exercise, medications, and the time of testing. Consuming a light meal was found to reduce blood eosinophils between 2 and 4 h after eating, with an average 23% reduction at 4 h (from 130 to 100 cells/ μ L). Exercise also reduces blood eosinophil counts. For example, a symptom-limited exercise test in COPD patients reduced blood eosinophils at 2 h, with normalization by 24 h. In Puebla, Mexico in 2019 we compared two groups of patients in Asthma and COPD clinic, this two groups were: One group of severe COPD patients [6] and other group healthy subjects [6] workers for the clinic, the age of the patient were 45–60 years and we found that the eosinophil count was similar in the COPD group and the control group. A study was carried out in the Asthma and COPD clinic of the City of Puebla in a Private Angeles Hospital, the presence of two groups of patients with COPD and another as a control group of health workers, and we obtained very interesting data from the account of the eosinophils in a stable state of the patients, since they came voluntarily on a normal and stable day to take the eosinophil count and what were our results: the following: 2 groups of patients with COPD 1 group with 6 patients and the second group with 8 healthy workers. The patients with COPD were severe but in a stable and controlled state and presented an eosinophil count between 144 to 240 cells, and the group of health workers with an eosinophil range between 102 and 192 cells. This finding in this small cohort of patients as a pilot study allows us to see that patients with severe COPD may have low eosinophil ranges because they are stable and controlled just like healthy workers and subsequently be able to use the eosinophil range in some exacerbation of patients who may present an increase in eosinophils and change the therapy, this small work carried out in a particular clinic allows us to conclude that serious patients who have a stable state really have eosinophils in the normal range and the increase of 300 cells is really a figure in which we can make changes in therapy, but on the other hand, in stable patients, it would not be appropriate to take hematic biometry in the stability consultations because it would not be case knowing that the eosinophil count remains normal and only in an exacerbation take them to determine changes in current therapeutics. We concluded that in asthma patients the eosinophil count is variable than the COPD patients [8–10].

11. What is the utility of eosinophils in two prevalent respiratory diseases today?

As described earlier in this chapter, eosinophils are in these times of progress in the treatment of asthma and COPD one of the important pillars at different stages of the disease, as described earlier, approximately 4 years ago we did not have a marker that we allow you to change our decisions in the therapy of these patients in the stable phase or in exacerbations, it seems that its use is very bleak in stable patients, but already established a little more scientific in its use in exacerbations, every patient shows us one of the possible use of eosinophils in the whole path of the disease either in a stable phase or in exacerbation. In the definition of the disease its integration is clearly not useful, as well as in the epidemiological phase, but not in the diagnostic phase where it can be important to emphasize the phenotypes in the two diseases such as in asthma: eosinophilic asthma and in COPD as eosinophilic COPD. In the clinic it has not contributed great importance and we do not think

it is relevant to know eosinophilia to determine if it is asthma or COPD even the spirometry is still the most important pillar of the diagnosis. in the classification of the disease it is of the utmost importance to determine if it is stable or exacerbated, as well as in the treatment that is vital to start steroid treatment, we know in asthma it is the pillar treatment of the disease not so in COPD but it allows to differentiate those responders to corticosteroids. Eosinophils at present and thanks to studies we can clearly establish its use at the beginning of the use of some biological medication to those patients with severe or exacerbated disease, as you know the exacerbations are those that deteriorate the disease and give a poor prognosis. As biomarker for biological initiation it is vital, as it has also been demonstrated in its use in the follow-up of patients, as part of the response to the treatment already established. There are still unknowns about the use of these cells in stable patients, we are developing a writing of the results of a pilot work on the values of eosinophils in stable patients with serious disease and healthy patients, these results will be shortly where we can show that in the stable patient there is still controversy in the use of treatment in patients with eosinophilia [10].

12. Conclusion

Asthma and COPD are two chronic diseases linked to exacerbations and possible quality of life of patients, the introduction of eosinophils as biomarkers in the evolution of the disease has opened a promising panorama as a biomarker in the classification of patients, their severity, prognosis and presence of exacerbations. Eosinophilia in these diseases is a reality and as pulmonologists we have a duty to always carry out that scrutiny that allows us to characterize our patients and to prescribe the appropriate treatment always taking into account the possible use of biologics in patients with severe disease. Both asthma and COPD are complex, heterogeneous conditions comprising a wide range of phenotypes, some of which are refractory to currently available treatments. These phenotypes and identification of biomarkers with which to recognize to guide an appropriate treatment for researchers and clinicians. The potential of blood eosinophils nowadays has potential and much attention in medical research to choose the optimal and correct treatment. In asthma, the rationale for their use as such is more clearly defined, with several well-controlled studies demonstrating that patients with higher eosinophil counts are prone to more severe disease and poorer outcomes. As a result, new biologic therapies have been developed to tailor treatment to these patients. In COPD, high blood eosinophil counts may predict a favorable response to ICS on top of LABA/LAMA, especially in patients with a history of frequent exacerbations, but the exact position and the definition of clinically significant eosinophilia is need to be more studied for the use of blood eosinophils for the identification of patients who may benefit from targeted treatments (**Table 1**). the use of eosinophils in clinical practice in COPD needs to be evaluated in prospective studies before firm conclusion and demonstrated in stable patients [10]. Eosinophilic inflammation is a stable longitudinal phenotype in a substantial proportion of COPD patients, which can be predicted over 12 months by an initial blood level measurement. The need for biomarkers to identify patients who may benefit from treatments in airways disease. As more treatment options are becoming available, we need to research and choose the biomarkers like elements or activation states of eosinophilic inflammation and will support the selection of treatment we need to control the patient in asthma and COPD. These events are seasonal in nature and relate to bacterial etiology and considerate the weather to take the sample [11].

Utility	Asthma	COPD
In definition	-	-
In epidemiological decision	-/+	-
In diagnosis	+/-	-
In clinic	+	+
In classification	+	-
In exacerbations	+	+
In treatment	++	++
In biological treatment	+++	+
Following	++	+
Stable	+	+/-

Table 1.
Utility of eosinophil as a biomarker in clinic.

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