Severe asthma and biologics: managing complex patients

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Abstract

Bronchial asthma is a chronic airway inflammatory disease of the respiratory tract that varies in terms of clinical presentations (phenotypes) and distinct underling pathophysiological mechanisms (endotypes). The definition of phenotype/endotype is crucial tak-ing into account the availability of novel biologic agent dedicated to patients who do not respond to conventional therapies. Although patients suffering from type 2 severe asthma significantly benefit from treatment with biologics no responders patients have been identified. Comorbidities increase the symptoms of asthma and complicate the overall management of the disease. The assessment and treatment of comorbidities is a crucial step and they the appropriate management may improve asthma symptoms and morbidity. Among comorbidities certainly chronic rhinosinusit with nasal polyps, obesity, bronchiectasis and immune defects represent a group of clinical conditions that negatively impact on asthma control despite a correct treatment. Although asthma is frequently characterized by an increase of blood eosinophils that releasing mediators and cytokines are involved in the inflammatory processes of airways wall, in patients with very high blood eosinophil levels it is opportune to be very careful in discerning whether it is a case of isolated severe eosinophilic asthma or a case of asthma in EGPA disease. In addition, hypereosinophilia can be the consequence of specific biological treatment as in the case of dupilumab. In this paper we have outlined the clinical features of those patients with severe asthma in which the management of the disease can be more complex.

Key words: Biologicals. Severe asthma. Dupilumab induced hypereosinophilia

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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 eosinofílico en el seno de una granulomatosis eosinofilica 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.

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Introduction

Bronchial asthma (BA) is a chronic airway inflammatory disease of the respiratory tract that varies in terms of clinical presentations (phenotypes) and distinct underling pathophysiological mechanisms (endotypes) [1,2]. Asthma can be categorized as type 2 (eosinophilic) or non-type 2 (non-eosinophilic) endotype [3,4]. The type 2 inflammatory process is the result of the involvement of T helper type 2 (Th2) cells, type 2 innate lymphoid cells (ILC2), mast cells, eosinophils and structural cells of the airway walls, all of them producing several cytokines, including interleukin (IL)-4, IL-5, IL-9 and IL-13 [5]. Similarly, type 2 inflammation plays a pivotal role in chronic rhino-sinusitis with nasal polyps (CRSwNP), one of the most important comorbidities of severe asthma. The definition of phenotype/endotype of both asthma and CRSwNP, is crucial taking into account the availability of novel biologic agents dedicated to patients who do not respond to conventional therapies [6-8]. Although patients suffering from type 2 severe asthma and/or CRSwNP significantly benefit from treatment with biologics in terms of clinical improvement and steroid-sparing effect, no responders patients have been demonstrated [9,10]. In addition, although in long-term studies the safety profile of biologicals used in asthmatic patients has been clearly confirmed, in a proportion of treated patients, some issues may emerge such as adverse infusion reactions, increased risk of infections, or the appearance of a paradoxical hyper-eosinophilia [11]. In this paper we have outlined the clinical features of those patients with severe asthma in which the management of the disease can be more complex.

1. When a severe asthma patient may be more complex?

1.1. Asthma with associated CRSwNP

Comorbidities increase the symptoms of asthma and complicate the overall management of the disease. In the evaluation of patients with asthma the assessment and treatment of comorbidities is a crucial step and they the appropriate management may improve asthma symptoms and morbidity. CRSwNP has been reported to be a frequent comorbidity of severe asthma [12]. Symptoms of loss of smell, nasal congestion and/or nasal obstruction, and rhinorrhea have a significant impact on social and physical quality of life (QoL). In fact, the presence of CRSwNP in asthmatic patients is associated with worsening of asthma outcomes, more specifically with an increased risk of exacerbations and of oral corticosteroids (OCS) use [13-15]. In a large study population the multivariable analysis demonstrated that CRS remained significantly associated with exacerbation frequency, even after adjustement for age, sex, medication adherence, BMI (body mass index), blood eosinophil count (BEC), and IgE levels [16]. Moreover, CRS exerts a more pronounced effect on asthma symptoms in patients with a 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 to treat 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 (AERD) [20]. A deep of attention must certainly be dedicated to the characterization of CRSwNP, typically sustained by a type 2 inflammation which represents about 80% of the cases, whereas CRSsNP is often characterized by type 1 or type 3 inflammation [21-23]. In a recent systematic review, the complexity of the disease has been found taking into account that 150 genetic variants have been identified in 99 genes involved in the pathogenesis of NP [24].

Asthma and CRS may share type 2 inflammatory pathways and similar histological alterations. In fact, in patients with CRSwNP, in addition to diffuse tissue eosinophilia and eosinophilic aggregates, basement membrane thickening, sub-epithelial oedema and fibrosis, goblet cell hyperplasia with mucin hypersecretion, are evident in a process similar to airway remodeling in asthma [25]. Of note, has been shown that biologics administered in severe asthmatic patients, have a greater clinical effect in the subgroup of patients with concomitant CRSwNP. Mepolizumab reduced the annual exacerbation rate in patients with severe eosinophilic asthma versus placebo regardless of NP status, but to a greater degree in those with NP (80%) than without NP (49%), as shown in the meta-analysis of the MUSCA and MENSA studies, including 936 patients, 166 out of them (18%) presented with NP at baseline [26]. The ANANKE study supports previous CALIMA and SIROCCO responder analysis, 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 as yet about an increased impact of NP at baseline on their efficacy in type 2 asthma.

In clinical practice, it is common to experience that patients reach a good clinical response for asthma symptoms, but not for CRS, as reported in some small case series [31].

Moreover, in individual patients, biological mechanisms underpinning asthma and CRS can be only partially similar, not only in terms of severity but also in terms of cellular and molecular “actors” driving the inflammatory process.

1.2. Asthma in obese patients

Obesity-associated asthma is a more difficult-to-treat, poorly controlled phenotype with worse morbidity and mortality outcomes. In fact, it has been shown that obesity is linked to frequent exacerbations, and increased use of OCS [32-35]. In addition to an ongoing suboptimal control of asthma, it has been found that obese patients experience significantly higher acute severity, including overall mechanical ventilation use and longer hospital length-of-stay, when compared to non-obese patients

[33]. The importance of the presence of an obese status in asthma patients seems to affect the expression of T2 biomarkers largely used for defining the eligibility criteria for currently available biologics. Indeed, it has been demonstrated that the increase of BMI is associated with FeNO reduction, independent of steroid 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, able to promote a Th2 response, mast cell degranulation and airway remodeling [36]. Adiponectine (ADPN) is one of the most important adipocytes-derived factors due to its multiple biological functions and the observation that low serum ADPN levels in obese asthmatics, particularly in women, has been described [37]. In fact, ADPN: (i) inhibits apoptosis of epithelial cells after cell injury and promotes repair and proliferation of the basal bronchial cells; (ii) reduces the tumor necrosis factor (TNF)-α induced secretion of chemokines by monocytes/macrophages (CCL2) and mastocytes (CXCL1); (iii) in ovalbumin-induced mouse model of airways inflammation, ADPN overexpression is able to counteract IL-13 action,; (iv) ADPN overexpression reduces mucus secretion by inhibiting the expression of omentin and MUC5AC; (v) inhibits the IL-33-stimulated NF-κB pathway and IL-13 production by ILC2s; (vi) reduces eotaxin-promoted eosinophil chemotaxis and adhesion; (vii) increases the secretion of IL-10 in peripheral T regulatory (Treg) cells, particularly in a Th2 milieu [38-46].

The non-type 2 pattern of inflammation shows increasing importance 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 disease, although eosinophilic inflammation is sometimes present in this form of asthma [47]. Interferon (IFN)-related signaling pathways were overrepresented in obese asthmatics, compared with both healthy controls and non-obese asthmatics. These pathways are induced by various IFN-inducing factors such as leptin hormone [48,49]. In obese asthmatics the severity and frequent exacerbation asthma episodes might be further influenced by the increased susceptibility to respiratory viral infections [50].

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The obesity can also negatively impact the clinical effects of biologics because the body weight is a clinically relevant covariant that may modify pharmacokinetic of these drugs [51,52]. The pharmacokinetics (PK) may be divided into four basic processes as absorption, distribution, metabolism, and excretion. These nonspecific general processes, affect the amount of active drug that reaches intact the target of action and, therefore, influences its activity. Unlike conventional drugs, mAbs used in asthma can be administered exclusively via intravenous or subcutaneous. The subcutaneous absorption can be reduced by pre-systemic elimination due to the activity of soluble peptidases, the endothelial endocytosis and subsequent lysosomal degradation, the interaction with the phagocytic immune cells in the lymph nodes [53].

After distribution in the tissue, mAbs are mainly eliminated 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, as it is easy to understand, the treatment of obese patients with severe asthma cannot be separated from undertaking a dietary strategy to reduce body weight and to limit the impact of obesity has on the various aspects previously discussed.

For monoclonal antibodies (mAbs) administered via the subcutaneous (SC) route, 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 that may be more difficult in obese patients [53]. Very few data are available about this topic. Even though body weight seems to explain the between-subject variability in dupilumab PK in patients with asthma, no dose adjustment is recommended with regard to body weight, given the limited difference in efficacy/safety across the weight categories [54]. Similarly, body weight (as well as high-titer antidrug antibodies, see below) was identified as relevant covariate influencing the PK of benralizumab, thus suggesting a more rational selection of dosage regimens in asthma patients [55].

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Therefore, it has been highlighted that the correct phenotyping of the obese asthma patient should to enable us to develop a rational therapeutic plan, including both the pharmacological approach and specific anti-obesity therapies including bariatric surgery [56].

1.3. Oral corticosteroids (OCS)-dependent patients

Inhaled corticosteroids (ICS) represent the first-line therapy for patients with persistent asthma because inhibit almost every aspect of the airways inflammatory process [57]. ICS are effective in most patients with asthma, irrespective of age or asthma severity. They not only control asthma symptoms and improve lung function but also prevent exacerbations and may reduce asthma mortality and the irreversible changes in airway function that occur in some patients [58]. However, a proportion of asthmatic patients develop a dependence 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]. Asthmatic patients with type 2-low inflammation are characterized by a low response to OCS. Whereas most patients with persistent eosinophilic inflammation tend to well respond to OCS [60]. Although severe asthmatic patients with OCS dependence are a small proportion of the general asthmatic population, they represent a large burden on health care costs, with an important increase in morbidity, hospitalization, mortality and side effects [61]. Several molecular mechanisms have been identified that may contribute to the resistance of cells to the anti-inflammatory effects of corticosteroids in severe asthma, with mechanisms differing between patients [62]. Glucocorticoid (GC) resistance may result from defects at different levels in GC signaling, such as reduced glucocorticoid receptor (GR) expression, reduce GC binding to GR, impaired nuclear translocation, or altered co-factor 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 as FeNO and blood eosinophils. For patients with OCS-dependent asthma who are more likely to have a type 2 phenotype is advisable to perform repeated measures by using a supervised OCS-taper approach avoiding the risk to induce an exacerbation.

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OCS-sparing potential has been demonstrated by three biologics approved for treatment of severe asthma (benralizumab, dupilumab, and mepolizumab), however the lack of head-to-head trials with these treatments, do not allow any conclusive considerations about the preferential choice in OCS-dependent patients. Matching-adjusted indirect comparison (MAIC), that allows for comparison of treatments across clinical trials demonstrated that, after adjustment for differences in baseline population characteristics, reductions in OCS dosage, percentages of patients achieving OCS elimination, and annual asthma exacerbation rates were comparable between mepolizumab, dupilumab, and benralizumab. [65]

1.4. Hypereosinophilic/EGPA patients

The normal adult healthy range of eosinophils in blood is appreciated to be about at 30-330 cells/μL (median: 120 cells/μL in males and 100 cells/ μL in females) [66]. The degree of eosinophilia is defined using the absolute number of circulating eosinophils in blood. Eosinophilia and hyper-eosinophilia are defined as a count greater than 500 and 1500 cells/μL, respectively [67]. Asthma is frequently characterized by an increase of BEC that, releasing several mediators and cytokines, are involved in the pathological tissue processes such as epithelial damage, smooth muscle hypertrophy, impaired tissue repairment, thus promoting chronic airways remodeling and airflow obstruction [68-70]. In a retrospective analysis was found that patients with systemic eosinophilia ≥400 cells/μL, especially when associated with airway eosinophilia (≥3%) were more likely to have worse lung function, symptoms and impairment of QoL [71]. In a large cohort study it has been shown that exacerbation rate increases progressively with ascending categories of blood eosinophil count, when compared with reference category of 200 cell/μL or less [72]. High BEC is typical of eosinophilic granulomatosis with polyangiitis (EGPA), an eosinophilic necrotizing systemic vasculitis, classically associated with severe asthma and nasal polyps [73]. Taking into account that EGPA could represent a possible evolution of eosinophilic form of severe asthma, although a specific cut-off of BEC has

not been defined, in patients with "high/very high" blood eosinophils it is opportune to be very careful in discerning whether it is a case of isolated severe eosinophilic asthma or a case of asthma in EGPA disease [74]. Of note, asthma, CRS and blood eosinophilia could anticipate the overt vasculitis for years [75]. It is also important to take into account that BEC at baseline may influence the choice of the biological for asthma treatment, not only in terms of response, but also because anti-IL-4Rα chain mAb (dupilumab) may induce, as will be discussed, a further increase of blood eosinophils, at least in a proportion of patients [76]. In fact, dupilumab treatment, now use 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]. In the large majority of reported data, it has been observed a rapid increase in BEC and a spontaneous decrease, regardless of dupilumab maintenance, although hyper-eosinophilia persisted in a proportion of patients [78]. After all, some patients from asthma trials developed severe eosinophil-related manifestation such as "hyper-eosinophilic syndrome' and "chronic eosinophilic pneumonia" [79-81]. Differently from asthma patients, no clinical impact of hyper-eosinophilia was reported in atopic dermatitis (AD) patients [82]. While data are missing from trials [83-86], in real-life study blood hyper-eosinophilia has been reported in about 15% of AD patients treated with dupilumab [87]. The different clinical consequences among asthma and AD raised the question why this occurs. So far, the mechanisms underlying hyper-eosinophilia upon dupilumab remain unclear. The observed increase of blood eosinophils was hypothesized to be due to the inhibition of IL-4/IL-13 signaling. Both cytokines induce the expression of adhesion molecules on endothelial cells, a crucial step in the migration of eosinophils in tissue [88-91]. Dupilumab, by blocking the biological effects of both cytokines, downregulates the expression of these adhesion molecules. Therefore, eosinophils can move from the bone marrow to the blood, as this process is mediated by IL-5, but cannot leave from the blood to the tissue. However, although 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 that the increase of eosinophils is usually non-

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persistent. Finally, the interference with the adhesion of eosinophils to endothelial cells, should prevent the tissue infiltration that instead may complicate some cases of dupilumab-induced hyper-eosinophilia [77,80]. Some possible explanations derive from experimental models. 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 due to the low levels of IL-13 that may result in an increase in NF-κβ, which in turn increases synthesis of IL-5, similarly to what has been observed in non-allergic asthmatics with high levels of IL-5 and eosinophils despite low IL-4 levels [92,93].

From a clinical point of view, it is important to suggest that in patients with higher baseline BEC, a monitoring of the value is advisable after the start of dupilumab. More careful evaluation is recommended in patients switched from an anti-IL-5 or anti-IL-5R mAbs to dupilumab. In fact, the disappearance of the IL-5 axis blockade can favor an unexpected expansion of the eosinophilic population however inhibited by the previous biological treatment. Similar attention must been dedicated to OCS-dependent asthmatic/CRSwNP patients in which the rapid reduction of the steroid dose, made possible by dupilumab therapy, can be complicated by BEC increase.

In Figure 1 a flow-chart for the clinical management of dupilumab treated is proposed.

1.5. 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 the development of bronchiectasis [94,95]. Respiratory infections are strongly linked to asthma exacerbations, as clearly demonstrated by several data [96-99]. A neglected but frequent comorbidity of asthmatic patients is represented by antibody deficiencies, characterized by low serum levels of one 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, so creating a vicious cycle. Is evident as antibody deficiency and bronchiectasis can be considered strong risk

factors for severe asthma outcomes, if left untreated [97-99]. The prevalence of antibody deficiency in patients with obstructive airways disease and bronchiectasis is certainly underestimated and carries a significant burden of disease [101,102]. In asthmatic patients, data on primary antibody deficiency prevalence are not clearly defined, although in a large cohort study it has been estimated of about 5.5% [103]. Severe asthma patients, especially if they experienced frequent respiratory infections, should be submitted to a screening to exclude concomitant bronchiectasis and humoral immune defects. Although Ig replacement therapy (IRT) is the standard therapy for severe forms of primary immunodeficiency, due to effectiveness in reducing the recurrence and the severity of infections, the hospitalizations and the mortality, it's not universally recommended for the management of minor defects [104]. Some recent data suggest that IRT could be effective in reducing respiratory infections and hospitalizations also in IgG subclasses deficiency [105], but the effect of IRT on asthma exacerbations and the presence of steroid sparing effect due to reduction of respiratory infections has been scarcely investigated except for small case series [104,106].

In a real-word retrospective study, including 16 patients with severe eosinophilic asthma and copresence of bronchiectasis, mepolizumab effectively improves asthma symptoms control evaluated by ACT, reduces annual exhacerbation rate and corticosteroids intake, showing that the presence of bronchiectasis does not limit the effectiveness of mepolizumab [107]. Similarly, a case series of patients with bronchiectasis and eosinophilic inflammatory endotype, treated with mepolizumab (n=12) or benralizumab (n=9) showed a significant reduction of blood eosinophils as well as a significant improvement of FEV1, symptom burden and QoL [108]. Additional results are available for a few number of cases treated with dupilumab and omalizumab [109].

1.6. Patients non responding to biologics

Currently available biologics for severe asthma are indicated for patients with eosinophilic or allergic asthma phenotypes. In the pivotal studies of the currently approved biologics, exacerbation

rates markedly were reduced by the most efficacious dose regimen versus placebo [78, 110-113]. In a real-life studies an even more pronounced positive effects to biological treatments has been observed [114]. Super response was observed in a proportion of patients and was predicted by shorter asthma duration and higher FEV1 and tended to be associated with adult-onset asthma, absence of CRSwNPs, and lower BMI [113]. However, a proportion of patients (about 15%) do not achieve a control of asthma and/or nasal symptoms and can be classified as non-responders, based on the discontinuation of biological treatment after less than two years because of clinical worsening with either increased symptoms, decreased FEV1, or increased OCS use [115, 9, 10]. The remaining patients are defined partial responders who did not fulfill the criteria of non-responders but experienced residual disease manifestations even after two years of treatment, including inadequately controlled symptoms of asthma or rhinosinusitis, persistent airflow limitation, or OCS dependency [9]. The incomplete responses could be due to irreversible remodeling of upper and lower airways [116,117]. In some patient residual asthma symptoms without evidence of eosinophilic inflammation may be caused by comorbidities such as dysfunctional breathing, obesity, bronchiectasis, or cardiovascular disease, but also by the impact of airways remodeling despite the abrogation of airway eosinophilia [118, 119]. In fact, it has been clearly demonstrated how asthma (and CRSwNP) remodeling profoundly depends on IL-4/IL-13 axis irrespective to eosinophils [120]. We must underline that until now no definitive consensus exist on the definition of the clinical characteristics of non-responder patients to a specific biological drug as well as the duration of the observation period to define a responder or non-responder. Recent guidelines recommend re-evaluation of response after 4-6 months, but probably a longer observation period or a composite index that takes into account other parameters seems to be preferable to judge the reduction in exacerbations. For suboptimal response, can be useful to re-assess airway inflammation and airway hyper-responsiveness or lung function.

Several reasons of a no response to a biological treatment can be identified: i) no correct phenotype assessment at baseline; ii) clinical impact of concomitant comorbidities; iii) incomplete capacity of the biological drug to abrogate the airway process; iv) long-term history of asthma diseases

with irreversible histological and functional consequences (airways remodeling; fixed airflow obstruction); v) no adherence to biological treatment (patient in home therapy); vi) development of neutralizing anti-drug antibodies (Table 1) [121-125]. In fact, biologicals, including mAbs, are structurally immunogenic, and the formation of antibodies [anti-drug antibodies (ADA)]. The loss of response to biologicals observed in a proportion of treated patients may be explained by immune-complexes formation between mAbs and ADAs, leading to their increased clearance reducing the half-life and serum level or by the inhibition of the drug activity by blocking the active site for target recognition (neutralizing ADAs) [126].

During mepolizumab treatment in the RCT, anti-mepolizumab antibodies were detected in 2-5% of patients but neutralising ADA were not detected [127,128].

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

In dupilumab treated patients the rate of persistent ADA response range from 2.1% to 4.2% with higher and lower dose, respectively [78].

Concerning benralizumab, ADA production was detected in a higher proportion of patients (15%) although there were not an association with hypersensitivity reactions or reduced efficacy [130]. Overall, mAbs used for severe asthma appear to present less immunogenicity in comparison to those used in rheumatic and intestinal disorders [131], although no data in real-life are available, exploring the real impact on efficacy of biologicals in severe asthma patients.

From a clinical point of view, in non-responder patients to a specific biological drug a switch to an alternative drug can be considered.

In table 2 a possible switching strategy is proposed although the new biological agent anti-stromal lymphopoietin (TSLP) tezepelumab mAb has not been considered taking into account recent introduction in step 5 of the GINA guidelines and the lack of real-life data [76].

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2. Conclusions

Although therapy with biological drugs has allowed clinical control to be achieved even in patients with severe type 2 asthma unresponsive to so-called conventional therapy, it is known, however, that a proportion of patients are characterized by the presence of comorbidities that hinder and make more the therapeutic management of these subjects is complex. Therapeutic success, even if based on the use of biological drugs, cannot be separated from the treatment of the comorbidities themselves. In addition, potentially expected undesirable events such as dupilumab-induced hypereosinophilia should not in themselves hinder treatment but must be adequately managed to ensure continuation of therapy as much as possible in order to achive the expected benefits.

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Tables

Table 1. Reasons of partial or no response to biological treatment

- No adherence to standard therapy
- Comorbidities: dysfunctional breathing, immunodeficiency, obesity, deconditioning, bronchiectasis, cardiovascular disease
- irreversible remodeling of upper and lower airways
- Individual differences in pharmacokinetics of the drugs
- formation of anti-drug antibodies

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Table 2. Switching strategy in biologicals non-responder patients

Non response to:	Preferential switch to:	When is prevalent:
DUPILUMAB (anti-IL-4Rα)	Mepolizumab/Reslizumab	Increase of BEC; eosinophilic asthma at baseline
	Benralizumab	Increase of 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	FEV1< 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	FEV1< 80% and perennial allergen sensitization
OMALIZUMAB (anti-IgE)	Dupilumab	High FeNO*; low FEV1; OCS dependency
	Mepolizumab	Eosinophilic asthma at baseline
	Benralizumab	Eosinophilic asthma at baseline

ADA: anti-drug antibodies; BEC: blood eosinophils count; FeNO: Fractional exhaled nitric oxide; FEV1: Forced expiratory volume in 1 sec.; OCS: oral corticosteroids

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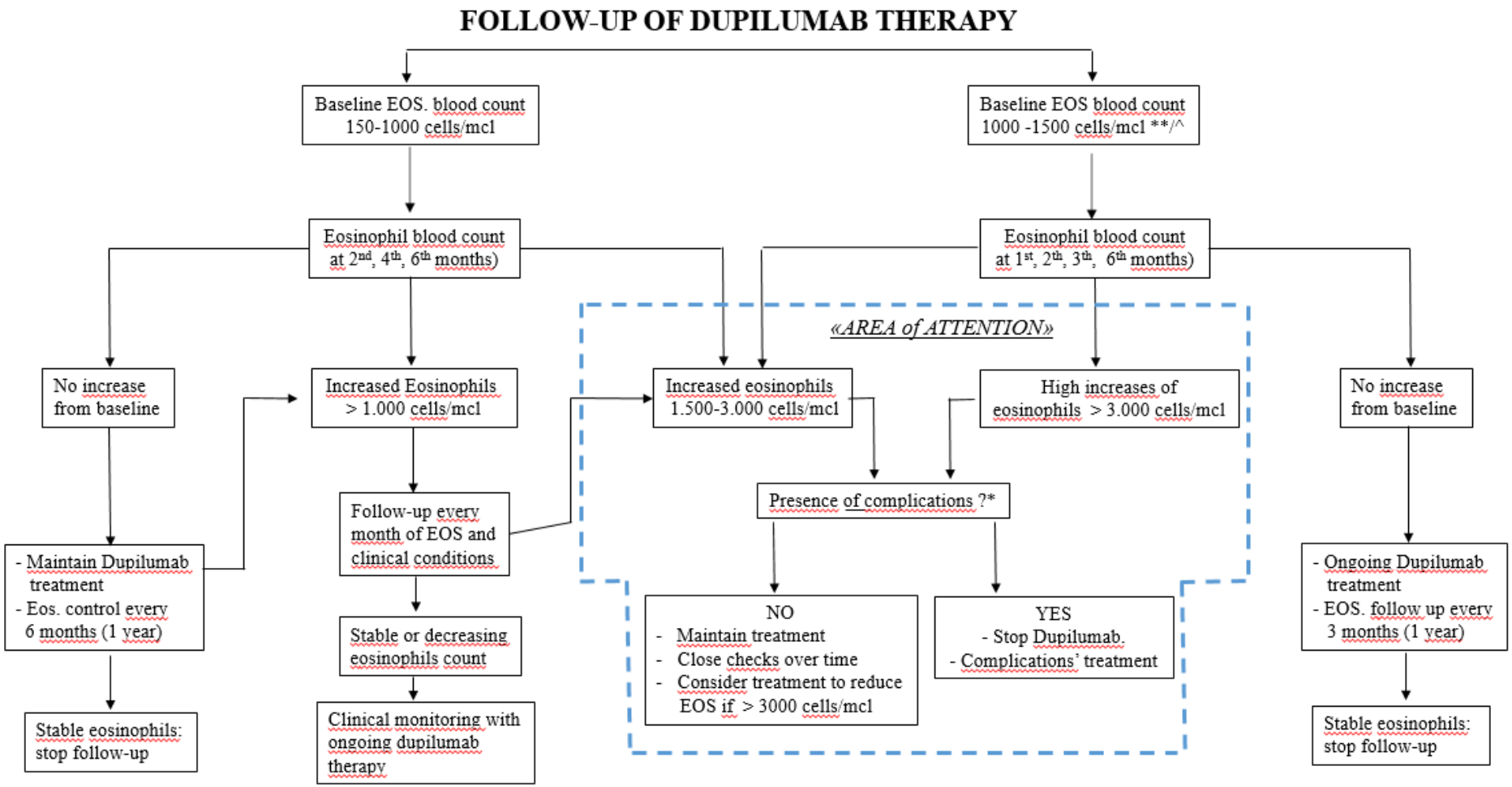
Figure. Follow-Up of Dupilumab Therapy.



* Worsening of asthma symptoms; Exclude pulmonary infiltrates; ANCA (anti-neutrophilic cytoplasmic antibodies) detection, Exclude other hypereosinophilic syndromes symptoms/organ involvement
** In Oral corticosteroids (OCS)-dependet patients with high eosinophils count, slow reduction of OCS dosage
^ Patients with more than 1500 eosinophils at baseline should not receive dupilumab (no data from clinical trials available)

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