EDITORIAL

Refractory Asthma: the Ongoing Debate

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Refractory asthma is defined as asthma with persistent symptoms or asthma with frequent or serious exacerbations accompanied by persistent airflow obstruction despite high doses of corticosteroids. Other equivalent designations would be difficult-to-control asthma or treatment-resistant asthma. In the process of arriving at a classification of refractory asthma, other processes with similar symptoms need to be ruled out, potentially aggravating factors need to be controlled, and adherence to therapy needs to be optimal.[1] Most patients with refractory asthma consult the pneumologist after having undergone many different treatments. Although refractory asthma patients are quite a small group (5%-10% of the total), they need to be identified given that they account for at least half of the overall costs associated with the disease.[2] Refractory asthma may be classified in any one of the clinically severe asthma groups.[3] Most refractory asthmatics have persistent diurnal and nocturnal symptoms; other asthmatics show few symptoms on a routine basis but present with severe exacerbations. From the clinical point of view, the range of refractory asthmas include: *a)* brittle asthma, with wide and/or brusque peak flow variability; *b)* asthma with accelerated loss of lung function; *c)* asthma with permanent airflow limitation; *d)* asthma with copious expectoration; and *e)* asthma with varying responses to corticosteroids.

When a patient with refractory asthma visits the specialist, he or she is usually symptomatic. Consideration of the problem from scratch is recommended, and the first step is to determine whether the patient really has asthma. In the differential diagnosis of the triad of cough, wheeze, and breathlessness, other diseases such as chronic obstructive pulmonary disease (COPD), cystic fibrosis, vocal chord dysfunction, sleep apnea, Churg-Strauss syndrome, left ventricular failure, and allergic bronchopulmonary mycosis should be ruled out. The required battery of tests includes a bronchial challenge and dilatation test of hyperresponsiveness, skin prick tests for typical aeroallergens, chest x-ray, blood and sputum eosinophil counts, serum immunoglobulin E levels, fungal radioallergosorbent test, and—for obese patients—a polysomnograph. In this initial evaluation of the patient, computed tomography (CT) of the facial sinuses and 24-hour monitoring of esophageal pH is recommended in order to rule out sinusitis and gastroesophageal reflux. Once an asthma diagnosis is certain, the next step consists of ruling out poorly controlled asthma; for this purpose, a study of previous medical history is essential,[4] as asthma severity will be determined by the minimum medication required to achieve adequate control of symptoms.[5] This process requires a period of strict monitoring in order to determine the severity of the asthma. It also requires monitoring of at least some of the bronchial inflammation markers (sputum eosinophil levels, exhaled nitric oxide, and airway hyperresponsiveness), an evaluation of possible environmental (eg, tobacco) and occupational agents, and strict adherence to high-dose anti-inflammatory treatment. During this monitoring period, which may last 6 to 12 months, 2 problems may interfere with the patient's control of the disease: a failure to comply with treatment and the presence of comorbidities.

Adherence to therapy and an optimal method for administering medicine constitute the first goals in ensuring that a patient with refractory asthma is correctly classified. Enough emphasis cannot be placed on the problem of therapeutic adherence. López Viña[6] underlined the need to understand each asthma patient's psychology and genuine willingness to change behavior. This author also pointed to the need for ongoing care by the physician, who should provide a written self-management program for asthmatics that involves regular measurements of peak flow. It has been demonstrated that most exacerbations are preceded by a clinical deterioration prodrome that lasts 3 to 5 days,[7] and so patients need to be able to immediately recognize a worsening of their asthma. In a study by Woolcock et al[8] of asthma monitored by means of frequent airway hyperresponsiveness measurements, study group subjects who received strictly monitored corticosteroid treatment showed a 10-to-100-fold decrease in the severity of airway hyperresponsiveness in comparison to a control group; this reduction,

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however, was only achieved after 5 to 15 months' treatment with inhaled corticosteroids. The authors concluded that the greater efficacy of treatment in the study group was due fundamentally to adherence to the antiinflammatory treatment program. The fact, moreover, that a substantial amount of time is needed to reduce bronchial hyperresponsiveness is yet another reason for strictly monitoring poorly controlled asthma.

The second reason patients fail to control their asthma is the possible coexistence of factors that may worsen the course of their disease, such as upper airway illness, gastroesophageal reflux, hyperventilation, psychiatric disorders, hyperthyroidism, and excessive use of β_2-agonists.[9] It is crucial to check for the existence of such factors, since asthma control will undoubtedly benefit greatly from control over any associated aggravating factors.[10] It is also crucial to investigate medications that may potentially aggravate asthma, such as non-steroidal antiinflammatory drugs and β-blockers.[11] A recent English study of 100 patients with difficult-to-treat asthma indicated that 32% of them were misdiagnosed, were non-adherent to treatment, or had psychiatric problems.[12] Only once adherence to treatment has been ensured and once comorbidities have been ruled out can a diagnosis of refractory asthma be postulated for a patient who continues to be symptomatic despite receiving high does of inhaled corticosteroids and long-acting β-agonists.

Heaney et al[13] identified certain characteristics that predicted a diagnosis of refractory asthma for a patient with a probability of 93%. These were a need to inhale a dose of more than 2000 μg daily of beclomethasone, previous assessment by a respiratory specialist, and—before bronchodilation—forced expiratory volume in 1 second (FEV_1) less than 70% predicted. The doubt remains, however, as to whether a refractory asthma phenotype really exists—a question which the ENFUMOSA cross-sectional multicenter study[14] aimed to answer. Designed to define a clinical phenotype of chronic severe asthma patients, that study identified the following characteristics of subjects in the chronic severe asthma group compared to the well-controlled asthma group: predominantly female, body mass index in the obesity range, a lesser degree of atopy, a significantly higher ratio of residual volume to total lung capacity, greater hypoxemia, and a lower ratio of carbon monoxide diffusing capacity to alveolar volume. This led the authors to conclude that there may be an important component of small airways disease in severe asthma, which in turn may indicate excessive airway remodeling. The same study pointed to the fact that poorly controlled asthma may be characterized by a suboptimal or diminished sensitivity to corticosteroids. It also revealed a predominantly neutrophilic inflammation in the sputum of severe asthmatics that was not present in the sputum of well-controlled asthmatics. This would corroborate the hypothesis that, in poorly controlled asthma, 2 types of bronchial inflammation are possible, namely, inflammations in which either eosinophils predominate or neutrophils predominate. It is not known whether neutrophils contribute to the pathophysiology of refractory asthma or whether, in fact, their presence reflects improved neutrophil survival in response to high doses of corticosteroids.

From the 2 aforementioned studies it can be deduced that patients with poorly controlled asthma are likely to have both bronchial inflammation that is resistant to conventional treatment and reduced lung function.

An asthma patient with persistent eosinophilic inflammation may be classified as having steroid-resistant or steroid-dependent asthma. In either case, treatment with high doses of corticosteroids is necessary in order to overcome the resistance induced by the activating protein-1 transcription factor, which blocks the glucocorticoid receptors.[15] Glucocorticoid receptor sensitivity may be restored by high doses of oral corticosteroids in an induction phase, and this phase may then be followed up by a maintenance phase at a lower dose. The fact that glucocorticoid receptor sensitivity may be restored was recently demonstrated in a double-blind trial[16] of a single injection of triamcinolone. In just 2 weeks excellent results were obtained in terms both of reducing percentage eosinophilic sputum levels and in improving FEV_1. In view of the fact that some asthmatics are only partially resistant to corticosteroids, the ATS Workshop on Refractory Asthma[1] recommends doubling the dose for a further 2 weeks if the standard corticosteroid test of 40 mg of prednisone daily for 2 weeks fails to produce a positive result. The efficacy of corticosteroid treatment may also be negatively affected by overuse of β-adrenergic agents; in such a context, resistance to corticosteroids may develop and the effect will increase as the β-adrenergic dose is reduced.[17]

Patients with refractory asthma often fail to normalize lung function in response to corticosteroid or β-agonist treatment. This could be because—despite a relatively normal FEV_1 at baseline—they may rapidly destabilize (ie, brittle asthmatics), or because they have irreversible airway obstruction. An irreversible FEV_1 result in a corticosteroid trial may lead to diagnostic confusion between asthma and COPD. Patients with brittle asthma, however, have a positive bronchodilator test and spontaneous variation in peak flow. The precise nature of permanent airway obstruction in some asthmatics is unknown, although epidemiological studies have demonstrated a gradual loss in lung function that is more pronounced in patients with late-onset asthma, and even more marked in smokers.[18] Lung function irreversibility is believed to be due to structural changes in the airways, a fact which would seem to be corroborated by chest CT studies, which have revealed an increase in emphysemic areas and in bronchiectasis in patients with more severe asthma.[19] Given that permanent lung function damage is the most outstanding feature of refractory asthma, this kind of asthma may logically be considered to be similar to

COPD in its physiology; in other words, a parallel may be drawn between irreversible airway obstruction and airway remodeling that is difficult to reverse. It is only to be expected, therefore, that satisfactory control will be difficult. Finally, the situation may also be complicated by the fact that some patients may indeed have both asthma and COPD.[20]

For patients with refractory asthma who remain symptomatic despite conventional treatment at high doses and control of concomitant illness, some studies have demonstrated modest but inconclusive effects for treatment with antiinflammatory and immunomodulating drugs such as phosphodiesterase inhibitors, cytokine antagonists, methotrexate, gold salts, cyclosporine, intravenous gamma-globulin, and macrolides. However, none of these drugs have been demonstrated to produce an improvement in bronchial hyperresponsiveness and further studies are needed to establish the risk-benefit ratio for their use.[21,22] The ENFUMOSA[14] study detected a significant increase in urinary leukotriene E4 levels among severe asthma patients compared to controlled asthma patients; this would suggest that antileukotriene agents may be useful for the treatment of severe asthma. Omalizumab, a monoclonal anti-immunoglobulin E antibody, has produced promising results in patients whose asthma remains poorly controlled despite high doses of corticosteroids. It is quite feasible that this drug will be included in the therapeutic arsenal for severe asthma in the future, as it seems to have a high degree of efficacy in that context.[23]

In conclusion, refractory asthma needs to be diagnosed on the basis of an initial meticulous evaluation that rules out processes other than asthma, detects comorbidities, and strictly monitors adherence to therapy that enhances the potency of combined corticosteroid, β-agonist and antileukotriene therapy until the best possible lung function is attained and symptoms disappear.

Many questions remain to be answered in relation to precisely how asthma evolves. For example, clinical remission as determined by established tests may not fully correspond to full remission of disease. In a 30-year cohort study of asthmatic patients by Vonk et al,[24] 57% of subjects with clinical remission continued to present with abnormal bronchial hyperresponsiveness and/or a reduced lung function. The doubt thus remains whether or not such anomalies represent irreversible sequelae of asthma on the airway structures. The hypothesis that a patient may develop refractory asthma because of a failure to control the initial bronchial inflammation is disturbing. That hypothesis is similar, in fact, to what happens to the smoker in the subclinical phase: progressive lesions develop in peripheral airways and eventually result in accelerated deterioration in FEV_1.

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