

Response to monoclonal antibodies in asthma: definitions, potential reasons for failure and therapeutic options for suboptimal response

Running title: Response to monoclonal antibodies in asthma

Pérez de Llano L¹, Cisneros C^{2,3}, Domínguez-Ortega J^{4,5}, Martínez-Moragón E⁶, Olaguibel JM^{5,7,8}, Plaza V^{5,9,10,11}, Quirce S^{4,5}, Dávila I^{12,13,14}

1. Respiratory Service, Hospital Universitario Lucus Augusti. EOXI Lugo, Monforte, Cervo, Spain
2. Respiratory Medicine Department, Hospital La Princesa, Madrid, Spain
3. Instituto de Investigación Sanitaria Princesa (IIS-IP), Madrid, Spain
4. Department of Allergy, La Paz University Hospital, IdiPAZ, Madrid, Spain
5. CIBER de Enfermedades Respiratorias (CIBERES), Madrid, Spain
6. Respiratory Service, Hospital Universitario Dr Peset, Valencia, Spain
7. Allergy Department, Hospital Universitario de Navarra. Pamplona, Spain
8. Instituto de Investigaciones de Navarra (IDISNA), Pamplona, Spain
9. Respiratory Medicine Department, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain
10. Institut de Investigació Biomèdica Sant Pau (IIB Sant Pau), Barcelona, Spain
11. Facultat Medicina, Universitat Autònoma Barcelona, Spain
12. Allergy Service, Hospital Universitario de Salamanca, Spain
13. Instituto de Investigación Biosanitaria de Salamanca (IBSAL), Salamanca, Spain
14. Departamento de Ciencias Biomédicas y del Diagnóstico. Facultad de Medicina, Universidad de Salamanca, Salamanca, Spain

Corresponding:

José M Olaguibel

Hospital Universitario de Navarra

c/ Irunlarrea 3, 31008 Pamplona

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi:

10.18176/jiaci.0857

Abstract

Real-life data reveal that more than half of severe asthma patients treated with monoclonal antibodies (mAbs) do not achieve a complete response. Response to mAbs must be assessed holistically, considering all the clinically meaningful therapeutic goals, not just exacerbations or oral corticosteroid reduction. There are two different ways of measuring the response to mAbs: one, qualitative, classifies patients according to the degree of disease control they have achieved, without explaining how much a given patient improves relative to his baseline (pre-mAb) clinical situation; the other, quantitative, scores the changes occurred after treatment. Both methods are complementary and essential to making clinical decisions on whether to continue treatment. Several potential causes of suboptimal response to mAbs have been described: incorrect identification of the specific T2 pathways, comorbidities that reduce the room for improvement, insufficient dose, autoimmune phenomena, infections, change of the initial inflammatory endotype, and adverse events. Once a suboptimal response has been confirmed, a well-structured and multifaceted assessment of the potential causes of failure should be performed, considering, in particular, the resulting inflammatory process of the airway after mAb therapy and the presence of chronic or recurrent infection. This investigation should guide the decision on the best therapeutic approach. This review aims to help clinicians gain insights into how to measure response to mAbs and proceed in suboptimal response cases.

Key words: Severe asthma. Omalizumab. Mepolizumab. Reslizumab. Benralizumab. Dupilumab. Tezepelumab. Response.

Resumen

Los estudios clínicos en vida real revelan que más de la mitad de los pacientes con asma grave, tratados con anticuerpos monoclonales (mAb), no logran una respuesta completa. La respuesta a los mAbs debe evaluarse de manera integral, considerando todos los objetivos terapéuticos clínicamente significativos y no solo las exacerbaciones o la reducción de corticosteroides orales. Existen dos formas diferentes de medir la respuesta a los mAbs: una, cualitativa, que clasifica a los pacientes según el grado de control de la enfermedad que han logrado, sin explicar cuánto mejora un determinado paciente con respecto a su situación clínica basal (pre-mAb); la otra, cuantitativa, la cual puntúa los cambios ocurridos después del tratamiento. Ambos métodos son complementarios y claramente esenciales a la hora de tomar decisiones clínicas sobre la continuación del tratamiento con estos fármacos biológicos. Se han descrito varias causas posibles de respuesta subóptima a los mAbs que son: la identificación incorrecta de las vías T2 específicas, las comorbilidades que reducen el margen de mejora, una dosis insuficiente, fenómenos autoinmunes, infecciones, cambio del endotipo inflamatorio inicial y la aparición de efectos adversos. Una vez que se ha confirmado una respuesta subóptima, se debe realizar una evaluación bien estructurada y polifacética de estas posibles causas del fracaso, considerando, en particular, el proceso inflamatorio residual de las vías respiratorias tras la terapia con mAb y la presencia de infecciones crónicas o recurrentes. Esta evaluación es la que debe guiar las decisiones sobre el mejor enfoque terapéutico. Esta revisión tiene como objetivo ayudar a los clínicos a obtener un conocimiento más profundo sobre cómo medir la respuesta a los mAbs y cómo proceder con los pacientes que presenten una respuesta subóptima.

Palabras clave: Asma grave. Omalizumab. Mepolizumab. Reslizumab. Benralizumab. Dupilumab. Tezepelumab. Respuesta.

Introduction

Severe asthma (SA) affects approximately 5% to 10% of the asthmatic population [1]. The exact proportion of patients with severe uncontrolled asthma (SUA) remains to be settled. However, it has been estimated that 3.9% of all the patients seen at hospital asthma units in Spain are affected by SUA [2]. A study based on data from the largest real-life SA cohort showed that the proportion of eosinophilic asthma (83.8%) is larger than previously estimated [3], a finding with practical implications since several monoclonal antibodies (mAbs) that target this phenotype have demonstrated effectiveness in improving the clinical condition of SUA patients [4]. However, virtually all pivotal clinical trials supporting the approval of the different mAbs were designed to evaluate their effect on specific outcomes such as exacerbations or systemic corticosteroid use, although real-life demands a different approach: evaluating the response from a holistic perspective that considers all the clinically meaningful therapeutic goals. Since there are no head-to-head studies and many individual factors may influence the response in each patient, this article reviews recent scientific evidence on the response to mAbs in SUA and the management in case of suboptimal response.

1. The concept of response to monoclonal antibodies

Two approaches can be considered when treating a patient: disease remission and response to treatment. The concept of disease remission has been recently introduced in asthma treatment by an expert consensus [5] that distinguished between clinical remission (12 or more months without significant symptoms measured by an appropriate instrument, lung function optimization or stabilization, patient/provider's

agreement on remission, and no use of systemic corticosteroids) and complete remission (clinical remission and objective resolution of inflammation and, if appropriate, negative bronchial hyperresponsiveness). Both could be achieved while on treatment or without it. Prospective studies designed to analyse whether complete remission offers advantages to patients compared to clinical remission are needed.

Concerning treatment response, a task force of experts on SA suggested a traffic light system to classify responses into three categories: super-responders, intermediate responders, and non-responders [6]. Since then, several classifications of response to mAbs have been proposed, all establishing different qualitative response levels (Table 1). There is broad agreement on the need to include four main domains in response definition: severe exacerbations, oral corticosteroids (OCS) use, symptoms, and FEV1. However, there remains a significant discrepancy about the stringency of the criteria required to classify a patient as a "super-responder," "complete responder," or "patient in remission" (Table 1) [7-13]. From a clinician's point of view, it seems reasonable to require the elimination of severe exacerbations, OCS withdrawal, and achieve symptom control and normal pulmonary function to categorize a patient as a "complete responder." However, this is not always feasible: patients may suffer from adrenal insufficiency preventing complete removal of OCS, may have comorbidities (obesity, anxiety...) that negatively impact the results of symptoms' questionnaires, or may have fixed bronchial obstruction due to remodeling phenomena or smoking habit. Therefore, it is a challenging but necessary task for a clinician to establish the maximum potential improvement in a patient. It can be challenging to determine the best possible FEV1 in an asthmatic individual; an oral corticosteroid test can be helpful in some patients, but it is not well-standardized, and mAbs have shown to improve pulmonary function in

steroid-treated patients. With these caveats in mind, our proposal to qualitatively estimate response is summarized in Figure 1.

A qualitative response classification does not explain how much a given patient improves relative to his baseline (pre-mAb) clinical situation. The FEV₁, Exacerbations, Oral corticosteroids, and Symptoms (FEOS) Score (available at feoscore.com) has been developed to quantify response in SUA patients who are being treated with mAbs [14].

This instrument assigns relative weights to four clinically relevant domains (oral corticosteroid dose, severe exacerbations, symptoms, and pulmonary function) available in specialized asthma units and primary care (Figure 2). The range of responses runs from 0 (worsening) to 100 (best possible response). The higher the score, the larger the response. The quantification of achieved improvement depends on baseline disease burden. Patients with poorer asthma control before mAb initiation can obtain higher scores after treatment than those with better pre-treatment clinical conditions: the worse the clinical status before treatment, the greater the room for improvement.

Both methods of assessing response to mAbs -qualitative and quantitative- are complementary and essential to making clinical decisions on whether to continue treatment. Classifying a patient as a complete responder or non-responder is relatively easy. The real challenge for clinicians is whether to maintain or switch a mAb in cases of partial response, which is the situation most frequently found. In this scenario, the FEOS score can be helpful by quantifying how much the patient improved compared with pre-treatment (Figure 3).

Response in terms of symptoms, lung function or corticosteroid reduction can be estimated 4-6 months after starting treatment with a mAb [8]. To assess the effect on

exacerbations, a period of 12 months is recommended. In practical terms, if a patient does not achieve a complete response at 4-6 months, it is not expected that he/she will do so later

2. *Real-life response to monoclonal antibodies in SA*

Data from real-life studies conducted outside the controlled environment of a clinical trial complement the available evidence by reflecting patient diversity and can help us make clinical decisions. They provide results on the effectiveness of an intervention by assessing how well it works when applied in a day-to-day healthcare setting. They often show better results than clinical trials because there is no placebo comparator group (they analyze clinical changes between the baseline situation and that achieved after treatment), and they help us to assess response and long-term safety. Since it is impossible to list all the real-life studies published with the different mAbs, we will only list the most relevant ones.

Omalizumab: A meta-analysis included 86 real-life studies of patients with severe allergic asthma treated with omalizumab for more than 16 weeks. The global treatment efficacy evaluation (GETE) was good/excellent in 77% of patients at 16 weeks and in 82% of patients at 12 months. The mean improvement in FEV₁ was 160, 220, and 250 mL at 16 weeks, six months, and 12 months, respectively. There was a decrease in the Asthma Control Questionnaire (ACQ) score at 16 weeks (-1.14), six months (-1.56), and 12 months (-1.13) after omalizumab treatment. Omalizumab significantly reduced the annualised rate of severe exacerbations (RR: 0.41, 95% CI: 0.30-0.56), the proportion of patients receiving OCS (RR: 0.59, 95% CI: 0.47-0.75) and number of unscheduled medical

visits (mean difference: -2.34, 95% CI: -3.54 to -1.13) at 12 months compared to baseline [15].

Mepolizumab: A prospective multicentre, observational study was designed to determine the 2-year effectiveness and safety of mepolizumab treatment for patients with severe eosinophilic asthma in Greece. The authors found that mepolizumab therapy significantly reduced the annual rate of exacerbations and OCS use and improved asthma control and lung function after two years of treatment. However, only 19.5% of the patients were classified as "super-responders" (no severe exacerbations, no need for OCS, ≥ 6 points increase in Asthma Control Test: ACT, and ≥ 400 mL increase in FEV1) [16].

Reslizumab: A retrospective study included 208 patients who had received at least one dose of reslizumab in Spain. Complete control was achieved in 40% of patients at 52 weeks (no exacerbations, ACT >19 , and no maintenance glucocorticoids). Treatment with reslizumab led to a significant reduction in exacerbations (from a median of 3 to 0), use of OCS (from 54.8% to 18.5%), and significant symptom improvement in the entire treated population (ACT increased from 12 ± 4 to 20 ± 5). Seventy-five percent of patients continued treatment for two years [8].

Benralizumab: Kavanagh et al. found that the response rate with benralizumab in a cohort of 130 patients was 86.2% after 48 weeks of treatment. The response was defined as $>50\%$ reduction in the annualized rate of exacerbations and, for patients requiring maintenance OCS, $>50\%$ reduction in daily glucocorticoid dose. In addition, 43.8% of patients were exacerbation-free during the study, and 51.4% of corticosteroid-dependent patients were able to discontinue treatment [17]. In a real life study with 74 patients included, Poznasky et al. [18] observed sub-optimal response to benralizumab

in 27% of severe glucocorticosteroid-dependent patients with asthma and eosinophilia. The majority of exacerbations were non-eosinophilic, mostly neutrophilic, and associated with airway infections.

Dupilumab: A US real-life study included 72 patients treated with dupilumab for at least 12 months with a median of 13 months. 94.4% experienced a significant improvement in their asthma: ACT increased by 6 points, and FEV1 improved by 181 mL. More importantly, 20 patients (27.8%) who had failed treatment with other mAbs responded to dupilumab. Of the nine patients on systemic corticosteroids, 66.7% discontinued them [19].

Altogether, these real-life data confirm the effectiveness of mAbs in treating SA. Nevertheless, they also reveal that more than half of patients do not achieve a complete response.

3. Potential reasons for failure to achieve a complete response

Several potential causes of suboptimal response to monoclonals have been described

3.1. Incorrect identification of a T2-high endotype (endotype unresponsive to monoclonal antibodies). Heterogeneity of the T2 response (different pathways involved).

Bronchial asthma -especially SA- is a heterogeneous disease in which many of the mechanisms and genes involved are far from being understood, and some are entirely unknown. It seems plausible that the application of omics in the clinic could help us to increase precision in the near future, but in any case, the true endotyping of the patient is still very far from the point of routine clinical care. The T2/non-T2 dichotomy is

somewhat artificial [20,21], and other forms of phenotyping, such as the study of the dynamics of bronchial obstruction, could be much more relevant for the follow-up and management of patients with severe obstructive diseases [22].

In any case, the so-called non-T2 phenotype is a mixed bag that encompasses mechanisms as diverse as neutrophilic asthma as a consequence of infections, pauc-inflammatory asthma, or mast cell infiltrates in the muscle layer and its consequent bronchial hyperreactivity, for which no specific markers are available, and that has been found in both T2 and non-T2 asthma [21]. Even available markers are notably influenced by therapy or environmental factors. The sensitivity of FeNO to inhaled or oral corticosteroids is well known, as well as the marked decrease in its levels induced by the smoking habit, and extreme elevations, often with little clinical expression, are sometimes linked to exposure to aeroallergens, especially those from animals. The relationship between blood and tissue eosinophilia is also far from robust, especially in cases of SA treated with systemic corticosteroids. Finally, the treatment with mAbs can distort these biomarkers, one of the most paradoxical cases being hypereosinophilia induced by dupilumab, as will be discussed later, and normal blood eosinophil counts on anti-IL5 mAbs may be associated with poor asthma control and sputum eosinophilia.

Conversely, raised blood eosinophil counts on anti-IL4R mAb may be associated with good asthma control [23]. At the same time, the use of mAbs is helping us to discover the real implication of the different mechanisms of the disease in a given patient. In this sense, the simultaneous involvement of the IL5 and IL-4/IL-13 pathways is already very well documented [24] (figure 4), and there are recent clinical examples that could justify the need for dual therapy [25].

3.2. *Concomitant diseases*

Concomitant diseases are another possible reason for poor response to mAbs. It is well known that patients with SA associate other diseases or comorbidities in more than 90% of the cases [26].

Although a correct diagnosis and treatment must be carried out in all patients with not controlled SA before starting mAb treatment [27], the control of these comorbidities is not always possible. Therefore, they may continue being the cause of poor asthma control or suboptimal response to mAbs. An adequate approach to concomitant diseases (o comorbidities) in a specialized asthma unit improves the control and clinical results, but not in all cases [28]. Diseases such as obesity, gastroesophageal reflux, anxiety-depression, and even refractory nasal polyps can continue being present in subjects with asthma, producing symptoms and exacerbations even in patients with mAbs. In long-term studies evaluating the response to mAbs [7], partial response to anti-IL5 agents (almost 70%) has been seen in subjects with poorer lung function or uncontrolled sinus disease.

Characteristics of asthma and chronic obstructive pulmonary disease (COPD) often coexist in the same patient. It has been called "asthma-COPD overlap" (ACO). In the last years, there has been a growing interest in characterizing it; however, there is no unanimous agreement regarding its definition and characteristics. GesEPOC-GEMA consensus defines ACO as the existence of persistent chronic airflow limitation (essential to confirm the diagnosis) in a patient who is a smoker or ex-smoker (main risk factor) and presents clinical, biological, or functional characteristics of asthma [29]. ACO represents approximately 10%-40% of COPD and 15%-35% of asthmatic patients [30].

A recent study from the GEMA-DATA register (a Spanish multicentre observational initiative with retrospective and prospective data collection) that evaluates the effectiveness of mAbs in a real-life setting observed that patients with ACO treated for at least 12 months with monoclonal antibodies reach worse outcomes than asthma patients. The percentage of "controlled" patients was significantly lower in ACO patients than only asthmatic ones (16.7% vs. 39.7%). The percentage of patients with ≥ 1 exacerbation and ≥ 1 corticosteroid bursts was significantly higher in ACO patients (70.8% vs. 2.3% and 83.3% vs. 37.5%, respectively). However, there were no significant differences between groups in the asthma control test (ACT) scores [31].

Other clinical trials in COPD patients with eosinophilic phenotype did not show good results in reducing exacerbations with mAb treatment [32,33]. A post hoc study of patients treated with omalizumab reported similar improvements in exacerbation rate and symptom control in patients with ACO or only asthma [34].

3.3. *Insufficient dose*

Insufficient drug levels, either systemically or at the target organ, may be theoretically responsible for the lack of efficacy of mAbs. There have been some concerns, for example, that the monthly dose of mepolizumab 100 mg SC may be too low to reach effective airway drug levels in some SA patients [35]. Blood eosinophils are effectively suppressed, but blood eosinophil progenitors (EoPs), airway eosinophils, and airway EoPs can only be marginally decreased [36]. In parallel, IL-5 is also produced by type 2 innate lymphoid cells (ILC2s) residing in the airways [37]. This locally derived airway IL-5 produced by ILC2s may not be effectively suppressed by low-dose mepolizumab, which may allow for in situ airway eosinophilopoiesis, leading to persistent airway eosinophilia

and poor asthma control despite treatment with this mAb. However, on the other hand, weight-adjusted reslizumab was shown to lead to asthma control and significant airway eosinophil reduction in 10 patients with poor response to mepolizumab [38]. In another scenario, patients with a high body mass index (BMI) appear to have lower omalizumab serum peak concentrations which have been linked with poorer response in patients with chronic spontaneous urticaria [39].

3.4. *Autoimmune phenomena*

In SA, hypereosinophilia has been observed in between 4% and 25% of patients treated with dupilumab, being transient in most cases. However, persistent cases of symptomatic hypereosinophilia consistent with eosinophil granulomatosis with polyangiitis (EGPA), eosinophilic pneumonia, eosinophilic vasculitis, or sudden worsening of asthma symptoms have been described [40]. Cases of EGPA have been reported with all mAbs, including anti-IL-5 and leukotriene receptor antagonists, in publications or the Eudravigilance database. In many cases of EGPA, it appears during systemic steroids tapering or after switching from an anti-IL-5 mAb to dupilumab, suggesting that systemic steroids or the anti-IL-5 were masking the vasculitis. Blockade of the IL-4/IL-13 pathway causes a reduction of eosinophil migration and blood accumulation by inhibiting eotaxin-3, VCAM-1, and TARC without simultaneously inhibiting eosinophilopoiesis; a plausible explanation of this hypereosinophilia which has been recently reviewed by Olaguibel et al. [41].

In severe eosinophilic prednisone-dependent asthmatics, suboptimal treatment response to anti-IL-5 mAbs has also been linked to airway autoimmune phenomena. The presence of sputum anti-eosinophil peroxidase immunoglobulin (Ig) G was a predictor

of suboptimal response, and an increase in sputum C3c (a marker of complement activation) and deposition of C1q-bound/IL-5-bound IgG were observed in sputa of those patients who worsened on therapy, suggesting an underlying autoimmune-mediated mechanism [42].

On the other hand, all biological agents are theoretically immunogenic since they are not endogenous to the treated individual. Anti-drug antibodies (ADA) can potentially neutralize the corresponding drugs, thus reducing treatment efficacy, as has been shown in rheumatoid arthritis [43]. Data from five mepolizumab studies yielded a 1% to 9% incidence of ADA [44]; however, there is no standardization across different ADA analytical detection methods, and information about the impact of ADAs on pharmacokinetic or pharmacodynamic properties is very scarce.

3.5. Infections

Eosinophils help in the defense against both bacteria -through their phagocytic [45], bactericidal [46], and DNA trapping functions [47]- and viruses (expressing surface TLRs that recognize viral nucleic acids and presenting virus antigens to CD8+ T-cells) [48]. It has therefore been speculated that anti-eosinophilic (anti-IL-5) treatments may favor respiratory infections[49]. However, this effect has neither been observed in clinical trials of anti-IL-5 (see section 3.7) nor in other studies carried out in vivo in humans [50]. Moreover, anti-IL-5 has not been associated with an increased risk of COVID-19 [51,52]. Not all asthma exacerbations are caused by an increase in uncontrolled bronchial inflammation due to failed mAb therapy. Respiratory infections are a frequent cause of exacerbations; one study has reported that 80% of infections in patients treated with benralizumab were infectious [18], while the MEX study has shown that exacerbations

were infectious in up to 53% of patients treated with mepolizumab [53]. Infectious exacerbations were characterized by sputum neutrophilia and elevated blood C Reactive Proteine (CRP), while eosinophilic ones showed sputum and blood eosinophilia. However, FeNO measurement has emerged as the preferred method to discriminate between inflammation (≥ 50 ppb) and infection (≤ 20 ppb) [53].

Although it could be argued that patients become infected because inflammation is not well controlled, understanding the infectious (neutrophilic) or inflammatory (eosinophilic) nature of exacerbations potentially has therapeutic implications. The mAb therapy of the patients suffering eosinophilic exacerbations should be switched, while azithromycin (for several months) could be added in patients with infectious exacerbations maintaining the same mAb. Thus, identifying the cause of an exacerbation needs to become part of routine clinical practice. However, further studies are undoubtedly needed to confirm the suitability of this therapeutic strategy based on the exacerbation nature.

3.6. *Inflammatory endotype changes*

The inflammatory endotype of asthma does not usually remain stable over time. In approximately 50% of patients, it varies, mainly due to external factors such as intercurrent respiratory infections or smoking [54,55], and less frequently due to treatment aimed at reducing bronchial or blood eosinophilia [56,57]. The fact that this variability seems more frequent in patients with SA [57] may call into question the indication, for some patients, of treatment with mAbs prescribed based on a specific phenotype.

Given the failure to successfully treat SA with mAb therapy, certain possibilities must be considered and actions undertaken (see section 4). Given that one cause of therapeutic failure is a variable initial inflammatory state, re-evaluation is advisable [58]. Therefore, in addition to re-determining the usual biomarkers, an inflammatory cell count in induced sputum is recommended, as this would provide more precise information on bronchial events. For this purpose, the patient should be referred to a specialized center with an accredited asthma unit.

Of various changes in the pheno-endotype, it is not unusual to find that initial traits or biomarkers of the T2-high phenotype are no longer evident due to the action of, for instance, anti-IL-5 treatment. The patient would continue with uncontrolled asthma and present a concomitant T2-low phenotype, logically not controlled with anti-IL-5 treatment. Therefore, treatment of the T2-low asthma phenotype [58] should be considered, e.g., by including azithromycin [59] or by performing bronchial thermoplasty [60].

3.7. *Adverse events*

In real life, the appearance of adverse events may be another reason patients do not experience clinical improvement with mAb treatment [61]. Adverse events, like myalgia and/or fatigue, may be confused with the worsening of their asthma.

Sometimes symptoms or exacerbations appear in cortico-dependent patients when mAbs are started because of the corticoid dose reduction. It may also happen that when the dose of corticoids is reduced, new symptoms of another disease such as ABPA or EGPA [62,63] appear. That may be because these diseases can be masked by systemic corticosteroid use.

Sometimes, the decrease in the dose of systemic corticosteroids can also cause new symptoms due to adrenal insufficiency. Thus, symptoms can be confused with worsening asthma, especially if it is not adequately monitored by measuring basal cortisol and appropriately replaced with hydrocortisone [64].

3.8 Mucus plugging

It has been shown that mucus plugs occur in at least 1 of 20 lung segments in 58% of subjects with asthma and only 4.5% of controls, persist over time, correlate with FEV1, and contribute to mechanisms of chronic airflow obstruction [65]. In addition, it has been published that controlling eosinophilic bronchial inflammation with anti-T2 therapies improves ventilation defects, measured by inhaled gas magnetic resonance imaging (MRI), in adults with prednisone-dependent asthma[66]. MRI ventilation-defect-percent and mucus score values before therapy were significant variables in a model for ACQ 6 score improvements after benralizumab injection [67]. Altogether, these data suggest that the persistence of mucus plugs might cause a suboptimal response to mAbs. However, it remains to be established whether changes in the mucus score before and after monoclonal antibody (mAb) treatment correlate to response to these drugs and whether the mucus score after mAb treatment differs between complete responders and suboptimal responders.

4. How to proceed in the event of suboptimal response. Switching and combining monoclonal antibodies

As mentioned above, every patient's response to mAbs in SA is not equal. There is a broad spectrum of responses, with patients classified as having an excellent response to

those without any improvement. Since choosing the optimal treatment for each patient is crucial, all recommendations to manage a suboptimal response should be interpreted considering the patient, his/her preferences, personal and clinical circumstances, and expectations. Once a suboptimal response has been assessed, a well-structured and multifaceted approach should be performed, considering all the items which have been aforementioned in this manuscript (for example, the presence of a co-morbidity, such as obesity, that limits symptomatic response to treatment, or the existence of a specific allergy that causes symptoms or exacerbations). Those issues will be critical to better choose between two possible and realistic options: switching to another mAb targeting the same or an alternative mechanism or, on the other hand, considering an add-on therapy with a new mAb.

As there are no head-to-head comparative studies with mAbs in the treatment of asthma, indirect treatment comparisons using different approaches have been performed [68-72]. The main problem of this type of study is the different inclusion and exclusion criteria. Maybe a comparison of efficacy matching blood eosinophil counts could be valid. According to Pavord et al. [73], in patients with a baseline peripheral blood count of 300 eosinophils/ μ L or higher, improvement of exacerbations seems similar with all approved mAbs, whereas dupilumab tended to be associated with more significant improvement in FEV1. However, many questions are still unclear concerning the role of biomarkers in monitoring efficacy and response to mAbs, particularly of peripheral eosinophilia, since a decrease in eosinophil counts in peripheral blood is not always associated with a good clinical response [74]. There is emerging evidence that induced sputum may be more reliable in monitoring response to treatment than peripheral eosinophil counts. Mukherjee et al. demonstrated that in 65 suboptimal

responders to anti-IL-5 therapy (reslizumab or mepolizumab), 78% presented $\geq 3\%$ of eosinophils in sputum samples, while only seven had blood eosinophils upon 400 cells/ μL . The presence of sputum anti-eosinophil peroxidase IgG was a predictor of suboptimal response in these patients [42]. In a very short cohort of 10 prednisone-dependent patients with severe eosinophilic asthma, treatment with standard doses of mepolizumab was prescribed for at least one year, and weight-adjusted intravenous reslizumab was superior in attenuating airway eosinophilia with associated improvement in asthma control [38].

Many recent anti-IL-5 and IL-5R studies have included SA patients previously on omalizumab treatment, showing relevant benefits in clinical outcomes (38.2% in the REDES study with mepolizumab; 35.1% in a Spanish real-life study with reslizumab and 19% in the Italian Registry ANANKE) [8, 75,76]. However, very few publications assess the effectiveness of switching to anti-IL-5/IL-5R in non-responders to omalizumab in real-life conditions. In Italy, 33 patients with SA not controlled by omalizumab experienced benefits by switching to mepolizumab with only slight increases in economic costs [77].

Other studies have also explored the effect of switching to another mAb on residual disease after blocking the IL-5 pathway. The ORBE study, an observational, retrospective, multicentre study in real-life conditions in Spain, characterized the patient profile and evaluated the effectiveness of at least the first three benralizumab doses in 19 severe eosinophilic asthma patients, refractory to anti-IL5 mAbs [78]: 88.9% of the included patients had been previously treated with mepolizumab, and 11.1% with reslizumab, although in some cases, there was a washout period between previous treatment and benralizumab treatment initiation at the investigator's discretion. The

study suggested an improvement in some clinical outcomes (exacerbations and OCS withdrawal). Interestingly, although effective depletion of eosinophils was achieved in most cases (mean 0.8 (2.8) cells/ μ l), 11% of patients were defined as non-responders. In contrast, 14% of patients were considered super-responders, suggesting that peripheral eosinophil counts do not predict nor discriminate the response to treatment. At the same time, some other issues, such as differences in dosing interval, mode of administration, or cellular target, could explain those clinical benefits of switching. Similarly, a more extensive British case series (33 patients) examining the clinical effectiveness of benralizumab in patients previously treated with mepolizumab showed that switching might benefit patients with suboptimal response to mepolizumab, particularly those with unidentified airway infection or an IL-13 dominant type-2 pathway [79]. Furthermore, 70 German patients receiving anti-IL-5 drugs with inadequate response were switched to anti-IL-5R therapy, significantly reduced OCS (from 32 patients to 19), and improved asthma control (ACT from 16 to 19) and FEV1 (from 61% to 68%) [80]. However, there have been published isolated cases of patients who responded to mepolizumab and not to benralizumab, probably explained by the development of anti-drug antibodies to benralizumab (10% of patients in the BORA study) [81]. There is much more scarce evidence regarding switching from other mAbs to dupilumab in real-life settings. A recent Japanese case series (16 patients) showed that dupilumab significantly reduced the number of annual exacerbations from 3.4 ± 4.1 to 1.6 ± 2.7 (/person-year, $p < 0.01$) at the last follow-up regardless of previous mAb use, but tended to worsen by 24 months in patients with prior mAb prescription. Furthermore, BEC transiently increased, suggesting that this issue should be monitored

carefully in patients who previously received anti-IL-5/IL-5r drugs [82]. In contrast, other authors found clinically valuable responses with dupilumab in this setting [83].

Finally, it is recommended to offer a more rapid initiation of the new agent, particularly for more symptomatic patients who experience frequent exacerbations, although there are not sufficient published data regarding the necessity of a washout period. In the ZEPHYR-1 Study, a registry that characterized SEA patients treated with benralizumab, among patients switching from omalizumab, there was a median of 76.5 days between the last omalizumab record and the first benralizumab dose [84]. Among patients switching from mepolizumab, there was a median of 78.0 days. By contrast, the OSMO study showed that most patients with uncontrolled SA on omalizumab achieved a beneficial response, without safety issues, after directly switching to mepolizumab [85]. Patients with SA may require aggressive therapy that targets multiple relevant pathways. The potential benefit of treating these patients with multiple targeted agents should be considered and studied for efficacy, cost-effectiveness, and safety [86]. Combination or dual therapy with mAbs may be considered in severe, refractory, poorly controlled asthma that responds only partially to one of them. Combination therapy may also treat typical comorbidities, such as atopic dermatitis, nasal polyposis, and chronic urticaria. Several single case reports have been published [86-92], including several cases of allergic bronchopulmonary aspergillosis [93,94]. The most common dual therapy reported is omalizumab and mepolizumab [86-93]. Dual therapy with dupilumab and anti-IL-5/R might be an option when anti-IL-5/R treatment alone is insufficient to achieve asthma control or when symptomatic hypereosinophilia occurs under dupilumab treatment [94]. In another scenario, mAbs can be combined to treat SA and an unrelated disease [25, 95].

The most extensive study published with dual mAb therapy reports a total of 25 patients, 15 concomitantly received two mAbs approved for SA (8 were treated for comorbidities), and the other ten patients received one mAb for asthma and another for an unrelated disease [25]. All patients received dual therapy safely, with no reported adverse effects.

In summary, the combination of mAbs may be safe and appropriate for severe persistent asthma and comorbid conditions. The mechanisms of action of the chosen mAbs must be complementary (greater experience with omalizumab + anti-IL-5). If dual therapy is considered appropriate for a selected patient, mAbs must be started sequentially, ensuring both the necessity of the second drug and the tolerability of each agent. Although the safety of combination mAbs for asthma has not been yet established, the data published so far are reassuring [25]. Cost is another important consideration, but dual therapy can be cost-effective by reducing SA exacerbations, hospitalizations, and lost work or school productivity.

A new class of biologicals is currently being developed for treating severe asthma, called anti-alarmins. The best-known alarmins are TSLP (thymic stromal lymphopoietin), interleukin-25, and interleukin-33. These cytokines are released by the epithelial cells of the respiratory tract in response to stimulation with allergens, air pollutants, and viruses, inducing an increase in inflammatory activity at a high point in the inflammatory cascade [96].

Tezepelumab, a human anti-TSLP monoclonal antibody, has just been approved for treating severe asthma in the USA by the FDA. The EMA is already studying the dossier of pivotal trials, so its commercialization in Europe is also expected in a few months.

Tezepelumab, at a dose of 210 mg, administered subcutaneously every four weeks, significantly reduced the annualized rate of asthma exacerbations and improved lung function, disease control, and quality of life in patients with severe asthma regardless of whether or not they have classic markers of the T2 phenotype such as elevated blood eosinophils or FeNO in exhaled air [97]. Tezepelumab also rapidly reduced blood eosinophil counts, FeNO, gradually decreased serum total IgE levels and attenuated airway responsiveness to mannitol [98]. All this with a good safety profile, comparable to placebo. In a mechanistic transbronchial biopsy study, tezepelumab also significantly reduced the number of eosinophils, but not the number of neutrophils, mast cells, or T cells in airway submucosa [99]. All these data point to its use in a wide range of patients with severe asthma regardless of their phenotype, although, for the time being, it has not shown its ability to save steroids, and we do not have real-life studies of its use as a substitute for other drugs, biological or in their combination [96].

Regarding the use of anti-alarmins in combination, a recent randomized, double-blind trial showed that Itepekimab, an anti-IL 33, was as effective as dupilumab in maintaining asthma control, reducing exacerbations, and improving lung function. However, combining both drugs did not produce significantly better results in any of these parameters than monotherapy [100].

As a graphical summary, Figure 5 suggests therapeutic options for patients with a suboptimal response to mAbs.

Conflicts of interest

LPLL reports grants, personal fees and non-financial support from AstraZeneca, personal fees and non-financial support from GSK, grants and personal fees from TEVA, personal fees and non-

financial support from Novartis, personal fees and non-financial support from Chiesi, personal fees from Sanofi, personal fees from Menarini, grants and personal fees from Esteve, personal fees from MSD, personal fees from TECHDOW PHARMA, grants and non-financial support from FAES, personal fees from Leo-Pharma, personal fees from GEBRO and personal fees from GILEAD.

CCS in the last three years received honoraria for speaking at sponsored meetings from AstraZeneca, GSK, Sanofi, Chiesi, Novartis and Mundipharma. Received help assistance to meeting travel from AstraZeneca, Chiesi, Sanofi, Novartis and Gebro. Act as consultant for GSK, Sanofi and Astra. And received funding/grant support for research projects from GSK, Astrazeneca.

JDO has received funding for research, honoraria for consultancy and conferences from AstraZeneca, Chiesi y GSK; honoraria for consultancy and conferences from Bial, Novartis, Sanofi and Teva; and speaker fees from ALK, LETI Pharma and Mundipharma.

EMM reports grants, personal fees and non-financial support from AstraZeneca, personal fees and non-financial support from GSK, personal fees from TEVA, personal fees from Novartis, personal fees and non-financial support from Chiesi, personal fees from Sanofi, personal fees from Menarini, personal fees from MSD, personal fees from GEBRO and personal fees from GILEAD.

JMO in the last three years received honoraria for speaking at sponsored meetings from AstraZeneca, , GSK and Mundi-Pharma. Act as a consultant for AstraZeneca and Eversens. Received funding/grant support for research projects from SANOFI and Eversens

VP in the last three years received honoraria for speaking at sponsored meetings from Astrazeneca, Boehringer-Ingelheim, Chiesi, Gebro, GSK and Sanofi. Received help assistance to meeting travel from Astrazeneca and Chiesi. Act as a consultant for Astrazeneca, GSK, and

Sanofi. And received funding/grant support for research projects from a variety of Government agencies and not-for-profit foundations, as well as AstraZeneca, Chiesi and Menarini.

SQG has been on advisory boards for and has received speaker honoraria from ALK, Allergy Therapeutics, AstraZeneca, Chiesi, GlaxoSmithKline, Leti, Mundipharma, Novartis, Sanofi and Teva.

IDG has received payment for lectures, including service on speaker's bureaus from Allergy Therapeutics, Astra-Zeneca, Chiesi, Diater, GSK, Leti, MSD, Novartis, Roche, Sanofi, Teva; for consultancy from Allergy Therapeutics, ALK-Abello, Astra-Zeneca, GSK, Merck, MSD, Novartis, Sanofi and Thermofisher Diagnostics; and grants for Thermofisher Diagnostics.

Financial sources

The authors declare that no founding was received for the present study.

References

1. Varsano S, Segev D, Shitrit D. Severe and non-severe asthma in the community: a large electronic data base analysis. *Respir Med*. 2017;123:131-9.
2. Quirce S, Plaza V, Picado C, Vennera M, Casafont J. Prevalence of uncontrolled severe persistent asthma in pneumology and allergy hospital units in Spain. *J Investig Allergol Clin Immunol*. 2011;21:466-71.
3. Heaney LG, Perez de Llano L, Al-Ahmad M, Backer V, Busby J, Canonica GW, et al. Eosinophilic and Noneosinophilic Asthma: An Expert Consensus Framework to Characterize Phenotypes in a Global Real-Life Severe Asthma Cohort. *Chest*. 2021;160(3):814-30.
4. Agache I, Beltran J, Akdis C, Akdis M, Canelo-Aybar C, Canonica GW, et al. Efficacy and safety of treatment with biologicals (benralizumab, dupilumab, mepolizumab, omalizumab and reslizumab) for severe eosinophilic asthma. A systematic review for the EAACI Guidelines - recommendations on the use of biologicals in severe asthma. *Allergy*. 2020;75(5):1023-42.
5. Menzies-Gow A, Bafadhel M, Busse WW, Casale TB, Kocks JWH, Pavord ID, et al. An expert consensus framework for asthma remission as a treatment goal. *J Allergy Clin Immunol*. 2020 Mar;145(3):757-65.
6. Buhl R, Humbert M, Bjermer L, Chanez P, Heaney LG, Pavord I, et al. Severe eosinophilic asthma: a roadmap to consensus. *Eur Respir J*. 2017;49: 1700634.
7. Eger K, Kroes JA, Ten Brinke A, Bel EH. Long-Term Therapy Response to Anti-IL-5 Biologics in Severe Asthma-A Real-Life Evaluation. *J Allergy Clin Immunol Pract*. 2021;9(3):1194-200.

8. Pérez de Llano LA, Cosío BG, Lobato Astiárraga I, Soto Campos G, Tejedor Alonso MÁ, Marina Malanda N, et al. Asthma Control in Patients with Severe Eosinophilic Asthma Treated with Reslizumab: Spanish Real-Life Data. *J Asthma Allergy*. 2022;15:79-88. doi: 10.2147/JAA.S340562.
9. Menzies-Gow A, Hoyte FL, Price DB, Cohen D, Barker P, Kreindler J, et al. Clinical Remission in Severe Asthma: A Pooled Post Hoc Analysis of the Patient Journey with Benralizumab. *Adv Ther*. 2022.39(5):2065-84.
10. Álvarez-Gutiérrez FJ, Blanco-Aparicio M, Plaza V, Cisneros C, García-Rivero JL, Padilla A, et al. Consensus Document for Severe Asthma in Adults. 2020 Update. Available at: <https://www.elsevier.es/en-revista-open-respiratory-archives-11-articulo-documento-consenso-asma-grave-adultos--S265966362030014X>. Accessed: 25th March 2022.
11. Wechsler ME, Peters SP, Hill TD, Ariely R, DePietro MR, Driessen MT, et al. Clinical Outcomes and Health-Care Resource Use Associated With Reslizumab Treatment in Adults With Severe Eosinophilic Asthma in Real-World Practice. *Chest*. 2021;159(5):1734-46. doi: 10.1016/j.chest.2020.11.060.
12. Kavanagh JE, Hearn AP, Dhariwal J, d'Ancona G, Douiri A, Roxas C, et al. Real-World Effectiveness of Benralizumab in Severe Eosinophilic Asthma. *Chest*. 2021;159(2):496-506. doi: 10.1016/j.chest.2020.08.2083.
13. Upham JW, Le Lievre C, Jackson DJ, Masoli M, Wechsler ME, Price DB, et al. Defining a Severe Asthma Super-Responder: Findings from a Delphi Process. *J Allergy Clin Immunol Pract*. 2021;9(11):3997-4004.
14. Pérez de Llano L, Dávila I, Martínez-Moragón E, Domínguez-Ortega J, Almonacid C, Colás C, et al. Development of a Tool to Measure the Clinical Response to Biologic

Therapy in Uncontrolled Severe Asthma: The FEV₁, Exacerbations, Oral Corticosteroids, Symptoms Score. *J Allergy Clin Immunol Pract.* 2021;9(7):2725-31. doi: 10.1016/j.jaip.2021.01.033.

15. Bousquet J, Humbert M, Gibson PG, Kostikas K, Jaumont X, Pfister P, et al. Real-World Effectiveness of Omalizumab in Severe Allergic Asthma: A Meta-Analysis of Observational Studies. *J Allergy Clin Immunol Pract.* 2021;9(7):2702-14.

16. Kallieri M, Zervas E, Fouka E, Porpodis K, Mitrova MH, Tzortzaki E, et al. RELight: A two-year REal-Life study of mepolizumab in patients with severe eosinophilic asTHma in Greece: Evaluating the multiple components of response. *Allergy.* 2022 May 20. Online ahead of print.

17. Kavanagh JE, Hearn AP, Dhariwal J, d'Ancona G, Douiri A, Roxas C, et al. Real-World Effectiveness of Benralizumab in Severe Eosinophilic Asthma. *Chest.* 2021;159(2):496-506.

18. Poznanski SM, Mukherjee M, Zhao N, Huang C, Radford K, Ashkar A, et al. Asthma exacerbations on benralizumab are largely non-eosinophilic. *Allergy.* 2021;76:375–9.

19. Nowsheen S, Darveaux JI. Real-world efficacy and safety of dupilumab use in the treatment of asthma. *Ann Allergy Asthma Immunol.* 2021;127(1):147-9.

20. Seys SF, Long MB. The quest for biomarkers in asthma: challenging the T2 versus non-T2 paradigm. *Eur Respir J.* 2022;59(2):2102669. Doi: 10.1183/13993003.02669-2021.

21. Sparreman Mikus M, Kolmert J, Andersson LI, Östling J, Knowles RG, Gámez C, et al. Plasma proteins elevated in severe asthma despite oral steroid use and unrelated to Type-2 inflammation. *Eur Respir J.* 2022;59(2):2100142. doi: 10.1183/13993003.00142-2021.

22. Delgado-Eckert E, James A, Meier-Girard D, Kupczyk M, Andersson LI, Bossios A, et al. Lung function fluctuation patterns unveil asthma and COPD phenotypes unrelated to type 2 inflammation. *J Allergy Clin Immunol.* 2021;148:407-19. DOI: 10.1016/j.jaci.2020.12.652.
23. Koenderman L, Hassani M, Mukherjee M, Nair P. Monitoring eosinophils to guide therapy with biologics in asthma: does the compartment matter? *Allergy.* 2021;76:1294-7.
24. Kaur R, Chupp G. Phenotypes and endotypes of adult asthma: Moving toward precision medicine. *J Allergy Clin Immunol.* 2019;144,1–12.
25. Lommatzsch M, Suhling H, Korn S, Bergmann KC, Schreiber J, Bahmer T, et al. Safety of combining biologics in severe asthma: Asthma-related and unrelated combinations. *Allergy.* 2022. Online ahead of print.
26. Hekking PP, Amelink M, Wener RR, Bouvy ML, Bel EH. Comorbidities in difficult-to-control-asthma. *J Allergy Clin Immunol Pract.* 2018;6:108-13.
27. GEMA 5.0. Spanish Guideline on the Management of Asthma. *J Investig Allergol Clin Immunol.* 2021;31(Supp 1).
28. Tay TR, Lee J, Radhakrishna N, Hore-Lazy F, Stirling R, Hoy R, et al. A structured approach to specialist-referred difficult asthma patients improves control of comorbidities and enhances asthma outcomes. *J Allergy Clin Immunol Pract.* 2017;5:956-64.
29. Plaza V, Alvarez F, Calle M, Casanova C, Cosio BG, Lopez-Vina A, et al. Consensus on the Asthma-COPD Overlap Syndrome (ACOS) Between the Spanish COPD Guidelines (GesEPOC) and the Spanish Guidelines on the Management of Asthma (GEMA). *Arch Bronconeumol.* 2017;53(8):443-9.

30. Mekov E, Nuñez A, Sin SS, Rhee CK, Maselli DJ, Coté A, et al. Update on Asthma-COPD Overlap (ACO): A narrative review. *International Journal of Chronic Obstructive Pulmonary Disease*. 2021;16:1783-99.
31. Pérez de Llano L, Dacal D, Marina N, Plaza V, Gullón JA, Muñoz-Esquerre M, et al. The response to biologics is better in patients with severe asthma than in patients with asthma-COPD overlap syndrome. *Journal of Asthma and Allergy*. 2022;15:363-9.
32. Pavord ID, Chanez P, Criner GJ, Kerstjens KAM, Korn S, Lugogo N, et al. Mepolizumab for eosinophilic chronic obstructive pulmonary disease. *N Engl J Med*. 2017;377:1613-29.
33. Criner GJ, Celli BR, Brightling CE, Agusti A, Papi A, Singh D, et al. Benralizumab for the prevention of COPD exacerbations. *N Engl J Med*. 2019;381:1023-34.
34. Hanania NA, Chipps BE, Griffin NM, Bongin Yoo B, Iqbal A, Casale TB, et al. Omalizumab effectiveness in asthma-COPD overlap: post hoc analysis of PROSPERO. *J Allergy Clin Immunol*. 2019;381:1629-33.
35. Cormier M, Chaboillez S, Lemiere C. Secondary loss of response to mepolizumab in severe eosinophilic asthma. *J Allergy Clin Immunol Pract*. 2020;8:736-8.
36. Sehmi R, Smith SG, Kjarsgaard M, Radford K, Boulet LP, Lemiere C, et al. Role of local eosinophilopoietic processes in the development of airway eosinophilia in prednisone-dependent severe asthma. *Clin Exp Allergy*. 2016;46:793-802.
37. Smith SG, Chen R, Kjarsgaard M, Huang C, Oliveria JP, O'Byrne PM, et al. Increased numbers of activated group 2 innate lymphoid cells in the airways of patients with severe asthma and persistent airway eosinophilia. *J Allergy Clin Immunol*. 2016;137:75-86 e78.

38. Mukherjee M, Aleman Paramo F, Kjarsgaard M, Salter B, Nair G, LaVigne N, et al. Weight-adjusted Intravenous Reslizumab in Severe Asthma with Inadequate Response to Fixed-Dose Subcutaneous Mepolizumab. *Am J Respir Crit Care Med*. 2018;197:38-46.
39. Ghazanfar MN, Bartko EA, Arildsen NS, Poulsen LK, Jensen BM, Enevold C, et al. Omalizumab serum levels predict treatment outcomes in patients with chronic spontaneous urticaria: A three-month prospective study. *Clin Exp Allergy*. 2022;52:715-8.
40. Eger K, Pet L, Weersink EJM, Bel EH. Complications of switching from anti-IL-5 or anti-IL-5R to dupilumab in corticosteroid-dependent severe asthma *J Allergy Clin Immunol Pract*. 2021;9(7):29135.
41. Olaguibel JM, Sastre J, Rodriguez JM, Del Pozo V. Eosinophilia induced by blocking the IL-4/IL-13 pathway. Potential mechanisms and clinical outcomes. *J Investig Allergol Clin Immunol*. 2022: Ahead of print.
42. Mukherjee M, Forero DF, Tran S, Boulay ME, Bertrand M, Bhalla A, et al. Suboptimal treatment response to anti-IL-5 monoclonal antibodies in severe eosinophilic asthmatics with airway autoimmune phenomena. *Eur Respir J*. 2020;56(4):200011.
43. Prado MS, Bendtzen K, Andrade LEC. Biological anti-TNF drugs: immunogenicity underlying treatment failure and adverse events. *Expert Opin Drug Metab Toxicol*. 2017 Sep;13(9):985-95.
44. Ortega HG, Meyer E, Brusselle G, Asano K, Prazma CM, Albers FC, et al. Update on immunogenicity in severe asthma: Experience with mepolizumab. *J Allergy Clin Immunol Pract*. 2019 Sep-Oct;7(7):2469-75.
45. Cline MJ, Hanifin J, Lehrer RI. Phagocytosis by human eosinophils. *Blood*. 1968;32, 922-34.

46. Yazdanbakhsh M, Eckmann CM, Bot AA, Roos D. Bactericidal action of eosinophils from normal human blood. *Infect Immun*. 1986;53:192–8.
47. Mukherjee M, Lacy P, Ueki S. Eosinophil extracellular traps and inflammatory pathologies—Untangling the web! *Front. Immunol*. 2018;9: 2763.
48. Phipps S, Lam CE, Mahalingam S, Newhouse M, Ramirez R, Rosenberg HF, et al. Eosinophils contribute to innate antiviral immunity and promote clearance of respiratory syncytial virus. *Blood*. 2007; 110:1578–86.
49. Samarasinghe AE, Melo RC, Duan S, Le Messurier KS, Liedmann S, Surman SL, et al. Eosinophils Promote Antiviral Immunity in Mice Infected with Influenza A Virus. *J. Immunol*. 2017;198:3214–26.
50. Gleich GJ, Klion AD, Lee JJ, Weller PF. The consequences of not having eosinophils. *Allergy*. 2013;68:829–35.
51. Hanon S, Brusselle G, Deschamphelire M, Louis R, Michils A, Peché R, et al. COVID-19 and biologics in severe asthma: data from the Belgian Severe Asthma Registry. *Eur Respir J*. 2020;56(6):2002857.
52. Rial MJ, Valverde M, del Pozo V, González-Barcala FJ, Martínez-Rivera C, Muñoz X, et al. Clinical characteristics in 545 patients with severe asthma on biological treatment during the COVID-19 outbreak. *J Allergy Clin Immunol Pract*. 2021;9(1):487-89.e1.
53. McDowell PJ, Diver S, Yang F, Borg C, Busby J, Brown V, et al; Medical Research Council: Refractory Asthma Stratification Programme (RASP-UK Consortium). The inflammatory profile of exacerbations in patients with severe refractory eosinophilic asthma receiving mepolizumab (the MEX study): a prospective observational study. *Lancet Respir Med*. 2021 Oct;9(10):1174-84.

54. Schleich FN, Manise M, Sele J, Henket M, Seidel L, Louis R. Distribution of sputum cellular phenotype in a large asthma cohort: predicting factors for eosinophilic vs neutrophilic inflammation. *BMC Pulm Med*. 2013 Feb 26;13:11. doi: 10.1186/1471-2466-13-11.

55. Suárez-Cuartín G, Crespo A, Mateus E, Torrejón M, Giner J, Belda A, et al. Variability in Asthma Inflammatory Phenotype in Induced Sputum. Frequency and Causes. *Arch Bronconeumol*. 2016;52(2):76-81.

56. Zaihra T, Walsh CJ, Ahmed S, Fugère C, Hamid QA, Olivenstein R, et al. Phenotyping of difficult asthma using longitudinal physiological and biomarker measurements reveals significant differences in stability between clusters. *BMC Pulm Med*. 2016;16(1):74.

57. Kupczyk M, Dahlén B, Sterk PJ, Nizankowska-Mogilnicka E, Papi A, Bel EH, et al. BIOAIR investigators. Stability of phenotypes defined by physiological variables and biomarkers in adults with asthma. *Allergy*. 2014;69(9):1198-204.

58. Agache I, Akdis CA, Akdis M, Canonica GW, Casale T, Chivato T, et al. EAACI Biologicals Guidelines-Recommendations for severe asthma. *Allergy*. 2021;76(1):14-44.

59. Gibson PG, Yang IA, Upham JW, Reynolds PN, Hodge S, James AL, et al. Effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma (AMAZES): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2017;390(10095):659-68.

60. Bonta PI, Chanez P, Annema JT, Shah PL, Niven R. Bronchial thermoplasty in severe asthma: best practice recommendations from an expert panel. *Respiration*. 2018;95(5):289-300.

61. Jackson K, Bahna SL. Hypersensitivity and adverse reactions to biologics for asthma and allergic diseases. *Expert Rev Clin Immunol*. 2020;16(3): 311-9.

62. Wechsler ME, Wong DA, Miller MK, Lawrence-Miyasaki L. Churg-strauss syndrome in patients treated with omalizumab. *Chest*. 2009;136:507-18.
63. Kopač P, Rotar Ž, Novljan MP, Škrbat S. Eosinophilic granulomatosis with polyangiitis evolution during severe eosinophilic asthma treatment with benralizumab. *J Allergy Clin Immunol Pract*. 2020;8:2448-49.
64. Suehs CM, Menzies-Gow A, Price D, Bleecker ER, Canonica GW, Gurnell M, et al. Expert Consensus on the Tapering of Oral Corticosteroids for the Treatment of Asthma A Delphi Study. *Am J Respir Crit Care Med*. 2021;203:871–81.
65. Dunican EM, Elicker BM, Gierada DS, Nagle SK, Schiebler ML, Newell JD, et al. Mucus plugs in patients with asthma linked to eosinophilia and airflow obstruction. *J Clin Invest*. 2018;128(3):997-1009.
66. Svenningsen S, Eddy RL, Kjarsgaard M, Parraga G, Nair P. Effects of Anti-T2 Biologic Treatment on Lung Ventilation Evaluated by MRI in Adults with Prednisone-Dependent Asthma. *Chest*. 2020;158(4):1350-60.
67. McIntosh MJ, Kooner HK, Eddy RL, Jeimy S, Liciskai C, Mackenzie CA, et al. Asthma Control, Airway Mucus, and 129Xe MRI Ventilation After a Single Benralizumab Dose. *Chest*. 2022:S0012-3692(22)00424-X]
68. Cockle SM, Stynes G, Gunsoy NB, Parks D, Alfonso-Cristancho R, Wex J, et al. Comparative effectiveness of mepolizumab and omalizumab in severe asthma: an indirect treatment comparison. *Respir Med*. 2017;123:140-8.
69. Iftikhar IH, Schimmel M, Bender W, Swenson C, Amrol D. Comparative efficacy of anti-IL-4, IL-5 and IL-13 drugs for treatment of eosinophilic asthma: a network meta-analysis. *Lung*. 2018;196:517-30.

70. Bourdin A, Husereau D, Molinari N, Golam S, Siddiqui Mohd K, Lindner L, et al. Matching-adjusted indirect comparison of benralizumab versus interleukin-5 inhibitors for the treatment of severe asthma: a systematic review. *Eur Respir J*. 2018;52:1801393.
71. Busse W, Chupp G, Nagase H, Albers FC, Doyle S, Shen Q, et al. Anti-IL-5 treatments in patients with severe asthma by blood eosinophil thresholds: indirect treatment comparison. *J Allergy Clin Immunol*. 2019;143:190-200. e20.
72. Bateman ED, Khan AH, Xu Y, Guyot P, Chao J, Kamat S, et al. Pairwise indirect treatment comparison of dupilumab versus other biologics in patients with uncontrolled persistent asthma. *Respir Med*. 2022;191:105991. doi: 10.1016/j.rmed.2020.105991. Epub 2020 Apr 29. PMID: 35090688.
73. Pavord ID, Hanania NA, Corren J. Controversies in Allergy: Choosing a Biologic for Patients with Severe Asthma. *J Allergy Clin Immunol Pract*. 2022;10(2):410-9.
74. Salter B, Lacy P, Mukherjee M. Biologics in asthma: a molecular perspective to precision medicine. *Front Pharmacol*. 2021;12:793409.
75. Domingo Ribas C, Carrillo Díaz T, Blanco Aparicio M, Martínez Moragón E, Banas Conejero D, Sánchez Herrero MG; REDES Study Group REal world. Effectiveness and Safety of Mepolizumab in a Multicentric Spanish Cohort of Asthma Patients Stratified by Eosinophils: The REDES Study. *Drugs*. 2021;81:1763-74.
76. Menzella F, Bargagli E, Aliani M, Bracciale P, Brussino L, Caiaffa MF, et al. ChAracterization of ItaliaN severe uncontrolled Asthmatic patieNts Key features when receiving Benralizumab in a real-life setting: the observational rEtrospective ANANKE study. *Respir Res*. 2022;23:36.

77. Carpagnano GE, Resta E, Povero M, Pelaia C, D'Amato M, Crimi N, et al. Clinical and economic consequences of switching from omalizumab to mepolizumab in uncontrolled severe eosinophilic asthma. *Sci Rep.* 2021;11:5453.
78. Martínez-Moragón E, García-Moguel I, Nuevo J, Resler G, ORBE study investigators. Real-world study in severe eosinophilic asthma patients, refractory to anti-IL5 biological agents treated with benralizumab in Spain (ORBE study). *BMC Pulm Med.* 2021;21:417.
79. Kavanagh JE, Hearn AP, d'Ancona G, Dhariwal J, Roxas C, Green L, et al. Benralizumab after sub-optimal response to mepolizumab in severe eosinophilic asthma. *Allergy.* 2021;76:1890-3.
80. Drick N, Milger K, Seeliger B, Fuge J, Korn S, Buhl R, et al. Switch from IL-5 to IL-5-Receptor α Antibody Treatment in Severe Eosinophilic Asthma. *J Asthma Allergy.* 2020;13:605-14.
81. Busse WW, Bleecker ER, FitzGerald JM, Ferguson GT, Barker P, Sproule S, et al. Long-term safety and efficacy of benralizumab in patients with severe, uncontrolled asthma: 1-year results from the BORA phase 3 extension trial. *Lancet Respir Med.* 2019;7(1):46-59.
82. Numata T, Araya J, Miyagawa H, Okuda K, Takekoshi D, Hashimoto M, et al. Real-World Effectiveness of Dupilumab for Patients with Severe Asthma: A Retrospective Study. *J Asthma Allergy.* 2022;15:395-405.
83. Mümmeler C, Munker D, Barnikel M, Veit T, Kayser MZ, Welte T, et al. Dupilumab Improves Asthma Control and Lung Function in Patients with Insufficient Outcome During Previous Antibody Therapy. *J Allergy Clin Immunol Pract.* 2021;9(3):1177-85.e4.

84. Chung Y, Katial R, Mu F, Cook EE, Young J, Yang D, et al. Real-world effectiveness of benralizumab: results from the ZEPHYR 1 Study. *Ann Allergy Asthma Immunol*. 2022 Mar 2:S1081-206(22)00131-4.
85. Liu MC, Chipps B, Munoz X, Devouassoux G, Bergna M, Smith SG, et al. Benefit of switching to mepolizumab from omalizumab in severe eosinophilic asthma based on patient characteristics. *Respir Res*. 2021;22:144.
86. Ortega G, Tongchinsub P, Carr T. Combination biologic therapy for severe persistent asthma. *Ann Allergy Asthma Immunol*. 2019;123(3):309-11.
87. Dedaj R, Unsel L. Case study: A Combination of mepolizumab and omalizumab injections for severe asthma. *J Asthma*. 2019;56(5):473-4.
88. Domingo C, Pomares X, Morón A, Sogo A. Dual monoclonal antibody therapy for a severe asthma patient. *Front Pharmacol*. 2020;11:587621.
89. Fox HM, Rotolo SM. Combination anti-IgE and anti-IL5 therapy in a pediatric patient with severe persistent asthma. *J Pediatr Pharmacol Ther*. 2021;26(3):306-10.
90. Volpato M, Nowak S, Bourrain JL, Demoly P, Ahmed E, Bourdin A, et al. The six million dollar man. *ERJ Open Res*. 2021;7:00341-2020.
91. Caskey JR, Kaufman D. Dual biologic therapy in a patient with severe asthma and other allergic disorders. *BMJ Case Rep*. 2021;14(5):e242211.
92. Altman MC, Lenington J, Bronson S, Ayars AG. Combination omalizumab and mepolizumab therapy for refractory allergic bronchopulmonary aspergillosis. *J Allergy Clin Immunol Pract*. 2017;5(4):1137-9.
93. Laorden D, Zamarrón E, Domínguez-Ortega J, Romero D, Quirce S, Álvarez-Sala R. Successful long-term treatment combining omalizumab and anti-IL-5 biologics in allergic

bronchopulmonary aspergillosis. Arch Bronconeumol. 2022 Jan 7:S0300-2896(22)00001-1.

94. Briegel I, Felicio-Briegel A, Mertsch P, Kneidinger N, Haubner F, Milger K. Hypereosinophilia with systemic manifestations under dupilumab and possibility of dual benralizumab and dupilumab therapy in patients with asthma and CRSwNP. J Allergy Clin Immunol Pract. 2021;9(12):4477-9.

95. Mahar PD, Zubrinich CM, Manuelpillai N, Foley P. Combination treatment with monoclonal antibodies: Secukinumab, benralizumab and dupilumab for the combined management of psoriasis and severe asthma. Australas J Dermatol. 2021;62(4):506-8.

96. Brusselle GG, Taichman DB, Koppelman GH. Biologic Therapies for Severe Asthma. New England Journal of Medicine. 2022;386(2):157-71.

97. Menzies-Gow A, Corren J, Bourdin A, Chupp G, Israel E, Wechsler ME, et al. Tezepelumab in Adults and Adolescents with Severe, Uncontrolled Asthma. New England Journal of Medicine. 2021;384(19):1800-9.

98. Sverrild A, Hansen S, Hvidtfeldt M, Clausson C-M, Cozzolino O, Cerps S, et al. The effect of tezepelumab on airway hyperresponsiveness to mannitol in asthma (UPSTREAM). European Respiratory Journal. 2022;59(1):2101296.

99. Diver S, Khalfaoui L, Emson C, Wenzel SE, Menzies-Gow A, Wechsler ME, et al. Effect of tezepelumab on airway inflammatory cells, remodelling, and hyperresponsiveness in patients with moderate-to-severe uncontrolled asthma (CASCADE): a double-blind, randomised, placebo-controlled, phase 2 trial. The Lancet Respiratory Medicine. 2021;9(11):1299-312.

100. Wechsler ME, Ruddy MK, Pavord ID, Israel E, Rabe KF, Ford LB, et al. Efficacy and Safety of Itepekimab in Patients with Moderate-to-Severe Asthma. *New England Journal of Medicine*. 2021;385(18):1656-68.

Accepted Article

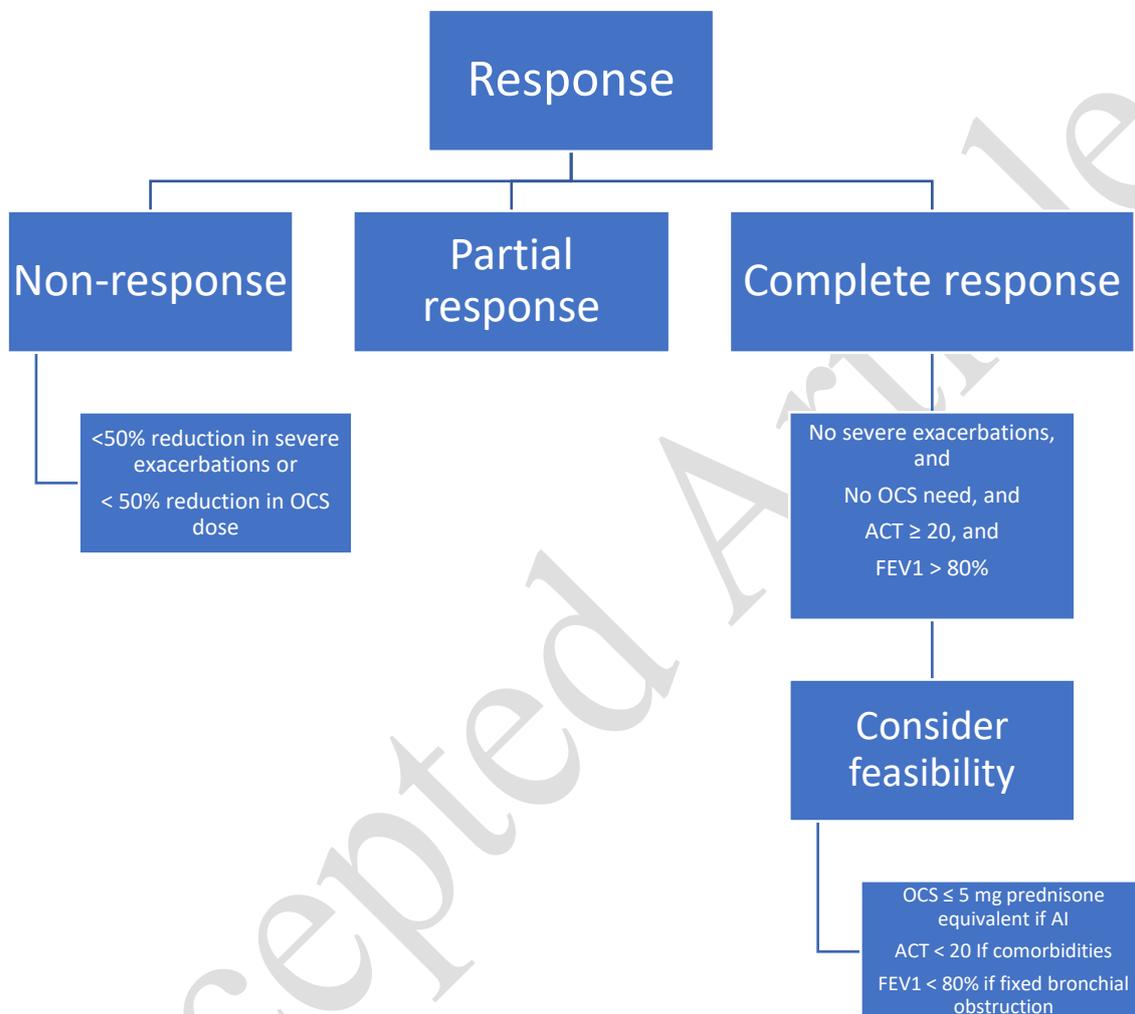
Table 1. Different qualitative categories of response according to published reports.

Publication	Categories of response
Eger et al. [7]	Super-responders: no chronic OCS use, no OCS bursts in the past three months, ACQ <1.5, FEV1 ≥80% predicted, FeNO <50ppb, and complete control of comorbidities (CRS, NP, chronic otitis, allergic rhinoconjunctivitis, and atopic dermatitis).
Pérez de Llano et al. [8]	Complete response: no chronic OCS use, no severe exacerbations, and ACT ≥ 20.
Menzies-Gow et al. [9]	Clinical remission: no OCS use, no severe exacerbations, ACQ-6 ≤0.75, and pre-BD FEV1 increase ≥ 100 mL.
Spanish Respiratory Society [10]	Complete response: no chronic OCS use, no severe exacerbations, ACT ≥ 20, FEV1 ≥ 80%. Asthma control: no chronic OCS use, ≤1 severe exacerbation, ACT ≥ 20, FEV1 < 80%.
Wechsler et al. [11]	Excellent response: 0 CAEs during months 2–7 post-reslizumab initiation. Clinically meaningful response: did not meet criteria for category 1, ≥ 50% reduction in CAEs AND any of the following: · ≥ 50% reduction in average maintenance OCS dose (mg/day) or discontinued maintenance OCS use · ≥ 5% improvement in FEV1 percent predicted · ≥ 3-point improvement in ACT score · ≥ 0.5-point improvement in ACQ score
Kavanagh et al. [12]	Responder: ≥ 50% reduction in severe exacerbations and OCS dose.
Upham et al. [13]	Super-responder: improvement in three or more criteria, at least two of which should be major criteria

	<p>*Major SR criteria: exacerbation elimination, a significant improvement in asthma control (two or more times the minimal clinically important difference), and cessation of maintenance of oral steroids (or weaning to adrenal insufficiency).</p> <p>*Minor SR criteria: 75% exacerbation reduction, having well-controlled asthma, and 500 mL or greater improvement in FEV1.</p>
--	---

Abbreviations: ACT: Asthma control test; ACQ: Asthma control questionnaire; ACQ-6: Asthma control questionnaire of 6 items; CAE: Clinical asthma exacerbation; CRS: Chronic rhinosinusitis; FeNO: Fraction of exhaled nitric oxide; FEV1: Forced expiratory volume in one second; NP: Nasal polyps; OCS: oral corticosteroids.

Figure 1. Proposal to qualitatively classify response to mAbs.



Abbreviations: AI: Adrenal insufficiency; ACT: Asthma control test; FEV1: Forced expiratory volume in one second; OCS: oral corticosteroids.

Figure 2. The FEOS score to quantify response to mAbs.

Criteria	Select	Points
Maintenance systemic corticosteroid dose: change with respect to baseline		
Increase [‡]	<input type="checkbox"/>	0
No change [£]	<input type="checkbox"/>	14
Reduction < 50%	<input type="checkbox"/>	24
Reduction between 50% and 100%	<input type="checkbox"/>	29
Complete withdrawal	<input type="checkbox"/>	38
Severe exacerbations: change with respect to the previous 12 months		
Increase*	<input type="checkbox"/>	0
No change [†]	<input type="checkbox"/>	11
Reduction <50%	<input type="checkbox"/>	22
Reduction between 50% and 100%	<input type="checkbox"/>	27
100% Reduction	<input type="checkbox"/>	38
ACT questionnaire: change with respect to baseline		
ACT total score decrease	<input type="checkbox"/>	0
< 3 points increase	<input type="checkbox"/>	5
≥ 3 points increase, but total score <20	<input type="checkbox"/>	9
ACT ≥ 20	<input type="checkbox"/>	13
Pre-bronchodilator FEV1: change with respect to baseline		
>100 ml decrease	<input type="checkbox"/>	0
No change or <100 ml and <10% increase	<input type="checkbox"/>	5
≥ 100 ml increase and 10%, but < 80%	<input type="checkbox"/>	9
FEV1 ≥80%	<input type="checkbox"/>	11
		Total score

Abbreviations: ACT: Asthma control test; FEV1: Forced expiratory volume in one second;

OCS: oral corticosteroids.

Figure 3. Integration of qualitative and quantitative approaches in assessing the response to biologics in asthma.

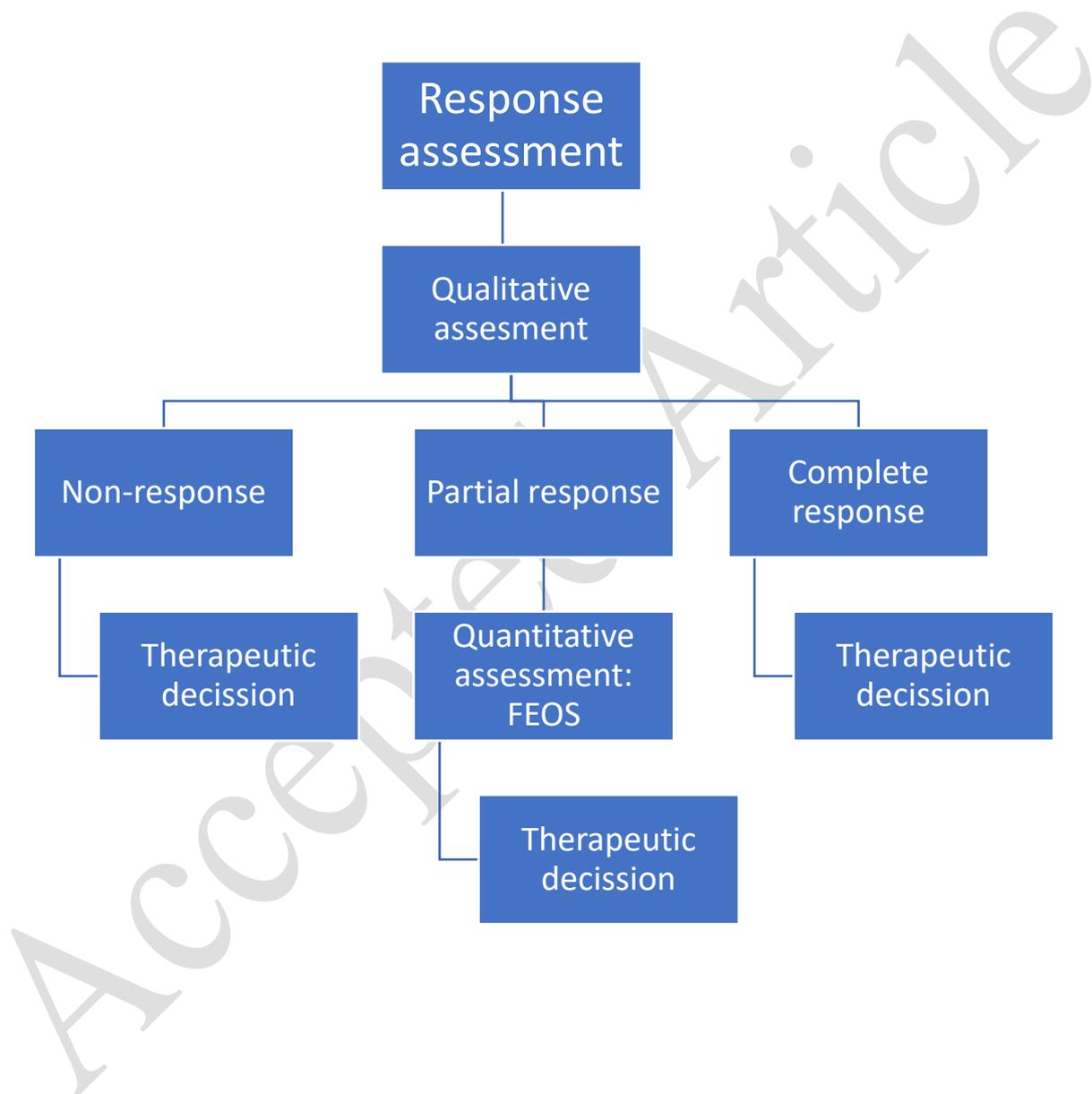


Figure 4. Distribution of T2-high biomarkers in a population of severe asthma patients.

Data (unpublished) from the Spanish Registry GEMA-DATA.

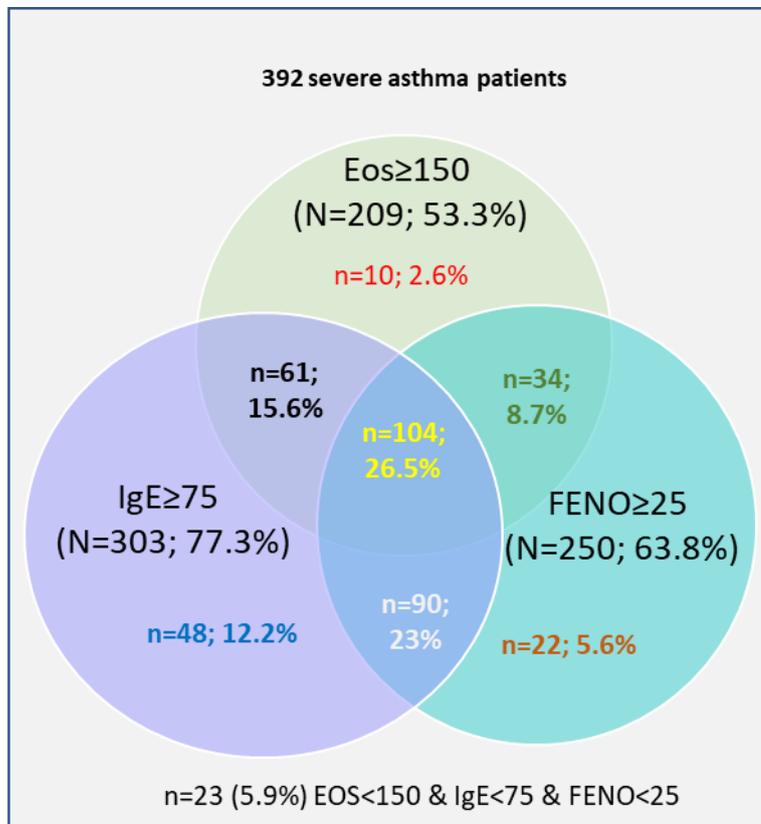
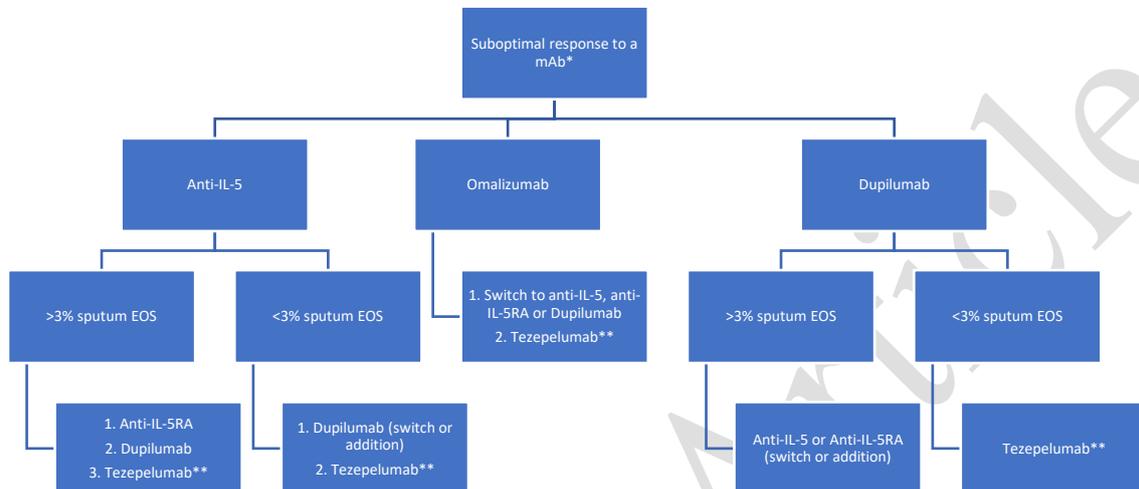


Figure 5. Therapeutic options in cases of suboptimal response to mAbs. No preference order is indicated, except if there is a numbered list.



*In a suboptimal response to a mAb, determine whether it is due to infection or uncontrolled inflammation. In case of infection, consider adding azithromycin or switching to another mAb. In the case of inflammation, the recommendation is to follow the algorithm.

** Tezepelumab is not indicated in patients receiving maintenance OCS. In addition, there is no experience in the failure of other mAbs.