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EDITORIAL

ASTHMA AND SEVERE ASTHMA MANAGEMENT IN THE CLINICAL PRACTICE

Combined approach to define the clinical impact and decision making in asthmatics

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In the population of patients suffering from bronchial asthma accurate diagnosis should precede an appropriate and proportional access to medications. Current European Respiratory Society (ERS) and American Thoracic Society (ATS), and GINA guidelines for severe asthma[1-3] recommend as first choice high dose inhaled corticosteroids (ICS) and long-acting bronchodilators (long-acting beta-2 agonists [LABA] with/without long acting muscarinic antagonist [LAMA]) or as alternatives, leukotriene modifiers, theophylline as controller according to the patient's severity.[1-3] Combination treatment with some of these agents and, and in particular ICS, LABA, and LAMA, now available in a single inhaler,[4] may be required to put and maintain control disease in severe asthmatics. Even if in a small but clinically demanding patients, particularly allergic or with type-2 profile, new biologic therapies may be required.[5]

Insights of asthma and severe asthma have improved over the last years, following the application of precision medicine as the driving approach.[5] Notwithstanding, much more knowledge gap still remains to fill both in terms of biology and immunology throughout the course of the disease, which includes matching appropriate therapies with specific phenotypes and endotypes.

The most important advance over the last 20 years is the better understanding of severe asthma not as a continuum worsening starting from mild asthma, but as a different disease entity,[1, 3, 5, 6] to be phenotyped beyond the classical identification of reversible respiratory symptoms/airway obstruction and bronchial hyperresponsiveness.[7] This has led scientific community to better identify and define what severe asthma is, *i.e.* "asthma which requires treatment with high dose corticosteroids (CSs), plus a 2nd controller, to remain controlled or which remains uncontrolled despite this therapy."[1, 3]

Despite improvement in definition, prevalence of severe asthma remains undefined with only rough and variable estimates (5% to 10%) among all the asthmatics individuals,[6, 8] with a clear predominance in the early childhood or mid-adulthood.[9] This uncertainty relies on the possible gap between clinical or physiological confirmation (current or previous reversible airway obstruction with spirometry or methacholine challenge), and biologic testing such as biomarkers for type 2 (T2) inflammation, blood/sputum eosinophils, nitric oxide fraction (FeNO), in exhaled air, serum IgE antibodies,[10] or other biomarkers of autoimmunity for differential diagnosis,[11] and even the treatment adherence or symptoms control.[12]

Most important, an accurate phenotypic/endo-

typic diagnostic assessment also requires search and management of comorbidities (*e.g.* sinus disease, nasal polyps, gastro-esophageal reflux, atopic dermatitis, etc.) which is nowadays essential in order to best match asthma profile with the therapeutic options that actually include biologic medications.[13] To this scope, the Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes (U-BIOPRED) study has defined strategies to accurately assess the T2 phenotyping of asthma patients.[14] However, little is known about the trajectories of these identifiable phenotypes based on monitoring both the clinical and biological characteristics. Similarly, no definitive conclusions are still available about the predictive role of any of these biomarkers, once assessed earlier, in terms of the disease course.[15]

To date there are five registered and available biologic therapies for patients with severe asthma.[5] These approved monoclonal antibodies differ in patient's response according to their specific targets and have shown efficacy in response to an abnormal rise in T2 systemic inflammation and/or circulating IgE in allergic individuals. Remarkably, outside a specific T2 inflammatory response, the so called low-T2 asthmatics still do not have any definitive response of adequate therapies such as biologics or other drugs (*i.e.* azithromycin), nor different physical approaches such as bronchial thermoplasty could be widely recommended.[16] Genetic or molecular mechanisms associated with these phenotypes/endotypes remain poorly understood.[5]

Final, and most important on the clinical ground, still several patients suffer from sudden acute asthma attacks by not responding to usual and/or specific biologic therapies. Which potentially leads patients to respiratory distress and death.[17]

With this review series published as a journal special issue on severe asthma, we aim at updating the actual knowledge in adult asthma. Experts and opinion leaders were therefore invited to contribute to a shared editorial plan. The journal editor's choice in this series was to mix-up narrative with systematic reviews according to the different topics included.

Tagliabue *et al*.,[18] from Genoa, Italy, provide a narrative review on the epidemiology of severe asthma and international registries. Ricciardolo *et al*.,[19] from Turin, Italy, and Malta, are presenting a systematic review on asthma phenotypes/endotypes. Biddiscombe and Usmani,[20] from London, UK, offer an overview of delivery and compliance with inhaled therapy in asthma. Edris and Lahousse[21] from Ghent, Belgium, have systematically reviewed all papers on the use of monoclonal antibodies to treat type 2 asthma. Correia-de-Sousa *et al*.,[22] from Portugal, are tackling the management of asthma in primary health care. Lastly, Bosi *et al*.,[23] from Modena, Italy, investigated the management of critically ill asthma attacks.

The general aim with this series is to highlight the main key points that actually drive the most appropriate management of patients with bronchial asthma and severe asthma in particular. We are confident that the series' content will enable readers to update information in order to translate knowledge into a best practice for specialists and even for current practitioners. With regard to this, in particular, a special focus was placed on how to manage asthmatic individuals in the primary care, including treatment compliance, which is one of the pivotal aspect that has been reported recently by a joint European task force.[24]

As for the premises above, large room was given to the most relevant aspect dealing with the patient's phenotyping and the advanced personalized therapy offered by the available monoclonal antibodies pointing out their expanded role with the syndromic aspects of the disease in adults. Last, but not least, a specific focus and attention on the acute asthma attack has been given since still several individuals come to emergency unaware of this risky condition to their life.

Overall, this series of reviews would like to raise awareness on a very serious condition, namely bronchial asthma, which is still underestimated for its consequences. In particular, integrating approach in those patients not controlled should prompt a better understanding of a possible specific phenotype, in relation to important biological/immunological/genetic pathways and clinical characteristics such as age, onset, and other clinical features.

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