Severe Asthma and Biologics: Managing Complex Patients

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Abstract

Bronchial asthma is a chronic inflammatory disease of the respiratory tract that varies in terms of clinical presentations (phenotypes) and distinct underlying pathophysiological mechanisms (endotypes). The definition of phenotype/endotype is crucial, given the availability of novel biologic agents for patients who do not respond to conventional therapies. Although patients with type 2 severe asthma benefit significantly from treatment with biologics, nonresponders have been identified. Comorbidities worsen the symptoms of asthma and complicate management of the disease. The assessment and treatment of comorbidities is a crucial step, and appropriate management may improve asthma symptoms and morbidity. Among comorbidities, those with a marked negative impact on control despite appropriate treatment include chronic rhinosinusitis with nasal polyps, obesity, bronchiectasis, and immune deficiency. Although asthma is frequently characterized by increased blood eosinophils that release mediators and cytokines and are involved in inflammation of the airway wall, in patients with very high blood eosinophil levels, we must differentiate between isolated severe eosinophilic asthma and asthma in eosinophilic granulomatosis with polyangiitis. In addition, hypereosinophilia may result from specific biological treatment, as in the case of dupilumab. We outline the clinical features of patients with severe asthma whose disease is complex to manage.

Key words: Biologics. Severe asthma. Dupilumab-induced hypereosinophilia.

Resumen

El asma bronquial es una enfermedad inflamatoria crónica de las vías respiratorias que varía en términos de presentaciones clínicas (fenotipos) y distintos mecanismos fisiopatológicos subyacentes (endotipos). La definición de fenotipo/endotipo es crucial teniendo en cuenta la disponibilidad de nuevos agentes biológicos dedicados a pacientes que no responden a las terapias convencionales. Aunque los pacientes que padecen asma grave tipo 2 se benefician significativamente del tratamiento con productos biológicos, no se han identificado específicamente pacientes que respondan. Las comorbilidades aumentan los síntomas del asma y complican el manejo general de la enfermedad. La evaluación y el tratamiento de las comorbilidades es un paso crucial y su manejo adecuado puede mejorar los síntomas y la morbilidad del asma. Entre las comorbilidades, ciertamente, la rinosinusitis crónica con pólipos nasales, la obesidad, las bronquiectasias y los defectos inmunológicos representan un grupo de condiciones clínicas que impactan negativamente en el control del asma, a pesar de un correcto tratamiento. Aunque el asma se caracteriza frecuentemente por un aumento de los eosinófilos en sangre que liberan mediadores y citocinas que están implicados en los procesos inflamatorios de la pared de las vías respiratorias, en pacientes con niveles muy elevados de eosinófilos en sangre es crucial ser muy cuidadoso en discernir si se trata de un caso aislado de asma eosinofílica grave o un caso de asma eosinofílica en el seno de una granulomatosis eosinofílica con poliangeitis (EGPA). Además, la hipereosinofilia puede ser consecuencia de un tratamiento biológico específico como es el caso del dupilumab. En este trabajo hemos esbozado las características clínicas de aquellos pacientes con asma grave en los que el manejo de la enfermedad puede ser más complejo.

Palabras clave: Biológicos. Asma severa. Hipereosinofilia inducida por dupilumab.

Introduction

Bronchial asthma (BA) is a chronic inflammatory disease of the respiratory tract that varies by clinical presentation (phenotype) and distinct underlying pathophysiological mechanisms (endotype) [1,2]. In terms of endotype, asthma can be categorized as type 2 (eosinophilic) or non–type 2 (noneosinophilic) [3,4]. The type 2 inflammatory process is the result of the involvement of type 2 helper T (T_H2) cells, type 2 innate lymphoid cells, mast cells, eosinophils, and structural cells of the airway walls, all of which produce several cytokines, including interleukin (IL) 4, IL-5, IL-9, and IL-13 [5]. Similarly, type 2 inflammation plays a pivotal role in chronic rhinosinusitis with nasal polyps (CRSwNP), a major comorbidity of severe asthma. The definition of the phenotype/endotype of both asthma and CRSwNP is crucial, given the availability of novel biologic agents for patients who do not respond to conventional therapies [6-8]. Although patients with type 2 severe asthma and/or CRSwNP benefit significantly from treatment with biologics in terms of clinical improvement and corticosteroid-sparing effect, nonresponders have been identified [9,10]. In addition, although the safety profile of biologics used in asthmatic patients has been clearly confirmed in long-term studies, some treated patients may experience adverse infusion reactions, increased risk of infection, and paradoxical hypereosinophilia [11]. In this paper, we outline the clinical features of patients with severe asthma whose management is more complex.

Complexity of Management of Severe Asthma

Asthma Associated With CRSwNP

Comorbidities increase the symptoms of asthma and complicate disease management. In the evaluation of patients with asthma, assessment and treatment of comorbidities is a crucial step, and appropriate management may improve symptoms and morbidity. CRSwNP has been reported to be a frequent comorbidity of severe asthma [12]. Symptoms such as loss of smell, nasal congestion and/or obstruction, and rhinorrhea have a significant impact on social and health-related quality of life. In fact, the presence of CRSwNP in asthmatic patients is associated with worsening of asthma outcomes and, more specifically, with an increased risk of exacerbations and need for oral corticosteroids (OCS) [13-15]. In one large study population, the multivariable analysis demonstrated that CRS remained significantly associated with frequency of exacerbation, even after adjustment for age, sex, adherence, body mass index, blood eosinophil count (BEC), and IgE levels [16]. Moreover, CRSwNP exerts a more pronounced effect on asthma symptoms in patients with more severe asthma at baseline [17]. Patients with CRSwNP generally have a high symptom burden, with a clinical history of repeated sinus surgery. In addition, it has been demonstrated that OCS are most consistently recommended as acute oral therapy for patients with moderate-to-severe CRSwNP [18,19]. Of note, asthma and CRSwNP are often associated with aspirin/nonsteroidal anti-inflammatory drug exacerbated respiratory disease [20]. There is a clear need for characterization of CRSwNP, which is typically characterized by type 2 inflammation in about 80% of cases, whereas CRS without NP is often characterized by type 1 or type 3 inflammation [21-23]. In a recent systematic review, the complexity of the disease was illustrated by the identification of 150 genetic variants in 99 genes involved in the pathogenesis of NP [24].

Asthma and CRS can share type 2 inflammatory pathways and similar histological alterations. In fact, in CRSwNP, in addition to diffuse tissue eosinophilia and eosinophilic aggregates, the disease is characterized by basement membrane thickening, subepithelial edema and fibrosis, and goblet cell hyperplasia with mucin hypersecretion, which comprise a process similar to airway remodeling in asthma [25]. Of note, biologics administered in severe asthma have a more marked clinical effect in the subgroup of patients with concomitant CRSwNP. Mepolizumab has been shown to reduce the annual exacerbation rate in patients with severe eosinophilic asthma compared with placebo regardless of NP status, albeit to a greater degree in those with NP (80%) than in those without NP (49%), as demonstrated in the meta-analysis of the MUSCA and MENSA studies, which included 936 patients, 166 of whom (18%) presented with NP at baseline [26]. The ANANKE study supports the previous CALIMA and SIROCCO responder analyses, where CRSwNP was identified as a clinical characteristic of enhanced response to benralizumab [27,28]. Both dupilumab and omalizumab have demonstrated efficacy in the treatment of CRSwNP [7,8,29,30], although no data are available with respect to an increased impact of baseline NP on their efficacy in type 2 asthma.

In clinical practice, patients often achieve a good clinical response with respect to asthma symptoms, but not for those of CRS, as reported in a small case series [31]. Moreover, in individual patients, the biological mechanisms underpinning asthma and CRS may only be partially similar, not only in terms of severity, but also in terms of the cellular and molecular actors driving the inflammatory process.

Asthma in Obese Patients

Obesity-associated asthma is a difficult-to-treat, poorly controlled phenotype, with poor outcomes in terms of morbidity and mortality. In fact, it has been shown that obesity is linked to frequent exacerbations and increased use of OCS [32-35]. In addition to suboptimal control of asthma, obese patients experience significantly higher acute severity, including the need for mechanical ventilation and longer hospital stay than nonobese patients [33]. In asthma, obesity seems to affect expression of the type 2 biomarkers used mainly for defining the eligibility criteria for biologics. Indeed, it has been demonstrated that increased body mass index is associated with reduced FeNO, independent of the corticosteroid dose, with important implications for tailoring treatment in the era of precision medicine [35]. From a pathogenic perspective, adipocytes produce a large panel of factors, including immune-modulating molecules, which promote a T_H2 response, mast cell degranulation, and airway remodeling [36]. Adiponectin is a major adipocyte-derived factor owing to its multiple biological functions, and low serum adiponectin levels have been reported to be play a key role in obese asthma patients,

particularly in women [37]. In fact, adiponectin has a series of functions. First, it inhibits apoptosis of epithelial cells after cell injury and promotes repair and proliferation of bronchial basal cells. Second, it reduces the tumor necrosis factor (TNF) α–induced secretion of chemokines by monocytes/macrophages (CCL2) and mastocytes (CXCL1). Third, overexpression of adiponectin has been shown to counteract the action of IL-13 in an ovalbumin-induced mouse model of airway inflammation. Fourth, overexpression of adiponectin reduces mucus secretion by inhibiting the expression of omentin and MUC5AC. Fifth, it inhibits the IL-33–stimulated NF-κB pathway and production of IL-13 by type 2 innate lymphoid cells. Sixth, it reduces eotaxin-promoted eosinophil chemotaxis and adhesion. Finally, it increases the secretion of IL-10 in peripheral T regulatory (Treg) cells, particularly in a T_H2 milieu [38-46].

The non–type 2 pattern of inflammation is increasingly important in obese asthmatic patients. In fact, the major obesity-associated asthma phenotype is characterized as late-onset, severe, and difficult-to-treat type 2–low inflammation, although eosinophilic inflammation is sometimes present in this form of asthma [47]. Interferon-related signaling pathways are overrepresented in obese asthmatics, compared with both healthy controls and nonobese asthmatics. These pathways are induced by various interferon-inducing factors such as leptin hormone [48,49]. In obese asthmatics, the severity and frequent exacerbation of asthma episodes might be further influenced by increased susceptibility to respiratory viral infections [50].

Obesity can also negatively impact the clinical effects of biologics because body weight is a clinically relevant covariant that may modify the pharmacokinetics of these drugs [51,52]. Pharmacokinetics covers 4 basic processes, namely, absorption, distribution, metabolism, and excretion. These nonspecific general processes affect the amount of active drug that reaches the target of action intact and, therefore, influences its activity. Unlike conventional drugs, the monoclonal antibodies (mAbs) used in asthma can be administered exclusively via the intravenous route or the subcutaneous route. Subcutaneous absorption can be reduced by presystemic elimination owing to the activity of soluble peptidases, endothelial endocytosis and subsequent lysosomal degradation, and interaction with the phagocytic immune cells in the lymph nodes [53].

After distribution in tissue, mAbs are eliminated mainly via catabolism following endocytosis and transport to the lysosome. A protective mechanism for IgG molecules, including mAbs, consists in the recycling of the molecules through the interaction with FcRn localized in the endosomes. Therefore, treatment of obese patients with severe asthma must be accompanied by a dietary strategy to reduce body weight and limit the impact of obesity on the aforementioned aspects.

For mAbs administered subcutaneously, as in the case of those used in severe asthma, absorption into the systemic circulation first requires convective transport of the mAb through the interstitial space into the lymphatic system, which may prove more difficult in obese patients [53]. Very few data on this topic are available. Even though body weight seems to explain the between-patient variability in the pharmacokinetics of dupilumab in asthma, no dose adjustment is recommended with regard to body weight, given the limited difference in efficacy and safety across the weight categories [54]. Similarly, body weight, as well as high-titer antidrug antibodies (see below), was identified as a relevant covariate influencing the pharmacokinetics of benralizumab, thus highlighting the need for a more rational selection of dosage regimens in asthma patients [55].

Therefore, correct phenotyping of the obese asthma patient should enable us to develop a rational therapeutic plan, comprising both a pharmacological approach and specific antiobesity therapies, including bariatric surgery [56].

Oral Corticosteroid–Dependent Patients

Inhaled corticosteroids constitute the first line of therapy for patients with persistent asthma because they inhibit almost every aspect of the airway inflammatory process [57]. Inhaled corticosteroids are effective in most patients with asthma, irrespective of age or disease severity. They not only control asthma symptoms and improve lung function, but also prevent exacerbations and may reduce asthma-associated mortality and the irreversible changes in airway function that affect some patients [58]. However, a proportion of asthmatic patients become dependent on OCS, ie, they are forced to use frequent courses of OCS to treat exacerbations or a daily dose to control symptoms, despite proper inhalation therapy [59]. Asthma patients with type 2–low inflammation are characterized by a low response to OCS. Most patients with persistent eosinophilic inflammation, on the other hand, tend to respond well to OCS [60]. Although OCS-dependent patients with severe asthma account for a small proportion of the general asthmatic population, they generate considerable health care costs, with a notable increase in morbidity, hospitalization, mortality, and adverse effects [61]. Several molecular mechanisms contribute to the resistance of cells to the anti-inflammatory effects of corticosteroids in severe asthma, with mechanisms differing between patients [62]. Resistance to corticosteroids may result from defects at different levels in glucocorticoid signaling, such as reduced glucocorticoid receptor expression, reduced binding of glucocorticoids to their receptor, impaired nuclear translocation, or altered cofactor activity [63,64]. From a clinical point of view, it is important to consider that OCS may interfere with the correct detection of available and validated biomarkers, such as FeNO and blood eosinophils. For patients with OCS-dependent asthma who are more likely to have a type 2 phenotype, it is advisable to perform repeated assessments using a supervised OCS-tapering approach to avoid the risk of exacerbation.

OCS-sparing potential has been demonstrated by 3 biologics approved for treatment of severe asthma, namely, benralizumab, dupilumab, and mepolizumab, although the lack of head-to-head trials with these treatments prevents us from drawing conclusions on the optimal choice in OCS-dependent patients. Matching-adjusted indirect comparison, which enables comparison of treatments across clinical trials, demonstrated that, after adjustment for differences in baseline population characteristics, similar findings were recorded for mepolizumab, dupilumab, and benralizumab in terms of reductions in OCS dosage, percentage of patients discontinuing OCS, and annual asthma exacerbation rates [65].

Hypereosinophilic/EGPA Patients

The normal adult range of eosinophils in blood is 30-330/μL (median, 120/μL in men and 100/μL in women) [66]. The degree of eosinophilia is defined using the absolute number of circulating eosinophils in blood. Eosinophilia and hypereosinophilia are defined as a count greater than 500 and 1500/μL, respectively [67]. Asthma is frequently characterized by an increase in BEC that leads to release of several mediators and cytokines that are involved in pathological tissue processes such as epithelial damage, smooth muscle hypertrophy, and impaired tissue repair, thus promoting chronic airway remodeling and airflow obstruction [68-70]. A retrospective analysis found that patients with systemic eosinophilia ≥400/μL, especially when associated with airway eosinophilia (≥3%), were more likely to have worse lung function, symptoms, and impairment of health-related quality of life [71]. A large cohort study showed that the exacerbation rate increases progressively with ascending categories of BEC when compared with the reference category of ≤200/μL [72]. High BEC is typical of eosinophilic granulomatosis with polyangiitis (EGPA), a necrotizing systemic eosinophilic vasculitis that has classically been associated with severe asthma and nasal polyps [73]. Given that EGPA could represent the progression of an eosinophilic form of severe asthma in patients with high/very high BEC (although no specific BEC cut-off has been defined), care should be exercised when differentiating between isolated severe eosinophilic asthma and asthma in EGPA [74]. Of note, asthma, CRS, and blood eosinophilia could anticipate overt vasculitis for years [75]. It is also important to remember that BEC at baseline may influence the choice of biologic for asthma treatment, not only in terms of response, but also because the anti-IL-4Rα chain mAb dupilumab can induce a further increase in BEC, at least in a proportion of patients (see below) [76]. In fact, dupilumab, which is now used in several clinical conditions, may be associated with an increase in BEC, as shown by the phase 3 studies in which 4% to 14% of patients developed predominantly asymptomatic blood eosinophilia [77]. Most reported data reveal a rapid increase and a spontaneous decrease in BEC regardless of dupilumab maintenance, although hypereosinophilia persisted in a proportion of patients [78]. Some patients from asthma trials developed severe eosinophil-related manifestations such as hypereosinophilic syndrome and chronic eosinophilic pneumonia [79-81]. In contrast with asthma patients, no clinical impact of hypereosinophilia was reported in patients with atopic dermatitis (AD) [82]. While data are missing from trials [83-86], one real-life study reported blood hypereosinophilia in about 15% of AD patients treated with dupilumab [87]. The differences in clinical consequences between asthma and AD lead us to ask why this occurs. The mechanisms underlying hypereosinophilia in therapy with dupilumab remain unclear. The increase in BEC was hypothesized to be due to the inhibition of IL-4/IL-13 signaling. Both cytokines induce expression of adhesion molecules on endothelial cells, a crucial step in the migration of eosinophils in tissue [88-91]. By blocking the biological effects of these cytokines, dupilumab downregulates expression of the adhesion molecules. Therefore, eosinophils can move from bone marrow to blood, as this process is mediated by IL-5, but cannot move from blood to tissue, and while this may be a possible explanation, additional mechanisms are likely to be involved, as suggested by the fact that not all patients develop eosinophilia and the increase in BEC is usually nonpersistent. Finally, interference with the adhesion of eosinophils to endothelial cells should prevent the tissue infiltration that may instead complicate some cases of dupilumab-induced hypereosinophilia [77,80]. Experimental models may provide explanations. In fact, while IL-4 antibody is able to reduce eosinophilic infiltration in the lung, IL-13–/– mice treated with ovalbumin and anti–IL-4 neutralizing antibody have more eosinophilic lung infiltrates than wild-type mice owing to the low levels of IL-13 that may result in an increase in NF-κβ, which in turn increases synthesis of IL-5, much in the same way as in nonallergic asthma patients with high levels of IL-5 and eosinophils despite low IL-4 levels [92,93].

From a clinical point of view, patients with higher baseline BEC should be monitored after initiation of dupilumab. More careful evaluation is recommended in patients who switched from an anti–IL-5 or anti–IL-5R mAb to dupilumab. In fact, the disappearance of IL-5 axis blockade can favor unexpected expansion of the eosinophil population, no matter how much it is inhibited by the previous biologic. Similar attention must be given to OCS-dependent asthma/CRSwNP patients, in whom the rapid reduction of the corticosteroid dose, made possible by dupilumab, can be complicated by the increase in BEC.

The Figure provides a proposal for the clinical management of dupilumab.

Patients With Asthma, Antibody Deficiency, and Bronchiectasis

The clinical hallmark of antibody deficiency is the presence of recurrent upper and lower respiratory tract infections resulting in anatomical injury with bronchiectasis [94,95]. Respiratory infections are strongly linked to asthma exacerbations, as clearly demonstrated elsewhere [96-99]. Antibody deficiency is a neglected but frequent comorbidity of asthma. It is characterized by low serum levels of 1 or more immunoglobulin (Ig) class and/or one or more IgG subclasses [100]. Viral and bacterial infections are highly prevalent in antibody-deficient patients, and patients with bronchiectasis are more prone to develop respiratory infections, thus creating a vicious cycle. If left untreated, antibody deficiency and bronchiectasis can be considered strong risk factors for severe asthma outcomes [97-99]. The prevalence of antibody deficiency in patients with obstructive airway disease and bronchiectasis is certainly underestimated, and this comorbidity carries a significant disease burden [101,102]. In asthma patients, data on the prevalence of primary antibody deficiency are not clearly defined, although one large cohort study has estimated this to be about 5.5% [103]. Severe asthma patients, especially those who experience frequent respiratory infections, should undergo screening to exclude concomitant bronchiectasis and humoral immune defects. Although immunoglobulin replacement therapy is the standard approach for severe forms of primary immunodeficiency, its effectiveness in reducing the recurrence and the severity of infections, hospitalizations, and

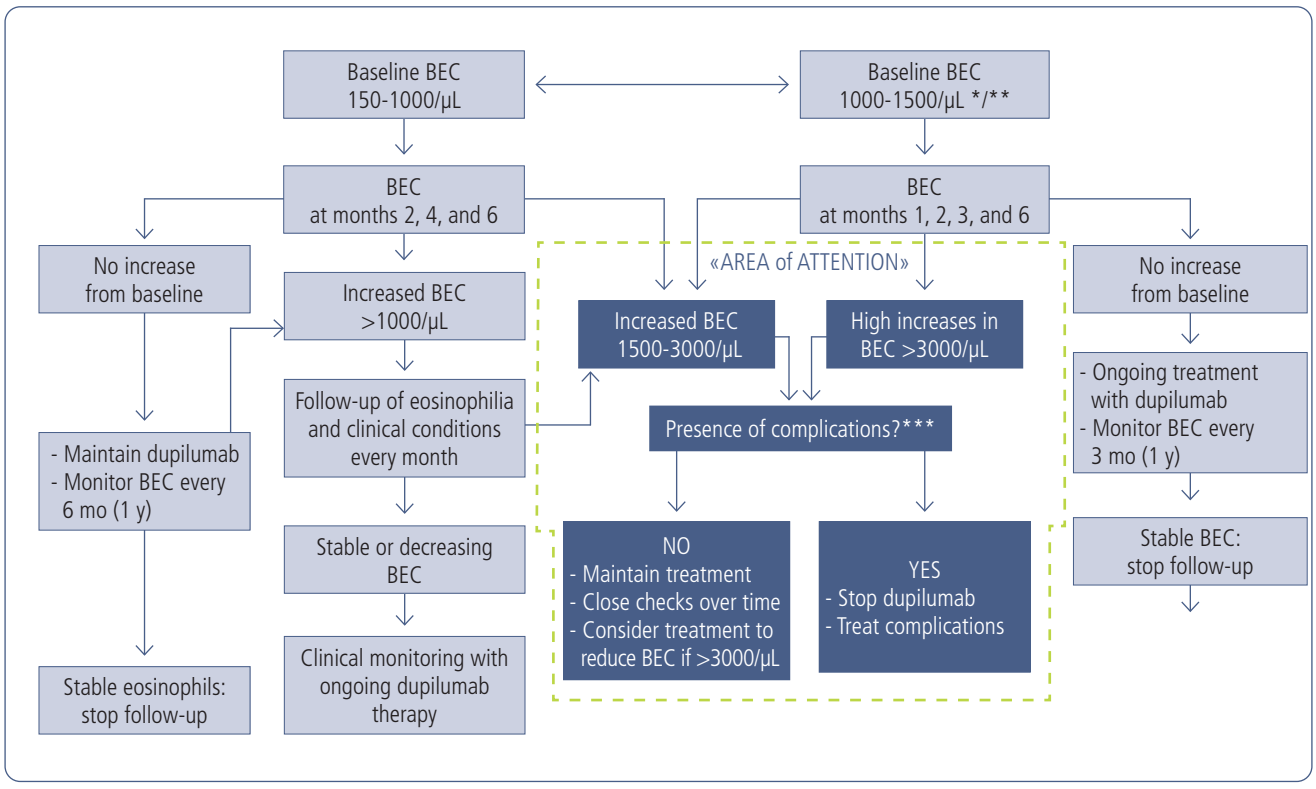

Figure. Proposal for the clinical management of dupilumab. BEC indicates blood eosinophil count. *In oral corticosteroid–dependent patients with high BEC, slow reduction of oral corticosteroid dosage. **Patients with more than 1500/µL at baseline should not receive dupilumab (no data from clinical trials available). ***Worsening of asthma symptoms. Exclude pulmonary infiltrates, antineutrophilic cytoplasmic antibodies, other hypereosinophilic syndromes, symptom/organ involvement.

mortality means that it is not universally recommended for the management of minor defects [104]. Recent data suggest that immunoglobulin replacement therapy could be effective in reducing respiratory infections and hospitalizations in IgG subclass deficiency [105], although the effect of this approach on asthma exacerbations and the corticosteroid-sparing effect due to reduction of respiratory infections have only been investigated in small case series [104,106].

In a realword retrospective study of 16 patients with severe eosinophilic asthma and copresence of bronchiectasis, mepolizumab effectively improved control of asthma symptoms (as per the Asthma Control Test score) and reduced the annual exacerbation rate and corticosteroid intake, showing that the presence of bronchiectasis does not limit the effectiveness of mepolizumab [107]. Similarly, a significant reduction in BEC and a significant improvement in FEV_1, symptom burden, and health-related quality of life were observed in a case series of patients with bronchiectasis and the eosinophilic inflammatory endotype treated with mepolizumab (n=12) or benralizumab (n=9) [108]. Additional results are available for a low number of cases treated with dupilumab and omalizumab [109].

Patients Not Responding to Biologics

Currently available biologics for severe asthma are indicated for patients with eosinophilic or allergic asthma phenotypes. In the pivotal studies of currently approved biologics, exacerbation rates were markedly reduced by the most efficacious dose regimen compared with placebo [78,110-113]. In a real-world study, an even more pronounced positive effect has been observed for biological treatments [114]. Superresponse was observed in a proportion of patients and was predicted by shorter asthma duration and higher FEV_1 and tended to be associated with adult-onset asthma, absence of CRSwNP, and lower body mass index [113]. However, a proportion of patients (about 15%) do not achieve control of asthma and/or nasal symptoms and can be classified as nonresponders, based on the discontinuation of biologics after less than 2 years because of clinical worsening with increased symptoms, decreased FEV_1, or increased OCS use [9,10,115]. The remaining patients are defined as partial responders who did not fulfill the criteria for nonresponders but experienced residual disease manifestations even after 2 years of treatment, including inadequately controlled symptoms of asthma or rhinosinusitis, persistent airflow limitation, and OCS dependency [9]. The incomplete response could be due to irreversible remodeling of the upper and lower airways [116,117]. In some patients, residual asthma symptoms without evidence of eosinophilic inflammation may be caused by comorbidities such as dysfunctional breathing, obesity, bronchiectasis, and cardiovascular disease, but also by the impact of airway remodeling despite the abrogation of airway eosinophilia [118,119]. In fact, it has been clearly demonstrated

how asthma (and CRSwNP) remodeling largely depends on the IL-4/IL-13 axis, irrespective of eosinophils [120]. Importantly, no consensus has been reached on the definition of the clinical characteristics of nonresponders to a specific biologic or on the duration of the observation period to define a responder or a nonresponder. Recent guidelines recommend re-evaluation of response after 4-6 months, although a longer observation period or a composite index that takes into account other parameters might be preferable if we are to judge the reduction in exacerbations. For suboptimal response, it can be useful to reassess airway inflammation and airway hyperresponsiveness or lung function.

The various reasons why a patient does not respond to a biological treatment are as follows: (*i*) no correct assessment of phenotype at baseline; (*ii*) clinical impact of concomitant comorbidities; (*iii*) incomplete ability of the biologic to abrogate the airway process; (*iv*) long-term history of asthma with irreversible histologic and functional consequences (airway remodeling, fixed airflow obstruction); (*v*) no adherence to biologics (patient administering therapy at home); and (*vi*) development of neutralizing antidrug antibodies (Table 1) [121-125]. In fact, biologics, including mAbs, are structurally immunogenic and may be hampered by the formation of antibodies (antidrug antibodies [ADA]). The loss of response to biologics observed in a proportion of treated patients may be explained by the formation of immune complexes between mAbs and ADAs, leading to their increased clearance and reducing the half-life and serum level or through the inhibition of drug activity by blocking the active site for target recognition (neutralizing ADAs) [126].

Table 1. Reasons for Partial or No Response to Biologics.

No adherence to standard therapy
Comorbidities: dyspnea, immunodeficiency, obesity, deconditioning, bronchiectasis, cardiovascular disease
Irreversible remodeling of upper and lower airways
Individual differences in drug pharmacokinetics
Formation of antidrug antibodies

Randomized clinical trials revealed antimepolizumab antibodies in 2%-5% of patients but did not identify neutralizing ADAs [127,128].

ADAs have been reported in 11% of mepolizumab-treated patients, even though there was no correlation between the presence of ADAs and adverse events and no apparent marked changes in the pharmacokinetic or blood eosinophil profiles. In fact, all samples were negative for neutralizing antibodies [129].

In dupilumab-treated patients, the rate of a persistent ADA response ranged from 2.1% to 4.2% with the high and low doses, respectively [78].

Concerning benralizumab, ADA production was detected in a higher proportion of patients (15%), although no association with hypersensitivity reactions or reduced efficacy was identified [130]. Overall, mAbs used for severe asthma appear to be less immunogenic than those used in rheumatic and intestinal disorders [131]; however, no real-life data are available on the impact of biologics on efficacy in severe asthma patients.

In clinical practice, a switch to an alternative drug can be considered in patients who do not respond to a specific biologic.

Table 2 presents a possible switching strategy, although the new thymic stromal lymphopoietin blocker tezepelumab has not been considered given its recent introduction in step 5 of the GINA guidelines and the lack of real-world data [76].

Conclusions

Although therapy with biologics has enabled control of symptoms, even in patients with severe type 2 asthma

Table 2. Switching Strategy in Patients Who Do Not Respond to Biologicals.

No response to	Preferential switch to	When prevalent
Dupilumab (anti-IL-4Rα)	Mepolizumab/Reslizumab	Increased BEC, eosinophilic asthma at baseline
	Benralizumab	Increased BEC, eosinophilic asthma at baseline
	Omalizumab	FEV_1 <80% and perennial allergen sensitization
Benralizumab (anti-IL-5R)	Mepolizumab/Reslizumab	ADA+
	Dupilumab	High FeNO, atopy; low FEV_1, OCS dependency
	Omalizumab	FEV_1 <80% and perennial allergen sensitization
Mepolizumab/Reslizumab (anti-IL-5R)	Benralizumab	ADA+, Persistence of BEC >150 and baseline BEC >300
	Dupilumab	High FeNO, low FEV_1, OCS dependency
	Omalizumab	FEV_1< 80% and perennial allergen sensitization
Omalizumab (anti-IgE)	Dupilumab	High FeNO, low FEV_1, OCS dependency
	Mepolizumab	Eosinophilic asthma at baseline
	Benralizumab	Eosinophilic asthma at baseline

Abbreviations: ADA, antidrug antibody; BEC, blood eosinophil count; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; OCS, oral corticosteroids.

that does not respond to so-called conventional therapy, a proportion of affected patients are characterized by the presence of comorbidities that hinder and complicate therapeutic management. The success of therapy, even if based on biologics, cannot be separated from the treatment of the comorbidities themselves. In addition, expected undesirable events, such as dupilumab-induced hypereosinophilia, should not in themselves hinder treatment but must be adequately managed to ensure continuation of therapy where possible in order to achieve the expected benefits.

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Conflicts of Interest

AM has received consulting fees and honoraria for lectures from AstraZeneca, Chiesi, GSK, Novartis, and Sanofi. CM has received honoraria for lectures from Chiesi, GSK, Guidotti, Menarini, and Novartis and consulting fees from AstraZeneca, GSK, and Sanofi. AV has received honoraria for lectures from AstraZeneca, Chiesi, GSK, Novartis, and Sanofi and received consulting fees from GSK.

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