

Original article

Sublingual immunotherapy in daily medical practice: effectiveness of different treatment schedules – IPD meta-analysis

Jochen Sieber

Stallergènes GmbH, Kamp-Lintfort, Germany

**Juliane Köberlein
Ralph Mösges**University of Cologne, Institute of Medical Statistics,
Informatics and Epidemiology, Cologne, Germany**Address for correspondence:**

Dr. Jochen Sieber, Stallergènes GmbH,
Carl-Friedrich-Gauss-Str. 50, 47475 Kamp-Lintfort,
Germany.
Tel.: +49 2842 9040-112; Fax: +49 2842
9040-2112; HSieber@stallergenes.de

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Abstract**Objective:**

To compare the effectiveness of perennial and co-seasonal high-dose sublingual immunotherapy (SLIT) treatments as well as ultra-rush and classical titrations in a real-world setting for pollen allergens.

Methods:

An individual patient data (IPD) meta-analysis was performed of three open, prospective observational studies on high-dose SLIT using IR-standardised allergen extracts in patients with allergic rhinitis with and without asthma.

Results:

In total, 1052 patients aged 24.9 years (mean) were treated with SLIT and included in this IPD meta-analysis. Individual studies and total data pool analyses revealed consistent improvements in rhinoconjunctivitis symptom scores. Stratified analyses revealed consistent improvements in symptomatic score and medication score regardless of the type of sensitisation and type of treatment. Ultra-rush titration resulted in considerably more pronounced improvement in symptom scores than classical titration, possibly due to better compliance of patients receiving that supervised titration. Adverse events occurred in 24% of patients during titration and in 18% of patients during maintenance treatment. The vast majority of events (89% and 87%) were mild-to-moderate, predominantly local symptoms in the oral cavity. There were no differences detected between the study titration or treatment schedules. No serious adverse reactions were reported. Nearly all patients (88%) decided to continue SLIT after completion of the studies.

Conclusion:

High-dose SLIT with seasonal allergens given as co-seasonal or perennial treatment appears to be effective and well-tolerated in daily medical practice. Improved compliance under ultra-rush titration and seasonal SLIT treatment may further enhance effectiveness. Randomised controlled trials are requested for the further evaluation of these findings.

Introduction

Allergic rhinitis is a symptomatic disorder of the nose induced after allergen exposure by an immunoglobulin E (IgE)-mediated inflammation of the membranes lining the nose^{1,2}. The recommendation to use sublingual-swallow immunotherapy (SLIT) in children and adults with allergic rhinitis evolved over several years based on the following key publications: the World Health Organization (WHO) position paper on allergen immunotherapy³, the Allergic Rhinitis and its Impact on Asthma (ARIA) Workshop Group paper in collaboration with the WHO (2001)¹ and its 2008 update², the Cochrane

review of SLIT for allergic rhinitis based on 22 studies involving 979 patients (children and adults)⁴, a meta-analysis evaluating the efficacy of SLIT in the treatment of allergic rhinitis in children and adolescents aged 3–18 years⁵, and the World Allergy Organization position paper on sublingual immunotherapy⁶. The optimal dose for the sublingual treatment of allergic rhinoconjunctivitis to grass pollen could be identified⁷ and a sustained effect of SLIT on symptoms after treatment cessation was shown⁸. In contrast, subcutaneous immunotherapy (SCIT) is effective in children and adults, but it is burdened by the risks of side-effects². These side-effects may be life-threatening².

Over the past 10 years, the allergen doses used for SLIT increased up to 1125 times the dose commonly administered with SCIT⁹. A meta-analysis showed that the incidence of adverse events associated with SLIT were not dose-dependent¹⁰. Twenty-five controlled studies on SLIT were subdivided into two groups: studies using low allergen doses ranging from 1 to 50 times the dose commonly administered with SCIT (13 studies) and studies with high allergen doses ranging from 50 to 500 times the dose administered with SCIT (12 studies). 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.

Traditional SLIT dosing regimens consisted of an induction phase lasting a couple of months followed by a maintenance phase of years. More than 10 years ago, a rush pre-seasonal treatment schedule reaching the maintenance dose in 15 days with twice-daily administrations was studied in 34 adult patients with grass pollen-induced allergic rhinoconjunctivitis and shown to be safe and well-tolerated¹¹. More recently, an ultra-rush high-dose SLIT regimen reaching the maintenance dose of 300 IR (index of reactivity) allergen extract within 90 min (30–90–150–300 IR) proved to be safe in adult patients allergic to cypress¹² or grass pollen⁸. During the ultra-rush titration phase, only local adverse events such as mouth and tongue itching occurred in both the SLIT and placebo groups. Up to the present, ultra-rush high-dose SLIT regimens were evaluated in four studies with children^{13–16}. The empirically derived recommendation to titrate SLIT as well as SCIT seems to be still valid, because a direct start with the maintenance dose may lead to anaphylactic reactions¹⁷.

Controlled clinical trials that focus on efficacy and safety as their specific aim are often conducted under tightly-controlled research conditions. These studies often involve very select patient populations, the results of which cannot be extended to all patients with allergic rhinitis. Studies of clinical effectiveness have evolved in response to the need for more real-world information about treatment alternatives and patient outcomes.

The authors performed an individual patient data (IPD) meta-analysis of three open, prospective observational studies on high-dose SLIT using standardised allergen extracts (Staloral 300; Stallergènes S.A., Antony, France) in patients with allergic rhinitis to compare the effectiveness of perennial and co-seasonal treatments as well as ultra-rush and classical titrations.

Methods

Study drug

Standardised allergen extracts in aqueous solution were used for SLIT. Biological activity of the extract was assessed in comparison with an internal standard *in vitro* and *in vivo*, and expressed as an index of reactivity (IR)¹⁸. The allergen extracts used contained allergens of the following allergen groups: grasses (predominantly sweet vernal grass, cocksfoot, rye grass, timothy, meadow grass), rye, weeds, trees (predominantly birch, alder, hazel).

Patient selection

All three studies recruited patients with a medical history of allergic rhinitis or rhinoconjunctivitis with or without mild-to-moderate asthma. Due to the observational character of the trials, no strict inclusion and exclusion criteria could be applied. The patient selection was based on the recommendations in the summary of the product characteristics (SmPC). Therefore, as main characteristics of the patients, positive skin prick tests to at least one of the aforementioned allergens and presence of specific IgE ≥ 0.7 kU/L were required as well a positive clinical history for the respective allergen. Patients with severe asthma should not be included. Co-sensitisation to perennial or seasonal allergens was allowed.

Study design

Study 1 (perennial treatment with classical titration)

From November 2000 to March 2002, 451 patients aged 2–80 years were treated in Germany. Classical SLIT titration started at 1 IR, reached the daily maintenance dose of 150 IR on day 24, and was followed by a maintenance phase at 150 IR once daily (OD) for 5 days a week (Monday to Friday).

Study 2 (co-seasonal treatment with ultra-rush titration)

From January 2003 to October 2003, 254 patients aged 9–72 years were treated in Germany. Ultra-rush titration at the beginning of the season reached the maintenance dose within 90 min (30–60–120–240 IR) and was followed by a co-seasonal maintenance phase at 240 IR OD.

Study 3 (perennial or co-seasonal treatment)

From September 2000 to December 2003, 358 patients aged 3–78 years were treated in Germany (279 patients), Switzerland (50 patients), and Italy (30 patients) with either a co-seasonal or perennial schedule. Classical SLIT titration started at 10 IR reached the daily maintenance dose of 240 IR OD on day 11. The titration was either started at the beginning of the respective season or in autumn in the year before the pollen season. It was followed by a maintenance phase with either 240 IR daily until the end of the season or 240 IR on alternate days perennially.

The co-seasonal treatment in the respective studies started at the anticipated beginning of the pollen seasons based on the local pollen calendars. The perennial treatment started in autumn of the year preceding the pollen season to be evaluated. In all three studies, patients were asked for a retrospective assessment of symptoms during the previous year at initiation of SLIT. At the end of the evaluated season, symptoms during SLIT were assessed. The combined rhinoconjunctivitis symptom score consisted of the six symptoms sneezing, rhinorrhea, nasal pruritus, nasal congestion, ocular pruritus, and watery eyes. Mild, moderate, and severe intensity of the individual symptoms were scored as 1, 2, and 3, respectively. Moreover, the use of concomitant symptomatic medications such as antihistamines, mast cell stabilisers, and oral or local corticosteroids was scored as 1, 2, and 3 for once weekly, several times weekly, and several times daily uses, respectively for each medication.

Data analysis

To avoid any bias upon data consolidating, only variables which were assessed in all three studies were chosen for the analysis file, i.e. the rhinoconjunctivitis scores during the year before SLIT and during SLIT, respectively. A pre-defined protocol described the processing of the different variable groups both during the synthesis process and subsequent to it. Following data synthesis, the data sets were examined with respect to plausibility and occurrence of errors. If it was not possible to rectify the variables of a data set, missing values were assumed. After plausibility control, patient data sets with less than 50% of all data necessary for the calculation of analysis parameters were planned to be excluded from the final analysis file. None of the data sets was actually excluded.

The following variables were available for analysis:

- Demography (age, gender, duration of rhinitis, sensitisation)
- Allergen extract used for SLIT (kind of allergens, start and end of titration phase, kind of titration, i.e. ultra-rush versus classical)

- Symptom scores (severity and frequency of rhinoconjunctivitis symptoms)
- Symptomatic medication use
- Adverse events during titration and maintenance phase (type and severity)
- Decision to continue/discontinue SLIT after the first year of treatment

The three studies were first analysed individually. A subsequent analysis of the total data pool was used for descriptive statistics. In both cases, the statistical analysis was primarily based upon descriptive and explorative data analysis methods. The demographic data were checked for homogeneity among studies, and ordinal parameters were examined by means of contingency tables. Both the Kruskal–Wallis test and the Mann–Whitney U-test were used to examine differences between studies.

During stratified analysis, the studies were used both individually as well as summarised in a total data pool. The evaluation of each study with a subsequent synthesis of the results served to estimate the overall effect. In the analysis of the total data pool, calculations of the overall effect and analysis of variance (ANOVA) for possible influencing factors were performed.

The total data pool was stratified as follows:

- (1) Monosensitisation vs. polysensitisation
- (2) Perennial treatment vs. co-seasonal treatment
- (3) Classical titration over 11–24 days vs. ultra-rush titration within 2 h
- (4) Patients without asthma vs. patients with asthma
- (5) Various age groups (≤ 10.3 ; 10.3–21.4; 21.4–36.6; > 36.6 years of age)
- (6) Various durations of disease (≤ 1.2 ; 1.2–3.1; 3.1–6.4; > 6.4 years)
- (7) Seasonal rhinitis vs. perennial rhinitis (based on timelines of clinical symptoms)
- (8) Birch pollen allergen extract vs. tree pollen allergen extract (mixture of birch, alder, hazel) in patients with tree pollen allergy
- (9) Five-grass pollen allergen extract vs. allergen extracts containing various grasses, grains, and rye pollen in patients with grass pollen allergy
- (10) Tree pollen allergen extract vs. allergen extracts containing tree, grass, and weed pollens
- (11) Grass pollen extract vs. allergen extracts containing tree, grass, and weed pollens

The efficacy of individual strata was compared using two-sided statistical tests. Differences were considered statistically significant at a p -value of less than 0.05.

Estimation of the study-specific effects and examination for homogeneity

The estimations of effects were based on symptom scores and use of concomitant medications. These parameters are

Table 1. Demographic and treatment data.

	Study 1	Study 2	Study 3	Total
Treatment schedule (titration)	Standard titration	Ultra-rush titration	Standard titration	N.A.
Treatment schedule (duration)	Perennial (<i>n</i> = 451)	Co-seasonal (<i>n</i> = 254)	Perennial (<i>n</i> = 203) or co-seasonal (<i>n</i> = 149)	N.A.
Mean cumulative dose (IR)	12,100	13,600	Perennial 32,400 co-seasonal 28,700	N.A.
Gender 'male' (%)	56.1	36.7	53.7	50.7
Gender 'female' (%)	43.9	63.3	46.3	49.3
Mean age (years)	20.0	38.3	21.7	24.9
Mean duration allergic rhinitis (years)	4.4	10.0	4.3	5.6

ordinal numbers. Nevertheless, procedures for continuous variables were applied, a widely used approach for meta-analyses. Weighted mean differences were calculated and checked for homogeneity. Variability in patient characteristics and conduct of the studies were used to explain heterogeneous study-specific effects.

Estimation of the pooled effect

The overall effect was estimated using the 'inverse variance' method. For homogeneous and heterogeneous study-specific effects, the 'fixed effect' and 'random effects' models were used.

Pooled analysis

Significant differences in efficacy between strata appeared were analysed by ANOVA for possible influencing factors. A model with constant and random variable effects was applied. The variable 'study affiliation' constituted the random variable effect.

Results

In total, 1052 patients aged 2–80 years (mean age $\pm$ standard deviation: 24.9 ± 16.6 years) and treated with the IR-standardised sublingual allergen extract were included in this IPD meta-analysis. There were 521 male and 507 female patients. In 24 patients, the gender was not reported. Significant differences between studies 1 and 2 as well as 2 and 3 ($p < 0.001$) were detected for both age (Mann–Whitney U-test) and gender (chi-squared test). Mean overall duration of allergic rhinitis was 5.6 years with significant differences between studies. Demographic data are shown in Table 1. 69% of patients had only seasonal allergic rhinitis, 31% additionally rhinitis caused by perennial allergens. The majority of patients were sensitised to tree (57%) and grass pollens (including cereals and rye, 62%) [sensitised to grass alone: 8.2%]; 41% were polysensitised; 42% of patients had coexisting allergic asthma. The overall mean duration of SLIT was 19 weeks with substantial differences between studies: 9 weeks in

study 2 and 26 weeks in study 3. The most frequently used allergen extracts contained tree pollens from the Betulaceae family (49.9%) and grass pollens from the Pooideae family (41.6%). The remaining prescriptions contained weeds alone or in mixture with tree or grass pollens.

Efficacy results

Results of individual studies and total data pool

Compared to the retrospectively assessed rhinoconjunctivitis symptom score of the previous year, the mean overall improvement in the score was 2.3 during the investigational period. Figure 1 displays the severity of rhinoconjunctivitis symptoms in the pooled analysis. Figure 2 displays the individual studies' rhinoconjunctivitis symptom scores. Figure 3 displays the concomitant use of symptomatic medications in individual studies. Similar results were seen for the individual groups of symptomatic medications, i.e. antihistamines, mast cell stabilizers, and corticoids.

Results of stratified analyses

Rhinoconjunctivitis symptoms improved during SLIT to a similar extent during co-seasonal and perennial treatments (Figure 4). Compared with classical titration, ultra-rush titration resulted in numerically better results for the improvement of rhinoconjunctivitis symptoms. (Figure 5). However, the difference was not significant ($p = 0.09$). The same applied to the reduction in concomitant use of symptomatic medications (Table 2).

Age and duration of allergic rhinitis or sensitisation status did not have any significant influence on the improvement of rhinoconjunctivitis symptoms. The use of symptomatic medications was reduced to a greater extent in younger patients and patients with a shorter history of allergic disease (Table 3).

The type of causative allergen(s) did not reveal any conclusive results suggesting the preferred use of a particular combination of allergens in therapeutic extracts used in high-dose SLIT.

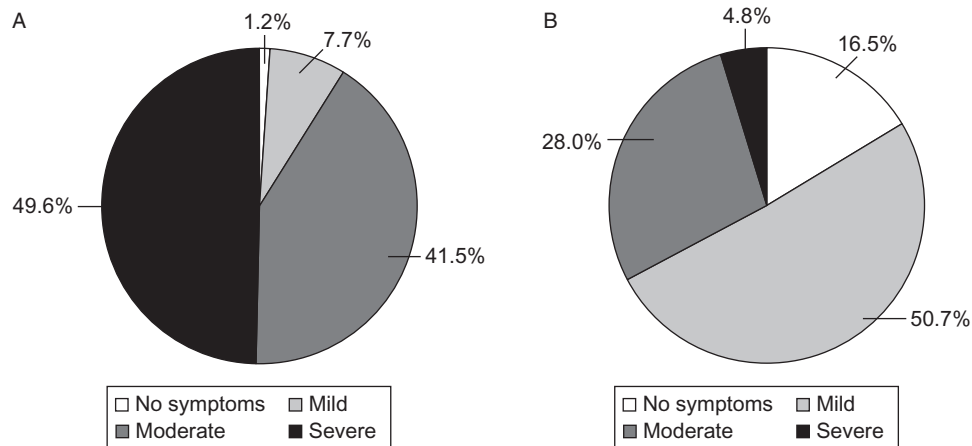


Figure 1. Percentage of patients with different grades of severity of rhinoconjunctivitis symptoms (pooled analysis). A. Previous year; B. Treatment year.

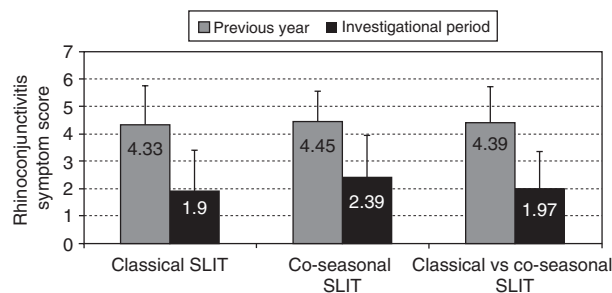


Figure 2. Rhinoconjunctivitis symptom scores (individual studies, mean, SD); p -values for differences between baseline and investigational period <0.0001 for all treatment modalities.

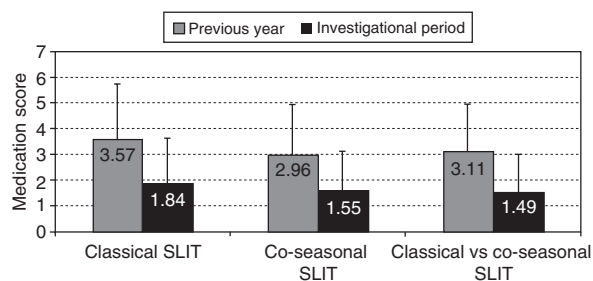


Figure 3. Total score for concomitant use of symptomatic medication (individual studies, mean, SD); p -values for differences between baseline and investigational period <0.0001 for all treatment modalities.

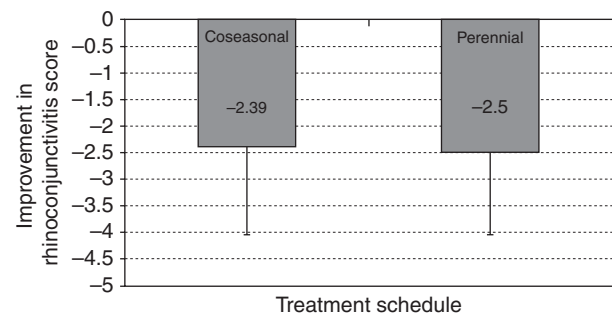


Figure 4. Rhinoconjunctivitis scores stratified by treatment schedule (mean, SD, $p=0.09$ for difference between groups).

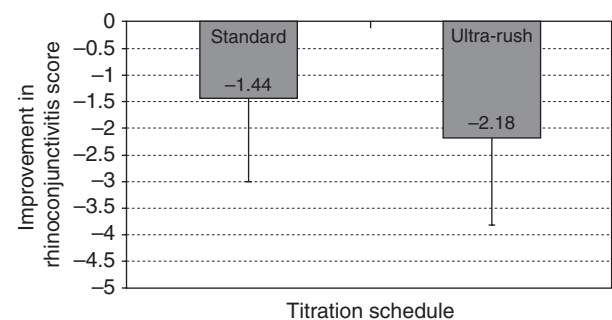


Figure 5. Rhinoconjunctivitis scores stratified by titration (mean, SD, $p=0.09$ for difference between groups).

Safety

Adverse events occurred in 24% of patients during titration and in 18% of patients during maintenance treatment. The vast majority of events (89 and 87%) were mild to moderate, predominantly local symptoms in the oral cavity. There were no differences detected between the different titration or treatment schedules. No serious adverse reactions were reported. Nearly all patients (88%) decided to continue SLIT after completion of the studies.

Discussion

The authors performed an IPD meta-analysis of three open, prospective observational studies on high-dose SLIT using IR-standardised allergen extracts in patients with allergic rhinoconjunctivitis with and without asthma to compare the effectiveness of perennial and co-seasonal treatments as well as ultra-rush and standard titrations. Individual studies and total data pool analyses

Table 2. Changes of medication scores in stratified analyses.

Variable	Stratum	n	Mean	SD	p-value
Sensitisation	Mono-sensitised	553	2.05	1.51	0.965
	Poly-sensitised	387	2.02	1.44	
Asthma	Concomitant asthma	373	1.93	1.51	0.099
	w/o concomitant asthma	501	2.07	1.41	
Disease duration	<1.2 years	211	1.73	1.31	<0.001
	1.2–3.1 years	217	1.81	1.39	
	3.1–6.4 years	220	2.22	1.47	
	>6.4 years	214	2.51	1.64	
Age	<10.3 years	232	1.67	1.35	<0.001
	10.3–21.4 years	235	1.94	1.37	
	21.4–36.6 years	245	2.34	1.48	
	>36.6 years	236	2.22	1.61	

Table 3. Changes of rhinoconjunctivitis scores in stratified analyses.

Variable	Stratum	n	Mean	SD	p-value
Sensitisation	Mono-sensitised	553	2.28	1.59	0.965
	Poly-sensitised	387	2.40	1.67	
Asthma	Concomitant asthma	373	2.31	1.62	0.099
	w/o concomitant asthma	501	2.40	1.60	
Disease duration	<1.2 years	211	2.39	1.64	0.325
	1.2–3.1 years	217	2.45	1.68	
	3.1–6.4 years	220	2.30	1.57	
	>6.4 years	214	2.23	1.72	
Age	<10.3 years	232	2.24	1.55	0.430
	10.3–21.4 years	235	2.50	1.60	
	21.4–36.6 years	245	2.30	1.57	
	>36.6 years	236	2.27	1.75	

revealed consistent improvements in rhinoconjunctivitis symptom scores.

Stratified analyses revealed consistent improvements in rhinoconjunctivitis symptom scores as well as symptomatic medication score regardless of the type of sensitisation and type of treatment. This confirms that what has been shown regarding the efficacy in poly- versus monosensitised patients in randomised controlled trials^{7,19} can also be expected in daily medical practice. The same effectiveness of co-seasonal and perennial SLIT treatment may have an impact on the yearly treatment cost of hyposensitisation. Whether the restriction of the treatment duration to the pollen season, i.e. the time of the symptoms may lead to an improved compliance remains to be evaluated. Ultra-rush titration resulted in considerably more pronounced improvements in symptom scores. It is not clear at the moment whether this may be attributed to a presumed better compliance of patients receiving this form of supervised titration or whether it is due to the fact that ultra-rush titration accelerates the time until the onset of efficacy as has previously been shown for ultra-rush venom immunotherapy²⁰ which may even have diminished the difference in the cumulative doses. On the other hand, the lack of precise drug accountability in non-interventional trials such as the ones in the current

meta-analysis makes it difficult to estimate this effect. Controlled trials are requested to confirm this finding.

It may be further noted that due to the non-interventional character of the trials, a placebo treatment was not foreseen. However, the 'placebo effect' is usually a rescue medication effect or an effect of fewer symptoms during an absence of exposure²¹. The reduction of scores in the observational trials included in this IPD meta-analysis is comparable to what has been shown in randomised placebo-controlled trials with similar SLIT preparations^{8,22} and results of the present study were essentially in line with results of other observational studies on SLIT in children and adults^{23–26}. The effectiveness of SLIT in daily medical practice compares with the efficacy seen in controlled clinical trials^{4,27}.

The trials in this IPD meta-analysis were prospective observational studies with a retrospective assessment of the symptoms in the pollen season before the treatment and observation period. This approach was chosen for practical reasons and is considered robust because the retrospective assessment of seasonal symptoms has been evaluated in a study with birch-pollen allergic patients²⁸. Here, symptoms were assessed by the same four-point verbal descriptor scale as was used in the present studies. The retrospective assessment could detect the impact of SIT on nasal and eye

symptoms. The authors concluded that retrospective assessment of symptoms tends to over-rate average symptom severity, but appears sufficiently sensitive to detect treatment efficacy.

Traditionally, medical decisions are primarily based on the evidence of clinical efficacy and safety, i.e. evidence from controlled clinical trials that focus on efficacy and safety as their specific aim. Efficacy is measured under tightly-controlled research conditions. These studies often involve highly selected patient populations, the results of which cannot be extended to all patients with allergic rhinitis. Studies of clinical effectiveness have evolved in response to the need for more real-world information about treatment alternatives and patient outcomes.

For 2 decades now, the concepts of efficacy and effectiveness have been examined from the viewpoints of the traditions and philosophies of health-care research and social programme evaluation²⁹. For the development of health-promotion programmes, eight phases of research are suggested: basic research, hypothesis development, pilot applied research, prototype evaluation studies, efficacy trials, treatment effectiveness trials, implementation effectiveness trials, and demonstration evaluations²⁹. The great need is to consider trials which are more effective, and which test the value of medical measures under more real-world conditions compared with controlled clinical trials²⁹.

RCTs with placebo and an active comparator are designed to assess the safety and efficacy of drugs and the design of such RCTs emphasises internal validity over generalisability³⁰. The active comparison with a control group was not possible in the present study because of the non-interventional character of observational studies, but comparisons with placebo are not necessary in meta-analyses, while head-to-head evaluations are becoming more common when the effectiveness of different treatments are being compared.

Effectiveness studies, in which treatments are studied under real-world conditions, usually account more for generalisability to actual users, but data may be biased in other ways³⁰. As there were no confounding factors identified by the ANOVAs performed in this IPD meta-analysis, the authors trust in the validity of the current effectiveness assessments.

Combining data for a systematic review of the literature can be accomplished by either a meta-analysis of published results or a pooled analysis of primary data. Until recently, it was customary for meta-analysis to be carried out using the aggregated summary of studies published in journals, especially randomised controlled trials. Meta-analysis of such aggregated data is limited because randomised controlled trials only measure efficacy and not effectiveness and a meta-analysis of aggregated results published in a journal is limited to the outcome and exposures reported.

Because of this it is becoming more feasible to obtain the full study datasets from the original researchers, making a synthesised overview using information at the patient level possible. This has become known as meta-analysis of individual patient data (IPD), although other terms such as 'mega-analysis' or 'pooled analysis' have been used. To-date, these IPDs have largely been carried out on RCT data but there is a growing potential for combining observational data^{31,32}. The results presented in this article had been generated in an IPD meta-analysis of observational studies. The techniques used to perform such meta-analysis are often similar to those used for RCTs. Observational studies are prone to a greater degree of bias than RCTs. Nevertheless this study design was used to generate conclusions about the effectiveness of SLIT in daily practice and to evaluate with this approach, not just the efficacy of the intervention. To ensure the quality of analysis, two common approaches^{31,32} for an IPD meta-analysis were used and all available observational studies concerning the investigated drug collected.

Conclusions

High-dose SLIT with seasonal allergens given as seasonal or perennial treatment appears effective and well-tolerated in daily medical practice. Improved compliance under ultra-rush titration and seasonal SLIT treatment may further enhance effectiveness. Randomised controlled trials are requested for the further evaluation of these findings.

Transparency

Declaration of funding

Stallergènes GmbH provided funding for this research and subsequent papers.

Declaration of financial/other relationships

J.S. has disclosed that he is an employee of Stallergènes. R.M. has disclosed that he has been a speaker or consultant or has received research or other funding from several pharmaceutical companies in addition to Stallergènes. J.K. has no conflicts of interests that are directly relevant to the content of this manuscript.

Some peer reviewers receive honoraria from CMRO for their review work. The peer reviewers of this paper have disclosed that they have no relevant financial relationships.

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