

Future aspects of pharmacological treatment to inhibit the allergic march

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Introduction

Pharmacotherapy has become the mainstay of management of established allergic disease. While allergen avoidance is clearly important and occasionally allergen immunotherapy can be of value, for the majority of patients it is necessary to employ pharmacotherapeutic approaches. Unfortunately none of these treatments have any impact on the progression of the allergic march. Furthermore, there is no evidence that any pharmacological intervention modifies the natural history of allergic disease. Nevertheless, pharmacotherapy has been highly effective in suppressing symptoms and improving the quality of life, lung function and bronchial hyperresponsiveness. Hitherto, such therapy has only been employed after the onset of symptoms. The question, therefore, arises as to whether any form of pharmacotherapy, if it is employed early enough, can modify the evolution of the disease process and have an impact on the allergic march. However, very few studies have actually been conducted and published.

Asthma

Asthma constitutes the most common, severe and sometimes life-threatening manifestation of allergic disease which has increased in prevalence at an alarming rate in affluent communities throughout the world. Despite highly effective pharmacotherapy to control asthma, no cure has

been identified and the natural history progresses irrespective of treatment. Children with infrequent episodic asthma do not have any abnormality of lung function compared with non-asthmatic controls after 28 years' follow-up irrespective of the use of prophylaxis (1). However, the converse is also true, that the degree of lung function abnormality and bronchial hyperresponsiveness at presentation with wheezing are the main predictors of ongoing disease with abnormal lung function and persistent hyperresponsiveness as an adult, irrespective of therapy even with inhaled steroids (2).

Studies of airway immunohistopathology in established asthma have shown that inflammation, particularly involving eosinophils and mast cells, is present even during relatively asymptomatic periods (3). A paradigm has evolved that continuing inflammation contributes to a remodelling process in which collagen is laid down below the epithelial basement membrane and in the lamina propria together with hypertrophy of smooth muscle which produces an irreversible component of airflow limitation (4). However, a number of studies in early childhood have suggested that much, if not all, of the immunopathology of asthma is established very early in the evolution of disease and is very likely to be present even before the first symptoms are manifest (5). Studies in adults have shown that the inflammation indices in the airways of asthmatics correlate reasonably well with the

degree of bronchial hyperresponsiveness (6). It has been shown that bronchial hyperresponsiveness can develop as early as 4 weeks of age in those born to atopic asthmatic parents, long before there are any symptoms (7). As bronchial hyperresponsiveness is a risk factor for later asthma (8), the implication of this is that the airway inflammation of asthma is established a long time before this disease produces symptoms.

My own group have shown that there is no correlation between the degree of either eosinophilic infiltration of the lamina propria nor the thickness of the lamina reticularis as a component of remodelling with either the severity of disease or its duration (5). This would be consistent with the concept that the airway immunopathology is established before symptoms are manifest. Under such circumstances, it is then likely that conventional pharmacotherapeutic approaches to treatment will not modify natural history even if introduced early after the onset of symptoms. Thus attention must now focus on presymptomatic intervention to try and halt the allergic march. While environmental modification and immunomodulation are likely to be the most effective long-term strategy in this respect, consideration of the use of currently available pharmacotherapeutic approaches is certainly appropriate, as these will be more acceptable interventions in the short term with an established track record in relation to efficacy and safety considerations.

Potential targets

Atopic dermatitis

Many studies have shown that atopic dermatitis is a common precursor to the development of asthma (9). This is perhaps, therefore, the most obvious target for presymptomatic anti-asthma preventive strategies. In infants with mild to moderate atopic dermatitis, between 40% and 50% will eventually develop some degree of asthma. In those with a more severe dermatological problem, the overwhelming majority will have asthma and this probability increases if there is a first-degree relative with atopic disease. If the atopic dermatitis is associated with persistent egg sensitivity, then the specificity for subsequent asthma is extremely high (10). More recently, it has been shown that atopic dermatitis associated with either grass pollen, house dust mite or cat sensitivity also confers a very considerably increased risk of asthma development (11). However, only 50% or less of the

ultimate asthmatics will have had previous atopic dermatitis.

Allergic rhinitis

It is generally believed that allergic rhinitis is a problem that follows rather than precedes asthma. However, this is not always the case and certainly in children beginning to develop signs of seasonal rhinoconjunctivitis there is a significant risk of the subsequent development of seasonal asthma, which might form a second target for therapeutic intervention (12).

IgE and IgE antibodies

While a raised total IgE in the cord blood is highly specific for the early development of atopic disease, it is unfortunately not very sensitive (13). Indeed, long-term follow-up studies would suggest that the sensitivity is so low that this is an inappropriate screening test. Whether or not the use of IgE antibody measurements and also, indeed, skin prick testing will have any greater value in prediction remains to be established. Nevertheless, subgroups of infants sensitised to aeroallergens such as house dust mite do have a high risk of developing asthma (14).

Family history

It has been well shown that while a first-degree relative with atopy confers a high risk for developing atopic disease and asthma, the vast majority of the future asthmatics will not come from families with a positive history (15). This focuses on the need to identify accurate predictors of disease which are hitherto not available.

Bronchial hyperresponsiveness

The implication from studies of bronchial hyperresponsiveness is that this is yet another index indicating an increased risk of subsequent asthma (8). However, this is neither highly specific nor necessarily particularly sensitive. Intercurrent viral infection may have a transient effect on hyperresponsiveness which will confound the discriminatory capacity of this test which furthermore, in infancy is extremely difficult to measure without highly sophisticated lung function testing equipment.

Summary of targets

For the present, it is inevitable that trials conducted to identify pharmacotherapeutic interventions as prophylaxis in halting the allergic

march will focus on high-risk groups using a combination of the markers identified to have some degree of specificity, which will include the presence of atopic dermatitis and/or allergic rhinitis and/or evidence of sensitisation to inhalants or egg. However, in the longer term, better markers of future asthma will facilitate wider application of preventive strategies.

Ketotifen

There are two published trials showing a significant beneficial effect of ketotifen in the prevention of asthma. One study recruited 121 infants with atopic dermatitis and treated them in a double-blind parallel group study with either ketotifen or placebo for 1 year. After 1 year, only 13% of the actively treated infants had developed asthma, where the figure in the placebo treated patients was 42%. This was a highly significant difference but was only apparent in those infants who not only had atopic dermatitis but also a raised total IgE level (16).

There is one other trial of ketotifen which was employed in a double-blind trial in 95 infants with a family history of asthma, and a raised total IgE level. After 3 years' treatment, 9% of the actively treated patients had three or more respiratory illnesses suggesting a diagnosis of asthma, compared with 35% in the placebo group (17).

Despite these two encouraging trials, little attempt was made to follow up on these observations. In part, this was because there were concerns that ketotifen had some adverse effects in increasing appetite and weight gain, and causing some degree of somnolence and irritability in small children. More recently, however, with the advent of newer non-sedating antihistamines, the concept has again been raised and trials are now in progress using both cetirizine and loratidine. Results using the former drug have now been published (11).

Cetirizine

Early Treatment of the Atopic Child (ETAC) has been a multi-centre double-blind randomised placebo-controlled trial of the use of cetirizine at a dose of 0.25 mg/kg administered twice daily compared with matching placebo to prevent the onset of asthma in infants with atopic dermatitis. Infants were recruited between 1 and 2 years of age and were maintained on the treatment for 18 months. While there were no differences between active and placebo therapy in the intention to

treat population, subgroup analysis of those with evidence of sensitivity to either house dust mite or grass pollen at recruitment showed a significantly lower cumulative prevalence of asthma over 18 months of active treatment compared with placebo. This was a very considerably significant effect, with a reduction of asthma by 50% in the grass pollen sensitised group and 40% in the house mite sensitive group (11).

There were also some potential benefits of cetirizine in the treatment of the primary condition, namely the atopic dermatitis. Patients on active treatment required significantly less other antihistamines which were primarily prescribed to reduce pruritis. Furthermore, the active treatment significantly reduced the frequency of acute urticaria and reduced the requirement for high potency topical steroids in those children with more severe eczema. This provided some justification for the use of the treatment even for the primary problem, notwithstanding its potential to prevent or halt further development of the atopic march (18).

Unlike the ketotifen study, ETAC have continued follow-up of the children beyond the treatment period. Preliminary analysis of 18-month post-treatment shows that there was no rebound in asthma prevalence when the treatment was stopped in the active group and after a full 3 years (18 months of treatment), there was still a significant difference in asthma prevalence in the grass pollen sensitised group. Most importantly, this trial has also shown that the intervention is extremely safe (18). Indeed, the trial has provided information which is quite unique in relation to assessment of safety of any pharmacotherapy in infancy.

Potential mechanisms of action of antihistamine

It is difficult to conceive how a simple H1 receptor antagonist would have an effect in preventing or inhibiting the allergic march from atopic dermatitis to asthma. However latterly, studies have shown that a number of antihistamines best exemplified with cetirizine have additional properties which might explain their efficacy.

A number of antihistamines have been shown to prevent the upregulation of the intercellular adhesion molecule 1 (ICAM-1) after stimulation with allergen (19). This has been demonstrated specifically in the eye. Cetirizine has also been shown to inhibit the upregulation of VCAM-1 and to inhibit eosinophil migration into allergen challenged tissues either in the skin, nose or eyes. Probably as a consequence of prevention of

upregulation of ICAM-1. Antihistamines have been shown to reduce the susceptibility of cells to infection with rhinovirus which, of course, gains access to cell by ligation with ICAM-1 (20). It is, therefore, tempting to speculate that inhibiting upregulation of adhesion molecules would prevent migration of inflammatory cells into the airway and thereby retard or even prevent the development of asthma. While the eosinophil continues to be the main focus of attention, ICAM-1 is also important in relation to neutrophil adhesion. Our own studies have shown that the neutrophil may well be an important initiator of inflammation in the asthmatic airway of young children (21). Thus inhibition of trafficking of both cells may well be important. However, the adhesion molecules are also important in facilitating cell-to-cell communication which, therefore, might have a more fundamental effect on the sensitisation process.

Other drugs

There are no published trials of the use of other pharmacotherapeutic approaches for the primary prevention of allergic disease. However, it is interesting to speculate on which pharmacotherapies might have some value given their properties.

Sodium cromoglycate

Sodium cromoglycate was developed for the treatment of asthma. Its mechanism of action has always been in doubt. However, among other properties, it inhibits IgE-dependent mast cell release of pro-inflammatory mediators, to a certain extent, it interferes with inflammatory cell trafficking in allergen challenge tissue, and has an inhibitory effect on certain neuronal reflexes which may be important in triggering bronchospasm in asthma (22). Perhaps the property of sodium cromoglycate which would be most valuable in considering preventive strategies is its effect on IgE production. It has been shown that it will inhibit the gene deletional switching from IgM to IgE production which, of course, is triggered by IL-4 and IL-13 and clearly is an important component of the development of allergic sensitisation and subsequent disease (23).

The key issue in relation to sodium cromoglycate, however, is to achieve adequate concentrations in the relevant target tissues. Whether or not it will be possible *in vivo* remains to be established by study. Certainly it is worthy of further investigation. Clearly, in consideration of employment of any pharmacotherapeutic intervention in early infancy, the primary considera-

tion is safety. Sodium cromoglycate has an unparalleled record of safety by comparison with any other drug used for any other disease.

Leukotriene receptor antagonists

The cysteinyl leukotrienes are an important group of mediators in asthma. They not only trigger bronchospasm but also are chemotactic for eosinophils. Since the advent of cysteinyl leukotriene receptor antagonists, it has become clear that the lipoxygenase pathway is very important in the pathogenesis of asthma, at least in some patients (24). Hitherto, the safety record for the receptor antagonists has been good in childhood and studies are under way to establish their safety and efficacy even in infant wheezers (25). There will, therefore, be the potential to study this group of drugs as a preventive strategy. Given that they may well have some benefit for the treatment of allergic rhinitis and atopic dermatitis, there is little doubt that trials will evolve in the near future. There is some evidence that there is at least an additive effect of the leukotriene receptor antagonists with potent H1 receptor antagonists (26) and perhaps the best first trial should combine the two medications.

Inhaled steroids

Given the highly efficacious and relatively safe pharmacotherapeutic profile for inhaled corticosteroids in the treatment of children with asthma, it is tempting to consider the use of such agents in a preventive strategy. Indeed, it has been suggested that the earlier inhaled steroids are introduced after the onset of symptoms, the less the adverse effect of the disease on lung growth and, therefore, increase in lung function (27). However, the very much longer-term follow-up studies would suggest that hitherto inhaled steroids have not had a major impact on long-term outcomes (2). This may, of course, be because the treatment has been used too late.

However, some have expressed considerable concern about potential adverse effects of early use of inhaled corticosteroid (28). There are at least theoretical reasons to believe that steroids could have an effect on lung growth when used under 2 years of age, while new alveolus formation is still proceeding at a rapid rate. At least one animal study has indicated that this is a potential adverse effect (29). Furthermore, at least, *in vitro*, steroids can be shown to increase rather than decrease IL-4 dependent gene deletional switching in B cell IgE production (30).

Thus for the present, consideration of the use of inhaled corticosteroids in the inhibition of the atopic march should be shelved. The only published trial of asthma prevention that has attempted very early use of ICS (and indeed SCG) after the first wheeze in infancy observed no effect compared with placebo, but the treatment period was very short (31). Later use of either ICS or nedocromil sodium in childhood asthma even for 4–6 years has no impact on post-bronchodilator lung function compared with placebo, despite appreciable improvements in symptom control (32). This again highlights the need for earlier interventional preventive strategies.

Summary

Hitherto, most trials investigating strategies to inhibit the atopic march have focused on allergen avoidance. In the long-term, it is likely that immunomodulatory approaches will have the best chance of success. However, in the interim there is every justification for investigating pharmacotherapeutic approaches. Many drugs currently available for the treatment of atopic disease have properties which might render them valuable in preventive strategies. The newer generation antihistamines are the only group that have been investigated and shown to have some effects in preventing the development of asthma in infants with atopic dermatitis. Future studies will need to focus on other combinations of drugs including the leukotriene receptor antagonists and perhaps cromones.

References

1. OSWALD H, PHELAN PD, LANNIGAN A, et al. Childhood asthma and lung function in mid-adult life. *Pediatr Pulmonol* 1997; 23: 14–20.
2. GERRITSEN J, KOETER GH, POSTMA DS, et al. Airway responsiveness in childhood as a predictor of outcome of asthma in adulthood. *Amer Rev Respir Dis* 1991; 143: 1468–72.
3. BEASLEY R, ROCHE WR, ROBERTS JA, HOLGATE ST. Cellular events in the bronchi in mild asthma and after bronchial provocation. *Am Rev Respir Dis* 1989; 139: 806–17.
4. LAITINEN LH, HEINO M, LAITINEN A, et al. Damage to the airway epithelium and bronchial reactivity in patients with asthma. *Am Rev Respir Dis* 1985; 131: 599–606.
5. WARNER JO. Bronchial hyperresponsiveness, atopy, airway inflammation and asthma. *Pediatr Allergy Immunol* 1998; 9: 56–60.
6. SONT JK, HAM J, VAN KRIEKEN JM, et al. Relationship between the inflammatory infiltrate in bronchial biopsy specimens and clinical severity of asthma in patients treated with inhaled steroids. *Thorax* 1996; 51: 496–502.
7. YOUNG S, LE SOUEF PN, GEELHOED GC, et al. The

influence of a family history of asthma and parental smoking on airway responsiveness in early infancy. *N Engl J Med* 1991; 324: 1168–73.

8. LE SOUEF P. Infant lung function, bronchial responsiveness and the development of asthma. *Pediatr Allergy Immunol* 2000; 11 (suppl 13): 15–18.
9. SALOB S, ATHERTON D. Prevalence of respiratory symptoms in children with atopic dermatitis attending pediatric dermatology clinics. *Pediatrics* 1993; 91: 8–12.
10. KULIG M, BERGMANN R, TACKE V, et al. Long lasting sensitization to food during the first two years precedes allergic airway disease. *Pediatr Allergy Immunol* 1998; 9: 61–7.
11. ETAC Study Group. Allergic factors associated with the development of asthma and the influence of cetirizine in a double blind randomised placebo controlled trial. First results of ETAC. *Pediatr Allergy Immunol* 1998; 9: 116–24.
12. ANDERSON HR, POTTIER AC, STRACHAN DP. Asthma from birth to age 23: incidence and relationship to prior and concurrent atopic disease. *Thorax* 1992; 47: 537–42.
13. CRONER S, KJELLMAN N-IM. Development of atopic disease in relation to family history and cord blood IgE levels – 11 year follow-up in 1654 children. *Pediatr Allergy Immunol* 1990; 1: 14–21.
14. DELACOURT C, LABBE D, VASSAULT A, et al. Sensitization to inhalant allergens in wheezing infants is predictive of the development of infantile asthma. *Acta Paediatr Scand* 1994; 49: 843–7.
15. BERGMANN RL, BERGMANN KE, WAHN U. Can we predict atopic disease using perinatal risk factors? *Clin Exp Allergy* 1998; 28: 905–7.
16. IKURA Y, NASPITZ CK, MIKAWA H, et al. Prevention of asthma by ketotifen in infants with atopic dermatitis. *Ann Allergy* 1992; 68: 233–6.
17. BUSTOS GJ, BUSTOS D, BUSTOS GJ, ROMERO O. Prevention of asthma with ketotifen in pre-asthmatic children; a 3 year follow-up study. *Clin Exp Allergy* 1995; 25: 568–73.
18. SIMONS FER. Prospective long term safety evaluation of the H1 receptor antagonist, cetirizine, in very young children with atopic dermatitis. *J Allergy Clin Immunol* 1999; 104: 433–40.
19. CIPRANDI G, PASSALACQUA G, CANONICA GW. Effect of H1 antihistamines on adhesion molecules; a possible rationale for long term treatment. *Clin Exp Allergy* 1999; 29 (suppl 3): 49–53.
20. GWALTNEY JM, DRUCE HM. Efficacy of brompheniramine maleate for the treatment of rhinovirus colds. *Clin Infect Dis* 1997; 25: 1188–94.
21. MARGUET C, JOUEN-BOEDES F, DEAN TP, WARNER JO. Bronchoalveolar cell profiles in children with asthma, infantile wheeze, chronic cough or cystic fibrosis. *Am J Respir Crit Care Med* 1999; 159: 1533–40.
22. HOSHINO M, NAKAMURA Y. The effect of inhaled sodium cromoglycate on cellular infiltration into the bronchial mucosa and the expression of adhesion molecules in asthmatics. *Eur Respir J* 1997; 10: 858–65.
23. LOH RKS, JABARA HH, GEHA RS. Sodium cromoglycate inhibits $\Sigma\mu\leftarrow\epsilon$ deletional switch recombination and IgE synthesis in human B cells. *J Exp Med* 1994; 180: 663–71.
24. CHUNG KF. Leukotriene receptor antagonists and biosynthesis inhibitors: potential breakthrough in asthma therapy. *Eur Respir J* 1995; 8: 1203–13.
25. KNORR B, MATZ J, BURNSTEIN JA, et al. Montelukast for chronic asthma in 6–14 year old children. *JAMA* 1998; 279: 1181–6.

26. REICIN A, WHITE R, WEINSTEIN SF, et al. Montelukast, a leukotriene receptor antagonist, in combination with loratadine, a histamine receptor antagonist, in the treatment of chronic asthma. *Arch Intern Med* 2000; 160: 2481–8.
27. AGERTOFT L, PEDERSEN S. Effects of long-term treatment with an inhaled corticosteroid on growth and pulmonary function in asthmatic children. *Respir Med* 1994; 88: 373–81.
28. PEDERSEN S, WARNER JO, PRICE JF. Early use of inhaled steroids in children with asthma. *Clin Exp Allergy* 1997; 27: 995–1006.
29. KLEBL FH, WEBER G, KALDEN JR, NUSSLEIN HG. *In vitro* and *in vivo* effects of corticosteroids on IgE and IgG subclass secretion. *Clin Exp Allergy* 1994; 24: 1022–9.
30. ZIPG G, LACK G, HARBECK RJ, et al. The *in vivo* effects of glucocorticoids on IgE production. *J Allergy Clin Immunol* 1994; 94: 222–30.
31. REIJONEN TM, KORPPI M. One-year follow-up of young children hospitalised for wheezing; the influence of early anti-inflammatory therapy and risk factors for subsequent wheezing and asthma. *Pediatr Pulmonol* 1998; 26: 113–19.
32. The Childhood Asthma Management Program Research Group. Long term effects of budesonide or nedromil in children with asthma. *N Engl J Med* 2000; 343: 1054–63.