



Long-term efficacy of specific subcutaneous, short-term MPL adjuvant immunotherapy over three treatment and three follow-up years, as measured by quality of life

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Abstract

Background Apart from allergen avoidance, specific immunotherapy (SIT) is the only causal treatment for pollen allergy diseases. Its efficacy and tolerability have been demonstrated in numerous studies on adults and children. There are fewer studies, however, evidencing a long-term treatment effect and the effect of treatment on patients' quality of life (QoL).

Patients and methods The aim of this prospective, noninterventional postmarketing surveillance (PMS) study was to document QoL with, and long-term effect of, an MPL (monophosphoryl lipid A)-adjuvanted allergoid involving four injections over 3 treatment years and 3 follow-up years. In the period from 2006–2012, 223 pollen-allergic individuals from 12 centers were evaluated annually. The patients completed standardized questionnaires on QoL for each pollen season. Symptoms documented in the QoL questionnaire were temporally aligned with data from regional pollen traps.

Results Patients with allergy to pollen from early bloomers (birch, alder, hazel), as well as patients with grass/rye allergy, showed a continuous improvement in treatment effect over the 3 treatment years and a good carry-over effect in follow-up years 1–3.

Conclusion Short-term MPL adjuvant therapy showed good efficacy at 3 years following treatment completion and is suited to the long-term improvement of patient QoL.

Keywords Quality of life · Allergic rhinoconjunctivitis · Allergic asthma · Long-term effect · Medication use · SIT

Abbreviations

AQLQ	Asthma Quality of Life Questionnaire
DBPC	Double-blind placebo-controlled
DEGS	Study on Adult Health in Germany (<i>Studie zur Gesundheit Erwachsener in Deutschland</i>)
EMA	European Medicines Agency (formerly EMEA)
IgE	Immunoglobulin E

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MAR	Missing at random
ML	Maximum likelihood
MPL	Monophosphoryl lipid A
PAT	Preventive allergy treatment
PMS	Postmarketing surveillance study
QoL	Quality of life
RAST	Radioallergosorbent test
RQLQ	Rhinoconjunctivitis Quality of Life Questionnaire
SCIT	Subcutaneous immunotherapy
SIT	Specific immunotherapy
SLIT	Sublingual immunotherapy

Introduction

The lifetime prevalence of allergic rhinoconjunctivitis in the German population is estimated to be 14.8% and 8.6% for allergic asthma (Study on Adult Health in Germany DEGS1, German Federal Law Gazette 2013). In the German federal state of Brandenburg, for example, 11.7% of school leavers in 2015 suffered from a clinically manifest allergic respiratory disease (www.gesundheitsplattform.brandenburg.de).

Against this backdrop, preventive measures and therapies that treat the root cause of this widespread disease are of considerable importance in terms of health care. There are numerous studies on the efficacy of specific immunotherapy (SIT). The majority of these studies evaluated SIT on the basis of symptom and medication scores. No reliable laboratory parameters for monitoring and evaluating its clinical effect are available as yet. While appreciating the extensive study material that already exists, there are two important aspects of SIT that have been less well documented: the patient's perception of their health and life status and the carry-over effect years following treatment completion.

Objectives

Our study followed the development of allergy-related symptoms over a 3-year period of subcutaneous im-

muno-therapy (SCIT), followed by a 3-year follow-up. Primary target parameters were changes to quality of life (QoL) and the long-term efficacy of short-term SCIT using an MPL adjuvant allergoid in pollen-allergic individuals. Other target parameters included medication use, tolerability, and adherence.

Study design

The study was an open, prospective postmarketing surveillance (PMS) study on a large patient collective, and evaluation was carried out by both the physician and patients.

Methods

In 2006, 223 patients in whom SIT was indicated for rhinoconjunctivitis and/or asthma in allergy to pollen from early blooming trees or grasses were recruited from 12 practices. The guideline-adherent [27] diagnostic work-up included mandatory prick testing and/or optional specific IgE detection using RAST (radioallergosorbent test) with a minimum class 2 finding. The clinical relevance of allergens that tested positive in skin or in vitro testing was established on the basis of patient history using standardized questions: type, severity, and duration of symptoms, onset in which months; any additional sensitization to perennial or mould allergens (exclusion criterion). Provocation testing was also optional in the case of doubt. Patients were provided with detailed information on the planned study and endorsed the physician's documentation as well as their own documentation compiled using a standardized and validated questionnaire (Rhinitis Quality of Life Questionnaire [RQLQ] and Asthma Quality of Life Questionnaire [AQLQ]) according to Juniper ([1, 2]; Fig. 1). After a thorough baseline evaluation prior to treatment initiation, patients were interviewed and evaluated annually by their physician both during and shortly before the end of the pollen season and given a QoL questionnaire to complete independently.

Fig. 1 Overview of the AQLQ and RQLQ questionnaires

RQLQ (Rhinoconjunctivitis Quality of Life Questionnaire)	AQLQ (Asthma Quality of Life Questionnaire)
No impairment whatsoever ranging to severely impaired (0–6)	No impairment whatsoever ranging to severely impaired (0–6)
- Activities (at home and work, contact with others, sex, hobbies, outdoor activities, activities with pets) - Sleep - General symptoms (reduced performance, weakness, fatigue, difficulties concentrating, headache) - Practical problems (frequent nose-blowing, eye-rubbing) - Nasal symptoms - Eye symptoms - Mental well-being	- Strenuous or moderately strenuous activities - Sleep - Symptoms or impairments due to: chest tightness, cough, shortness of breath, wheezing, gasping, difficulties exhaling, clearing of the throat, increased sensitivity to cigarette smoke, dusts, air pollution, odors - Concerns, anxiety - Overall impairment in activities

Patients

At the start of data collection, case report forms for 132 tree pollen-allergic patients and 91 grass pollen-allergic patients aged between 7 and 69 years (median 33 years) were documented. Of these patients, 58% were female and 42% male. All patients suffered from allergic rhinoconjunctivitis. In addition, 41% of the tree pollen-allergic patients and 32% of the grass pollen-allergic patients suffered from asthma. None of the patients had undergone hyposensitization during the 3 years prior to study initiation.

Disease severity was evaluated prior to treatment initiation on the basis of patient self-assessment using a point system of 0–12 for rhinoconjunctivitis and 1–2 for asthma.

The percentage of tree pollen-allergic patients that rated the initial severity of their rhinoconjunctivitis as 8–12 was almost 20% higher compared with the grass pollen-allergic individuals (71% versus 53%). The percentage of asthma patients was also higher in the tree pollen-allergic group compared with the grass pollen-allergic group (40.9% versus 31.9%).

The distribution of asthma severity (grade 1 or 2) was comparable in both groups.

The median disease duration prior to treatment initiation was 6 years.

Treatment

All patients received preseasonal SIT consisting of a tyrosine-adsorbed allergoid plus 50 µg MPL in four injections at incremental doses according to the product information.

Statistical analysis

When evaluating the time course, analysis of the QoL questionnaire was performed according to Juniper [1, 2] using a longitudinal model in which the model parameters were estimated according to the maximum-likelihood principle. This approach yielded valid results even in the case of incomplete datasets assuming a drop-out structure according to MAR (missing at random) [3, 4] and is therefore superior to usual variance analysis procedures. The children's questionnaires according to Juniper were not analyzed separately due to low numbers ($n = 3$) and were included instead in the overall evaluation. All calculations were performed using the SAS Institute software Proc Mixed (Version 9.1, 2007). A third-order polynomial with a significant estimated value was chosen as the modeling approach.

Results

Adherence/compliance

In total, 84.8% of tree pollen-allergic and 80.2% of grass pollen-allergic patients completed the 3-year therapy. Follow-up in the third year following the completion of SIT was possible in 67% of tree pollen- and 63% of grass pollen-allergic patients. There was no shift in the gender ratio (58% female, 42% male).

Percentage of asthmatic patients with tree pollen allergy

Of 54 patients with pre-existing asthma at the start of treatment (41% of $n = 132$), 49 could be followed-up in the second year, 41 in the third, 35 in the fourth, 32 in the fifth, and 31 in the sixth year.

Between the second treatment year and third follow-up year, new-onset asthma symptoms were recorded in 11 patients, i.e., 8.8% of 132 patients. By contrast, 7 patients no longer reported asthma symptoms during the treatment and follow-up periods (13% of 54).

Grass pollen allergy patients

Of 29 patients with pre-existing asthma at the start of treatment (32% of $n = 91$), 28 could be followed-up in the second year, 25 in the third, 21 in the fourth, 20 in the fifth, and 18 in the sixth year.

Between the second treatment year and third follow-up year, new-onset asthma symptoms were recorded in 5 patients, i.e., 5.5% of 91 patients. By contrast, 7 patients no longer reported asthma symptoms during the treatment and follow-up periods (7% of 29).

Quality of life

Data compiled from the patient questionnaires showed a marked improvement in QoL during the three treatment years, as well as a stable carry-over effect for up to 3 years following SIT completion (follow-up), in both tree pollen-allergic and grass pollen-allergic patients.

RQLQ: Rhinoconjunctivitis Quality of Life Questionnaire

A total of 28 parameters in seven main groups were rated by patients, each on a scale of 0 ("no impairment whatsoever") to 6 ("extremely impaired") and statistically analyzed as normalized or partial totals (also on a scale of 0–6). In each treatment cycle, the questions related to: (a) the middle and (b) the end of the relevant pollen season. The relevant time window for each questionnaire was determined at short notice based on pollen counts and meteorological conditions.

Mean total scores ($\pm$ standard deviation) of 3.4 ± 0.9 (trees) and 3.0 ± 1.0 (grasses) were seen prior to SIT initiation. Following the first treatment cycle, results (maximum-likelihood estimators [ML estima-

Fig. 2 Total rhinitis score for tree pollen-allergic patients from 2007–2012. Values in the treatment and follow-up years are each for the middle and the end of the season

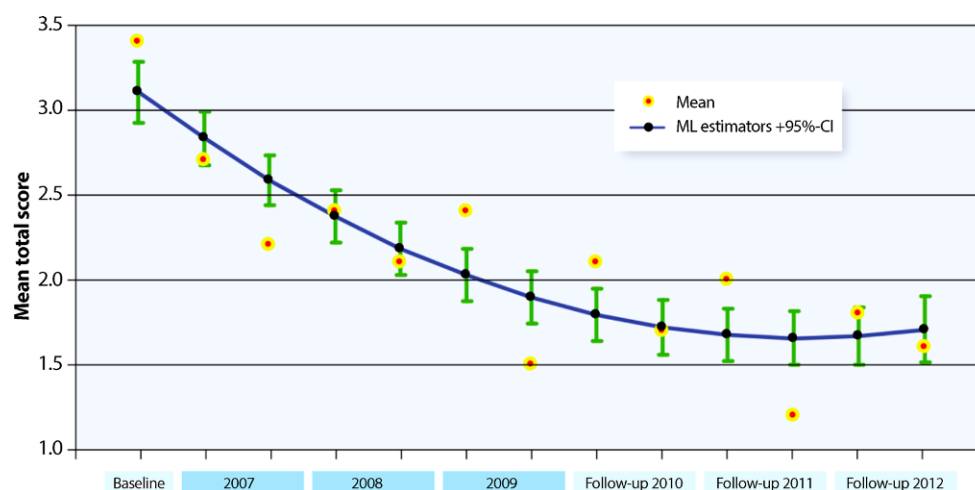
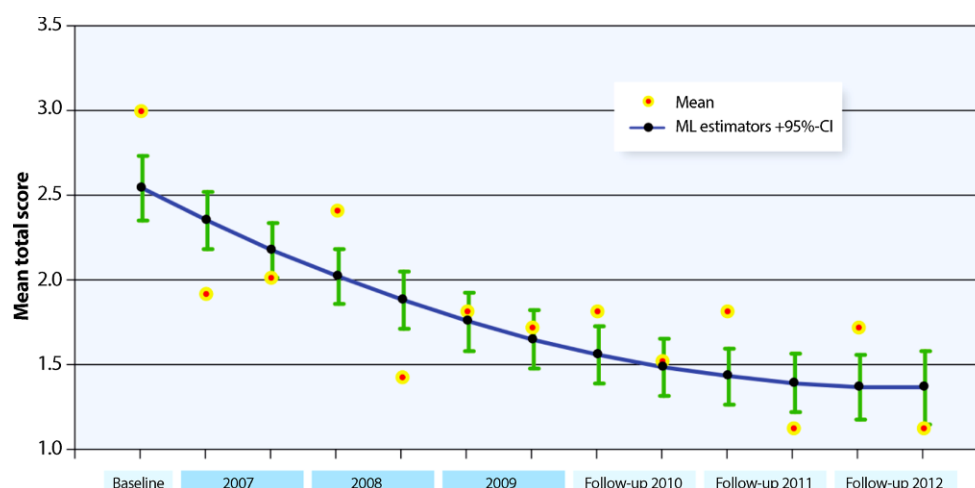


Fig. 3 Total rhinitis score for grass pollen-allergic patients from 2007–2012. Values in the treatment and follow-up years are each for the middle and the end of the season



tors]) were on average 17% (trees) and 15% (grasses) lower; following the second treatment cycle, these were 30% and 27% lower, respectively. Following the third treatment cycle, a mean reduction of 39% and 36%, respectively, was seen compared with baseline estimations, corresponding to a mean improvement of 1.2 (tree pollen) and 0.9 (grass pollen) score levels (significant changes in both allergy groups; $p < 0.0001$).

This status remained stable during follow-up between 2010 and 2012.

Figs. 2 and 3 show changes in the rhinitis total score for both grass and tree pollen patients.

AQLQ: Asthma Quality of Life Questionnaire

A total of 32 parameters in the patient questionnaire were summarized as total scores or partial totals (four factors) on a six-point scale (0 = “no impairment whatsoever” to 6 = “fully impaired”). In order to maintain equivalent scales for rhinitis and asthma, the item values on the asthma scale were inverted from the original: 1 = “fully impaired” to 7 = “no impairment whatsoever.” This resulted in no change in the statistical characteristics of the asthma scale.

Mean total scores ($\pm$ standard deviation) of 2.4 ± 1.2 (trees) and 2.4 ± 1.0 (grasses) were seen prior to SIT initiation. Following the first treatment cycle, results (ML estimators) were on average 20% (trees) and 23% (grasses) lower; following the second treatment cycle, these were 35% and 39% lower, respectively. Following the third treatment cycle, a mean reduction of 45% and 49%, respectively, was seen compared with baseline estimations, corresponding to a mean improvement of at least one score level (significant change; $p < 0.0001$).

This status changed for both allergens by the end of the follow-up period (2012) in the form of a non-significant average increase by 0.2 score levels.

Figs. 4 and 5 show the changes in the total asthma score for both grass and tree pollen patients.

Medication use

During end of season-appointments, the physician asked patients about their use of symptomatic anti-allergy agents (systemic antihistamines; cortisone, antihistamine, and anticongestive nose drops; cortisone- and antihistamine-containing eye drops; cortisone-,

Fig. 4 Total asthma score for tree pollen-allergic patients from 2007–2012. Values in the treatment and follow-up years are each for the middle and the end of the season

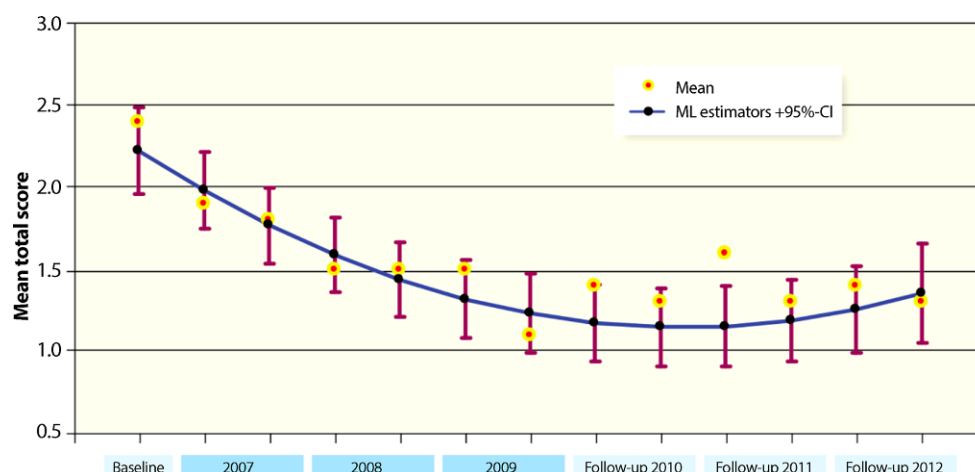
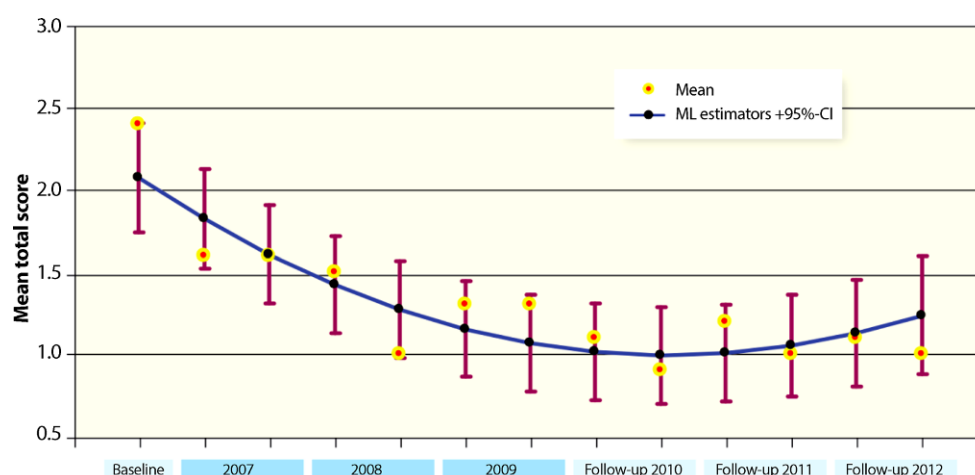


Fig. 5 Total asthma score for grass pollen-allergic patients from 2007–2012. Values in the treatment and follow-up years are each for the middle and the end of the season



DNCG-, and sympathomimetic-containing asthma sprays) during the previous pollen season, and the information was semiquantitatively analyzed: regularly (two to three times per week or more); often (once a week), occasionally (two to three times per month), never (Fig. 6).

During the 2006 pollen season, 72.7% of tree pollen patients and 72.5% of grass pollen patients used anti-allergy drugs “regularly”. Following the third therapy year, these percentages diminished to 12% (trees) and 1% (grasses), followed by an increase to 28% (trees) and 9% (grasses) in the third follow-up year. The improvement was significant (Wilcoxon matched pairs test; $p < 0.0001$) in all six observational years for both allergens.

Tolerability

Adverse or unexpected local and systemic events were documented in detail and recorded statistically in accordance with reporting obligations. Side effects were predominantly mild and local in nature. Two reactions were classified as “severe”; one of these cases involved painful swelling as well as hardening and erythema at

the injection site, the other hyposmia (delayed reaction, causality unlikely).

In addition, the physician carried out a general assessment at the end of each treatment cycle during the 3 treatment years. The tolerability of treatment using tree pollen allergens was rated as “very good” or “good” for 85.6% of patients in the first treatment cycle, 90.2% in the second, and 98.2% in the third. Grass pollen allergens received similar ratings: physicians estimated tolerability to be “very good” or “good” in 93.4% of patients in the first treatment cycle, 97.5% in the second, and 100% in the third.

Discussion

Our study followed changes in allergy-related symptoms during 3-year SCIT and 3-year follow-up. The long-term clinical effect of SIT is one of its most important efficacy parameters and one that has been demonstrated in only a handful of studies. In order to evaluate the efficacy of SIT, the European Medicines Agency (EMA) [5] recommends analyzing – above and beyond symptom scores and medication use – aspects of QoL. In addition to the typical physical symptoms of allergic rhinoconjunctivitis (e.g., sneezing, watery

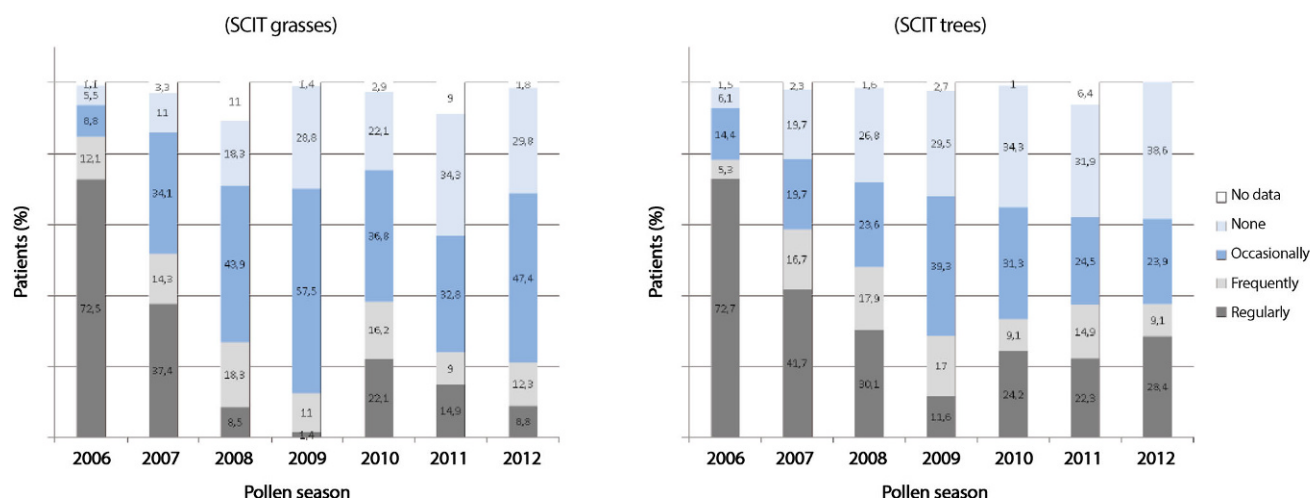


Fig. 6 Use of antiallergic medication for subcutaneous immunotherapy (SCIT) in grass and tree pollen allergic patients

nasal secretion, nasal blockage, conjunctivitis) and bronchial asthma, widely varying parameters, such as sleep behavior, physical activity, concentration, and practical everyday activity, effect well-being and life satisfaction on an individual basis. In order to get a picture of these highly differing dominant parameters, which also vary in terms of severity, a number of working groups have developed disease-specific questionnaires. We used the Rhinitis Quality of Life Questionnaire and the Asthma Quality of Life Questionnaire according to Juniper. These questionnaires have been developed and extensively validated for SIT [1, 2].

It is thanks to these QoL assessments that the extent of impairment caused by chronic disorders, such as allergic disease, is less underestimated today. Allergies have a significant negative effect not only on individual well-being, but also on economic and social aspects of life. Recent investigations demonstrate the effect of allergy-related concentration disorders, fatigue, and loss of energy on work performance, school performance, social contact, and safety [6–11].

Subscores in the rhinoconjunctivitis questionnaire in our study revealed the parameters “practical problems”, “activities”, and “nasal problems” to be particularly burdensome from a patient perspective. These findings tally with other studies that have worked with the Juniper Rhinitis Quality of Life Questionnaire [12–14].

In order to document disease-specific information, it is important to be aware of current allergen exposure. The vast majority of patients included in the study lived and worked within a 50-km radius of pollen traps belonging to the Johanner Hospital im Fläming, Treuenbrietzen, Germany, mostly in rural areas. Physicians and patients were given narrow timeframes for data collection, depending on pollen counts at the Treuenbrietzen pollen station or the Bonn center for regional data at the time. We hoped that by comparing certain threshold values for pollen

levels at the start of the season, meteorological conditions at the time, and experience from previous years we would be able to identify reliably peak exposure times for patients. However, it became apparent that the specified time period of 7–10 days, as compared with the data subsequently mapped by the German Meteorological Service, was unable to yield sufficiently predictive forecasts of the actual maximum pollution levels.

A growing number of factors capable of affecting pollen levels and allergic potency are being identified, even in microclimates. For example, grass pollen studies show that, if humidity is high, pollen can fragment while still in the pollen sac, thereby forming respirable particles. High levels of these are released particularly if humid conditions are followed by dry weather [26]. One can also assume that, after high pollen counts followed by rain and despite only low pollen counts in pollen traps, the pollen lying on the ground ruptures and respirable allergenic particles are released into ambient air. It is possible that the use of personal pollen samplers and precise day-to-day data recordings are required in order to show convincing correlations.

Allergic pollen asthma in adults is predominantly associated with allergic rhinoconjunctivitis; in our patient population, all asthmatics also suffered from rhinoconjunctivitis. By considering treatment results separately, one obtains practice-relevant information, in particular for SIT.

In all, 54 (41%) of tree pollen-allergic and 29 (32%) of grass pollen-allergic patients included in the study additionally suffered from asthma. As in the rhinoconjunctivitis patients, a significant improvement in QoL was achieved under treatment in both allergen groups. The total score (ML estimators) among asthma patients with tree pollen allergy dropped from 2.2 prior to treatment to 1.2 following the third year of treatment. In the third follow-up year, 6 years after treatment initiation, the score still

showed an improvement at 1.3 compared with the baseline score. The corresponding figures for asthma patients with grass pollen allergy were a score reduction from 2.08 prior to treatment to 1.07 following the third treatment year and to 1.1 in the third follow-up year.

A number of new-onset asthma cases were seen over the course of the study, whereas asthma resolved in other patients (see results, percentage of asthmatic patients).

A comparison of the scant numbers available for asthma onset years following SIT completion is generally difficult due to the varying study designs and parameters. We suggest to consider results from the Preventive Allergy Treatment (PAT) study [15] 7 years following SIT completion: new-onset asthma was seen in 25% (16 of 64) of children who were asthma-free at baseline (versus 24 of 53 children, i. e., 45% in the no-SIT control group).

Medication use, as annually assessed by physicians, showed a clear trend toward improvement in both allergen groups. Medication use dropped continuously up to treatment completion and then stabilized – at a significantly lower level versus baseline – up to the end of follow-up 3 years following treatment completion.

A number of prospective studies, albeit of varying design, have investigated whether and for how long treatment success persists following SIT completion [12–20]. Double-blind placebo-controlled (DBPC) studies showing evidence of efficacy for up to 3 follow-up years are only available for more recent sublingual immunotherapy (SLIT) preparations, which were already subject to the stringent regulations of the Therapy Allergen Ordinance at the clinical trial stage [24]. Studies on the long-term effects on asthma and new-onset asthma were carried out in children in particular. With the exception of three children, our patient population comprised adults. The new regulations on presenting placebo-controlled treatment outcomes over several follow-up years will yield greater insight into the long-term efficacy of SIT. Compared with randomized studies, acceptance and reliability in PMS studies are inherently limited in their ability to define causalities, particularly due to the wholly desirable mean variation in patient parameters in daily practice. Nevertheless, PMS will remain an indispensable instrument of open studies in large practice collectives. With regard to the study discussed here, the fact that it dispensed with an integrated base year should be viewed critically.

One of the main problems encountered in all long-term observational studies is motivating as many patients as possible to participate up to the designated study end. In our study, we observed treatment adherence of 93% among tree pollen-allergic patients in the second and 85% in the third year of treatment. The grass pollen-allergic group showed treatment adherence of 90% in the second and 80% in the third

year of treatment. These figures are extremely good compared with the literature [21, 22]. At the end of the 3-year follow-up period, 67% of tree pollen- and 63% of grass pollen-allergic patients were still available to answer questions and complete the questionnaire. These results were undoubtedly due to the well-maintained physician–patient relationship and good acceptance of the short-term configuration, involving only four injections per year and requiring relatively little logistical effort on the part of patients.

Ensuring and maintaining patient compliance and adherence are treatment-relevant tasks of the physician and largely determine the success of SIT. A model based on vaccination methods could be extremely helpful in guaranteeing success even after treatment completion: if a patient experiences reduced effectiveness, a repeat treatment cycle of only 1 year is performed as a “booster dose” [18, 19, 23]. A more recent study with the preparation used in this study shows that a one-off booster cycle of four injections 4–8 years following SCIT in patients experiencing renewed symptoms significantly improves the clinical picture [25].

The question arose in conjunction with this study as to whether a treatment duration of 3 years is in actual fact sufficient for all patients. If it became established procedure for allergy patients to visit their physician annually following completion of their basic treatment, the duration of SIT could be made dependent on treatment effect.

Conclusion

This 6-year PMS-study demonstrates that QoL and medication use in patients undergoing short-term immunotherapy with an allergoid experience a marked and relevant improvement and remain stable over a 3-year follow-up period compared with baseline findings. In addition, patients with manifest allergic asthma benefit from this form of SIT. Patients undergoing short-term immunotherapy (four injections/year within 3 to maximum 8 weeks) demonstrate high treatment adherence.

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Conflict of interest U. Rabe, J. Altengarten, E. Benke, A. Erdmann, A.-P. Erdmann, G. Fiedler, S. Hofmann, B. Jasch, U. Kallien, S. Knuppe-Andree, H.-J. Lüdcke, K. Lohse and M. Piller declare that they have no competing interests.

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