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A prospective study of asthma desensitization in 1,182 children, 592 asthmatic children and 590 nonatopic controls

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Abstract. – *Background:* **The aim of this prospective study was to evaluate the prevalence of allergic asthma and or rhinitis (AR) in 1182 children. Systemic reactions (SRs) to asthma desensitization, previously, specific immunotherapy (SIT) in children with allergic asthma and or AR are scarcely known.**

Materials and Methods: Since 1999, we have consecutively enrolled all children ranging in age from 3 to 11 years attending our Division because affected with severe asthma (592). Controls were 590 nonatopic children matched for age and sex recruited from our outpatient clinic. The study children were treated with a personalized asthma desensitization, the controls were treated with all usual medications. The parents of all children gave their informed consent. Data were analyzed using the X2 method

Results: **The 592 atopic children with severe asthma, 370 males and 222 females, aged 3.5 to 10.5 years, tested positive for Der p and Der f (47.1%) or for pollen allergens (52.9%). We have demonstrated a high increase of ashma incidence, since at the start there were 135 asthmatic children and 215 during 2000, with a 62.5% increase. During 2001 there were 242 children, with a 88.8% increase compared to 1999. All of these children were subjected to asthma desensitization, previously SIT (SARM, Roma). At the third yearly control, the study children had a significantly greater reduction as regards days (p = 0.0001) and nights (p = 0.0005) without asthma and drug usage (p = 0.0003) compared with drug-treated children. The number of SPTs and/or sIgE to inhalants also decreased, spirometry data were also notably improved The clinically adverse events only were mild or transient.**

Discussion: **The positive results obtained in this large study add to its safety in our opinion because the children were followed by their doctors also on the basis of "as frequently as needed". Accordingly, the early onset of childhood asthma emphasizes that an early treatment is the only means to significantly abate the march of atopic asthma. We have documented an unexpected prevalence of pediatric asthma that should by evaluated in light of the very early asthma development in children which is present even before asthma would be diagnosed based on clinical symptoms The causes of this dramatic increment (10.4%/month in the last six months) may be identified chiefly in the worldwide increase in air pollution and secondhand tobacco smoke.**

Key Words:

Pediatric asthma, Asthma desensitazion, SIT reactions, Increased asthma prevalence.

Introduction

Systemic reactions (SRs) to specific immunotherapy (SIT) have been reported since 1911, when this therapy was introduced into clinical practice[1], and subsequently many other reports have discussed the occurrence of such reactions[2-8]. A number of fatalities after SIT have been also rarely reported, since Lamson in 1924 first described a death from anaphylaxis after SIT[9-11]. The prevalence of SRs in adults has been estimated between 5% and 44% for grass SIT[12-14], and between 7 and 50% for mite SIT[4,8,15], whereas at present there are a few data in children[16,17]. According to these studies performed on a small number of children with asthma, SR rate was actually zero using a mite extract[16], and between 80 to 100% using a highly purified and standardized mold extract[17].

Exposure to high levels of allergen during early life might contribute to the rising prevalence of pediatric asthma. Dramatic worldwide variations in asthma prevalence have been found especially of severe forms of asthma, whose frequency was found by us between 62% and 88% according to the year. The aim of this study was to evaluate the results of the desensitization to respiratory al-

lergens in 1182 children with asthma and or rhinitis (AR) and a possible upsurge of such disease. We also discuss the issue of possible reaction during SIT administration.

Materials and Methods

Since 1999, we have consecutively enrolled all children ranging in age from 2.5 to 7.5 years attending our Division because affected with severe asthma. Inclusion criteria were as follows physical examination, positive skin-prick test (SPTs), specific IgE (sIgE) to inhalant allergens, and spirometry. Controls were 590 nonatopic children matched for age and sex recruited from our outpatient clinic. Inclusion criteria were as follows physical examination, positive skin-prick test (SPTs), specific IgE (sIgE) to inhalant allergens, and spirometry. The study children were treated with a personalized asthma desensitization, the controls were treated with all usual medications. The parents of all children gave their informed consent. Data were analyzed using the X2 method The children were observed for 30 minutes following the treatment. Facilities for emergency treatment were at immediate disposal. The doctor had to record on a special chart the date, the administered dose, the type of SR, the time of onset of symptoms, the severity of the SR (score 1-3), its duration and the type of emergency treatment and the outcome.

X2 method was used for the statistical analysis .

Results

The study included 1,182 children. The 592 atopic children with severe asthma, 370 males and 222 females, aged 2.5 to 7.5 years (mean 3.9 years) tested positive for Der p and Der f (47.1%) or for pollen allergens (52.9%). In particular, initially there were 135 such children and 215 during 2000, with a 62.5% increase. During 2001 there were 242 children, with a 88.8% increase compared to 1999 (p = 0.0001) with an increased incidence of pediatric asthma. All of these children were subjected to asthma desensitization, previously SIT (SARM, Roma). The 592 atopic children with severe asthma, 370 males and 222 females, aged 3.5 to 10.5 years, tested positive for Der p and Der f (47.1%) or for pollen allergens (52.9%). All of these children were subjected to asthma desensitization, previously SIT (SARM, Roma). At the third yearly control, the study children had a significantly greater reduction as regards days (p = 0.0001) (Figure 1) and nights (p = 0.0005) (Figure 2) without asthma and drug usage (p = 0.0003) (Figure 3) compared with drug-treated children. The number of SPTs and/or sIgE to inhalants also decreased, spirometry data were also notably improved. We have recorded no SRs but a complete cure in 97% of cases, The clinically adverse events only were mild or transient

Discussion

This study, performed on a large population of children, 85% with allergic asthma and 15% with AR, shows a zero prevalence of SRs to SIT. Asthma desensitization in early life may modify the development of the immune response to allergens We point out that in this study SIT was administered by the prescribing pediatric allergist, and only to some patients by a non-allergist primary practitioner, always supervised by the prescribing Pediatric Allergists, and instructions covering detailed precautions were given. This may have minimized the risk of reactions. The pretty good outcome of the local reactions due to prompt, appropriate treatment strongly indicates that SIT is safe when administered by a well trained physician. Specialists in allergy

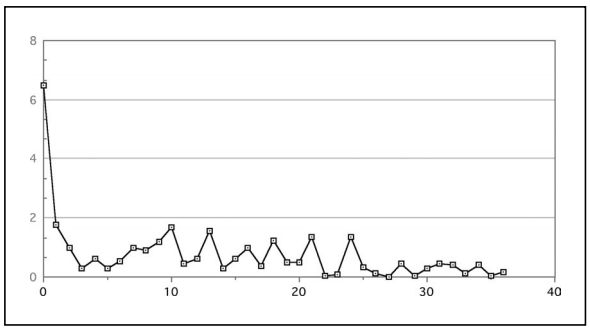

Figure 1. Mean percentage of days with asthma in SIT-treated children.

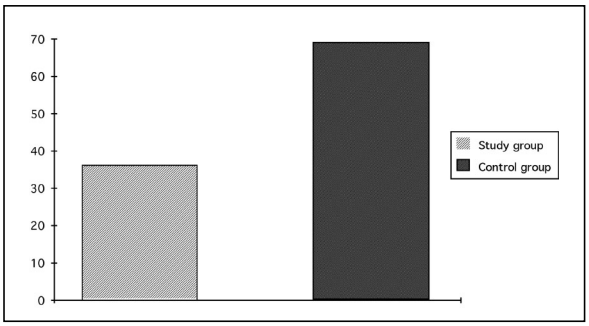

Figure 2. Mean percentage of nights with asthma in 1182 children. Comparison between SIT-treated children and controls. $p = 0.0005$.

are trained to modulate the dose of the allergenic extract according to different situations, such as patient sensitivity, bronchial hyperreactivity, current asthma, severity of symptoms and allergen exposure, thus remarkably reducing the risk of SRs. In addition, they are both trained to recognize the premonitory symptoms of anaphylaxis and to promptly handle anaphylaxis if it occurs.

Several risk factors for SRs have been recently identified: some are related to the patient (symptomatic asthma, recent respiratory infection, bronchial hyperreactivity), whereas others are related to the environment (allergen exposure, such as during the pollen season) or to errors in the administration of SIT: inadvertent errors in dosage, inadvertent intravenous administration, inappropriate dose increase despite recent symptoms or prior SR, switch to a new vial extract, dosing during the allergen season[7,10,11,22]. Although the enrolled children received SIT even during the pollen season when the allergen exposure was maximum, no SRs occurred. In addition, no SR could be associated with allergen exposure in all cases who experienced systemic reactions. Recent respiratory infections and current asthma were exclusion criteria from injections, as well as any other acute affection. Therefore the careful examination of the children each time before injection played a significant role in minimizing the SR prevalence.

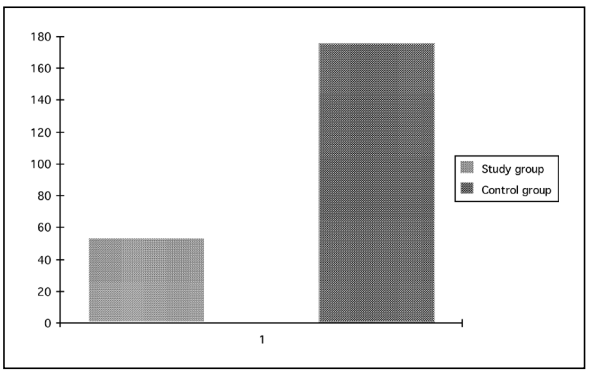

Figure 3. Mean drug usage for asthma attacks in 1182 children. Comparison between SIT-treated children and controls. $p = 0.0003$.

Nevertheless, despite all precautions, SRs may occur at any time in the course of SIT, even when the patient has been receiving the same maintenance dose of extract for years, and even when SIT is appropriately administered[7,10,11,22]. In the present study, local reactions occurred in 37/41 patients (90.2%) with the maintenance dose, previously tolerated, and only in 4/41 patients (9.8%) during dose build-up. In studies in adults, most SRs occurred during dose build-up[4,8]. According to previous surveys[4,11,22], this study shows that mite extract triggered a significant higher number of reactions ($p < 0.0001$) in comparison with pollens extract. Although several studies have demonstrated the relative safety of SIT[18], it is imperative that the occurrence of severe reactions are reduced to a minimum. A retrospective study performed by Lockey et al[10] in the USA showed that over the period 1945-1985 seven deaths to SIT occurred in children. Seventeen fatalities associated with SIT for the years 1985-1989 were reported from members of the American Academy of Allergy and Immunology[22]. Three of the 17 patients who died were children[22]. Onset of anaphylaxis occurred within 30 minutes in all the patients but one[22]. Therefore the risk of fatal reactions appears to be increased in patients with asthma and the risk is further increased when the patient with asthma is steroid-dependent; has required hospital or emergency room visits for treatment; is experiencing increased bronchospasm; or has compromise of another vital system (eg. cardiovascular)[22]. It has been shown by the Committee on Safety of Medicines that 26 deaths due to SIT occurred between 1957 and 1986 in England11 however none in children. These surveys have confirmed the risk factors for SR, previously mentioned. The time of onset of SRs is a matter of great importance, because it defines the

appropriate waiting period in the office following the injection[19,22]. Asthma desensitization is the only one that may modify the natural course of allergic asthma, since it interferes with the underlying immunological mechanism. A such intervention in early life may modify the development of the immune response to allergens. The positive results obtained in this large study add to its safety in our opinion because the children were followed by their doctors also on the basis of "as frequently as needed". Accordingly, the early onset of childhood asthma emphasizes that an early treatment is the only means to significantly abate the march of atopic asthma. The causes of this dramatic increment (10.4%/month in the last six months) may be identified chiefly in the worldwide increase in air pollution and secondhand tobacco smoke. Levine[2] reported that 50% of SRs occurred within 30 minutes following the administration of the extract. In the 63 deaths reported in the USA over 29 years, shock occurred within 20 minutes in 27 cases, between 20 and 30 minutes in 2 cases and after 30 minutes in 4 cases, whereas there was no information available for the other cases[10,22]. The UK Committee on Safety in Medicines recommends that patients remain under medical observation for 2 hours after the administration of SIT[11] because among the 26 reported deaths in adults 76% occurred within 20 minutes; 15% between 20 and 120 minutes; 4% between 2 and 4 hours; and 4% between 6 and 36 hours[11]. The causal relationship between SIT and fatalities becomes less convincing when the onset of symptoms occurs several hours following the injection. The administration of SIT, according to this recommendation, is extremely difficult or even impossible. However, the Executive Committee of the American Academy of Allergy and Clinical Immunology recommends an observation period of 20 minutes[19,21]. This period may be increased for high-risk patients. The Working Group of the International Union of Immunological Societies and the WHO recommended keeping patients under medical observation for 30 minutes[20]. Most of the deaths from anaphylactic shock can be avoided if SIT is administered, or carefully supervised, by a well-trained allergist[7,23]. The prompt availability of equipment and medicine for emergency treatment and physicians skilled in the treatment of anaphylaxis are mandatory for the correct management of SRs[23]. The equipment must be listed and checked every week and the expire date of the medicines should be noted in order to provide for their substitution. The prompt recognition of SRs and the immediate use of epinephrine are the mainstay of management of systemic allergic reactions.

In conclusion, our study indicates that asthma prevalence has a unremitting upsurge, and that SIT has desensitized a great number of asthmatic children. Several studies by ours demonstrate that no immediate reaction occur when SIT is prescribed, and supervised by allergists, and administered only by physicians skilled in the management of anaphylaxis[24-30]. The upsurge in pediatric asthma is dramatized by the recent paper by Pohunek et al[31] demonstrating that even in mild forms of asthma there is eosinophilic inflammation and airway remodelling which occur early in the natural history of pediatric asthma and are present even before asthma would be diagnosed based on clinical symptoms. A such intervention in early life may modify the development of the immune response to allergens. The positive results obtained in this large study add to its safety in our opinion because the children were followed by their doctors also on the basis of "as frequently as needed". Accordingly, the early onset of childhood asthma emphasizes that an early treatment is the only means to significantly abate the march of atopic asthma. The causes of this dramatic increment (10.4%/month in the last six months) may be identified chiefly in the worldwide increase in air pollution and secondhand tobacco smoke.

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