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Uncontrolled severe asthma: starting from the unmet needs

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In the last decades bronchial asthma has represented a main focus of both basic and pharmacological research. In fact, the knowledge about pathophysiological mechanisms and phenotypes as well as the treatment opportunities have substantially increased [1]. In particular, the introduction of biologic drugs for severe asthma is leading a revolution in terms of pharmacological therapy, by paving the way to the precision medicine approach [1].

Nevertheless,, asthma management still represents a challenge worldwide. Particularly severe asthma and asthma control are the main unmet needs in the field [2]. The last, which is actually independent of asthma severity, is even more impacting when it regards severe asthma. In fact, although severe asthma represents a small proportion of the overall asthma prevalence, it substantially contributes to the global burden of the disease, especially when uncontrolled [2,3]. Many aspects of individual and community life may be affected by severe uncontrolled asthma (SUA). The article by Chen and co-workers in *Curr Med Res Opin* points out the major criticisms related to SUA, such as its epidemiology, clinical features, the impact of the novel therapies in term of efficacy and costs [3]. Some shadows still characterize the knowledge about severe asthma, and probably limit its optimal management. Starting from the basics, how frequent severe asthma is?

Although the prevalence of asthma is globally well known, ranging from 6% to 9% of the general population [2], the frequency of severe asthma and SUA is still poorly defined. Actually, the impressively large range of its frequency, from 1.8 to 38% reported by different studies [3,4] suggests that the topic is still controversial. This reflects deep differences in terms of population samples, definitions and methodology, as well as the complexity of this sort of research. In fact, even though the ERS/ATS guidelines on severe asthma have quite recently clarified some controversial aspects and are currently the most accepted ones [5], the identification of severe asthmatic patients cannot rely on easy and immediate tools such as

questionnaires or patient reported outcomes only, but it implies a careful and experienced evaluation of clinical (exacerbations, use of oral steroids) and functional parameters, as well as the correct intake of the prescribed treatments. On one side, an involvement of GPs and other specialists is required for the emersion of severe asthmatic patients who still miss a correct assessment of their disease. On the other side, it implies a widely shared knowledge about the disease, and requires a long journey in terms of training. Alternatively, the analysis of large electronic databases including asthmatic patients can detect the ones with severe asthma according to the medications dispensed and the health resources utilized [2,4]. But still, this way is not free of biases, especially if the data come from a specialist setting.

Severe asthma definition itself includes some critical aspects. From a clinical point of view the grading system of asthma severity is mainly based on the recurrence of exacerbations as well as the need of oral steroids as an add on treatment [5]. However, a standardized definition and grading of exacerbations are still lacking [5]. Furthermore, while asthma-related hospital admissions can be considered a proxy of severe exacerbations in the frame of a difficult to treat asthma, the access to Emergency department may be due to acute relapses of uncontrolled but not truly severe asthma [6,7]. In fact, according to our personal data almost 50% of Emergency Department admissions for asthma were coded as green or white at the triage [8]. Most of those patients were immigrants, who sought the Emergency Department as easiest access to the NHS, independently from the severity of the disease.

As far as severe asthma treatment is concerned, the introduction of biologics has for sure represented a relevant step forward, and the growing number of new drugs in the field will increase the chances for an optimal control in more patients [1]. Although an improvement in terms of pulmonary function has not been systematically assessed in patients treated with biologics, a significant reduction of the number of exacerbation and of the use of OCS represent the most positive outcomes [1]. Nevertheless, some substantial limitations still contribute to the burden of SUA. First of all, the available biologic treatments and the upcoming ones only target allergic and eosinophilic asthma [1]. In fact, Th2 high phenotype accounts for the biggest proportion of severe asthma, but still Th2 low phenotype is not negligible, also because it is usually characterized by a reduced response to ICS and OCS [9]. Second, a proportion of patients, ranging from 20% to 30%, do not respond to the treatment despite the eligibility criteria are fully matched [10]. In the era of "Precision Medicine" the issue of "non responders" is crucial for the biologic treatments sustainability, under a clinical and economic perspective [3]. The evaluation of the clinical response itself might be complex and includes many aspects, which differently characterize each patient [1]. For instance, lung function is generally considered the hallmark of asthma control, but talking about severe asthma, exacerbations and the frequent use of OCS are the most relevant aspects, in terms of both asthma severity grading and treatment response evaluation [5]. In fact, lung function itself maybe not so linearly related to the recurrence and the severity of exacerbations. Furthermore, the effect of a biologic treatment on lung function should be evaluated according to different risks factors such as duration of the disease, current or previous smoking habit, presence of comorbidities. At the same time concomitant comorbidities, such as obesity or psychiatric conditions, may negatively affect the perception of the functional improvement due to the treatment. Higher eosinophil count has been also related to a more severe disease [11] but the individual intrinsic variability of this parameter [12] has to be taken into account. Likewise, the effect on the quality of life is controversial [3], being perhaps more relevant in allergic asthma. However, the perception of QoL improvement can be affected by several patient-related conditions, such as duration of the disease, type of job, hobbies, and psychological aptitudes [1,3]. Therefore, patients with more active style of life or shorter length of the disease, or younger, like allergic patients, might better appreciate the clinical improvement due to the biologic treatment. Furthermore, a substantial lack of correlation between different parameters can be observed during the treatment course in some cases. In the case of mepolizumab, although a significant reduction of blood eosinophils can be

observed in every treated patient, the response in terms of lung function or FeNO value can present a great variability [13]. The observation suggests possible different targets for the same class of drugs. Thus, besides the effect on exacerbations and the use of OCS, the clinical response assessment should be tailored on the specific patient profile before deciding to continue, stop or change an on-going treatment. Investigating the association between some specific asthma sub-phenotype and the grade of the clinical response might be helpful in improving the patient selection step, which currently represents the more critical issue in the field of biologics. In other words, reliable biomarkers able to predict the clinical response to a biologic drug are still lacking [14]. Such biomarkers would be particularly helpful in the case of patients potentially eligible for more than one treatment. For example, a patient presenting high levels of eosinophils and a history of severe allergic asthma with sensitization to perennial allergens could be addressed to both anti IgE and anti IL5 biologics; the choice between the two treatment options is mainly based on a clinical ground and on the expertise of the clinician prescribing the drug [15]. Reducing the risk of a non-response would be optimal also for the treatment sustainability, including clinical and economic issues. The costs of the new biologic treatments represent a major drawback [3]. However, the cost/benefit ratio is certainly reduced by the decrease of ED access and hospitalizations. At the same time, the lower use of OCS, reported in most of studies carried out with OMZ and anti IL 5 therapies limits the costs due to the OCS side effects. This is particularly true for patients who are on regular treatment [16], but also an intermittent use is responsible for systemic side effects [17] as well as regular ICS at high dosages [18]. A further perspective that can be taken in account is the efficacy of the biologic treatments on concomitant comorbidities, which can further positively impact on costs. This is the case of patients with concomitant nasal polyposis, who are frequently treated with OCS and surgical intervention for relapses [19]. Another potential issue to be taken into consideration in severe asthma management is the long-term safety of biologics. Differently from OMZ, the anti IL5 monoclonal has been recently introduced in the real-life practice. For OMZ the risk of the development of cancer [20] has been denied, but a significant association with cardiovascular diseases has been reported in the United States [21]. Therefore, a strict surveillance over the time is needed, and the assessment of biologics safety has to be a priority in the national severe asthma networks.

In conclusion, we have extremely effective therapeutic options for the management of SUA but not so effective tools for optimally select the right strategy. Furthermore, the knowledge about asthma pathophysiological mechanisms should be oriented to the early identification of asthma phenotypes which will evolve in severe and potentially difficult to control asthma so that preventive treatments, maybe including some biological treatment and for sure immunotherapy when indicated, could be initiated in a preventive perspective, before a potentially irreversible stage.

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