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Efficacy and safety of sublingual immunotherapy with grass monomeric allergoid: comparison between two different treatment regimens

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Key words

Rhinitis, asthma, grass pollens, sublingual immunotherapy, SLIT, monomeric carbamylated allergoid

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Summary

Background: *Sublingual immunotherapy (SLIT) with monomeric carbamylated allergoid proved to be well tolerated, safe and effective in patients with respiratory allergy. Standard administration regimens are expected to require a long time before clinical benefit can be appreciated. We investigated whether pre-seasonal and perennial regimens differently affect the clinical efficacy of grass pollen SLIT.* ***Methods:*** *Adult patients with allergic rhino-conjunctivitis with/without mild intermittent asthma due to grass pollen were included into this open prospective study and randomised to receive SLIT with a continuous regimen (Group 1: 1,000 AU/week for the entire study period) or a pre-seasonal regimen (Group 2: 5,000 AU/week for 10 weeks/year for 2 years), or on demand drug therapy alone (Group 3) for two years. At entry (November 2005), at the end of the first and second pollen season, a Visual Analogue Scale (VAS) was used to assess patients' well-being. Symptom score and drug consumption were evaluated during the seasons. Methacholine challenge was performed at study entry and conclusion. Adverse events were recorded along the whole study duration.* ***Results:*** *Thirty-two patients were divided into Group 1 (n=10), Group 2 (n=11) and Group 3 (n=11). A significant VAS improvement was observed in both SLIT groups, after the first and second pollen season, compared to baseline and to Group 3 ($p<0.05$). Less symptoms and need for medications resulted during the second season ($p<0.05$). No relevant variations in bronchial hyper-reactivity have been observed between the three groups. Only 2 patients experienced local or mild reactions in SLIT groups.* ***Conclusion:*** *Both pre-seasonal and continuous regimen of SLIT with monomeric allergoid turned out effective and safe, suggesting that a pre-seasonal course with 5,000 AU/week for 10 weeks may represent a convenient option in patients with grass pollen allergic rhinitis with/without mild intermittent asthma. Further research is urgently needed to consolidate these preliminary evidences.*

Introduction

Sublingual immunotherapy (SLIT), which has been recognized as an effective treatment for respiratory allergy (1-3), is gaining an increasing credibility as a viable alternative to subcutaneous immunotherapy (SCIT).

In several European countries, SLIT provides the standard of care for patients receiving immunotherapy. As for

SCIT, SLIT demonstrated its efficacy in numerous randomized controlled trials, and some evidences suggest a possible effect in hampering the natural course of the disease (4). Despite the exact mechanisms of SLIT remain partially unclear, some similarities with SCIT have been described. SLIT results in profound immunological changes in the responses to allergens, characterized by a down-modulation of the Th-2 responses and induction of regulatory cells, producing IL-10 (4-7).
The main advantages of SLIT are its favourable safety profile and the self-management, which make it more convenient for patients. No fatalities have ever been reported in more than 20 years of trials and clinical use, severe adverse events are rare and only few cases of anaphylaxis were observed with high dose SLIT with native allergens (8-12).
Carbamylated monomeric allergoids for sublingual use are chemically modified allergens characterized by reduced IgE binding activity, responsible for a lower allergenicity, with preserved immunogenicity (13). The safety profile of allergoids SLIT has been shown to be higher as compared to SCIT, since systemic and anaphylactic reactions are nearly virtually absent, as documented by clinical trials and post-marketing studies (14-16). The clinical efficacy of sublingual allergoids in respiratory allergy due to seasonal and perennial allergens has been documented in different clinical trials and recently summarized in a systematic review (17).
It has been argued that compliance to the treatment may represent a relevant drawback for SLIT (18). Being the treatment for the most part self-administered at home, a concrete risk for patient's discontinuation seems realistic, and some reports suggest worrying conclusions (19). For this reason strategies to favour the adherence to treatment are strongly encouraged. Patients' education and short term follow-up seem to be beneficial (20). Also shortened treatment courses, which would also have economical implications, are expected to provide further advantages.
The aim of the present study was to investigate whether, in a population of allergic patients with seasonal rhinoconjunctivitis with/without mild intermittent asthma, due to grass pollen, two different administration regimens (pre-seasonal *vs* perennial) affect in a different way the clinical efficacy of SLIT, in comparison to pharmacological treatment alone.

Materials and methods

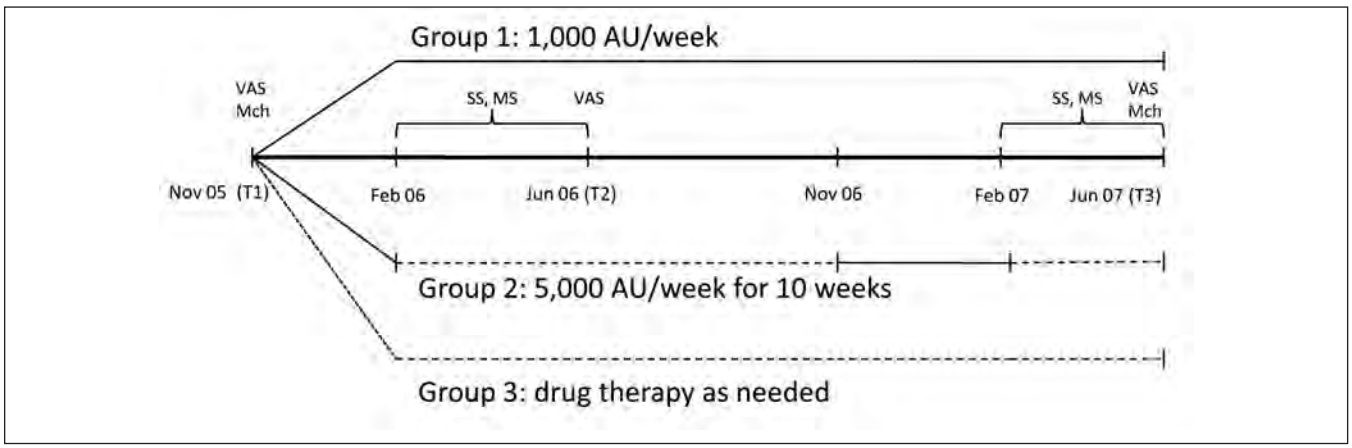
Study design

This is a prospective, randomized, open controlled trial with three parallel groups. Adult patients with rhinitis with/without mild intermittent asthma were enrolled to receive two different administration schemes of SLIT or drug therapy alone on demand. Patients undergoing SLIT were allowed to receive rescue medications in case of acute symptoms.
Patients were evaluated at enrollment (November 2005) to assess their baseline conditions and inclusion/exclusion criteria. The clinical assessment, through a Visual Analogue Scale (VAS), was adopted as primary outcome to evaluate the treatment efficacy. Patients were asked to grade the severity of their symptoms retrospectively, referred to the previous 12 months at enrollment (T1), referred to the previous 6 months after the 1st pollen season (end of June 2006, T2) and after the 2nd pollen season (end of June 2007, T3). Co-primary outcomes were the changes in global symptoms (sneezing, itching, rhinorrea, nasal congestion, ocular symptoms, cough, asthma symptoms), in medication consumption, during the pollen seasons, and secondary outcome the response to methacholine challenge at the second year of treatment. The study design is described in Figure 1.
The study receive approval by the Ethical Committee of Ravenna ASL (Ravenna, Italy).

Patients

Inclusion criteria were: a) age between 18 and 70 years; b) presence of clinical symptoms of allergic rhinitis with/without mild intermittent asthma, solely during the grass pollen season for at least 2 years; c) sensitization to grass pollen, confirmed by skin test (wheals >3mm) or specific IgE assay (Class >II). Rhinitis was diagnosed on a clinical basis according to ARIA guidelines (21). Mild intermittent asthma was diagnosed according to GINA guidelines (22) as episodes of wheeze, chest tightness, dyspnoea, or cough responding to inhaled salbutamol. Asthmatic patients had to have normal spirometric results with FEV1 greater than 79% of the predicted value at entry.
Exclusion criteria were as follows: previous immunotherapy courses; FEV1 less than 80% of predicted value or persistent asthma; major anatomic alterations of the upper airways (polyps, septal deviation, and turbinate hypertro-

Figure 1 - Study design. (SS=symptoms score; MS=medication score; VAS=visual analogue scale; Mch=methacholine challenge)



phy); major systemic or autoimmune diseases, malignancies, psychiatric disorders, and pregnancy; treatment with beta-blockers.
All patients had to sign an informed consent before entering the study.

Investigational treatment

SLIT was a grass pollen monomeric carbamylated allergoid (Lais®, Lofarma SpA, Milan, Italy), biologically standardised in allergenic units (AU) and prepared as orosoluble tablets (allergoid SLIT). The tablets had to be taken in the morning at empty stomach and kept under the tongue for 1-2 minutes until dissolution before swallowing.
In November 2005, the build-up phase lasted 16 days and 25 AU, 100 AU, 300 AU and 1000 AU tablets were used. Subsequently the patients have been treated for two years either with a maintenance dosage of 1,000 AU/week (i.e. 1 tablet once a week) in a continuous regimen (Group 1) or 5,000 AU/week (i.e. 1 tablet 5 times a week) for 10 weeks/year pre-seasonally (Group 2), according to a computer-generated randomisation list. The total amount of allergoid given during the maintenance phase was about 50,000 AU/year in both the groups.
A third group of patients (Group 3) was randomly allocated to receive on demand pharmacotherapy alone for the whole study duration.
The on demand therapy, allowed to all patients for acute symptoms relieve, included: cetirizine tablets 10 mg once daily, intranasal fluticasone propionate 50 μg (2 spray per nostril/die), inhaled salbutamol 100 μg (2-3 puff as needed), prednisone 25 mg tablet (in case of refractory symptoms and for a maximum of 3 days).

Clinical evaluation

Patients were required to fill-in a specific Visual Analogue Scale (VAS) exploring the degree of patient well-being and, although indirectly, the severity of the rhinitic symptoms retrospectively. In our study the maximum level of well-being was 10 and the minimum was 0. The VAS had to be filled-in at entry (T1), at the end of the first season (T2) and at the end of the second one (T3).
In addition, patients were asked to record daily in a monthly diary card during the season, the disease-related symptoms and the rescue medication intake (daily reflective assessment). A global symptom score was calculated on the basis of the occurrence of the following symptoms: sneezing, itching, rhinorrea, nasal congestion, ocular symptoms, cough and asthma symptoms. Each of them could be scored from 0 (absent) to 3 (very troublesome).
The drug consumption was scored monthly: 0 points if no drug was assumed in that month, 1 points if the assumption was scarce (i.e. no more than 5 days with the need of a rescue therapy in that month), 2 points if this was in the average (i.e. no more than 10 days with the need of a rescue therapy in that month) and 3 points if this was elevated (i.e. more than 10 days with the need of a rescue therapy in that month). At the end of the study, a cumulative drug consumption was calculated correcting in respect to the drug class, being the clinical effects of drugs of different magnitude and duration: the lowest score (1 point) was given to bronchodilator, an intermediate score (2

point) to antihistamines and topical steroids, the highest score (3 point) to oral corticosteroids.
All patients were also required to report in a separate diary any untoward effect. Adverse events (AE) were subdivided into local AE (oral itching, swelling of tongue) and systemic AE (asthma, rhinitis, urticaria, abdominal pain/diarrhoea, anaphylaxis).

Methacholine challenge

The methacholine test (Mch) was performed in all patients, at T1 and T3 (therefore before the 1st and at the end of 2nd pollen season respectively), with patients free of inhaled bronchodilators for at least 12 hours. Increasing doses of methacholine (30 - 60 - 120 - 240 - 390 - 690 - 1,260 - 2,490 μg) were administered until a decrease of 20% in FEV1 or whenever the maximum dose (cumulated dose of 2,490 μg) were reached.
The test was considered positive if patient responded with a provocation dose (PD_{20}) lower than 1,600 μg. The grade of hyper-reactivity (BHR) was considered mild if PD_{20} ranged between 1,600 and 800 μg, moderate if between 800 and 400 μg and severe if between 400 and 200 μg (20).

Statistical analysis

The primary efficacy endpoint was the average VAS score change during the grass pollen season, and the power calculation was based on this endpoint. A difference between groups of at least 30% can be discovered with a 5% significance level and a power of 70% with a sample size of 10 subjects in each arm. With an estimated dropout of 20%, approximately 12 subjects were to be included in each treatment arm. The Wilkinson Signed Ranks test for intergroup comparison was used to evaluate the changes of VAS, symptom-medication score and MCh in comparison to baseline values. The Mann-Whitney U test was used to determine whether the values of a particular variable differ among the three groups and to analyse these differences.

Results

Patients

Thirty-three adult patients, coming to Lugo Hospital (Ravenna, Italy), suffering from allergic rhinitis with/without intermittent asthma were enrolled in the study and randomised to receive SLIT with a perennial regimen (Group 1: 1,000 AU/week for the entire study period) or a pre-seasonal regimen (Group 2: 5,000 AU/week for 10 weeks/year for two years), or as needed drug therapy alone (Group 3).
The baseline characteristics of the patients are described in Table 1. No statistically significant difference between groups in the considered parameters was observed.
One patient from Group 1 dropped out after a few days of treatment for adverse events. Ten patients received the lower weekly dose of the allergoid SLIT, 11 patients the higher one and the remaining 11 the on demand pharmacotherapy. Some patients were sensitized to other allergens (house dust mite =6), compositae (n=2), olive (n=5), dog epithelia (n=3), cat epithelia (n=6), birch pollen (n=3), but had no symptoms out of the grass pollen season.

Build-up Phase, Drop-outs and Safety

Patient tolerated well the 16-day build-up phase and the following maintenance therapy. Only 2 patients reported adverse events. The first one, from Group 1, had an episode of lips paresthesia and one of sore-throat with burning, both occurring immediately after the tablet assumption. The second patient, from Group 2, referred an episode of cough and one of nocturnal asthma. Only the first patient interrupted the study because of the described adverse events.

VAS

The statistical analysis was performed on 32 patients (mean age 29±10.1 years, 13 females) belonging to Group 1 (n=10), Group 2 (n=11) and Group 3 (n=11). The VAS changes are described in Figure 2. In respect to the previous year (T1), a significant VAS improvement in both Group 1 and Group 2 was observed after one (T2) and two years of treatment (T3), compared to the baseline values and to the Group 3 ($p<0.05$), while no improvement was seen in Group 3.

Global symptom score

During the first allergen season the three groups showed comparable levels of clinical symptoms. Group 1 and Group 2 experienced a lower global symptoms score (mean/ds: 6.60/2.41 and 9.18/5.06 respectively) in comparison to Group 3 (mean/ds: 20.27/4.15) during the second pollen season ($p<0.05$), with no significant difference between Group 1 and Group 2 (Fig. 3).

Table 1 - Patients' baseline characteristics

	Group 1	Group 2	Group 3
Patients	10	11	11
Sex (M/F)	4/6	8/3	7/4
Mean age	26.5±10.4	31.6±11.6	31.2±8.3
Weight	69.3±15.2	73.9±9,8	74.0±16.7
Height	164,5±13,9	162,8±16,2	159,4±13,8
Disease			
Rhinitis	8	5	5
Rhinitis and Asthma	2	6	6
Allerge			
Grass	10	11	11
Dermatophagoides	2	3	1
Compositae	1	1	-
Olive	2	2	1
Birch	1	2	-
Dog	2	1	-
Cat	4	1	1
Disease onset (years) [mean SD]	7.40 (5.27)	11.82 (8.06)	10.55 (6.56)
Seasonal disease onset (n. of patients)	10	11	11
VAS previous season (T1) [mean (SD)]	28.10 (13.07)	35.73 (21.55)	36.55 (8.77)
Lung function [mean (SD)]			
FEV_1 (L)	3514.0 (896.76)	3772.7 (915.52)	3486.4 (764.65)
CV	4395.0 (941.76)	5000.0 (1278.3)	4738.2 (1047.9)
Mch challenge positive	1	3	4

Figure 2 - VAS mean values assessed at baseline (referred to the previous season), after the first and the second pollen season in the 3 groups of patients (mm = millimetres)

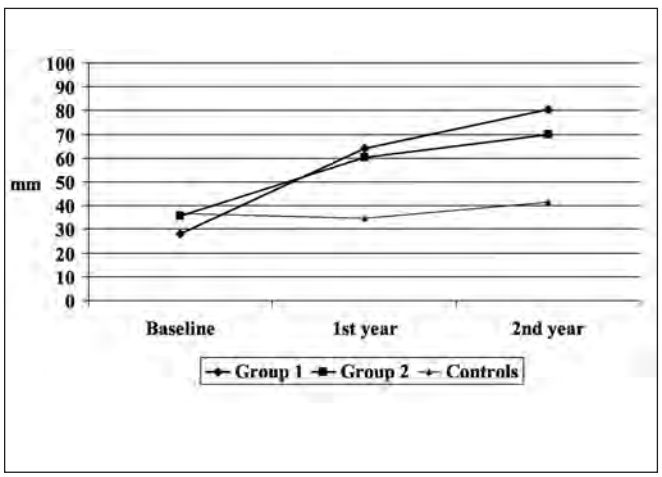


Figure 3 - Global symptom score in the 3 groups of patients at the 1st and the 2nd year.

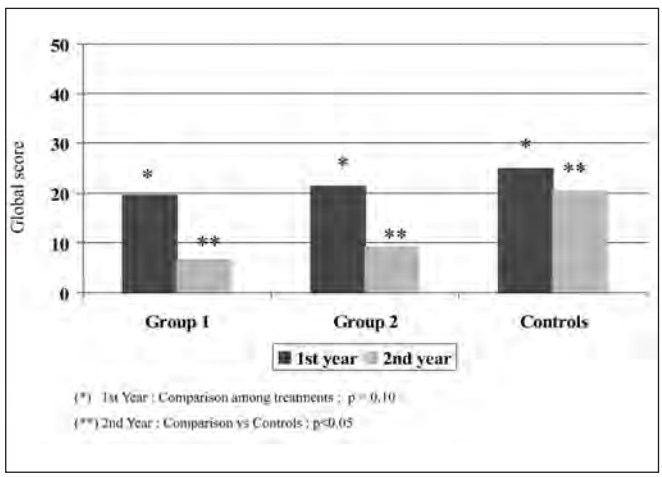
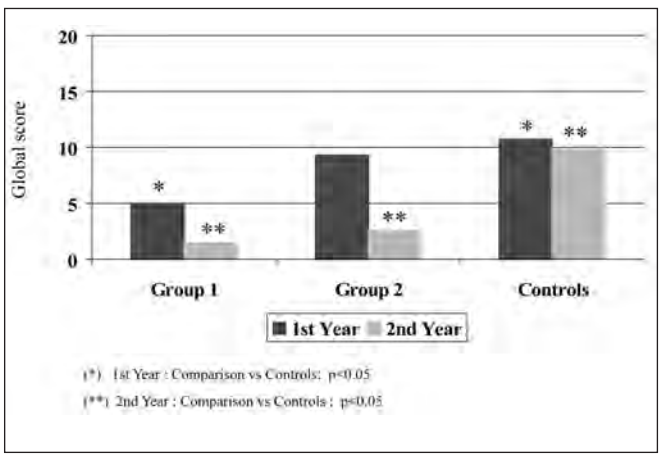


Figure 4 - Global medication score in the 3 groups of patients at the 1st and the 2nd year



Drug consumption

With respect to the control group , only group 1 showed a lower on demand therapy request during the first pollen season. The assumption was significantly lower in both SLIT groups (mean/ds: 1.40/1.07 and 2.45/3.56 respectively) compared to control group (mean/ds: 9.82/3.82) during the second season ($p<0.05$), with no significant difference between Group 1 and Group 2 (Fig. 4).

Methacholine challenge

Concerning methacholine test response, in Group 1 9/10 patients were negative at T1 and 8/10 remained negative at T3. In Group 2 8/11 patients were negative at T1 and 7/11 remained unchanged at T3, while 2 passed from negative to positive and 2 *vice versa*. No change was seen between T1 and T3 in Group 3 in which 7/11 patients were negative. Difference between the three groups in their changes from T1 to T3 were not statistically significant ($p=0.29$).

Discussion

One of the most important and debated aspects of SLIT is the regimen of administration. Among the published trials, various maintenance regimens were used (once daily, on alternate days, weekly), according to empirical considerations (4). For pollen allergens, the administration regimen can be pre-seasonal (start before and stop at the beginning of the pollen season), seasonal (start and end with the pollen season), continuous (all year, independent of the pollen season), or pre-co-seasonal (start before the pollen season end continue until the end of it), although no study directly compared these alternatives and there is no consensus on which is the best option (23). Moreover, recent trials have shown that the clinical efficacy is dependent in part on the duration of the pre-seasonal phase, with 8 weeks the minimum required to achieve a good efficacy (24).

The present study compared two different regimen of carbamylated grass allergoid SLIT for two years, using as control the on demand pharmacological treatment alone, to investigate if a pre-seasonal administration may differently affect the clinical outcome in respect to a continuous administration in adult patients with rhinitis with/without asthma.

Both regimens produced a similar improvement in patient's wellbeing during the first and the second year of treatment, with respect to drug therapy alone. In fact a significantly greater VAS improvement in both SLIT groups at the end of two consecutives pollen seasons was observed in respect to the previous year.

In the second year also the levels of global symptoms and drug assumption were in favour of the two SLIT groups, without significant intergroup difference. The reason why this clinical improvement was seen only after the second year of treatment, in respect to VAS is unclear. An hypothesis may be that the sensitivity of VAS assessment (that is more subjective) could have been enhanced in the context of an open fashion study. Furthermore some authors suggests that the changes in VAS score might accurately reflect changes during treatment that are not completely clear (25). On the other hand VAS correlates with the severity of the disease but provides a psychometric evaluation based on patient's level of agreement to a predefined statement. Finally we cannot exclude that the lack of a short-term evaluation for VAS may have affected our findings, despite that, to our knowledge, no time cut-off has ever been defined to discriminate the time-extension of its reliability. In any case the consistent result for both VAS, symptoms and medication use assessments during the second year of treatment suggests that a prolonged SLIT course is desirable, despite the optimal duration still remains to be defined.

In respect to allergen specific BHR, aspecific BHR is frequently less affected as by the pollen season as by immunotherapy courses (26, 27). Anyway during the pollen season it could be expected an increase in aspecific BHR,

due to the increased amount of allergen exposure. We observed the response to Mch challenge in order to detect the eventual protective effect of immunotherapy on such increase, but no variation in the three groups between study entry (before the pollen season) and conclusion (end of 2007 pollens season) was observed. A possible explanation is given by the fact that methacholine challenges could have not been performed at pollen peaks. It was argued, in fact, that the intensity and the duration of allergen exposure is a critical aspect to determine detectable changes in non-specific BHR, due to a persistent and relevant IgE-mediated bronchial inflammation (28).

These consideration could also explain the discrepancy among the number of patients with historical asthmatic symptoms (2 in group 1, 6 in groups 2 and 3) and the number of patients with positive Mch test after the second pollen season (2 in group 1, 3 in group 2 and 4 in group3).

In our observation a continuous treatment regimen with grass allergoids 1000 AU/week did not show particular advantages in respect to a pre-seasonal regimen at the dose of 5000AU/week for 10 weeks. This aspect can suggest that the cumulative dose of SLIT for pollen allergy could be more important than the treatment duration in order to achieve the clinical benefit.

Considering the adverse events occurrence, the higher dose regimen resulted well tolerated as well, confirming the general safety profile of SLIT with monomeric allergoids. This can probably be ascribed to the low IgE-binding property of the active ingredient, which prevents the IgE-mediated allergen presentation by dendritic cells to Th2 cells, which is the an essential mechanism for explaining the large increase of allergen-specific IgE observed in the course of SLIT with native grass allergen (29, 30).

The interpretation of our results should take into consideration the existence of some methodological weakness. In fact a small sample size was included, the study was open, some patients were polisensitized and the pollen count could not be monitored along the study to verify pollen exposure and seasonal peaks. As a consequence of this also the Mch test could not be performed at pollen peak.

Further no data on patients' adherence to the treatment were collected from the count of the returned blisters.

Although the trial had a prospective design, some of these flaws can be imputable to deviations from study protocol, due to issues relaying with a real-life management.

Another weak point of our investigation is related to the arbitrary score given to the on demand therapy in relation to its monthly usage. Moreover, concerning symptoms scores, a prospective baseline period of observation (at least 1 season) was not used to include patients with an appropriate minimum number of symptoms before being randomised, and to exclude patients without a clear increase in symptoms during the season. On the other hand our patients were asymptomatic at baseline and referred suffering only in the grass pollen season, partially justifying the absence of a run-in period.

Finally the absence of placebo arm may have played a role in detecting a significant benefit, because its effect could account for a relevant part of the observed changes (31). Furthermore, the lack of a direct comparison with placebo does not allow an estimation of the clinical relevance of the observed improvements, since a difference in symptoms of at least 20% in respect to placebo is commonly adopted as minimal relevant magnitude.

All these limitations could have been responsible for overestimated results, but also for missing the differences between the effect of a higher dosage given in a shorter period of time in comparison with a lower dosage given in a longer period of time, differences that were observed in previous studies as a result of a dose-response effect (30, 32).

Our findings suggest that a shorter maintenance course with higher weekly dose of allergoids SLIT could be convenient in respect to a continuous one with lower doses. However, due to the numerous limitations that we discussed, a cautious approach is desirable in drawing conclusions. If these observations will be confirmed in the context of larger double blind controlled randomized trials adopting symptoms-plus-medication combined score as primary outcomes and other measures to reduce bias, our consideration could have a series of important practical implications. In fact a shorter course, resulting well tolerated and able to achieve a comparable clinical benefit of a continuous one, is expected to meet patients' preference and compliance. We already mentioned that strategies aimed at favouring the adherence to the treatment are strongly encouraged to ensure its overall efficiency. Moreover concrete advantages in term of economic implications could derive from a reduced number of monitoring visits.

For these reasons studies directly comparing the different SLIT dosing regimens are urgently needed to prove the more convenient course of administration, including duration.

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