

What are the candidate groups for pharmacotherapeutic intervention to prevent asthma?

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Despite the development of many new therapies for the treatment of asthma, the prevalence of this disease is still increasing in many areas of the world. Today no intervention is able to completely cure asthma but chronic therapies could decrease its severity. Moreover, asthma is one of the most common chronic diseases of childhood and its pharmaco-economic burden is huge. Epidemiologic studies have identified some of the major factors involved in the pathogenesis and evolution of asthma. Several prevention programs have been developed in different countries with various success rates. Most of those interventions were based on allergen avoidance. From studies aimed at controlling early asthma and from epidemiologic data, we have learned to identify high-risk groups, e.g. the atopic child with allergic asthma, with a family history of asthma or allergy-related disease and early sensitization to aeroallergens. Only a few prospective studies aimed at preventing the onset of asthma have been published. With ketotifen, Iikura et al. could prevent the onset of asthma after a 1-year period in patients suffering from atopic dermatitis. Another study has been published by Bustos et al. concerning children with a family history of allergy and high total IgE levels. Those studies involved about 100 patients. No follow-up data has been published for either of them. Recently, the first results from the ETAC[®] (Early Treatment of the Atopic Child) trial have been reported. This study involved 817 atopic children with atopic dermatitis and a family history of atopy: cetirizine halved the number of patients developing asthma in the subgroups (200 children) sensitized to house dust mite (51.5% versus 28.6%) or pollen (58.8% versus 27.8%). The optimal target for pharmaceutical intervention to prevent asthma would seem to be high risk patients: children with atopic dermatitis, a family history of asthma or atopic disease and early sensitization to aeroallergens. Primary prevention in whole populations (e.g. starting even before the onset of atopic dermatitis or allergen sensitization) does not at present appear to be a realistic approach.

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Today asthma is one of the more important chronic diseases in the world in terms of numbers of patients and costs. Despite the development of many new medications for the treatment of asthma, the mortality and morbidity of the disease have not decreased (1, 2). Moreover, the number of hospitalizations is still appearing to increase.

Asthma starts very early in life in many patients. Wheezing disappears spontaneously before the sixth birthday in a majority of them (3).

For years, asthma has been recognized as an inflammatory disease. In the last few years there has been major progress in our understanding of the physiopathology of the disease and its

treatment. The inflammatory cascade is starting to be well-explored. This immunologic phenomenon implies different cells and pathways. New families of medications have been developed based on some of these pathways, e.g. leukotriene antagonists (4). Today neither intervention nor medication is able to definitively cure asthma. Symptoms can be controlled or reduced. During treatment, the occurrence of wheezing can be diminished using corticosteroids, but it reappears when treatment is stopped.

Atopic diseases are complex and multifactorial with interaction between genetic factors, environmental exposure to allergens and non-specific factors. Asthma is one atopic disease as are atopic dermatitis and allergic rhinoconjunctivitis. The relationship between food allergy and atopy is still less clear. The first years of life seem to be of major importance for the atopic diseases (5).

Prevention of asthma

Risk factors for developing asthma have been identified by several epidemiologic studies (6, 7). Childhood asthma is a complex syndrome implicating multiple risk factors at the same time. This complexity justifies the high-risk strategy approach (8) involving allergen avoidance and early pharmacotherapeutic interventions. Attempts at prevention by allergen avoidance have produced conflicting results. Moreover, such prevention is very difficult or quite impossible to manage in daily practice (9). Therefore early pharmacotherapeutic interventions are of major interest but they need to meet specific requirements, including clinical efficacy, easy administration, good tolerability and safety, as these medications will be given for long periods in relatively healthy patients.

Pharmacotherapeutic interventions in asthma

Medications active in the treatment of mild asthma are the drugs of choice for such an approach. High-risk patients have been the best targets for such early intervention. Very little is known about the long-term safety of these medications, especially in children.

A number of studies designed for the prevention of asthma attacks in already asthmatic patients have been published. These studies are not true preventive interventions.

Pharmacotherapeutic prevention of asthma in childhood

Cromolyn (10, 11) as well as loratadine (12) and cetirizine (13) have often been used in rather small studies but we have not found any studies focused on the prevention of asthma in non-asthmatic patients. The majority of studies have confirmed the ability of these drugs to reduce the number of asthmatic attacks in mild allergic asthma.

Iikura et al. (14) tried to prevent the onset of asthma with a 1-year treatment with ketotifen or placebo in 121 children suffering from atopic dermatitis. Those children, aged between 1 month and 36 months at inclusion, did not have any wheezing before randomization. In the group of patients with high total IgE, the number of asthmatic patients was significantly reduced. In another study by Bustos et al. (15), 100 children up to 2 years of age were treated in a double-blind way for 3 years with ketotifen or placebo. Patients with a family history of asthma or allergic rhinitis in at least one of the parents or grandparents and elevated serum total IgE were included. A decrease of 25% (35/9) in the number of asthmatic patients was observed in the ketotifen group. No difference was found between treatment groups in IgE levels before, during and at the end of the trial. To our knowledge, no data regarding adverse effect or follow-up without study medication have been published for the last two studies. In accordance with the conclusions of the authors, this preventive effect is probably related to the anti-inflammatory properties of the compound.

The ETAC[®] trial

Recently, the first efficacy results of the ETAC trial (16) (Early Treatment of the Atopic Child) have been published. ETAC was a prospective, randomized, double blind, parallel group and placebo-controlled trial of cetirizine. Over a 2-year period, 817 infants aged 1–2 years who suffered from atopic dermatitis and with a family history of atopy in one direct relative were included. Detailed history regarding related risk factors including total IgE and five specific IgE serum levels were recorded at baseline and at regular intervals. Excluded were infants with asthma, or with a history, after 6 months of age, of any episode of wheezing or more than one episode of nocturnal cough (three consecutive nights with sleep disturbances). The study was coordinated by a Scientific Advisory Board (SAB) consisting of independent clinicians and

scientists not involved as investigators and blind to the treatment randomization. Infants were treated for 18 months with relatively high doses of an oral solution of cetirizine (0.25 mg/kg body weight b.i.d.) or placebo. The primary end point was the number of children developing asthma, defined as three independent episodes of nocturnal cough with sleep disturbances or wheezing. All data were recorded by the parents/guardians on diary cards and validated by the investigator at the next visit. Thereafter all data were reviewed by an independent Data Review Committee including SAB members.

Results from the placebo group confirmed that 40% of those children developed asthma at the end of the 18-month therapy as hypothesized in the protocol for this high-risk group. Moreover, infants with raised baseline level of serum total IgE or specific IgE antibodies against egg, cow milk, house dust mite, cat dander and grass pollen (Pharmacia CAP[®] System, Pharmacia & Upjohn, Uppsala, Sweden) had an increased relative risk of developing asthma. This increase was statistically significant in children with total IgE, or sensitized to house dust mite or cat dander (as was already known from other studies), but also in children sensitized to grass pollen (a new finding). This last predictor was the strongest one. There was no difference (cetirizine 150/398 (37.7%) versus placebo 151/397 (38.0%)) between the two groups in the total number of children developing asthma. In the active group, however, in the subgroups of children sensitized to grass pollen and/or house dust mite (i.e. 20% of the study population), treatment with cetirizine halved the number of patients developing asthma (respectively 58.8% versus 27.8% and 51.5% versus 28.6%) (Fig. 1).

Different statistical analyses confirmed those findings.

Safety was assessed by physical examination, adverse events recording, blood sampling including hematologic, renal and hepatic parameters (four times during the study) analyzed by a central laboratory (Institut Pasteur de Lille, Lille, France), ECG recorded three times and read by one single cardiologist. The safety profile was similar in the two treatment groups.

Conclusions

In these clinical trials, the groups who seem to respond better to the preventive treatment are those with:

- positive family history of atopy in a first degree relative;
- a personal history of atopic dermatitis;

- elevated IgEs (total or specific against pollen or house dust mite).

Big specific multicenter and well-standardized trials are required in order to confirm and clarify these findings. This preventive approach seems to be very promising. Further work has to be done to better identify the populations at highest risk of developing asthma, including their genetic profile. This would allow true primary prevention even before the onset of atopic dermatitis or allergen sensitization.

Primary prevention in whole populations (e.g. starting even before the onset of atopic dermatitis or allergen sensitization) does not appear today to be a realistic approach.

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