Therapeutic options for severe asthma

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Abstract

As the overall prevalence of asthma has escalated in the past decades, so has the population of patients with severe asthma. This condition is often difficult to manage due to the relative limitation of effective therapeutic options for the physician and the social and economic burden of the disease on the patient. Management should include an evaluation and elimination of modifiable risk factors such as smoking, allergen exposure, obesity and non-adherence, as well as therapy for co-morbidities like gastro-esophageal reflux disease and obstructive sleep apnea. Current treatment options include conventional agents such as inhalational corticosteroids, long acting β_2 agonists, leukotriene antagonists, and oral corticosteroids. Less conventional treatment options include immunotherapy with methotrexate, cyclosporine and tacrolimus, biological drugs like monoclonal antibodies, tumor necrosis factor-α blockers and oligonucleotides, phosphodiesterase inhibitors, antimicrobials and bronchial thermoplasty.

Key words: severe asthma, treatment.

Introduction

Asthma is a chronic inflammatory disorder of the airways associated with bronchial hyper-responsiveness (BHR), reversible airflow limitation and recurrent symptoms of wheezing, chest tightness and cough. Etiologies includes genetic and environmental factors that together create a state of persistent inflammation of the lower respiratory tract that can be worsened by various trigger factors like allergen exposure, smoking, drugs and exercise. Cross-sectional surveys estimate that the prevalence of asthma has increased by about 38% in the past two decades [1]. Explanations for this increased prevalence include a parallel rise in the prevalence of obesity [2] and allergic rhinitis1, as well as the levels of air pollution [3].

According to the WHO/NHLBI Global Initiative for Asthma (GINA) guidelines, asthma is best classified according to the level of clinical control into controlled, poorly controlled and uncontrolled [4]. Previously asthma was classified as mild, moderate and severe based on the severity of symptoms, degree of lung impairment and amount of medication required. While mild and moderate asthma can be successfully managed with traditional therapy using β_2-agonists and corticosteroids [5], severe asthma remains a clinically, socially and economically difficult condition to manage, with patients suffering from frequent exacerbations and intolerable

symptoms, leading to significantly higher healthcare costs [6, 7] compared to their less severe counterparts.

Various criteria for defining severe asthma have been put forth by many organizations and clinicians worldwide. For the purpose of this paper, severe asthma shall be understood to refer to the state of asthma in which clinical symptoms of asthma persist in an uncontrolled manner, despite the highest level of therapy advocated in the WHO/NHLBI GINA guidelines [5]. Thus, severe asthma is a broad term and encompasses "difficult asthma", "uncontrolled asthma" and "refractory asthma". As multiple definitions exist, the prevalence of severe asthma has been difficult to determine. However, it can be estimated that approximately 3% [8, 9] of the asthma population suffers from this condition. Although this may seem a small proportion, the magnitude of clinical difficulty to those managing such individuals is often enormous.

Treatment of modifiable factors

Obesity

Thompson et al suggested that obesity is much more common among asthmatics with severe symptoms, as about 75% of the patients attending an emergency room for asthmatic symptoms were either overweight or obese [10]. Possible factors involved in this relationship include mechanical compression of ventilation with a resultant compromise in functional residual capacity, tidal volume and tidal bronchodilation [11], altered levels of the inflammatory mediators leptin [12] and adinopectin [13], decreased response to inhaled corticosteroids [14] and airway smooth muscle dysfunction [15]. As studies of such individuals indicate that weight loss aids in the symptomatic relief of asthma [16, 17], all obese asthmatics should be advised to lose weight as a part of their management plan.

Allergen exposure

Exposure to environmental, industrial and food allergens plays a crucial role in the pathogenesis of severe asthma. Studies of serum IgE levels to common allergens (cockroaches, house dust mite and Alternaria) show a linear dose-response relationship to asthma morbidity, which includes both increased exacerbations as well as increased need for medication [18]. It is also evident that continual exposure to allergens causes a dramatic decline in lung function by augmenting airway inflammation and remodeling, leading to chronic airway injury that will not effectively respond to pharmacotherapy with corticosteroids [19]. As individuals with severe asthma are already in a compromised state with regards to increased risk of exacerbations and decreased effectiveness of medications, avoidance of all known allergens should be insisted upon. Lifestyle modification like moving to high-altitude locations where there is a lower level of allergens [20] should also be considered.

Smoking

Research has consistently demonstrated that smoking plays a pivotal role in the development of severe asthma [21 , 22] Individuals presenting to an emergency room for the treatment of asthma were 60% more likely to be smokers than not [22]. Asthmatics who are also smokers, have an enhanced rate of decline in their lung function [23] as well as diminished responsiveness to corticosteroids [24], when compared to their non-smoking counterparts. It is of the utmost importance that these patients abstain from smoking.

Drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) and β-blockers have for long been implicated as triggering factors for the exacerbation of asthma. Aspirin in particular is associated with severe asthma [25] due to perturbations in arachidonic acid metabolism, resulting in an imbalance between pro-inflammatory and anti-inflammatory mediators. Aspirin may also have a stimulatory effect on fibrosis, which can lead to irreversible obstruction and considerably diminished lung function [26]. In a study conducted with 500 asthma patients, 15% were discovered to have aspirin intolerance, of which they were previously unaware, suggesting that provocation tests for aspirin should be performed to detect Aspirin Exacerbated Respiratory Disease (AERD) [27]. Patients with AERD were reported to have a higher incidence of severe asthma (66%) and an increased history of intubation (20%) when compared to their non-aspirin sensitive counterparts [26]. Patients with severe asthma are thus advised to abstain from aspirin and its derivatives although the selective cyclooxygenase-2 inhibitors celecoxib and etericoxib have been shown to be safe [28, 29]. Additionally, montelukast 10mg daily has been shown to be beneficial in the treatment of aspirin intolerant patients [30, 31].

Another class of drugs that has been incriminated as a trigger factor for asthma exacerbation is β-blockers. Bronchoconstriction, through the inhibition of β receptors, was an unacceptable adverse effect of these popular anti-hypertensive drugs and they were thus avoided in asthmatic patients. However, recent evidence indicates that not only are some cardioselective β-blockers acceptable for use in asthmatics, but that some, nadalol in particular, have been shown to have a beneficial effect when combined with corticosteroids in the treatment of asthma [32, 33]. However, the decision to start

a severe asthmatic on therapy with any β-blocker should always be undertaken with extreme caution.

Infections

Viral infections, chiefly influenza, play an important role in worsening of the severity of asthma by various mechanisms including increased bronchial hyper-responsiveness, mucus production and airway remodeling [34]. Therefore, influenza vaccinations, which have been demonstrated to be safe in asthmatics, should be administered to all patients with asthma [35, 36].

Similarly, the association between severe asthma and *Hepatitis C* has been also been pointed out in recent studies [37].

Persistent infections with atypical bacteria are also involved in severe asthma. In a recent study, 52% of patients with severe asthma tested positive for *Mycoplasma pneumoniae*, demonstrating the importance of the diagnosis and treatment of this infection [38]. Diagnosis should be carried out by polymerase chain reaction (PCR) assays, which have been shown to be the most sensitive test [38] and treatment should be with clarithromycin [39]. Chronic infection with *Chlamydia pneumoniae,* which is also associated with more severe disease [40, 41], should be tested for and treated with effective medications such as doxycycline, erythromycin or a fluroquinolone [42].

Non-adherence

Compliance with medication regimens and treatment plans poses a major problem in the management of severe asthma. Recent evidence indicates that up to 37% of patients with severe asthma admit to being non-compliant and that interventions aimed at improving compliance were able to decrease rates of hospital admission and dosages of prescribed steroids [43]. In-depth patient education [44], electronic monitoring of inhaled steroid use [45] and assessment of prescription filling [46] are methods which, although time consuming, have been demonstrated to improve the adherence to medication and ultimately asthma control. The role of long acting steroids in improving compliance is also of importance, as data suggests that injectable betamethasone [47, 48] and dexamethasone [49, 50] may have a role in the management of asthma. However, as sufficient research on its therapeutic efficacy in severe asthma is not available, further studies are necessary before using them in non-compliant severe asthmatics.

Treatment of co-morbidities

Gastro-esophageal reflux disease (GERD), obstructive sleep apnea (OSA), and sinus diseases are among the most significant co-morbidities associated with severe asthma [51]. One in four asthmatics (25.4%) [52] suffers from GERD, which not only aggravates asthma symptoms, but also increases the frequency of exacerbations. Thus, symptomatic patients should be thoroughly evaluated and treated with acid suppressive therapy, preferably a proton pump inhibitor [53, 54].

Teodorescu *et al*. reported that the presence of OSA was associated with a 3.6 times higher chance for having poorly controlled asthma [55]. Approximately 63% of children with severe asthma also have OSA [56]. Possible mechanisms associated with the increase in severity include an increase in the level of leukotrienes resulting in bronchospasm. In severe asthmatics, adenotonsillectomy [57, 58] in the pediatric age group and continuous positive airway pressure (CPAP) [59-61] in adults are methods to control OSA.

Both rhinitis and sinusitis are also associated with severe asthma [62] and their treatments have shown to improve lung function in such patients [63, 64].

Pharmacotherapy

Conventional therapy

Baseline drugs used to treat the more aggressive forms of asthma include one or more of the following: inhaled corticosteroids (ICS), long acting β_2-agonists (LABA), leukotriene modifiers and sustained-release theophyllines [5]. Adding LABA to ICS is widely used as combination drugs and are more effective in improving lung function, asthma symptoms, and decreasing the use of rescue therapy than increasing the dose of ICS alone [65, 66]. When combined, LABA augments the anti-inflammatory action of ICS at a molecular level [67, 68]. In severe asthmatics, when used alone, high doses of ICS are required, reaching up to 1-2 mg/day of beclomethasone dipropionate (BDP), which can lead to serious systemic side effects such as osteoporosis, cataract, and bruising [69, 70]. Thus, newer formulations consisting of smaller particle size preparations of these combination drugs (e.g. beclomethasone and formoterol) have been developed, which are able to reach more distal airways compared to standard preparations, resulting in less absorption from the proximal air passages and fewer systemic side-effects [71]. These new formulations allow much lower doses of both drugs to be used with an equivalent effect on the airways [72].

Leukotriene modifiers suppress the inflammatory process in asthma by decreasing the pro-inflammatory effect of leukotrienes. The leukotriene receptor antagonist, montelukast, usually given at a starting dose of 10 mg/day, is a safe [73] and effective alternative to increasing the dose of ICS and is associated with a significant improvement

in morning peak expiratory flow [74]. Montelukast is also particularly effective in asthmatic patients with allergic rhinitis [75]. Zileuton, another modifier, exerts its action by decreasing the amount of leukotriene production through inhibition of the enzyme 5-lipoxygenase. Zileuton is also an effective alternative to increasing the dose of steroids. O'Connor *et al*. reported a 12% increase in the forced expiratory volume in 1 s (FEV_1) when Zileuton 400 mg QID was added to 200 μg of BDP given twice daily [76]. However, zileuton has been associated with hepatotoxicity and interacts with drugs such as theophylline and warfarin, and thus should be prescribed cautiously [77].

Theophylline, a methylxanthine and a phosphodiesterase inhibitor has both bronchial smooth muscle relaxation and anti-inflammatory properties. Sustained release theophylline 300-600 mg/day in combination with BDP 250 μg BID has been shown to be as effective as 500 μg of BDP in increasing the mean morning and evening peak expiratory flow rate (PEFR) as well as the mean FEV_1 values in moderate to severe asthmatics [78]. Nevertheless, as it associated with multiple drug interactions and adverse effects [79], patients should be regularly monitored for any untoward consequences from this therapy.

Tiotropium, an anti-cholinergic drug, has also been used as add-on drug in the treatment of severe asthma [80]. In a recent study of severe, uncontrolled asthmatics already receiving ICS and LABA, Kerstjens *et al*. demonstrated that the addition of once-daily tiotropium (5 μg or 10 μg) to their usual regimen resulted in a significant improvement in their FEV_1 [81].

Despite the treatment options above, physicians are still unable to control asthma in a minority of patients and are forced to keep increasing the doses of their prescribed medications and eventually add oral corticosteroids to their regimen. Prednisone, the most commonly used oral corticosteroid, is administered at doses that are in proportion to the severity of asthma symptoms. Although effective, oral corticosteroids are associated with numerous adverse effects with high doses and long term therapy. Therefore their use is limited and physicians are forced to find steroid-sparing medications to treat such patients.

Cromoglycates like nedocromil and cromolyn sodium while useful in the management of some patients with mild-moderate asthma are not effective enough to be of benefit to patients with severe asthma [4].

Immunotherapy

Methotrexate, an inhibitor of the enzyme dihydrofolate reductase, is an anti-metabolite used in a variety of immune-mediated diseases. It plays a role in the treatment of severe asthma as a steroid-sparing agent. However, as there is little evidence available regarding the use of methotrexate in severe asthma, its use is controversial. Studies demonstrate that when given at a dose of 10 mg weekly, methotrexate is able to control asthma to the extent of reducing the dose oral corticosteroids by up to 50% [82, 83]. A 6% improvement in FEV_1 has also been reported with its use [84]. However, as a variety of gastrointestinal, neurological, hematological, and respiratory side-effects [85] are possible, further studies are required before advocating methotrexate as a safe and effective steroid-sparing agent. It is advised that only physicians with an expertise in severe asthma administer methotrexate with vigilant monitoring throughout its course, using their judgment to decide whether the benefit of methotrexate therapy is worth the risk in each individual patient.

Cyclosporine A is an immunosuppressant drug which acts by inhibiting the release of inflammatory mediators from mast cells and basophils. Studies using a daily dose of 5 mg/kg of cyclosporine have shown a beneficial effect in the treatment of steroid-dependant asthma [86, 87]. Notable benefits of cyclosporine include an improvement in PEFR [88, 89], as well as an increase in FEV_1 [88, 90]. However due to the serious side effects [89] such as hirsutism, hypertension and renal impairment, as well as the lack of sufficient experimental data, cyclosporine should be reserved for judicious use in the most serious cases.

Tacrolimus [91], azathioprine [92, 93] and auranofin [94] are other drugs that have been reported to be useful in the treatment of severe asthma. However, sufficient data is not available to affirm their safety and efficacy.

Biological drugs

Omalizumab, a monoclonal antibody directed again IgE, is an effective and well-tolerated drug that can be administered to patients with severe asthma. Studies have demonstrated up to 68% decline in exacerbations with the addition of omalizumab to the treatment regimen of severe asthmatics [95]. In addition to decline in the rate of exacerbations, significantly fewer emergency room visits and improved asthma symptoms have also been reported [96-98]. Administration is via an injection of 0.016 mg/kg per IU/ml of serum IgE [99] and the commonest side effects that have been reported include local injection site reactions and lower respiratory tract infections [97]. However, recent concerns about the development of anaphylaxis with the use of this drug have made physicians cautious about its use.

CD23 is a cell-surface molecule that is thought to influence IgE production. IDEC-152, an IgG1 anti-CD23

antibody has been shown to be safe and decrease serum total IgE in patients with mild-moderate persistent allergic asthma in a phase I, placebo controlled trial. However, after a single dose, there was no significant change in the FEV_1 or the PEFR [100].

IgE synthesis is suppressed by inhibition of the cytokines IL-4 and IL-13. Altrakincept, an IL-4 receptor given by inhalation has been shown to be effective and have some steroid-sparing effect in patients with moderate asthma [101]. Pitrakinra, a mutated IL-4 protein that blocks IL-4 and IL-13, when given either by subcutaneous injection or by inhalation has been shown to reduce the response to inhaled allergens in patients with mild asthma [102]. Lebrikizumab, an IL-13 antibody, has been shown to improve lung function in poorly controlled severe asthmatics especially in those that had a high pretreatment level of serum periostin [103].

Mepolizumab, a monoclonal antibody targeting IL-5 has been reported to decrease the number of asthma exacerbations as well as blood and sputum eosinophils, suggesting a unique role in the therapy of the eosinophilic variant of severe asthma [104-106]. Nair *et al*. demonstrated that a monthly intravenous infusion of 750 mg reduced the requirement of prednisone in as well [107]. However, sufficient data is not available to determine the safety of the drug in severe asthmatics.

Daclizumab, a humanized monoclonal antibody directed against the CD25 subunit of IL-2 receptor, is emerging as a potential agent in the therapy of severe asthma. Busse *et al*. reported that intravenously administered daclizumab led to improvements in FEV_1, daytime asthma symptoms and exacerbation rate [108].

Current studies with etanercept, a TNF-α inhibitor, have not shown any benefit in the therapy of severe asthma [109, 110] although perhaps further in-depth studies may prove the drug to be more beneficial. In addition, golimumab, a monoclonal antibody targeting TNF-α, was not only shown to have no role in asthma therapy, but also to increase the risk of severe infections and malignancies [111]. At this time, both these drugs are not therapeutic options for asthma.

Antisense oligonucleotides and interference RNA are also coming to light as innovative therapeutic options for asthmatics. These drugs act by targeting RNA transcripts, and consequentially, specific gene products [112, 113]. Currently, EPI-2010 and TPI ASM8 are antisense oligonucleotides which have undergone clinical trials and have been reported to be safe and effective in mild asthmatics [112]. Due to their relative safety, they are drugs which may be effective in severe asthma in the future.

PDE-4 inhibitors

An emerging class of drugs is the phosphodiesterase-4 inhibitors. Their anti-inflammatory action is exerted through enzyme inhibition, resulting in an elevation of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) levels, thereby suppressing inflammation at the cellular level [114]. Two drugs, cilomilast and roflumilast, have been undergoing trials to determine their clinical efficacy in the treatment of asthma. Roflumilast has been shown to have better efficacy and safety profile with tolerable gastrointestinal side effects [115] with evidence supporting its ability to produce improvements in FEV_1 and PEFR at a dosage of 100-500 μg in patients with mild-moderate asthma [116]. However further trials are necessary to demonstrate its effectiveness in severe asthma.

Antimicrobials

Currently, clarithromycin is gaining popularity in the treatment of severe asthma over the previously preferred troleandomycin, and is supported by the study conducted by Simpson *et al*. concluding that clarithromycin therapy, 500 mg twice daily, is able to attenuate IL-8 levels as well as neutrophil activation in severe asthmatics [117]. Additionally, as clarithromycin plays a key role in the treatment of the commonly concomitant infections due to *Chlamydophila pneumoniae* and *Mycoplasma pneumoniae*, its antimicrobial property may be beneficial in severe asthma.

Itraconazole, 200 mg twice daily, has been reported to improve the quality of life in those asthmatics that have been sensitized to fungal infections [118].

Miscellaneous therapies

Nebulized heparin has been shown to significantly reduce the late allergic response to allergen in asthmatic subjects which may be due to its anti-inflammatory activity [119].

Oral gold has been to shown to have a small role in decreasing the glucocorticoid dose in steroid-dependent asthmatics [120]. However, this effect is of probably limited clinical significance and given the side-effects of gold and the necessity for monitoring, gold has no role in the treatment of severe asthma.

A variety of other drugs like colchicine, hydroxychloroquine, immunoglobulin, dapsone and Chinese herbal medicines have been used over the years but none of them have ever been shown to have any clear benefit in patients with asthma.

Similarly, dietary alterations like low calorie or elimination diets, magnesium supplementation, diets rich in omega-3 or omega-6 fatty acids and antioxidant supplementation have never been shown to have any benefit in patients with asthma.

Evidence to support other nonpharmacologic interventions like biofeedback and relaxation tech-

niques, acupuncture, chiropractic manipulation, massage therapy and breathing exercises are limited by the absence of well designed clinical trials and therefore cannot be recommended at this time.

Bronchial thermoplasty

Bronchial thermoplasty (BT) is a recently developed bronchoscopic procedure in which radiofrequency energy is used to reduce bronchial smooth muscle wall thickness. In a randomized double-blinded trial, Castro *et al.* reported that more patients who had undergone BT had an improvement in their Asthma Quality of Life Questionnaire (AQLQ) score compared to those who had not (79% vs. 64%) [121]. Additionally, their study, which consisted of 3 bronchoscopic procedures carried out 3 weeks apart, demonstrated a 32% reduction in the rate of exacerbations in patients who had undergone BT compared to the control group. Immediate adverse effects that occurred include worsening of asthma symptoms and upper respiratory tract infections [121], but studies indicate that in the long term, BT is a safe procedure for severe asthmatics [122]. With the support of more clinical data, BT may eventually become a preferred therapeutic choice in severe asthma.

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