Controversies and Dilemmas in Severe Asthma

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Abstract

As severe asthma is a rather common respiratory disease, with a heavy burden for the patient, the health system and society, it is important to recognize it and apply modern biological therapy if indicated. As in today's approach to asthma management, we tend no more to "me too medicine", but to individual therapy in personalised and precise medicine. This article is dealing with some controversies and dilemmas in the field. After introducing biological therapy in the early 2000s, systemic glucocorticoids became the second option for patients with severe asthma. Starting with the controversy about accurate asthma diagnosis, then the question of where patients with severe asthma are hiding, thirdly, are we treating those patients appropriately and comprehensively, and finally, are we emphasising enough the necessity of smoking cessation? After reviewing the facts, and considering the extensive discussion exposed in controversies, a similar analysis brought up a few dilemmas, i.e. how could we precisely define severe asthma phenotypes, how should we distinguish asthma from COPD in middle-aged smoking patients, and how to make the right personalized choice of biologicals. There is also the dilemma about age - how old (or young) should the patient be for the indication for biologicals, and lastly, the length of treatment which is appropriate to assess a patient's response to biologicals ("responder" or "non-responders").

Keywords: asthma, diagnostics, precision medicine, smoking cessation, response to therapy assessment

Introduction

Asthma is the most frequent chronic respiratory disease[1], with almost 1 in 8 children and 1 in 12 adults affected[2]. Asthma has a great impact on the person, the health system and society. Therefore, investigating asthma from different angles is important, as is dealing with controversies and dilemmas in the field.

The First Controversy in Asthma Always Starts with Asthma Diagnosis

There is a substantial number of patients with an *incorrect diagnosis* of asthma. Around 2% of *misdiagnosed* patients were thought to have asthma, but instead, they had other serious diseases (like tracheal stenosis, and coronary artery disease...). A significant part of these patients was *frequently diagnosed with asthma without sufficient evidence, which is not beneficial for the patient (over-diagnosis)*- around 33% of patients had innocent diseases (i.e. rhinitis, GERB, anxiety etc.)[3]. Some of the patients also had a *failure of recognising asthma* (*underdiagnosis)*. In the general population of younger subjects < 44 years who on a questionnaire reported respiratory symptoms

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compatible with asthma, around 32% of the asthma was confirmed by further examination i.e. methacholine challenge testing, skin prick tests and serum IgE measurement (4). Although in older patients >65 years, a lower percentage of underdiagnosed asthma was found - in 15% of them. This fact is very important, because, in older patients with typical asthma symptoms, asthma is a rarely perceived physician-diagnosed disease, even in those patients who had< 10 pack-years of smoking or no history of congestive heart failure[5]. Independent risk factors for asthma misdiagnosis are spirometry underutilization and missing data on pack-years of smoking[6].

An even bigger problem is the diagnosis of severe asthma. There is a significant delay in some severe asthma patients until the right diagnosis of severe asthma is established. The most logical possible explanations are twofold: the appearance of disease with atypical presentations of asthma in persons with parallel conditions (like obesity), and secondly - some patients are "poor perceivers" (although there are also medical professionals failing to recognize the disease). There are asthma patients that never have wheezing, some never cough, but most of them have dyspnea. As dyspnea can be a manifestation of many diseases, the most often from cardiac origin, it is not surprising that some patients for many years do not perform any pulmonary diagnostics. Of course, heart diseases are the most common pathology in the elderly, so they are often present as a comorbidity, but are not necessarily the leading etiology. As many patients smoke and their obstructive disease is presented for the first time during an exacerbation, they immediately receive a COPD diagnosis, which has been going on for years. From personal experience, a certain number of "COPD" patients disclosed their asthma features after usage of a single or dual bronchodilator therapy in COPD became more regular, and somewhat earlier patients were advised to discontinue ICS from their therapy. The fact is that in most of those patients careful medical history should determine asthma immediately. Respiratory symptoms were present from childhood, they had sensitisation to perennial allergens, they were treated for asthma in youth, or have eosinophilia etc. "Lack of careful history taking is intellectually lazy, it is too expensive, so should be condemned."[7]

"Poor perceivers" are those patients with asthma who do not report symptoms when their FEV_1 dropped by 20%[8]. In the group with an established asthma diagnosis in this study of 1155 subjects, 6% were poor perceivers of dyspnea, while in the group which did not have physician-diagnosed asthma despite verified airways obstruction, 26% were poor perceivers. Both under and overdiagnosis of asthma lead to significant risks to patients, and every effort should be undertaken to establish a proper diagnosis[9].

It is usually stated that 5-10% of all asthma patients have severe asthma[10]. Since 2016, the Global initiative for asthma (GINA) has stated that asthma is a heterogeneous disease[11]. Asthma heterogeneity can be seen in diverse clinical presentations, different responses to treatment, and different pathophysiological features and findings due to various pathogenic mechanisms, which lead to multiple asthma phenotypes.

Here Comes the Second Controversy: Where are Those Patients With Severe Asthma Hiding?

There is an unmet need for standardisation of the referral pathway leading to early identification of patients with severe or difficult-to-treat asthma[12]. A possible solution for better referral to asthma specialists is better communication with emergency departments (ER).Patients discharged from the emergency departments after an acute asthma exacerbation episode should be referred to an asthma specialist, either a pulmonologist, allergist or pediatrician. Another possibility is also better access to the general practitioner's (GP's) pool of "problematic" asthma patients. Patients are

often put on a short course of OCS, without an individualised strategy for the patient during the high-risk period after an emergency room or hospital visit. Around 29% of asthma patients, who are using high doses of ICS, also take harmfully high doses of oral steroids of more than 0.429 per year[13]. Oral steroids have devastating effects on a person's health – an annual cumulative dose of 2 grams of oral steroids is associated with adverse side effects, like diabetes, osteoporosis, arterial hypertension, cataracts, depression, but also adrenal insufficiency - the side effect of which we are thinking the least[14].

There are also obstacles and barriers to diagnosing severe asthma patients. Here I refer to all kinds of medical doctors, GPs' and all different specialists, including pulmonologists. We have to ask ourselves: are we appropriately listening to our patients? Are we asking the right questions? Do we perform objective measurements, like questionnaires, PEF or other lung function measurements, do we detect airflow variability, FeNO, blood and sputum eosinophilia, skin prick tests etc. Are we actively looking for other diseases similar to severe asthma from a differential diagnosis (ANCA test, total and specific IgE to *Aspergillus fumigatus,* computed tomography HRCT, nasal polyps, drug sensitivities etc)? There is a lot of room for improvement in this area.

Extrapolation of results from the database to the general Dutch population: there are about 6000 patients with severe asthma who are candidates for biologic treatment – 1.5% of the entire asthma patient population (13). If we try to estimate the situation for Croatia, with 4,087,843 inhabitants (according to the mid-2018 estimate by the Croatian Bureau of Statistics) the asthma prevalence is 5.28%, as it was shown to be a European prevalence[15] (although there are epidemiological data that the asthma prevalence in schoolchildren in Croatia is higher - 6.02%–6.9%[16,17]), there are 215,838 asthmatics; among them there should be at least 5% of severe asthmatics, which is 10,792 patients. Not all of them are candidates for biological therapy; eligible are only those asthma patients who are prone to exacerbations or who need oral steroids for treatment.

In the entire asthma population, one-quarter of the patients are prone to exacerbations, not all of them, but 10% have severe asthma[18]. Prone to asthma exacerbations means more than two or three (some authors count four - still there is no consensus on the number of asthma exacerbations per year). A patient is said to have suffered from a severe exacerbation if any of the following are present: either systemic steroids had been used to treat the attack, the maintenance dose was required to be escalated for at least 3 days; or an emergency visit due to asthma had to be made to a health-care facility, during which systemic steroids were administered[19]. The same severe asthma population revealed that more than a third of those patients do not have asthma exacerbation at all. The most important risk factors for asthma exacerbations were BMI, gastroesophageal reflux, rhinosinusitis and blood eosinophils. Expenses for the 5% of patients prone to exacerbation make up almost 50% of the total exacerbation burden[20]. Until now, different cohort analyses did not reveal a single phenotype of patients prone to exacerbations[21]. It seems that patients became prone to exacerbations when having an increased underlying biological risk, and when he or she is exposed to a certain environment with allergens, pollution or stress[22].

There are 30% of patients with severe asthma who need oral steroids for their treatment to prevent their asthma from becoming uncontrolled, or for improvement in symptoms and prevention of exacerbations[23].

If we account for these facts, and if this is a similar situation in Croatia (we do not have solid statistical data about severe asthma) there are around 3500 patients with severe asthma who are prone to exacerbations

or are permanently on oral steroid therapy. As half of them have type 2 inflammation[24], then it is reasonable to assume that there are 1780 patients in Croatia eligible for some kind of biological therapy.

If we consider a different count, parallelly, in Croatia as in the Netherlands, where 1.5% of all asthma patients are eligible for biologicals, we get similar numbers. In Croatia, 1.5% of all asthma patients consist of 3237 individuals. Half of those patients are 1618 patients with severe asthma who are allergic or have eosinophilic asthma, or have asthma with type 2 inflammation - all of them are eligible for either anti-IgE, antiIL-5 or anti-IL-4/IL-13 biological therapy.

We investigated Croatian pulmonologists' attitudes toward the prescription of biologicals in severe asthma patients, to identify reasons for the discrepancy between the number of eligible severe asthma patients and proper biological treatment. Biologics can be prescribed only by a pulmonologist following specific guidelines proclaimed by the National Health Insurance (Croatian Health Insurance Fund, CHIF) and has to be approved by the Hospital Medicines Committee (HMC). We found that regular treatment with systemic glucocorticoids and frequent acute exacerbations were the most frequent major indications for biologics in severe asthma patients, 91.7% and 82.1%, respectively, followed by frequent ER visits or hospitalizations (53.6%). The average period from establishing the indication for biologic therapy until the actual application was estimated to be 2 months, significantly shorter in university hospitals (58 vs. 105 days, $z=2.255$, $p=0.024$) but without a difference between regions ($p=0.561$). A significant number of pulmonologists reported that some of their patients did not receive biological treatment for their severe asthma during the last 12 months even though they needed it: due to inappropriate diagnosis (64.3%), strict administrative directions for the reimbursement by the Croatian Health Insurance Fund (70.2%), and limited hospital resources (57.1%). Croatian pulmonologists also identified the problem of financial restrictions at the level of hospitals. When we examine the guidelines prescribed by CHIF, poor lung function (FEV1 <60% expected) is for all biologics one of the key criteria that had to be fulfilled. In international guidelines, poor lung function is not mentioned for indications for biologicals or it is restricted to FEV1 ≤80%. Therefore, negotiations with CHIF based on pharmaco-economic and health-related quality of life (HRQoL) criteria should be initiated to implement less stringent criteria for the reimbursement of biologics according to internationally recommended guidelines[25].

Third controversy: Are we Emphasizing the Necessity of Smoking Cessation Enough?

Asthma is not considered a disease of high mortality. Still, each day there are 3-6 deaths from asthma, as reported in Brazil[26]. Investigations have proven that decreasing the number of smokers also decreases the prevalence of respiratory deaths[27].

Tobacco smoke from cigarettes has many toxic compounds such as acrolein, acetaldehyde, and formaldehyde, which contribute to respiratory irritation[28]. Tobacco can increase the prevalence of allergic diseases, like asthma, allergic rhinitis and atopic dermatitis. It could precipitate allergic sensitization directly – by affecting the IgE production on a cellular level, or indirectly – by increasing the permeability of respiratory epithelium[29]. In the research conducted on Croatian citizens, we have found a statistically significant increased prevalence of allergic diseases and increased level of total IgE, both in active and passive smokers as opposed to non-smokers[30]. Active smoking increases the inflammatory process with cell infiltrations, especially eosinophils[31]. The clinical picture of asthma in smokers is more severe in terms of symptoms, with more frequent exacerbations than in asthmatic non-smokers[7]. Secondhand smoking leads to

more severe airway obstruction and greater hyper-responsiveness[32].

It is obvious that smoking negatively influences asthma -it aggravates symptoms and treatments for exacerbation, increases inflammation and decreases the possibility of asthma control. That is why physicians and all other health care professionals should exert the greatest effort to bring the awareness about harmful effects of tobacco smoking to our patients.

It is important to build a national capacity for smoking cessation policy, which the World Health Organization (WHO) summarizes in a document[33]. There are enumerated measures influencing the demand for tobacco products (like taxation and legislation) and other interventions directly targeted to facilitate the changes in tobacco user attitudes and behaviour (like Quit and Win competition, mass media communications campaign, telephone help-line etc.). At the individual level the most recommended is the 5A strategy[34]:

1. *Ask*: Identify and document the tobacco-use status of every patient at every visit.
2. *Advis*: In a clear, strong, and personalized manner, urge every tobacco user to quit.
3. *Assess*: Is the tobacco user willing to make a quit attempt at this time?
4. *Assist*: For the patient willing to make a quit attempt, use counselling and pharmacotherapy to help him or her quit.
5. *Arrange*: Schedule follow-up contact, preferably within the first week after the quit date, in person or by telephone.

It would take only a few minutes to speak to patients and learn about their tobacco use and habits. We should help the smoker to understand the health risks of smoking. Tobacco is the single greatest preventable cause of disease and premature death. Stop smoking is the best thing one could do for his or her health.

Dilemmas in Severe Asthma

First Dilemma: How Could we Precisely Define a Severe Asthma Phenotype?

The real-world situation in medical praxis is concerning. Around half (1/2) of the physicians in the world do not have an approach to diagnostic tools satisfying for establishing an accurate diagnosis. Around one third (1/3) of the patients in the world receive inappropriate treatment, and around one quarter (¼) of patients have potential life-threatening side-effects because of inappropriate treatment.

Today, defining severe asthma phenotypes is a process based on a biomarker-driven approach[35]. Asthma phenotypes with underlying mechanisms became the centre of asthma research as there are efficient phenotype-driven therapies available. This therapy is usually biological[36, 37], but also includes macrolides, which are a successful therapy in uncontrolled asthma[38] (although the immunomodulatory effect of azithromycin was proven more than a decade ago in healthy persons[39]) and other airways diseases such as chronic obstructive pulmonary disease.

Precisiondefinition of severe asthma phenotype is crucial for applying personalized medicine[40].

For that purpose, we should combine medical history, physical examination, biomarkers and imaging methods. In medical history the most important is the age when an asthma diagnosis was established. Other factors to take into consideration are: whether it is childhood or adulthood asthma (early-onset or late-onset asthma), if there are allergies or any drug sensitivities, is there a family history of allergies, is there a smoking habit or obesity present, which comorbidities does the patient have, especially nasal polyps, and carefully monitoring of a steroid side effect, like arterial hypertension, diabetes mellitus, depression, adrenal insufficiency or cataracts. Among biomarkers for clinical praxis, the most important are total and specific

immunoglobulin E (IgE), eosinophils in blood and (induced) sputum, alsofractional exhaled nitric oxide (FeNO). It is important to find fungi in sputum if they are present and to distinguish if it is just sensitisation (SAFS - severe asthma fungal sensitisation), or colonisation and/or invasion (like ABA – allergic bronchopulmonary aspergillosis). Imaging like radiography or computed tomography (CT scan) will disclose bronchiectasis, eosinophilic infiltrates, also eosinophilic granulomatosis with polyangiitis (EGPA), as well as signs of bronchiolitis or mucoid impactions. In some cases, it will be necessary to perform bronchoscopy for a differential diagnosis or to remove thick and sticky eosinophilic secretion in the airways.

Second Dilemma: How Should we Distinguish Asthma From COPD in Middle-aged Smoking Patients?

The answer to this question at the beginning lies in detailed anamnesis, which no single diagnostic test could replace. A connection of symptoms to certain triggers, like allergen exposure worsening respiratory symptoms, or coexistence of respiratory symptoms with comorbidities like eosinophilic lung infiltrate, rhinosinusitis with or without nasal polyps, urticaria, atopic dermatitis, psoriasis, fungi sensitisation, etc., should be associated to asthma. Also, an allergy should always be looked for, or an aspirin sensitivity, as well as multiple episodes of respiratory symptoms during childhood and family history of allergies, whether in predecessors or descendants.

Another important factor, after medical history data, is lung function variability. The situation is not so clear when there is fixed airway obstruction (FAO) or persistent airflow limitation (PAL). Asthma and COPD are syndromes consisting of several endotypes and phenotypes, consequently comprising a spectrum of diseases[41].

It is very difficult to distinguish whether chronic airflow limitation is due to asthma or a CD, especially in smokers and the older population. Prevalence of FAO is higher in more severe degrees of asthma, in severe or difficult-to-treat asthma there are 55% to 60% of patients with FAO; of them fulfiling the criteria for COPD (42).When we compare asthma patients with asthma with and without FAO, those with FAO are more likely to be male and to have a longer asthma duration[43]. Mannino et al. found that up to 30% of subjects with airflow obstruction have a history of asthma rather than COPD, but reversibility was not assessed in this epidemiologic survey, which could make this number even higher[44].

Third Dilemma: How to Make the Right Personalized Choice of Biologicals?

As phenotype may or may not be associated with underlying disease mechanisms, clinical phenotypes alone are not precise enough to guide targeted immune-modulator therapy without a "biologic" marker to reveal underlying biologic heterogeneity[45].This means that the mandatory choice of biologicals is biomarkers, total and specific immunoglobulin E (IgE), eosinophils in blood and (induced) sputum, as well as fractional exhaled nitric oxide (FeNO). When we take everything into account, clinical and laboratory aspects, together with functional tests and imaging, we can make a responsible choice.

Still, there are a few problems to be resolved. We need to develop biomarkers, which could lead us to a more precise choice of which biological therapy to start with, which will have a better predictive value for responsiveness to biologics. Also, those biomarkers should be predictive for effective monitoring, or to give a signal when to stop biologics. Not to mention how important it is to find new biomarkers for the T2-low asthma phenotype (or non-T2 endotype), after which a search for an effective treatment could become a more realistic option for such patients.

Fourth Dilemma: Age. How Old (or Young) Should Our Patients be for Indication for Biologicals?

Allergic asthma is usually an early-onset (during childhood, before the age of 12 years), but not necessarily, while eosinophilic asthma is usually a late-onset, but also not necessarily. In children, after the age of 6 years, omalizumab showed good tolerability and safety, while anti-IL-5 treatment mepolizumab and benralizumab are recommended after the age of 12 years (reslizumab after the age of 18), as well as dupilumab with the indication for severe asthma[46]. Registries of severe asthma patients show that the average age of severe asthma patients receiving biologicals is older than 50 years, with a median of 56 years (with the oldest patient at the age of 83 years)[47]. In the group of late-onset severe asthma, there is also a group of patients with a "Non-T2 high" phenotype. They have neutrophils in induced sputum and are steroid-resistant. At this moment of medical science development, this group will not benefit from any of today's known biologicals[45]. Once again, the most important factor is to distinguish and properly define the asthma phenotype, to identify all comorbidities, the level of symptoms with the quality of life achieved with standard asthma treatment and good adherence, and to assess the potential benefit of biologic therapy. This should be done in a precise medical manner, personally in just that patient, with defined goals in asthma treatment by the patient himself[48], while chronological age is the least important factor.

Of course, our goal is also to find younger patients, able to work, or to improve their education, to ensure them a full life, by preventing exacerbations and airway remodelling with the least damage and side effects of medical treatment of their asthma.

Fifth Dilemma: Length of Treatment Appropriate to Assess a Patient's Response to Biologicals ("Responder" or "Non-responders")

We do not have a universally accepted definition of response to biologicals in severe asthma. There is no one parameter most important in an evaluation. Most experts agree that it is necessary to assess different asthma elements during follow-up, from the clinical point (frequency of exacerbations, symptom score), lung function, therapy dosages that patients need to control asthma symptoms, as well as inflammatory biomarkers values[49]. In the present-day perspective, it is also essential to have shared decision making. The importance of a conversation should be emphasized, which will define the patient's goals in biological treatment–that together,the patient and his physician should decide what the asthmatic person would like to improve with his asthma[48].

Responses to biological drugs in severe asthma are defined as super responders, partially responders and non-responders[50]. In this group of 114 Dutch patients with severe asthma treated with antiIL-5 therapy, it was established that 14% of super responders, after two years of follow-up had no residual manifestation of asthma. The majority consisted of partial responders, 69%, who have some asthma symptoms occasionally, while the smallest group were non-responders, 11% of patients whose asthma showed clinical worsening. Amongthe experienced residual manifestations of the disease most often were uncontrolled asthma symptoms, impaired lung function, and uncontrolled sinonasal symptoms.

A reasonable period for assessment of biological treatment response in severe asthma patients is one (the first) year of treatment (12 months), enough to count the number of exacerbations, oral steroid dosage, asthma control, eosinophilia, and estimate trends in lung function.

Different health care providers and insurance companies have different indications as well as rules for assessing the efficacy of biological therapy in severe asthma, sometimes even medically and scientifically non-logical and not correct. An example is that in some countries if a patient during omalizumab treatment for the first 4 months could not stop oral steroids, he or she is considered a non-responder, which is wrong. Many studies conducted with any biological treatment have revealed that more than a third of patients with severe asthma could not stop their steroid treatment (51), despite step 5 GINA treatment, good adherence and proper inhaler technique applied, with administered biologicals in concordance with asthma phenotype and type 2 inflammation (although 80% of patients significantly reduce steroid dosage[52]). Although patients could not stop steroids, they experience other benefits from biologicals, like less frequent exacerbations and overall quality of life, so it is an injustice to withdraw omalizumab after such a short period of treatment. GINA strategy suggests that 4 months should be adequate for assessment of mepolizumab response, but NICE guidelines indicated 12 months of treatment of mepolizumab[53].

The next question is about the duration of biological treatment when a person has at least a partial response. Some countries have the rule to quit biologicals after 2 years of treatment, despite good response, which is considered too short in the asthma scientific community. There are not many studies published on the length of biological treatment, as well as what happens after the discontinuation of biological therapy. Results from the Spanish severe asthma registry have shown that the effects of 6 years of omalizumab may persist after discontinuation of therapy in 60% of patients for at least 4 years[54]. There are no published data with results for other biologicals because they are of a shorter time in real life praxis with severe asthma patients' therapy. It is of utter importance to assess the duration of therapy seriously, with all sides and on a multidisciplinary basis, i.e. clinically, functional measurements, and laboratory biomarkers, as well as to discuss with the patient, and only then the proper decision should be made.

Sixth Dilemma: Should we Treat a Patient With Severe Asthma and Another Significant Disease, Like Allergic Broncho-pulmonary Aspergillosis (ABPA), or Eosinophilic Granulomatosis with Polyangiitis (EGPA)?

Biologics have been used in recent years to treat ABPA and EGPA in patients with severe asthma. However, robust clinical evidence of biological therapy efficacy in severe asthma with allergic broncho-pulmonary aspergillosis (ABPA) is lacking and still out of the label[55]. ABPA develops in susceptible patients whose airways are colonized with *Aspergillus fumigatus*. ABPA develops in 1-5% of asthmatic patients or 2-15% of patients with cystic fibrosis.

Biologics are used in patients with severe asthma and ABPA who have frequent acute exacerbations, who did not have a response to antifungal medication and in patients with stage IV ABPA (steroid-dependent asthma). All biologicals available for severe asthma have been applied, anti-IgE (omalizumab), anti-IL-5 (mepolizumab and benralizumab), and anti IL4/13(dupilumab). In all treated groups an improvement has been shown, with fewer exacerbations and symptoms with a steroid-sparing effect. The best improvement was found in lung function measured by FEV_1 in the vast majority of patients, where an improvement of more than 10% has been considered clinically relevant based on patient perception[56]. With the purpose to avoid hyper-eosinophilia, dupilumabwas introduced simultaneously with oral steroids[57].

EGPA became an indication for targeted biological anti-IL-5 treatment, with the

first FDA approval in 2017 for mepolizumab, but in a higher dose of 300 mg subcutaneously (sc.), while in Europe it is still not approved for this indication of EGPA, and not in this higher dose (just in a dose of 100 mg for severe asthma[58]). EGPA is always connected with asthma, hyper-eosinophilic syndrome, often rhinosinusitis with nasal polyps, as well as damage to two or more organs due to necrotising vasculitis of small vessels (heart, lung, skin, kidneys, gastrointestinal or nervous system). With the purpose of induction or maintenance of remission or preventing relapse or refractory EGPA, higher dosages of mepolizumab were applied. Further studies of EGPA treatment with "asthma-tailored" dosages (100 mg sc. every 4 weeks (q4 w) instead of 300 mg sc.q4w) have shown an improvement also clinically and in reducing steroid burden. It has been proven that anti-IL-5 treatment (besides mepolizumab, also benralizumab[59] and reslizumab is not approved for routine usage for patients yet, but a promising clinical trial has been published[60]) improves sinonasal scores, reduces asthma symptoms, improves lung function, decreases blood eosinophil count, and significantly decreases steroid dosage.

Conclusion

Severe asthma often has anatypical presentation, so first, we have to be sure which disease we are treating, and with which comorbidities. Efforts should be addressed to adherence, proper inhaler technique, and then the right treatment to the right patient at the right time. Due to the heterogeneity of asthma, and the fact that some biomarkers do not differ between clinical phenotypes, clinical phenotypes alone are not precise enough to guide targeted biological therapy. Mandatory for the choice of biologicals are biomarkers values, total and specific immunoglobulinE (IgE), eosinophils in blood and (induced) sputum, as well as fractional exhaled nitric oxide (FeNO). When we take everything into consideration, including clinical and laboratory aspects, together with functional tests and imaging, we can make a personalized choice of treatment, with a reasonable chance for significant improvement for our severe asthma patients. Still, there are many controversies and dilemmas in the field.

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