

Efficacy of sublingual specific immunotherapy in intermittent and persistent allergic rhinitis in children: an observational case–control study on 171 patients. The EFESO-children Multicenter Trial

Acquistapace F, Agostinis F, Castella V, Kantar A, Novembre E, Perrone MR, Pietrasanta M, Sambugaro R, Milani M. Efficacy of sublingual specific immunotherapy in intermittent and persistent allergic rhinitis in children: an observational case–control study on 171 patients. The EFESO-children Multicenter Trial. *Pediatr Allergy Immunol* 2009.
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Sublingual-specific immunotherapy (SLIT) is considered as a valid treatment of respiratory allergies. However, there are few data on large sample size regarding its clinical role in 'real life' in term of reduction of symptoms, rescue medications and prevention of asthma in patients suffering from allergic rhinitis (AR) especially in children. We performed a multicenter, case–control study to evaluate the effect of SLIT in children (age 6–18 yr) with intermittent or persistent AR. 171 children (27% girls and 73% boys) with AR due to seasonal or perennial allergens were enrolled in a multicenter case–control study. Cases ($n = 90$) were defined as patients with intermittent (64%) or persistent (36%) AR who were treated for at least two consecutive years with specific SLIT with the related allergen extracts (SLITone[®] ALK-Abellò). Controls ($n = 81$) were defined as sex-age- and type of allergen matched AR children who were never treated with specific immunotherapy and had no asthmatic symptoms at the beginning of observation period. Main outcomes of the study were the rhinoconjunctivitis symptom score (SS) (sneezing, rhinorrhea, nasal itch, congestion, ocular itch and watery eyes) with a ranging scale from 0 (= no symptoms) to 3 (= severe symptoms) and the medication score (MS) evaluating symptomatic drug intake (antihistamine and inhaled corticosteroids). SS and MS were evaluated at the end of the observational period in relation with the period, considering the last 12 months, in which patients suffered the highest symptoms levels (i.e., peak of relevant pollen season (seasonal AR) or during the period of maximum allergen exposure in case of perennial AR). Secondary outcome of the study was the development of asthma symptoms during the observation period. SS (mean \pm SD) was 4.5 ± 2.5 in cases and 9.0 ± 3.0 in controls (-50%) ($p = 0.0001$). MS (mean \pm SD) was 2.5 ± 1.9 and 3.6 ± 2.1 in the case and control groups, respectively (-31%) ($p = 0.0001$). At the end of the observation period asthma symptoms were present in 14 subjects in the case group (15%) and in 20 children (24%) in the control group ($p = 0.13$). New skin sensitizations appeared in 6% of cases ($n = 2$) and in 36% ($n = 12$) of the controls ($p = 0.001$). The EFESO trial shows that a 2-yr once daily SLIT treatment in children with intermittent or persistent AR is associated with lower symptom and medication scores in comparison with subjects treated with symptomatic drugs only.

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Key words: sublingual immunotherapy; pediatric patient; allergic rhinitis; case–control trial; asthma prevention

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Accepted 12 January 2009

Sublingual-specific immunotherapy (SLIT) is considered as a valid treatment of respiratory allergies (1). SLIT is safer and easier to administer than subcutaneous immunotherapy, and might be an equally efficacious alternative (2, 3). Randomized control trials (4, 5) and meta-analyses (6) have evaluated the efficacy of SLIT showing that it could reduce symptoms and symptomatic drug consumption in subjects with allergic rhinitis and or asthma (7, 8). However there is little clinical data evaluating the effectiveness of SLIT, i.e., its clinical role in 'real life' in term of reduction of symptoms, rescue medications, prevention of asthma particularly in pediatric patients suffering from allergic rhinitis (AR) (9). We therefore performed a multicenter, case-control cross-sectional study to evaluate the effectiveness of SLIT in children with seasonal or perennial AR in comparison with symptomatic drugs treatment only.

Methods

Patients

A total of 171 children with diagnosis of allergic rhinitis, both intermittent and persistent, according to ARIA guidelines (1), were enrolled in a case-control cross-sectional multicenter trial. Cases ($n = 90$) (mean age 12 ± 3 yr, 73% male) were defined as patients with intermittent (64%) (allergy to grass, ragweed or trees) or persistent (36%) (allergy to house dust mite, cat or dog and/or Parietaria) AR who had been treated for at least two consecutive years (one vial daily) with specific SLIT with the related allergen extracts (*SLITone*[®]; ALK-Abellò, Lainate, Italy). Controls ($n = 81$) (mean age: 11 ± 2 yr) were defined as sex-age- and type of allergen matched AR subjects who had never been treated with specific immunotherapy. In addition, both cases and controls had no asthmatic symptoms at the beginning of observation period.

Study design

This study was set up as an observational case-control cross-sectional multicenter trial. The trial involved eight Pediatric Allergy Units in Italy. The study was approved by the Institutional review board at each center and complied with the provision of the Declaration of Helsinki, Good Clinical Practice guidelines and local law and regulations. Parents of participants provided written informed consent.

Study outcomes

The main outcomes of the study were the 6-item rhinoconjunctivitis symptom score (SS) (sneezing, rhinorrhea, nasal itch, congestion, ocular itch and watery eyes) with a ranging scale from 0 (=no symptoms) to 3 (=severe symptoms) and the medication score (MS) evaluating symptomatic drug intake (antihistamine and inhaled corticosteroids). SS was evaluated according to WAO and EAACI guidelines (10). MS was calculated according to Valovirta et al. (11). SS and MS were evaluated at the end of the observational period in relation with the period, taking in consideration the last 12 months, in which patients suffered the highest symptoms levels (i.e. peak of relevant pollen season in case of seasonal AR or during the period of maximum allergen exposure in case of perennial AR). Seasonal allergies were defined as allergies toward: grass, trees or ragweed. Perennial allergies were defined as allergies toward house dust mite, pets and parietaria (due to its very long pollen season). The secondary outcome of the study was the development of asthma symptoms during the observation period and the developing of new sensitizations. The presence of asthma was evaluated using the ISAAC 'questionnaire (12) performing the following question at the end of the observational period: 'Have you had wheezing or whistling in the chest in the last 12 months?' New sensitizations (one or more) were evaluated performing a standard 10-allergen SPT test at the end of the observational period and comparing historical data for each patient evaluated.

Statistical analysis and sample size calculation

The study protocol and the statistical analysis plan specified that comparison of symptoms and MSs between cases and controls as to be considered as the primary efficacy outcome of the trial. The Power calculation assumed a difference between cases (subjects treated with SIT) and control (subject treated with symptomatic drugs only) in the SS of at least -2.4 ± 3.4 with an effect size of 0.7. This assumption provided a 95% power at an alpha level of 0.01 for a sample size of at least 80 evaluable patients per group. Analysis was performed using SPSS statistical package Version 13, Chicago, Illinois, USA. The Shapiro-Wilk test was used to evaluate the normal distribution of continuous variables (symptom and MSs). The Mann-Whitney test was utilized to compare SS and MS between cases and control. The chi-square test was used for categorical

variables such as frequency of asthma cases and new sensitizations between cases and controls.

Results

Between March 2006 and December 2007, 171 pediatric patients were enrolled in the EFESO trial. A total of 90 subjects represented the cases group and 81 subjects the control group. Table 1 shows the main demographic and clinical characteristics of the case and control subjects enrolled in the study. The two populations were comparable according to a matched case-control study design. In particular age, sex distribution, type of AR and polysensitized patients were equally distributed in the two groups.

Symptom score

In the study population as a whole, SS was 4.5 ± 2.5 and 9.0 ± 3.3 in cases and controls, respectively (-50%) (Fig 1). The absolute difference was 4.5 (95% CI of the difference: from 3.5 to 5.5). This difference was statistically significant (Mann-Whitney test; $p = 0.0001$).

Medication score

In the study population as a whole, MS was 2.5 ± 1.9 and 3.6 ± 2.1 in the cases and control groups, respectively (-31%) (Fig 2). The absolute difference was 1.1 (95% CI of the difference: from 0.5 to 1.8). This difference was statistically significant (Mann-Whitney test; $p = 0.0001$).

Development of asthma

At the end of the observation period, asthma symptoms were present in 15% of cases and in 24% in the control group ($p = 0.13$).

Development of new sensitization in monosensitive patients

At the beginning of the observation period 36 subjects in the cases group (40%) and 34 in the

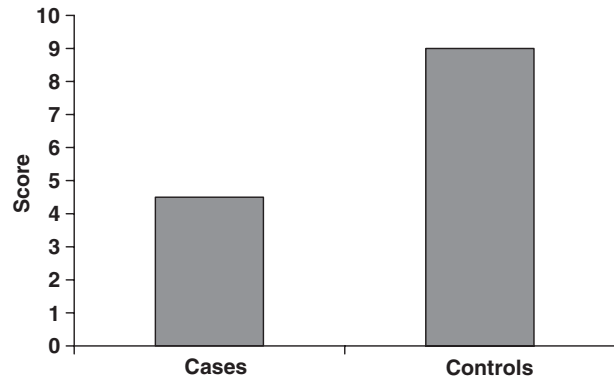


Fig. 1. Symptom score in cases (n = 90) and controls (n = 81). $p = 0.0001$; cases vs. controls; Mann-Whitney test.

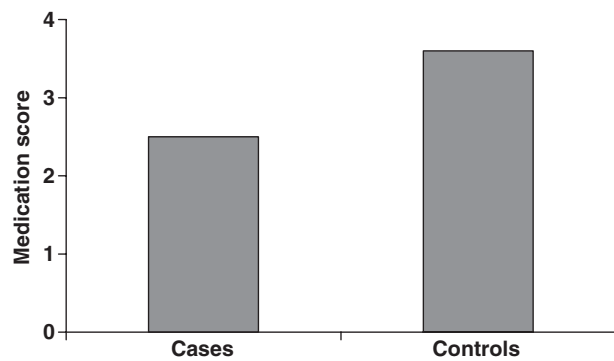


Fig. 2. Medication score in cases (n = 90) and controls (n = 81). $p = 0.0001$; cases vs. controls; Mann-Whitney test.

control group (42%) were monosensitized patients. At the end of the observation period 34 subjects (94%) in the cases group remained monosensitized in comparison with only 22 (64%) patients in the control group ($p = 0.001$). Therefore, new skin sensitizations appeared in 6% of cases (n = 2) and in 36% (n = 12) of the controls.

Discussion

Randomized controlled trials (RCT) have shown that SLIT is an effective treatment in patients suffering from allergic respiratory diseases such as AR and allergic asthma (13, 14). The efficacy of SLIT has been confirmed also by several meta-analyses (4, 5, 15). SLIT is able to reduce symptoms and symptomatic drug consumption (4). However, there is little data evaluating the effectiveness of SLIT, i.e., its clinical role in 'real life' in term of reduction of symptoms, rescue medications, prevention of asthma particularly in pediatric patients

Table 1. Demographic and clinic characteristics of cases and controls

	Cases n = 90	Controls n = 81
Age (years), mean (SD)	11 (3)	12 (3)
Boys/girls	65/25	59/22
Mild allergic rhinitis (%)	44	52
Mild-severe allergic rhinitis (%)	56	48
Seasonal allergic rhinitis (%)	54	53
Perennial allergic rhinitis (%)	46	45
Monosensitive patients (%)	40	42
Polysensitive patients (%)	60	58

suffering from AR. Our trial has shown that sublingual immunotherapy in pediatric patients with AR significantly improved clinical outcome (less symptoms and less medication intake) in comparison with children treated with symptomatic drugs only. Some limitation should be taken into account when considering the result of our study. In particular the EFESO trial is a case-control cross sectional study. Double-blind RCT have often been considered as the reference standard for evaluating the efficacy of therapeutic and preventive interventions (16). However, RCT are addressed to evaluate the efficacy, instead of the effectiveness, of a particular treatment strategy (17). In some circumstances the clinical results from RCT could have a low generalization (so called external validity) regarding the applicability of the data obtained in the everyday unselected patient population (18). This is of particular relevance if respiratory allergies and the effect of SIT are to be considered. The main clinical effects of SIT are in general obtained in the long-term (19). Compliance to the treatment could be a crucial aspect (20). In such circumstances a more practical approach, i.e., studies evaluating the effectiveness of treatment, could be more appropriate. Observational non-randomized studies have a role when RCT are not available, and, even when RCT are available, to quantify effectiveness and other real world experiences. It is in general considered that non-randomized studies overestimate the benefits of treatment. However some authors, performing meta-analyses of randomized trials and meta-analyses of observational studies for the same topics, concluded that well-designed observational studies do not overestimate effects of treatment compared with randomized trials (21). The main objective of the EFESO-children trial was to assess the clinical effectiveness of SLIT in an unselected population of pediatric subjects with AR treated or not with SLIT. Some researches have stated that observational studies can provide the same answers as RCT if their biases and other limitations are understood and, where possible, overcome (22). Therefore, when performing a case-control study a crucial methodological aspect is to enroll two groups with high comparability regarding all the potential confounding variables in order to reduce potential selection bias. If pre-treatment characteristics of the patients in the treated group (i.e., cases) and untreated groups (i.e., controls) are properly balanced the results of observational studies showing a beneficial effect of therapy are more convincing (23). Cases and control subjects

enrolled in the EFESO trial were comparable for all the clinical and demographic characteristics considered. In addition, another relevant potential bias could be associated to the fact that the EFESO trial was an open study. Therefore in assessing the primary outcome (i.e., symptoms) it is not possible to rule out the tendency of the investigator to overestimate (or underestimate) the clinical effect of SLIT. However the evaluation of SS was measured addressing specific questions to the patient, operating therefore in a 'single-blind' condition. Furthermore, the study was conducted in 8 centers. The tendency and the direction of the effects of SLIT on symptom and MS resulted quite similar in all the participating centers. Furthermore, in both cases and controls we have observed a similar behavior regarding SS in seasonal AR patients in comparison with perennial AR subjects (data not shown), thus supporting the consistency of the SS measurements. The other primary outcome of the EFESO trial was the MS which was evaluated using objective data (clinical and medical records). We did not find a significant difference in asthma development between children treated or not with SIT in this study. However, we found a lower incidence of new asthma development in the case group (15% vs. 24%; a 38% reduction) in comparison with control. Asthma development was a secondary endpoint of the EFESO study. Therefore the sample size was calculated in relation with the primary endpoint (i.e., symptoms and MS). Probably a larger sample size (i.e., more than 600 patients in total) or a longer follow-up observational period should have been needed to find a significant difference between SLIT treated children and controls for this clinical end-point. In the Novembre trial (24), a 3-yr SLIT treatment in allergic children was associated with a 57% relative reduction in the risk to develop asthma in comparison with controls with an incidence of asthma in SLIT treated children of 17%, similar to the incidence we observed in cases group (15%) in our study. In conclusion, the EFESO trial shows that a 2-yr SLIT treatment in children with seasonal or perennial AR is associated with lower symptom and MSs in comparison with allergic children treated with symptomatic drugs only. SLIT is also associated with a significant lower incidence of new skin sensitizations in comparison with allergic patients not treated with SIT. Our data reinforces the concept that specific immunotherapy could be considered a causal treatment of respiratory allergies.

Acknowledgments

This study was funded by ALK-Abellò Italy. MM is an employee of ALK-Abellò. MM was involved in the study protocol writing and logistic of the trial. He was not involved in data management and analysis.

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