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Clinical relevance of non-grass pollens respiratory allergies in Italy and effects of specific sublingual immunotherapy: The Rainbow Trial, a multicentre 3-year prospective observational study

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Key words

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Summary

Objective: *We evaluated, by means of a multicentre, prospective observational trial, the severity in term of symptoms and symptomatic drugs use and the presence of asthma in subjects with tree or cypress or olive, or ragweed or parietaria allergy and we evaluated also the efficacy of a consecutive 2-year specific sublingual immunotherapy treatment.* ***Patients and Methods:*** *Consecutive patients suffering of respiratory allergies (rhinoconjunctivitis and/or mild moderate asthma) due to one of the described allergens were enrolled. During the specific relevant pollen seasons for each allergens nose and eye symptoms and medication scores (SS and MS) were evaluated. Global score (GS) was calculated as the sum of SS and MS. An Asthma symptom score if present, were also, calculated. A total of 162 patients were enrolled in 14 Italian Allergic Clinics .Patients were treated with the relevant specific sublingual immunotherapy (SLITOne, ALK) for two consecutive pollen seasons.* ***Results:*** *At baseline prevalence of allergies was the following: tree 18% (30 patients); ragweed 14% (23 patients); olive 7% (11 patients); cypress 7% (12 patients) and pellitory 53% (86 patients). At baseline asthma was detected in 65 patients (40%). Asthma was more common in polisensitive subjects in comparison with mono-sensitive (51% vs. 30%). According to allergen type, asthma was present in 47% of pellitory allergic patients, in 45% of olive allergic subjects, in 38% of ragweed allergic patients, in 26% of tree allergic patients and only in 9% of cypress allergic subjects. In pellitory, olive and ragweed allergic patients the frequency of asthma was statistically significant (P=0.0055) higher in comparison with other groups. At baseline GS mean (SD) in the whole population was 17(7). GS during the following 2 consecutive seasons with SLIT treatment decreased significantly (P=0.0001) to 9 (5) and to 7 (5), respectively (a reduction of 59% in comparison with baseline). In patients with asthma the mean clinical score decreased significantly from baseline value of 2.7 to 0.3 at the end of the observation period. No serious adverse events were reported. Local side effects, mainly oral itching, were reported by 14% of patients and were mild and transient in nature.* ***Conclusion:*** *In this population pellitory, olive and ragweed allergies are associated with a more severe clinical picture in comparison with tree and cypress allergy. A two-year SLIT treatment was associated with a significant reduction in SS, MS, GS and asthma score in comparison with baseline. SLIT was also safe and well tolerated.*

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Introduction

In addition to grass allergy, several pollen sensitizations such as tree, olive, cypress, ragweed and pellitory are quite common in Mediterranean area (1). Specific geographical distribution of these allergens is also well known. Furthermore, these allergens are commonly the cause of respiratory allergic clinical manifestations such as rhinitis and asthma (2). So far the are few data regarding the clinical impact of these allergies in term of symptoms and risk of asthma. In patients with seasonal allergens induced respiratory allergies, such as allergic rhinitis and allergic asthma, sublingual immunotherapy (SLIT) is considered clinically effective (3). However there are no many studies that support the clinical efficacy (especially in the mid-term) of specific sublingual immunotherapy in the treatment of seasonal non-grass allergies such as, trees, ragweed olive, cypressus and pellitory (4).

Study Aim

We evaluated, by means of a multicentre, prospective 3-consecutive pollen seasons observational trial, the severity in term of symptoms and symptomatic drugs use and the presence of asthma in subjects with tree, cypress or olive, or ragweed or pellitory allergy. We also evaluated the clinical efficacy of specific sublingual immunotherapy (SLIT) in term of symptoms, medication and clinical global score during a treatment for 2-consecutive pollen seasons.

Study Design

This study was set up as an observational prospective multicenter trial. The trial involved a total of 14 Allergy Units in Italy. Six Centres were located in the North, 5 in the Centre and 3 in the South Regions of the country. 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. Participants provided oral informed consent.

Subjects and Methods

Consecutive patients suffering from respiratory allergies due to one of the following seasonal allergens: tree (Betula, Alnus and Corylus); olive (Olea *europea*) ; cypress (Cupressus *arizonica*); ragweed (Ambrosia *artemisifoli*a) or pellitory (Parietaria *judaica*) were enrolled in 14 Italian Allergic Clinics.

Patients selection

Main eligibility criteria were as follows: men or women 10–65 years of age with at least 2 years' clinical history of allergic rhino-conjunctivitis and/or mild-to-moderate asthma (according to ARIA (5) and GINA guidelines (6), respectively) with respiratory symptoms suggestive of the relevant allergen exposure (i.e. symptoms in February-March for tree allergy, April-May-June for cypress allergy, June-July for Olive allergy, September-August for ragweed, March-July for pellitory allergy, according also to the geographical location); a positive skin prick test against the relevant allergen extract (SPT; ALK-Abellò) with a wheal diameter >3 mm; specific IgE against the relevant allergen, (IgE class ≥2); no clinical history of chronic sinusitis or allergic rhinitis and/or asthma because of allergens such as house dust mite or Alternaria *alternata*; no clinical history of severe asthma (Global Initiative for Asthma 2002 step 4 and FEV1 <80% of expected value after treatment with inhaled corticosteroids and short-acting beta 2-agonists); and no previous treatment by allergen-specific immunotherapy within the previous 5 years. Pregnancy was an exclusion criterion. After the baseline evaluation, patients were assigned to SLIT treatment with the relevant allergen extract (SLITOne®, ALK-Abellò, Denmark) one vial per day without up-dosing for 2 consecutive years (dosage regimen: 5 to 7 time per week).

Study Outcomes

The main outcomes of the study were the 6-item rhinoconjunctivitis symptom score (SS) (sneezing, rhinorrea, 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 (7). During the relevant pollen season symptom and medication scores (SS and MS) were evaluated. Global score (GS) was also calculated as the sum of SS and MS. Asthma symptoms score (cough, wheezing, dyspnea; with a ranging scale from 0 (=no symptoms) to 3 (=severe symptoms), if present, were also, calculated. A to-

tal of 162 patients were enrolled. SS, MS were measured during relevant pollen seasons for 3 consecutive years (baseline and after 1 and 2 years of SLIT treatment).

Statistical Analysis

The study protocol and the statistical analysis plan specified that comparison of symptoms and medication score between baseline and end of the observation period as to be considered as the primary efficacy outcome of the trial. 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 (SS, MS and GS). The Wilcoxon test was utilized to compare SS, MS and GS between different times of evaluation (baseline vs. first year of SLIT treatment and vs. end of the study evaluation period). The chi-square test was used for categorical variables such as frequency of asthma. According to the design of the trial (prospective observational study) a formal sample size calculation was not performed. However the aim of the trial was to enrol at least 150 allergic patients in order to have a representative sample of these kinds of non grass seasonal allergies. For missing data the LOCF method (Last Observation Carried forward) was used.

Results

The study started in January 2007 and was concluded in June 2010. A total of 162 non-grass pollen-allergic subjects (78 men and 84 women) were enrolled; the mean (SD) age was 31 (13) years. Table 1 describes the main demographic and clinical variables of the study population. Mono-sensitive patients were 54% (87 out of 162) and poli-sentitive 46% (75 out of 162). Allergic rhinitis was classified as moderate-severe in 68% of the patients (110 patients out of 162). At baseline poli-sensitive patients tended to have a more severe clinical manifestation pattern in comparison with mono-sensitive subjects. SS was 13±5 in poli-sensitive subjects and 11.5±5 in mono-sensitive patients but this difference was of borderline significance (P=0.07 Mann-Whitney test). No differences were observed in the medication score between mono and poli-sensitive patients. Distribution of allergies was the following: tree 17% of population; ragweed 17%; olive 8%; cypress 11%; pellitory 43%. A total of 65 out of 162 (40%) reported current asthma at baseline. Asthma was more prevalent in poli-sensitive subjects (51%) in comparison with mono-sensitive patients (30%) (P=0.008, Chi-square test). According to allergen type, at the baseline visit, asthma was detected in 47% of pellitory allergic patients, in 45% of olive allergic subjects, in 38% of ragweed allergic patients, in 26% of tree allergic patients and only in 9% of cypress allergic subjects. In pellitory, olive and ragweed allergic patients the frequency of asthma was statistically significant (P=0.0055 Chi-square Test) higher in comparison with tree and cypress allergic subjects. Allergy to pellitory, olive or ragweed was associated with an Odd Ratio of 3.1 (95% CI from 1.3 to 7.0) to have asthma in comparison with tree or cypress allergic subjects. GS was higher in pellitory and olive allergic patients (18±8 and 18.4±4 respectively) in comparison with other groups (15±5). These differences however were not statistically significant.

Clinical Efficacy of SLIT

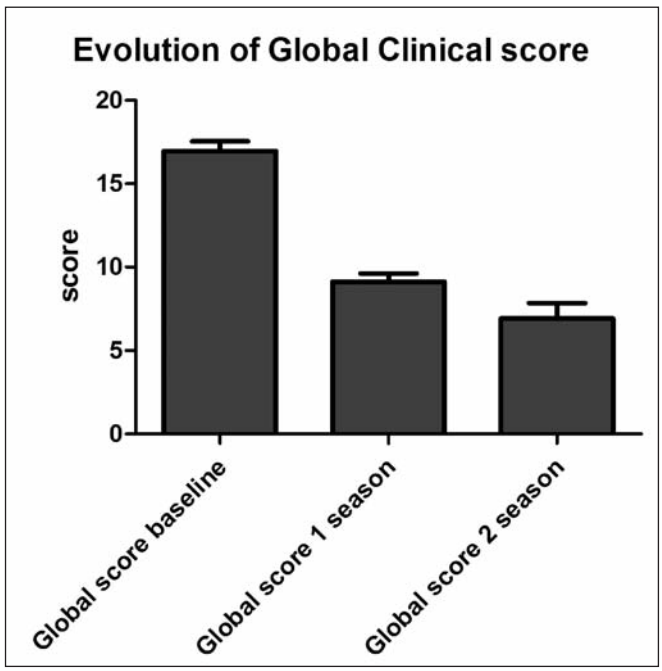
Clinical data for 1 and 2 pollen seasons after SLIT were available for 139 and 131 patients respectively (80% of

Table 1 - Main Demographic and Clinical Characteristics at baseline

Total Population enrolled	162
Men/Women	78/84
Age, years ; mean(SD)	31 (13)
Duration of Allergic Disease; years, mean(SD)	8 (5)
Type of respiratory allergy	
Rhinitis only, n (%)	46 (29)
Rhinitis and conjunctivitis, n (%)	51 (31)
Rhinitis and Asthma, n (%)	25 (16)
Rhinitis, conjunctivitis and asthma, n (%)	33 (20)
Asthma only, n (%)	7 (4)
Any asthma n (%)	65 (40)
ARIA Classification of Rhinitis	
Moderate/Severe, %	68%
Mild %	32%
Allergic to Trees (Betula, Corylus, Alnus)	30
Allergic to Ragweed (Ambrosia artemisifolia)	23
Allergic to Cypress (Cupressus arizonica)	12
Allergic to Olive (Olea europea)	11
Allergic to Parietaria judaica	84
Monosensitised patients, n (%)	87 (54)
Polisensitised patients, n (%)	75 (46)
Symptom Score at baseline (scale from 0 to 18)	11 (4)
Medication Score at baseline (scale from 0 to 18)	6 (4)
Global Score, mean (SD)	17 (7)
Asthma symptoms score, mean (SD)	2.7 (2)

the baseline population.) GS, in the population as a whole, during the following 2 consecutive seasons with SLIT treatment decreased significantly (P=0.0001, Wilcoxon Test) to 9 (5) and to 7 (5), respectively, with a reduction of 59% in comparison with baseline (Figure 1). In the population as a whole SS, mean (SD) decreased significantly from 11 (4) to 4 (3) at the end of study period with a reduction of 64%. In mono-sensitive patients (N=87) mean percent reduction of SS with SLIT was more pronounced in comparison with poli-sensitive patients but the difference was not statistically significant. MS decreased from 6 to 3 after SLIT treatment; a 50% reduction. In figure 2 the SS at baseline and after 2 consecutive pollen seasons with SLIT for groups of type of allergy are showed. SLIT treatment was associated with a significant reduction of SS irrespective of the causative allergen. However clinical efficacy of SLIT was more pronounced in tree and pellitory allergic patients (80% of SS reduction) in comparison with ragweed, cypress and olive allergic subjects (30%-50% of SS reduction). Clinical efficacy of SLIT was observed both in mono-sensitive and poli-sensitive subjects without any significant difference in the amount of percentage reduction of GS in comparison with baseline. At baseline in the 65 patients reporting asthma symptoms the mean (SD) asthma clinical score was 2.7(2). At the end of the observation period this score was significantly reduced to 0.3 (0.6). A total of 30 patients (46%) with asthma at baseline reported no asthmatic symptoms at the end of the observational study period.

Figure 1 - Evolution of Global Clinical Score. Entire Population



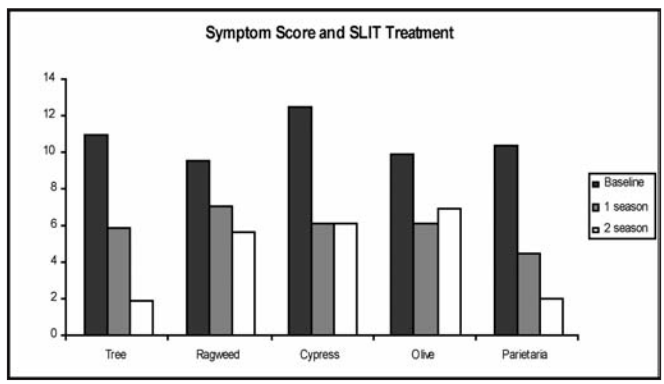
Safety and Tolerability of SLIT

A total of 38.880 SLIT doses were administered during the observation period of the Rainbow study. No serious adverse events were reported. Local mild and transient side effects, mainly oral itching, were reported by 14% of patients (23 out of 162). In 7 patients (4.3% of the study population) more than one local side effect was reported. Oedema of the lips, mild and transient, were reported in 2 patients. The majority of local side effects lasted less than 10 days after treatment start.

Discussion

Respiratory allergy is probably the most common IgE mediated disease (8). Its prevalence in the general population in industrialized countries is reported to range between 10% and 20% (9). Pollen allergy has also a remarkable clinical impact all over Europe, and there is a body of evidence suggesting that the prevalence of respiratory allergic reactions induced by pollens in Europe has been on the increase in the past decades (10). Grass pollen is by far the most important cause of pollinosis throughout the European continent, including the Mediterranean area (11). Between 8% and 35% of young adults in countries of the European Community show IgE serum antibodies to grass pollen allergens. Grass allergy is also the most common form of pollen sensitization in Italy, affecting 17% of the population (12). However tree, ragweed, olive, cypress

Figure 2 - Evolution of Symptom Score during SLIT Treatment and Type of Allergy



and pellitory are very common sensitization observed in both European and Italian population (13). These kind of sensitization present a clear geographical pattern (tree and ragweed in the North of the country, whereas olive, cypress and pellitory sensitization are more common in the centre and south of Italy). Birch is the major pollen-allergen-producing tree in northern Europe and North Italy (14,15). Olive pollen is considered as one of the most important causes of respiratory allergic disease in the Mediterranean region (16). In southern Italy, the frequency of positivity to olive pollen allergens among all skin prick test-positive patients is 13.49% in adults and 8.33% in children (17). Cypress releases an enormous amount of anemophilous pollen and it has been recognized to be responsible for a large part of total annual amount of airborne pollen in several Mediterranean areas (18). In cypress allergic patients asthma prevalence seems to be very low (19). Also in our study asthma prevalence in these patients was 9%. Parietaria is the main allergenic genus of the Urticaceae family (20). The most important species are Parietaria *judaica* and Parietaria *officinalis*. Parietaria *judaica* grows mainly in coastal Mediterranean areas. In some areas, like south of Italy, some patients have year-long symptoms. Sensitization to Parietaria *judaica* markedly increased the risk of developing asthma. Epidemiological studies show that bronchial asthma is present in 52% of the monosensitized Parietaria patients (21). This prevalence was also confirmed by our study in which asthma in pellitory allergic patients was reported in 47% of the cases. Ragweed has long been recognized as a significant cause of allergic rhinitis (22). A large random skin test survey demonstrated that 10% of the US population was ragweed-sensitive (23). More recently, Ambrosia pollen levels were significantly related to asthma and rhinitis in a study based on a symptoms diary and peak expiratory flow rates (24). In our study ragweed allergic patients presented a high symptom score and a prevalence of asthma of 38%. Asthma and rhinitis are often co-morbid conditions (25). Also our epidemiological study showed that asthma is observed in 40% of non-grass pollen allergic patients. In the Rainbow study sensitizations to Parietaria *judaica,* olive and ragweed are associated with a higher frequency of asthma in comparison with tree and cypress allergic patients. Polosa et al (26) have shown that pellitory sensitization increased by 4 times the risk to have asthma in comparison with non pellitory allergic subjects. In our population allergic rhinitis was classified as moderate-severe in 68%, suggesting that also these kind of pollinosis could have a great impact on quality of life of allergic patients. Polisensitization in the Rainbow sample was observed in up to 46% and these subjects have a higher prevalence of asthma in comparison with mono-sentitive patients. The Rainbow Study is, in our knowledge, the first large prospective observational epidemiological trial addressing the clinical impact of respiratory allergies induced by non-grass pollen allergens and evaluating the clinical efficacy of specific sublingual immunotherapy 2-year consecutive treatment.

Conclusion

Non-grass respiratory allergies in Italy are a relevant clinical problem. In patients enrolled in the Rainbow study with sensitization to non-grass seasonal pollens, clinical manifestation of respiratory allergy are generally relevant. Rhinitis was considered moderate-severe in the majority of the patients (68%). In this population asthma could be observed in up to 47% of the sample. In the Rainbow study population pellitory, olive and ragweed allergies have been associated with a more severe clinical picture in comparison with tree and cypress allergy. The Odd Ratio for current asthma in patients with pellitory, olive and ragweed was higher in comparison with the other groups. A two-year specific SLIT treatment was associated with a significant reduction in SS, MS, GS and asthma score in comparison with baseline, irrespective of allergen type sensitization. SLIT was as effective in mono-sensitive as in poli-sensitive subjects. In addition 46% of patients with asthma symptoms at baseline have no respiratory symptoms after a 2-year treatment with specific SLIT.

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