Review Article

CHANGING PARADIGMS IN THE TREATMENT OF ASTHMA

Loh Li Cher *MD,* IMU Lung Research, International Medical University

Abstract

Significant changes have occurred in relation to how chronic asthma is being treated. Emphasis has now shifted from viewing asthma as a condition of smooth muscle dysfunction to one of chronic inflammation. As such, anti-inflammatory therapy forming the cornerstone of treatment represents the first important milestone in the evolution of asthma treatment. For this purpose, inhaled corticosteroid (ICS) is by far the most effective anti-inflammatory therapy. Another important milestone is the recognition of the superiority of adding long-acting β_2-agonist (LABA) to ICS over escalating ICS dose alone or other forms of add-on therapies in treating asthmatic patients not responding to regular ICS alone. The effectiveness of adding LABA to ICS in treating asthma logically led to combining the two drugs into one single inhaler (salmeterol/fluticasone and budesonide/formoterol) that has the attractiveness of being user-friendly and ensuring that ICS is not missed out. The unique property of formoterol that allows for repetitive flexible dosing paved way to the concept of using Symbicort for both regular maintenance dosing and as required rescue medication. This revolutionary approach has been recently shown to provide improved asthma outcome, achieved at an overall lower or at least comparable corticosteroid intake, and may represent another evolutionary step in the treatment strategy of chronic asthma.

Keywords: Asthma treatment, airway inflammation, corticosteroid, long-acting β_2-agonist

Loh LC. Changing paradigms in the treatment of asthma. The Family Physician 2005;13(3):5-9

Introduction

Over the last 15 years, significant advancement in the understanding of asthma pathophysiology has led to important paradigm shifts in our approach to treating asthma. Despite being an 'old' condition, asthma still captures world-wide attention by its significant morbidity and mortality. It probably reaches its pinnacle in mid-1990s when many countries reported significant increase in asthma incidence, mortality and morbidity,[1] prompting the establishment of a global panel of expert clinicians in 1995 under the auspices of World Health Organization and National Heart, Lung and Blood Institute, USA, to discuss strategies of preventing and treating asthma. The international group and its work are enshrined as the Global Initiative for Asthma or GINA.[2] Malaysia also has its representative there.

Address for correspondence: Associate Professor Loh Li Cher, Department of Medicine, International Medical University, Jalan Rasah, 70300 Seremban, Negeri Sembilan Darul Khusus, Malaysia. Tel: 06-7677798, Fax: 06-7677709, Email: loh@imu.edu.my

Funding: None
Conflicts of Interest: The author has received honorarium for lectures delivered and travel support for medical conferences from GlaxoSmithKline, AstraZeneca and MSD Malaysia.

To date, asthma affects around 100 million people world-wide and incurs significant healthcare cost and burden in all countries. Developed economies may expect between 1 and 2% of total healthcare expenditures to be spent on asthma alone.[2] A large scale epidemiological survey conducted globally estimated the 12-month prevalence rates of adolescent asthmatics to be between 5 and 15% in most countries.[3] In some countries like United Kingdom and Australia, the rates were reported to be over 25%. In Malaysia, the Second National Health and Morbidity Survey between 1996 and 1997 reported prevalence rates of 4.5% and 4.1% for childhood and adult asthma, respectively.[4] There is presently no data on the trend of asthma mortality for Malaysia. The nearest available data comes from Singapore that showed evidence for increasing asthma deaths in children between age 5 and 14 from the mid 1970s to the mid 1990s.[5] This trend has since been reversed, largely attributable to large-scale nationwide education and improved treatment strategies.

This review focuses on the important 'evolutions' in asthma treatment strategies in the past 15 years. Most of these paradigm shifts took place in tandem with some of the crucial research discoveries in asthma pathophysiology.

The central role of airway inflammation in asthma

The first important milestone in the treatment of asthma was the recognition of the central role of airway inflammation in asthma. Although inhaled corticosteroids (ICS) were introduced as early as in 1970s, the central role of airway inflammation was not fully appreciated until in 1992 when Laltinen LA and colleagues in their landmark study[6] demonstrated airway inflammation from bronchoscopic biopsies of patients with mild asthma. They also showed that three months treatment with inhaled budesonide, compared with placebo, completely restored the bronchial mucosa integrity and improved lung function. Thus the findings provided crucial evidence that resolution of airway inflammation is translated into improved lung function, and challenged the traditional view that asthma is primarily a disease of smooth muscle dysfunction causing variable airflow limitation.[7] Since then, there have been an abundance of evidence for airway inflammation in asthma of all severities and that resolution of this inflammation leads to improved lung function, symptom control and reduced asthma exacerbations.[8] Recently, regular use of low-dose ICS was shown to be associated with reduced risk of death from asthma, suggesting that targeting airway inflammation is the correct way forward.[9]

The central role of airway inflammation in asthma is now so firmly established that GINA would define asthma as 'a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role'. It continues to state that 'The chronic inflammation causes an associated increase in airway hyper-responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning.'[2] While still a subject of some debate, the definition suggests that airway inflammation in asthma is foundational and that all clinical and physiologic manifestations of asthma emit from this. Current consensus among experts postulates that chronic inflammation that is left unchecked will lead to airway remodeling and fibrosis. The latter is observed in many chronic asthmatic patients in whom airway obstruction is not fully reversible and who respond poorly to all forms of asthma therapy. The inflammatory cells that have received much attention are the eosinophils, mast cells and CD4+ T lymphocytes of T Helper Type 2 (Th2) subset.[8,10] These cells, particularly the CD4 Th2 cells, respond well to the effects of corticosteroids, thus explaining why among various anti-inflammatory agents that have been tested, corticosteroids are still the most effective anti-inflammatory therapy in asthma.[10]

The superiority of the addition of long-acting β_2-agonist to inhaled corticosteroids

Riding on the wave of evidence that airway inflammation is crucial to treat and that ICS is effective, it is logical to increase the dose of ICS in patients in whom asthma is still inadequately controlled on lower dose ICS alone. Greening and colleagues in their landmark study in 1994,[11] compared the effect of doubling ICS dose *vs.* addition of a long-acting β_2-agonist (salmeterol) to ICS at existing dose in asthmatic patients not responding to low dose ICS alone. The finding was surprising in that combining LABA and ICS produced a significantly superior beneficial effect, compared with escalating ICS dose alone. Doubts on whether this response was genuine and safe have now been largely dispelled by larger scale randomized controlled studies in favour of the addition of a LABA (either salmeterol or formoterol) than escalating ICS dose alone,[12,13] This superior beneficial effect is not confined to improved lung function alone but also to better symptom control, reduced asthma exacerbations and improved health-related quality of life.

Most studies to date showed that LABA alone does not generally have much anti-inflammatory activity,[14] although formoterol has been shown to have some effect on plasma leakage[15] and on mast cells.[16] The latter can provide some rationale for the additive beneficial effect when formoterol is added to ICS. The more attractive theory, however, involves the concept of synergism, resulting from the interaction of corticosteroids and β_2-agonist at a molecular level, thus allowing a reduced concentration of corticosteroids for an equal response.[17] One recent study by Roth M and colleagues[18] showed that the combination of lower doses of corticosteroids and LABA resulted in a synchronized activation of the transcription factors and an enhanced anti-proliferative effect on human bronchial airway smooth muscles cells, proposing yet another possible molecular mechanism whereby synergism can occur.

Another attraction for using a combined ICS and LABA is the avoidance of side-effects brought about by high doses of inhaled corticosteroids. Steroid phobia is well recognized and is responsible for the many problems associated with treatment compliance in many patients. It is only recently that the issue of dose-response relationship of ICS being highlighted from the scientific perspective. It showed that like in most drugs, the dose-response curve is relatively flat at higher doses of ICS. Most of the therapeutic benefit of ICS is probably achieved at doses around 400 μg a day of beclomethasone or its equivalence in patients with mild-to-moderate asthma.[19] Such consideration

lend momentum to the current thinking of keeping ICS dose low while adding a second asthma drug like LABA.

Potential role of Symbicort as single inhaler therapy

The superiority of combining LABA and ICS to treat asthma logically led to the development of placing both drugs into one single inhaler. This development has the potential of improving treatment compliance and ensuring that the intake of corticosteroid, the key anti-inflammatory drug, is not missed out. The two that are available in the market are Seretide (combining fluticasone and salmeterol) and Symbicort (combining budesonide and formoterol). The efficacy of combining both drugs into one single inhaler, compared to giving both separately, has been tested and shown to be equivalent.[20,21] In asthma management guidelines, both Seretide and Symbicort can be used from Step 3 chronic asthma treatment, i.e. moderate persistent asthma.

The interesting discovery that formoterol has additional rapid onset bronchodilator effect,[22,23] led to research as to whether it can be also used as rescue medication, similar to that of short-acting β_2-agonist like salbutamol and terbutaline. In fact, the bronchodilator effect of formoterol has also been shown to be dose-dependant[22] and its systemic side effect is not 'cumulative' despite its ability to maintain a long period of bronchodilation.[24] Such unique properties of formoterol, in contrast to salmeterol, are attributable to differences of receptor affinity and the physico-chemical properties between formoterol and salmeterol.[25] These properties of formoterol (i.e. rapid onset of action and possibility of repetitive flexible dosing without 'accumulation' of systemic side-effects) are ideally positioned for the revolutionary approach aptly called the 'Single Inhaler Therapy'.

'Single Inhaler Therapy' (SIT) proposes that Symbicort be used for regular maintenance therapy as well as for rescue medication in patients with persistent asthma. It drastically simplifies the treatment regime from using three inhalers (ICS and LABA for regular maintenance therapy and short-acting β_2-agonist for rescue medication) to using just one inhaler (Symbicort). It is revolutionary in that rescue medication is always been reserved for using short-acting β_2-agonist and the idea of administering extra long-acting bronchodilation and corticosteroids during rescue treatment may appear unnecessary and potentially harmful. Aalbers and colleagues[26] were the first to explore the potential of using Symbicort as adjustable maintenance dosing in patients with moderate persistent asthma. They showed that such an approach with Symbicort produced better outcome, compared with using Seretide or Symbicort as conventional fixed maintenance dosing, in terms of symptom control and severe exacerbation rates. More importantly, this better outcome was achieved with lower overall drug load and with no increase in the incidence of side effects. With regards to using Symbicort as SIT, one randomised controlled study by Scicchitano R and colleagues,[27] primarily designed to address the issue of safety, showed that compared with using the conventional approach of inhaled budesonide as regular maintenance dosing and inhaled terbutaline as rescue treatment, SIT approach was safe and conferred greater efficacy in some aspects of asthma outcomes at an overall lower ICS dose. The landmark study that directly compared using Symbicort as conventional regular maintenance dosing and terbutaline as rescue medication, with using Symbicort as both maintenance and rescue medication (i.e. SIT approach), was conducted by O'Byrne and colleagues.[28] They showed that in patients with moderate persistent asthma, Symbicort SIT approach was superior in terms of lung function and exacerbation rates. Again, this was safe and was achieved with comparable mean daily ICS and fewer days with systemic steroid.

At the time of this writing, it remains to be seen as to how this revolutionary Symbicort SIT approach will impact on the current strategy of treating asthma. It is the unique properties of formoterol that allow this approach. As such, any extensive adoption of Symbicort SIT approach can radically affect the use of other asthma medications that are still considered effective therapies. This is likely to be a topic of intense discussion in the very near future.

Leukotriene modifiers as a new class of drugs for asthma

Among the many new drugs that have been tried on for asthma, leukotriene modifiers represent the most important development as a new class of drugs in the past 25 years.[29] Leukotrienes are leukocyte-generating lipid mediators that promote airway inflammation and induce bronchoconstriction. Inhibiting its effects is shown to benefit asthmatic patients. Presently, the most widely available leukotriene modifier is a leukotriene receptor antagonist, montelukast.

While its anti-inflammatory effect is not as potent as that of ICS,[30] leukotriene modifiers are useful alternatives to ICS in patients unreceptive to ICS for whatever reasons. It seems to particularly benefit patients with exercise-induced and aspirin-intolerant asthma, a finding that has prompted the

recommendation of such uses in treatment guidelines.[2] More recently, the advocacy that airway inflammation is continuous from nose to lung[31] suggests that leukotriene receptor antagonist (LTRA) should be used more widely for patients with both asthma and allergic rhinitis. It is theoretically superior to inhalational therapies in treating small airways bronchoconstriction.[32] Also, its huge advantage of being an oral medication is particularly appealing to some patients like the young and very old who struggle with inhaler devices. Its protean roles continue to evolve, as exemplified by the recent finding that it can protect young paediatric patients from wheezing illness after viral RSV bronchioliits.[33] However, in terms of add-on treatment for patients not adequately controlled on ICS alone, it is shown to be generally less effective than using LABA.[34] Because of these, the exact position on the use of LTRA remains to be clearly defined in the near future.

Management of asthma in Malaysia today

There is evidence that anti-inflammatory agents, primarily ICS, are under-prescribed in patients with chronic asthma in Malaysia.[35,36] A recent population-based survey of three large cities in Malaysia, which formed part of a larger study of Asia-Pacific countries, showed that only 10% of all asthmatic patients surveyed and only 17% of the severe persistent asthmatics among them were prescribed an ICS.[36] Although the situation may be rapidly changing as indicated by a nation-wide survey of prescribing patterns among Malaysian doctors,[37] it is likely that still more clinicians and patients require education on the disease of asthma being inflammatory in nature and that this inflammation is chronic, thus requiring regular anti-inflammatory therapy for a period of time.

The issue of cost and treatment compliance is always pertinent in the management of any chronic disease, and as such, Malaysian asthmatic patients are no exception. Single inhalers containing both ICS and LABA are shown to be more cost-effective than using these two drugs in separate inhalers[21] and can improve compliance. Symbicort SIT approach simplifies the treatment in patients with moderate-to-severe persistent asthma and can easily make an impact in treatment of asthma here in Malaysia.

Conclusions

In the past 15 years, there has been important 'evolutions' as to how asthma should be treated based on the rapidly expanding understanding of its disease pathophysiology. In view of the significant economic and individual burden brought about by asthma world-wide, there is very little excuse for clinicians and patients not to take full advantage of these modern therapies and treatment strategies. Despite the many milestones achieved, the modern treatment of asthma continues to evolve. Some of the exciting research horizons include the development of potential strategies to prevent asthma or changing its natural history. Even so for now, the prospect of having good and effective anti-asthma treatment has already become a reality and should be taken full advantage of.

References

1 Masoli M, Fabian D, Holt S, et al. The global burden of asthma: executive summary of the GINA Dissemination Committee report. Allergy. 2004 May;59(5):469-78. [PubMed]

2 GINA Workshop Report (Updated 2004). Global Strategy for Asthma Management and Prevention. NIH Publication No 02-3659 Issued January, 1995. National Heart, Lung and Blood Institute, USA.

3 Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Lancet. 1998;351(9111):1225-32. [PubMed]

4 National Health and Morbidity Survey 1996-1997 Volume II. Executive Summary: Asthma. Public Health Institute, Ministry of Health Malaysia 1997.

5 Ng TP, Tan WC. Temporal trends and ethnic variations in asthma mortality in Singapore, 1976-1995. Thorax. 1999 Nov;54(11):990-4. [Full text]

6 Laitinen LA, Laitinen A, Haahtela T. A comparative study of the effects of an inhaled corticosteroid, budesonide, and a beta 2-agonist, terbutaline, on airway inflammation in newly diagnosed asthma: a randomized, double-blind, parallel-group controlled trial. J Allergy Clin Immunol. 1992 Jul;90(1):32-42. [PubMed]

7 Kaliner MA. How the current understanding of the pathophysiology of asthma influences our approach to therapy. J Allergy Clin Immunol. 1993;92(1 Pt 2):144-7. [PubMed]

8 Busse WW. Inflammation in asthma: the cornerstone of the disease and target of therapy. J Allergy Clin Immunol. 1998 Oct;102(4 Pt 2):S17-22. [PubMed]

9 Suissa S, Ernst P, Benayoun S, et al. Low-dose inhaled corticosteroids and the prevention of death from asthma. N Engl J Med. 2000 Aug;343(5):332-6. [Full text]

10 Larche M, Robinson DS, Kay AB. The role of T lymphocytes in the pathogenesis of asthma. J Allergy Clin Immunol. 2003 Mar;111(3):450-63. [PubMed]

11 Greening AP, Ind PW, Northfield M, et al. Added salmeterol versus higher-dose corticosteroid in asthma patients with symptoms on existing inhaled corticosteroid. Lancet. 1994 Jul;344(8917):219-24. [PubMed]

12 Pauwels RA, Lofdahl CG, Postma DS, et al. Effect of inhaled formoterol and budesonide on exacerbations of asthma. Formoterol and Corticosteroids Establishing Therapy (FACET) International Study Group. N Engl J Med. 1997 Nov;337(20):1405-11. [Full text]

13 Shrewsbury S, Pyke S, Britton M. Meta-analysis of increased dose of inhaled steroid or addition of salmeterol in symptomatic asthma (MIASMA). BMJ. 2000;320:1368-73. [Full text]

14 Howarth PH, Beckett P, Dahl R. The effect of long-acting beta2-agonists on airway inflammation in asthmatic patients. Respir Med. 2000 Oct;94 Suppl F:S22-5. [PubMed]

15 Baluk P, McDonald DM. The beta 2-adrenergic receptor agonist formoterol reduces microvascular leakage by inhibiting endothelial gap formation. Am J Physiol. 1994;266(4 Pt 1):L461-8. [PubMed]

16 Nials AT, Ball DI, Butchers PR, et al. Formoterol on airway smooth muscle and human lung mast cells: a comparison with salbutamol and salmeterol. Eur J Pharmacol. 1994 Jan;251(2-3):127-35. [PubMed]
17 Barnes PJ. Scientific rationale for inhaled combination therapy with long-acting beta2-agonists and corticosteroids. Eur Respir J. 2002 Jan;19(1):182-91. [Full text]
18 Roth M, Johnson PR, Rudiger JJ, et al. Interaction between glucocorticoids and beta2 agonists on bronchial airway smooth muscle cells through synchronised cellular signalling. Lancet. Oct 26;360(9342):1293-9. [PubMed]
19 Holt S, Suder A, Weatherall M, et al. Dose-response relation of inhaled fluticasone propionate in adolescents and adults with asthma: meta-analysis. BMJ. 2001;323:253-6. [Full text]
20 Chapman KR, Ringdal N, Backer V, et al. Salmeterol and fluticasone propionate (50/250 microg) administered via combination Diskus inhaler: as effective as when given via separate Diskus inhalers. Can Respir J. 1999 Jan-Feb;6(1):45-51. [PubMed]
21 Rosenhall L, Borg S, Andersson F, et al. Budesonide/formoterol in a single inhaler (Symbicort) reduces healthcare costs compared with separate inhalers in the treatment of asthma over 12 months. Int J Clin Pract. 2003 Oct;57(8):662-7. [PubMed]
22 Palmqvist M, Persson G, Lazer L, et al. Inhaled dry-powder formoterol and salmeterol in asthmatic patients: onset of action, duration of effect and potency. Eur Respir J. 1997 Nov;10(11):2484-9. [Full text]
23 Pauwels RA, Sears MR, Campbell M, et al. Formoterol as relief medication in asthma: a worldwide safety and effectiveness trial. Eur Respir J. 2003 Nov;22(5):787-94. [Full text]
24 Totterman KJ, Huhti L, Sutinen E, et al. Tolerability to high doses of formoterol and terbutaline via Turbuhaler for 3 days in stable asthmatic patients. Eur Respir J. 1998 Sep;12(3):573-9. [Full text]
25 Lotvall J. Pharmacological similarities and differences between beta2-agonists. Respir Med. 2001 Aug;95 Suppl B:S7-11. [PubMed]
26 Aalbers R, Backer V, Kava TT, et al. Adjustable maintenance dosing with budesonide/formoterol compared with fixed-dose salmeterol/fluticasone in moderate to severe asthma. Curr Med Res Opin. 2004;20(2):225-40. [PubMed]
27 Scicchitano R, Aalbers R, Ukena D, et al. Efficacy and safety of budesonide/formoterol single inhaler therapy versus a higher dose of budesonide in moderate to severe asthma. Curr Med Res Opin. 2004 Sep;20(9):1403-18. [PubMed]
28 O'Byrne PM, Bisgaard H, Godard PP, et al. Symbicort Single Inhaler Therapy compared with a fixed higher dose budesonide and fixed dose Symbicort in asthma. Am J Respir Crit Care Med. 2005 Jan 15;171(2):129-36. [PubMed]
29 Kemp JP. Recent advances in the management of asthma using leukotriene modifiers. Am J Respir Med. 2003;2(2):139-56. [PubMed]
30 Ducharme FM. Inhaled glucocorticoids versus leukotriene receptor antagonists as single agent asthma treatment: systematic review of current evidence. BMJ. 2003;326:621. [Full text]
31 Lipworth BJ, White PS. Allergic inflammation in the unified airway: start with the nose. Thorax. 2000 Oct;55(10):878-81. [Full text]
32 Bjermer L, Diamant Z. The use of leukotriene receptor antagonists (LTRAs) as complementary therapy in asthma. Monaldi Arch Chest Dis. 2002 Feb;57(1):76-83. [PubMed]
33 Bisgaard H. A randomized trial of montelukast in respiratory syncytial virus postbronchiolitis. Am J Respir Crit Care Med. 2003 Feb 1;167(3):379-83. [Full text]
34 Ringdal N. Long-acting beta2-agonists or leukotriene receptor antagonists as add-on therapy to inhaled corticosteroids for the treatment of persistent asthma. Drugs. 2003;63 Suppl 2;21-33. [PubMed]
35 Lim TO, Suppiah A, Ismail F, et al. Morbidity associated with asthma and audit of asthma treatment in out-patient clinics. Singapore Med J. 1992 Apr;33(2):174-6. [PubMed]
36 Lai CK, De Guia TS, Kim YY, et al. Asthma control in the Asia-Pacific region: the Asthma Insights and Reality in Asia-Pacific Study. J Allergy Clin Immunol. 2003 Feb;111(2):263-8. [PubMed]
37 Loh LC, Wong PC. Asthma prescribing practices between government and private doctors in Malaysia - A nationwide questionnaire survey. Asian Pac J Allergy Immunol. 2005 Mar;23(1):7-17.[PubMed]

Editor's note: Symbicort is a trademark of AstraZeneca, Seretide is a trademark of GlaxoSmithKline