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Current issues for establishing inhaled corticosteroids as the antiinflammatory agents of choice in asthma

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Airway inflammation appears to be present even in the mildest of asthma, and inhaled corticosteroids now form the mainstay of asthma therapy. Inhaled corticosteroids largely avoid the adverse effects associated with oral steroids and are now recommended in newly detected disease. Inhaled corticosteroids reduce airway inflammation, airway hyperresponsiveness, and the symptoms of asthma and improve lung function, irrespective of the patient's age or asthma severity. Several different inhaled corticosteroids are available as therapeutic options for the treatment of asthma, and these include fluticasone propionate, beclomethasone dipropionate, and budesonide. The efficacy and safety of inhaled corticosteroids are compared in this article, and inhaled corticosteroid therapy is also compared with other therapies. Recently, there has been a consensus that the optimal use of inhaled corticosteroids for asthma management is using a "start high—go low" approach, and the reasons for this are discussed. (*J Allergy Clin Immunol* 1998;101:S427-33.)

Key words: *Inhaled corticosteroids, inflammation, asthma, side effects, airway hyperresponsiveness*

Glucocorticoids are the most effective therapy available for asthma, and inhaled corticosteroids largely avoid the adverse effects associated with oral steroids. With the recognition that airway inflammation is present even in the mildest of asthma, inhaled corticosteroids are now recommended in newly detected disease and have become the mainstay of asthma treatment in many countries.¹⁻³ Despite their proven efficacy in asthma control, the use of inhaled corticosteroids has been

Abbreviations used

AHR:	Airway hyperresponsiveness
BDP:	Beclomethasone dipropionate
FP:	Fluticasone propionate
NO:	Nitric oxide

tempered by concern about systemic side effects, so less effective therapies are often preferred, particularly in the treatment of pediatric asthma. There are several important issues involved in the use of inhaled corticosteroids for asthma.

INFLAMMATION IN ASTHMA

Asthma involves inflammation of the airways in all patients with symptomatic disease. This inflammation is characterized by an infiltration of eosinophils and the presence of activated T-lymphocytes (predominantly CD4+ cells) and degranulated mast cells.³ Bronchial biopsy studies have demonstrated this inflammatory response in patients with very early disease and in episodic asthma at times when symptoms are not present.⁴ There is also evidence for structural changes in the airways of asthma patients, including increased thickness of the basement membrane as a result of deposition of collagen, increased thickness of the airway smooth muscle layer, increased numbers of blood vessels, and hyperplasia of mucus-secreting cells.⁵ This structural remodeling is likely to be the result of uncontrolled chronic inflammation in the airways.

More recently, other techniques have confirmed that inflammation is present in mild asthma. Induction of sputum with hypertonic nebulized saline provides a method for studying the inflammatory response in asthma.⁶ Induced sputum from patients with mild asthma

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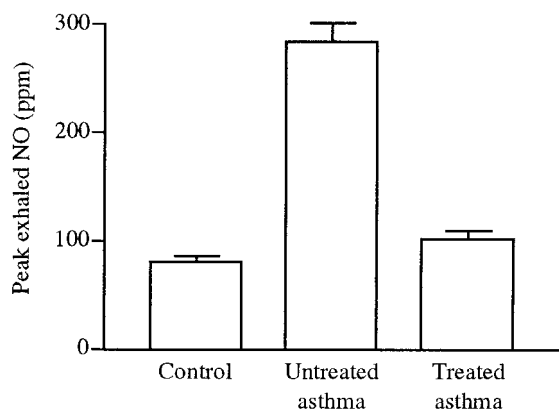


FIG. 1. Peak exhaled nitric oxide (NO) concentrations in control ($n = 67$), untreated asthma ($n = 61$), and treated asthma ($n = 52$) groups.¹¹ *Untreated asthma*, no inhaled corticosteroids; *Treated asthma*, regular inhaled corticosteroids. Results are expressed as mean $\pm$ SEM.

shows the presence of eosinophils and eosinophil granule proteins.^{6,7} We have also demonstrated the same inflammatory profile in children with asthma. Exhaled nitric oxide has been used to investigate inflammation in airways of patients with asthma.⁸ Inflammatory cytokines induce expression of the enzyme inducible NO synthase (iNOS) in epithelial cells,⁹ and this enzyme has increased expression in airway epithelial cells and inflammatory cells of airways from asthma patients.¹⁰ We have demonstrated, using bronchoscopic sampling, an increase in the amount of NO in exhaled air of patients with mild asthma who are untreated¹¹ and that this increase is derived from the lower respiratory tract.¹²

Inflammation of the airways accounts for all of the clinical features of asthma. Airway inflammation leads to airway hyperresponsiveness, which allows triggers such as exercise and exposure to an allergen to narrow airways with resultant wheeze and dyspnea. Inflammation may sensitize and activate sensory nerves in the airway, resulting in cough and chest tightness, which are common and troublesome symptoms of asthma. Thus inflammation is central to clinical asthma.

MECHANISM OF ACTION OF STEROIDS

Although inhaled corticosteroids are the most effective therapy known for asthma, their precise mechanism of action is not yet fully understood. Important advances have been made in elucidating some of the molecular and cellular actions of steroids that are relevant to their anti-asthma effects.¹³

Inhaled corticosteroids are highly lipophilic and rapidly enter target cells of the airway and bind to cytosolic glucocorticoid receptors. In human airways, there is a high level of glucocorticoid receptor expression in epithelial cells and in endothelial cells of bronchial vessels.¹⁴ Binding of the glucocorticoid to the glucocorticoid receptor results in rapid localization to the nucleus, where the glucocorticoid receptor binds to DNA at

specific consensus sites, termed glucocorticoid response elements (GREs), on the upstream promoter sequence of steroid-responsive genes. This results in increased (or occasionally decreased) transcription of a particular gene. It is likely that altered transcription of many different genes is involved in the anti-asthma effect of steroids.¹⁵ Perhaps their most important action is inhibition of transcription of the genes for the inflammatory proteins (cytokines, inflammatory enzymes, inflammatory receptors) involved in asthmatic inflammation.¹⁵ Recently, it has been demonstrated that the glucocorticoid receptor may bind directly to transcription factors that are activated by cytokines and other inflammatory signals. Thus, proinflammatory cytokines go on to activate the transcription factors nuclear factor-kappa B (NF- κ B) and activator protein-1 (AP-1). NF- κ B and AP-1, when activated within the nucleus, bind to response elements on the promoter sequence and thus regulate the transcription of certain genes.¹⁶ NF- κ B and AP-1 also bind to the activated glucocorticoid receptor within the nucleus, and through this protein-protein interaction, corticosteroids may inhibit the cellular actions of cytokines.¹⁵

Inhaled corticosteroids inhibit the expression of iNOS by blocking NF- κ B, which is required for its induction. This is reflected by a reduction in exhaled NO in patients with asthma treated with inhaled corticosteroids (Fig. 1).¹¹ A double-blind, placebo-controlled study of inhaled budesonide has demonstrated a significant reduction of exhaled NO in patients with mild asthma.¹⁷ Furthermore, in patients treated with inhaled corticosteroids, a reduction in steroid dose results in an increase in exhaled NO before any change in symptoms or lung function is observed.¹⁸ Thus exhaled NO may be a useful means of monitoring the level of control of inflammation in asthma, and because the test is noninvasive it may be used in patients of all ages.

Steroids may have direct inhibitory effects on many of the cells involved in asthmatic inflammation, including macrophages, T-lymphocytes, eosinophils, and epithelial cells.¹⁹ Airway epithelial cells are likely to be a major target for inhaled corticosteroids because these cells release multiple inflammatory mediators that may amplify airway inflammation. Several studies have directly demonstrated the anti-inflammatory effect of inhaled corticosteroids through the use of bronchial biopsies in asthma patients. There is a marked reduction in the numbers of mast cells, macrophages, T-lymphocytes, and eosinophils in the epithelium and submucosa after 1 to 3 months of inhaled steroid therapy.²⁰⁻²⁴ Furthermore, the characteristic epithelial shedding and goblet cell hyperplasia observed frequently in the biopsies of asthma patients is reversed after treatment with inhaled corticosteroids,²⁰ and one study has demonstrated a reduction in the thickened basement membrane.²⁴ These cellular effects of steroids are summarized in Fig. 2.

Asthma is characterized by asthma hyperresponsiveness (AHR) to many apparently unrelated stimuli, and this is related to airway inflammation. By reducing

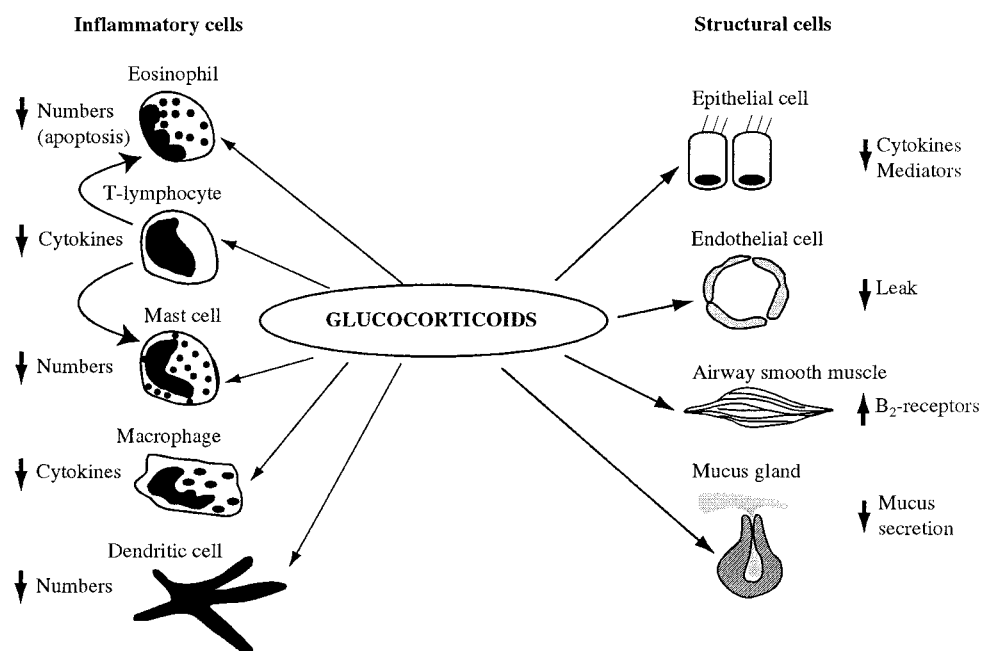


FIG. 2. Various cellular effects of glucocorticoids and their role in the control of asthma.

airway inflammation, inhaled corticosteroids consistently reduce AHR both in adults and in children with asthma.²⁵ Long-term treatment with inhaled corticosteroids reduces responsiveness to histamine, cholinergic agonists, allergen challenge (early and late allergic responses), exercise, fog, cold air, bradykinin, adenosine, and irritants such as sulphur dioxide and metabisulphite. The reduction in AHR takes place over several weeks and may not be maximal until after several months of therapy. The magnitude of the reduction varies between patients but is in the order of one to two doubling dilutions for most allergen challenges and often fails to return to the normal range. This may reflect suppression of the inflammation, but there is persistence of structural changes that cannot be reversed by steroids. Inhaled corticosteroids not only make the airways less sensitive to spasmogens but they also limit the maximal airway narrowing in response to a spasmogen.²⁶

CLINICAL EFFICACY

Inhaled corticosteroids are very effective at controlling symptoms of asthma in patients of all ages and severity.^{1, 27, 28} Inhaled corticosteroids were first introduced to reduce the requirement for oral steroids in patients with severe asthma, and many studies have confirmed that in the majority of patients inhaled corticosteroids can completely replace oral steroids. As experience has been gained with inhaled corticosteroids, they have been introduced in patients with milder asthma, with the recognition that inflammation is present even in patients with mild asthma.²⁹ Inhaled anti-inflammatory drugs have now become first-line

therapy in any patient who needs to use a β_2 -agonist inhaler more than once a day, and this is reflected in national and international guidelines for the management of chronic asthma.³⁰⁻³² In patients with newly diagnosed asthma, inhaled corticosteroids (budesonide 600 μg twice daily) reduced symptoms and β_2 -agonist inhaler usage and improved peak expiratory flows. These effects persisted over the 2 years of the study, whereas in a parallel group treated with inhaled β_2 -agonists alone there was no significant change in symptoms or lung function.³³ In a separate study, patients with mild asthma treated with a low dose of inhaled steroid (budesonide 200 μg twice daily) showed a progressive improvement in lung function over several months and showed fewer symptoms, with many patients becoming asymptomatic.³⁴ Similarly, inhaled beclomethasone dipropionate (400 μg twice daily) improved asthma symptoms and lung function, and this was maintained over the 30 months of the study.³⁵ There was also a significant reduction in the number of exacerbations. Although the effects of inhaled corticosteroids on AHR may take several months to reach a plateau, the reduction in asthma symptoms occurs more rapidly.³⁶ Inhaled corticosteroids effectively control asthmatic inflammation but need to be taken regularly. When inhaled corticosteroids are discontinued there is usually a gradual increase in symptoms and airway responsiveness back to pretreatment values,³⁶ although in some patients with mild asthma who have been treated with inhaled corticosteroids for a long time, symptoms may not recur.³⁷

Inhaled corticosteroids are equally effective in chil-

dren. In an extensive study of children 7 to 17 years of age, there was a significant improvement in symptoms, peak flow variability, and lung function compared with a regular inhaled β_2 -agonist that was maintained over the 22 months of the study,³⁸ but asthma deteriorated when the inhaled corticosteroids were withdrawn.³⁹ There was a high proportion of dropouts (45%) in the group treated with inhaled β_2 -agonist alone.

Some patients with asthma develop an element of irreversible airflow obstruction, but the pathophysiological basis of these changes is not yet fully understood. It is likely that they are the result of chronic airway inflammation and may be prevented by treatment with inhaled corticosteroids. There is some evidence that the annual decline in lung function may be slowed by the introduction of inhaled corticosteroids.⁴⁰ Recent evidence suggests that the early use of corticosteroids may prevent irreversible changes in lung function in adults and children.^{41, 42} Patients started on inhaled budesonide (1200 μ g daily) at the time of onset of their asthma had better lung function than patients treated for 2 years with an inhaled β_2 -agonist.⁴¹ Indeed, the longer the inhaled steroid was delayed after onset of asthma, the worse the lung function in adults and children.^{42, 43} This argues strongly for the early introduction of inhaled corticosteroids in adults and children rather than initial treatment with other treatments that may not suppress the inflammation in the airways.

ADVERSE EFFECTS

The main reason for the reluctance to use inhaled corticosteroids, particularly in children, has been concern over systemic effects.⁴⁴ Inhaled corticosteroids have probably been studied more carefully than any other therapy, and there is now much reassuring evidence for their safety.²⁷ Systemic effects arise from absorption from the gastrointestinal tract, but this is largely eliminated by the use of large volume spacers or by the use of fluticasone propionate, which is completely metabolized in the liver after absorption from the gut. All currently available inhaled corticosteroids are absorbed from the lung directly into the systemic circulation. This systemic absorption is inevitable. However, the systemic absorption does not appear to have any adverse effect on bone metabolism or on growth at the doses of inhaled steroid that most patients require. Studies examining the systemic effects of inhaled corticosteroids in normal volunteers and patients with asthma of varying severity have demonstrated that irrespective of the inhaled steroid used, there are minimal systemic effects (even when using the most sensitive indicators) at doses of ≤ 400 μ g for children and ≤ 800 μ g for adults. At higher doses than these there is some evidence of systemic effects, although this is less noticeable with budesonide and FP than with BDP. Even at doses of up to 2000 μ g daily there is little evidence of any adverse effects, although occasional patients may have idiosyncratic responses. It is important that such studies are conducted using asthma patients because there is some evidence that

systemic absorption is less in asthma patients than in normal volunteers; it is possible that this is related to more central deposition of the inhaled drug. In the future it is possible that inhaled corticosteroids with even fewer systemic effects will be developed,⁴⁵ although existing inhaled corticosteroids given by new delivery systems are virtually free of systemic effects at the doses the vast majority of patients require.

COMPARISON BETWEEN INHALED CORTICOSTEROIDS

Several inhaled corticosteroids are currently available for the treatment of asthma, although their availability varies between countries. There have been relatively few studies comparing efficacy of the different inhaled corticosteroids, and it is important to take into account the delivery system and the type of patient under investigation when such comparisons are made. In the United States, BDP, flunisolide, and triamcinolone are currently available, but there have been no studies comparing these corticosteroids at different doses. Budesonide, which is widely available in many countries, has been compared with BDP in adults and children, and the two corticosteroids appear to have comparable antiasthma effects at equal doses, whereas FP is approximately twice as potent as either steroid.^{2, 27} Budesonide and FP have a lower oral bioavailability than BDP as a result of their extensive hepatic first-pass metabolism.

The most important issue for the long-term use of inhaled corticosteroids, particularly when used in patients with mild asthma, is the therapeutic ratio, that is, the ratio of therapeutic benefit to adverse effects. This has been extensively investigated, and the safety of inhaled corticosteroids has been studied in greater detail than almost any other class of drug in current clinical practice.²⁷ There is no convincing evidence that the doses of inhaled corticosteroids used for the treatment of mild asthma have any clinically important adverse effects in adults or children. Budesonide and FP have less systemic effects than BDP at equivalent antiasthma doses. FP is approximately twice as potent as budesonide and hence should be used at half the dosage. Whether there are differences between budesonide and FP will require careful long-term follow-up studies.

COMPARISONS WITH OTHER THERAPIES

No other antiasthma therapy is as effective at controlling the disease as glucocorticoids, but other treatments may reduce the requirement for inhaled corticosteroids and thus reduce the need for high doses. Cromones (sodium cromoglycate and nedocromil sodium) are much less effective at controlling asthma than inhaled corticosteroids, although these drugs may sometimes be useful in patients with mild asthma.⁴⁶ However, from biopsy studies, there is little convincing evidence that cromones reduce inflammation in asthma patients.⁴⁷ Furthermore, because their duration of action is short, these treat-

ments must be given at least four times daily, which is a major disadvantage compared with once- or twice-daily treatment with inhaled corticosteroids.

Short-acting β_2 -agonists (such as salbutamol and terbutaline) do not control asthma as effectively as inhaled corticosteroids in either adults or children.^{33, 38} There is no evidence to suggest that they reduce inflammation of airways in asthma.²⁰ The long-acting inhaled β_2 -agonist salmeterol appears to give better control of asthma when added to 400 or 800 μg BDP compared with increasing the dose of BDP to 1000 μg daily.^{48, 49} This suggests that the inhaled corticosteroids have a relatively shallow dose-response curve or that these doses are near the top of the curve and that this bronchodilator has an additional effect. Whether this is due to its bronchodilator action, its mast cell stabilising effect, or an action on airway edema is not yet clear.

Theophylline when used alone does not control asthma as effectively as inhaled corticosteroids and is associated with more frequent side effects.⁵⁰ Recent studies suggest that theophylline may have anti-inflammatory effects in asthma at relatively low doses.^{51, 52} Theophylline may be useful in controlling asthma in patients with more severe disease, and controlled studies designed to compare the effect of adding a low dose of theophylline to an inhaled steroid (budesonide 800 μg daily) show a better effect on asthma control than doubling the dose of inhaled steroid.⁵³

Antileukotrienes (leukotriene receptor antagonists and 5'-lipoxygenase inhibitors) have a useful clinical effect in controlling asthma symptoms, improving lung function, and reducing the need for inhaled β_2 -agonist rescue therapy.⁵⁴ However, their efficacy is clearly less than that seen with inhaled corticosteroids, and it is uncertain whether they can affect the inflammatory process. Surprisingly, glucocorticoids, even at high doses orally, do not appear to inhibit leukotriene production in asthma, even after allergen challenge.⁵⁵ It is possible that the residual abnormalities in airway function that remain in some patients after high doses of inhaled corticosteroids are due to continued leukotriene production and would respond to an antileukotriene.

OPTIMAL USE OF INHALED CORTICOSTEROIDS

Although inhaled corticosteroids have revolutionized asthma therapy, there are some patients whose asthma is not well controlled even at high doses. Poor compliance with inhaled corticosteroids is a common problem.⁵⁶ This might be improved by reducing the dose frequency to once daily, but only when daily doses of ≤ 400 μg are needed.⁵⁷

The dose-response curve for clinical effect of inhaled corticosteroids reaches a plateau relatively quickly, so there is little improvement after increasing the dose, whereas systemic absorption increases more steeply. In some studies no dose-response has been observed,⁵⁸ and in others most of the effects of the inhaled corticosteroids have been achieved at low doses.⁵⁹ This may, in part, be dependent on the parameter of efficacy that is being measured. Thus although the dose-response curve

for improvement in lung function may be flat, that for reduction in asthma exacerbations may be steeper. Some parameters may be more sensitive to control by corticosteroids, whereas higher doses are needed to suppress sputum eosinophilia (A. Jatakanon, S. Kharitonov, P.J. Barnes; unpublished observations). The dose-response to inhaled corticosteroids may vary, depending on the severity of asthma and the amount of inflammation. This is probably a consequence of the induction of steroid resistance by cytokines, so that larger doses of corticosteroids are required when inflammation is greater.

Previous guidelines suggested that inhaled corticosteroids should be started at a low dose and progressively increased until asthma control is achieved. This is contrary to clinical practice and to common sense. Because inhaled corticosteroids have a slow onset of action, patients whose asthma is not controlled lose confidence in the treatment, and this is likely to decrease compliance. It would be more sensible to start at a dose that is likely to be effective and then lower this to the minimal dose needed to maintain control.⁶⁰ This approach is logical in the light of our current understanding of the mechanism of action of steroids. Steroids activate glucocorticoid receptors, which act as functional antagonists of transcription factors that regulate increased transcription of genes such as inflammatory cytokines and enzymes in asthma. If there is active inflammation of the airways, a high level of transcription factors bind to glucocorticoid receptors, so steroids are less effective and cannot effectively gain control of the inflammatory response. Higher doses of steroids overcome this by blocking the activated transcription factors, allowing more glucocorticoid receptors to become available to block the inflammatory response. Once control is achieved, this can be maintained with lower doses of steroids. Although there are no clinical trials comparing the two approaches of high-to-low versus low-to-high inhaled corticosteroids, there are studies that demonstrate that the dose of inhaled steroid can be reduced once control is achieved.^{41, 42} The "start high—go low" approach is recommended in the recent revision of the British Thoracic Society Guidelines for Asthma Management.⁶¹ It may be seen as similar to the treatment of hematologic malignancies, in which there is an initial induction phase, but once the patient is in remission, therapy is switched to maintenance therapy at a lower dosage to maintain control.

Most patients should be started on inhaled corticosteroids at a dose of 400 μg twice daily and should be treated with this dose for at least 3 months, because this is a time when most of the benefit of the inhaled steroid is obtained. The dose of inhaled steroid should then be reduced according to a simple step-down regime. In a few patients the initial dose of corticosteroids may be too low and it may be necessary to increase the dose. In patients with more severe asthma it is necessary to start treatment with oral steroids to obtain control initially; in these patients inhaled corticosteroids should be started at the same time.

REFERENCES

1. Barnes PJ. Anti-inflammatory therapy in asthma. *Annu Rev Med* 1993;44:229-49.
2. Barnes PJ. Inhaled glucocorticoids for asthma. *N Engl J Med* 1995;332:868-75.
3. Barnes PJ. Cytokines as mediators of chronic asthma. *Am J Respir Crit Care Med* 1994;150:S42-9.
4. Laitinen LA, Laitinen A, Haahtela T. Airway mucosal inflammation even in patients with newly diagnosed asthma. *Am Rev Respir Dis* 1993;147:697-704.
5. Knox AJ. Airway re-modelling in asthma: role of airway smooth muscle. *Clin Sci* 1994;86:647-52.
6. Pizzichini E, Pizzichini M, Efthimiadis A, Evans S, Morris MM, Squillance D, et al. Indices of airway inflammation in induced sputum: reproducibility and validity of cell and fluid-phase measurements. *Am J Respir Crit Care Med* 1996;154:308-17.
7. Keatings VM, Collins D, Scott DM, Barnes PJ. Differences in interleukin-8 and tumor necrosis factor- α in induced sputum from patients with chronic obstructive pulmonary disease or asthma. *Am J Respir Crit Care Med* 1996;153:530-4.
8. Barnes PJ, Kharitonov SA. Exhaled nitric oxide: a new lung function test. *Thorax* 1996;51:218-20.
9. Robbins RA, Barnes PJ, Springall DR, Warren JB, Kwon OJ, Buttery LDR, et al. Expression of inducible nitric oxide synthase in human bronchial epithelial cells. *Biochem Biophys Res Commun* 1994;203:209-18.
10. Hamid Q, Springall DR, Riveros-Moreno V, Chanez P, Howarth P, Redington A, et al. Induction of nitric oxide synthase in asthma. *Lancet* 1993;342:1510-3.
11. Kharitonov SA, Yates D, Robbins RA, Logan-Sinclair R, Shinebourne E, Barnes PJ. Increased nitric oxide in exhaled air of asthmatic patients. *Lancet* 1994;343:133-5.
12. Kharitonov S, Chung KF, Evans DJ, O'Connor BJ, Barnes PJ. Increased exhaled nitric oxide in asthma is derived from the lower respiratory tract. *Am J Respir Crit Care Med* 1996;153:1773-80.
13. Barnes PJ. Molecular mechanisms of steroid action in asthma. *J Allergy Clin Immunol* 1996;97:159-68.
14. Adcock IM, Gilbey T, Gelder CM, Chung KF, Barnes PJ. Glucocorticoid receptor localization in normal human lung and asthmatic lung. *Am J Respir Crit Care Med* 1996;154:771-82.
15. Barnes PJ, Adcock IM. Anti-inflammatory actions of steroids: molecular mechanisms. *Trends Pharmacol Sci* 1993;14:436-41.
16. Barnes PJ, Adcock IM. Transcription factors in asthma. *Clin Exp Allergy* 1995;27(suppl 2):46-9.
17. Kharitonov SA, Yates DH, Barnes PJ. Regular inhaled budesonide decreases nitric oxide concentration in the exhaled air of asthmatic patients. *Am J Respir Crit Care Med* 1996;153:454-7.
18. Kharitonov SA, Yates DH, Chung KF, Barnes PJ. Changes in the dose of inhaled steroid affect exhaled nitric oxide levels in asthmatic patients. *Eur J Respir Dis* 1996;9:196-201.
19. Schleimer RP. Effects of glucocorticoids on inflammatory cells relevant to their therapeutic application in asthma. *Am Rev Respir Dis* 1990;141:S59-69.
20. Laitinen LA, Laitinen A, Haahtela T. A comparative study of the effects of an inhaled corticosteroid, budesonide, and of a β_2 -agonist, terbutaline, on airway inflammation in newly diagnosed asthma. *J Allergy Clin Immunol* 1992;90:32-42.
21. Djukanovic R, Wilson JW, Britten YM, Wilson SJ, Walls AF, Roche WF, et al. Effect of an inhaled corticosteroid on airway inflammation and symptoms of asthma. *Am Rev Respir Dis* 1992;145:699-74.
22. Jeffery PK, Godfrey RW, Adelroth E, Nelson F, Rogers A, Johansson S. Effects of treatment on airway inflammation and thickening of basement membrane reticular collagen in asthma. *Am Rev Respir Dis* 1992;145:890-9.
23. Burke C, Power CK, Norris A, Condez A, Schmekel B, Poulter LW. Lung function and immunopathological changes after inhaled corticosteroid therapy in asthma. *Eur Respir J* 1992;5:73-9.
24. Trigg CJ, Manolistas ND, Wang J, Calderon MA, McAvlay A, Jordan SE, et al. Placebo-controlled immunopathological study of four months inhaled corticosteroids in asthma. *Am J Respir Crit Care Med* 1994;150:17-22.
25. Barnes PJ. Effect of corticosteroids on airway hyperresponsiveness. *Am Rev Respir Dis* 1990;141:S70-6.
26. Bel EH, Timers MC, Zwinderman AH, Dijkman JH, Sterk PJ. The effect of inhaled corticosteroids on the maximal degree of airway narrowing to methacholine. *Am Rev Respir Dis* 1991;143:109-13.
27. Barnes PJ, Pedersen S. Efficacy and safety of inhaled steroids in asthma. *Am Rev Respir Dis* 1993;148:S1-26.
28. Konig P. Inhaled corticosteroids—their present and future role in the management of asthma. *J Allergy Clin Immunol* 1988;82:297-306.
29. Barnes PJ. A new approach to asthma therapy. *N Engl J Med* 1989;321:1517-27.
30. Sheffer AL. National Heart Lung and Blood Institute National Asthma Education Programme Expert Panel Report: guidelines for the diagnosis and management of asthma. *J Allergy Clin Immunol* 1991;88:425-534.
31. Sheffer AL. International consensus report on diagnosis and management of asthma. *Clin Exp Allergy* 1992;22(suppl 1):1-72.
32. British Thoracic Society. Guidelines on the management of asthma. *Thorax* 1993;48(suppl):S1-24.
33. Haahtela T, Jarvinen M, Kava T, Kirivanta K, Koskinen S, Lehtonen K, et al. Comparison of a β_2 -agonist terbutaline with an inhaled steroid in newly detected asthma. *N Engl J Med* 1991;325:388-92.
34. Juniper EF, Kline PA, Vanzieleghe MA, Ramsdale EH, O'Byrne PM, Hargreave FE. Effect of long term treatment with an inhaled corticosteroid (budesonide) on airway hyperresponsiveness and clinical asthma in nonsteroid-dependent asthmatics. *Am Rev Respir Dis* 1990;142:832-6.
35. Kerrebijn KF, Van Essen-Zandvliet EEM, Neijens HJ. Effect of long-term treatment with inhaled corticosteroids and beta-agonists on bronchial responsiveness in asthmatic children. *J Allergy Clin Immunol* 1987;79:653-9.
36. Vathenen AS, Knox AJ, Wisniewski A, Tattersfield AE. Time course of change in bronchial reactivity with an inhaled corticosteroid in asthma. *Am Rev Respir Dis* 1991;143:1317-21.
37. Juniper EF, Kline PA, Vanzielegmen MA, Hargreave FE. Reduction of budesonide after a year of increased use: a randomized controlled trial to evaluate whether improvements in airway responsiveness and clinical asthma are maintained. *J Allergy Clin Immunol* 1991;87:483-9.
38. Van Essen-Zandvliet E, Hughes MD, Waalkens HJ, Duiverman EJ, Pocock SJ, Derrebijn KF. Effects of 22 months of treatment with inhaled corticosteroids and or beta $_2$ -agonists on lung function airway responsiveness and symptoms in children with asthma. *Am Rev Respir Dis* 1992;146:547-54.
39. Waalkens HJ, Van Essen-Zandvliet EE, Hughes MD, et al. Cessation of long-term treatment with inhaled corticosteroids (budesonide) in children with asthma results in deterioration. *Am Rev Respir Dis* 1993;148:1252-7.
40. Dompeling E, Van Schayck CP, Molema J, Folgering Van Grusven PM, Van Weel C. Inhaled beclomethasone improves the course of asthma and COPD. *Eur Respir J* 1992;5:945-52.
41. Haahtela T, Jarvinen M, Kava T, Kirivanta K, Koskinen S, Lehtonen K, et al. Effects of reducing or discontinuing inhaled budesonide in patients with mild asthma. *N Engl J Med* 1994;331:700-5.
42. Agertoft L, Pedersen S. Effects of long-term treatment with an inhaled corticosteroid on growth and pulmonary function in asthmatic children. *Respir Med* 1994;5:369-72.
43. Selroos O, Pretalcho A, Lofroos AB, Riska A. Effect of early and late intervention with inhaled corticosteroids in asthma. *Chest* 1995;108:1228-34.
44. Kamada AK, Szeffler SJ, Martin RJ, Booshey HA, Chinchilli VM, Druzen JM, et al. Issues in the use of inhaled steroids. *Am J Respir Crit Care Med* 1996;153:1739-48.
45. Brattsand R, Axelsson B. New inhaled glucocorticosteroids. In: Barnes PJ, editor. *New drugs for asthma*. Vol. 2. London: IBC Technical Services; 1992:192-207.
46. Thomson NC. Nedocromil sodium: an overview. *Respir Med* 1989;83:269-76.
47. Manoliitis ND, Wang J, Devalia J, Trigg CJ, McAuley AE, Davies

- RJ. Regular albuterol, nedocromil sodium and bronchial inflammation in asthma. *Am J Respir Crit Care Med* 1995;152:1925-30.
48. Greening AP, Ind PW, Northfield M, Shaw G. Added salmeterol versus high-dose corticosteroid in asthma patients with symptoms on existing inhaled corticosteroid. *Lancet* 1994;344:219-24.
49. Woolcock A, Lundback B, Ringdal N, Jacques L. Comparison of addition of salmeterol to inhaled steroids with doubling the dose of inhaled steroids. *Am J Respir Crit Care Med* 1996;153:1481-8.
50. Tinkelman DG, Reed CE, Nelson HS, Offord KP. Aerosol beclomethasone dipropionate compared with theophylline as primary treatment of chronic, mild to moderately severe asthma in children. *Pediatrics* 1993;92:64-77.
51. Barnes PJ, Thomson NC. Neural and humoral control. In: Barnes PJ, Rodger IW, Thomson NC, editors. *Asthma: basic mechanisms and clinical management*. London: Academic Press; 1992. p. 343-58.
52. Kidney J, Dominguez M, Taylor PM, Rose M, Chung KF, Barnes PJ. Immunomodulation by theophylline in asthma: demonstration by withdrawal of therapy. *Am J Respir Crit Care Med* 1995;151:1907-14.
53. Evans DJ, Taylor DA, Zetterstrom O, Chung KF, O'Connor BJ, Barnes PJ. Low dose inhaled steroid plus theophylline vs high dose inhaled steroid in the control of asthma. *N Engl J Med* 1997;337:1412-8.
54. Chung KF. Leukotriene receptor antagonists and biosynthesis inhibitors: potential breakthrough in asthma therapy. *Eur Respir J* 1995;8:1203-13.
55. Dworski R, Fitzgerald GA, Oates JA, Sheller JR. Effect of oral prednisone on airway inflammatory mediators in atopic asthma. *Am J Respir Crit Care Med* 1994;149:953-9.
56. Bosley CM, Parry OT, Cochrane GM. Patient compliance with inhaled medication: does combining beta-agonists with corticosteroids improve compliance? *Eur Respir J* 1994;7:504-9.
57. Jones AH, Langdon CG, Lee PS, Lingham SA, Nankani JP, et al. Pulmicort Turbohaler once daily as initial prophylactic therapy for asthma. *Respir Med* 1994;88:293-9.
58. Hummel S, Lehtonen L. Comparison of oral steroid sparing by high-dose and low-dose inhaled steroid in maintenance treatment of severe asthma. *Lancet* 1992;340:1483-7.
59. Dahl R, Lundbäck B, Malo J, Mazza JA, Nieminen MM, Saarglainen P. A dose-ranging study of fluticasone propionate in adult patients with moderate asthma. *Chest* 1993;104:1352-8.
60. Barnes PJ. Inhaled glucocorticoids: new developments relevant to updating the Asthma Management Guidelines. *Respir Med* 1996;90:379-84.
61. British Thoracic Society. The British guidelines on asthma management. *Thorax* 1997;52(suppl 1):S1-21.