

Asthma: primary therapies

Inflammation and its control are key to the management of asthma.

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Asthma is now established as a chronic inflammatory disorder of the airways.¹ The characteristic symptomatology is a consequence of this inflammation and the associated bronchial hyper-responsiveness (BHR). It therefore follows that control of the inflammation and relief of bronchial narrowing are the principal therapeutic strategies necessary for effective control of asthma. The most effective anti-inflammatory medication remains corticosteroids and for bronchodilatation β_2 adrenoceptor agonists; these are the primary therapies.

Some of the problems that bedevil asthma are that, as yet, we have no simple tools to monitor airway inflammation and that both doctors and patients underestimate asthma severity and do not treat optimally. Numerous studies across the world have documented widespread suboptimal asthma control because of these inadequacies.^{2,3}

However, reasonable surrogates of control are the clinical therapeutic endpoints or goals as developed by GINA (the Global Initiative for Asthma – Table I). The achievement of as many of these aims as possible correlates well with suppression of the disease process and normalisation of functional capacity.

Table I. Therapeutic end-points in asthma control

- Minimal or no symptoms either during the day or night
- Minimal need for rescue medication (SABA)
- Normal lung function (PEFR)
- No acute attacks
- Normal lifestyle
- Minimal side-effects of therapy

Inhaled corticosteroids (ICS)

Corticosteroids remain the cornerstone of asthma therapy. One must remember that there are a multitude of pathways and mediators that orchestrate asthmatic inflammation and that one needs to have an agent that has a broad range of anti-inflammatory effects – only corticosteroids possess this property.¹ Anti-leukotrienes and theophylline have much narrower anti-inflammatory targets and can be complementary but cannot compare with steroids. These two drugs also have bronchodilator properties that act via different mechanisms.

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Monitoring airway inflammation

As alluded to earlier, monitoring disease activity in asthma is not easy as it usually involves invasive bronchoscopic techniques or specialised equipment. Two techniques/measurements may gain wider acceptability in the future: nitric oxide (NO) determination and induced sputum.

Nitric oxide is generated in the airways and can be detected in exhaled breath. Initially a fairly large apparatus was used to measure NO but with improvements in technology a small portable machine has been developed that has brought the cost down considerably. The device measures F_{ENO} (fractional expired NO) concentration and reasonably accurately reflects airway inflammation.⁴ Adjusting the dose of ICS according to F_{ENO} has led to good asthma control at lower cumulative steroid doses.

Induced sputum (obtained by encouraging sputum production following hypertonic saline nebulisation) has been extensively used to study the airway milieu. One study looked at sputum eosinophils sequentially⁵ – again titrating ICS according to the sputum eosinophil count resulted in improved asthma outcomes compared with clinical criteria.

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Modulation of inflammation by corticosteroids

An increasing number of small protein and other molecules that participate in airway inflammation, viz. cytokines, chemokines, growth factors etc., are being characterised. In general, there is no need for clinicians to know the details of any of these mediators. It suffices to appreciate that, as mainly protein molecules, their production is governed by nuclear programming. Thus an agent

that is able to influence nuclear transcription will be able to alter mediator production and attenuate inflammation – this is precisely what corticosteroids do.

The corticosteroid receptor (CR) resides in the cytoplasm of cells in an ‘inactive’ state. When corticosteroids enter cells and bind to the receptor, this new complex is actively transported into the nuclear compartment. Here, direct and indirect interactions occur, the latter via transcription factors. The complex binds to the promoter regions of numerous genes that control inflammatory mediator production. In this way, pro-inflammatory mediator production is switched off and anti-inflammatory mediator production is stimulated; the net effect is to dampen inflammation.

With regard to utilising induced sputum, bronchial biopsy and bronchoalveolar lavage (BAL) with clinical correlates, the following has been documented:

- a profound effect in decreasing eosinophils, lymphocytes, cytokines, nitric oxide and other mediators
- subsidence of symptoms, bronchial hyper-responsiveness and the risk of exacerbations
- a decrease in basement membrane thickening and the regular and extensive deposition of collagen beneath the sub-epithelial layer
- improvement in lung function – as inflammation subsides, resting bronchomotor tone changes and the airways spontaneously dilate; bronchodilator responses are often also better.

These effects in decreasing fibrosis and inflammation are thought to prevent airway remodelling and to attenuate the ‘fixed obstruction’ that might accompany chronic severe asthma. In this respect they are considered ‘disease modifying’ (Table II).

Table II. Corticosteroids help achieve the goals of asthma therapy

- Decrease airway inflammation
- Decrease bronchial hyper-responsiveness
- Improve symptoms
- Improve pulmonary function
- Decrease rate of exacerbation
- ‘Disease modifying’

ICS are also available in different potencies related to their receptor affinities. Thus budesonide, fluticasone propionate and ciclesonide are almost twice as potent as beclomethasone. In more severe asthma,

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it may be prudent to use a more potent steroid rather than increasing the dose of beclomethasone.⁶ Ciclesonide is activated in the lung and therefore does not cause the oropharyngeal side-effects of the other steroids and would be preferred if these are troublesome. It is always recommended to gargle the mouth after use of ICS and/or to use a spacer device. The metered-dose inhaler (MDI) remains the most effective way to deliver CS to the lung, as smaller doses can be delivered to the site of disease. By this route, systemic side-effects are negligible; it is over-reliance on systemic steroids that is potentially hazardous – they should be the very last option in chronic asthma.

As regards BHR, higher doses of ICS for longer periods are required to decrease reactivity.⁷ Control of BHR is associated with superior short- and long-term outcomes in asthma. Clinicians should consider the cost-effectiveness when contemplating high-dose steroids in this situation.

With reference to alternative controller therapy, leukotriene modifiers and theophylline have more selective anti-inflammatory properties and most guidelines relegate them to second-line treatment. They should not be used as monotherapy but added on to ICS. Trials with these agents were powered for non-inferiority – ICS were clearly superior in a range of pharmacological actions.

ICS have traditionally been delivered by MDI containing chlorofluorocarbons (CFCs). Despite the small deleterious effect on the environment of CFCs, they will in due course be completely banned. To circumvent this, dry-powder inhalers (DPIs) and a new propellant have been developed: hydrofluoroalkane (HFA). These inhalers have smaller particle sizes that allow more distal deposition and other properties that doctors will need to become familiar with. Clinically, some of them have increased effectiveness compared with CFC inhalers.

Bronchodilator therapy

Beta₂-adrenoceptor agonists relax bronchial smooth muscle and are the best bronchodilator medication. Short-acting agents (SABA) act within minutes and for up to 6 hours while long-acting agents (LABA) provide effective bronchodilatation for 12 hours and longer. If patients are uncontrolled on SABA and ICS at a dose equivalent to 400 - 800 µg budesonide/day, it is appropriate to add LABA.^{8,9} This combination results in improved asthma control and reduces the chances of acute attacks. Apart from sustained bronchodilatation, one of the reasons for the enhanced effect is the synergy between LABA and ICS (Fig. 1). At a molecular level LABA have also been found to increase CS-CR translocation to the nucleus to augment anti-inflammatory

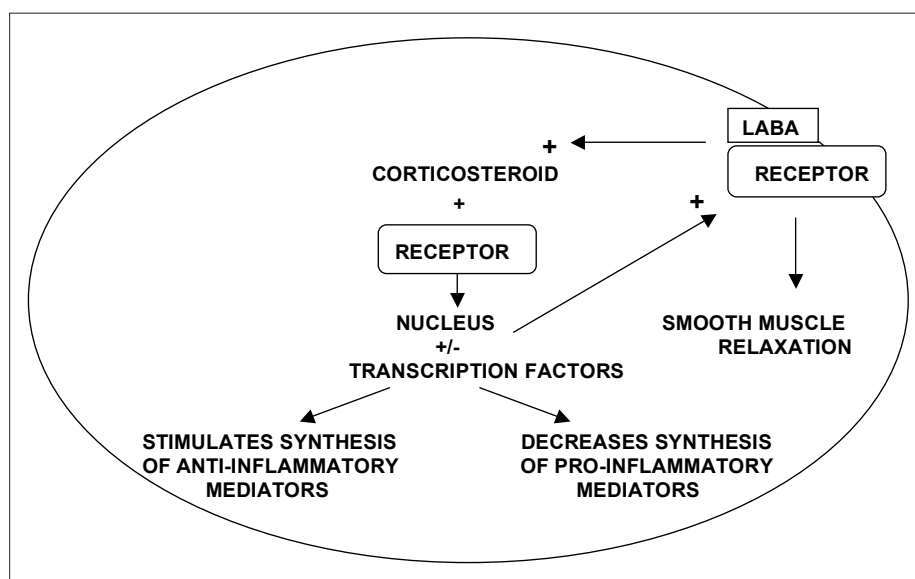


Fig. 1. The principal mode of action of corticosteroids. Corticosteroids work by attaching to receptors that translocate to the nucleus, thereby modulating inflammatory mediator production. LABA, in addition to causing prolonged smooth-muscle relaxation, also promote (+) this nuclear translocation, thus augmenting the anti-inflammatory response. Steroids in turn synergistically increase beta₂-adrenoceptor number and function.

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effects described previously. CS in turn have a positive effect on beta-receptors. They increase the production of beta-receptors, improve their function and resist the development of tolerance. Thus the composite effect of this combination is to attain levels of control usually achieved with higher doses (usually double) of corticosteroids.

The beta₂-adrenoceptor has also been well studied and categorised. Single amino acid substitutions in the receptor give rise to polymorphisms.¹⁰ Intriguingly, this is sufficient to change the physical characteristics of the receptor. Some of the features that have been described include resistance or susceptibility to down-regulation, nocturnal asthma and augmentation of the beta-agonist response. While these help to explain asthma phenotypes and therapeutic responses, they probably have negligible therapeutic repercussions.

LABA have also attracted totally unnecessary negative publicity in respect of asthma mortality. Well-conducted clinical trials and audits have shown no link to asthma deaths.¹¹ Inappropriate prescribing, over-reliance on bronchodilator therapy, inadequate use of ICS and poor asthma control are unequivocally linked to serious adverse outcomes. Thus LABA can be prescribed with confidence and should always be added to baseline ICS treatment.

Combination inhalers

The effectiveness of combination treatment has led to the single-device concept where both medications have become available as fixed combination inhalers: fluticasone propionate and salmeterol (Seretide) and budesonide and formoterol (Symbicord).

These provide clinical control equivalent to the monocomponent inhalers. Combination inhalers offer many advantages. They are more convenient (especially in a situation of polypharmacy with co-morbidity) by simplifying the treatment regimen and aiding adherence. An important advantage is that patients cannot default on ICS because when the inhaler is used for its bronchodilator capacity, the steroid is co-administered. A landmark trial in asthma, the GOAL study (Gaining Optimal Asthma Control) utilising Seretide achieved unprecedented levels of asthma control. Most subjects achieved complete or a very well-controlled status of their clinical condition.

The combination inhaler with formoterol can also be used for acute relief of symptoms, as it is rapidly acting as well. This approach has culminated in the SMART concept (Symbicord and reliever therapy). The idea here is that instead of a short-acting beta-agonist, the patients take extra inhalations of the maintenance combination inhaler during periods of increased symptoms (that possibly heralds an exacerbation) to prevent such attacks. So, when patients need relief from bronchospasm they take additional doses of ICS as well. Clinically, this approach has resulted in excellent asthma control, with fewer exacerbations and an overall reduced cumulative steroid dose over time.

Combination inhaler therapy will undoubtedly be the principal strategy for asthma control for the foreseeable future.

References

1. Barnes PJ. How corticosteroids control inflammation. *Br J Pharmacol* 2006; 148: 245-254.
2. Rabe KF, Vermeire 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.

3. Lange P, Ulrik CS, Vestbo J. Mortality in adults with self reported asthma. Copenhagen City Heart Study Group. *Lancet* 1996; 347: 1285-1289.
4. Montuschi P, Mondino C, Koch P, *et al.* Effects of Montelukast treatment and withdrawal on fractional exhaled nitric oxide and lung function in children with asthma. *Chest* 2007; 132: 1876-1881.
5. Green RH, Brightling CE, McKenna S, *et al.* Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. *Lancet* 2002; 360: 1715-1721.
6. Ayres JG, Bateman ED, Lundback B, Harris TAJ. High dose fluticasone propionate, 1 mg daily, versus fluticasone propionate, 2 mg daily, or budesonide, 1.6 mg daily, in patients with chronic severe asthma. *Eur Respir J* 1995; 8: 579-586.
7. Currie GP, Fowler SJ, Lipworth BJ. Dose response of inhaled corticosteroids on bronchial hyper-responsiveness: a meta-analysis. *Ann Allergy Asthma Immunol* 2003; 90: 194-198.
8. Sin DD, Man J, Sharpe H, *et al.* Pharmacological management to reduce exacerbations in adults with asthma: a systematic review and meta-analysis. *JAMA* 2004; 292: 367-376.
9. Masoli M, Weatherall M, Holt S, Beasley R. Moderate dose inhaled corticosteroids plus salmeterol versus higher doses of inhaled corticosteroids in symptomatic asthma. *Thorax* 2005; 60: 730-734.
10. Tattersfield AE, Hall IP. Are beta2-adrenoceptor polymorphisms important in asthma? – An unraveling story. *Lancet* 2004; 364(9444): 1464-1466.
11. Barnes PJ. Scientific rationale for using a single inhaler for asthma control. *Eur Respir J* 2007; 29: 587-595.
12. Bateman ED, Boushey HA, Bousquet J, *et al.* for the GOAL Investigators Group. *Am J Respir Crit Care Med* 2004; 170: 836-884.
13. Lundborg M, Wille S, Bjermer L, *et al.* Maintenance plus reliever budesonide/formoterol compared with a higher maintenance dose of budesonide/formoterol plus formoterol as reliever in asthma: an efficacy and cost-effectiveness study. *Curr Med Res Opin* 2006; 22: 809-821.

In a nutshell

- Anti-inflammatory therapy is the cornerstone of therapy in asthma.
- Corticosteroids are the most effective anti-inflammatory agents.
- Corticosteroids are available in different potencies – more severe disease is best managed with a more potent steroid.
- Clinical therapeutic endpoints (the goals of asthma management) are a useful surrogate of control of airway inflammation and narrowing.
- Inhaled corticosteroids plus long-acting β -antagonist are the most effective agents for uncontrolled asthma.
- Most MDIs contain CFCs – these are being phased out and replaced with HFA/dry-powder devices.
- MDIs are the best way to deliver therapy as small, effective doses can be delivered to the appropriate site, making them cost-effective and limiting systemic side-effects.
- Patient education and reinforcement is crucial – the better patients utilise their MDIs the better the clinical effect.