

SHORT REPORT

Direct comparison between continuous and coseasonal regimen for sublingual immunotherapy in children with grass allergy: A randomized controlled study

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Keywords

continuous regimen; coseasonal regimen; grass pollen; respiratory allergy; sublingual immunotherapy.

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Abstract

Background: Pre-seasonal, pre-coseasonal and continuous regimens of immunotherapy have been proposed, but their efficacy was never compared. This phase IV open study was designed to compare the clinical efficacy of a continuous and a coseasonal sublingual immunotherapy (SLIT) for grass allergy over 3 years.

Methods: Children with rhinitis/asthma because of grass were randomized to SLIT given continuously (all year long) or coseasonally. The treatment started in October 2005 in the continuous SLIT group and in March 2006 in the coseasonal group. Diary cards for clinical symptoms (from 0 = none to 3 = severe), and drug intake were recorded from March to June in 2005 (baseline), 2006 2007, and 2008. Specific IgE and IgG4 were evaluated every year.

Results: Eighty children (age range 8–16) were randomized and 72 completed the study. In the first year, the symptom + medication score improved by 44% in the continuous group and by 20% in the coseasonal group ($p = 0.04$). Symptoms, chest symptoms, and drug intake separately showed a greater decrease vs. baseline in the continuous group. In the second year, the global score decreased in both groups with no significant difference, whereas symptom score decreased more in the continuous group. In the 3rd year, there was no difference in clinical parameters between the two groups. Specific IgG4 were significantly higher vs. baseline since the 1st year in the continuous group and since the 2nd in the coseasonal group.

Conclusion: In grass pollen allergy, the continuous regimen performs better than the coseasonal in the first season, whereas in the subsequent years, the two regimens are nearly equivalent.

Sublingual immunotherapy (SLIT) is currently accepted as a safe and effective treatment for respiratory allergy in adults and children. The proofs of efficacy and safety SLIT come from more than 60 randomized placebo controlled trials, several meta-analyses, and numerous post-marketing surveys (for review see 1). In addition, SLIT has been shown capable of conferring a long-term protection and may have a preventative effect on development of asthma (2). Nonetheless, there are several practical aspects of SLIT that still need to be better addressed, including, the optimal maintenance dose, clearly identified only for grass (2), the compliance (3),

and the treatment regimen to choose, especially in the case of pollen allergies. In fact, effective pre-seasonal, pre-coseasonal, and continuous regimens have been proposed in various trials (4). On the other hand, continuous treatments entail certain inconveniences for patients who have symptoms only during the pollen season, and in addition would represent a not negligible economic burden. In this regard, no direct comparison between continuous and seasonal regimen has been carried out so far. Based on this, we designed a clinical trial to compare the efficacy (and safety) of continuous vs. coseasonal SLIT, in children with grass pollen

allergy, suffering from hay fever and asthma. The changes vs. baseline in clinical parameters were compared between the two groups. Adverse events and immunological parameters were also evaluated.

Methods

Study design

The phase IV study was designed as randomized, open, with two parallel groups. Because the two treatments are commercially available, and the study was not intended to demonstrate the efficacy of SLIT per se, the Ethical Committee denied the permission to have a placebo group for 3 years. Patients were recruited during the 2005 pollen season (baseline) and randomized (according to a computer-generated list) to receive continuous (CON-SLIT) or coseasonal (COS-SLIT) sublingual immunotherapy for 3 years. Clinical and immunological parameters were assessed at baseline and in the three following seasons. All the parents signed an informed consent. The coordinator (LM) was in charge on patient's supervision and was responsible for reporting any reaction and/or side effects.

Patients and diagnosis

Children with respiratory allergy solely because of grass pollen were enrolled. Inclusion criteria were: (i) history of rhinoconjunctivitis/asthma only during the grass pollen season in the last 2 years; (ii) unsatisfactory control of symptoms in the previous year, despite a guideline-based therapy; (iii) positive skin prick test to grass pollen extract; and (iv) class ≥ 2 serum-specific IgE to *Timothy*. Exclusion criteria were: (i) sensitization to pollens with overlapping seasons (e.g. Parietaria or Olive); (ii) previous grass immunotherapy; (iii) forced expiratory volume in 1 s (FEV1) below 75% of predicted value; (iv) symptoms or non-specific bronchial hyperresponsiveness to methacholine out of the pollen season [provocative concentration (PC20) below 2 mg/ml]; and (v) systemic diseases and/or chronic treatment with systemic corticosteroids.

The diagnosis of asthma was established on the basis of at least three physician-diagnosed episodes of wheezing/breath difficulty during the two previous grass pollen seasons (5). Skin prick tests were performed according to current guidelines (6), using a panel of commercial extracts (Stallergenes SA, Antony Cedex, France).

Immunotherapy and concomitant treatments

The CON-SLIT started in October 2005 and was continued until June 2008. The COS-SLIT started each year (2006–2008) on the first days of the pollen season and was given until the end of June. The extract was a mix of five grasses, including Timothy, Sweet vernal, Ryegrass, Cock's foot, and Meadow grass (Staloral; Stallergenes SA), prepared in vials at the concentration of 300 IR/ml (14 mcg/ml Phl p 5). The buildup lasted 6 days, then the maintenance dose of six

drops was given 5 days/wk. The up-dosing was performed under the supervision of a physician. In the case of side effects, the dose was properly delayed/reduced. Patients/parents were regularly contacted every 2 months to check the adherence, and control visits were scheduled every 4 months.

Allowed medications were: nedocromil sodium eye drops three times a day, desloratadine (one tablet or 5 ml syrup daily), intranasal levocabastine, and inhaled salbutamol on demand. Patients/parents were instructed to use the medications regularly to control symptoms. In the case of severe symptoms, a 5-day course of oral prednisone (1 mg/kg) was allowed.

Clinical evaluation

Symptoms were recorded daily from March to June. The season 2005 represented the baseline for subsequent comparisons. The severity of symptoms was graded from 0 to 3 for: chest (breathlessness, cough, wheezing, and tightness), nose (sneezing, obstruction, and rhinorrhea), eyes (itching, redness, lacrimation, and swelling). Medications were scored 1 point for each local administration (nedocromil eye drops, intranasal antihistamine, or inhaled salbutamol) and two points for each systemic administration (desloratadine and prednisone). The sum of symptoms plus medication score (SMS) was calculated for analysis. The scores were also analyzed separately. At the end of each season, the physicians and the patients provided an overall assessment of their symptoms, compared to the previous season, using a VAS scale from +3 = much better to -3 = much worse. The pollen counts of the area of Messina were obtained from the local aerobiology service and expressed as weekly mean of pollen grains/cubic meter of air. A Burkard pollen trap (VPPS 2000; Lanzoni, Bologna, Italy) was used.

Immunological parameters

Blood samples for the measurement of specific antibodies were obtained before randomization and at the end of each season. *Phleum Pratense*-specific IgE and IgG4 antibodies were determined by the ImmunoCAP method (Pharmacia, Uppsala, Sweden). Results were expressed in kU/l for IgE and $\mu\text{g/ml}$ for IgG4.

Statistical analysis

The sample size was determined based on the SMS, considering a proportion difference between treatments of 25% (arbitrarily chosen), a significance level of $\alpha = 0.05$ and a power of $1 - \beta = 0.8$. Thus, a number of at least 30 subjects per arm completing the third grass pollen season were required. Two-tailed Mann-Whitney tests were used to compare the percentage reductions in symptoms/medication intake vs. baseline in each group. The same tests were used to analyze specific IgE and IgG4. p values < 0.05 were considered significant.

Results

Patients

Eighty children (43 boys, mean age 12 years, age range 8–16 years) were enrolled and randomly allocated to the two groups, which resulted homogeneous as shown in Table 1. Eighteen patients were skin positive to mites, but they were included because had no perennial clinical symptom and their PC20 was > 2 mg/ml in autumn. The pollen counts were similar in 2005, 2006, 2007, and 2008 (Fig. 1).

Seventy-two of 80 children (90%) completed the study. In the COS-SLIT group, there were five dropouts, four because of adverse reactions. In the CON-SLIT group, there were three dropouts, one because of recurrent abdominal pain. All patients who completed the study had the full data set. The maintenance dose had to be reduced in three CON-SLIT patients and in four COS-SLIT patients because of the persistence of local side effects.

Clinical efficacy

Of the pollen seasons, all patients were symptom-free and used no drugs. During the pollen season 2006, symptoms scores, medication scores, and chest symptoms resulted to be significantly lower than at baseline in the CON-SLIT group ($p = 0.001$, 0.007 , and 0.02 , respectively). In the COS-SLIT group, a significant reduction vs. baseline was found only for medication scores ($p = 0.05$). When comparing the two groups in 2005 and 2006 (Fig. 2), the SMS was reduced by 44% in the CON-SLIT and by 20% in COS-SLIT ($p = 0.04$). The symptom scores fell by 39% in the CON-SLIT and 15% in COS-SLIT group ($p = 0.02$), the medications fell by 60% and 18%, respectively ($p = 0.03$), and chest symptoms were

Table 1 Demographic and clinical data of patients

	Treatment	
	Continuous sublingual immunotherapy (CON-SLIT)	Coseasonal sublingual immunotherapy (COS-SLIT)
Total no of patients	40	40
Female	16	21
Male	24	19
Age (mean in years)	11	12
Age (range in years)	8–16	8–16
Mean duration of allergy (years)	5.2	4.10
Monosensitized to grass	30	32
Intermittent asthma	26	28
Mild persistent asthma	14	12
Drop out	3	5
Specific IgE (kU/l), median, and IQR	11.2 (2.3–15.1)	9.9 (2.9–14.9)
Specific IgG4 (μ g/ml), median, and IQR	0.9 (0.2–2.1)	0.8 (0.1–1.8)

SLIT, sublingual immunotherapy.

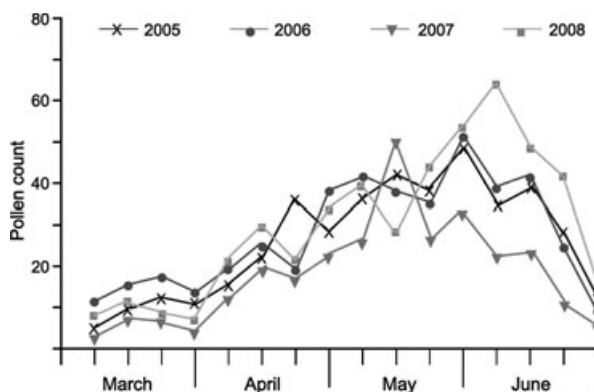


Figure 1 Weekly pollen counts for 2005, 2006, 2007, and 2008.

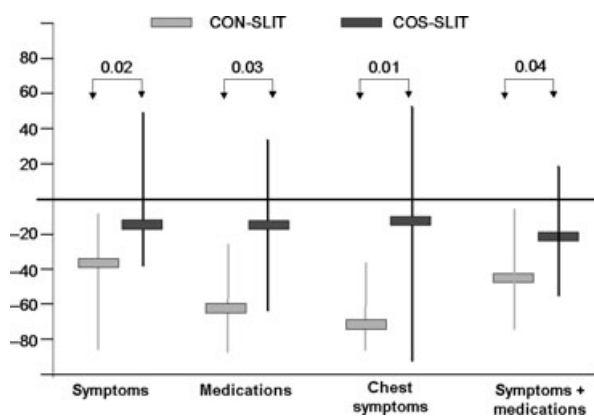


Figure 2 Percentage reduction (median and interquartile range) vs. baseline for symptoms plus medication score (SMS), symptoms score, medication score, and chest symptoms at the 1st year of treatment.

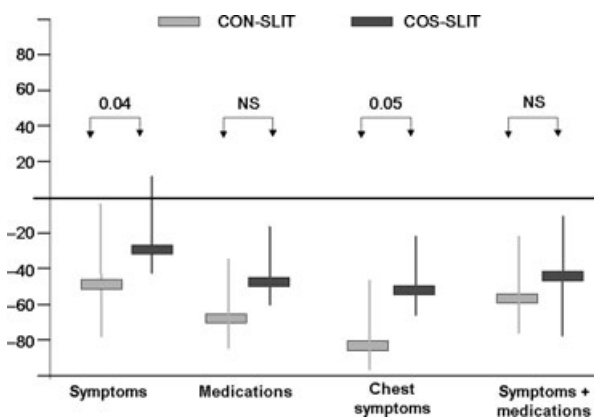


Figure 3 Percentage reduction (median and interquartile range) vs. baseline for symptoms plus medication score (SMS), symptoms score, medication score, and chest symptoms at the 2nd year of treatment.

reduced by 72% in the CON-SLIT and by 11% in the COS-SLIT group ($p < 0.01$). In 2007 (Fig. 3), SMS scores decreased vs. baseline by 59% in CON-SLIT and by 45% in COS-SLIT, with no significant difference between groups.

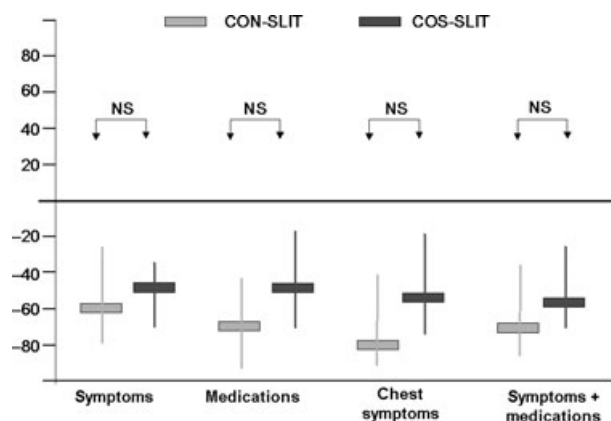


Figure 4 Percentage reduction (median and interquartile range) vs. baseline for symptoms plus medication score (SMS), symptoms score, medication score, and chest symptoms score at the 3rd year of treatment.

Symptom scores fell by 51% in the CON-SLIT and 34% in the COS-SLIT ($p = 0.04$), medication scores fell by 72% and by 49%, respectively ($p = \text{ns}$), and chest symptoms were reduced by 88% in the CON-SLIT as compared with 53% in COS-SLIT group ($p = 0.05$). During the third year, no significant differences between the two groups were seen in SMS, symptoms, chest symptoms, and drug intake score, which decreased from 45% to 80% vs. baseline (Fig. 4).

All the patients reported a perceived improvement at the end of each season, and the same was true for the doctor's evaluation (Fig. 5).

Immunological parameters

Timothy-specific IgE remained unchanged throughout the study, except for the first year, when a significant increase was observed in the CON-SLIT group only (not shown). An increase in specific IgG4 compared to baseline appeared in the CON-SLIT group since the first season ($p < 0.05$) and was maintained in the subsequent years. In the COS-SLIT group, the increase vs. baseline became significant only at the second season ($p < 0.05$). The inter-group comparison showed a significant difference in favor of the CON-SLIT group at the first and second year, with no difference at the third year (Table 2).

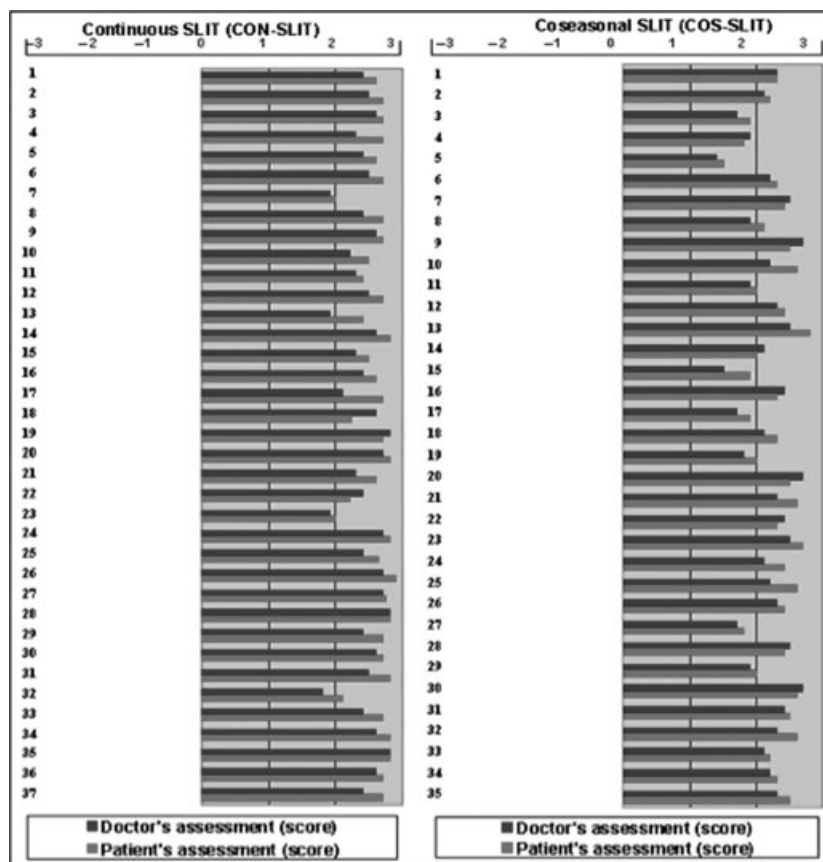


Figure 5 Patient-by-patient results of the self-assessment and doctor's assessment (VAS scale) of the overall efficacy of sublingual immunotherapy (SLIT). The bars represent the mean of the three seasons.

Table 2 Change in IgG4 over the study period µg/ml: inter-group comparisons

	CON-SLIT		COS-SLIT		Inter-group p
	Median	IQR	Median	IQR	
Baseline	0.9	0.2–2.1	0.8	0.1–1.8	0.278
Season 1	4.2	0.8–7.1	0.9	0.3–2.1	0.02
Season 2	9.3	2.8–18.5	2.9	0.6–5.2	0.001
Season 3	22.7	3.8–46.4	11.9	2.5–19.3	0.134

SLIT, sublingual immunotherapy.

Discussion

In recent years, SLIT has been extensively studied to assess its clinical efficacy. From the so-called big trials, it is now clear that SLIT achieves an improvement of symptoms invariably >20% vs. placebo, which is accepted as a reasonable efficacy threshold (7). Concerning the maintenance regimen, the efficacy of SLIT with grass pollen vaccines was demonstrated with coseasonal, pre-coseasonal, and continuous courses (4). The problem of the best maintenance regimen is of central importance to clinicians. In fact, a continuous regimen may pose problems of adherence and patients could be reluctant to take a treatment when they are symptom-free, out of the pollen season. In addition, a continuous treatment carries on a relevant economic cost, and this is of special importance in countries where SLIT is not reimbursed. In addition, it is not clear if a continuous treatment is more effective than an intermittent one in producing immunological changes, which are likely associated with the long-lasting and preventative effects.

However, no direct comparison between continuous and seasonal (either coseasonal or pre-coseasonal) regimen has been so far carried out. Therefore, we undertook this trial to compare from a clinical viewpoint the continuous and the coseasonal maintenance regimens. Because of the fact that the clinical effects of SLIT seem to increase over time (7, 8), we planned a 3-year observation period, to better appreciate

those effects. The study was not placebo controlled, because it was not aimed at demonstrating the efficacy of SLIT and the Ethical Committee did not accept a 3-year blinding and placebo for a phase IV study comparing two effective treatments. Our data indicate that the continuous treatment (pre-seasonal starting) with grass pollen SLIT, in children with seasonal respiratory allergy, performed better than the coseasonal treatment at the 1st year. The difference between regimens remained present also when asthma symptoms and drug intake scores were analyzed separately. On the other hand, the coseasonal treatment achieved an efficacy similar to the continuous regimen since the second pollen season, and at the third year of treatment, the efficacy was similar. This may be explained by the fact that the continuous group actually received also a pre-seasonal treatment (9). In this regard, a recent meta-analysis (10) on grass-SLIT evidenced that the efficacy is greater for a treatment's duration >12 months. SLIT was well tolerated by the majority of patients, although local side effects (itching/burning in the mouth, gastrointestinal symptoms) were frequent. In five cases, local symptoms imposed the discontinuation of SLIT. Concerning the immunological parameters, specific IgG4 increased since the first year with the CON-SLIT, whereas significant increase was observed after the second season of treatment in the COS-SLIT group.

In conclusion, it may be suggested that in grass allergy a pre-coseasonal regimen should be chosen at the first course of vaccination, then coseasonal courses are also a suitable option.

Funding and conflict of interest

None to declare for all Authors.

Author contributions

GBP and GP designed the study, collected, and analyzed the results and wrote the manuscript. LC, GC, DV, MV, and RDL did the clinical work, collected the data, and equally contributed to the revision of the manuscript.

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