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Medications for asthma management

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Abstract

Asthma is common lung condition that causes sporadic breathing difficulties due to swelling and narrowing of the tubes that carry air to and from the lungs. According to the World Health Organization (WHO), 23.5 crore people currently suffer from asthma and India has the largest number of asthma deaths in the world, contributing to 22.3% of all global asthma deaths. Despite the pathophysiology of asthma is better understood and there are reliable diagnostic tools and medications for its control, still it remains poorly managed in the clinical practice across the globe. This chronic inflammatory disorder cannot be cured, but proper diagnosis, treatment, careful observation, patient education regarding asthma and regular medical check up can be fruitful for its management and control. In regard to management, medications play a very important role to reduce the severity of this disease. Since, education for the management of asthma is an essential strategy, therefore, this article provides a review of current literature exploring the medications utilized to treat and manage the chronic asthma.

Keywords: Asthma, controllers, management, medications, patients, relievers

Introduction

Asthma is a chronic inflammatory disorder in which the airways narrow, swell and produce extra mucus (Holgate and Polosa, 2006) ^[26]. It is characterised by airway inflammation, persistent airways hyperresponsiveness (AHR) and intermittent, reversible airways obstruction (Gina, 2006; Bousquet *et al.*, 2000) ^[27] and leads to recurrent symptoms such as wheezing, dyspnea (shortness of breath), chest tightness and coughing (Global Initiative for Asthma (GINA): Global strategy for asthma management and prevention. 2009, Available at: <http://www.ginasthma.com> Accessed July 15, 2010). Although this chronic inflammatory disorder is localized in the lungs but it represents a component of systemic airway disease which involves the entire respiratory tract (Bourdin *et al.*, 2009) ^[2].

The true burden of Asthma in India is not known. Although earlier studies have reported a median prevalence of 3% (more than 30 million asthmatics in India), there is growing evidence to suggest that this may be a gross underestimate (Agarwal *et al.*, 2006) ^[3]. According to the World Health Organization (WHO), India has the largest number of asthma deaths in the world, contributing to 22.3% of all global asthma deaths (WHO, 2004). Further, Sundeep and co-authors (2015) have reported that asthma management in India still remains very poor, with a significant proportion of patients experiencing bothersome symptoms and worsened quality of life. Hence, there is a need for an urgent review of this situation and initiate active measures at local as well as national levels to improve asthma care in India.

The pathophysiology of asthma is generally associated with T helper cell type-2 (Th2) immune responses (Bousquet *et al.*, 2000) ^[27]. Elevation of Th2 cells in the airways release specific cytokines, including interleukin (IL)-4, IL-5, IL-9 and IL-13, that promote eosinophilic inflammation and immunoglobulinE (IgE) production by mast cells. Further, IgE production triggers the release of inflammatory mediators, such as histamine and cysteinyl leukotrienes, that cause bronchospasm (contraction of the smooth muscle in the airways), edema (swelling) and increased mucous secretion (mucous hypersecretion), leading the characteristic symptoms of asthma. The mediators and cytokines released during the early phase of an immune response to an inciting allergen, trigger a further inflammatory response (late-phase asthmatic response) that leads to further airway inflammation and bronchial hyperreactivity (Barnes and Pauwels, 1994) ^[31]. A number of chromosomal regions associated with asthma susceptibility have also been identified, such as those related to the production of IgE antibodies, expression of airway hyperresponsiveness, and the production of inflammatory mediators (Lemanske *et al.*, 2003) ^[28]. However, further study is required to determine the specific genes involved in asthma as well as the gene-environment interactions which cause disease expression.

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Despite a better understanding of the pathophysiology of asthma, presence of reliable diagnostic tools, availability of a wide array of effective and affordable inhaled drugs and simplified national and international asthma management guidelines, asthma still remains poorly managed in the clinical practice across the globe (Anderson *et al.*, 2015) [29]. To rule out this chronic inflammatory disorder, several classification of medications are used which reduce the inflammation in the airways and keep the asthma symptoms under control. Therefore, education on such medications used for asthma control is an essential strategy. The present review, therefore, explores the medications utilized to treat and manage the chronic asthma and reduce exacerbations. The medications used for the treatment of asthma can be classified as controllers and relievers. Controllers are the medications taken daily on long term basis which achieve control primarily through the anti-inflammatory effects while relievers are the medications used as on an as needed basis for quick relief of bronchoconstrictions and symptoms (Juniper *et al.*, 1990) [30].

Controller medications

Inhaled corticosteroids

Inhaled corticosteroids, ICS, also known as glucocorticosteroids, glucocorticoids, steroids are the most effective controllers used for the treatment of asthma (Patrick and Carolyn, 2008) [11]. They are the only drugs which effectively suppress the characteristic inflammation in asthmatic airways, even in very low doses (Barnes, 2010) [4]. Low-dose ICS monotherapy is the recommended first-line maintenance therapy for most children and adults with asthma. Regular use of ICS is reported to reduce symptoms and exacerbations, and improve lung function and quality of life. However, ICSs do not “cure” asthma, and symptoms tend to recur within weeks to months of ICS discontinuation. Therefore, long term treatment is generally required in most patients (Kalpan *et al.*, 2009; www.ginasthma.com, 2010; Loughheed *et al.*, 2010) [8, 32, 7].

Six ICSs, are currently available for clinical use which exhibit different pharmacokinetic/pharmacodynamic profiles and biologic characteristics. They are beclomethasone dipropionate, budesonide, flunisolide, fluticasone propionate, mometasone fumarate and triamcinolone acetate (Skoner *et al.*, 2008) [13]. Ciclesonide, a seventh ICS, is also available for the treatment of asthma, but the nasal-spray version of ciclesonide (Omnaris) was recently cleared for treatment of allergic rhinitis (Taylor *et al.*, 1999) [14]. Among the clinically used ICSs, fluticasone, budesonide, and mometasone are active drugs while beclomethasone dipropionate and ciclesonide are pro-drugs with active metabolites. Beclomethasone dipropionate bears relatively poor activity and is metabolized to 17-beclomethasone monopropionate, which is the main active constituent (Allen *et al.*, 2003) [1].

Leukotriene receptor antagonists (LTRAs)

The LTRAs belong to the new class of asthma medication and are considered as adjunct therapy for asthma patients (Antony, 2000). Montelukast and zafirlukast are effective for the treatment of asthma. These are generally considered to be safe and well tolerated. However, when used as monotherapy, these agents are less effective than ICS treatment. Therefore, they are usually reserved for patients who are unwilling or unable to use ICSs. LTRAs is also used as add-on therapy if asthma is uncontrolled despite the use of low-to-moderate

dose of ICS therapy. However, LTRAs are considered to be less effective than LABAs as add-on therapy in the adults (www.ginasthma.com, 2010; Loughheed *et al.*, 2010) [32, 7].

Combination inhalers

Combination inhalers are another medication option for people with poorly controlled asthma. They are a mixture of controller medication with a form of slow-acting reliever medication.

The combination of a LABA and ICS are highly effective in reducing asthma symptoms and exacerbations, and is the preferred treatment option in adolescents or adults whose asthma is inadequately controlled on low-dose ICS therapy, or in children over 6 years of age who are uncontrolled on moderate ICS doses (Loughheed *et al.*, 2010) [7]. Although there is no apparent difference in efficacy between ICSs and LABAs given in the same or in separate inhalers, combination ICS/ LABA inhalers are preferred because they preclude use of the LABA without an ICS, are more convenient and may enhance patient adherence. Three combination ICS/LABA inhalers are mostly used: Fluticasone & Salmeterol (Seretide), Budesonide & Formoterol (Symbicort) and mometasone & formoterol (Zenhale). Combination budesonide/formoterol has recently been approved for use as a single inhaler for both daily maintenance (controller) and reliever therapy in individuals 12 years of age and older. It should only be used in patients whose asthma is not adequately controlled with low-to-moderate ICS doses or whose disease severity warrants treatment with combination therapy (GINA, 2010; Loughheed *et al.*, 2010) [32, 7]. People requiring a combination inhaler should be reviewed regularly by their health care professional.

Theophylline

Theophylline is considered to be an oral bronchodilator with modest anti-inflammatory effects. Due to its frequent adverse events such as, gastrointestinal symptoms, loose stools, seizures, cardiac arrhythmias, nausea and vomiting, its use is generally reserved for patients whose asthma is uncontrolled despite an adequate trial of ICS, LABAs and/or LTRAs (GINA, 2010; Loughheed *et al.*, 2010) [32, 7].

The anti-inflammatory activities of theophylline are relevant to asthma. They include inhibition of cytokine synthesis and release, inhibition of inflammatory cell activation and microvascular leakage, and prevention of airway hyperresponsiveness induced by airway inflammation. It is reported to have immunomodulatory effect even at low plasma concentration (Barnes and Pauwels, 1994) [31].

Anti IgE therapy

The anti-IgE monoclonal antibody, omalizumab, is reported to reduce the frequency of asthma exacerbations by approximately 50%. The drug is administered subcutaneously once every 2-4 weeks and is approved for the treatment of moderate to severe, persistent allergic asthma in patients 12 years of age or older. Recently, omalizumab is reserved for patients with difficult to control asthma who have documented allergies and whose asthma symptoms remain uncontrolled despite ICS therapy (Loughheed *et al.*, 2010) [7].

Systemic corticosteroids

Systemic corticosteroids, such as oral prednisone, are generally used for the acute treatment of moderate to severe asthma exacerbations. While chronic systemic corticosteroid therapy may also be effective for the management of difficult

to control asthma, prolonged use of oral steroids are associated with well-known and potentially serious adverse effects and, therefore, their long-term use should be avoided if at all possible. Adverse events with short-term, high-dose oral prednisone are uncommon, but may include: reversible abnormalities in glucose metabolism, increased appetite, edema, weight gain, rounding of the face, mood alterations, hypertension, peptic ulcers and avascular necrosis (GINA, 2010)^[32].

Allergen specific immunotherapy

Allergen-specific immunotherapy involves the subcutaneous administration of gradually increasing quantities of the patient's relevant allergens until a dose is reached that is effective in inducing immunologic tolerance to the allergen. Despite its wide use for the treatment of allergic asthma, it is not universally accepted by all clinical practice guideline committees due to the potential for serious anaphylactic reactions with this form of therapy (Frew, 2010). A Cochrane review of 75 randomized controlled trials examining the use of allergen-specific immunotherapy in asthma management confirmed its efficacy in reducing asthma symptom scores and medication requirements, and improving airway hyperresponsiveness (Abramson *et al.*, 2003). Similar benefits have been noted with sublingual immunotherapy (Calamita *et al.*, 2006)^[23]. Evidences also suggest that allergen-specific immunotherapy may prevent the onset of asthma in atopic individuals (Grembiale *et al.*, 2000). It can be used prior to a trial of ICS therapy in patients with very mild allergic asthma and concomitant allergic rhinitis and as add-on therapy in patients using ICSs alone (Zielen *et al.*, 2010). Allergen-specific immunotherapy may also be considered in patients using combination inhalers, ICS/LTRAs and/or omalizumab if asthma symptoms are controlled. Since allergen-specific immunotherapy carries the risk of anaphylactic reactions, it should only be prescribed by physicians who are adequately trained in the treatment of allergy and the injections must be given in clinics that are equipped to manage possible life-threatening anaphylaxis.

Reliever medications

Reliever means "rescue". Reliever medication works quickly and is used to treat acute symptoms. The major advantage of relievers type of medications is that it can be inhaled the drugs so delivered directly into the airways, producing higher local concentrations with significantly less risk of systemic side effects (Kemp, 1999). This type of medications work fastly to widen the airways so that asthmatic patients can feel easier to breathe again. They open up the airway by relaxing the tightened airway muscles. (Zhao *et al.*, 2015). Thus, they act quickly to reverse bronchoconstriction and relieve its symptoms (Joseph *et al.*, 1996).

Inhaled rapid-acting beta₂-agonists are the most preferred reliever medications for the treatment of acute symptoms (O'Byrne *et al.*, 2005) and can be given in both adults and children of all ages (Williams *et al.*, 1998). β agonists are divided into three classes namely : Short-Acting β Agonists (SABAs) –e.g. Salbutamol, Terbutaline; Long-Acting β Agonists (LABAs) –e.g. Salmeterol, Formoterol, Olodaterol, Vilanterol and; Ultra-Long Acting β Agonists (ultra-LABAs).-e.g. Ultra-Indacaterol. SABAs should only be taken on an as needed basis for symptom relief. Increased use (i.e., 3 or more times per week) indicates worsening control and signals the need to reassess treatment to achieve control of

symptoms.

Among LABAs, formoterol has a rapid onset of action and, therefore, may be used for acute symptom relief. However, LABA monotherapy is reported to be associated with an increased risk of asthma-related morbidity and mortality, thus, formoterol should only be used as a reliever in patients 12 years of age or older who are on regular controller therapy with an ICS (GINA, 2010; Kaplan *et al.*, 2009; Loughheed *et al.*, 2010)^[32, 8, 7]. Budesonide/formoterol in a single inhaler has been found to be effective maintenance and reliever agent in both adults and children. It has also been found to be safe and more efficacious than fixed-dosing (Saleh, 2008)^[12].

Short-acting anticholinergic bronchodilators, such as ipratropium bromide, may also be used as reliever therapy for asthma. However, these agents appear to be less effective than inhaled rapid-acting beta₂-agonists and, therefore, should be reserved as second-line therapy for patients who are unable to use SABAs. They may also be used in addition to SABAs in patients experiencing moderate to severe asthma exacerbations. Furthermore, chronic, short-acting anticholinergic bronchodilator therapy is not recommended for use in children (Loughheed *et al.*, 2010)^[7].

Conclusion

Asthma is a common chronic inflammatory disorder characterised by airway inflammation, persistent airways hyperresponsiveness (AHR) and intermittent, reversible airways obstruction that leads to recurrent symptoms such as wheezing, dyspnea (shortness of breath), chest tightness and coughing. The management for diagnosed asthma may be achieved through the use of avoidance measure and pharmacological interventions. The medications are classified as controllers and relievers. ICS are the most effective controllers used for the treatment of asthma. Beside ICS used alone as effective controller, its combination with LABA are also highly effective in reducing asthma symptoms and exacerbations. The LTRAs are considered as adjunct therapy for asthma patients. Further, theophylline is another controller considered to be an oral bronchodilator with modest anti-inflammatory effects. An anti-IgE monoclonal antibody, omalizumab, is also prescribed to patients documented with allergies and whose symptoms remain uncontrolled despite ICS therapy. Systemic corticosteroids, such as oral prednisone, are used for the acute treatment of moderate to severe asthma exacerbations. But their prolonged use are associated with well-known and potentially serious adverse effects therefore, their long-term use should be avoided. Allergen-specific immunotherapy is a potentially disease-modifying therapy, but should only be prescribed by physicians with appropriate training in allergy. Patients with asthma should have a regular medical check up and adherence to therapy for its fruitful management and control.

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