Olea sublingual allergoid immunotherapy administered with two different treatment regimens

S. Leonardi[#], A. Arena*, R.W., M.E. Bruno[¥], P.M. Cannaò**, R.W.D'Anneo[§], P. Falagiani[¥], E. Gammeri*, G. Mistrello[¥], A. Nicolini[^], L. Ricciardi°, G. Valenti[ç], R.Longo[#,] M. La Rosa[#].

[#] Pediatric Broncho Pneumology Unit,Department of Pediatrics , University, Catania, Italy

[¥] Scientific Department, Lofarma S.p.A., Milano, Italy

** Allergology Ambulatory, Acireale (CT), Italy

§ Respiratory Centre Disease, Papardo Hospital, Messina, Italy;

* Respiratory Centre Disease, ASL 5, Messina, Italy;

[^] O. U. of Paediatrics, OMPA Hospital, Ragusa, Italy

° Allergology Department, University, Messina, Italy

[ç] Pneumology Service, ASL 10, Palermo, Italy

Correspondence:

Dr. Salvatore Leonardi
Department of pediatrics, University, Catania, Italy
Tel: …+390953782764……
Fax: +390953782385……
E-mail: …leonardi@unict.it……

ABSTRACT

Background: Sublingual immunotherapy (SLIT) with monomeric carbamylated allergoid administered in accordance with the standard regimen has proven to be effective and safe. Achieving clinical benefit, however, requires a lengthy period of time so it is not very suitable for short-lasting allergies. We thus performed this study to compare an administration protocol starting in the co-seasonal period (with a 4-day build-up phase) with a pre-co-seasonal scheme to verify if the former regimen provides the same benefit in a shorter period of time. *Methods and results:* The prospective, randomised, drug therapy-controlled study was conducted in 33 rhinitic patients monosensitised to *Olea* with or without asthma. Ten patients were assigned to the co-seasonal therapy with 5,000 AU/week for 6 weeks, 11 to the pre-co-seasonal therapy with 3,000 AU/week for 10 weeks, and 12 to drug therapy. They were treated from April or May to June 2008. A Visual Analogue Scale (VAS) was performed at baseline and after treatment to assess the well-being of the patients. Drug consumption was evaluated by means of a monthly diary. There was greater VAS improvement in both the SLIT groups versus the controls, but it was statistically significant only in the co-seasonal group ($p<0.01$). Furthermore, there was a reduction in the rescue medication only in the co-seasonal SLIT ($p<0.05$ versus drug therapy). One mild adverse event was observed. *Conclusions:* The allergoid SLIT was shown to be effective and safe in *Olea* allergy in particular when a co-seasonal regimen was used.

Key-words: Allergen, Allergic Rhinitis, Asthma, Carbamylated allergoid, Olea allergy, Sublingual co-seasonal immunotherapy

INTRODUCTION

Specific sublingual immunotherapy (SLIT) with monomeric allergoid (allergoid SLIT) has been shown to be clinically effective and safe in many clinical studies (1-7). However, the standard induction build-up phase is rather time-consuming requiring anywhere from a maximum of 14 weeks (traditional schedule) to a minimum of 16 days (semi-rush schedule). The build-up phase of SLIT has in fact been designed according to the same criteria used for injective immunotherapy, where side effects are frequent, local and systemic, severe and even life-threatening in some rare cases. The safety profile of SLIT and the allergoid SLIT in particular has been shown to be much higher compared to injective immunotherapy, and systemic and anaphylactic reactions are nearly virtually absent, as documented by clinical trials and post-marketing surveillance studies (1-8). Yet, we still do not know whether the use of higher dosages of the allergoid SLIT during the maintenance period can lead to faster effects and/or to increased efficacy without compromising the good tolerability of the product.

The objectives of this study were as follows: 1) to evaluate the possibility of simplifying the initial build-up phase of the allergoid SLIT by shortening the induction phase to 4 days; 2) to verify if this therapy, given co-seasonally for 6 weeks, i.e. from May to mid-June, can be as effective and safe as the pre-co-seasonal SLIT used in *Olea* allergic patients; 3) lastly, to investigate if the rapidity of effect and/or the efficacy of the allergoid SLIT could be further increased, using a maintenance dosage of 5,000 AU/week for the co-seasonal therapy and yet maintain the safety/tolerability profile of the lower dose tested in this study, i.e. 3000 AU/week used pre-co-seasonally. This dosage was chosen as it proved to be more effective of that of 1000 AU/week in a previous study conducted in patients allergic to Pellitory with both the SLIT started in the co-seasonal period (9).

It should be noted that *Olea* allergy, which is present in southern Mediterranean countries, has a very short pollination period that lasts from from May to June, which makes it particularly suitable for testing these three hypothesis.

MATERIALS AND METHODS

This prospective, randomised open study was conducted in three parallel groups receiving either two different dosages and regimens of SLIT or the standard chronic pharmacotherapy normally taken for rhinitis and/or mild persistent asthma. All the three groups were allowed to receive the rescue medication specified in the study protocol in addition to their assigned therapy in the case of urgent need but only for a very short period of time. All patients were evaluated at entry to assess their baseline conditions. The parameters used to evaluate treatment efficacy were the Visual Analogue Scale (VAS) which was performed at baseline and at the end of the study and drug consumption, which was measured before and after treatment.

Patients

Thirty-three patients suffering from rhinitis and/or mild persistent asthma and never having previously received any form of specific immunotherapy were enrolled in the study. The patients' characteristics at baseline are described in Table 1. Ten patients (2M, 8F, mean age 24±13 years) were treated co-seasonally and received the higher dose of the allergoid SLIT, 11 patients (7M, 4F, mean age 26±14 years) were treated pre-co-seasonally and received the lower dose, while the remaining 12 patients (5M, 7F, mean age 23±14 years) received the standard chronic pharmacotherapy. All 33 patients were monosensitised to *Olea* as confirmed by a positive (>3mm) skin prick test response only to *Olea* (among a panel of nine extracts produced by Lofarma S.p.A., Milan, Ital: *Olea*, Grass, Mugword, Pellitory, Cat, Birch, *Alternaria*, *Aspergillus*, House Dust Mite) and positive CAP assay results (class II or greater) (CAP System EIA, Pharmacia, Uppsala, Sweden). Moreover they had to experienced exacerbation of their symptoms only during the *Olea* season (April and May). Subjects suffering from systemic or immunological diseases, major anatomical alterations of the upper airways, renal insufficiency, coronary heart disease, neurological or psychiatric diseases, receiving chronic steroid or beta-blocker treatments were excluded as were pregnant women. All patients signed an informed consent before entering the study.

Investigational treatment

SLIT is a monomeric carbamylated allergoid (Lais®, Lofarma SpA Milan, Italy) (10) biologically standardised in allergenic units (AU) and prepared as orosoluble tablets (allergoid SLIT). The tablets were taken in the morning on an empty stomach and kept under the tongue for 1-2 minutes to dissolve before swallowing. During the 4-day build-up phase ten 300 AU tablets were used. The treatment regimen during the up-dosing was as follows: 1 tablet on the first day, 2 tablets on the second day, 3 tablets on the third day and 4 tablets on the fourth day, totalling 3,000 AU in four days. The patients were subsequently randomised to receive either with a maintenance dosage of 3,000 AU/week (i.e. one 1000 AU tablet 3 times per week) or 5,000 AU/week (i.e. one 1000 AU tablet 5 times per week). SLIT was administered in the first group pre-co-seasonally for 10 weeks (30,000 AU total) and in the second group co-seasonally for 6 weeks (30,000 AU total). Since all the patients were monosensitised they were treated only for *Olea.*

The standard chronic pharmacotherapy consisted of antihistamines (cetirizine or loratadine tablets 10 mg, once daily) and long-term intranasal steroids (fluticasone propionate, 125 µg, 2 sprays per nostril/day), together with long-acting bronchodilators (salmeterol, 100 µg/day) for patients with asthmatic symptoms as well.

The rescue medication, which was administered for symptomatic control only in the case of urgent need and for no more than three days, was as follows in all three groups: cetirizine or loratadine tablets 10 mg, two or more tablets/day, inhaled salbutamol 100 µg, 2-3 puffs or more/day, intranasal fluticasone propionate 250 µg, 2 or more sprays per nostril/day.

Clinical evaluation

Patients were required to complete a specific graduated scale known as the Visual Analogue Scale (VAS) which here explores more the degree of patient well-being than the severity of his allergic symptoms during the SLIT as recently described by Bousquet et al. (11). In the present study the maximum level of well-being was 10 and the minimum was 0. The VAS was completed upon study entry and at the end of treatment, i.e. after one month treatment in the 5000 AU and in the

pharmacological group and after two months in the 3000 AU group. The VAS was chosen because it is very simple to use and much faster to perform than the Standardized Rhinitis Quality of Life (RQLS) and the Nasal/Conjunctival scoring system (e.g. TNNS).

Rescue medication consumption received a score of 1 point if no drug was consumed during that month, 2 points for low consumption (i.e. needing no more than 5 days of rescue therapy during that month), 3 points for average consumption (i.e. needing no more than 10 days of rescue therapy during that month), and 4 points for high consumption (i.e. needing more than 10 days of rescue therapy during that month) regardless of the kind of drug. The cumulative symptomatic drug intake score was then recalculated at the end of the study by the doctor, with each kind of drug being scored separately and differently from the others (antihistamines = 1, inhaled salbutamol = 2 and inhaled steroids =3). This was done in order to obtain a more uniform and realistic global score, belonging these drugs to different classes and having thus a different clinical effect.. A similar system was recently employed also by other authors (12).

All patients were also required to record any side effects in a separate diary. Adverse events (AE) with the allergoid SLIT were subdivided into local AE (oral itching, swelling of tongue) and systemic (asthma, rhinitis, urticaria, abdominal pain/diarrhoea, anaphylaxis).

Statistical analysis

The Wilcoxon Signed Ranks Test was used to evaluate the changes of VAS versus the baseline values. The Mann-Whitney test for intergroup comparison was used (Mixed model through SAS 9.1 version package) to determine whether the values of a particular endpoint differed amongst the three populations (3,000 AU versus 5,000 AU versus control),

P values less than 0.05 were considered significant.

RESULTS

Build-up Phase, Drop-outs and Safety

Both the 4-day induction build-up phase and the 1 or 2-month maintenance therapy were tolerated very well by all the patients. Furthermore, none of the patients interrupted the study due to adverse events.

VAS

The VAS results are described in Figure 1. At baseline there were no statistically significant differences amongst the three groups even though the patients treated with the 5,000 AU had a slightly higher VAS than the other two groups. An increase in VAS values was observed in all the three study groups after treatment versus baseline, but the increase obtained by SLIT was more pronounced than that observed with the drug therapy. Considering the results obtained amongst the three different groups, it is worth noting that only the score obtained with the co-seasonal SLIT was statistically better than the scores observed in the controls ($p<0.05$), whilst no statistically significant differences were observed either between the two SLIT groups or between the pre-co-seasonal SLIT and the controls.

Drug consumption

There was a reduction in the consumption of rescue medication versus baseline only in the 5,000 AU group ($p<0.05$). Drug consumption in the 3,000 AU group increased slightly, and the increase was also more pronounced in the control group (Figure 2).

DISCUSSION

The regimen used for the induction build-up phase in this study is particularly short, i.e. 4 days, and starts with a 300 AU dose. This means that only two types of tablets titrated to 300 and 1000 AU need to be used, thus greatly simplifying the initial treatment and preventing dosage errors. The maintenance phase can also begin much earlier with this regimen, possibly providing a great advantage with respect to the time taken to reach clinical benefit. The regimen used in this study consisted of administering a cumulative dose of 3,000 AU in 4 days, slightly lower than the regimen (4,000 AU) used by Rossi & Monasterolo in their ultra-rush up-dosing study, in which

the administration of all the dosages lasted only 20 minutes (4). The administration of such high dosages in a short period of time did not cause any significant adverse reactions in either study. Similar results were obtained in studies conducted by Gammeri et al. and D'Anneo et al., in which 6,000 AU were administered in three days (9,13). On the whole, these data confirm the good tolerability and safety of the allergoid SLIT, even when it is administered over a very short period of time. This can probably be ascribed to the low IgE-binding activity of the active ingredient (10) which prevents the IgE-mediated allergen presentation by dendritic cells to T_H2 cells, which is the key mechanism for explaining the large increase of allergen-specific IgE observed in the course of SLIT with native grass allergens (14). On the contrary, a gradual decrease of allergen-specific IgE was observed during the course of SLIT with Dermatophagoides carbamylated allergoid (15).

With respect to efficacy, a correlation can be seen between the SLIT dose, the clinical effects and the mode of administration. Both the SLIT groups were shown to be more effective than the controls and, in fact, there was a greater VAS improvement in both SLIT groups at the end of treatment versus the pharmacological therapy even if this improvement was statistically significant only in the co-seasonal group ($p<0.05$) and a reduction in drug consumption was observed only with the 5,000 AU dose. In our opinion this could be a possible demonstration of the greater rapidity of effect of a higher dosage given in a shorter period of time in comparison to a lower dosage given in a longer period of time (i.e. started not immediately before the pollen season).

A dose-response effect regarding the effectiveness of SLIT has been previously described by other authors in studies performed with SLIT tablets (14,16) . In our case, however, besides the increase in absolute efficacy, what emerges from our data is the rapidity of effect obtainable by increasing the rapidity of administration, i.e. giving the same amount of allergen in a shorter period of time. This time-response effect was also previously observed by Di Gioacchino et al. in an immunological study comparing the effects on IL-10 and other cytokines (INF-γ, IL-4, IL-6,

IL-2, TNF-α) of two different allergoid SLIT induction schemes, one lasting 14 weeks and the other 16 days. It emerged that the faster regimen, in which the tablets were consumed more closely to each other, was associated with a greater change in the above parameters regardless of the total amount of allergen administered (17).

In the present study, the speed of administration during the build-up phase was the same in the two groups, so it was not able to influence the results between the two SLIT regimens. The total amount of allergen administered was also the same in the two groups, but both the frequency of administration and the weekly dose were different, so it is difficult to understand if it has been the higher weekly dose or the higher administration frequency that determined the greater clinical improvement seen in the co-seasonal group. On the other hand, this choice was mandatory to maintain the total amount of allergen equal between the two SLIT groups, so making them comparable, even if a potential bias due to the open label design of the study cannot be excluded.

Although these limits and the fact that the present study was conducted in only 33 patients, it showed, in any case, that, by increasing the frequency of the SLIT administration and thus its dosage per week, a superior clinical benefit in a shorter period of time can be achieved, i.e. 6 weeks instead of 10.

Considering that the maximum pollination period for *Olea* in southern Italy ranges from May to June, when allergic symptoms in most patients become worse, on the basis of our data, we can state that a maintenance dosage based on the administration of 1,000 AU five time a week started just before the beginning of the pollination period, i.e. in May, could be more advisable than a more traditional regimen of 1,000 AU three time a week started pre-seasonally, i.e. in April, and continued during the season, to obtain a more rapid and higher clinical benefit without any significant adverse reactions. Another important aim of shortening the therapy can be to allow the patients to start the SLIT immediately before the season. In this way also those patients that arrive late to the doctor can be treated.

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TABLES TITLES

Table 1: Patient characteristics at baseline

FIGURES LEGEND

Figure 1: VAS mean values ± SD at baseline and after treatment in the 3 groups of patients

Figure 2: Drug consumption ± SD at baseline and after treatment in the 3 groups of patients. The medication used was scored according to monthly consumption and drug class.