Prevention strategies for asthma — secondary prevention

Secondary prevention of asthma is defined as intervention(s) for infants and children who are at high risk for the development of asthma but who have not yet developed asthma symptoms or signs. These patients have a family history of allergic disease and 1 or more of the following: atopic dermatitis or eczema, allergic rhinitis, food allergy, bronchial hyperreactivity, blood eosinophilia, elevated total IgE levels, elevated allergen-specific IgE, or skin-test reactivity to specific allergens.[1–3]

Literature review

The evidence base for effective measures in the area of secondary prevention of asthma is small. All of the studies identified in a MEDLINE search are included in this review. Criteria for diagnosis of asthma are those described by the individual investigators.

Current evidence

Evidence-based therapeutic interventions for the secondary prevention of asthma fall into 3 categories:

- pharmacologic treatment[4–22]
- control of environmental allergens and environmental tobacco smoke[23–27]
- allergen-specific immunotherapy[28–32]

Pharmacologic treatment

H_1-antihistamine medications are of limited therapeutic benefit when administered in the usual doses to those with established asthma.[4] Nevertheless, in 3 prospective, double-blind, placebo-controlled studies,[5–8] the first-generation H_1-antihistamine ketotifen and the second-generation H_1-antihistamine cetirizine, both of which have anti-allergic and anti-inflammatory properties,[4,9] were used with some success in the secondary prevention of asthma.

In a double-blind, parallel-group, placebo-controlled study,[5] 121 infants and children with atopic dermatitis, who were 1–36 months old at study entry, received ketotifen twice daily for 1 year; the dose for those <14 kg was 0.8 mg and for those 14–23 kg the dose was 1.2 mg. At the end of this time, only 13.1% of the ketotifen-treated children had asthma in contrast with 41.6% of the placebo-treated children ($p < 0.001$); however, the beneficial effect of ketotifen was observed only in children who had a raised total serum IgE level at study entry. Adverse effects, including sedation, were noted in the ketotifen-treated children. Children with atopic dermatitis frequently have elevated total IgE; however, IgE does not correlate with asthma in the absence of atopic dermatitis. Adverse effects, including sedation, were noted in 6 of the 61 ketotifen-treated children compared with 0 of the 60 children in the placebo group. Subsequent trials to support this approach have not been published and ketotifen is seldom used.

In a subsequent double-blind, placebo-controlled, parallel-group study,[6] 100 pre-asthmatic infants with a family history of allergy and elevated total serum IgE levels were treated with ketotifen at a dose of 0.5 mg every 12 h for those ≤3 years of age and 1 mg every 12 h for those >3 years of age. Treatment was continued for 3 years. At the conclusion of treatment, 9% of the 45 infants who were given ketotifen had developed asthma and 35% of the 40 children given placebo had developed asthma ($p = 0.003$). Adverse effects were not discussed in the report of the study.

In a larger, rigorously designed, randomized, double-blind, placebo-controlled investigation[7] (the Early Treatment of the Atopic Child [ETAC] study) of 817 children aged 12–24 months at entry, cetirizine in a dose of 0.25 mg/kg or matching placebo was given twice daily for 18 months. There was a 6-month double-blind follow-up and an additional 36-month open follow-up. At entry, no child had a history of wheezing, nocturnal cough or pulmonary disease of any kind. Asthma was defined as 3 episodes of nocturnal cough with sleep disturbance or wheezing separated by at least 7 days in a clinical setting where asthma was likely and other conditions had been excluded.

In contrast to placebo, cetirizine treatment delayed asthma onset in children sensitized to house dust mites (HDMs) (35 of 68 v. 16 of 56, $p = 0.005$) and in those sensitized to grass pollen (20 of 34 v. 10 of 36, $p = 0.002$), although not in the entire group enrolled in the study (intention-to-treat population; 150 of 398 v. 151 of 397).[7] In the grass pollen-sensitized children, the effect was sustained for 36 months after treatment was discontinued ($p = 0.008$). In the children sensitized to HDMs, there was a gradual narrowing of the difference between cetirizine and placebo treatments in terms of cumulative prevalence of asthma at the end of 36 months, but no evidence of a rebound after the treatment was stopped ($p = 0.04$). The effect on prevention of asthma symptoms, which was maintained after cetirizine treatment was discontinued, was attributed to down-regulation of ICAM-1 expression and eosinophilic inflammation.[8,9] In the placebo-treated children, there was a significantly higher risk of the development of asthma in those sensitized to grass pollen, HDM, cat or egg allergen at study entry.[8]

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In the ETAC study, cetirizine also had a topical glucocorticoid-sparing effect in atopic dermatitis[10] and decreased the frequency of acute urticaria episodes, which occurred in 5.8% of the cetirizine-treated children in contrast with 16.2% of the placebo-treated children.[11] Unlike the preventative effect against asthma, the preventative effect against urticaria disappeared when treatment was stopped. Despite the relatively high cetirizine dose administered (0.25 mg/kg twice daily), the long-term safety profile was excellent and there were no adverse effects on growth, behaviour, psychosocial or cognitive development, as rigorously assessed during active treatment and follow-up using validated instruments, including the McCarthy Scales of Childrens' Ability.[12–14]

There are 2 additional relevant studies. A 24-month study in which loratadine prevented viral upper respiratory tract infections and associated wheezing and coughing in children aged 24–30 months has been completed but not yet published.[15] A long-term, prospective, randomized, double-blind, placebo-controlled study of levocetirizine (the pharmacologically active enantiomer of the racemate cetirizine), 0.125 mg/kg twice daily, in children aged 12–24 months is also underway.

Prospective, randomized, double-blind, placebo-controlled pharmacologic interventions are needed to test other classes of medications, including inhaled glucocorticoids[16] and oral leukotriene modifiers,[17] which are effective in infants and young children with an established diagnosis of asthma, but have not been studied for their secondary prevention effects in high-risk children who have not yet developed asthma. Also, the topically applied calcineuron inhibitors, such as pimecrolimus and tacrolimus, introduced recently for relief of skin inflammation in infants and children with atopic dermatitis or eczema are of interest with regard to their potential role in the secondary prevention of asthma.[18] The possibility that allergen exposure might decrease responsiveness to pharmacologic treatment needs to be explored further.[19] In addition, new immunomodulators, which appear to be safe and effective in clinical trials in humans, should eventually be studied for the secondary prevention of asthma in at-risk individuals. Examples of these interventions include anti-IgE with[20] or without[21] specific allergen immunotherapy, cytokine antagonists[21] and DNA vaccines, including immunostimulatory sequences with[23] or without specific allergen.

Overall, studies of secondary prevention have been disappointing, but in children already sensitized to HDM or grass pollen allergens who do have atopic dermatitis, treatment with cetrizine may have some benefit.

Infection, environmental allergens and environmental tobacco smoke

The long-term ramifications of the amount, timing and extent of exposure to infections, environmental and food allergens and environmental tobacco smoke and other respiratory irritants and the complex interactions of these factors with genetic factors are currently incompletely understood.[1] Although sensitization of children can be prevented by avoidance of environmental allergens, such as HDMs,[24] there is no evidence that this is associated with secondary prevention of asthma. However, most research efforts in this area to date have focused on primary and tertiary prevention, rather than secondary prevention.[1,25,26]

The association between passive smoking and asthma in children, including asthma development and asthma severity, is well-documented.[27] However, it should be noted that although avoidance of tobacco smoke exposure in at-risk infants and children is logical and universally recommended by physicians, there are no studies proving that avoidance of passive smoking is useful in the secondary prevention of asthma. Moreover, long-term changes in parental smoking habits are difficult to achieve.[28]

Allergen-specific immunotherapy

Allergic rhinitis often precedes the onset of asthma. A 2-year rigorously designed, prospective, randomized, double-blind, placebo-controlled study[28] followed 44 patients, mean age 19 years (range 10–38 years), with a documented history of perennial atopic rhinitis, but no history of asthma and normal pulmonary function tests, who were monosensitized to HDM (*Dermatophagoides pteronyssinus*) and had no other allergies. In this group, *D. pteronyssinus* immunotherapy reduced the progression of rhinitis to asthma and prevented an associated increase in bronchial hyperreactivity. After 1 year of treatment, patients receiving immunotherapy had increased PD_{20} FEV_1 for methacholine (2.88-fold increase, 95% CI 2.09–3.98) and showed further improvement after 2 years (OR 4.1, 95% CI 2.09–5.7). At the end of the study, the PD_{20} FEV_1 was within the normal range for 50% of the treated patients ($p < 0.0001$) and significantly higher in this group than in those receiving placebo ($p < 0.0001$); PD_{20} FEV_1 > 8 mmol versus 2.9 mmol. None of the patients treated with immunotherapy developed asthma, yet 9% of those given placebo did. The investigators concluded that immunotherapy administered to carefully selected, monosensitized patients with perennial allergic rhinitis but no asthma reduces airway responsiveness and thus holds some promise for secondary prevention of asthma.

In another study,[29] 205 children, mean age 10.7 years (range 6–14 years) with grass or birch pollen allergy (or both) but without any other clinically important allergy or asthma needing daily medications were randomly chosen to receive allergen-specific immunotherapy for 3 years or assigned to an open control group. After 3 years, among those without asthma, the treated children had significantly fewer asthma symptoms, as evaluated by clinical diagnosis (OR 2.52, 95% CI 1.3–5.1). The results of methacholine bronchial provocation tests improved significantly in the

treatment group during the winter (PC_{20} OR 2.75, 95% CI 1.2–6.3), but not during the allergy season (PC_{20} OR 1.43, 95% CI 0.8–2.7). The investigators concluded that immunotherapy can reduce the development of asthma in children with seasonal rhinoconjunctivitis. However, the conclusions that can be drawn from this randomized, clinical trial are limited by the fact that it was not double-blind or placebo-controlled and that, before the start of immunotherapy, 20% of the children likely had mild asthma, although they did not need daily treatment.

In other studies that were prospective, but not randomized, double-blind or placebo-controlled,[30,31] and in a retrospective study,[32] the investigators concluded that allergen-specific immunotherapy may prevent the onset of new sensitization in children with respiratory symptoms and monosensitization to HDMs.

Implications for research

1. Future research should consist of appropriately timed and adequately powered, randomized, double-blind, placebo-controlled studies of the following: additional H_1-antihistamines with anti-allergic, anti-inflammatory effects; additional classes of pharmacologic treatment, such as inhaled glucocorticoids, leukotriene modifiers and topical calcineuron inhibitors; new immunomodulators, such as anti-IgE; and allergen-specific immunotherapy.
2. Also needed are randomized, controlled studies of the role of avoidance of environmental allergens and tobacco smoke in the secondary prevention of asthma.

References

1. Wahn U, von Mutius E. Childhood risk factors for atopy and the importance of early intervention. *J Allergy Clin Immunol* 2001;107(4):567-74.
2. Kulig M, Bergmann R, Klettke U, Wahn V, Tacke U, Wahn U. Natural course of sensitization to food and inhalant allergens during the first 6 years of life. *J Allergy Clin Immunol* 1999;103(6):1173-9.
3. National Asthma Education and Prevention Program expert panel report: guidelines for the diagnosis and management of asthma update on selected topics — 2002. *J Allergy Clin Immunol* 2002;110(5 suppl.):S141-219.
4. Simons FE. Is antihistamine (H_1-receptor antagonist) therapy useful in clinical asthma? *Clin Exp Allergy* 1999;29(suppl. 3):98-104.
5. Iikura Y, Naspitz CK, Mikawa H, Talaricoficho S, Baba M, Sole D, et al. Prevention of asthma by ketotifen in infants with atopic dermatitis. *Ann Allergy* 1992;68(3):233-6.
6. Bustos GJ, Bustos D, Bustos GJ, Romero O. Prevention of asthma with ketotifen in preasthmatic children: a three-year follow-up study. *Clin Exp Allergy* 1995;25(6):568-73.
7. 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. Early Treatment of the Atopic Child. *Pediatr Allergy Immunol* 1998;9(3):116-24.
8. Warner JO, ETAC Study Group. A double-blind, randomized, placebo-controlled trial of cetirizine in preventing the onset of asthma in children with atopic dermatitis: 18 months' treatment and 18 months' posttreatment follow-up. *J Allergy Clin Immunol* 2001;108(6):929-37.
9. Leurs R, Church MK, Taglialatela M. H_1-antihistamines: inverse agonism, anti-inflammatory actions and cardiac effects. *Clin Exp Allergy* 2002;32(4):489-98.
10. Diepgen TL, Early Treatment of the Atopic Child Study Group. Long-term treatment with cetirizine of infants with atopic dermatitis: a multi-country, double-blind, randomized, placebo-controlled trial (the ETAC trial) over 18 months. *Pediatr Allergy Immunol* 2002;13(4):278-86.
11. Simons FE. Prevention of acute urticaria in young children with atopic dermatitis. *J Allergy Clin Immunol* 2001;107(4):703-6.
12. Simons FE. Prospective, long-term safety evaluation of the H_1-receptor antagonist cetirizine in very young children with atopic dermatitis. *J Allergy Clin Immunol* 1999;104(2 pt 1):433-40.
13. Stevenson J, Cornah D, Evrard P, Vanderheyden V, Billard C, Bax M, et al. Long-term evaluation of the impact of the h_1-receptor antagonist cetirizine on the behavioral, cognitive and psychomotor development of very young children with atopic dermatitis. *Pediatr Res* 2002;52(2):251-7.
14. de Longueville M, Deruyter B. RR, QT, and QTc in 799 infants aged 1-2 years. *J Allergy Clin Immunol* 1998;101:S198.
15. Grimfeld A, Holgate ST, Adam D, Bonini S, Borres M, Canonica GW, et al. Preventive study phase I results: loratadine treatment reduces wheezing episodes in children at risk for recurrent upper respiratory infections. *Allergy* 2000;55(Suppl 63):242.
16. Baker JW, Mellon M, Wald J, Welch M, Cruz-Rivera M, Walton-Bowen K. A multiple-dosing, placebo-controlled study of budesonide inhalation suspension given once or twice daily for treatment of persistent asthma in young children and infants. *Pediatrics* 1999;103(2):414-21.
17. Knorr B, Franchi LM, Bisgaard H, Vermeulen JH, LeSouëf P, Santanello N, et al. Montelukast, a leukotriene receptor antagonist, for the treatment of persistent asthma in children aged 2 to 5 years. *Pediatrics* 2001;108(3):E48.
18. Nimmagadda SR, Szefler SJ, Spahn JD, Surs W, Leung DY. Allergen exposure decreases glucocorticoid receptor binding affinity and steroid responsiveness in atopic asthmatics. *Am J Respir Crit Care Med* 1997;155(1):87-93.
19. Milgrom H, Fick RB Jr, Su JQ, Reimann JD, Bush RK, Watrous ML, et al. Treatment of allergic asthma with monoclonal anti-IgE antibody. *N Engl J Med* 1999;341(26):1966-73.
20. Kuehr J, Brauburger J, Zielen S, Schauer U, Kamin W, Von Berg A, et al. Efficacy of combination treatment with anti-IgE plus specific immunotherapy in polysensitized children and adolescents with seasonal allergic rhinitis. *J Allergy Clin Immunol* 2002;109(2):274-80.
21. Barnes PJ. Cytokine-directed therapies for asthma. *J Allergy Clin Immunol* 2001;108(2 suppl):S72-6.
22. Simons FER, Shikishima Y, van Nest G, Eiden JJ, HayGlass KT. Allergen-selective redirection of immunoregulatory responses in ragweed-allergic humans using Dynavax Amb a 1 immunostimulatory oligodeoxyribonucleotide conjugate (AIC). *J Allergy Clin Immunol* 2003;111(2 pt 2):S267.
23. Arshad SH, Bojarskas J, Tsitoura S, Matthews S, Mealy B, Dean T, et al. Prevention of sensitization to house dust mite by allergen avoidance in school age children: a randomized controlled study. *Clin Exp Allergy* 2002;32(6):843-9.
24. Liu AH, Murphy JR. Hygiene hypothesis: fact or fiction? *J Allergy Clin Immunol* 2003;111(3):471-8.
25. von Mutius E, Martinez FD. Prevention of allergic disease in childhood. In: Adkinson NF Jr, Yunginger JW, Busse WW, Bochner BS, Holgate ST, Simons FER, editors. *Middleton's allergy: principles and practice*. 6th ed. St. Louis: Mosby; 2003:1169-74.
26. Cook DG, Strachan DP. Health effects of passive smoking. 10. Summary of effects of parental smoking on the respiratory health of children and implications for research. *Thorax* 1999;54:357-66.
27. Irvine L, Crombie IK, Clark RA, Slane PW, Feyerabend C, Goodman KE, et al. Advising parents of asthmatic children on passive smoking: randomised controlled trial. *BMJ* 1999;318(7196):1456-9.
28. Grembiale RD, Camporota L, Naty S, Tranfa CME, Djukanovic R, Marsico SA. Effects of specific immunotherapy in allergic rhinitic individuals with bronchial hyperresponsiveness. *Am J Respir Crit Care Med* 2000;162(6):2048-52.
29. Moller C, Dreborg S, Ferdousi HA, Halken S, Host A, Jacobsen L, et al. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). *J Allergy Clin Immunol* 2002;109(2):251-6.
30. Pajno GB, Barberio G, De Luca F, Morabito L, Parmiani S. Prevention of new sensitizations in asthmatic children monosensitized to house dust mite by specific immunotherapy. A six-year follow-up study. *Clin Exp Allergy* 2001;31(9):1392-7.
31. Des Roches A, Paradis L, Menardo JL, Bouges S, Daures JP, Bousquet J. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. VI. Specific immunotherapy prevents the onset of new sensitizations in children. *J Allergy Clin Immunol* 1997;99(4):450-3.
32. Jacobsen L, Dreborg S, Moller C. Immunotherapy as a preventive treatment [abstract]. *J Allergy Clin Immunol* 1996;97:232.