Response to Monoclonal Antibodies in Asthma: Definitions, Potential Reasons for Failure, and Therapeutic Options for Suboptimal Response

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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 only reduction of exacerbations and oral corticosteroids. There are 2 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 the baseline (pre-mAb) clinical situation; the other, quantitative, scores the changes occurring after treatment. Both methods are complementary and essential to making clinical decisions on whether to continue treatment. The various potential causes of suboptimal response to mAbs include incorrect identification of the specific T2 pathways, comorbidities that reduce the room for improvement, insufficient dose, autoimmune phenomena, infections, change in 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, with emphasis on 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. The present review aims to help clinicians gain insights into how to measure response to mAbs and proceed in cases of suboptimal response.

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); y 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 percentage of patients with severe uncontrolled asthma (SUA) remains to be determined. 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 frequency of eosinophilic asthma (83.8%) is larger than previously estimated [3]. This finding has practical implications, since several monoclonal antibodies (mAbs) that target the eosinophilic 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 the effect on specific outcomes, such as exacerbations and systemic corticosteroid use, although daily clinical practice demands a different approach, namely, evaluating the response from a holistic perspective that considers all the clinically meaningful therapeutic goals. Since there are no head-to-head studies and the response in an individual patient may be influenced by many individual factors, this article reviews recent scientific evidence on the response to mAbs in SUA and management in case of suboptimal response.

2. 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 was 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, optimization or stabilization of lung function, 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 are needed to analyze whether complete remission offers patients advantages other than clinical remission.

Concerning response to treatment, a task force of experts on SA suggested a traffic light system to classify responses into 3 categories: super-responders, intermediate responders, and nonresponders [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 4 main domains in the definition of response: severe exacerbations, oral corticosteroid (OCS)

Table 1. 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 previous 3 months, ACQ <1.5, FEV_1 ≥80% predicted, FeNO <50 ppb, 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 prebronchodilation FEV_1 increase ≥100 mL.
Álvarez-Gutiérrez et al [10]	Complete response: no chronic OCS use, no severe exacerbations, ACT ≥20, FEV_1 ≥80%. Asthma control: no chronic OCS use, ≤1 severe exacerbation, ACT ≥20, FEV_1 <80%.
Wechsler et al [11]	Excellent response: 0 CAEs during months 2-7 after initiation of reslizumab. 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/d) or discontinued maintenance OCS use – ≥5% improvement in FEV_1 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 3 or more criteria, at least 2 of which should be major criteria *Major super-responder criteria: elimination of exacerbations, significant improvement in asthma control (2 or more times the minimal clinically important difference), and cessation of maintenance of oral corticosteroids (or weaning to adrenal insufficiency). *Minor super-responder criteria: 75% reduction in exacerbations, well-controlled asthma, and 500 mL or greater improvement in FEV_1.

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; FEV_1, forced expiratory volume in 1 second; NP, nasal polyps; OCS, oral corticosteroid.

use, symptoms, and FEV_1. However, significant discrepancies surround 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, before a patient can be categorized as a complete responder, it seems reasonable to require the elimination of severe exacerbations, withdrawal of OCS, symptom control, and normal pulmonary function. However, this is not always feasible: patients may experience adrenal insufficiency preventing complete removal of OCS, comorbidities (eg, obesity, anxiety) that negatively impact the results of symptom questionnaires, or fixed bronchial obstruction due to remodeling phenomena or smoking. Therefore, it is a challenging but necessary task for a clinician to establish the maximum potential improvement a patient can achieve. It can be challenging to determine the best possible FEV_1 in an asthmatic individual; an OCS challenge test can be helpful in some patients, although this is not well-standardized, and mAbs have been shown to improve pulmonary function in corticosteroid-treated patients. With these caveats in mind, our proposal to qualitatively estimate response is summarized in Figure 1.

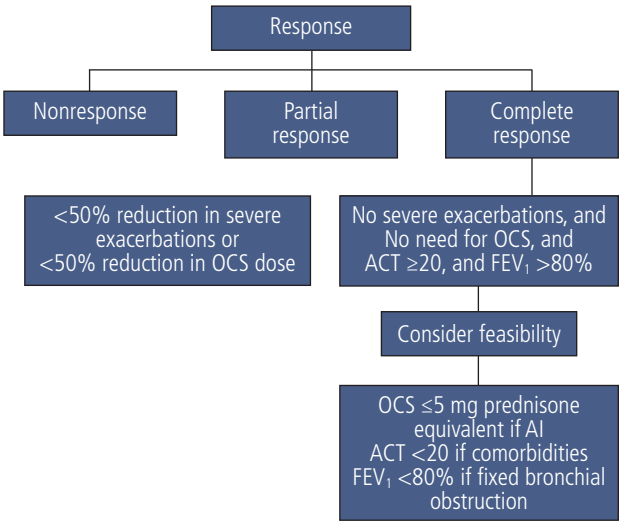

Figure 1. Proposal for qualitative estimation of response to mAbs. AI indicates adrenal insufficiency; ACT, Asthma Control Test; FEV_1, forced expiratory volume in 1 second; OCS, oral corticosteroids.

Classification of a qualitative response does not explain how much a given patient improves relative to his/her baseline (pre-mAb) clinical situation. The FEV_1, Exacerbations, Oral corticosteroids, and Symptoms (FEOS) Score (available at feosscore.com) has been developed to quantify response in SUA patients who are being treated with mAbs [14]. This instrument assigns relative weights to 4 clinically relevant domains (oral

Table 2. Quantifying the Response to mAbs: The FEOS Score

Criteria	Select	Points
Maintenance systemic corticosteroid dose: change with respect to baseline		
Increase[a]		0
No change[b]		14
Reduction <50%		24
Reduction between 50% and 100%		29
Complete withdrawal		38
Severe exacerbations: change with respect to the previous 12 mo		
Increase[c]		0
No change[d]		11
Reduction <50%		22
Reduction between 50% and 100%		27
100% Reduction		38
ACT questionnaire: change with respect to baseline		
ACT total score decrease		0
<3-point increase		5
≥3-point increase, but total score <20		9
ACT ≥ 20		13
Prebronchodilator FEV_1: change with respect to baseline		
>100 mL decrease		0
No change or <100-mL and <10% increase		5
≥100-mL increase and 10%, but <80%		9
FEV_1 ≥80%		11
	Total score	

Abbreviations: ACT, Asthma control test; FEOS, FEV_1, Exacerbations, Oral corticosteroids, and Symptoms; FEV_1, forced expiratory volume in 1 second; OCS, oral corticosteroids.
[a]Or if the patient was not receiving systemic corticosteroids and started the drug.
[b]Or if the patient was not receiving systemic corticosteroids and remained without them.
[c]Or at least 1 if the patient was free of severe exacerbations.
[d]Or if the patient was free of exacerbations and continued to have no severe exacerbations

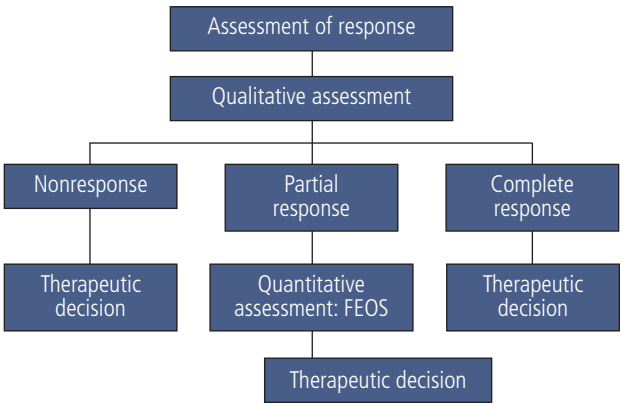

Figure 2. Integration of qualitative and quantitative approaches in assessing the response to biologics in asthma. FEOS indicates FEV_1, Exacerbations, Oral corticosteroids, and Symptoms Score.

corticosteroid dose, severe exacerbations, symptoms, and pulmonary function) and can be used in specialized asthma units and primary care (Table 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 the improvement achieved depends on baseline disease burden. Patients with poorer asthma control before initiation of mAbs can obtain higher scores after treatment than those with better pretreatment clinical conditions: in other words, 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 nonresponder is relatively easy. The real challenge for clinicians is whether to maintain or switch a mAb in cases of partial response, which is the most common situation. In this scenario, the FEOS score can prove to be helpful by quantifying how much the patient improved compared with before treatment (Figure 2).

Response in terms of symptoms, lung function, or reducing the corticosteroid dose 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.

3. Real-life Response to Monoclonal Antibodies in SA

Data from real-life studies conducted outside the controlled environment of a clinical trial complement available evidence by reflecting patient diversity and can facilitate clinical decision making. Real-life studies enable us to assess the effectiveness of an intervention in a day-to-day health care 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). In addition, 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 list only the most relevant ones.

- *Omalizumab:* One 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 FEV_1 was 160, 220, and 250 mL at 16 weeks, 6 months, and 12 months, respectively. There was a decrease in the Asthma Control Questionnaire (ACQ) score at 16 weeks (–1.14), 6 months (–1.56), and 12 months (–1.13) after treatment with omalizumab. Omalizumab significantly reduced the annualized 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 the 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 multicenter, observational study was designed to determine the 2-year effectiveness and safety of mepolizumab for patients with severe eosinophilic asthma in Greece. The authors found that mepolizumab significantly reduced the annual rate of exacerbations and OCS use and improved asthma control and lung function after 2 years of treatment. However, only 19.5% of the patients were classified as super-responders (no severe exacerbations, no need for OCS, ≥6-point increase in the Asthma Control Test [ACT] score, and ≥400 mL increase in FEV_1) [16].
- *Reslizumab:* A retrospective study included 208 patients who had received at least 1 dose of reslizumab in Spain. Complete control was achieved in 40% of patients at 52 weeks (no exacerbations, ACT score >19, and no maintenance corticosteroids). Treatment with reslizumab led to a significant reduction in exacerbations (from a median of 3 to 0) and use of OCS (from 54.8% to 18.5%) and a significant improvement in symptoms in the entire treated population (ACT score increased from 12 [4] to 20 [5]). Seventy-five percent of patients continued treatment for 2 years [8].
- *Benralizumab:* Kavanagh et al [17] 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 a >50% reduction in the annualized rate of exacerbations and, for patients requiring maintenance OCS, a >50% reduction in daily corticosteroid 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. In a real-life study of 74 patients, Poznanski et al [18] observed a suboptimal response to benralizumab in 27% of severe corticosteroid-dependent patients with asthma and eosinophilia. Most exacerbations were noneosinophilic, mostly neutrophilic, and associated with airway infections.
- *Dupilumab:* A real-life study in the USA included 72 patients treated with dupilumab for at least 12 months

(median, 13 months). Of these, 94.4% experienced a significant improvement in their asthma: the ACT score increased by 6 points, and FEV_1 improved by 181 mL. More importantly, 20 patients (27.8%) who had failed treatment with other mAbs responded to dupilumab. Six of the 9 patients receiving systemic corticosteroids (66.7%) discontinued treatment [19].

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

4. Potential Reasons for Failure to Achieve a Complete Response

Several potential causes of suboptimal response to monoclonals have been described.

4.1 Incorrect Identification of a T2-High Endotype (Endotype Not Responding 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 clinical practice could improve precision in the near future; however, true endotyping of the patient is still very far from being used in 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 resulting from infections, pauci-inflammatory asthma,

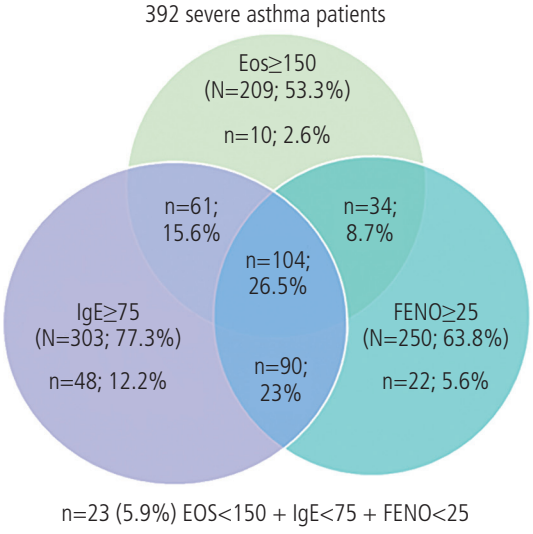

Figure 3. Distribution of T2-high biomarkers in a population of severe asthma patients. Data (unpublished) from the Spanish GEMA-DATA Registry. Eos indicates eosinophils; FENO, fractional exhaled nitric oxide.

and mast cell infiltrates in the muscle layer and the 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 and environmental factors. The sensitivity of FeNO to inhaled and oral corticosteroids is well known, as is the marked decrease in its levels induced by smoking. Moreover, extreme elevations, often with scant 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. This is particularly true in cases of SA treated with systemic corticosteroids. Finally, treatment with mAbs can distort these biomarkers, one of the most paradoxical cases being hypereosinophilia induced by dupilumab (see below), and normal blood eosinophil counts for anti–IL-5 mAbs may be associated with poor asthma control and sputum eosinophilia.

Conversely, raised blood eosinophil counts on anti–IL-4R mAbs may be associated with good asthma control [23]. At the same time, the use of mAbs is helping us to discover the real role of the different mechanisms of the disease in a given patient. In this sense, the simultaneous involvement of the IL-5 and IL-4/IL-13 pathways is already very well documented [24] (Figure 3), and there are recent clinical examples that could justify the need for dual therapy [25].

4.2 Concomitant Diseases

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

Although a correct diagnosis must be made and treatment administered in all patients with uncontrolled SA before starting mAbs [27], control of these comorbidities is not always possible. Therefore, they may continue to be the cause of poor asthma control or suboptimal response to mAbs. An adequate approach to concomitant diseases (or comorbidities) in a specialized asthma unit improves control and clinical results, but not in all cases [28]. Diseases such as obesity, gastroesophageal reflux, anxiety-depression, and even refractory nasal polyps may continue to be present in individuals with asthma, producing symptoms and exacerbations, even in those taking mAbs. In long-term studies evaluating the response to mAbs [7], a partial response to anti–IL-5 agents (almost 70%) has been seen in individuals with poorer lung function or uncontrolled sinus disease.

The characteristics of asthma and chronic obstructive pulmonary disease (COPD) often coexist in the same patient, ie, asthma-COPD overlap (ACO). In recent years, there has been a growing interest in characterizing ACO, although there is no unanimous agreement regarding its definition and characteristics. The GesEPOC-GEMA consensus defines ACO as the presence 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 is detected in approximately 10%-40% of COPD patients and in 15%-35% of asthmatic patients [30].

A recent study from the GEMA-DATA registry (a Spanish multicenter observational initiative with retrospective and prospective data collection) on the effectiveness of mAbs in a real-life setting observed poorer outcomes in patients with ACO treated for at least 12 months than in asthma patients. The percentage of "controlled" patients was significantly lower in ACO patients than in only asthmatic ones (16.7% vs 39.7%). The percentage of patients with ≥1 exacerbation and ≥1 corticosteroid burst 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 ACT scores [31].

Other clinical trials in COPD patients with an 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 those with ACO or only asthma [34].

4.3 Insufficient Dose

Insufficient drug levels, either systemically or in the target organ, may be 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]. While blood eosinophils are effectively suppressed, blood eosinophil progenitors, airway eosinophils, and airway eosinophil progenitors can only be marginally decreased [36]. In parallel, IL-5 is 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 enables in situ airway eosinophilopoiesis, leading to persistent airway eosinophilia and poor asthma control despite treatment with mepolizumab. However, weight-adjusted reslizumab was shown to lead to asthma control and significant airway eosinophil reduction in 10 patients with a poor response to mepolizumab [38]. In another scenario, patients with a high body mass index appear to have lower omalizumab serum peak concentrations, which have been associated with a poorer response in patients with chronic spontaneous urticaria [39].

4.4 Autoimmune Phenomena

In SA, hypereosinophilia has been observed in 4%-25% of patients treated with dupilumab and is transient in most cases. However, persistent cases of symptomatic hypereosinophilia consistent with eosinophilic 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 and in the Eudravigilance database. EGPA often appears during tapering of systemic corticosteroids or after switching from an anti–IL-5 mAb to dupilumab, suggesting that systemic corticosteroids or the anti–IL-5 were masking the vasculitis. Blockade of the IL-4/IL-13 pathway causes a reduction in eosinophil migration and blood accumulation by inhibiting eotaxin-3, VCAM-1, and TARC, without simultaneously inhibiting eosinophilopoiesis; a plausible explanation for this hypereosinophilia was recently reviewed by Olaguibel et al [41].

In severe eosinophilic prednisone-dependent asthmatics, a suboptimal response to anti–IL-5 mAbs has also been linked to airway autoimmune phenomena. The presence of sputum antieosinophil 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 was observed in the sputum of patients whose condition worsened with therapy, thus 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. Antidrug antibodies (ADAs) can potentially neutralize the corresponding drugs, thus reducing treatment efficacy, as shown in rheumatoid arthritis [43]. Data from 5 studies on mepolizumab yielded a 1% to 9% incidence of ADAs [44]; however, analytical methods for detection of ADAs are not standardized, and information about the impact of ADAs on pharmacokinetic or pharmacodynamic properties is very scarce.

4.5 Infections

Eosinophils help in the defense against bacteria (through their phagocytic [45], bactericidal [46], and DNA-trapping functions [47]) and viruses (expressing surface Toll-like receptors that recognize viral nucleic acids and presenting viral antigens to $CD8^+$ T cells) [48]. It has therefore been speculated that antieosinophilic (anti–IL-5) treatments may favor respiratory infections [49]. However, this effect has not been observed in clinical trials with anti–IL-5 agents (see Section 3.7) or in other studies carried out in vivo in humans [50]. Moreover, anti–IL-5 agents have 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 reported that 80% of infections in patients treated with benralizumab were infectious [18], while the MEX study showed 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 protein, while eosinophilic exacerbations were characterized by 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 should be switched in patients with eosinophilic exacerbations, while azithromycin could be added (for several months) in patients with infectious exacerbations maintaining the same mAb. Thus, identifying the cause of an exacerbation needs to become part of routine

clinical practice. Undoubtedly, further studies are needed to confirm the suitability of this therapeutic strategy based on the nature of the exacerbation.

4.6 Inflammatory Endotype Changes

The inflammatory endotype of asthma does not usually remain stable over time. It varies in approximately 50% of patients, mainly owing to external factors such as intercurrent respiratory infections and smoking [54,55] and less frequently 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 mAbs, certain possibilities must be considered, and actions undertaken (see Section 5). Re-evaluation is advisable in cases of therapeutic failure, which is a variable initial inflammatory state [58]. Therefore, in addition to redetermining 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.

As for 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, which, logically, is not controlled with anti–IL-5 treatment. Therefore, physicians should consider treatment of the T2-low asthma phenotype [58] by including azithromycin [59] or by performing bronchial thermoplasty [60].

4.7 Adverse Events

In real life, adverse events may be another reason patients do not experience clinical improvement with mAbs [61]. Adverse events such as myalgia and/or fatigue may be confused with worsening of asthma.

Symptoms or exacerbations may appear in corticosteroid-dependent patients when mAbs are started and a trial of corticosteroids dose reduction is launched. In addition, new symptoms of another disease such as allergic bronchopulmonary aspergillosis (ABPA) or EGPA may appear when the dose of corticosteroids is reduced [62,63], probably 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 this is not adequately monitored by measuring basal cortisol and the drug appropriately replaced with hydrocortisone [64].

4.8 Mucus Plugging

It has been shown that mucus plugs occur in at least 1 of 20 lung segments in 58% of persons with asthma and in only 4.5% of controls. These persist over time, correlate with FEV_1, and contribute to mechanisms of chronic airflow obstruction [65]. Controlling eosinophilic bronchial inflammation with anti-T2 therapies has been shown to improve ventilation defects, as measured by inhaled gas magnetic resonance imaging, in adults with prednisone-dependent asthma [66]. Magnetic resonance imaging ventilation defect percent and mucus score values before therapy were significant variables in a model based on improvements in the ACQ-6 score 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 treatment with mAbs correlate with a response to these drugs and whether the mucus score after treatment with mAbs differs between complete responders and suboptimal responders.

5 How to Proceed in the Event of a Suboptimal Response: Switching and Combining Monoclonal Antibodies

The spectrum of responses to mAbs is broad, ranging from excellent to no improvement. Consequently, not all patients with SA respond equally to this treatment. Since choosing the optimal treatment for each patient is crucial, all recommendations to manage a suboptimal response should be interpreted considering the patient and his/her preferences, personal and clinical circumstances, and expectations. Once a suboptimal response has been assessed, a well-structured and multifaceted approach should be adopted, taking into account all the items addressed above (for example, comorbidity, such as obesity, that limits symptomatic response to treatment or the presence of a specific allergy that causes symptoms or exacerbations). Consideration of these issues will facilitate the choice between 2 possible and realistic options: switching to another mAb targeting the same or an alternative mechanism; or administering add-on therapy with a new mAb.

As there are no head-to-head comparisons of mAbs in the treatment of asthma, indirect comparisons of treatment have been made using different approaches [68-72]. The main problem of this type of study is the different inclusion and exclusion criteria. A comparison of efficacy by matching blood eosinophil counts could prove valid. According to Pavord et al [73], in patients with a baseline peripheral blood eosinophil count of ≥300/μL, exacerbations seem to improve equally with all approved mAbs, whereas dupilumab tended to be associated with a more significant improvement in FEV_1. However, many questions on the role of biomarkers in monitoring efficacy and response to mAbs remain unanswered, particularly in the case 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 for monitoring response to treatment than peripheral eosinophil counts. Mukherjee et al [42] demonstrated that in 65 patients who responded suboptimally to anti–IL-5 therapy (reslizumab or mepolizumab), 78% presented ≥3% of eosinophils in sputum samples, while only 7 had blood eosinophils ≥400/μL. The presence of sputum antieosinophil peroxidase IgG was a predictor of suboptimal response in these patients. In a very small cohort

of 10 prednisone-dependent patients with severe eosinophilic asthma, treatment with standard doses of mepolizumab was prescribed for at least 1 year, and weight-adjusted intravenous reslizumab was superior in attenuating airway eosinophilia with an associated improvement in asthma control [38].

Many recent anti–IL-5/IL-5R studies have included SA patients previously receiving omalizumab and show 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 ANANKE Registry) [8,75,76]. However, very few publications assess the effectiveness of switching to anti–IL-5/IL-5R therapy in nonresponders to omalizumab in real-life conditions. In Italy, 33 patients with SA not controlled by omalizumab benefited from switching to mepolizumab, with only slight increases in economic costs [77].

Other studies have also explored the effect of switching to a different mAb in residual disease after blockade of the IL-5 pathway. The ORBE study, an observational, retrospective, multicenter study performed under real-life conditions in Spain, characterized the patient profile and evaluated the effectiveness of at least the first 3 benralizumab doses in 19 patients with severe eosinophilic asthma refractory to anti–IL-5 mAbs [78]: 88.9% of the patients had previously been treated with mepolizumab and 11.1% with reslizumab, although in some cases, at the investigator's discretion, there was a washout period between the previous treatment and initiation of benralizumab. The results suggested an improvement in specific clinical outcomes (exacerbations and withdrawal of OCS). Interestingly, although effective depletion of eosinophils was achieved in most cases after treatment with benralizumab (mean [SD], 0.8 [2.8]/μL), 11% of patients were defined as nonresponders. In contrast, 14% of patients were considered super-responders, suggesting that peripheral eosinophil counts do not predict or identify response to treatment. At the same time, the clinical benefits of switching could be explained based on other issues, such as differences in dosing interval, mode of administration, and cellular target.

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 a suboptimal response to mepolizumab, particularly those with unidentified airway infection or an IL-13–dominant type-2 pathway [79]. Furthermore, 70 German patients with an inadequate response to anti–IL-5 drugs were switched to anti–IL-5R therapy. OCS use was reduced significantly (from 32 patients to 19), and improvements were recorded for asthma control (ACT score increasing from 16 to 19) and FEV_1 (from 61% to 68%) [80]. However, there have been isolated cases of patients who responded to mepolizumab and not to benralizumab, probably owing to the development of antidrug antibodies to benralizumab (10% of patients in the BORA study) [81]. Evidence regarding the switch from other mAbs to dupilumab in real-life settings is scarcer. 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, $P < .01$) at the last follow-up, regardless of previous mAb use, although outcomes tended to worsen by 24 months in patients with a previous mAb prescription. Furthermore, blood eosinophil counts increased transiently, 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, the new agent should be initiated rapidly, particularly in more symptomatic patients who experience frequent exacerbations, although published data regarding the need for a washout period are insufficient. ZEPHYR-1, a registry study that characterized severe eosinophilic asthma patients treated with benralizumab, showed that among patients switching from omalizumab, there was a median of 76.5 days between the last dose of omalizumab and the first dose of benralizumab [84]. The median was 78.0 days among patients switching from mepolizumab. By contrast, the OSMO study showed that most patients with uncontrolled SA taking omalizumab achieved a beneficial response, without safety issues, after switching directly 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 be used to treat typical comorbidities, such as atopic dermatitis, nasal polyposis, and chronic urticaria. Several single case reports have been published [86-92], including cases of allergic bronchopulmonary aspergillosis [93,94]. The most common combination reported is that of omalizumab and mepolizumab [86-93]. The combination of 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 develops during therapy with dupilumab [94]. In another scenario, mAbs have been combined to treat SA and an unrelated disease [25,95].

The most extensive study published with combination mAb therapy reports on a total of 25 patients, of whom 15 concomitantly received 2 mAbs approved for SA (8 were treated for comorbidities), and the other 10 received one mAb for asthma and another for an unrelated disease [25]. All patients received combination 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 need for the second drug and the tolerability of each agent. Although the safety of combining mAbs for asthma has not yet been established, the data published to date are reassuring [25]. Cost is another important consideration, although combination therapy can prove cost-effective by reducing SA exacerbations, hospitalizations, and lost work or school productivity.

A new class of biologicals, the antialarmins, is currently being developed to treat SA. The best-known alarmins are

thymic stromal lymphopoietin (TSLP), IL-25, and IL-33. These cytokines are released by the epithelial cells of the respiratory tract in response to stimulation by allergens, air pollutants, and viruses, which induce an increase in inflammatory activity at a high point in the inflammatory cascade [96].

Tezepelumab, a human anti-TSLP monoclonal antibody, was recently approved for treating severe asthma in the USA by the United States Food and Drug Administration (FDA). Given that the European Medicines Agency (EMA) is already studying the dossier of pivotal trials, marketing of the drug in Europe is expected to commence in a few months. Administered subcutaneously at a dose of 210 mg every 4 weeks, tezepelumab 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 had classic markers of the T2 phenotype such as elevated blood eosinophils or FeNO in exhaled air [97]. Tezepelumab also rapidly reduced blood eosinophil counts and FeNO and gradually decreased serum total IgE levels and attenuated airway responsiveness to mannitol [98]. All this was achieved with a good safety profile, which was comparable to that of 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 the airway submucosa [99]. These data point to its use in a wide range of patients with severe asthma regardless of their phenotype. However, for the time being, it has not proven able to spare corticosteroids, and we do not have real-life data on its use as a substitute for other approaches, whether biological drugs or combination therapy [96].

Regarding the use of antialarmins in combination, a recent randomized, double-blind trial showed that itepekimab, an anti–IL-33 agent, 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 than monotherapy in any of these parameters [100].

As a graphical summary, Figure 4 suggests therapeutic options for patients with a suboptimal response to mAbs.

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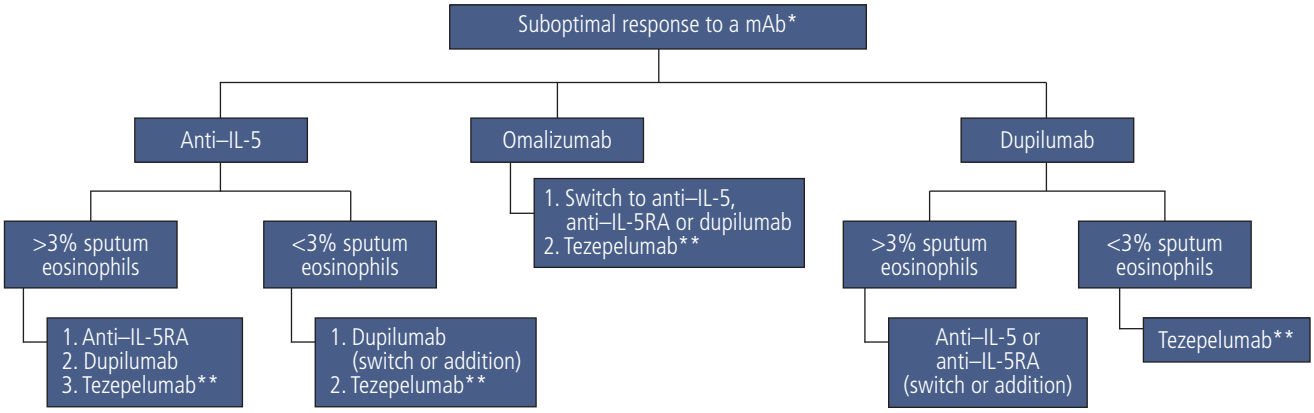
Conflicts of Interest

LPLL reports grants, personal fees, and nonfinancial support from AstraZeneca, personal fees and nonfinancial support from GSK, grants and personal fees from TEVA, personal fees and nonfinancial support from Novartis, personal fees and nonfinancial 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 nonfinancial support from FAES, personal fees from Leo-Pharma, personal fees from GEBRO, and personal fees from GILEAD.

In the last 3 years, CCS has received honoraria for speaking at sponsored meetings from AstraZeneca, GSK, Sanofi, Chiesi, Novartis, and Mundipharma. CCS has also received assistance with travel to meetings from AstraZeneca, Chiesi, Sanofi, Novartis, and Gebro. CCS has acted as a consultant for GSK, Sanofi, and AstraZeneca and received funding/grant support for research projects from GSK and AstraZeneca.

JDO has received funding for research and honoraria for consultancy and conferences from AstraZeneca, Chiesi, and GSK. JDO has also received 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 nonfinancial support from AstraZeneca, personal fees and nonfinancial support from GSK, personal fees from TEVA, personal fees from Novartis, personal fees and nonfinancial support from



*In the case of a suboptimal response to a mAb, determine whether it is due to infection or uncontrolled inflammation. In the 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 with failure of other mAbs.

Figure 4. Therapeutic options in cases of suboptimal response to mAbs. No order of preference is indicated, except if there is a numbered list. mAb indicates monoclonal antibody; OCS, oral corticosteroids.

Chiesi, personal fees from Sanofi, personal fees from Menarini, personal fees from MSD, personal fees from GEBRO, and personal fees from GILEAD.

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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.

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