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Review Article

Refractory Asthma : An Overview

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Abstract

Patients whose asthma is not adequately controlled despite treatment pose a major clinical challenge and it is an important health care problem. It carries several names; each one points to an aspect of the disease. Chronic severe asthma, steroid-dependent asthma, steroid-resistant asthma, difficult-to-control asthma and refractory asthma are some of these terminologies. Patients with severe refractory disease often require regular oral corticosteroid with an increased risk of steroid-related adverse events. Alternatively, immunomodulatory and biologic therapies may be considered, but they show wide variation in efficacy across studies, thus limiting their generalization. Managing asthma that is refractory to standard treatment requires a systematic approach to evaluate adherence, ensure a correct diagnosis, identify coexisting disorders and trigger factors. In future phenotyping of patients with severe refractory asthma will also become an important element of this systematic approach.

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Introduction

Bronchial asthma is a common disease of which most patients are adequately treated by standard therapy. However, a small but worrying group of patients whose asthma is not adequately controlled despite conventional strategies of combination of high dose inhaled corticosteroids and long-acting bronchodilators pose a major clinical challenge and an important health care problem. It carries several names; each one points to an aspect of the disease. Chronic severe asthma, steroid-dependent asthma, steroid-resistant asthma (SRA) difficult-to-control asthma, and refractory asthma are some of these terminologies[1].

Along with genuine causes, there are some other etiologies which can be further divided into three categories: (1) misdiagnosis where the problem is not bronchial asthma to start with, but another respiratory system pathology that is not appropriately addressed, e.g. bronchiectasis, endo-bronchial tumors and vocal cord dysfunction,[2] (2) comorbidity that worsen bronchial asthma and making it difficult to manage, e.g. chronic sinusitis, gastro-esophageal disease, sleep apnea syndrome, and congestive heart failure (CHF),[3] and (3) confounding factors, e.g. nonadherence with treatment, the presence of allergens at home or work and psychosocial problems making asthma difficult to treat[4]. Management of such patients includes confirmation of the diagnosis, evaluation of medication compliance, identification of factors that precipitate exacerbations as well as early assessment of progressive deterioration of the disease. Nonetheless, these patients often require long-term systemic corticosteroid treatment resulting in unwanted and potential serious side effects, such as osteoporosis, skin thinning, diabetes,

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hypertension and cataract formation. To avoid these effects of systemic steroid therapy, a number of alternative approaches consisting of uses of immune-suppressants and other agents with putative anti-inflammatory activity have been investigated and proposed.

Evaluation of severe refractory asthma

There are no validated algorithms to substantiate the most useful approach to the evaluation of the patient with suspected SRA, but some have been suggested[5]

A rational method would involve 3 main aspects: [5]

a) confirmation of severe asthma

b) evaluation of other conditions, coexisting conditions and trigger factors

c) evaluation of the severe asthma subphenotype

(a) Confirmation of severe asthma

Many aspects need to be considered here. At first one needs to obtain a detailed history from the patient including details of respiratory symptoms (including chest tightness, wheezing, cough, night-symptoms , exercise and environment related symptoms), the original diagnosis (including who, when, how and previous investigations), asthma-related morbidity (intensive care/hospital admissions, length of hospital stay, number of exacerbations per year, exacerbating factors and severity of symptoms), associated comorbidities (chronic rhinosinusitis, cardiac conditions, gastro oesophageal reflux, obesity, psychological factors etc), family history, smoking history and current medication including compliance, technique, intolerance to medications and new medications. Second, a thorough physical examination of both respiratory and cardiovascular systems is essential. Third, previous investigations, in particular full blood count, plain chest X-ray, total immunoglobulin E (IgE), autoimmunity, pulmonary function tests and saturation oximetry or some times arterial blood gases should be carefully reviewed and if necessary repeated. The pulmonary function tests should include actual and predicted values for forced expiratory volume in 1 second (FEV1) to document the presence of airflow limitation[6]. Simultaneous assessment of FEV1 reversibility is helpful. In addition, fall in FEV1 when tapering steroid treatment can also be used to document variable airflow limitation and steroid dependency. Occasionally, reversibility testing may not be conclusive and confirmatory tests including bronchial provocation challenges using methacholine or mannitol exhaled nitric oxide measurements and exercise testing may be required. In patients without positive challenge test with bronchial provocation, alternative diagnosis(es) should be considered. Further, more investigations to exclude other conditions should be considered.

(b) evaluation of other conditions, coexisting conditions and trigger factors:

(i) evaluation of other conditions (pseudoasthma):

Taking a detailed history may arouse suspicion of other conditions and appropriate investigations can confirm or exclude these. These conditions and appropriate investigations include the following: bronchoscopy for intrabronchial obstruction, laryngoscopy for vocal cord dysfunction during attack, blood gases during dysfunctional breathing/panic attacks, sputum culture for ABPA Aspergillus, HRCT scan for emphysema, D-dimer and Doppler ultrasound of the limbs for recurrent pulmonary embolism, CT pulmonary angiography for pulmonary arterial hypertension, transbronchial lung biopsy for bronchiolitis etc[7].

(ii) evaluation of coexisting conditions and trigger factors:

It has been reported that other conditions may coexist along side severe asthma and these may present, if untreated, with asthma-like symptoms like chronic rhinosinusitis, gastroesophageal reflux disease, psychosocial factors smoking, allergens and trigger factors and obesity [8]. Hence, coexisting conditions need to be carefully identified and managed, as it may improve the patients' symptoms and prevent further escalation of asthma.

c) evaluation of severe asthma subphenotype:

Phenotyping of patients with SRA is becoming increasingly important because it may help to guide current and possibly future treatments. However, the true significance of phenotyping SRA can be firmly established only when detailed

characterization of hundreds of patients will be completed and analyzed, as proposed in the newly established pan-European consortium Unbiased Bio markers for the Prediction of Respiratory Disease Outcome in Understanding Severe Asthma[9]. In clinical practice, most patients with severe asthma are by and large belonging to 3 categories: (1) those suffering from frequent severe exacerbations with relatively stable episodes between exacerbations (exacerbation prone asthma) (2) those who develop irreversible airflow obstruction (asthma with fixed airflow obstruction) and (3) those who depend on systemic corticosteroids for daily control of their asthma (steroid-dependent asthma). [5]

Management

Treatment of this type of asthma remains highly problematic. Regular systemic corticosteroids are often needed to minimize symptoms. Hence, patients not only are at risk of dying from their asthma, but also from the co-morbidities associated with the excessive steroid use. [10]

Patients with such severe disease that is unremitting to guideline-based management may be better looked after at dedicated clinics where patients would be assessed for alternative diagnoses and co-morbidities, adequately phenotyped using more specialized investigative methods and optimally managed with the best possible treatments available and where patients may also have facilitated access to a multidisciplinary team (physicians, ENT specialists, psychologists, pharmacists and specialist nurses). The choice and formulation of therapeutic agents to be used should be dictated by disease severity, therapeutic response, patient's co-morbidities and preferences, as well as on the agents' adverse event profile. These include standard therapies immunomodulatory agents, biological and other novel therapies.

A. Standard therapies

Standard treatment for patients with severe asthma includes high-dose inhaled corticosteroids (ICS) in combination with a long acting beta-2 agonist (LABA). LABA may reduce the dose of ICS by 57%[11]. More recently, an ICS with smaller particle size for more distal penetration of the airways to improve inflammation in smaller airways has been proposed, but its efficacy has yet to be evaluated in SRA[12]. Leukotriene antagonists may be beneficial in some patients with severe asthma, especially those with aspirin sensitivity[13]. Other drugs used in which reports of improvements in patients with SRA, but not assessed by randomized clinical trials, include anticholinergics, theophyllines, intravenous (IV) magnesium [14,15,16] . Hence, a trial of these agents may prove useful. Inspite of using these additional therapies, there is a sub group of patients with severe unremitting disease who require high doses of oral corticosteroids (OCS, 30 mg/day) on a daily basis to attain an adequate level of control of their symptoms and Qol. This subgroup of patients often exhibits deterioration of their asthma symptoms as soon as the dose of corticosteroids is tapered. Hence, reasonable control of their asthma can only be achieved at the cost of significant morbidity (eg, osteoporosis diabetes, hypertension, cataract formation, gastrointestinal GI) bleeding, myopathy, adrenal insufficiency, susceptibility to infections, weight gain, and skin thinning.

B. Immunomodulatory drugs

To curtail the necessity of prolonged OCS use and associated adverse effects, a trial with immunomodulatory drugs may be an option. Some of the agents that can be considered include methotrexate, cyclosporine A, and macrolide antibacterial [17]

Other agents have been investigated but are not commonly used and include azathioprine, gold, and IV IGs.

i) Methotrexate is the most clinically investigated immunological agents in severe asthma[17]. Methotrexate at 15 mg weekly for up to 28 weeks were reported to result in a significant OCS dose reduction, and in fact more than half of the patients came off their OCS completely[18,]

ii) Cyclosporine A

Cyclosporine A works by inhibiting the activation of T cells .Cyclosporine A at a dose of 5

mg/kg/day in SRA patients is equally effective as patients on a mean dose of .8.5 mg/day of prednisolone for a period of 12–36 weeks [19]

C. Omalizumab

IgE has central pathophysiological role in the development of allergic conditions by enhancing dendritic cell allergen uptake, and activation and release of inflammatory mediators by mast cells and basophils.[20] Omalizumab is a humanized IgE-specific monoclonal antibody that prevents inter action of IgE to FcR1receptors on effector cell. Studies evaluating over 2,500 patients have been conducted to assess the safety and efficacy of omalizumab in severe atopic asthmatics who had persisting symptoms despite optimum treatment. Studies have reported that the addition of omalizumab has beneficial improvements in the reduction of exacerbations, reduction in ED attendances, asthma-related QoL, asthma symptoms, lung function as well as reduction in steroid reliever usage.[21] Omalizumab is administered either 2-weekly or 4-weekly depending on the weight and IgE levels, in patients with an IgE level between 30–700 IU/ml over 25–52 weeks. Most of the adverse events were minor such as headaches, cough, GI symptoms, urticaria, and injection-site reactions

D. Bronchial thermoplasty

An increase in airway smooth muscle (ASM) is thought to be an important factor in severe and fatal asthma 22. Bronchial thermoplasty is the delivery of controlled thermal energy to the airway wall during several bronchoscopy procedures. The application of BT to the airways is an innovative treatment approach to reduce the broncho-constrictor response in asthma. Studies have demonstrated that BT results in reduction of the ASM.

Conclusion and the future

Managing asthma that is refractory to standard treatment requires a systematic approach to evaluate adherence, ensure a correct diagnosis, and identify coexisting disorders and trigger factors. In future, phenotyping of patients with SRA will also become an important element of this systematic approach because it could be of help in guiding and tailoring treatments. Treatment of SRA remains highly problematic and regular systemic corticosteroids are often needed to mini mize symptoms. Despite the unquestionable beneficial role of systemic corticosteroids for most patients with SRA, they do not seem to be effective in every patient and they are associated with severe adverse side effects. Moreover, immunomodulatory and biologic therapies reportedly lack high levels of efficacy, show wide variation in success rates across studies, and are associated with adverse side effects Cons equently, there is a compelling need for more effective drugs for these challenging patients. Identifying medications that reduce the need for systemic corticosteroids in patients with SRA should be a priority for the academic world and the pharmaceutical industry.

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