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Optimal Management of Severe/Refractory Asthma

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Abstract: Asthma is a chronic inflammatory disease of the airways, affecting approximately 300 million people worldwide. Asthma results in airway hyperresponsiveness, leading to paroxysmal symptoms of wheeze, cough, shortness of breath, and chest tightness. When these symptoms remain uncontrolled, despite treatment with high doses of inhaled and ingested corticosteroids, asthmatic patients are predisposed to greater morbidity and require more health care support. Treating patients with severe asthma can be difficult and often poses a challenge to physicians when providing ongoing management. This clinical review aims to discuss the definition, prevalence and evaluation of severe asthmatics, and provides a review of the existing pharmacologic and non-pharmacologic treatment options.

Keywords: severe asthma, refractory asthma, asthma management, difficult asthma

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Introduction

Asthma is a complex,¹ multi-factorial chronic airway disease, of all ages and both sexes. Severe asthma represents a heterogeneous group, with data from the Severe Asthma Research Program (SARP) describing five distinct phenotypes through cluster analysis.¹⁻⁸ The etiology of asthma involves genetic, environmental and inflammatory components. The principle pathophysiology of this chronic airway disease is chronic inflammation of the lower respiratory tract.⁹ The prevalence of asthma is increasing worldwide.¹⁰ Data from National Health Interview Surveys from Centers for Disease Control and Prevention (CDC) showed an increase in prevalence of asthma in the United States, from 7.3% in 2001 to 8.2% in 2009.¹¹ The Canadian National Population Health Survey showed that the prevalence of asthma in males and females >12 years in 1996/97 was 7.2% and in 2005 was 8.3%.¹² Asthma is twice as common in obese people as non-obese.¹³

Definition of severe/refractory asthma

The Canadian Asthma Consensus Guidelines defines asthma as “a disease characterized by paroxysmal or persistent symptoms of dyspnea, chest tightness, wheezing, sputum production and cough, associated with variable airflow limitation and airway hyperresponsiveness to endogenous or exogenous stimuli.”¹⁴ The Global Initiative for Asthma (GINA)¹⁵ diagnostic criteria similarly are airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning along with variable airflow obstruction which is often reversible either spontaneously or with treatment. Thus, the definition of asthma is quite general and relies on clinical and physiological parameters. It allows for the capture of numerous syndromes able to meet such criteria.¹⁶ In the face of this general definition, defining severe asthma becomes even more difficult.

Asthma, in clinical trials and clinical practice, is classified as mild, moderate and severe and is further sub-categorized as mild-persistent, moderate-persistent and severe-persistent based upon symptoms, need for rescue therapy or lung function. However, since the Canadian Asthma Consensus Conference in 1996,¹⁷ the concept of an asthma continuum was adopted. Asthma continuum reflects a dynamic

therapeutic approach that allows drug therapy to be adapted to the severity of the underlying illness and facilitates adjustment of the intensity of therapy to the degree of control achieved. In 1996, it was also agreed upon that asthma “control” and “severity” should be differentiated.^{17,18} Severity is defined by the minimum medication required to achieve adequate asthma control rather than by symptoms or abnormal lung function.^{17,18} Thus, severe asthma is defined as well controlled asthma symptoms on high to very high doses of inhaled corticosteroids, with or without the use of oral corticosteroids; and very severe asthma is defined as well or not well controlled asthma symptoms despite very high dose of inhaled and ingested corticosteroids and with or without requiring additional therapies. For this classification, the daily high and very high doses of inhaled corticosteroid (approximate equivalent doses) are defined as follows: High dose is beclomethasone dipropionate, 1000 to 2000 µg; fluticasone, 500 to 1000 µg; and budesonide, 800 to 1600 µg and very high dose is fluticasone, 1000 to 2000 µg and budesonide, 1600–3200 µg.

The term “refractory asthma” was agreed upon at the American Thoracic Society workshop.¹⁹ It is not meant to describe only patients with “fatal” or “near fatal” asthma, but it is meant to encompass the asthma subgroups previously described as “severe asthma,” “steroid-dependent and/or resistant asthma,” “difficult to control asthma,” “poorly controlled asthma,” “brittle asthma,” or “irreversible asthma.”¹⁹ Refractory asthma can be defined as per the American Thoracic Society guidelines when one or both major criteria and two minor criteria, described as follows, are fulfilled. The major criteria are: In order to achieve control to a level of mild-moderate persistent asthma: (1) Treatment with continuous or near continuous ($\geq 50\%$ of year) oral corticosteroids 2) Requirement for treatment with high-dose inhaled corticosteroids. The minor criteria are: (1) Requirement for daily treatment with a controller medication in addition to inhaled corticosteroids eg, long-acting β -agonist, theophylline or leukotriene antagonist (2) Asthma symptoms requiring short-acting β -agonist use on a daily or near daily basis (3) Persistent airway obstruction ($FEV_1 < 80\%$ predicted; diurnal peak expiratory flow (PEF) variability $> 20\%$) (4) One or more urgent care visits for asthma per year (5) Three or more oral steroid “bursts” per year (6) Prompt deterioration



with $\leq 25\%$ reduction in oral or inhaled corticosteroid dose (7) Near fatal asthma event in the past. To make the diagnosis of refractory asthma, it is necessary that other conditions have been excluded, exacerbating factors treated, and the patient felt to be generally adherent. For the purposes of definition of refractory asthma, the drug ($\mu\text{g}/\text{d}$) and the dose (puffs/d) are as follows: (a) Beclomethasone dipropionate $> 1,260 > 40$ puffs ($42 \mu\text{g}/\text{inhalation}$) > 20 puffs ($84 \mu\text{g}/\text{inhalation}$); (b) Budesonide $> 1,200 > 6$ puffs; (c) Flunisolide $> 2,000 > 8$ puffs; (d) Fluticasone propionate $> 880 > 8$ puffs ($110 \mu\text{g}$), > 4 puffs ($220 \mu\text{g}$); (e) Triamcinolone acetonide $> 2,000 > 20$ puffs.¹⁹

Prevalence of severe/refractory asthma

Definition of severe or refractory asthma is not uniform in the literature; hence it is difficult to estimate the true disease prevalence. Most asthma is mild to moderate and can be controlled by minimal medication which include inhaled β -agonists and inhaled corticosteroids. Only about 5%–10%, likely $< 5\%$,¹⁹ of total asthmatic subjects have difficult disease which requires higher doses medication to achieve adequate control or have persistent symptoms, asthma exacerbations and airway obstruction despite higher medication use.^{16,20} Thus, these severe asthmatic groups of subjects have greater morbidity and a disproportionate need for health care support compared with the less severe subset.²¹

Evidence-based Management of Severe/Refractory Asthma: Optimal General Management

The diagnosis of asthma should be confirmed, as misdiagnosis of asthma could be as high as 30%.²² Alternative diagnoses such as chronic obstructive pulmonary disease, left ventricular failure, localized obstruction, cystic fibrosis and/or vocal cord dysfunction should be ruled out.²⁰ Once the diagnosis of asthma is objectively confirmed, utilization of the concept of asthma continuum is a key in monitoring any asthma patient including severe/refractory asthma. Goals of care of severe/refractory asthma are: to prevent chronic and troublesome symptoms, to normalize pulmonary function, to maintain normal activity levels, to prevent exacerbations, to improve health-related quality of life and to provide optimal

pharmacotherapy with minimal or no adverse effects. General treatments must include patient education, development of an action plan, smoking cessation, and review of medication adherence and symptom triggers.

Asthma education

Asthma education with the help of an asthma educator or Certified Respiratory Educator²³ is very helpful in improving patient understanding and participation in asthma care. Key components of asthma education, as demonstrated with the Canadian experience, are individual teaching and group sessions.⁷ All asthmatics should be referred to asthma education centers after the physician has initiated asthma education. Basic information with practical applications should be provided, including: manifestations and mechanisms of asthma (inflammation vs. bronchoconstriction), inciters and inducers, environmental control/prophylaxis, goals of asthma treatment, medication use and side-effects, inhaler use, assessment of severity and control of asthma, use of an action plan, use and interpretation of peak flow measurements and information on available resources. Subjects should be provided with skills for self-management and telephone consultations or other visits with the health educator should be offered. Group sessions should include lectures and discussions on practical aspects of asthma in relation to management; and participation in a support group should be offered.⁷

Asthma action plan

A personalized self-treatment written Asthma Action plan guided by symptoms or peak flow meter should be developed in collaboration with the educator and the respirologist.¹⁹ The action plan should include instructions regarding the maintenance medication schedule, doses of rescue therapy for increased symptoms, and when and how to seek urgent or emergency care. A personalized action plan should give clear guidance to optimal asthma control vis-à-vis no/minimal shortness of breath, cough or wheezing, no/minimal limitation of physical activities, no night time awakenings and less than 15% variability in diurnal PEF. For all asthma patients, including those with severe/refractory asthma, inhaler technique should be reviewed and instruction included in action plan.



Smoking

Cigarette smoking is a very common airway irritant in many asthmatics and it reduces inhaled corticosteroids (ICS) effectiveness. A multidisciplinary approach to smoking cessation should be used in dealing with current smokers.²⁴ Smoke-free legislation passage and strict adherence is essential in asthma care. Introduction of the comprehensive smoke-free legislation in Scotland recently demonstrated that there was a reduction in the incidence of asthma among people who did not have occupational exposure to environmental tobacco smoke.²⁵

Adherence

Patient adherence to asthma care should be reviewed in each clinic visit. Significantly poor adherence (less than 50% prescription refill), especially to corticosteroid therapy, has been demonstrated in severe, difficult-to-control-asthma subjects. Poor adherence is identified badly by physician assessment and patient self report, thus, objective, surrogate and direct measures of adherence should be performed as part of a difficult asthma assessment and are important before prescribing expensive novel biological therapies.²⁶ A multi-level intervention using a simple concordance interview and a menu driven psycho-educational intervention strategy was studied in severe, difficult-to-control asthmatic subjects.²⁷ The menu driven intervention was designed and delivered by an experienced respiratory nurse with basic level psycho-therapy training. This model encompassed the Transtheoretical Model of Change, Motivational Interviewing and Cognitive Behavioural Therapy principles, providing a flexible short term intervention using patient's individual reasons for non-adherence as a guide to plan intervention content. The model used a non-confrontational technique which elicited self-motivation and provided a process to resolve ambivalence towards medication taking. This multi-level intervention technique was shown to be effective in improving adherence to asthma treatment. Most importantly, this relatively simple menu driven intervention strategy reduced prescribed daily dose of inhaled corticosteroid (ICS), rescue prednisolone courses, hospital admissions and reduced maintenance oral steroid dose in subjects on maintenance steroids.²⁷

Vaccination

Preventive vaccinations such as yearly influenza vaccines and pneumococcal polysaccharide vaccine are important for all asthmatic subjects and especially cigarette smokers.²⁸ A nested case-control study demonstrated that asthma is an independent risk factor for invasive pneumococcal disease and that the risk among persons with asthma was at least double that among controls.²⁹

Management of Comorbidities

Many comorbid conditions may occur with asthma especially gastroesophageal reflux disease (GERD), rhinitis/sinusitis, psychological disturbances, chronic infections, obstructive sleep apnea (OSA), obesity, and allergic bronchopulmonary aspergillosis (ABPA). Interaction of these comorbidities with asthma may be complex. Some of these comorbidities may change asthma phenotype,³⁰ they may complicate the course of asthma or may act as confounding factors in the diagnosis or assessment of asthma control.³¹ Social and environmental exposures may result into some comorbidities. Effect of these comorbidities on asthma may be variable and may alter response to asthma treatment. These comorbidities thus, needs to be assessed systematically and treated appropriately, especially in the presence of severe asthma as the prevalence of these comorbidities seems high.³¹

GERD

A randomized, placebo-controlled trial demonstrated no role of proton-pump inhibitors in severe asthmatics without any symptoms of reflux disease.³² Furthermore, the meta-analysis of all randomized controlled trials with proton-pump inhibitors and asthma demonstrated statistically significant improvement in the morning peak flow but such low magnitude improvement in peak-flow is unlikely to have any clinical significance.³³ Thus, proton-pump inhibitors can not be recommended for empirical use in asthmatics.

Obesity and OSA

Reduced response to standard asthma medications, including inhaled cortico-steroid and bronchodilators, in obesity might lead to severe asthma.³⁴ Reasons for this reduced response are not known. Weight loss does seem to improve asthma symptoms and peak



flow.³⁵ Obstructive sleep apnea may be associated with asthma and obesity. The relationship between asthma and obesity is not completely understood yet. However, OSA is associated with upper and systemic airway inflammation³⁶ and thus, could complicate asthma management.

Psychological disturbances

Psychological elements such as anxiety, depression and panic disorders are more frequent in severe asthmatics and thus need to be attended promptly.^{31,37} Moreover, psychological factors such as anxiety and depression are associated with poor adherence to inhaled asthma treatment and hence need special attention.³⁸

Allergic factors and ABPA

Allergic bronchopulmonary aspergillosis may complicate asthma control and could lead to central bronchiectasis.³⁹ Several allergic and non-allergic factors should be carefully examined at each clinic visit pertaining to home, social and occupational environments of severe asthmatic subjects because exposure to these factors can worsen asthma symptoms.⁴⁰ Unidentified allergens could be at home or at the work place. Allergens at home such as dust mites, cats, cockroaches and other domestic pets should be reviewed. There is little evidence in the literature that shows clinical benefit to using physical and chemical practices to reduce dust mite or pet allergens; further studies are required.⁴¹ Sensitization to molds has been identified as a risk factor for severe asthma in a multicentre epidemiological survey of 30 centers, and therefore should be reviewed.⁴²

Dietary factors such as dietary-salicylates, monosodium glutamate could be potential allergens. Drugs such as non-steroidal anti-inflammatory agents, including aspirin, and oral or ophthalmic β -blockers could be contributing to asthma trigger or severity. Exposure to allergens at the work place such as chemicals, fumes, dust vis-à-vis asthma severity on week-days vs. weekends and holidays is important in the history. Detailed occupational history to rule out occupational asthma is important.²⁰ Allergy testing can be considered to identify triggers and possibly prepare for immunotherapy. A Cochrane review performed by Abramson and colleagues showed immunotherapy reduces asthma symptoms, need for

asthma medication and bronchial hyper-reactivity. There is a possibility of developing local and systemic adverse events, including anaphylaxis, when undergoing this therapy.⁴³

Optimal Pharmacotherapy for Severe/Refractory Asthma

Mainstay pharmacotherapy for severe/refractory asthma is combination of inhaled corticosteroids (ICS) and one or two controller agents such as long acting β -agonists (LABA), leukotriene modifiers or oral theophylline.¹⁹ Recently, tiotropium bromide was demonstrated to be effective as an add-on controller therapy to ICS in uncontrolled asthma.⁴⁴ No studies have evaluated the benefits of multiple combinations of these alternative controllers. Thus, in the absence of data, clinicians should carefully monitor clinical parameters to assess the best combination of controller medications.¹⁹ If control is obtained and maintained for a three month period, the treatment regime can be stepped down to establish the lowest effective dose that maintains control.⁸

Use of corticosteroids in severe asthma

ICS have been shown in multiple studies, over four decades, to have efficacy in reducing asthmatic symptoms, improving quality of life, improving lung function, decreasing airway hyperresponsiveness, reducing frequency and severity of exacerbations and reduction in asthma related mortality.^{15,45} Inhaled corticosteroids have effective anti-inflammatory effects in patients with severe asthma.^{15,46} It is believed that steroids in the airway suppress the transcription, production and downstream effects of inflammatory cytokines. This results in a reduction of chronic inflammation in the airways of asthmatic patients.^{46,47} ICS primarily act upon the airway mucosa but are systemically absorbed via the lung at higher doses. They are metabolized mainly by the liver, and excreted via the gastrointestinal and genitourinary tracts.⁴⁸ Aiming for the lowest dose of ICS to achieve the best asthma control is important because, low dose ICS (<250 mcg fluticasone per day, or equivalent) acts locally on the airway mucosa with minimal side effects. At doses >500 mcg/day of fluticasone (or equivalent), local side effects become more apparent.⁴⁵ These include oropharyngeal candidiasis, dysphonia, and cough due to upper airway irritation.⁴⁵ All ICS



will further demonstrate systemic side effects with escalating doses.⁴⁹ These are generally less severe than those observed with the equivalent dose of oral steroids.⁴⁹ Lipworth's systematic review and meta analysis in 1999 revealed a greater dose-related systemic effect with fluticasone compared to other corticosteroids, especially with doses above 0.8 mg/day.⁴⁹ The systemic side effects exhibited by absorption of ICS via the lung include, easy bruising, adrenal suppression and decreased bone mineral density.^{15,49}

In severe persistent asthma, patients experience symptoms despite the use of low dose ICS and LABA's. While dose response curves for ICS seem to plateau at low to moderate doses, a report from the National Asthma Education and Prevention Program suggests that in severe cases, twice daily therapy with high dose ICS should be used, in addition to other measures of control.^{50,51} It is not entirely clear which optimal dose and combination of controller medications should be employed in severe/refractory asthma to produce the maximum clinical benefit.¹⁹ ICS, however, represent the cornerstone of maintenance therapy for patients with asthma.⁴⁵ Evidence indicates that over 90% of benefit from ICS is achieved at low doses (<250 mcg fluticasone per day, or equivalent).^{52,53} Before increasing the dose of ICS to moderate or high levels, add-on therapy with LABA's or LRTA's are recommended.⁴⁵ However, if patients continue to be refractory to this therapy, there is evidence that increasing the dose of ICS may be beneficial.⁵⁴ In fact, in patients with severe asthma who are already dependent on oral corticosteroids, therapy with high dose ICS (>500 mcg fluticasone per day or equivalent) can be beneficial for lung function and quality of life.⁵⁵ Further, increasing the ICS dose may allow for tapering and eventual removal of the oral corticosteroid.⁵⁵

Oral steroid therapy is indicated in the management of patients with severe refractory asthma, not responsive to step-wise conventional treatments.⁴⁵ The lowest dose possible should be maintained.¹⁹ Given the side effect profile of long term oral steroid usage, osteoporosis prevention should be addressed,⁴⁵ when prescribing oral steroid therapy.

Steroid resistance or insensitivity should be assessed if asthma remains uncontrolled despite high ICS dose and pre-bronchodilator FEV₁ < 70% predicted with persistence of bronchial reversibility.¹⁹ A one to two week trial of an oral steroid in divided

doses (40 mg/day or double the dose if already on oral steroid) is recommended, while observing the effect on morning pre-bronchodilator FEV₁.¹⁹ If the FEV₁ fails to increase by 15% (and 200 ml), the patient is considered steroid resistant.¹⁹ This trial also gives an opportunity to assess and address the issue of adherence to therapy. Subjects with severe/refractory asthma who remain symptomatic despite optimal application of conventional therapy and management of comorbidities, alternative therapies given below could be considered.

Steroid sparing agents

Due to the side-effect profile of systemic steroids, several alternative options have been evaluated in treating severe/refractory asthma. Cochrane review of randomized controlled trial determined that there was insufficient evidence to support the use of azathioprine, chloroquin, cyclosporine, gold or methotrexate in the treatment of chronic asthma as a steroid sparing-agent. For most of these agents the side-effect profile is not preferable.⁵⁶⁻⁶⁰ Add-on therapies such as macrolides, anti-IgE therapy (omalizumab), tumor necrosis factor- α inhibitors, cytokine receptor antagonists and bronchial thermoplasty are discussed below.

Macrolides

Macrolide antibiotics have shown immunomodulatory effects in neutrophilic lung diseases such as panbronchiolitis in East Asians and cystic fibrosis.⁶¹⁻⁶⁵ More recently, clarithromycin was demonstrated to modulate IL-8 and neutrophil accumulation in refractory asthmatics in a randomized trial. In addition, treatment with oral clarithromycin in a randomized placebo controlled trial has shown to reduce severity of bronchial hyperresponsiveness in asthmatics.⁶⁶ A double-blinded, randomized controlled trial of clarithromycin or placebo added to low dose fluticasone in sub-optimally controlled asthmatics, did not show any improvement in control of symptoms.⁶⁷ Thus, macrolide therapy may be an important additional therapy that could be used to reduce noneosinophilic airway inflammation, particularly neutrophilic inflammation, though clinical outcome benefit is still unclear.⁶⁸

Antifungal therapy

Sensitization to molds has been shown to be a risk factor for severe asthma.⁴² A randomized placebo



controlled trial by Denning and colleagues on severe asthmatics with fungal sensitization demonstrated by skin prick or specific IgE testing showed treatment with oral itraconazole (200 mg twice a day) over a 32 week period increased asthma related quality of life. Subjects with ABPA were excluded from this trial.⁶⁹ The mechanism by which antifungal therapy improves patient symptoms is not clearly understood. At this time, further research is required in patient selection and optimal duration of therapy.⁷⁰

Anti-IgE therapy (Omalizumab)

Immunoglobulin E (IgE) plays a pivotal role in the molecular pathway responsible for the allergic response.⁷¹ Previous literature has demonstrated that patients with asthma have elevated circulating IgE levels, which implies an allergic basis to the disease.⁷² In allergic asthma, aeroallergens sensitize and trigger an immune based allergic inflammatory response, mediated via IgE.⁷³ Given this, significant interest has been generated in targeting this molecule as a treatment in patients with allergic asthma who are not well controlled on conventional therapies.

Omalizumab is a humanized recombinant monoclonal anti-IgE antibody^{73,74} This antibody binds to free circulating IgE molecules in the bloodstream, thereby preventing IgE from binding to mast cells, basophils and other immune cells.^{74,75} Without surface bound IgE, immune cells cannot be activated by allergens. This results in a slowing of the allergic and inflammatory cascade.⁷⁶ Omalizumab also reduces the overall density of immune cell surface IgE receptors, creating less potential for immune cell stimulation.^{76,77} Further, studies indicate that Omalizumab does not bind to IgE receptors itself, and therefore cannot initiate an allergic and inflammatory response.⁷⁵

Omalizumab is administered subcutaneously and has a mean half-life of 26 days.^{76,78} Therefore, monthly administration of the drug is usually sufficient. Treatment dose is determined in accordance with body weight and serum total IgE levels prior to treatment.⁷⁶ Dosage adjustments during the course of therapy are required should there be significant changes in body weight.⁷⁸ Drug metabolism occurs primarily via the hepatic system, while the IgE molecules are degraded by the reticuloendothelial system. There are no controlled studies to evaluate the effect of Omalizumab in pregnant women, but animal studies have confirmed

no teratogenicity.⁶⁴ Omalizumab is recommended for use in pregnant women only if clearly required.⁷⁸

The most common side effects associated with subcutaneous injection of Omalizumab include headache, local injection site reaction and upper respiratory tract infection.⁷⁸ In post marketing surveillance data, anaphylactic reactions have also been reported as a side effect, with a frequency of 0.2%.⁷⁹ Anaphylaxis in this population manifested as symptoms of wheezing, shortness of breath, chest tightness, angioedema of the tongue and throat, hypotension, syncope, and hives.⁸⁰ While relatively uncommon, anaphylactic reactions were found to occur after the administration of the first dose, and up to one year after initiation of Omalizumab.⁸⁰ Other side effects, including malignant neoplasms, thrombocytopenia and parasitic infections, have also been evaluated.⁷⁹ Thus far, none of these side effects have shown direct statistical correlation with administration of Omalizumab.⁷⁹ Additional studies are currently underway to assess long term safety data for Omalizumab.⁷⁹

Several studies evaluating Omalizumab have demonstrated a clinical effect on markers of airway inflammation, exacerbation frequency, emergency room visits, asthma symptom severity, inhaled corticosteroid use, and quality of life in patients with moderate to severe asthma.^{73,81–86} A placebo controlled study by Djukanović and colleagues in 2004 demonstrated that treatment with Omalizumab for 16 weeks reduced serum IgE levels, IgE, cells in the airway mucosa, and sputum eosinophil counts in patients with mild to moderate asthma.⁸¹ Interestingly, this study did not demonstrate significant improvements in hyperresponsiveness to methacholine.⁸¹ A more recent study in 2010 involving patients with severe asthma again demonstrated an effect of Omalizumab on airway inflammation.⁸² This study demonstrated a reduction in airway expression of endothelin-1, an important mediator in airway inflammation and remodeling.⁸²

In addition to inflammatory markers, Omalizumab has also demonstrated efficacy in reducing the frequency of asthma exacerbations and inhaled corticosteroid requirements. This data comes from several studies, including two key randomized controlled trials.^{83,84} Both trials demonstrated a significant reduction in exacerbations and use of inhaled corticosteroids compared with placebo in moderate to severe, and severe asthmatics. In the INNOVATE study, a randomized control trial by Humbert and colleagues,



Omalizumab was shown to reduce emergency room visits and exacerbations, when added to high dose ICS and LABA therapy. This study also assessed severe asthmatics.⁸⁷ Asthma related quality of life has also been studied as an endpoint in patients treated with Omalizumab.^{85,86} Chipps and colleagues completed a pooled analysis of six controlled trials which revealed a significant clinically meaningful improvement in quality of life after treatment with Omalizumab.⁸⁵ This effect was seen in patients with severe asthma.

Given the clinical benefits of Omalizumab in patients with moderate to severe allergic asthma, cost effectiveness has also been evaluated. The baseline cost of Omalizumab is high, at \$10,000 to \$12,000 USD per year for patients receiving the minimum dose every 4 weeks.⁸⁸ Therefore, careful patient selection is paramount. A retrospective economic analysis published in 2004 calculated a cost of \$523 per day to achieve one successful symptom controlled day.^{88,89} From this cost perspective, they concluded that Omalizumab should be considered in severe asthmatics on maximal therapy with poorly controlled symptoms, who also experience hospitalization.^{88,89} A second study in 2007 evaluating cost effectiveness also concluded that Omalizumab was not cost effective for most patients with severe asthma, and suggested that physicians explore all options before turning to Omalizumab.⁹⁰

The recent 2010 Canadian Thoracic Society (CTS) consensus statement on the management of asthma discusses the use of Omalizumab in clinical practice.⁴⁵ Omalizumab is approved by Health Canada for the treatment of moderate to severe persistent allergic asthma in patients greater than 12 years of age.⁴⁵ Given the high cost, discussed above, specific criteria have been set forth for the use of Omalizumab. Patients must have difficult to control asthma, as confirmed by objective measures, documented allergy to aeroallergens, a serum total IgE level between 30 IU/mL and 700 IU/mL, and uncontrolled symptoms despite therapy with high dose ICS and one additional controller medication.⁴⁵ The updated GINA guidelines published in 2008 echo the indications for treatment set forth by the CTS. Given the available studies, Omalizumab has been shown to be safe add-on therapy.¹⁶

Anti-cytokine therapy

Tumor necrosis factor- α inhibitors were thought to be of benefit in the treatment of severe asthma. However,

in a large, double-blind, placebo-controlled, dose ranging trial with a monoclonal antibody to TNF- α , golimumab, demonstrated unfavorable risk-benefit ratio which led to premature discontinuation of the trial.⁹¹ Thus, TNF- α inhibitors do not seem to be a favorable therapeutic option for severe asthmatics.

Bronchial thermoplasty

More than 5 years ago, dog experiments revealed that bronchial thermoplasty might have therapeutic benefits for asthma subjects by reducing airway hyperresponsiveness.⁹² Bronchial thermoplasty is a bronchoscopic procedure where controlled radio frequency energy is delivered to the airways in order to reduce the airway smooth muscle mass and attenuate bronchoconstriction. This has now been tested in asthmatic subjects in randomized controlled trials. The earlier trials performed on moderately severe and severe asthmatic subjects were disappointing due to the notable adverse effects of the treatment and the lack of any effect on airway hyperresponsiveness.^{93,94} None the less, these trials demonstrated that bronchial thermoplasty was superior to usual care with respect to asthma control and asthma-related quality of life, with variable effects on peak expiratory flow, FEV₁, asthma symptoms, and symptom-free days. However, high potential of placebo effect could not be ruled out in these earlier trials.⁹⁵ A well powered, sham controlled, double-blind multi-center study hence was designed (AIR2) to evaluate the safety and effectiveness of bronchial thermoplasty in adult patients with severe asthma who were symptomatic, despite the use of high-dose standard care medications.⁹⁶ AIR2 did not meet the primary endpoint of minimal clinically important difference in asthma-related quality of life questionnaire score. Procedure related respiratory adverse events were more common in the thermoplasty group and 30% were classified as moderate to severe grade.⁹⁷ Thus, bronchial thermoplasty can not be offered to severe/refractory asthmatics as it has neither proven to be effective nor safe.

Conclusions

Severe/refractory asthma is likely to represent a heterogeneous population; however, the specific subtypes have not yet been well defined. A better understanding of these subtypes could potentially lead to improved treatment of severe asthmatics stratified by phenotypes. Severe asthma is a small subset of asthmatics;



however it presents with greater morbidity and a disproportionate need for health care support compared with less severe asthmatics. Thus, network approach to care and management of severe asthma is suggested.¹⁶ In Europe, nine European countries formed a European Network For Understanding Mechanisms Of Severe Asthma (ENFUMOSA)⁹⁸ and in the United States, four leading university centers are linked through the Severe Asthma Research Program (SARP).⁹⁹ In Canada, the Canadian Network of Severe Asthma (CSAN) is in the process of expansion and establishing consistent investigative protocols across all centers.¹⁰⁰ The Brussels's declaration demonstrates the need for change in asthma management and funding "real world" studies because of the substantial unmet clinical need which, in the 10% of patients with severe disease, accounts for approx. 50% of the health care costs.¹⁰¹ Continued global efforts and collaboration for further studies to understand severe/refractory asthma pathobiology and optimal treatment strategies are mandatory.

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