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Articolo di revisione / *Review article*

Brief practical guidelines for biologic prescriptions in severe asthma. Expert opinion

Brevi linee guida pratiche per le prescrizioni di biologico nell'asma grave. Opinione di Esperti

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Summary

This brief paper is intended to be a quick guide to prescribe biologics in severe asthma by following Global Initiative for Asthma (GINA) guidelines but also considering the author's personal opinions. The paper starts with the identification of candidates for biologic therapy examining next the biological markers to be taken into account for the phenotyping of inflammation. Finally, it indicates the type of biologic to be chosen. This guide also points out the possible signals that can allow us to identify patients with severe asthma that would otherwise be ignored. Furthermore, it tries to give some directions on how to proceed in order to select the right biologic in the cases where the overlapping of different phenotypes can be found or in non-T2 asthma.

Key words: severe asthma, biologic, guidelines, practical, prescription

Riassunto

Questo articolo vuole essere una breve e rapida guida per la prescrizione delle terapie biologiche nell'asma grave tenendo conto delle linee guida GINA e del punto di vista degli autori. Si parte dall'identificazione dei pazienti candidati alla terapia biologica e successivamente vengono considerati i marker biologici da misurare per effettuare la fenotipizzazione dell'infiammazione e quindi come scegliere il biologico giusto. La nostra guida vuole suggerire anche quali possono essere i segni/marcatori che possono permetterci di identificare pazienti con asma grave che altrimenti verrebbero ignorati. Inoltre, cerca di dare alcune indicazioni su come procedere per selezionare il giusto biologico nei casi in cui si riscontra la sovrapposizione di fenotipi di malattia diversi oppure nella forma non-T2 di asma.

***Parole chiave**: asma grave, biologico, linee guida, pratico, prescrizione*

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Identification of severe asthma patients

Uncontrolled asthmatic requiring treatments with multiple drugs (inhaled corticosteroids/long-acting beta2 agonists [ICS/LABA] + long-acting muscarinic antagonist [LAMA] +/- antileukotrienes) and high-dose ICS (step 5 of GINA guidelines), whose correct inhalation technique has been determined, with a good adherence to treatment and with comorbidities and aggravating factors under control, are considered as affected by an asth-

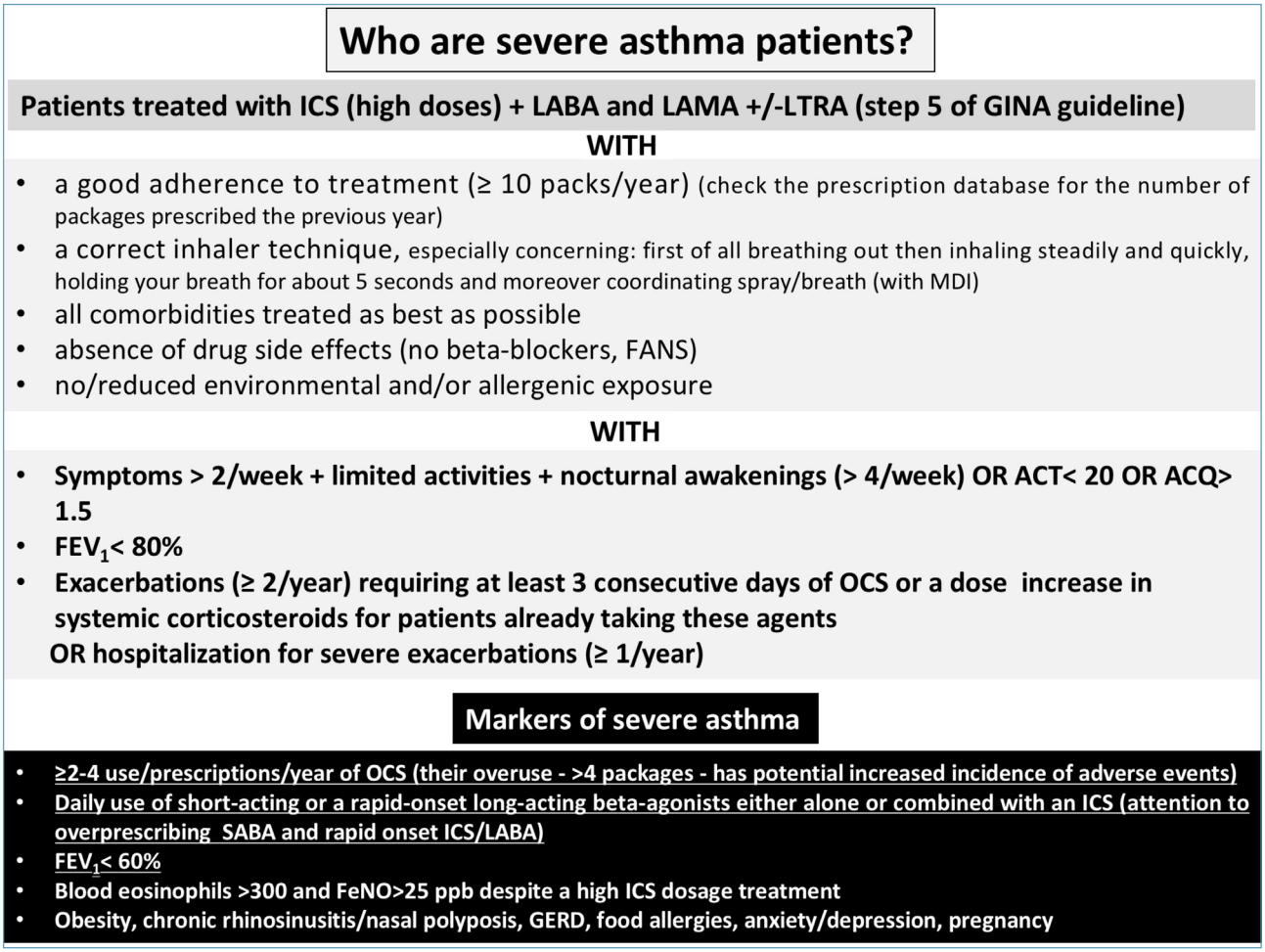

Figure 1. Characteristics of patients with severe asthma and clinical/biological markers identifying this condition.

ma phenotype defined as "severe" [1,2]. Failing to have control of severe asthma is defined by the presence of at least one of the following characteristics: a) patients show symptoms of uncontrolled asthma according to clinical questionnaires (Asthma Control Questionnaire [ACQ] ≥ 1.5 points or Asthma Control Test [ACT] < 20); b) they had two or more exacerbations in the previous year requiring a systemic corticosteroids treatment for ≥ 3 days or an increase in systemic corticosteroid doses for patients already taking them; c) or they need hospitalizations, intensive care unit stays, or mechanical ventilation for the exacerbations during the previous year [2]. Patients with the characteristics above indicated should be treated with a biological therapy (Fig. 1).

Severe asthma features

When dealing with an asthmatic using more than 2-4 packs/year of oral corticosteroids (obtained from the local pharmacy databases and/or family doctor's or reported by the patient during the visit), we may suspect a severe asthma case. The number of packages used by each patient can be searched for in the prescription database. An overuse of 4 oral corticosteroids (OCs) packs/year has a potential increased incidence of adverse events (osteoporosis, diabetes, others) [3]. Overprescribing short-acting beta-agonist (SABA) and rapid-action inhaled corticosteroid (ICS)/long-acting beta agonist (LABA) as needed during a regular treatment with ICS/LABA, should be carefully avoided. Daily use of short-acting or long-acting rapid-action β-agonists, either alone or combined with ICS, can be another severe asthma markers [4]. Such asthma phenotype should be suspected particularly when over-prescribing these drugs is associated with FEV_1 < 60%, blood eosinophils > 300/μL, fractional exhaled nitric oxide (FeNO) > 25 ppb despite a high ICS dosage treatment and especially when the following conditions are accompanied by obesity, chronic rhinosinusitis/nasal polyposis, bronchiectasis, obstructive sleep apnea (OSA) syndrome, gastroesophageal reflux disease (GERD), food allergies, anxiety/depression and pregnancy [2]. A large quantity of patients may not be recognized as severe asthmatics thus remaining undertreated with consequent exacerbations and higher costs associated with them (Fig. 1).

Diagnostic workup for the prescription of biological therapy

When the administration of biological therapy is being considered for severe asthma, it is important to define the phenotype in order to select the appropriate drug and identify the best candidate.

In order to proceed with the prescription of the biologic, one must first understand what type of inflammation characterizes asthma through the assessment of allergies and the measurement of some biomarkers. First of all, it is necessary to know the patient's allergic state. This evaluation should include a compatible medical history, a demonstration of the presence of allergies by skin prick tests and/or measurements of high levels of specific IgE serum or by specific exposure tests, when the clinician deems it necessary. Secondly, at least one peripheral eosinophil count is required to help characterize the presence of an asthma eosinophilic phenotype. Performing an eosinophil count in sputum may provide additional information. Another biomarker to be measured is FeNO, whose increase represents the expression of the activation of interleukin-4 (IL-4) and interleukin-13 (key cytokines of type 2 inflammation) at the bronchial epithelium level (detected by FeNO) (Fig. 2). The above said biomarker identifies "type 2 asthma" phenotype.

How to choose the right biological treatment

1) Omalizumab should be considered for patients with severe uncontrolled allergic asthma (allergy being demonstrated by skin prick tests and/or IgE values, allergen symptoms induced and childhood-onset asthma) with serum IgE ≥76 UI/ml, FEV_1<80%, at least two exacerbations during the previous year and/or with a continuous treatment of oral corticosteroids taken to control the disease.

2) While the use of an IL-5 and/or an IL-5 receptor inhibitor (mepolizumab or benralizumab) is recommended for the following:

Patients with severe uncontrolled eosinophilic asthma with at least two exacerbations during the previous year and/or continuous treatment of oral corticosteroids taken to control the disease and with:

a) Mepolizumab: blood eosinophils > 150 cells/μL and > 300 cells/μL in the last year, especially when associated

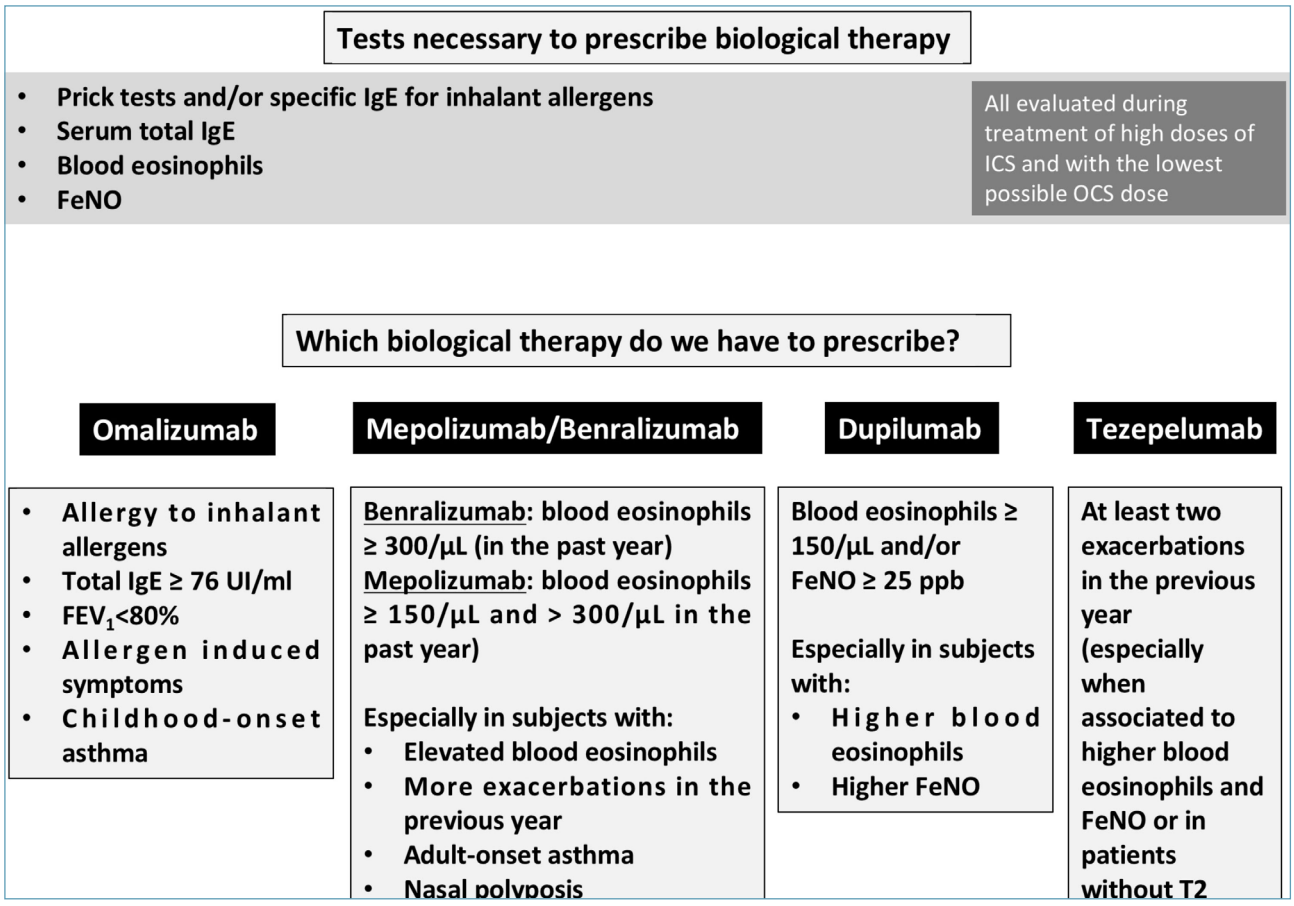

Figure 2. Tests necessary to prescribe biologics and which of these to prescribe.

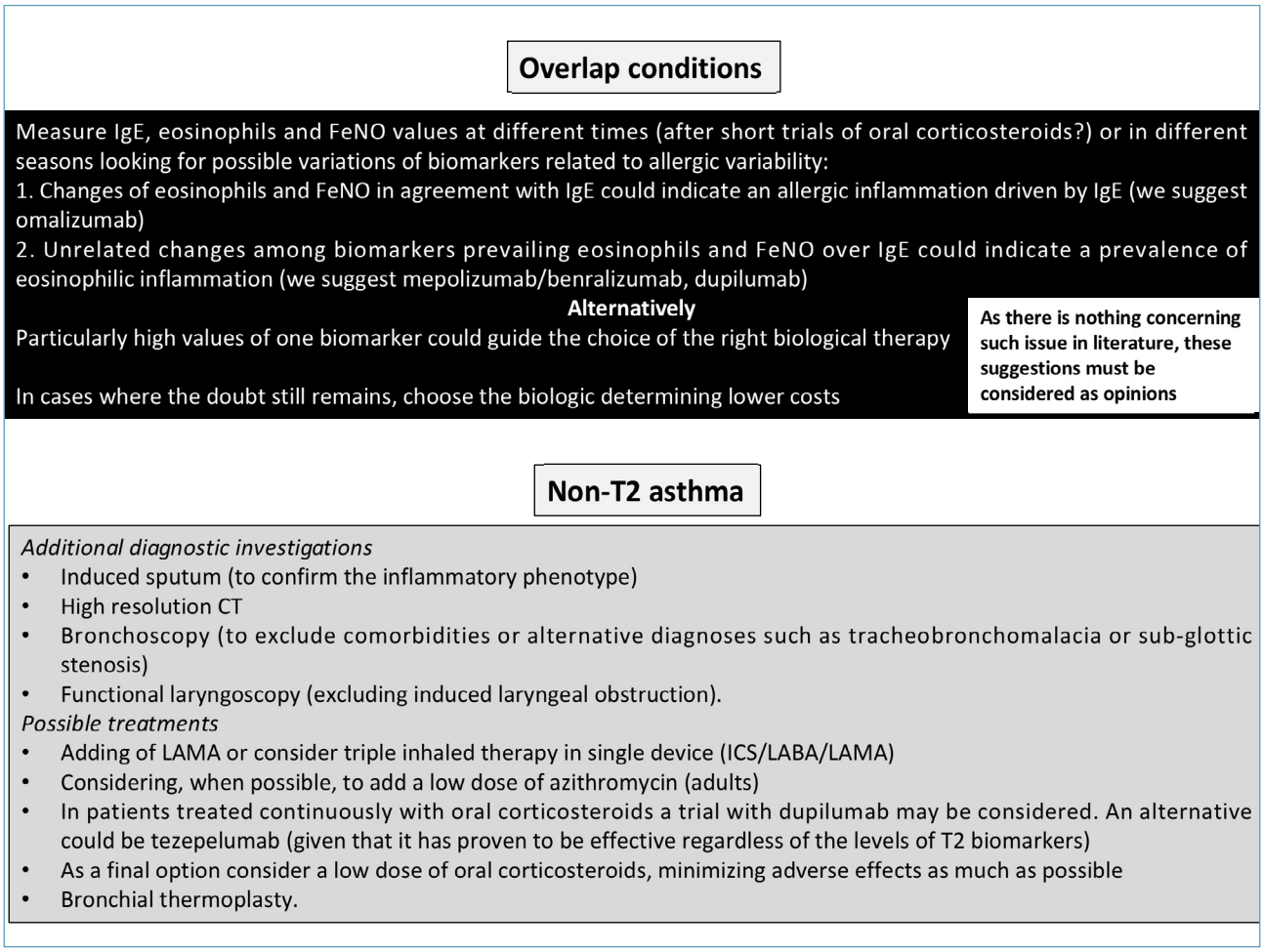

Figure 3. Which biologics to consider in overlap (allergic/eosinophilic) and in non-Th2 asthma.

to higher number of exacerbations, elevated blood eosinophils, nasal polyposis and to an older age asthma onset.

b) Benralizumab: blood eosinophils > 300 cells/μL in the last year especially when associated to higher number of exacerbations, elevated blood eosinophils, nasal polyposis and to an older age asthma onset.

3) The IL-R4α/IL-13Rα inhibitor (dupilumab) is indicated for patients aged ≥12 years with moderate-to-severe asthma who have a TH2-high phenotype (characterized by levels of FeNO > 25 ppb and/or peripheral blood eosinophils > 150/μL and ≤1500/μL), with at least two asthma exacerbations in the past year and/or with dependence on oral corticosteroids for at least 6 months. The presence of elevated eosinophils, elevated FeNO could be predictive of clinical efficacy with dupilumab. The presence of nasal polyposis could also be a marker of efficacy. If hypereosinophilia is found (blood eosinophilis > 1500 μL) consider causes such as eosinophilic granulomatosis with polyangiitis (EPGA).

4) Patients with at least two disease exacerbations during the past year may also be candidates for treatment with anti-TSLP (tezepelumab) especially if associated with the presence of elevated levels of circulating eosinophils and higher FeNO. It must be said that anti-TSLP may be also considered in patients who have no elevated T2 markers (Fig. 3).

In case of lack of clinical/functional response after 6-12 months it is necessary to switch to another biologic, always taking into account what is stated above.

What should be done in case of overlapping conditions?

We know that a subgroup of severe asthmatics is eligible for more than one biologic treatment targeting T2 inflammation. These patients constitute what we call the "overlap" endotype (eosinophilic/allergic). The magnitude of such asthmatics in the total population affected by severe asthma is not well-known. It has been recently observed that in the non-subtype-selected population of moderate-to-severe asthmatics, 78.0% had allergic asthma; of these, 39.5% had eosinophilic asthma and 29.5% had type 2 asthma. Among patients

with eosinophilic asthma (40.6% of total), 75.8% had the allergic phenotype while 41.3% had the type 2. Among individuals with type 2 asthma (28.3% of the total), 81.1% had allergic asthma while 59.2% had eosinophilic asthma [5]. This study shows how frequently we have to face the problem of which biologic has to be chosen. Furthermore, there are no head-to-head comparisons among the various biologics and therefore it remains challenging to decide on the treatment to be selected for a "biologic-naïve" patient with an overlap endotype [6]. Moreover, there are no studies evaluating possible co-administrations of biologics with different mechanisms for individuals presenting the above said endotype.

It must be said that both mepolizumab and benralizumab were effective in reducing exacerbations and improving lung function and asthma control regardless of IgE levels and atopic status [7-9]. A recent real-life study observed also that improvements in FEV_1%, FEF_{25-75}%, exacerbation numbers, blood eosinophil (BE) counts, fractional exhaled nitric oxide (FeNO) (ppb), percentages of patients that stopped/reduced short-acting β2-agonists (SABAs) or oral corticosteroid (OC), were similar after one year of mepolizumab treatment in allergic and non-allergic severe eosinophilic asthmatics [10]. Another real-world study indicated that, in both allergic and non-allergic subjects, benralizumab showed a similar effectiveness in severe eosinophilic asthma, regardless of SPT positivity or negativity [11]. Dupilumab also reduced severe exacerbation rates, improved FEV_1 and asthma control, and suppressed type 2 inflammatory biomarkers in patients with uncontrolled, moderate-to-severe asthma with or without evidence of the allergic type [12]. On the other hand, FeNO ≥ 20 ppb or serum eosinophils ≥ 260 cells/μL may predict good asthma response to anti-IgE treatment [1,14]. Also dupilumab showed a greater efficacy in patients with elevated baseline blood eosinophil counts (≥300 cells/μL) and fractional exhaled nitric oxide [13]. Obviously, a significantly high blood eosinophil number can also predict a better response to anti-IL-5 and anti-IL-5R antibodies [15, 16]. At the moment, there is no clear evidence of the clinical effectiveness of tezepelumab in patients with asthma overlap (allergic/eosinophilic). Although the response was higher in patients exhibiting the highest levels of blood eosinophils and FeNO, as compared to placebo, tezepelumab reduced exacerbations regardless of the baseline blood eosinophil counts, exhaled nitric oxide (FeNO) level and atopic status [17-19].

Therefore, all biologics may be used to treat the overlap asthma phenotype. However, we should choose the biological treatment that could give us the best clinical-functional response on a specific patient. Consequently, it would be necessary to know whether allergic, eosinophilic or type 2 inflammation is prevailing: clinicians may choose omalizumab if an allergic phenotype is predominant, anti-IL-5/anti-IL-5R if an eosinophilic phenotype is prevalent, dupilumab in case of type 2 asthma phenotypes (FeNO particularly elevated) or anti-TSLP in patients with higher blood eosinophils/FeNO or, on the contrary, in subjects with no elevated T2 markers. Such method of choice might lead us to select the most effective biologic. However, we need to identify new biomarkers that can allow us to choose the best biologic in order to obtain the greatest efficacy especially in overlap allergic/eosinofilic asthmatics. Targeted studies aimed at identifying these indicators more precisely are needed, as they would allow us to select the best biologic that may lead to obtaining not only a better clinical response to treatment but also a "complete clinical asthma remission" (the absence of the need for oral corticosteroids, symptoms, exacerbations or attacks, and pulmonary function stability) [20] on a larger number of patients.

Another aspect to consider is the association of severe asthma with bronchiectasis. The co-presence of bronchiectasis (BE) in severe eosinophilic asthma (SEA) is common. In fact, 25-68% of patients with severe asthma have comorbid bronchiectasis [21-25]. Several studies have demonstrated that mepolizumab or benralizumab effectively improved asthma outcomes in patients with SEA + BE [24-27]. In fact, although to a lower extent, all studies have highlighted an improvement in terms of lung function, symptoms, exacerbations, and OC sparing [25-27]. Therefore, in the presence of SEA + BE overlap, antieosinophilic biologics should be considered.

Practical suggestions

Since asthma is mainly allergic, when choosing the biologic, we should try to understand whether the eosinophilic or T2-type inflammation (FeNO) is linked to allergy (dependent on IgE variations) or, vice versa, are not connected with IgE changes (waived by allergy).

Identifying the type of the prevailing inflammation could lead us to choose the most effective biologic.

Therefore, it is always necessary to evaluate whether there is an allergy at the basis of the elevated values of eosinophils and FeNO; in other words, that these biomarkers are not actually secondary to the allergy-induced IgE increases. Consequently, it could be useful to measure the various biomarkers in different periods/seasons, when allergenic stimulation may change, in order to highlight the allergy-induced variations of the eosinophils and/or FeNO correlated with the IgE value modifications thus confirming that the latter stimu-

lates eosinophils/FeNO changes. In this case, we suppose that omalizumab should be prescribed. On the contrary, if there are no relationships between IgE and eosinophils/FeNO, with the latter continuing to be high at various measurements, regardless of IgE or the seasonality of the patient's allergies, other biologics should be chosen (Fig. 2).

Even brief trials with oral corticosteroids might lead to an elucidation of the type of inflammation (allergic/eosinophilic) responsible for severe asthma, although this hypothesis is not supported by any evidence. Persisting high IgE levels, despite the use of corticosteroids, may confirm strong allergenic stimuli that could point towards the choice of omalizumab. On the contrary, a persistence of a high eosinophilia or high FeNO values could indicate a prevalent eosinophilic inflammation or a predominant T2 phenotype that could lead to the choice of other biologics. However, it could happen that continuous therapy with OCs could reduce/normalize biomarkers and consequently mask a type 2 inflammation leading to a failure/erroneous classification of the patient. A suspension/reduction of OC or an analysis of biomarkers measured in the pre-OC period could better guide the choice of the right biologic.

Obviously, if, after 6-12 months of treatment with a biologic, a significant clinical/functional improvement cannot be observed, the biological therapy should be changed. The persistence of elevated blood eosinophils during treatment with omalizumab could be a marker of poor therapeutic efficacy of this biologic [28]. This together with a reduced clinical response must be taken into consideration for a possible replacement of omalizumab with another biologic.

Furthermore, in case the choice is not an easy one, it would be better to focus on a biologic leading to lower costs.

Patients without evidence of type 2 inflammations

Non-T2 asthma is defined as a non-eosinophilic disease without the presence of type 2 inflammatory markers (a count of blood eosinophils lower than 150 cells/μL and FeNO < 25 ppb with no evidence of allergies). Type 1, type-17 inflammations and the neutrophilic form seem to affect approximately 20-30% of all asthmatics [28]. No study identified an effective treatment for these phenotypes [2,29]. In the case of a patient with absence of biomarkers, we must consider further diagnostic investigations such as induced sputum, to confirm the inflammatory phenotype, high resolution CT, bronchoscopy, to exclude comorbidities or alternative diagnoses like tracheobronchomalacia or sub-glottic stenosis. Therefore, it is necessary to perform a functional laryngoscopy with the aim of excluding induced laryngeal obstruction. As regards therapy, the addition of LAMA should be considered if it has not already been added to the therapy. Adding a single-inhaler triple therapy (ICS/LABA/LAMA) could also be considered since it could significantly reduce exacerbations even in patients without evidence of type 2 inflammation biomarkers. We would also need to take into account adding a low dose of azithromycin in adults [30,31]. However, before doing this we to have exclude the presence of a possible mycobacteriosis, to check the QTc segment with an ECG and consider potential antibiotic resistance. As regards therapy with biologics, in case these patients are still undergoing an oral corticosteroid treatment, we should take into account a dupilumab therapy (Fig. 3). This because of the results obtained with dupilumab in a trial dealing with patients affected by glucocorticoid-dependent severe asthma without minimum requirements for blood eosinophils (< 150 cells/mm^3) or FeNO (< 25 ppb) [32]. Among patients with a baseline blood eosinophil count of less than 150 cells/mm^3, add-on therapy with dupilumab significantly reduced the oral glucocorticoid dose of 50% in comparison with placebo, whereas the rate of severe asthma exacerbations was 60% lower than the rate obtained with placebo and the FEV_1 was higher by a least-squares mean value of 0.24 liters in patients with glucocorticoid-dependent severe asthma [32].

We could also use tezepelumab, given that it has proven to be effective regardless of T2 biomarkers levels. Indeed, in the phase 3 randomized controlled NAVIGATOR trial of severe asthmatics with recurrent exacerbations, 1,061 patients were randomized to tezepelumab or placebo. After 52 weeks, tezepelumab reduced the annualized severe asthma attack rate by 56% compared with placebo in the intention-to-treat population. The reduction was observed predominantly in people with type 2 inflammatory asthma, but remained statistically significant in the subgroup with low type [2 17,33]. As a final option, in case of no response to the biologic, we should consider the administration of a minimal effective dose of oral corticosteroids in order to considerably minimize their possible induced adverse effects. Alternatively, we should take into account a bronchial thermoplasty [34] (Fig. 3).

Conclusion

To date, there is a treatment indication with biologic only for severe uncontrolled asthma characterized by frequent exacerbations. Excessive consumption of oral corticosteroid/salbutamol packets could be severe asthma markers. GINA guidelines give us an indication of when a patient needs a biologic therapy. However,

they are not clear about the one to be chosen in overlap cases, where it can be often difficult to select the right biologic to treat severe asthma. Even for non-T2 asthma, there is currently no treatment but only possible options, therefore, for this reason, only a specialist physician with experience in treating severe and poorly controlled asthma can initiate a biologic treatment. In case of therapeutic failure with a biologic, it would be mandatory to choose another one in order to guarantee these patients the best possible control.

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