Chronic persistent asthma: A review of medicines in the step-up approach

Irusen EM, FCP(SA), PhD

Respiratory Division, Internal Medicine, Faculty of Health Sciences, University of Stellenbosch and Tygerberg Academic Hospital

Correspondence to: Prof EM Irusen, e-mail: eirusen@sun.ac.za

Abstract

The medications used in asthma have been the subject of intense study over the last three decades. We now have extensive insights into their structure, regulation, receptors and mechanisms of action. Their intersection with the complexity of asthma inflammation has also been well characterised. In parallel, good quality pharmaceutical trials have informed national guidelines and patient-centered outcomes have been explored. With this therapeutic armamentarium the practitioner should aim to achieve the goals of asthma therapy that are focused on clinical and lung function parameters. The concept of complete asthma control is the current benchmark.

Airway inflammation is the fundamental problem in asthma and, logically, anti-inflammatory therapy in the form of inhaled corticosteroids is the single most important intervention. The importance of appropriate use of inhaler devices cannot be sufficiently emphasised. The clinician carefully titrates this treatment utilising additional medications for synergy and to modulate side-effects and costs. The contemporary standard of asthma care is a single inhaler with a combination of inhaled corticosteroids (ICS) and long-acting beta adrenoceptor agonists. The alternative is to add leukotriene modifiers to ICS therapy; there are special circumstances when this may be more appropriate. Poor inhaler use and concomitant allergic rhinitis are examples when supplementation with anti-leukotriene agents would be prudent. With whatever therapeutic strategy, regular education of the patient, tailoring of medication and monitoring of asthma are still crucial to ensure that the goals of asthma control are achieved and maintained in the long term.

Ⓟ **This article has been peer reviewed. Full text available at www.safpj.co.za** **SA Fam Pract 2008;50(4):28-36**

Introduction

Allergic sensitisation in atopic individuals sets the stage for the initiation and perpetuation of a series of events at cellular level in the bronchi and lungs that manifest as asthma. Over the last 20 years a bewildering number of genetic factors and a veritable arsenal of inflammatory pathways and mediators have been and continue to be discovered.[1,2] The clinician does not, in general, need to encompass this complexity – suffice to appreciate that at the core of asthma is the interaction of these components – airway inflammation. This is associated with bronchial hyper-responsiveness and episodic airway narrowing that are expressed in the clinical diagnosis of asthma. Pari pasu with the scientific research has been the concomitant elucidation of pharmacologic mechanisms and the therapeutic choices are now beyond question.

Corticosteroids

Corticosteroids (CS) have emerged as the most effective anti-inflammatory agents for chronic persistent asthma.[3] The end result of a variety of inflammatory stimuli is to programme the nuclei of immune cells towards the production of a host of pro-inflammatory mediators and to overwhelm anti-inflammatory mechanisms. We now understand that the best way to counteract this deleterious state is to administer corticosteroids. Steroids act through both genomic and non-genomic pathways.[4] Some of the non-genomic actions control inflammatory pathways. However, their principal action is genomic. This is initiated by the entry of steroids into cells and their subsequent linkage and activation of cytoplasmic (hitherto inactivated) glucocorticoid receptors (GR). These activated complexes translocate to the nucleus where binding to the promoter regions of DNA associated with the production of pro-inflammatory mediators is substantially reduced. Simultaneously the production of anti-inflammatory mediators is enhanced - the net effect is a dampening of inflammation.

Steroids are best administered by the inhaled route; this allows for targeted therapy at the site of disease and a substantial decrease in dosage (it is oral steroids that are primarily associated with the well known Cushingoid phenotype – not the inhaled form). Interestingly, one of the problems of inhaled therapy is that they are rapidly cleared from the airways by the bronchial circulation. One of the reasons that CS remain resident in the airways for a longer time is because they induce bronchial mucosal vasoconstriction thus impairing clearance of the medication.[5] We should remember that historically, steroid potency was determined by the McKenzie skin test.[6] Here, steroids are applied topically to the skin and their potency measured by the area of blanching induced (through vasoconstriction); for

equivalent concentrations of drugs, the larger the area, the more potent the steroid. This property of steroids likely improves the clinical effectiveness in the airways in asthma.

Another method to increase steroid activity is to develop agents that bind with increased affinity to the receptor: the stronger and longer the association with the GR, the more prolonged the anti-inflammatory effect.[7] Des-ciclesonide (the active moiety of ciclesonide [Alvesco®]), fluticasone propionate and budesonide are amongst the most potent in this regard. This relative receptor affinity translates to dose equivalents of ICS. (Table I)

Table I: Clinical dose-equivalents of different corticosteroids

Steroid Preparation	Clinical Dose-equivalents
Beclomethasone dipropionate	250 μg
Budesonide	200 μg
Fluticasone propionate	100 μg
Ciclesonide	80 μg

The clinical dose-equivalents of different corticosteroids used in asthma are based on their relative receptor affinities for the steroid receptor. The more avid the binding, the more potent the clinical effect.

The final mechanism whereby steroids have an increased duration of action is reversible esterification.[8] Here, when a dose of steroid is administered, some molecules bind immediately to GR whilst others bind to fatty acid esters in the tissue which then acts as a "reservoir" of the drug. They can dissociate from the ester and become available to bind to GR at the later stage after the initially GR bound drug has been metabolised. This is relevant for budesonide and ciclesonide.
Despite their potency, the vast majority of inhaled steroids need currently to be given twice daily.
Ultra-long acting steroids that will remain bound to the steroid receptor for up to 24 hours allowing for once daily dosing are in development.

Assessing the efficacy of ICS

We do not, as yet, have simple tools to measure airway inflammation. The clinician uses surrogate markers. As inflammation is brought under control there is an accompanying decrease in asthma symptoms and the need for short-acting rescue β_2 agonist use (salbutamol). Thus the doctor deduces the degree of airway inflammation by the frequency of salbutamol usage; frequent, daily use is an indication to increase the ICS dose. The second way to monitor airway inflammation is serial peak expiratory flow rate (PEFR) monitoring.

Again, as inflammation subsides, the airways *spontaneously* dilate. Therefore reviewing pre-bronchodilator PEFR over time reflects the adequacy of ICS treatment. Determining post- bronchodilator PEFR is also useful: the magnitude of change may also be dependent on inflammation – the better the control, the better the bronchodilator response. One can then, over time, determine the personal best lung function that the patient should achieve and maintain.
ICS are extremely safe. There is negligible systemic toxicity with conventional doses (again it is inadequate control of asthma and the need to use systemic steroids that contribute to systemic adverse effects). With high dose ICS there is a very low prevalence of cataracts, skin bruising, growth problems and adrenal suppression. Local side-effects such as pharyngeal candidiasis and laryngeal problems can be avoided with spacer devices and mouth gargling. If, despite these measures, these remain problematic, then an agent such as ciclesonide should be tried as it is mainly activated in the lungs and not at the level of the pharynx.

β_2-adrenoceptor agonists

β_2-adrenoceptor agonists work via cell surface β_2-receptors that signal via cyclic AMP to cause smooth muscle relaxation. These are available as either short acting or long acting formulations (SABA or LABA). SABA may be used as needed or regularly – the former being advocated because of the concerns over tolerance. However, a large meta-analysis has shown no differences with either approach; clinical outcomes are equivalent with no danger of precipitating exacerbations with regular use.[9] Occasionally, regular treatment produces better asthma control scores.[10]

One of the disadvantages with as needed SABA prescription is under-usage. It is well known that some asthmatics are under-perceivers of airway narrowing.[11] These subjects fail to appreciate a reduction of up to 50% of airflow and hence do not use SABA when they ought to be doing so. Again, regular PEFR monitoring will alert clinicians to this problem; if the PEFR is low and the patient denies symptoms, these patients, in particular, should take their SABA regularly.

If subjects do not achieve asthma control at a dose of 400-800 μg/d of budesonide/equivalent, then international and national guidelines recommend the addition of LABA as the best therapeutic option.[12,13]

Those follow the excellent control and reduction in exacerbations seen with ICS/LABA.
The reason for this observation lies in the in-vitro demonstration of the pharmacological synergy of these two agents. CS increases the production and improves the function of beta adrenergic receptors [14, 15] and LABA augment the anti-inflammatory action of corticosteroids. The latter is achieved by increasing the translocation of activated steroid receptors into the nucleus to block inflammatory mediators. [16, 17] The prolonged bronchodilator properties of LABA did raise the concern that they may mask inflammation, however, provided an adequate dose of corticosteroids is used, it is now proven that this does not occur and that the synergy results in improved pathological control.[18]

When compared to leukotriene modifiers a Cochrane meta-analysis has shown superiority of LABA in improving lung function and symptoms, need for rescue therapy and exacerbation reduction. [19] LABA have an excellent safety profile and reports of their association with asthma mortality are completely unjustified. Formal audits of their use have shown no link with asthma mortality. [20, 21] Deficiencies in healthcare delivery and improper prescribing are contributors to asthma mortality. [22] It has long been established that over-reliance or exclusive prescription of bronchodilators alone are linked to asthma mortality. It is always imprudent not to utilise ICS in chronic asthma.

Combination LABA+ ICS products

Fixed dose single inhaler devices that contain both ICS and LABA are also very effective in achieving asthma control.[23] A major problem that bedevils asthma is the frequent occurrence of non-adherence of the ICS inhaler with separate inhalers.[24] The convenience of a single inhaler improves compliance and ensures that patients do not omit their ICS treatment. Simplifying the regimen is an important principle, particularly in the face of poly-pharmacy when there are co-morbid conditions.

Two effective strategies using combination inhalers are possible:

i) *Step-up fixed dose regimen with sequential increasing of the ICS component to achieve control (Seretide® and Symbicord®):* In the GOAL study (Gaining Optimal Asthma Control), Seretide® was compared to fluticasone propionate and as needed salbutamol. [25] The fixed dosed strategy resulted in dramatically improved levels of asthma control that was attained faster and with lower steroid doses than with fluticasone alone.

ii) *The Single Inhaler Therapy (SIT) utilising the SMART approach-(Symbicord® for maintenance and reliever therapy):* Here, the patient uses the combination inhaler twice a day and importantly, the same inhaler for rescue use.[26] It would appear counter intuitive that the approach seems to be driven by symptoms; real world experience has shown otherwise. Clinical control as measured by symptom free days, day and night scores and exacerbation rates compares favourably to fixed dose regimens.[27] The rationale is that the need for rescue with SABA is frequently a signal of increased inflammation and that both agents are needed when there are wheezing episodes. Thus the correct timing of the increased need and dosage of steroids appears to support the hypothesis. In addition to good control, the overall steroid dose over time is also reduced compared to conventional regimens.[27]

Leukotrienes modifiers

Arachidonic acid peroxidation results in either prostaglandin or leukotriene (LT) synthesis. Both play a role in asthma but the development of novel agents to modify LT actions has provided new insights into asthma. LTs mediate both allergic inflammation and bronchoconstriction.[28]

However, being highly selective, they do not have the wide spectrum of anti-inflammatory effects that ICS have and should not be used as monotherapy. Conversely, ICS have little or no effect on the leukotriene pathway.[29] Leukotriene antagonists are therefore appropriately prescribed as add on therapy to 400-800μg budesonide. Long term clinical trials have demonstrated their non-inferiority to other strategies for combination therapy.

In the COMPACT study, (Clinical Outcomes with Montelukast as a Partner Agent to Corticosteroid Therapy) patients not controlled on budesonide 800 μg alone were compared to the guideline strategy of doubling the dose of budesonide (1600 μg) or the addition of 10 mg montelukast.[30] Montelukast promptly improved baseline lung function (because of its bronchodilator properties) and showed identical trends in improvement in all components of asthma control compared to the higher dose ICS. Similar observations have been reported with zafirlukast.[31]

In the CASIOPEA study montelukast was added to symptomatic subjects on budesonide 400–1600 μg daily.[32] Morning PEFR and asthma-free days increased, with fewer nocturnal awakenings, a reduction in SABA usage and a mild reduction in exacerbations also being documented. Importantly, some subjects with normal lung function were still able to achieve additional benefits. This emphasises the need to assess asthma control in a composite manner and that benefits over and above lung function are possible. Thus the prescription of this class of drug is preferable to doubling the dose of ICS.

The IMPACT study (Investigation of Montelukast as a Partner Agent for Complementary Therapy) demonstrated equivalent efficacy in asthma outcomes between salmeterol and montelukast when added to low dose fluticasone propionate.[33] Other advantages/roles for anti leukotrienes are

1. Oral use. This is particularly useful for those who cannot use/comply with inhaled therapy
2. Exercise induced asthma
3. Aspirin sensitive asthma (this is exclusively leukotriene mediated) [34]
4. Negligible side-effects
5. Concomitant allergic rhinitis

Co-existent allergic rhinitis and asthma reinforces the "united airway" hypothesis where the one entity has an influence on the other. It has been postulated that uncontrolled allergic rhinitis influences the manifestation of asthma. Studies with montelukast have lent credence to this. Firstly, it can be as effective as antihistamines and allow a dose reduction of nasal corticosteroids in allergic rhinitis.[35] More importantly, when the allergic rhinitis is treated with montelukast, asthma control as measured by symptom scores, SABA usage, oral or ICS dosage and healthcare utilisation, all decreased.[36]

Anti leukotrienes agents are extremely safe; there is probably no causal association with the Churg-Strauss Syndrome (CSS). A review of all putative reports have suggested that the use of leukotriene modifiers and concomitant reduction in corticosteroids unmasked a pre-existing Churg Strauss diagnosis or that the leukotriene modifiers were initiated in patients who were in the process of developing CSS.[37]

Theophylline

Theophylline probably mediates its effects via adenosine receptors and now that it is established that at therapeutic doses no phosphodiesterase inhibition occurs, this mechanism, in asthma, should no longer be perpetuated.[38] It has bronchodilator and anti-inflammatory properties as well; the latter effects being seen at lower doses than conventionally used.[39] However, these features are weak and hence theophylline should not be considered as the sole controller agent for asthma.

Theophylline can also have significant gastrointestinal, cardiac and neurological side-effects especially with other drugs that interfere with its hepatic metabolism viz cimetidine and some macrolides and quinolones. These, coupled with the safety and clinical superiority of LABA as add-on therapy to ICS, have relegated theophylline to the last choice when considering additional therapy. However, because they are relatively cheaper, they are more commonly used. When considering their prescription, the slow-release preparations are preferred. They are also beneficial in more severe asthmatics where they have been shown to be equivalent to doubling the dose of ICS.[41] They can also be steroid-sparing thus limiting the adverse-effect profile in oral- steroid dependent asthmatics.[42]

Anti-cholinergic agents

Anti- cholinergic agents work by blocking muscarinic receptors resulting in bronchodilation.[43] However, they are less potent as SABA and when used in combination may produce little additional benefit.[44] Therefore the effectiveness of their prescription should be objectively measured and only maintained if a positive effect is documented. Situations that may permit their usage include the older asthmatic, severe asthma, intolerance to SABA and nocturnal symptoms.[43]

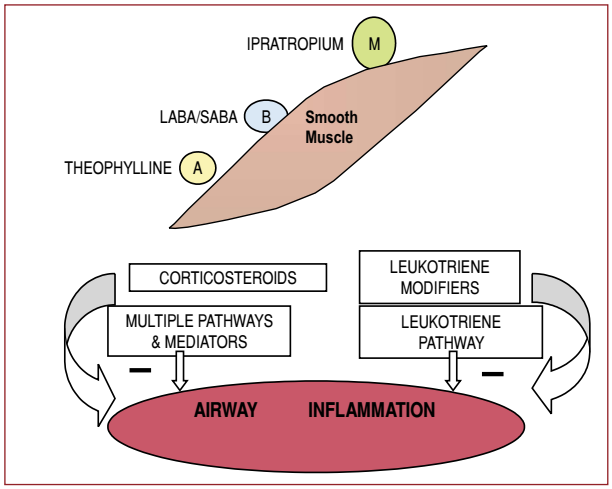
Other medications

The cromones such as sodium cromoglycate and nedocromil sodium have weaker anti-inflammatory properties than corticosteroids, limited

long-term efficacy data and currently have a minor role in the treatment of asthma.[45]

As regards oral steroids, these can have considerable side-effects and should not be used routinely. Their ease of use and relative cost have led to widespread abuse especially among patients who prefer to self -medicate. One should always consider adequate education and oral-steroid sparing strategies to limit complications. Short courses are appropriate for exacerbations and the minimal effective maintenance dose in the very difficult to treat asthmatic.

Figure I: Diagram to illustrate the dual components of asthma: smooth muscle constriction and airway inflammation



Bronchodilatation: Theophylline acts via adenosine receptors (A), LABA/SABA via β_2- adrenoceptors (B) and ipratropium via muscarinic (M) receptors.
— Denotes inhibition.

Clinical practice and asthma

One would imagine that with the knowledge expounded thus far, there would be no problems with asthma control. This couldn't be further from the truth. Appropriate understanding of the disease process and pharmacology should allow us to achieve the therapeutic targets that are the composite of asthma control (Table II). But, as with all areas of medicine, there are numerous barriers to effective clinical practice. Repeated audits of adherence to guidelines, prescriptions and patient experiences have revealed that we are far from optimising asthma care.[46] What are some of the major issues? Firstly, many doctors are not aware of the clinical studies, do not prescribe according to guidelines and accept sub-optimal asthma control. Secondly, patients have also decreased their expectations and accept that they will continue to have symptoms that limit their lifestyles. Thirdly, the clinicians and scientists themselves confuse colleagues when performing studies where asthma outcomes are not standardised or calibrated to therapy.[47,48]

Table II: Therapeutic targets in asthma

Complete amelioration of symptoms
Minimal need for rescue SABA use
Normal or personal best lung function
No exacerbations
No lifestyle restrictions
Reduced likelihood of side-effects of therapy

The New England Journal of Medicine suggested that intermittent ICS usage was satisfactory when this strategy failed dismally in a package of asthma control parameters.[48] Szefler et al,[47] studied the numbers of patients responding to ICS and montelukast and found it to be a maximum of 40% and 23% respectively. However, a response was defined as a pre-bronchodilator $FEV_1 \geq 7.5\%$; most of the subjects were mild asthmatics with FEV_1 approximately 100% and therefore it is conceivable that this value could not be improved upon. In clinical practice almost all asthmatics will have some response to steroids. Finally, health systems need to support and fund the most cost effective therapies. This is not currently the case.

Conclusion

Addressing inflammation is the most important aspect of asthma treatment. The doctor uses his understanding of asthma therapies and surrogate clinical markers to decide whether the goals of asthma have been met. The importance of education and training in proper inhaler technique must not be under estimated. Poor asthma control is frequently a consequence of poor technique and adherence. One could prescribe the most innovative medication and inhaler device but these would be completely ineffective if not used appropriately. A useful maxim to patients is "the better you use your inhaler, the better the relief you'll experience and the better will be your quality of life".

References

1. Goetzl EJ. Changing paradigms in the immunological science of allergy: 2008. Curr Allergy Asthma Rep 2008; 8: 28-31.
2. Hawkins GA, Peters SP. Pharmacogenetics of asthma. Methods Mol Biol 2008; 448: 359-78.
3. Barnes PJ. Corticosteroids: the drugs to beat. Eur J Pharmacol 2006; 533: 2-14.
4. Ito K, Getting SJ, Charonne CE. Mode of glucocorticoid actions in airway disease. Scientific World Journal 2006: 6: 1750-69.
5. Horvath G, Wanner A. Inhaled corticosteroids: effects on the airway vasculature in bronchial asthma. Eur Respir J 2006; 27:172-87.
6. Mendes ES, Pereira A, Danta I, Duncan RC, Wanner A. Comparative bronchial vasoconstrictive efficacy of inhaled glucocorticosteroids. Eur Respir J 2003; 21: 989-93.
7. Rohatagi S, Appajosyula S, Derendorf H, et al. Risk-benefit value of inhaled glucocorticoids: a pharmacokinetic/ pharmacodynamic perspective. J Clin Pharmacol 2004; 44:37-47.
8. Colice GL. The newly developed inhaled corticosteroid ciclesonide for the treatment of asthma. Expert Opin Pharmacother 2006; 7: 2107-17.
9. Walters EH, Walters J. Inhaled short acting beta2-agonist use in chronic asthma: regular versus as needed treatment. Cochrane Database Syst Rev 2003; (2): CD001285.
10. Chapman KR, Kesten S, Szelai JP. Regular vs as-needed inhaled salbutamol in asthma control. Lancet 1994; 343: 1379-82.
11. Teeter JG, Bleecker ER. Relationship between airway obstruction and respiratory symptoms in adult asthmatics. Chest 1998:113: 272-7.
12. Global initiative for asthma management and prevention 2006. www.ginasthma.org (Accessed 10/06/08)
13. Lalloo U, Ainslie G, Wong M, et al. Guidelines for the management of chronic asthma in adolescents and adults. SA Fam Pract 2007; 49: 19-31.
14. Collins S, Caron MG, Lefkowitz R. β2-adrenergic receptors in hamster smooth muscle cells are transcriptionally regulated by glucocorticoids. J Biol Chem 1988; 263: 9067-70.
15. Koto HM, Mak JC, Haddad CD, et al. Mechanisms of impaired beta-adrenoceptor-induced airway relaxation by interleukin -1 beta in vivo in the rat. J Clin Invest 1996; 98: 1780-87.
16. Eickelberg O, Roth M, Lorx R, et al. Ligand independent activation of the glucocorticoid receptor by the β2-adrenergic receptor agonists in primary human lung fibroblasts and vascular smooth muscle cells. J Biol Chem 1999; 274: 1005-10.
17. Roth M, Rudiger JJ, Bihl MP, et al. The β2-agonist formoterol activates the glucocorticoid receptor in vivo. Eur Respir J 2000; 16: 437S.
18. Sue-Chu M, Wallin A, Wilson S, et al. Bronchial biopsy study in asthmatics treated with low-and high- dose fluticasone propionate (FP) compared to low-dose FP combined with salmeterol. Eur Resp J 1999; 14: 124s.
19. Ducharme FM, Lasserson TJ, Cates CJ. Long-acting beta2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma (review). Cochrane Database of Systematic Reviews 2006, Issue 4. Art No.: CD003137. DOI: 10.1002/14651858.CD003137.pub3.
20. Mann RD. Salmeterol: a study by prescription-event monitoring in a UK cohort of 15,407 patients. J Clin Epidemiol 1996; 49: 247-50.
21. Bateman E, Nelson H, Bousquet J, et al. Meta-analysis: effects of adding salmeterol to inhaled corticosteroids on serious asthma-elated events. Ann Intern Med June 2008 epub.

22. Near Fatal Asthma: what have we learned? Castro M. Chest 2002; 121: 1394-5.
23. Douill I, Price D, Thomas M, et al. Cost-effectiveness of salmeterol xinafoate/fluticasone propionate combination inhaler in chronic asthma. Curr Med Res Opin 2007; 23:1147-59.
24. Partridge MR, van der Molen T, Myseth SE, Busse WW. Attitudes and actions of asthma patients on regular maintenance therapy: the INSPIRE study. BMC Pulm Med 2006; 6:13.
25. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma ControL study. Bateman ED, Boushey HA, Bousquet J, Busse WW, Clark TJH, Pauwels RA, Pedersen SE for the GOAL Investigators Group. Am J. Respir Crit. Care Med 2004; 170: 836-44.
26. Barnes PJ. Scientific rationale for using a single inhaler for asthma control. Eur Respir J 2007; 29: 587-95.
27. Bousquet J, Boulet LP, Peters MJ, et al. Budesonide/formoterol for maintenance and relief in uncontrolled asthma vs. high-dose salmeterol/fluticasone. Respir Med 2007; 101: 2437–46.
28. Austen KF. The cysteinyl leukotrienes: where do they come from? What are they? Where are they going? Nat Immunol. 2008; 9: 113-5.
29. Dworski R, Fitzgerald GA, Oates JA, et al. Effect of oral prednisone on airway inflammatory mediators in atopic asthma. Am J Respir Crit Care Med 1994; 149: 953-59.
30. Price DB, Hernandez D, Magyar P, et al. Randomised controlled trial of montelukast plus inhaled budesonide versus double dose inhaled budesonide in adult patients with asthma. Thorax 2003; 58: 211-16.
31. Nayak AS, Anderson P, Charous BL, Williams K, Simonson S. Equivalence of adding zafirlukast versus double –dose inhaled corticosteroids in asthmatic patients symptomatic on low dose inhaled corticosteroids. J Allergy Clin Immunol 1998; 101: S233.
32. Vaquerizo MJ, Casan P, Castillo J, et al. Effect of montelukast added to inhaled budesonide on control of mild to moderate asthma. Thorax 2003; 58:204-11.
33. Bjermer L, Bisgaard H, Bousquet J, et al. Montelukast or salmeterol combined with an inhaled steroid in adult asthma: design and rationale of a randomized, double-blind comparative study (the IMPACT- Investigation of Montelukast as a Partner Agent for Complementary Therapy-trial). Respir Med 2000; 94: 612-21.
34. Dursun AB, Woessner KA, Simon RA, Karasoy D, Stevenson DD. Predicting outcomes of oral aspirin challenges in patients with asthma, nasal polyps, and chronic sinusitis. Ann Allergy Asthma Immunol. 2008; 100: 420-5.
35. Lagos JA, Marshall GD. Montelukast in the management of allergic rhinitis. Ther Clin Risk Manag 2007; 3: 327–32.
36. Borderias L, Mincewicz G, Paggiaro P L, et al. Asthma control in patients with asthma and allergic rhinitis receiving add-on montelukast therapy for 12 months: a retrospective observational study. Curr Med Res Opin 2007; 23: 721–30.
37. Keogh KA. Leukotriene receptor antagonists and Churg-Strauss syndrome: cause, trigger or merely an association? Drug Saf 2007; 30: 837-43.
38. Ezeamuzie CI. Involvement of A3 receptors in the potentiation by adenosine of the inhibitory effect of theophylline on human eosinophil degranulation: possible novel mechanism of the anti-inflammatory action of theophylline. Bio Pharmacol 2001; 61: 1551-59.
39. Barnes PJ. Theophylline. New perspectives for an old drug. Am J Respir Crit Care Med 2003; 167: 813-18.
40. Tee AKH, Koh MS, Gibson PG, Lasserson TJ, Wilson AJ, Irving LB. Long-acting beta$_2$-agonists versus theophylline for maintenance treatment of asthma. Cochrane Database of Systematic Reviews 2007, Issue 3. Art No.: CD001281. DOI:10.1002/14651858.CD001281.pub2.
41. Ukena D, Harnest U, Sakalauskas R, et al. Comparison of addition of theophylline to inhaled steroid with doubling of the dose of inhaled steroid in asthma. Eur Respir J 1997; 10: 2754-60.
42. Markham A, Faulds D. Theophylline. A review of its potential steroid sparing effects in asthma. Drugs 1998; 56(6): 1081-91.
43. Restrepo RD. Use of inhaled anticholinergic agents in obstructive airway disease. Respiratory Care 2007; 52: 833-51.
44. Westby M, Benson M, Gibson P. Anticholinergic agents for chronic asthma in adults. Cochrane Database of Systematic Reviews 2004, issue 3. Art No.: CD003269. DOI: 10.1002/14651858.CD003269.pub2.
45. Szefler SJ, Nelson HS. Cromones: Alternative agents for anti-inflammatory treatment of asthma. J Allergy Clin Immunol 1998; 102: s23-35.
46. Rabe K, Vermiere PA, Soriano JB, Maier WC. Clinical management of asthma in 1999: the Asthma Insights and Reality in Europe (AIRE) study. Eur Respir J 2000; 16: 802-807.
47. Szefler SJ, Phillips BR, Martinez FD, et al for the Childhood Asthma Research and Education Network of the National Heart, Lung, and Blood Institute. Characterization of within-subject response to fluticasone and montelukast in childhood asthma. J Clin Allergy Immunol 2005; 115:233-42.
48. Boushey HA, Boushey HA, Sorkness CA, King TS, et al. Daily versus As-Needed Corticosteroids for mild persistent asthma. N Engl J Med 2005; 352: 1519-28.