

BRIEF REPORT

Observational study of sublingual specific immunotherapy in persistent and intermittent allergic rhinitis: the EFESO trial

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ABSTRACT

Background: Sublingual specific immunotherapy (SLIT) is a valid treatment for allergies. However, there are few data on a large sample size regarding its clinical role in 'real life'.

Study aim: We performed a multicentre, case-control study to evaluate the effectiveness of SLIT in patients with allergic rhinitis (AR).

Methods: A total of 305 patients with AR were enrolled. Cases ($n=154$) were defined as patients with intermittent (64%) or persistent (36%) AR who were treated daily for at least two consecutive years with specific SLIT. Controls ($n=151$) were defined as age-, sex- and type of allergen-matched AR subjects who were never treated with specific immunotherapy. The main outcomes of the study were the rhinoconjunctivitis symptom score (SS) and the symptomatic medication score (MS). SS and MS were evaluated

at the end of the observational period in relation to the peak of relevant pollen season or during the period of maximum allergen exposure in case of non-seasonal allergens.

Results: SS mean (SD) value was 5.1 (3.0) in cases and 9.3 (3.3) in controls (-43%) ($p=0.0001$). MS mean (SD) value was 2.6 (1.8) and 4.4 (2.6) in the case and control groups, respectively (-41%) ($p=0.0001$). At the end of the observation period, asthma-related symptoms were present in 8.5% of cases and in 20% in the control group ($p=0.01$).

Conclusion: The Efficacia nella rinite allergica di SLITOne (EFESO) trial shows that SLIT treatment in AR is associated with lower SS and MS in comparison with controls. SLIT is also associated with a lower incidence of asthma and new sensitizations. As this was an observational study, our results need to be confirmed in randomized, double-blind, controlled trials.

Introduction

Sublingual specific immunotherapy (SLIT) is considered a valid treatment for respiratory allergies¹. SLIT is safer and easier to use than subcutaneous immunotherapy, and might be an equally efficacious alternative². Randomized controlled trials (RCTs)³ and meta-analyses⁴ have evaluated the efficacy of SLIT showing that it could reduce symptoms and symptomatic drug use in subjects with allergic rhinitis

and/or asthma⁵. However, there are few data on a large sample size evaluating the effectiveness of SLIT, i.e. its clinical role in 'real life' in terms of reduction of symptoms, rescue medications, prevention of asthma and new sensitization in patients suffering from allergic rhinitis (AR)⁶. We therefore performed a multicentre, case-control, cross-sectional study to evaluate the effectiveness of SLIT in patients with persistent or intermittent AR in comparison with symptomatic drugs treatment approach only.

Methods

Patients

A total of 305 patients with diagnosis of AR (persistent or intermittent), according to ARIA guidelines¹, were enrolled in a case-control cross-sectional multicentre trial. Cases ($n = 154$) (mean age 21 years, 48% male) were defined as patients with intermittent (64%) or persistent (36%) AR who had been treated for at least 2 consecutive years (one vial daily) with specific SLIT with the related allergen extracts (SLITone)* Controls ($n = 151$) were defined as age-, sex- and type of allergen-matched AR subjects who had never been treated with specific immunotherapy. No symptoms of asthma were to have been present at the beginning of observation period. An additional inclusion criterion of EFESO study protocol stated that all patients (both cases and controls) should not have been treated in the past with specific immunotherapy.

Study design

This study was set up as an observational case-control cross-sectional multicentre trial. The trial involved 16 allergy clinic centres in Italy. The study was approved by the institutional review board at each centre and complied with the provision of the Declaration of Helsinki, good clinical practice guidelines and local law and regulations. All the participants provided written informed consent to participate in the trial.

Study outcomes

The main outcomes of the study were the six-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) for each symptom (the maximum SS was therefore 18) and the medication score (MS) evaluating symptomatic drug intake (antihistamine, nasal corticosteroids, inhaled corticosteroid, oral corticosteroid and β_2 bronchodilators) according to the following score: 0 = no use, 1: use 'as rescue' or 'as needed' medication; 2: use for less than 20 days; 3: use for more than 20 days during the pollen season or during the worst part of the year in relation with the type of allergy (the maximum MS was therefore 15). No patients (either in the control or the case groups) were treated with cromones or nasal antihistamines, as these drugs are not routinely prescribed by Italian allergologists. SS was evaluated according to World Allergy Organization (WAO) and European Academy of Allergy and Clinical Immunology (EAACI) guidelines⁷.

*SLITone is a registered product of ALK-Abellø

Medication score was calculated according to the method of Valovirta *et al.*⁸. SS and MS were evaluated at the end of the observational period in relation to the peak of relevant pollen season (pollen season 2007) or during the period of maximum allergen exposure in case of non-seasonal allergens. 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 International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire⁹ asking 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 ten-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 medication scores between cases and controls should be considered to be the primary efficacy outcomes of the trial. Power calculation assumed a difference between cases (subjects treated with SLIT) and control (subject treated with symptomatic drugs only) in the symptom score of at least -2.4 ± 3.4 with an effect size of 0.7. This assumption provided 90% power at an alpha level of 0.05 for a sample size of at least 120 evaluable patients per group. Analysis was performed using SPSS statistical package Version 13. The Shapiro-Wilk test was used to evaluate the normal distribution of continuous variables (symptom and medication scores). 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 use of symptomatic drugs, frequency of asthma cases and new sensitizations between cases and controls. Multiple logistic regression was used to examine the association between the development of asthma or new sensitizations with the following independent variables: age, sex, type of AR, severity of rhinitis (mild or moderate/severe), use of SLIT or symptomatic drugs only. Values are presented as mean (SD).

Results

Between March 2006 and December 2007, 305 patients were enrolled in the EFESO trial. A total of

154 subjects represented the cases group and 151 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, duration of allergy symptoms and type of AR and polysensitized patients were equally distributed in the two groups. However, a higher percentage of moderate-severe AR was observed in the cases in comparison with controls (56 vs. 48%), even if this difference was not statistically significant. The Table 2 summarizes the main results.

Symptom score

In the study population as a whole, SS mean value (SD) was 5.1 (3.0) and 9.3 (3.3) in cases and controls, respectively (-43%). The absolute difference was 4.2 (95% CI of the difference: from 3.4 to 4.8). This difference was statistically significant (Mann-Whitney test;

$p=0.0001$). The mean (SD) value of SS in the cases group was 5.4 (3.1) and 4.3 (2.7) for patients with intermittent and persistent AR, respectively. This difference was statistically significant ($p=0.039$). In the control group SS mean (SD) value in intermittent and persistent AR patients was 9.5 (3.3) and 8.0 (3.1), respectively. Again this difference was statistically significant ($p=0.024$). Taking into account the aetiology of AR, patients treated with SLIT showed a SS lower by 43% in intermittent and lower by 46% in persistent AR, respectively, in comparison with controls.

Medication score

In the study population as a whole, MS mean (SD) values were 2.6 (1.8) and 4.4 (2.0) in the cases and control groups, respectively (-41%). The absolute difference was 1.8 (95% CI of the difference: from 1.4 to 2.2). This difference was statistically significant (Mann-Whitney test; $p=0.0001$). In the cases, MS mean (SD) values in subjects with intermittent AR were 2.7 (1.9) and 2.0 (1.4) in patients with persistent AR. In the control group, MS mean (SD) values in subjects with intermittent and persistent AR were 4.4 (2.6) and 4.6 (2.9), respectively. Taking into account the aetiology of AR, patients treated with SLIT showed a MS lower by 39% for intermittent AR and lower by 57% for persistent AR when compared with controls. In addition, the percentage of patients with a $MS \geq 2$ (i.e., use for less than 20 days or use for more than 20 days during the period of maximum allergen load) for antihistamine drugs, nasal corticosteroids and inhaled corticosteroid and/or β_2 -agonists were significantly higher in controls in comparison with the cases. (Table 3).

Development of asthma-related symptoms

At the end of the observation period, asthma-related symptoms were present in 8.5% of cases and in 20% of the control group ($p=0.01$). All these patients were also under treatment with inhaled corticosteroids

Table 1. Demographic and clinical characteristics of cases and controls

	Cases <i>n</i> = 154	Controls <i>n</i> = 151
Age, years mean (SD)	22	23
Men/women	74/80	71/80
History of allergy, years, mean (SD)	14 (5)	15 (6)
Symptom score at the beginning, mean (SD)	7.6 (3.9)	7.2 (3.8)
Mild allergic rhinitis, <i>n</i> (%)	68 (44)	79 (52)
Moderated-severe allergic rhinitis, %	86 (56)	72 (48)
Intermittent allergic rhinitis, <i>n</i> (%)	98 (64)	95 (63)
Persistent allergic rhinitis, <i>n</i> (%)	56 (36)	56 (37)
Monosensitive patients, <i>n</i> (%)	66 (43)	62 (41)
Polysensitive patients, <i>n</i> (%)	88 (57)	89 (59)

Table 2. Main outcome results

		Cases	Controls	<i>p</i> -value (cases vs. controls)
Total population (cases = 154; controls = 151)	Symptom score, mean (SD)	5.1 (3)	9.3 (3.3)	0.0001
	Medication score, mean (SD)	2.6 (1.8)	4.4 (2.0)	0.0001
Intermittent AR (cases = 98; controls = 95)	Symptom score, mean (SD)	5.4 (3.1)	9.5 (3.3)	0.001
	Medication score, mean (SD)	2.7 (1.9)	4.4 (2.6)	0.001
Persistent AR (cases = 56; controls = 56)	Symptom score, mean (SD)	4.3 (2.7)	8.0 (3.1)	0.01
	Medication score, mean (SD)	2.0 (1.4)	4.6 (2.9)	0.01

Table 3. Percentage of patients with a medication score ≥ 2 (i.e., use for less than 20 days or use for more than 20 days during the period of maximum allergen load)

	Cases (154)	Controls (151)	p-value (chi-square test)
Antihistamine drugs	34%	76%	0.00001
Nasal corticosteroids	20%	45%	0.0001
Inhaled corticosteroid and/or β_2 -agonist	7%	19%	0.0029

and/or bronchodilators. In the multiple logistic regression analysis, development of asthma-related symptoms was significantly ($p=0.04$) associated only with type of treatment (symptomatic drugs only vs. SLIT), not with age, sex, severity of rhinitis and type of rhinitis.

New sensitizations

At the beginning of the observation period 66 subjects in the cases group (43%) and 62 in the control group (45%) were monosensitized patients. At the end of the observation period 63 subjects (95%) in the cases group were continuously monosensitized in comparison with 40 (64%) patients in the control group ($p=0.0001$). Therefore new skin sensitizations appeared in 5% of cases ($n=3$) and in 36% ($n=28$) of the controls. In the multiple logistic regression analysis, development of new sensitizations was significantly ($p=0.001$) associated only with type of treatment (symptomatic drugs only vs. SLIT), not with age, sex, severity of rhinitis and type of rhinitis.

Discussion

Randomized controlled trials have shown that SLIT is an effective treatment in patients suffering from allergic respiratory diseases such as allergic rhinitis and allergic asthma¹⁰. The efficacy of SLIT has also been confirmed by several meta-analyses^{4,5,11}. SLIT is able to reduce symptoms and symptomatic drug use¹². However, data regarding the efficacy of SLIT in the prevention of asthma and/or new sensitizations, coming from double-blind RCTs, is still lacking. Our trial has shown that sublingual immunotherapy in patients with allergic rhinitis is associated with a significantly better clinical outcome (less symptoms and less medication intake) in comparison with patients treated with symptomatic drugs alone. Furthermore, SLIT is associated with a significantly lower incidence of asthma comparison and the development of new sensitizations.

Some limitations should be taken into account when considering the results of the current study. In particular, the EFESO trial is a case-control cross-sectional study, whereas double-blind RCTs have often been considered to be the reference standard for evaluating the efficacy of therapeutic and preventive interventions¹³. However, RCTs are designed to evaluate the efficacy, rather than the effectiveness, of a particular treatment strategy¹⁴. In some circumstances the clinical results from RCTs could have a low generalization (so-called external validity) regarding the applicability of the data obtained in the everyday unselected patient population¹⁵. This is of particular relevance if respiratory allergies and the effect of SLIT are to be considered. The main clinical effects of SLIT are, in general, obtained in the long-term¹⁶. Compliance with the treatment could be a crucial aspect¹⁷. 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 RCTs are not available and when RCT are available to quantify effectiveness and other real-world experiences. It is generally 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 trials¹⁸. The main objective of the EFESO trial was to assess the clinical effectiveness of SLIT in an unselected population of subjects with allergic rhinitis treated or not with SLIT. Some researchers have stated that observational studies can provide the same answers as RCT if their biases and other limitations are understood and, where possible, overcome¹⁹. Therefore, when performing a case-control study a crucial methodological step is to enrol 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 almost identical the results of observational studies showing a beneficial effect of therapy are more convincing²⁰. 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 with 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. In fact both cases and controls were in a condition in which the treatment strategy chosen (symptomatic drugs only or SLIT) could be considered as a best treatment approach. Therefore it is unlikely that controls tended to overestimate the seriousness of their symptoms in comparison with cases.

In addition, the study was conducted in 16 centres. The magnitude of the effects of SLIT treatment on symptom and medication scores was comparable across all the centres. Furthermore, in both cases and controls we have observed a similar pattern regarding symptom score in intermittent AR patients in comparison with persistent AR subjects, 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). Another limitation of the EFESO trial is that no data were available for symptomatic medication use at the beginning of the observation period. Therefore it was not possible to calculate a basal MS. However, the EFESO inclusion criteria were that patients, both case and controls, should have been matched for AR severity and without asthmatic symptoms at the beginning of the observation period, so it is quite impossible that the MS at the beginning could have been different between the two groups. In the EFESO trial, we did not collect data regarding safety and tolerability of drug treatment regimens (symptomatic drugs and/or SLIT). SLIT, however, is considered very well-tolerated with side-effects being very uncommon. In patients with AR, no cases of anaphylaxis have been so far described during SLIT treatment²¹. A relevant clinical result of our study was the lower incidence of new asthma and new sensitizations development observed in SLIT-treated patients. However, these results should be considered and evaluated with caution, because these were secondary endpoints of our trial, and therefore, the sample size was not appropriately powered to detect these differences. In addition, the evaluation of the presence of asthma in the EFESO trial was performed using the ISAAC questionnaire and not using more objective diagnostic tools such as spirometry or metacholine bronchial reactivity test. This fact should lead to the conclusion that in our study SLIT could be associated with a lower incidence of wheezing in the last 12 months rather than a true reduction in the incidence of asthma. However, the ISAAC study considered the presence of wheezing as a sign of asthma. Furthermore, all the patients referring to wheezing were also under concomitant treatment with antiasthmatic drugs (inhaled corticosteroid and β_2 -agonist drugs). This aspect lends further support to the diagnosis of asthma.

Conclusion

The EFESO trial shows that a 2-year SLIT treatment in subjects with intermittent and persistent AR is associated with lower symptom and medication scores in comparison with subjects treated with symptomatic drugs only. SLIT treatment is also associated with a lower incidence of development of asthma-related symptoms, such as wheezing, and new sensitizations at the end of the observational period in comparison with allergic patients not treated with SLIT. This data reinforces the concept that specific immunotherapy could be considered a causal treatment of respiratory allergies. The EFESO results could also be useful in evaluating and calculating the sample size needed for the patients to be enrolled in forthcoming studies. According to the nature of this observational, non-randomized case-control study, however the results of the EFESO study should be confirmed in future trials adopting a randomized, double-blind, controlled design.

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