

Expert Opinion

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Development of an allergen extract for sublingual immunotherapy – evaluation of Staloral

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Background: Specific immunotherapy (IT) is an effective treatment for rhinitis and asthma caused by aeroallergens sensitization. Sublingual IT (SLIT) was introduced to solve the problem of systemic reactions to subcutaneous IT (SCIT) and developed to represent an actual treatment option. It is now generally accepted that allergen doses much higher than those administered by SCIT must be used to achieve clinical efficacy on allergic symptoms. **Objective:** To evaluate the characteristics of Staloral, an allergen extract produced by Stallergenes (Antony, France) in terms of practical administration, efficacy, safety and mechanism of action. **Methods:** Data were obtained from 20 double-blind, placebo-controlled studies using Staloral in patients sensitized to pollens and house-dust mites, and also from open studies concerning practical administration and the mechanism of action. **Results/conclusion:** Efficacy and safety of Staloral, as demonstrated by the revision of the studies, which used doses up to 1125 times those administered with SCIT, are very satisfactory and confer to this allergen extract optimal characteristics for treating patients with seasonal allergies due to pollens or with perennial symptoms induced by dust mites. The main mechanism of action is the interaction with dendritic cells of the oral mucosa and the subsequent tolerance induced in T cells.

Keywords: allergen extracts, efficacy, high dose, safety, Staloral, sublingual immunotherapy

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1. Introduction

Allergic respiratory diseases such as rhinitis and asthma demonstrate a worldwide increasing prevalence [1,2] and currently represent a relevant health and socio-economical burden [3]. Respiratory allergy is generally managed by, when feasible, allergen avoidance, by drug treatment, and by allergen specific immunotherapy (IT). Among these treatments, IT has the capacity, not shared by the other approaches, to change the natural history of allergy by modifying the immunological response toward tolerance to the specific allergen [4]. Traditionally, IT has been administered for many decades by the subcutaneous route, but the problem of adverse reactions to such form, uncommon but possibly severe and, rarely, fatal, lead to the development of noninjection routes and particularly to the introduction of sublingual immunotherapy (SLIT) [5]. SLIT has been demonstrated in a number of studies to be similarly effective but much better tolerated than subcutaneous immunotherapy (SCIT) [6]. Allergen extract to be used for IT should have all the relevant allergens from the naturally occurring source, such as pollen, house dust mites, moulds, or animal epithelia, in a known and reproducible composition. This requirement was not fulfilled for many years by extracts for SCIT, which were measured in arbitrary Units or in protein nitrogen units (PNU), but the introduction of SLIT in 1986 [7] took place when the process of allergen extract

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Box 1. Drug summary.

Drug name	Staloral
Phase	Launched
Indication	Allergy
Pharmacology description	Immunosuppressant/ stimulant
Route of administration	Alimentary, sublingual Alimentary, general
Pivotal trial(s)	A Phase III trial in 213 grass pollen allergy patients in Germany has closed and showed effectiveness over a 3-year period

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standardization, that is, with a known composition (adherent to the original material), well representing its allergen content, and constantly reproducible on a lot-to-lot basis, was already being used to ensure adequate quality of allergen products [8,9].

2. Standardization of Staloral

The process of standardization can be summarized as follows:

1. Collection and selection of raw materials. For pollens, sieving, drying, storage, supplier checking, receiving checking. For house dust mites, the cultivation is done by STALM-ITE APF®, a nutritive medium composed of amino acids and vegetal substrates without animal- or human-derived products, adherent to European Pharmacopoeia concerning the risk of viruses or prion transmission, and with no residual allergenicity.
2. Macroscopic and microscopic identification of components from raw materials
3. Comparison of the protein profile with the in-house reference by isoelectric focusing (IEF) or sodium dodecyl sulphate polyacrylamide gel electrophoresis (SDS-PAGE)
4. Dosage of the allergen activity in comparison with the in-house reference by ELISA inhibition
5. Dosage of major allergens, that is allergens recognized by more than 50% of patients allergic to the naturally occurring allergen source
6. Extraction in optimised conditions in Good Manufacture Processing for each type of extract
7. Clarifying filtration with elimination of extractive salts and low weight molecular substances
8. Adjustment of dosage of the allergen activity in comparison with the in-house reference
9. The IR (Index of reactivity) is a biological unit, a concentration of 100 IR is determined by the capacity of the allergen to elicit by skin prick test a geometric mean wheal

size of 7 mm diameter in 30 patients sensitive to the corresponding allergen.

In Europe, allergen extracts for SLIT are currently marketed by several manufacturers, thus the amounts of allergens are quite variable in the different products. Almost all the SLIT vaccines commercialized in Europe are standardized biologically or immunologically [10], but since the standardization methods are based upon in-house references, the different extracts are labeled in units that differ from manufacturer to manufacturer. On the other hand, during the last few years the availability of the content in micrograms of the major allergens have represented a significant improvement, since this allows rough comparison of the different therapeutic regimens.

3. Practical administration

The allergen extracts for SLIT in the pharmaceutical form of solutions can be delivered by drop-counters, pre-dosed actuators (mini-pumps) or disposable single-dose vials. Staloral 100 IR (Box 1) was initially administered by a drop-counter, but then a mini-pump pre-dosed actuator was introduced, the same used in Staloral 300. The allergen extract is usually administered in the morning before breakfast. The drops are kept under the tongue for few minutes and then swallowed (sublingual-swallow method). The acronym SLIT, unless otherwise stated, indicates the sublingual-swallow modality [11,12].

In Europe, in the past allergen mixtures were quite frequently used, but now the trend is to prescribe more and more monoreferences both for efficacy and safety issues [13-15].

3.1 Administration regimens

SLIT traditionally involves a build-up or up dosing phase (with gradually increasing doses) and a maintenance phase with the top dose [16]. The build-up phase in the past had a duration of up to 4 – 6 weeks, but the duration was progressively shortened. The extract is prepared in separate vials at different and increasing concentrations. Staloral is available as concentrations 10, 100 and 300 IR. Other concentrations are available for sensitive patients. The patient must start with the lowest concentration and gradually increase, according to the physician prescription, until the maintenance dose is reached. Rush and ultra-rush inductions have been proposed also for routine use, based on the safety profile of Staloral that is very favorable, also in children under the age of 5 years [17]. Ultra-rush schemes with a build-up shorter than 2 h have been reported in adults [18] and children [19], with encouraging results both for grasses [20] and mites [21].

The maintenance dose is generally the same for all patients, based on clinical results. The maintenance dose recommended for Staloral is 4 – 10 drops once daily, depending on the physician's choice. The use of the same dose for all patients is justified by the fact that, unlike with SCIT, the administration of very high amounts of allergens does

not provoke severe side effects. In the case of SLIT the concept of 'maximum tolerated dose' is hardly applicable, and the definition of maintenance dose is more appropriate.

The maintenance dose can be administered at variable time intervals but the once daily dose [22] simplifies the regimen by giving the maintenance dose as done with almost all drugs.

3.2 Criteria for starting and stopping

Staloral can be administered either pre-coseasonally (starting 2 – 4 months before and stopping at the end of the pollen season), coseasonally (only during the pollen season) or continuously. In the pre-coseasonal and coseasonal regimen, no dose reduction during the pollen season is usually applied, since there is no decrease in safety [20]. A recent study reported that a co-seasonal schedule based on a 300 IR/day administration repeated for 3 years had a carry-over effect following Staloral discontinuation [23]. On the other hand, for nearly-perennial or perennial allergens, continuous treatment is most frequently prescribed.

4. Clinical efficacy

The first studies on SLIT were conducted with very low or low doses [7,24], but in the ensuing years it was apparent that doses much higher – 50 – 100 times – than those administered with SCIT were needed to ensure clinical efficacy [25], introducing the concept of 'high-dose SLIT'. Staloral can be classified in this category because the ratio with the extract used for SCIT is higher than 50 – in most studies higher than 300 – for all allergens used. The first study on Staloral was conducted in patients allergic to grass pollen [26] and was followed by a number of studies dealing with the same pollen (three studies), olive pollen (one study), parietaria pollen (one study), birch (one study), ragweed pollen (two studies), and cypress pollen (two studies), and with *Dermatophagoides mites* (9 studies). In all studies with grass pollen the clinical efficacy of SLIT was demonstrated by significantly lower mean symptom/medication scores – the standard parameter of efficacy – in actively treated compared with placebo-treated adult patients [22,26,27] and children [23]. A significant efficacy was reported also in the studies with olive pollen in children [28], Parietaria pollen in children [29], ragweed pollen in adults and children [30,31], and birch pollen in adults [32], while in the two studies on adult patients with cypress pollinosis effectiveness was detected concerning quality of life [33], and medication but not symptom scores [34], that is, actively and placebo-treated patients had similar symptom scores but the latter had this outcome whilst consuming significantly more drugs.

Regarding dust mites, 7 of the 9 trials (4 in adults and 3 in children) achieved a significant improvement of allergic symptoms [35-41], while two studies, one in adults [42] and one in children [43] did not report a significant clinical advantage over placebo. The significant reduction of the allergen exposure obtained by dust control measures, as demonstrated by mite allergen measurement [42] and the fact that the

patients were already under optimal pharmacologic treatment [43] were claimed to account for such findings, respectively.

Table 1 lists all the published studies evaluating Staloral and Figure 1 depicts the evolution of the SLIT:SCIT ratio from the earliest to the most recent trials. These studies provided a consistent part of the data analyzed in the meta-analyses on efficacy of SLIT concerning both the overall results [6] and the data from subgroups formed by asthmatic patients [44] and children [45,46].

In such meta-analyses the clinical efficacy of SLIT was clearly demonstrated in terms of significantly lower symptom scores and significantly lower consumption of antiallergic drugs in actively treated than in placebo-treated subjects, and regarding adult and pediatric patients suffering from allergic rhinitis and allergic asthma. In the first meta-analysis dedicated to SLIT in allergic rhinitis, Staloral was the main contributor in terms of number of patients.

In two studies different doses of Staloral were compared, it was demonstrated that the 300 IR maintenance dose had optimal effectiveness in terms of clinical [30], and immunological [47] response.

5. Safety and tolerability

SLIT was proposed with the specific rationale of improving safety and therefore this issue is of particular importance. As known from the abundant literature, the majority of adverse events (AEs) involve the digestive system. Most of AEs can be easily managed by dose modification or, in cases of disturbing gastrointestinal reaction, by swallowing avoidance, that is spitting the extract after having kept it under the tongue [48]. It must be considered that SLIT is self managed at home by the patient and, therefore, the reporting of side effects is generally higher in clinical trials than in everyday clinical practice or post-marketing surveys.

It is of utmost importance that no fatality has ever been described. The most frequently described side effects in children and adults are the immediate onset of oral/sublingual itching after taking the dose, followed in frequency by stomachache, nausea or diarrhea. These events are mostly described as mild and self-resolving without dose adjustment or medical actions. Only exceptionally must SLIT be discontinued. Systemic side effects (e.g., asthma, rhinitis, urticaria, angioedema) are reported only occasionally in the available controlled studies. Also in children local oral side effects are frequent. In a study using a particularly high dose [29], the occurrence of nausea, stomachache and oral symptoms was 20% in the active group and 2% in controls.

André *et al.* in 2000 examined the safety of SLIT in the eight trials performed with Staloral available at that time [49]. These studies involved 690 subjects (347 active + 343 placebo), with 218 children aged 5 – 16 years (103 active + 115 placebo). The large majority of events were mild and their occurrence did not differ in active and placebo groups. The only differences were the oral and gastrointestinal side effects that were more

Table 1. Published studies of SLIT with Staloral.

Author, year (ref.)	Allergen	Maintenance	Protocol	Treatment duration	Major allergen Dose/month mean	SLIT/SCIT ratio
Sabbah, 1994 [26]	Grass pollen	Daily	Pre coseasonal	4 months		50
Vourdas, 1998 [28]	Olive pollen	Daily	Pre-coseasonal	2 yrs	675 µg Ole e 1	300
Clavel, 1998 [22]	Grass pollen	Daily	Pre-coseasonal	6 months	433.3 µg Phl p5	500
Pradalier, 1999 [27]	Grass pollen	Daily	Pre-coseasonal	4 months	233.8 µg Phl p 5	150
La Rosa, 1999 [29]	<i>Parietaria</i> pollen	3/week	Continuous	2 yrs	2187,5 µg Par j 1	375
Bousquet, 1999 [36]	Dust mites	3/week	Continuous	1 yr	175 µg Der p 1	450
Mungan, 1999 [37]	Dust mites	2/week	Continuous	1 yr		80
Guez, 2000 [42]	Dust mites	3/week	Continuous	2 yrs	91,7 µg Der p1	450
Bahceciler, 2001 [38]	Dust mites	2/week	Continuous	6 months	93.3 µg Der p1	70
Mortemousque, 2003 [39]	Dust mites	3/week	Continuous	2 yrs	91.7 µg Der p 1	450
Andr�, 2003 [30]	Ragweed pollen	3/week	Pre-coseasonal	7.5 months	4893.3 µg Amb a 1	200
Bowen, 2004 [31]	Ragweed pollen	Daily	Coseasonal	2.5 months	7305.7 µg Amb a 1	1125
Khinch, 2004 [32]	Birch pollen	3/week	Continuous	2 yrs	465.9 µg Bet v 1	175
Tonnel, 2004 [40]	Dust mites	Daily	Continuous	2 yrs	53,3 µg Der p 1	375
Niu, 2006 [41]	Dust mites	Daily	Continuous	6 months	283.3 µg Der p 1	1125
Di Rienzo, 2006 [33]	Cypress pollen	Daily	Pre-coseasonal	4 months		900
Lue, 2006 [35]	Dust mites	Daily	Continuous	6 months	283.3 µg Der p 1	1125
Vervloet, 2007 [34]	Cypress pollen	Daily	Coseasonal	4 months	6840 µg Jun a 1	1125
Pham-Thi, 2007 [43]	Dust mites	Daily	Continuous	18 months	383.3 µg Der p 1	1125
Ott, 2009 [23]	Grass pollen	Daily	Coseasonal	3 yrs	500 µg Phl p 5	1125

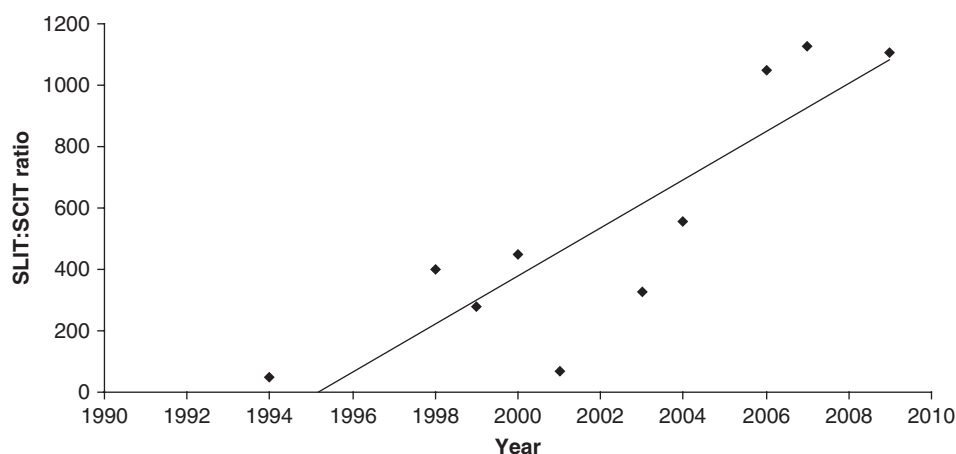


Figure 1. Sublingual immunotherapy:subcutaneous immunotherapy (SLIT:SCIT) ratios used from the earliest to the latest studies.

frequent in SLIT patients, although mild. The rate of side effects and dropouts was similar in adults and children.

In 2005 a systematic review of the published studies evaluated the occurrence of AEs according to the dose expressed as the ratio between SLIT and the equivalent SCIT [50]. Twenty-five studies were analysed altogether: 13 studies belonged to the low-dose group (doses ranging from 1 to 50 times the dose commonly administered with SCIT), and 12 belonged to the high-dose group (doses ranging from 50 to 500 times the dose administered with SCIT). Local reactions were significantly more frequent in the low-dose group than in the high-dose group ($p < 0.0001$), while there was no difference in the rate of systemic reactions. Severe systemic reactions were never reported. This review provided evidence that AE occurrence during SLIT, unlike during SCIT [51], is substantially not dose-dependent.

Recently, two cases of anaphylaxis were reported, but one case was actually not of the anaphylactic type (no respiratory or cardiovascular involvement, treatment with only antihistamines) [52], while the other concerned a 16-year old girl treated with a mix of *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* (50:50) who resumed SLIT, after a 3-week break in maintenance dose of 100 IR, with a high overdose of the extract [53].

Another notable demonstration concerned the possible use of high-dose SLIT in children younger than 5 years, that is the limit suggested for performing SCIT. An observational study with Staloral 300 was performed on 65 children, treated with SLIT with a build-up phase of 11 days, culminating in a top dose of 300 IR and a maintenance phase of 300 IR 3 times a week [17]. The allergens used were house dust mites in 42 patients, grass pollen in 11 patients, olive pollen in 5 patients, *Parietaria* pollen in 4 patients, and cypress pollen in 3 patients. All adverse reactions and changes in the treatment schedule were compared in two subgroups: children aged less than 5 years and more than 5 years. The average cumulative dose of SLIT was 36,900 IR. Adverse reactions were observed in 11 children, none of them severe enough to require discontinuation of immunotherapy. Six reactions occurred in the less than 5 years age group and 7 in the older age group, with no differences between these groups.

6. Mechanism of action

The therapeutic and preventative capacities of IT are related to its mechanisms of action [54]. In particular, IT has a demonstrated effect on allergic inflammation, which persists after its discontinuation, and modifies the natural history of allergy. The antiinflammatory effects of IT, including SLIT, is based on the ability to modify the phenotype of T cells, which in allergic subjects is characterized by a prevalence of the TH2 type, with production of IL-4, IL-5, IL-13, IL-17 and IL-32 cytokines [55]. IT-induced changes result in a TH1-type response (immune deviation) related to increased

IFN- γ and IL-2 production or reduced TH2 activity, through a mechanism of anergy or tolerance. It is now known that T cell tolerance is characterized by the generation of allergen-specific Treg cells, which produce cytokines such as IL-10 and TGF- β with immunosuppressant and/or immunoregulatory activity [56]. Recent studies suggest that the antiinflammatory mechanism of SLIT is similar to classical, subcutaneous IT [57,58], with a prominent role in SLIT for mucosal dendritic cells. Of note, in *in vitro* experiments was found that the internalization of allergens by Langerhans-like dendritic cells was dose-dependent [59]. The tolerance pattern promoted by dendritic cells and driven by Treg should account for the suppressed or reduced activity of inflammatory cells and for the isotypic switch of antibody synthesis from IgE to IgG, and especially to IgG4. The dose-dependence of the immunological response was also demonstrated in clinical studies on patients treated by SLIT with Staloral 300 [47]. Moreover, data obtained from biopsies clearly indicated that the pathophysiology of the oral mucosa plays a pivotal role in inducing tolerance to the sublingually administered allergen [60,61]. In particular, in subjects treated with high-dose SLIT by grass pollen Staloral 300 in biopsies carried out before SLIT there was a very low number of mast cells and eosinophils – the effector cells of allergic reactivity – both in the epithelium and subepithelium layers, and insignificant changes were detected after SLIT [61]. This shows the lack of allergic inflammation in the oral mucosa upon contact with the specific allergen and confirms the role of the mouth as a tolerogenic site, which is conceivable considering the different attitude of the mouth, where the antigens transit to undergo digestion, in respect to the airways or the skin, where antigen absorption is potentially dangerous [62]. However, this is a reasonable hypothesis but there is not yet firm proof of it.

7. Conclusion

Staloral is an effective treatment for rhinitis and asthma caused by sensitization to aeroallergens. It is now generally accepted that allergen doses much higher than those administered by SCIT must be used to achieve clinical efficacy on allergic symptoms. Such doses can be safely administered because the data on tolerability and safety of high-dose SLIT are reassuring. Efficacy and safety of Staloral, as demonstrated by 20 double-blind, placebo-controlled studies, which used doses up to 1125 times those administered with SCIT, are very satisfactory and confer to this allergen extract optimal characteristics for treating patients with seasonal allergies due to pollen or with perennial symptoms induced by dust mites.

8. Expert opinion

IT has unique characteristics for the treatment of respiratory allergy because is aimed at inducing tolerance to the responsible allergen(s) and at modifying the natural history of the disease and these goals cannot be reached by drugs, which have actions

limited to symptoms and are do not extend their effectiveness after discontinuation of treatment. SLIT is increasingly used in Europe and in some countries has become the most commonly used form of IT.

Still, there are possible developments to further increase the performance of SLIT, which consist of introduction of innovative tools for treatment monitoring and evaluation of the cost-effectiveness.

8.1 Introduction of innovative tools for treatment monitoring

Compliance is a pivotal issue in allergen immunotherapy. IT in any form requires substantial commitment by the patients, who must undergo regular (usually monthly) injections when SCIT is chosen, and daily (or very frequent) administration of the allergen extract when SLIT is chosen, for a prolonged time, generally at least three years.

According to established definitions, compliance is 'The extent to which a patient's behavior matches the prescriber's advice' and adherence is 'The extent to which the patient's behavior matches agreed recommendations from the prescriber' [63].

Early studies, when only the subcutaneous route was available, reported a low compliance, ranging from 45% to 60%, but the inconvenience of the demanding schedules used, with frequent injections, accounted for this outcome [64,65]. The use of more friendly schedules increased the compliance to about 90% [66].

SLIT has different compliance issues from SCIT, because it is administered at home by patients themselves and thus it is not affected by most causes reported for non-compliance to SCIT, having instead compliance problems similar to drug treatment. In some studies not specifically designed for compliance (for instance safety and tolerability analyses) was reported that treatment withdrawal is frequently caused by repeated local reactions in the mouth or at gastrointestinal level [6,48]. Studies specifically addressing the issue observed that a lack of compliance to SLIT may be caused by the erroneous perception that once allergic symptoms are improved, SLIT is no longer needed [67]. The overall compliance ranged from 72% to 85% [68,69], while the adherence value was between 75% and 97% [70,71].

It is evident that compliance to SLIT may be improved, to this aim a large group of Italian allergists was interviewed to identify the factors to implement in patient's management in future. The correct perception of clinical efficacy was considered the most important factor positively influencing adherence, followed by the possibility of reimbursement and by the absence of side effects [72].

8.2 Evaluation of the cost-effectiveness of SLIT

Currently, cost-effectiveness is an important matter in medicine. Some studies addressed this aspect in SLIT treatment with Staloral. The first published study dealt with the evaluation of cost effectiveness of SLIT in children with allergic rhinitis

and asthma, assessed by direct costs (drugs, specialists visits, and SLIT) and indirect costs (costs resulting from children's school and parental work loss). A substantial reduction was found in all outcome measures during SLIT compared with the previous period, indicating that high-dose SLIT may be effective in reducing the global cost of allergic rhinitis and asthma [73].

The second study was performed on a cohort of adults with pollen allergy and was conducted using a decision tree developed and populated with epidemiological and resource utilization data concerning about 2200 patients [74].

Target population were young adults suffering from pollen-induced rhinitis with or without asthma. Time perspective was established at 6 years in order to include long-term effectiveness of SLIT, and patients' data were collected from 25 Italian centers.

Main assessment criteria for the two different strategies were: i) costs, including the direct medical costs assessed in the National Health Service (NHS) perspective (visits, diagnostic procedures, drugs, SLIT and hospitalizations) and the direct plus indirect costs (lost working days) and patient out-of-pocket expenses assessed in the societal perspective; ii) effectiveness end-point, including: number of patients improved and number of asthma cases avoided; and iii) incremental cost per improved patient and incremental cost per asthma case avoided.

Cost analysis was performed in order to define the lowest cost strategy. A mean cost per patient treated over a period of 6 years was calculated for each therapeutic strategy and for each of the two perspectives studied. The SLIT strategy resulted in less expense in terms of both direct and indirect costs. The break-even point of SLIT, that is the time in which the overall cost of treatment for SLIT patients becomes lower than for patients receiving only drugs for the societal perspective was reached at year 4.

The third study evaluated the economics of SLIT in patients with pollen allergy and suffering from allergic rhinitis alone or associated with asthma compared with standard case controls [75]. This study was made with a longitudinal observational database operated by a network of Allergy centers. Patients were randomly assigned to SLIT (plus drugs as needed) or to treatment with drugs alone. The outcome measures included use of drugs, SLIT, visits and tests. Costs were assessed from the perspective of the Italian NHS.

The results showed that the overall per patient yearly cost of treatment was higher in SLIT patients, both in the whole sample (€311 versus €180/patient), in rhinitis (€288 versus €116) and rhinitis associated with asthma (€362 versus €230) sub-groups. Patients with rhinitis plus asthma generated more costs than those with rhinitis alone in both groups. Nevertheless, considerable savings were obtained in the cost of symptomatic drugs (-22% for rhinitis, -34% for rhinitis plus asthma) in SLIT patients, thus focusing the use of symptomatic drugs as an important indicator of effective allergy control. Previous efficacy studies provided evidence that SLIT can reduce the use of drugs, but this survey was the first

to demonstrate this outcome in a routine care population, in the medical practice environment of an observational study, and at the first year of treatment.

These studies clearly indicate that SLIT may be very beneficial to the healthcare system, in that either it could bring more clinical effectiveness at a reduced cost versus standard drug treatment, or it could bring extra benefit at an acceptable extra cost, thus fully accomplishing cost effectiveness. Still, considering the growing expectations of prescribers and

payers along with the spreading use of new technologies, further studies are needed to account for the different types of patients, management processes and healthcare settings [76].

Declaration of interest

Several of the co-authors are from Stallergenes (the manufacturer of staloral, the drug discussed in this paper). F Marcucci and C Incorvaia act as scientific consultants for Stallergenes.

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