The management of adults and children with moderate severity asthma

Jeena PM, MBChB, FCP (Paeds), FCP (Pulm)
Associate Professor, Department of Paediatrics and Child Health,
Nelson R Mandela School of Medicine, University of KwaZulu-Natal

Correspondence to: Prof P M Jeena, Email: jeena@ukzn.ac.za

Abstract

Moderate severity asthma occurs in approximately 10 to 15% of patients with chronic reversible airway obstruction and is defined by more than four daytime symptoms per week, more than four night time symptoms per month and peak expiratory flow rates of between 60 and 80% of predicted values. Currently recommended first line chronic maintenance treatment for children and adults for moderate severity asthma is the use of combination therapy of inhaled corticosteroids and long acting beta-2 agonists. Other agents such as leukotriene receptor antagonist, theophyllines and soluble TNF alpha-receptor blockers could be considered in special circumstances when adequate control is not obtained.

SA Fam Pract 2007;49(4): 28-32

INTRODUCTION

Asthma is a chronic disease with airflow limitation due to inflammation and smooth muscle bronchial constriction. According to the latest international guidelines, a major paradigm shift has occurred in the care of patients with asthma. The value of the classifications of patients according to their severity of disease for chronic maintenance management as intermittent or persistent (mild, moderate or severe) disease is being questioned. Recently asthma has been classified either as controlled or uncontrolled with treatment adjusted accordingly. For assessment of control, GINA utilises characteristics such as symptoms, usage of medication and variation of peak flow readings only, and these have been employed in the recent GOAL study to define well or total controlled asthma. These parameters alone do not give the complete picture of asthma control as other markers of allergic inflammation such as exhaled nitric oxide, eosinophic cationic protein, etc. and non- allergic inflammations, e.g. cytokines such as TNF alpha (neutrophilic inflammation) were not considered. In addition, methacholine challenge testing (degree of bronchial reactivity), lung biopsy (pathological severity of disease) and quality of life issues are not included in the evaluation of asthma control. With the addition of these markers and genetic studies of asthmatics, it may be possible within the next decade to accurately determine the specific type of asthma, the most appropriate therapeutic option and what adjustments we need to make in the medications to ensure optimal control. This would enhance the management model of stepping up or down therapy according to predefined targets of control rather than classifying patients into different severity categories.

IMPACT OF POORLY CONTROLLED ASTHMA

Uncontrolled childhood asthma has a significantly impact on quality of life issues related to parents and children. It results in school absenteeism, multiple visits to doctors and hospital admissions for the asthmatic and sleepless nights and work absenteeism for the parent/caregiver. Improved therapy that provides optimal control is available to provide a better quality of life for these family units

MODERATE SEVERE ASTHMA: CLASSIFICATION AND PREVALENCE

The current South African Thoracic Society and South African Childhood Asthma Working Group define moderate severe asthma in adults and children as more than four daytime symptoms per week, more than four night time symptoms per month and peak expiratory flow rates of between 60 and 80% of predicted values. Utilising this definition it is expected that approximately only 10 to 15% of asthma sufferers would be categorised as moderate severity asthmatics, the vast majority being mild persistent disease.

MANAGEMENT

Inhaled corticosteroids (ICS)

As asthma has predominantly been recognised as a disease of eosinophilic and IgE mediated inflammation, the cornerstone of management is the use of corticosteroids. The medications used in the management of adults and children of any age are similar with variations just in the drug doses required. The inhaled route is the preferred method of administration as the medication is required in the airways and lungs and utilisation in this form allows for a lower drug dosage with a better safety profile. The recommended drug dosage for adults with moderate severity disease is 500mg to 1000mg of beclomethasone dipropionate equivalent per day (medium dose) while half this dose is used in children. The major concern with the use of corticosteroids is the safety profile of these medications at high doses (> 1500 ug of BDP equivalent) of the inhaled medication or with recurrent or persistent use of the oral form of the drug.

Long acting Beta-2 agonist (LABA) and ICS

Over the last decade several large studies in adults have confirmed the benefit of commit ant use of inhaled long acting beta-2 agonist (LABA) with inhaled corticosteroids. The pivotal Greening study demonstrated that addition of a LABA to low dose inhaled corticosteroid (100 to 500mg BDP equivalent) had the same effect as using double the prescribed dose of steroids (500 to 1000mg BDP

equivalent corticosteroid per day). LABA potentiates the effect of corticosteroids by priming the glucocorticoid receptor and thus increasing activity while the corticosteriod induced replication of proteins important in producing beta-2 adrenoceptor and decreasing desensitisation of the beta-2 receptors. This self-perpetuating loop between LABA and corticosteroids allows for a lower dose of corticosteroids to be used to obtain control and is known as a steroid sparing effect. This effect is accentuated at a certain threshold value (flat dose response curve) for corticosteroids where the benefit of adding LABA is believed better than doubling the dose of corticosteroids.

Similar data has been shown in 6 double blind placebo controlled trials in childhood and adolescences. The addition of either LABA or placebo to corticosteroid therapy, statistical significant benefit in terms of bronchodilatation (benefit in symptom free days, FEV_1 and morning PEF) was seen with the LABA over the placebo; although the effects were not as marked as in adults. The comparison with doubling dose of steroids versus adding a LABA was assessed in two studies in children benefits in terms of symptom score, exacerbations rates, PEF and FEV_1 measurements and reduction in BHR were seen in the groups on LABA with inhaled corticosteroids. In summary LABA given in conjunction with appropriate inflammatory treatment particularly inhaled corticosteroids as a regular add-on treatment reduces the rate of exacerbations, decreases bronchial hyperactivity and is more advantageous than using either medication alone. Sekhsaria and colleagues found that a combination of fluticasone and salmeterol significantly reduce the number of emergency room visits and hospitalisations ($p<0.001$) in children with mean age of 35 months (range 5-60 months) with mild to moderate disease. The South African Childhood Asthma working group guidelines on chronic maintenance therapy for asthma recommends the use of combination therapy of a medium dose of corticosteroids and either LABA in children with moderate severity disease who are still symptomatic (step3).

Benefit of ICS and LABA administrated through a single device

Evidence that the administration of combination therapy of ICS and LABA was beneficial had led major pharmaceutical companies to produce these medications in a single device. Surprisingly, this intervention became a therapeutic advancement as studies of the combination medication in the single device were shown to be superior to providing each medication separately. Recently, in the GOAL and START studies, combination therapy is a single device was found to improve control of asthma in different severity of chronic asthma, raising the question of the usefulness of the clinical classification (mild, moderate and severe persistent disease). Based on these findings it would be prudent to classify asthma as controlled or uncontrolled with adjustment of medication accordingly. As a consequence of the bronchodilator and anti-inflammatory properties of the combination therapy and the added benefit of rapid acting long acting beta- 2 agonist formoterol, studies have suggested that the single device combination of budesonide and formoterol could be used as a controller (chronic maintenance) and reliever during an acute exacerbation. Although this seems an interesting prospect, it requires careful consideration as long-term airway inflammation may be masked by the repeated use of the LABA bronchodilator. This may result in underestimation of degree of uncontrolled asthmatic inflammation requiring increased dose of corticosteroids and could lead to unexpected asthma related deaths.

Other considerations as add-on medication to ICS for moderate severity asthma

Leukotriene receptor antagonists (LTRA)

These agents play a role in airway remodeling and decreasing eosinophil traffic and are considered mainly as anti-inflammatory medications. Malmestrom K et al has shown that inhaled corticosteroids are a more potent anti-inflammatory than leukotriene receptor antagonist. Glucocorticoids however, have little effect on the cysteinyl leukotriene pathway. The addition of a LTRA or doubling the dose of inhaled corticosteroids in the Compact study showed no difference in the outcome while the comparison of the addition of either LTRA or LABA in the cross over design in the Impact study showed equivalence in preservation of lung function in adult asthmatics with moderate severe disease. This suggests that leukotrienes do have a role to play in asthmatics with uncontrolled asthma where the threshold of risk – benefit ratio for cotricosteroids are reached. Furthermore it has a role to play in adults and children with specific phenotype asthma i.e. aspirin induced disease or viral induced wheeze (asthma).

Low dose theophyllines

The benefit of adding these agents to ICS in moderate severe disease has been demonstrated in studies by Evans et al. In a Cochran review of 6 studies evaluating the role of theophyllines, Wilson AJ et al showed that LABA was more effective than theophyllines although the latter being are much cheaper.

Newer agents: soluble TNF alpha receptor fusion protein

Given that TNF alpha is an important cytokine is asthmatic neutrophilic inflammation, the use soluble TNF alpha-receptor fusion protein such etanercept has recently shown benefit. In a placebo controlled trial of refractory asthmatics on corticosteroids, etanercept given twice weekly for 10 weeks showed improvement in asthma symptom scores, lung function, bronchial hyper-responsiveness and quality of life scores. No improvement was seen with allergic inflammation and the long-term safety of this medication still need to determined.

ADVERSE EFFECTS

Concerns over ICS

The safety of corticosteroids is dose related. High cumulative doses of steroids are associated with the more serious side effects of osteoporosis, blood abnormalities, cataracts, suppression of the hypothalamic pituitary axis. Low and medium doses of inhaled corticosteroids are safe and have minor side effects such as oral candidiasis and delayed growth (height). These can be limited by rinsing the contents of the mouth after inhalation of the corticosteroid. Suppression of the adrenal-cortical axis has been demonstrated with use of high doses and appropriate tests should be undertaken at regular intervals (6 monthly) in patients with high dose of steroids. Oral steroids carry a much higher risk for inducing adverse effects than inhaled steroids. In a recent study of children between 5 and 60 months of

age, a non-significant reduction of only 3.4% in height of children on combination therapy was noted with suppression more marked in males than females. Asthma itself has been noted to reduce onset of puberty and slow preadolescent growth velocity. The authors conclude that concerns over height should be viewed in relation to benefits of effective disease control from steroids. Moreover, suppression is temporary and childhood asthmatics ultimately reach their predicted adult height.

Concerns over LABA

Use as monotherapy

LABA have no effect on exhaled Nitric Oxide, eosinophil levels and on bronchial hyper reactivity (BHR) and are not anti-inflammatory and should not be used as monotherapy in persistent asthma.

Effect on bronchoprotection

LABA has a small effect on bronchial protection against exercise-induced bronchoconstriction or other irritants in children with regular use. This is unlike its effect when used as a single intermittent dose where better bronchodilatation and bronchoprotection has been noted. The concern that regular use of LABA would be associated with partial sub sensitivity of B2 adenoceptor due to decreased lymphocyte B2 receptor density (tolerance) and cross tolerance to SABA requires further clarification given the protective effect of corticosteroids. Steroids have a facillatory role of B2 receptor function and numbers and this counteract the effect of tolerance and limit the decrease in BHR. Tolerance is often seen with regular use of short acting b2 agonist and may translate into reduced bronchoprotection (decreased PC20 and increased bronchial hyper reactivity) that causes an increased clinical vulnerability to unprotected attacks while maintaining bronchodilatation and normal lung function.

Tolerability and safety

LABA are well tolerated without clinically important side effects even with long-term use. There side effect profile is similar to that of SABA. They are associated with tremors, palpitations, headaches, and nausea, and irritability, changes in blood glucose and plasma potassium levels. In the recent SMART trial from the USA, the use of LABAs were assumed to be associated with increased asthma related mortality in adults. However on closer analysis of the data, it was shown that this risk was only seen a certain subset of Afro-Americans who had a genetic predisposition to poor response to bronchodilation secondary to a higher prevalence of the arg –arg beta 2 receptor genotype. Also, the phenotype of these individuals and their lack of adherence to therapy contributed to the worse outcome.

Concerns over the use of leukotrienes

Although given as an oral medication, LTRA have been shown to be safe medications. A major concern was the increased incidence of Churg Struss syndrome following the introduction of zafirlukast in the USA. Closer examination of the data around these episodes indicated that the syndrome was more likely due to the withdrawal of corticosteroids rather than the use of the LTRA. Churg Struss syndrome has not been seen with use of Montelukast. Another adverse effect associated with LTRA was the development of hepatitis but not was mild and transient.

Concerns of the use of theophyllines

Major concern of theophyllines is the erratic absorption and variable drug levels with consequence idiosyncratic and drug dose dependant adverse effects. Cardiac arrthymias and palpitations have been observed with use.

CONCLUSIONS

Advances in our understanding of the clinical asthma is likely to change the way we consider managing patients with the different phenotypes of this disease entity, but for the moment, given our current knowledge and understanding of the condition, combination therapy with inhaled corticosteroids and long acting beta-2 agonist are the first line therapeutic option in adults and children with moderate severity asthma. In those not adequately controlled on this therapy, consideration of the use of a leukotriene receptor antagonist should be given especially if high combined doses of corticosteroids are in use. Further research of the use of soluble TNF alpha-receptor fusion proteins such etanercept in children and adults are required to best guide its use..

See CPD Questionnaire, page 41

Ⓟ This article has been peer reviewed

BIBLIOGRAPHY

1. Sekharia S, Alam M, Sait T, Starr B, Parekh M. Efficacy and safety of inhaled corticosteroids in combination with Long acting Beta 2 agonist in asthmatic children under 5. J Asthma 2004; 41: 575-82
2. Bisgaard H. Long –acting B2-agonists in management of childhood asthma: A Critical review of the literature. Ped Pulmonology 2000;29:221-34.
3. Greening AP et al. Added Salmeterol versus higher dose corticosteroids in asthma with symptoms on existing inhaled corticosteroids. Lancet 1994;344:219-24.
4. Bateman et al. Can guideline-defined asthma control be achieved. The gaining optimal asthma control study. ARJCCM 2004; 170:836-44.
5. Verberne AA et al. Addition of salmeterol versus doubling the dose of beclomethasone in children with asthma, The Dutch Asthma Study Group Am J Respir Crit Care Med 1998;158:213-9
6. Berry MA, Hargadon B, Shelley M et al. Evidence of a role of tumor necrosis factor alpha in refractory asthma. N. Engl. J Med 2006; 354: 697-710.
7. Malmstrom K, Rodriguez-Gomez G, Guerra J. Oral montelukast, inhaled beclomethasone and placebo for chronic asthma: a randomized controlled trial. Ann Intern Med 1999; 130: 487-95.