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Is mild asthma in real life always in the Green Zone?

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Asthma is a chronic inflammatory disease of the airways that is characterized by variable narrowing of the airways and symptoms of intermittent dyspnea, wheezing, and nighttime or early-morning coughing. Asthma is a major health problem throughout the world, affecting an estimated 315 million persons of all ages. Asthma is clinically heterogeneous, and its pathophysiology is complex. For convenience, asthma action plans are often broken down into three zones, usually based on peak flow meter recordings: green, yellow, and red according to the level of lung function impairment. Recent evidence shows that every asthmatic is potentially at risk for severe exacerbation independently of his/her zone, including the green zone. Furthermore, in real life scenario asthmatic patients can have poor perception of their symptoms or/and overestimate their level of asthma control, and this can obviously confound the clinical picture and favor sudden worsening of symptoms. To understand how to treat these patients, as well as how to assess their future risk, can make a difference in terms of clinical outcomes and prognosis. Following the suggestions and concerns recently published, who recently focused on the clinical management of mild asthma, we aimed at exploring strengthens and gaps in the daily management of the mildest forms of the disease, with a focus on alternative diagnostic and therapeutic strategies in approaching the "green" patient in clinical practice.

KEY WORDS: Asthma - Asthma, prevention and control - Diagnosis.

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The daily management of mild forms of asthma ideally relies on a self-management approach that is shared and accepted by patients and physicians. For convenience, asthma action plans are often broken down into three zones, usually based on peak flow meter recordings: green, yellow, and red according to the level of lung function impairment. In particular, the Green Zone should ideally be the ideal living condition, that is, "no asthma symptoms", meaning that the patient is able to perform usual activities and sleep without coughing, wheezing, or breathing difficulties, and the peak flow recording is above 80% of personal best. The patient living in the Green Zone is expected to suffer from mild forms of asthma, or alternatively mild asthmatics are expected to always live in the Green

TABLE I.—Critical topics in asthmatic patient suffering of mild asthma.

a) Most patients with asthma have mild persistent disease, which tends to be underdiagnosed and undertreated
b) The diagnosis of asthma is based on the presence of symptoms of dyspnea, cough, and wheezing and objective confirmation of variable airflow limitation that is at least partially reversible
c) For mild persistent asthma, regular controller treatment with low-dose inhaled glucocorticoids and rescue treatment with short-acting beta2-agonists, as needed, is recommended as the initial treatment
d) If asthma control is not achieved within 3 to 4 months, maintenance treatment should be stepped up with the addition of a second controller medication (long-acting beta2-agonist or leukotriene modifier) or with an increase in the dose of inhaled glucocorticoids
e) Ongoing patient education, written action plans, and regular follow-up visits to reassess asthma control and adjust therapy are integral to successful management
f) Regular treatment and therapy adherence are important also in mild asthmatic subjects, as it has been reported that a consistent number of subjects suffering from chronic respiratory diseases spontaneously quit the inhaled therapy [6]

Zone, but this is not the case. Indeed, a discrepancy exists between "fixed" asthma classification according to official documents of the scientific societies and real life conditions in which the asthmatic state can drastically and suddenly change, even in the mildest forms. Recent evidence shows that every asthmatic is potentially at risk for severe exacerbation;[1] furthermore, asthmatic patients can have poor perception of their symptoms or/and overestimate their level of asthma control. In real life scenario, not well controlled patients with asthma tend to consider themselves "completely" or "well controlled" despite their symptoms,[2] and this can obviously confound the clinical picture. To know how to treat these patients, but also how to assess their future risk, can make a difference in terms of clinical outcomes and prognosis.

Bel recently published an article that focuses on the clinical management of mild asthma.[3] Various therapeutic strategies are presented, followed by a review of official guidelines. The diagnosis of asthma, based on the presence of typical symptoms and on objective confirmation of variable airflow limitation that is at least partially reversible is clearly presented. Other recommendations from guidelines of The Global Initiative for Asthma (GINA) [4] and of the National Asthma Education and Prevention Program (NAEPP) of the National Heart, Lung, and Blood Institute [5] are reported, such as patient education, avoidance of triggers and pharmacological treatment. Finally, the article concludes with clinical recommendations on the interpretation of daytime and nighttime symptoms and exercise impairment, which suggest inadequate control. Before initiating daily controller treatment, the Author suggests a confirmation of the diagnosis of asthma by lung function assessment (spirometry or, in the absence of reversibility, through a bronchoprovocation challenge test with inhaled spasmogen). Furthermore, it is stressed that if the patient has a good response to low-dose inhaled glucocorticoids the dosage of inhaled medications should be further titrated to the lowest possible required to maintain asthma control. Following the suggestions and concerns that are raised by the article from Bel,[3] we aimed at exploring strengthens and gaps in the daily management of mild asthma, with a focus on alternative diagnostic and therapeutic strategies in approaching the patient in clinical practice.

Table I shows the critical topics in asthmatic patient suffering of mild asthma.

Strengthens and gaps: what is known and what should be known

The article by Bel has the merit of highlighting the clinical implications of mild asthma, and the consequences of uncontrolled disease in this stage. Most important, a careful revision of different therapeutic options is provided. Single-inhaler combination therapy, consisting of an inhaled glucocorticoid and a long-acting beta2-agonist,

is used for the treatment of patients with moderate asthma.[7] Whether this strategy is effective and safe in patients with mild asthma remains to be investigated. When adequate control of asthma is maintained at a low dose of inhaled glucocorticoids for 3 to 4 months, guidelines recommend stepping down the therapy. Proposed step-down strategies include a switch to intermittent use of inhaled glucocorticoids,[8] regular use of a leukotriene receptor antagonist, or once-daily single-inhaler combination therapy with a glucocorticoid and a long-acting beta2-agonist.[7] However, the most appropriate step-down strategy remains uncertain. In addition, the author does not mention the possibility of using an inhaled combination treatment consisting of an inhaled glucocorticoid and a long-acting, rapid onset beta2-agonist, as needed. The use of corticosteroid "as needed" or in "intermittent fashion" is interesting and requires deeper thinking. Perhaps, the "BEST" strategy [5] should be more widely evaluated, at least in the mild range of asthma severity, and tailored on the specific individual characteristics of the patient, as several studies showed similar efficacy in patients treated by chronic vs. intermittent therapy, and the interpretation of efficacy depends furthermore from the selected endpoint.[9-11] As mentioned earlier, this approach more accurately reflects the real life scenario.

Severe asthma exacerbations can occur even in patients with mild asthma that appears well controlled,[12] most often provoked by viral infections or exposure to known and unknown triggers. In this context, the use of biomarkers such as sputum eosinophil counts and exhaled nitric oxide levels is strongly advocated, but the role of these biomarkers in clinical practice remains uncertain.[13] In this regard, we suggest that mild asthmatics undergo, at least in their first assessment, a complete lung function evaluation (global spirometry and bronchoprovocation test). In these patients, the biological and functional involvement of small airways could occur, and should therefore be worth studying. Recent renewed interest underlines the role of the peripheral airways in asthma, being recognized as a relevant target for asthma treatment.[14]

In the current review all available tools that are actually used to manage mild asthma are clearly described, but the reader does not have the perception of a stepwise, and timely defined, approach. Short periods of loss of asthma control may occur as a result of exposure to nonspecific "triggers," such as fumes, pollution, strong smells, or exercise. Written action plans should be strongly implemented in daily clinical practice to prevent loss of asthma control. A large body of literature confirms the contribution of action plans in optimally managing asthma.[15] The asthma evaluation implies at each step a comprehensive lung function assessment. A stepwise approach to pharmacologic treatment, in which treatment is initiated and adjusted on the basis of ongoing assessments of the patient's level of asthma control, is presented and discussed, but it gets lost in an unlikely algorithm that can rarely be applied in clinical practice when treating mild forms of asthma. Furthermore, the effort to list all asthma medications and to classify them is somehow redundant and not crucial for the aims of the paper.

In the current review, the author claims that the role of specific immunotherapy in asthma, as compared with other treatment options, is relatively modest. This concept is not totally true:[16] actually, several clinical trials and meta-analyses on the efficacy of specific immunotherapy confirm the additional benefit provided by this approach,[17] mostly in mild allergic asthma. Specific immunotherapy has been shown to be effective in reducing asthma symptoms [18] and airway hyperresponsiveness,[19] in patients with a single, well-defined allergen, and in modifying the natural course of the disease,[18] and should therefore be considered not only when there is a substantial allergic contribution to patient's symptoms, and pharmacologic intervention and avoidance of environmental allergens have failed to control the asthma, but also when preventing the impact of the allergic rhinitis on asthma. This does not preclude the use of specific immunotherapy in conjunction

with pharmacological treatment. The one-airway concept is nowadays well accepted by the scientific community and based on strong epidemiological, functional and biological links.[20, 21] In addition, the two conditions share similar genetic and environmental risk factors.

As recently pointed out by Levy [22] in his comment on the article by Bel, the work-related phenotype is not included among the clinical manifestations of mild asthma. This is not a negligible issue, since occupational asthma accounts for up to 15% of asthma cases in adults.[23] In this respect, a careful investigation of the exposure to causative or triggering factors of asthma in the workplace can allow to adopt preventive strategies.

Unknown or underestimated issues in managing mild asthma

The therapeutic approach to mild asthmatic patients does not have to understate the presence of comorbidity i.e. upper airway obstructions, rhinitis, sinusitis, postnasal drip, nocturnal apnea. Sudden exacerbations of asthma could occur in patients in the Green Zone of control in presence of gastroesophageal reflux disease (GERD) and postnasal drip syndrome. According to current literature, pathological GERD can be found in 30% to 80% of patients with asthma. On the other hand, patients with esophagitis are more likely to have asthma than patients without esophagitis. In the ProGERD study,[24] the occurrence of asthma depended on longer GERD duration and was more prominent in male and older subjects while the type of GERD disease and weight and gender did not have significant relationship with asthma.[25] Another interesting systematic review (28 epidemiological studies) found a 59.2% weighted average prevalence of GERD symptoms in asthmatic patients, compared to 38.1% in controls. The corresponding prevalence of asthma in GERD patients was 4.6%, compared to 3.9% in controls.[26] One longitudinal study [27] showed a significant association between a diagnosis of asthma and a subsequent diagnosis of GERD, whereas the two studies that assessed whether GERD precedes asthma gave inconsistent results.[28] GERD should be considered in different asthma phenotypes: 1. asthmatic patients who initially present in adulthood, 2. asthmatic patients without an intrinsic component, 3. asthmatic patients not responding to bronchodilator or steroid therapy, 4. asthmatic patients featuring frequent exacerbations. Current guidelines recommend that physicians consider treating patients who have poorly controlled asthma for GERD, even without GERD symptoms. Recent data suggest that chronic treatment is not a useful practice for mild-to-moderate asthmatic patients.[29]

Sometimes, postnasal drip syndrome is associated with asthma as the thick mucus secretions drain from the back of the nose to the back of the throat, causing throat clearing, cough, and bronchial constriction Chronic sinusitis with nasal poliposis, even when not IgE mediated and not associated to acid acetylsalicylic sensitization, is significantly associated with lung function impairment and peripheral eosinophilia.[30] These data are suggestive not only of the occurrence of an independent risk factor for asthma exacerbations, but also of a defined asthma phenotype.

This knowledge and the clinical experience require the use of diagnostic procedures to confirm upper and lower respiratory diseases regardless of rhinitis or asthma symptoms. Consequently, optimal therapeutic effects will be achieved only if both levels are simultaneously treated. The Author underestimates the therapeutic role of intranasal glucocorticosteroids over oral H1-antihistamines and oral leukotriene receptors antagonists. A modern treatment of mild allergic asthma should be based on anti-inflammatory therapy on both levels, in particular with intranasal and inhalation corticosteroids and oral leukotriene receptors antagonists. This is supported by observations on the reduction in the rate of hospital admittance and emergency department visits for asthma exacerbations following nasal steroid treatment.[31, 32] Notably,

a systematic review on the efficacy of intranasal corticosteroid medications on asthma outcomes in patients with allergic rhinitis and asthma (for a total of 18 trials with a total of 2162 patients) has been published.[33]

The results of this study lend support to the unified airway theory, namely that treatment of the upper airway can significantly affect lower airway function. This was especially true, even if not conclusive, for outcomes measuring pulmonary function and bronchial hyper reactivity, suggesting that a decrease in upper airway inflammation may lead to a decrease in lower airway reactivity.[33-36] Beyond the therapeutic aspects, the lung functional evaluation remains a topic of debate among between general practitioners (GPs). In a recent investigation that involved GPs, it was reported that in presence of a chronic respiratory disease, in 37% of the cases were not prescribed spirometry (REF). We strongly believe that the prescription of lung function test should be implemented in order to improve the outcomes in mild asthmatic subjects. Diagnosis of mild asthma could be difficult or underestimated in those patients suffering from allergic rhinitis because usually they relate dyspnoea to nasal congestion and rarely refer bronchial symptoms to the doctor. Recently, a study was performed in a large group (1469 subjects) of adult allergic rhinitic patients to investigate the frequency of response to bronchodilation test and FEF25–75 values. Two third of the patients had significant response to bronchodilation tests and almost 20% had impairment of $FEF_{25-75\%}$ values (<65% predicted). This finding should be adequately considered as a precocious spirometry may allow the early detection of patients susceptible to develop asthma, and consequently to treat and monitor them.[37]

Open questions and potential scenarios

To better define the Green Zone, what we would like to know is whether leaving mild asthma untreated will eventually lead to more severe forms of the disease, both in terms of pathological changes (remodeling) and functional worsening (non reversible obstruction). This question would require a large randomized clinical trial lasting at least ten years, in which a group of asthmatics is left with rescue medication and the other undergoes regular steroid treatment. Biopsies should be performed at least at 2 year intervals. Unfortunately, such study is unethical and rather impossible to carry on, although it is envisaged as the unique opportunity to provide a definite answer to this dilemma.

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