

Efficacy of sublingual specific immunotherapy in patients with respiratory allergy to *Alternaria alternata*: a randomised, assessor-blinded, patient-reported outcome, controlled 3-year trial

Marcella Pozzan

Servizio di Allergologia ASL 16 Distretto 1, Padua, Italy

Massimo Milani

Medical Department ALK Abellò Lainate, Italy

Address for correspondence:

Dr Massimo Milani, MD, Via A. Nota 18,
20126 Milan, Italy.

Tel.: +390 293 763 356; Fax: +390 293 763 450;
masmilan2000@yahoo.it

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Abstract

Background:

Alternaria alternata (AA) sensitisation is a common cause of respiratory allergies such as rhinitis and asthma. So far there are no controlled double-blind trials evaluating the efficacy and safety of specific sublingual immunotherapy (SLIT) in AA allergies.

Objective:

To evaluate the efficacy of SLIT treatment in terms of clinical improvement and rescue medication usage in patients with confirmed AA respiratory allergy.

Subjects and methods:

A randomised, parallel group study in 52 subjects was conducted (32 men, mean age 20 ± 9 years) with clinically- and laboratory-confirmed AA respiratory allergies (allergic rhinitis with or without mild-to-moderate asthma). Patients were randomly assigned to SLIT treatment (SLITone *Alternaria*, ALK-Abellò, Denmark) one vial per day without up-dosing for 3 consecutive years ($n = 34$) or to a control group ($n = 18$) with a random allocation ratio of 2:1. Clinical improvement was assessed by evaluating patient-reported outcome (PRO) using a 6 cm visual analogue scale (0: extreme worsening; 3: no change; 6: extreme improvement). The VAS score was evaluated every year with an intra- and inter-group comparison. Rescue medication score (MS) was assessed by evaluating symptomatic drug consumption.

Results:

After 3 years the VAS score was 4.7 ± 0.8 in the SLIT group and 2 ± 1.6 in the control group ($p = 0.0002$). Clinical improvement was observed in 33 out of 34 subjects in the SLIT group (97%) and in 5 out of 18 in the control group (27%) ($p = 0.0001$; Fisher's exact test). The MS significantly ($p = 0.0001$) decreased in the SLIT group from 4.3 to 1.7 at the end of 3 years' treatment. In the control group MS increased from 3.4 to 4.0 by the end of the trial. No serious adverse events were observed in the either group. Six patients in the SLIT group (17%) reported side-effects, in general mild and transient. One patient prematurely discontinued the treatment due to gastrointestinal discomfort.

Conclusion:

The current study has shown that a 3-year course of SLIT is efficacious and well-tolerated in subjects with AA respiratory allergies.

Introduction

Background and study rationale

Alternaria alternata (AA) sensitisation is a common cause of respiratory allergies such as rhinitis and asthma¹. The association between AA allergen sensitisation and asthma is considered particularly strong² – AA sensitisation is also strongly associated with severe asthma³. In patients with seasonal allergen-induced respiratory allergies, such as allergic rhinitis and allergic asthma, sublingual immunotherapy (SLIT) is considered clinically effective⁴. However studies are lacking that support specific immunotherapy in the treatment of mould allergy. In particular there are no controlled double-blind trials evaluating the efficacy and safety of SLIT in AA allergies. In the recent World Allergy Association (WAO) SLIT position paper⁵, which reported on 60 double-blind placebo-controlled trials regarding efficacy of SLIT in the treatment of respiratory allergies, studies performed in AA allergic patients were not listed or included.

Study aim

The study aim was to evaluate the efficacy of SLIT after 3 years of treatment in terms of clinical improvement and rescue medication usage in patients with confirmed AA respiratory allergy (rhinitis with or without mild-to-moderate asthma).

Subjects and methods

A randomised, assessor-blinded, parallel-group study in 52 subjects was conducted (32 men, mean age 20 ± 9 years) with clinically and laboratory confirmed AA respiratory allergies.

Patient selection

Main eligibility criteria were as follows: men or women 10–65 years of age with at least 2 years' clinical history of AA-induced allergic rhinoconjunctivitis and/or mild-to-moderate asthma (according to ARIA⁶ and GINA⁷ guidelines, respectively) with respiratory symptoms suggestive of AA allergen exposure, i.e. symptoms in the late summer to autumn period; positive skin prick test against AA extract (SPT *Alternaria alternata*; ALK-Abellø) with a wheal diameter >3 mm; specific IgE against AA, (IgE class ≥ 2); no clinical history of chronic sinusitis or perennial or seasonal allergic rhinitis and/or asthma because of another allergen during – or potentially overlapping – the AA peak season; 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 β_2 -agonists); and no previous treatment by allergen-specific immunotherapy within the previous 5 years. Pregnancy was an exclusion criterion. Patients were randomly assigned to SLIT treatment (SLITOne *Alternaria alternata*, ALK-Abellø, Denmark) one vial per day without up-dosing for 3 consecutive years ($n = 34$) or to a control group ($n = 18$) with a random allocation ratio of 2:1. Patients in the control group were treated with symptomatic drugs only. SLIT was an AA extract standardised for Alt a 1 as the major allergen (cumulative monthly dose of $3.6 \mu\text{g/month}$).

Study design

The study was set up as a monocentre, randomised, assessor-blinded parallel-group trial. The study was approved by the institutional review board of the authors' 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. For patients aged <14 years of age, informed consents were obtained from the parents or tutors. For the treatment allocation of the participants, a computer-generated list of random numbers was used. Study protocol was approved by the local ethics committee.

Statistical analysis

The study protocol and the statistical analysis plan specified that comparison of visual analogue scale score (VAS) values between SLIT-treated patients and controls should be considered as the primary efficacy outcome of the trial. The power calculation assumed a difference between the two study groups in the VASs of at least -2.0 points with an effect size of 1.0. This assumption provided 95% power at an alpha level of 0.05 (two-tailed test) for a sample size of at least 50 evaluable patients in total (33 patients in the active group and 17 in the control group). Sample size calculation was performed using G*Power program Ver. 3.03 (Kiel, Germany). All statistical analyses were performed using SPSS statistical package Version 13. The Shapiro–Wilk test was used to evaluate the normal distribution of continuous variables. The Mann–Whitney test was utilized to compare VASs between treatment and control groups. Fisher exact test was used to compare categorical variables. For continuous variables, values are presented as mean (SD). Analysis was performed according to the intention-to-treat principle.

Study outcomes

In agreement with a recent position paper⁸, the authors decided to use a patient-reported outcome (PRO) as the

primary study aim. Therefore, the main outcome of the study was the 6 cm visual analogue scale (0: extreme worsening; 3: no change; 6: extreme improvement) evaluated at the end of the 3 years of treatment. Secondary efficacy endpoints included a rescue medication score (MS), evaluated each year, and the percentage of patients reporting significant clinical global improvement (comparison between end of trial and baseline). Clinical improvement was assessed with a 6 cm visual analogue scale (0: extreme worsening; 3: no change; 6: extreme improvement) performed every year in comparison with the baseline condition. In cases with allergic symptoms, subjects had access to symptomatic relief medication (oral antihistamine drugs, corticosteroid nasal spray, inhaled β_2 stimulants, inhaled corticosteroid, and oral corticosteroid) provided in a stepwise fashion depending on the persistence and severity of the symptoms. Use of relief medication was recorded in a patient diary card. The symptomatic medication score (MS) was assessed by evaluating symptomatic drug consumption at every year of treatment during the peak of AA allergen exposure. MS was rated according to the following criteria: use of antihistamine drug – 1 point; use of nasal corticosteroid drug – 1 point; inhaled corticosteroid – 1 point, inhaled β_2 stimulant – 1 point; oral corticosteroid – 2 points. In addition, 1 extra point was added if the use of a symptomatic drug lasted more than 20 consecutive days during AA peak allergen exposure. MS and VAS evaluation were performed by medical personnel unaware of the group allocation of the patient.

Results

Table 1 reports baseline patients' characteristics of the two study groups. A total of 52 subjects (32 men, 19 women; mean age 20 ± 9 years) were enrolled: 34 patients were assigned to SLIT treatment and 18 subjects were assigned to control groups with a random allocation ratio of 2:1. Figure 1 shows the study flow. All the randomised patients but one, completed the trial. The two study groups were

well balanced with regard to the main demographic and clinical characteristics. At baseline, ten patients out of 34 (29%) in the SLIT group suffered from rhinitis and asthma (mild-to-moderate). In the control group the percentage of patients with rhinitis and asthma was 38% (7 out of 18): this difference was not statistically different ($p=0.48$). Also the percentage of polysensitised patients was comparable between the two groups (82% in the SLIT and 83% in the control group). Moderate-to-severe allergic rhinitis, according to ARIA classification, affected 70% and 77% of the SLIT and control groups, respectively.

Primary outcome: After 3 years the VAS score in the SLIT group was 4.7 ± 0.8 and 2 ± 1.6 in the control group. This difference was statistically significant ($p=0.0002$; Mann-Whitney test).

Secondary outcomes: Clinical improvement was observed in 33 out of 34 subjects in the SLIT group (97%) and in five out of 18 in the control group (27%) ($p<0.0001$; Fisher's exact test). MS significantly decreased ($p=0.0001$; Mann-Whitney test) in the SLIT group from 4.3 to 1.7 at the end of the 3-year treatment period. In the control group MS increased from 3.5 to 4.0 at the end of trial (Figure 2). At the end of study period one patient out of 34 (3%) in the SLIT group was under treatment with inhaled corticosteroid in comparison with five out of 18 in the control group (27%) ($p=0.0077$ Fisher's exact test). Six patients in the SLIT group (17%) reported side-effects; in general mild and transient (mouth itching, gastrointestinal discomfort). One of these six patients discontinued the SLIT treatment after 8 months of treatment. No serious adverse events were observed in the two groups.

Discussion

Alternaria alternata is a common mould very frequently found as the causative agent of type I allergies in indoor and outdoor environments, particularly in regions with a warm climate⁹. Sensitivity to AA is a common cause of asthma¹⁰ but also upper respiratory tract symptoms can develop when high spore levels are present in the air. Generally, moulds first appear in the air in the spring, becoming most noticeable during the warmer months and usually disappear during colder months. Patients with allergy to moulds have symptoms from early spring through to the first frost. Epidemiological studies carried out in US and Europe have found that at least 4% of the paediatric population is sensitised to AA antigens^{11,12}. Sensitisation against AA is observed in up to 19% of patients with respiratory symptoms suggestive of allergic diseases¹³. *Alternaria* spores have been recognised as causing life-threatening episodes of asthma¹⁴. A large

Table 1. Baseline demographic and clinical characteristics for the two study groups.

	SLIT treated group (n=34)	Control group (n=18)	p value
Age (years) ($\pm$ SD)	18 ± 9	19 ± 10	n.s
Sex (men/women)	23/11	10/8	n.s
Asthma, yes/no (%)	10/24 (29%)	7/11 (38%)	0.48
Polysensitisation (%)	82%	83%	n.s
Moderate/severe rhinitis	70%	77%	0.40
<i>Alternaria</i> SPT (diameter of the wheal) mm	3.2	3.7	n.s

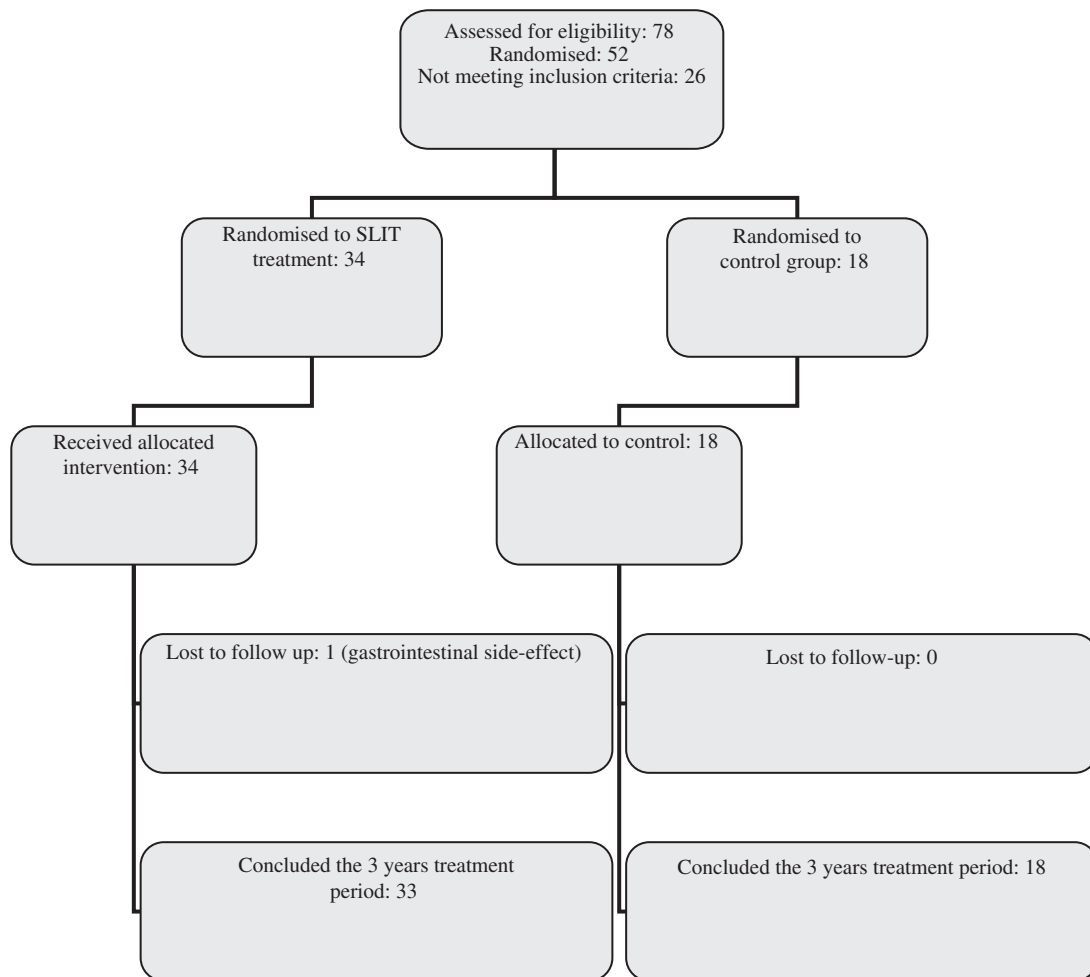


Figure 1. Study Flow.

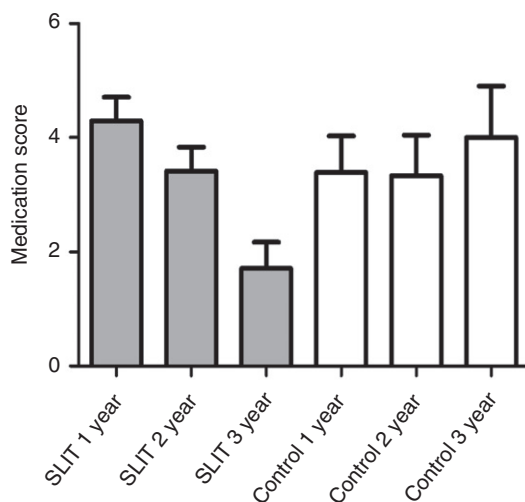


Figure 2. Changes in medication score during the 3 years of the study in the SLIT-treated group (grey bars) and in control group (white bars).

epidemiological study has shown that sensitisation to moulds is a powerful risk factor for severe asthma in adults¹⁵. In patients with severe asthma a sensitisation to AA is found in up to 8% of the cases¹⁶. Specific immunotherapy (SIT) is considered the only causative treatment of respiratory allergies such as rhinitis and asthma¹⁷. SIT is considered the only treatment with a carry-over effect and able to modify the clinical course of respiratory allergies¹⁸. SIT can also interfere with the development of the so called atopic march¹⁹. SIT is considered effective in the treatment of allergic seasonal rhinitis and asthma in both adults and children²⁰. Year-round (continuous immunotherapy) treatment with SLIT in both adults²¹ and children²² with perennial and seasonal respiratory allergic diseases has been shown to reduce significantly symptom and medication scores in 'well-designed' large sample size prospective studies. Standardised *Alternaria* extract administered with subcutaneous injections (SCIT) significantly

reduced symptoms and medication scores²³. However SCIT is associated with a high risk of systemic reactions in comparison with SLIT²⁴. Up to now, uncontrolled and open trials have been performed to evaluate the efficacy and safety of SLIT in AA allergies. In the recent WAO SLIT position paper⁵, which reported on 60 double-blind placebo-controlled trials regarding efficacy in the treatment of respiratory allergies, trials performed in AA allergic patients were not reported. In an open, 12-month uncontrolled trial Molina *et al.*²⁵ showed that sublingual immunotherapy with an AA extract was clinically effective in paediatric patients with asthma. The present study is so far the first randomised controlled trial which evaluates in the long term (i.e., 3 years) the efficacy of SLIT in respiratory allergy in *Alternaria alternata* sensitised patients. The major limitation of the present trial is that the study design was not double blind. However the evaluation of the primary outcome was performed with an assessor-blinded approach. Another factor is that the efficacy was not assessed using a validated symptom score. However the authors decided to define as the primary outcome of the trial a patient-reported outcome (PRO) as recently suggested⁸, using a VAS score. The expression 'patient-reported outcomes' (PROs) refers to 'any report coming from patients about a health condition and its treatment'²⁶. PROs are gaining increasing awareness and emphasis in clinical research and by regulatory bodies because of their relevance in the overall treatment efficacy assessment²⁷. An additional strength of the study to be taken in consideration is also the treatment duration (3 years). So far, uncontrolled or open trials were performed to evaluate the efficacy of SIT in AA allergic patient in the medium-long term. This is the first report evaluating the clinical efficacy of 3-year treatment of SLIT in patients with AA allergy.

Conclusion

The present study has shown that a 3-year course of SLIT is efficacious and well-tolerated in subjects with AA respiratory allergies. SLIT treatment is associated with a significant clinical improvement and a decrease in symptomatic drug treatment use.

Transparency

Declaration of funding

This trial was partially supported by ALK-Abellø with the supply of allergen extracts.

Declaration of financial/other relationships

M.M. has disclosed that he is an employee of ALK. He was involved in the study design and protocol preparation but not in the data analysis.

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References

- Holt PG, Macaubas C, Stumbles PA, et al. The role of allergy in the development of asthma. *Nature* 1999;402:B12-17
- Denning DW, O'Driscoll BR, Hogaboam CM, et al. The link between fungi and severe asthma: a summary of the evidence. *Eur Respir J* 2006;27:615-26
- Bush RK, Prochnau JJ. *Alternaria*-induced asthma. *J Allergy Clin Immunol* 2004;113:227-34
- Wilson DR, Lima MT, Durham SR. Sublingual immunotherapy for allergic rhinitis: systemic review and meta-analysis. *Allergy* 2005;60:4-12
- Canonica GW, Bousquet J, Casale T, et al. Sub-lingual immunotherapy: a World Allergy Association Position Paper 2009; *Allergy* 2009;64(Suppl 91):1-59
- ARIA Allergic rhinitis and its impact on asthma. ARIA workshop report. *J Allergy Clin Immunol* 2001;108(5 Suppl):1-205
- Masoli M, Fabian D, Holt S, et al. The global burden of asthma: executive summary of the GINA Dissemination Committee Report. *Allergy* 2004; 59:469-78
- Braido F, Bousquet PJ, Brzoza Z, et al. Specific recommendations for PROs and HRQoL assessment in allergic rhinitis and/or asthma: a GA(2)LEN task-force position paper. *Allergy* 2010;65:959-68
- O'Driscoll BR, Powell G, Chew F, et al. Comparison of skin prick tests with specific serum immunoglobulin E in the diagnosis of fungal sensitization in patients with severe asthma. *Clin Exp Allergy* 2009;39:1677-83
- Portnoy JM. Importance of mold allergy in asthma. *Curr Allergy Asthma Rep* 2008;8:71-8
- Hamilos DL. Allergic fungal rhinitis and rhinosinusitis. *Proc Am Thorac Soc* 2010;7:245-52
- Mari A, Schneider P, Wally V, et al. Sensitization to fungi: epidemiology, comparative skin tests, and IgE reactivity of fungal extracts. *Clin Exp Allergy* 2003;33:1429-38
- Randriamanantany ZA. *Alternaria* sensitization and allergic rhinitis with or without asthma in the French Six Cities study. *Allergy* 2010;65: 368-75
- O'Hollaren MT. Exposure to an aeroallergen as a possible precipitating factor in respiratory arrest in young patients with asthma. *N Engl J Med* 1991; 324:359-63
- Bartra J, Belmonte J, Torres-Rodriguez JM, et al. Sensitization to *Alternaria* in patients with respiratory allergy. *Front Biosci* 2009;14:3372-9
- Pulimood TB, Corden JM, Bryden C, et al. Epidemic asthma and the role of the fungal mold *Alternaria alternata*. *J Allergy Clin Immunol* 2007;120:610-17
- Bousquet J, Lockey R, Malling HJ. Allergen immunotherapy: therapeutic vaccines for allergic diseases. A WHO position paper. *J Allergy Clin Immunol* 1998;102:558-62
- Di Rienzo V, Marcucci F, Puccinelli P, et al. Long-lasting effect of sublingual immunotherapy in children with asthma due to house dust mite: a 10-year prospective study. *Clin Exp Allergy* 2003;33:206-10
- Pajno GB, Caminiti L, Vita D, et al. Sublingual immunotherapy in mite-sensitized children with atopic dermatitis: a randomized, double-blind, placebo-controlled study. *J Allergy Clin Immunol* 2007;120:164-70
- Penagos M, Compalati E, Tarantini F, et al. Efficacy of sublingual immunotherapy in the treatment of allergic rhinitis in pediatric patients 3 to 18 years of

- age: a meta-analysis of randomized, placebo-controlled, double-blind trials. *Ann Allergy Asthma Immunol* 2006;97:141-8
21. Milani M, Pecora S, Burastero S; EFESO Investigators Study Group. Observational study of sublingual specific immunotherapy in persistent and intermittent allergic rhinitis: the EFESO trial. *Curr Med Res Opin* 2008; 24:2719-24
 22. Acquistapace F, Agostinis F, Castella V, et al. Efficacy of sublingual specific immunotherapy in intermittent and persistent allergic rhinitis in children: an observational case-control study on 171 patients. The EFESO-children multicenter trial. *Pediatr Allergy Immunol* 2009;20:660-4
 23. Horst M, Hejjaoui A, Horst V, et al. Double-blind, placebo controlled rush immunotherapy with standardized *Alternaria* extract. *J Allergy Clin Immunol* 1990;85:460-72
 24. Olaguibel JM, Alvarez Puebla MJ. Efficacy of sublingual allergen vaccination for respiratory allergy in children. Conclusions from one meta-analysis. *J Invest Allergol Clin Immunol* 2005;15:9-16
 25. Molina C. Immunotherapy with an oral *Alternaria* extract in childhood asthma. Clinical safety and efficacy and effects on in vivo and in vitro parameters. *Allergol Immunopathol (Madr)* 2002;30:319-30
 26. Patrick DL, Burke LB, Powers JH, et al. Patient-reported outcomes to support medical product labeling claims: FDA perspective. *Value Health* 2007; 10(Suppl 2):S125-37
 27. US Department of Health and Human Services FDA Center for Drug Evaluation and Research. Guidance for Industry: patient reported outcome measures: use in medical product development to support labelling claims: draft guidance. *Health Qual Life Outcomes* 2006;4:79