Unconventional Treatment Options in Severe Asthma: An Overview

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ABSTRACT - In Canada, asthma is the leading cause of admission in hospital. About of 80% of the death from asthma is preventable. Severe asthma is defined as a patient with persistent symptoms despite the use of adequate controller therapy, including multiple courses of oral glucocorticosteroids. However, about 10% of patients with severe asthma remain poorly controlled despite optimal treatment and these patients have the greatest morbidity and mortality. The management of refractory severe asthma remains extremely challenging. For patients with refractory severe asthma, the adjunct therapies recommended by national guidelines only included oral glucocorticosteroid and anti-IgE antibody (omalizumab) therapy. Currently, there is limited published literature on the unconventional treatments such as methotrexate, cyclosporine, gold and antimicrobials treatments, for refractory severe asthma. The objective of this review article is to provide an updated therapeutic overview of unconventional treatment options for refractory severe asthma.

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INTRODUCTION

Asthma is defined as a chronic inflammatory disorder of the airways and is associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing (1, 2). In Canada, asthma is the leading cause of admission in hospital(3). About of 80% of the death from asthma is preventable(4, 5). Inhaled corticosteroids are the cornerstone treatment of asthma (2, 6).

Severe asthma is a complex syndrome with different clinical phenotypes(7-9). Severe asthma is defined as a patient with persistent symptoms despite the use of adequate controller therapy, including multiple courses of oral glucocorticosteroids(10). The WHO uniform definition for severe asthma is "uncontrolled asthma which can result in risk of frequent severe exacerbations (or death) and /or adverse reactions to medications and/or chronic morbidity (including impaired lung function or reduced lung growth in children"(11). Patients with severe asthma are divided into three groups: 1) untreated severe asthma, 2) difficult to treat severe asthma, 3) treatment resistant severe asthma. The last group of patients includes patients with asthma which control is not achieved despite the highest level of recommended treatment: refractory asthma and

corticosteroid-resistant asthma, and asthma for which control can be maintained only with the highest level of recommended treatment. The management of severe asthma must include:(11)

1. Accurate diagnosis with pulmonary expiratory flow rate or spirometry
2. Accurate assessment of severity
3. Assessment and prevention of risk factors
4. Assessment and control of comorbidities
5. Appropriate therapy including ICS, short-acting β_2-agonists and long acting β_2-agonists
6. Appropriate drug delivery devices
7. Assessment of control
8. Ongoing support in self-management and patient education
9. Well trained health professionals

The goal of asthma management is to achieve and maintain clinical control. Medications used to treat asthma are categorized in 2 groups: controllers and relievers. Controllers are medications which are taken on a scheduled daily basis for long-term; they include inhaled and systemic glucocorticosteroids,

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leukotriene modifiers, long-acting β_2-agonists in combination with inhaled glucocorticosteroids, sustained release theophylline, cromones and anti-IgE (2). Relievers are medications used on an as needed basis. They include rapid acting inhaled β_2-agonists, inhaled atni-cholinergics, short-acting theophylline and short-acting oral β_2-agonists (2). Inhaled glucocorticosteroids are currently are currently the most effective anti-inflammatory medications for the treatment of severe asthma. This have shown to reduce asthma symptoms, improved quality of life, improve lung function, decrease airway hyperresponsiveness, controlling airway inflammation, reduce frequency and severity of exacerbations (2). Many patients with severe asthma respond to a combination of high dose inhaled corticosteroids (fluticasone $\geq$ 1 mg/day or equivalent) and β_2-adrenergic receptor agonists (12-14). However, about 10% of patients with severe asthma remain poorly controlled despite optimal treatment and these patients have the greatest morbidity and mortality (9, 15, 16). The management of refractory severe asthma remains extremely challenging (17-19). These patients have poor quality of life and require multiple emergency room visits, hospitalizations and unscheduled physician visits (15, 20). For patients with refractory severe asthma, the adjunct therapies recommended by national guidelines only included oral glucocorticosteroid and anti-IgE antibody (omalizumab) therapy (2, 6). Currently, there is limited published literature on the unconventional treatments of refractory severe asthma (8, 21-23). The objective of this review article is to provide an updated therapeutic overview of unconventional treatment options for refractory severe asthma.

CURRENT UNCONVENTIONAL TREATMENT OPTIONS

Anti-infectives

Antibiotics

Macrolide antibiotics such as clarithromycin and azithromycin both inhibit bacterial protein synthesis by binding 50S submit of the 70S bacterial ribosome and exhibit anti-inflammatory effects (24-27). The macrolides have been shown to reduce IL-8 and neutrophils, major inflammatory mediator, in non-eosinophil asthma (28, 29). It has been suggested that there is an association between atypical bacterial infection such as Chlamydia pneumoniae and mycoplasma pneumoniae, and asthma (26, 30-33). Results from studies in both adults and pediatric patients showed that the presence of atypical infection is associated with increased inflammatory response to the airways (31, 34).

Studies on the use of macrolides in the treatment of systemic steroid-dependent asthma demonstrated that there was no significant difference between placebo and macrolide treatment with respect to FEV_1 improvement and or reduction in systemic glucocorticoid dose between the two groups (35). However, recent studies showed that the addition of a macrolide improved quality of life, increase FEV_1 from baseline, reduction in nocturnal symptoms, and reduction of neutrophil count (36-40).

Current clinical guidelines do not recommend the use of macrolides as routine treatment of refractory severe asthma. Nevertheless, there is increasing evidence to show that macrolides have a role in the management of severe asthma and asthma exacerbation (38, 39). There are, however, risks associated with the use of macrolides, mainly, the development of antibiotic resistance. Therefore, before initiating a macrolide in patients with severe asthma the discussion of risks versus benefits with patients is essential.

Anti-fungal

Allergic bronchopulmonary aspergillosis (ABPA) caused by hypersensitivity to *Aspergillus fumigates* manifest in patients with severe asthma (41). These patients also have a positive skin test to *Aspergillus fumigates* with increased serum IgE and IgG to *Aspergillus fumigates* (42). The standard treatment of inflammation for ABPA is the use of glucocorticosteroids. Recently, studies showed a reduction of inflammation, oral corticosteroid dose, total IgE, asthma exacerbation and an improvement of FEV_1 with the treatment of the azoles such as ketoconazole and itraconazole (43-45). Current recommendation is to consider itraconazole in patients who are not responding to oral corticosteroid or required a corticosteroid sparing drug (46).

Severe asthma fungal sensitization (SAFS) is a distinct asthma phenotype in severe asthma patients. Patients with SAFS have severe asthma and positive testing for fungal (*Alternaria alernata* or *cladosporium herbarum*) sensitization but

exclude ABPA. The sensitivity to molds is associated with asthma severity, hospitalization, and pulmonary hypersensitivity (32, 47-49). In addition, these molds are capable of germination, infection and colonization in the respiratory tract of patients with asthma (50). Clinical trials showed that the treatment with fluconazole resulted in significant improvement in lung function, quality of life, symptom scores and reduction in steroid requirement (51, 52). However, all of the monitoring parameters returned to baseline after the discontinuation of therapy (51). In general, fluconazole was well tolerated; however, the therapy is quite costly. It is recommended that the treatment of fluconazole should be patient specific.

Immunomodulating Agents

Methotrexate

Neutrophils are polymorphonuclear leukocytes and they play an important part in the immune system (53). They are the first line of defence against bacterial and fungal infections. Also, they play a major role in the inflammatory process by releasing inflammatory mediators which has a significant effect on patients with asthma (54).

Methotrexate is a folic acid antagonist with anti-neoplastic, immunosuppressive and anti-inflammatory effects; it is one of the most studied agents in asthma. The exact mechanism of methotrexate in asthma is unknown. It has been proposed that methotrexate may inhibit neutrophils (55-58). Some evidence suggested that methotrexate may enhance the sensitivity of monocytes to glucocortoids in severe asthma patients (59). The common doses used in the studies were 7.5 – 30 mg weekly. The duration ranges from 3 – 6 months.

Clinical trials evaluating the comparison of methotrexate with placebo demonstrated a modest steroid-sparing effect with methotrexate (60). The treatment of methotrexate was associated with significant hepatic and gastrointestinal side effects without much improvement in lung function or airway hyperresponsiveness.

A recent double-blind, randomized, placebo-control study of 46 severe asthma patient treated with methotrexate 10 mg/week for 12 months. The results showed a significant reduction (>50%) in steroid dose in the methotrexate group (61).

Common side effects were hepatic, gastrointestinal and oral ulcer but were transient and reversible.

It has been suggested that methotrexate should be given first consideration in patients whose symptoms are not controlled with long term oral glucocorticosteroid (21). However, the decision to initiate methotrexate must be based on risk versus benefit assessment for the patients.

Cyclosporine

Evidence supported the association with asthma symptoms and increased of eosinophils and T lymphocytes (62). Studies showed an increased of CD25+, CD4+ T lymphocytes in the peripheral blood of asthma patients who were unresponsive to oral corticosteroid as compared with asthma patients who were responsive to oral corticorsteroid (63-65).

Cyclosporine, a fungal metabolite, inhibits CD4+ T-cell activation (66-68). Randomized, placebo controlled trials showed a small reduction in daily oral corticorsteroid dose and slight improvement in lung function (66, 69-71). The duration of treatment in the studies was short with longest treatment period of 36 weeks (70). The studies did not examine the mechanism of action for cyclosporine by monitoring the inflammatory mediators. The most common side effects seen were elevation of diastolic blood pressure and serum creatinine that are reversible at the discontinuation of cyclosporine. Based on the current evidence and the safety profile, it is recommended that cyclosporine should not be routinely initiated in severe asthma patients, and should only be prescribed and monitored by trained specialist.

Gold

Gold sodium thiomalate, gold thioglucose, and auranofin are commonly used in gold therapy. It is an immunomodulator; the exact mechanism of action is unknown. It has been shown to reduce neutrophils and macrophage phagocytosis and lymphocyte reactivity (72) Clinical trials did not show clinical significant improvement in symptoms, pulmonary function tests, or reduction in oral steroid dose (73-76). The common dosing regimen used in the studies was 25 – 50 mg a week orally or intramuscularly. The common reported reversible side effects were gastrointestinal upset, diarrhea, pruritic rash, oral ulceration, proteinuria

and nephrotic syndrome. Given the lack of efficacy and associated toxicities, routine treatment with gold in severe asthma patients is not recommended. It should only be prescribed by experienced specialists.

Intravenous immune globulin (IVIG)

IVIG consists of pooled human plasma IgG antibodies. Studies demonstrated that the use of IVIG is effective in glucocorticoid dependent asthma patients (77-80). The exact mechanism of glucocorticosteroid sparing effects is unclear. It has been shown to suppress lymphocyte activation and cytokine dependent lymphocyte proliferation (79, 81, 82). IVIG improves glucocorticoid receptor sensitivity in patients who are glucocorticoid resistant (83).

Treatment with IVIG resulted in a reduction of asthma symptoms, oral steroid dose by as much as threefold and total serum IgE (78-80, 84). As an adjunctive therapy, IVIG, reduces glucocorticoid requirement, and hospitalization; but it does not improve lung function in patient with severe steroid dependent asthma (85).

In general, IVIG is well tolerated; common reported self-limiting side effects include headache and nausea. IVIG comes from pooled human plasma, although there is no risk of transmission of viral hepatitis, however, there is still a slight possibility of IVIG transmission of undefined viral infection. In rare cases, IVIG has been associated with interstitial nephritis and aseptic meningitis (86). Because IVIG contains a trace of IgA, IVIG should be avoided in patients with IgA deficiency as it could lead to anaphylactic reaction (87-90).

Azathioprine

Azathioprine is an immunosuppressive agent that reversibly reduces monocyte numbers in circulation and tissues (91), impairs synthesis of gamma globulin (IgM, IgG) (92), long term immunosuppression decreases the number of cutaneous Langerhans cells (93) impairs responses of helper T cell dependent B cells (94), impairs function of T suppressor cells (94) and impairs T cell lymphocyte function and IL-2 production (95). Because azathioprine has been shown to be effective in other inflammatory conditions, it is reasonable to expect that it would also be effective in patients with asthma. Nevertheless, there are limited studies to address the effectiveness of azathioprine in patients with asthma. Azathioprine did not improve FEV_1 or reduce asthma exacerbations (96). Due to insufficient evidence, it is recommended that more clinical trials are required to investigate the effectiveness of azathioprine in asthma patients.

Colchicine

Colchicine is an inexpensive anti-inflammatory, immunomodulating agent with very few adverse effects, has been in use for over 3000 years (97, 98). It is commonly used for treatment of gout. Colchicine exerts its anti-inflammatory action by interfering with leukocyte chemotaxis and lysosomal enzyme release, (99-101) and inhibiting histamine release from basophils (102, 103). The use of colchicine as an adjunct to oral or inhaled corticosteroid has been studied in patients with asthma. Results from studies failed to show improvement in clinical outcomes or reduction in corticosteroid dose in patients with mild to moderate asthma (104-108). Data from these studies failed to support the use of colchicine as an adjunct therapy in patients with glucocorticoid dependent asthma.

Dapsone

Dapsone is a sulfone antibiotic commonly used to treat leprosy. It interferes with the myeloperoxidase-hydrogen peroxide-halide mediated cytotoxic system in neutrophils resulting in inhibition of antibody adherence to neutrophils (109, 110). Currently, there is only one open label study of dapsone in 10 patients with asthma (111). The study showed that reduction of oral corticosteroid was possible in seven patients however all ten patients experienced dose-related hemolysis necessitated the discontinuation from the study. Due to the side effects and lack of efficacy evidence, dapsone is not recommended as an adjunct therapy.

Hydroxychloroquine

Hydroxychloroquine is used in malarial infection, rheumatoid arthritis and systemic lupus erythematosus. The proposed mechanism for hydroxychloroquine is that it inhibits phospholipase A2, and phagocytosis and decreases stimulation of

CD4+ lymphocytes (112). The possible anti-inflammatory properties are a result of decrease leukotriene and prostaglandin synthesis (113). Open label studies shown hydroxychloroquine had corticosteroid-sparing effects, improved FEV_1 and FVC and reduced IgE levels.(114, 115) Yet, in a double-blind placebo-controlled trial with nine patients, hydroxychloroquine failed to show oral corticosteroid-sparing effects and pulmonary function improvements (116). Overall, hydroxychloroquine was well tolerated. Although rare, it can cause irreversible retinal damage. Given that there is insufficient efficacy and safety data, hydroxychloroquine is not recommended as an adjunct in the treatment of asthma.

BIOLOGICS

Omalizumab

Basophil, mast cell and particularly eosinophil degranulation play a central role in allergic asthma which occurs in presence of high IgE level (117-119). Increased numbers of eosinophils are associated with the severity of asthma (120-122). Omalizumab (Xolair®, Genetech/Novartis) is a recombinant humanized monoclonal anti-IgE antibody that binds to the Fc-region of the IgE molecule, and so prevents IgE from interacting with high or low-affinity IgE receptors (FcεR1 and FcεR11) and resulting in a reduction of circulating free IgE (119, 123-125). Omalizumab also downregulates FcεR1 receptors in circulating basophils, in mast cells, and in circulating antigen presenting cells. This is believed to result in a downgrade of inflammatory responses mediated by helper T cells (125, 126). Omalizumab received approval by the US Food and Drug Administration (2003) and Health Canada (2005) for use in patients who are 12 years or older with moderate to severe persistent asthma, who are not controlled with inhaled corticosteroids, have an serum IgE 30–700 International Units (IU)·mL^{-1}, and also test positive for reactivity to a perennial airborne allergen. Currently, omalizumab is the only biologic approved for the treatment of asthma. Numerous clinical trials of patients with mild to severe allergic asthma showed omalizumab significantly reduced serum IgE, inhaled corticosteroid dose requirement and number of asthma exacerbations and improved quality of life compared to placebo (127). However, the author noted significant placebo effect in the

control group and questioned the true effects of omalizumab. Recent studies on adolescents and adults also showed similar results (128-130). Nevertheless, omalizumab has not shown to consistently improve lung functions. In general, omalizumab is well tolerated, but studies lack long-term safety data. According to the recent recommendations, omalizumab is an option in patients with severe allergic asthma with elevated serum IgE or demonstrated allergic sensitization (2).

Anti-tumor Necrosis Factor α

Tumor necrosis factor α are inflammatory cytokines released by mast cells,(131) and are elevated in patients with severe asthma (131-135). Patients who were given exogenous tumor necrosis factor α developed airway hyperresponsiveness and airway neutrophilia (136, 137). The exact mechanism of airway inflammation is unclear. It is believed that tumor necrosis factor α affects the airway smooth muscles by the release of cysteinyl leukotrienes C_4 and D_4, recruits both neutrophils and eosinophils, activation of T cells (138, 139) and enhancement of cytotoxic activities of the leukocytes (140, 141). Anti- tumor necrosis factor α monoclonal antibodies such as infliximab, and etanercept, have been studied in patients with refractory severe asthma evaluating FEV_1, FVC, quality of life, and number of exacerbations produced conflicting findings (134, 135, 142-144). A recent phase II randomized placebo-controlled trial with golimumab, a monoclonal antibody, in patients with severe persistent asthma failed to show benefits over placebo and was prematurely terminated at 24 weeks (145). Of concern, patients in the treatment group had increased serious side effects such as infections, and eight malignancies such as breast cancer, B cell lymphoma, melanoma, cervical carcinoma, renal cell carcinoma, colon cancer and basal cell carcinomas while none was reported in the placebo group. Similar infections and malignancies were reported in a recent study on the administration of infliximab for six months in patients with chronic obstructive pulmonary disease (146). In addition, there have been numerous reporting of malignancies in patients with rheumatoid arthritis treated with anti- tumor necrosis factor α (147-149). Although atni- tumor necrosis factor α remains a viable option in the treatment of refractory severe asthma, careful

evaluation of risks versus benefits must be taken in consideration before initiating these biologics.

OTHERS

Heparin

Heparin is a glycosaminoglycan commonly used for its anticoagulation effects. Heparin and heparin-like compounds are ubiquitous in the lung, intestine and liver (150). It is found in cytoplasm of mast cells as granules and it is released under inflammatory conditions such as asthma. It is hypothesized that heparin inhibits inositol triphosphate receptors which prevents mast cell degranulation, and histamine release (151-159). In patients with atopic asthma, plasma level of heparin, and heparin-like compounds are elevated resulting in altered platelet function. Early studies with high dose intravenous heparin in patients with asthma revealed subjective improvement of asthma symptoms but no objective improvement (160, 161). The results were confirmed with inhaled heparin (162). In subsequent studies, inhaled heparin inhibits bronchoconstriction in patients with exercise-induced asthma (163, 164). The effect is also seen with inhaled low molecular weight heparin, enoxaparin (165). Trials of inhaled heparin on bronchoconstriction effects caused by bronchostimulants such as methacholine, yield mixed results (166-168). Case reports of patients with corticosteroid resistant asthma responded to inhaled heparin during exacerbations (169).

No bleed complications or significant changes in partial thrombin time, or anti-Xa activities were reported in any of the studies. Nonetheless, the use of heparin for the anti-inflammatory properties is hindered by the fear of bleeding. The requirement of high dose of heparin to achieve anti-inflammatory effects limits its use in severe asthma patients. Currently, efforts are being devoted to develop chemically modified heparin without the anticoagulation effects (170). Thus far, all the studies are limited to small sample size. Larger prospective placebo-controlled studies are needed to determine efficacy and toxicity of heparin in patients with asthma.

Furosemide

Furosemide, a loop diuretic, inhibits the sodium/potassium/chloride co-transporter in the ascending loop of Henle which produces potent dieresis (171). The exact mechanism of furosemide in asthma is not known. It is not a bronchodilator as it does not inhbit acetylcholine, histamine or tachykinin induced bronchoconstriction (172, 173). It is proposed that furosemide reduce chloride channel activity which inhibits the release of inflammatory mediators such as histamine and leukotrienes by eosinophils (174).

Two small studies using inhaled furosemide in combination with lysine acetylsalicylate (LASA) demonstrated significant reduction in glucocorticosteroid requirement in patients with chronic asthma (175, 176). Studies evaluated the use of inhaled furosemide in acute asthma exacerbation yielded mixed results (177-180). A follow up case series showed clinical improvement in patients with severe asthma exacerbations who were unresponsive to conventional therapies (180). The current efficacy and toxicity data are lacking. Large double blinded placebo controlled trials are needed to establish the role of loop diuretics in the treatment of asthma.

CONCLUSION

There is significant co-morbidities exist in patients who are refractory to standard treatment.(181) The management of refractory severe asthma requires a systematic approach consists of correct diagnosis, identification of co-morbidities, patient specific treatment and assessment of adherence. Asthma severity is intertwined with the level of control, therapy prescribed and responsiveness to prescribed therapy (11). When considering the use of unconventional therapies for asthma, only trained and experienced pulmonologists should initiate these therapies. The weigh risks versus benefits and cost must be taken into account when making the decision.

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