Specific Sublingual Immunotherapy

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Citation

A Al-Shehri. *Specific Sublingual Immunotherapy*. The Internet Journal of Asthma, Allergy and Immunology. 2001 Volume 2 Number 2.

Abstract

The present long-term study shall determine the extent of reduction of intake of different classes of symptomatic medication under SLIT in patients with IgE-mediated allergic reactions to aeroallergens.

INTRODUCTION

The therapeutical principles of treating immunoglobulin-E mediated allergic reactions are based on medical symptomatic treatment and allergen avoidance as well as specific hyposensitization both as causal therapy.

In a large scale of controlled studies hyposensitization to inhaled allergens has been proved effective for patients with immunoglobulin-E mediated allergic reactions, especially to pollen and insect venom. Besides the parenteral and oral specific immunotherapy the sublingual administration of soluble allergen extracts for specific hyposensitization was proposed in the eighties [Holt et al. 1988, Scadding and Brostoff 1986].

Still the mechanisms of immunotherapy are not fully understood. Treating with grass-pollen allergens can dampen both early-phase and late-phase responses, the latter associated with reduction of infiltration of eosinophils into the airway mucosa [Holt et al. 1998]. Additionally the cytokine profile of the T-helper lymphocytes changes from the Th2 pattern towards the atopy-inhibitory Th1 profile. Holt et al. [1998] suggest that theoretically “prolonged treatment could imprint this response pattern into long-term Th-cell memory” so as to provide protection against allergic reaction to the same allergen. In addition to these “immune-deviation mechanisms” T-cells may either actively be suppressed or permanently removed.

Bousquet et al. [Clavel et al. 1995] as well as Tari et al. [1990] found a significant decrease of specific IgG4 under sublingual immunotherapy as often described under subcutaneous hyposensitization.

The oral mucosa is one important site to induce immunological tolerance to protein antigens. In sublingual immune therapy there is a repeated exposure of the mucosa to considerable amounts of modified allergens. This tolerance induction may give way for a down regulation of immune-inflammatory responses. In an experimental study of Van Wilsem et al. [1994] they postulated that the Langerhans cells of the oral epithelium act as antigen-presenting cells irrespective of the source and route of antigen administration. The possible interaction between these cells and local lymphocytes as well as conditions in the lymph nodes themselves may determine whether antigen contact leads to tolerance or activation. In another experimental study Seifert [1997] showed that the oral application of antigens induce a significant reduction of circulating antibodies which are partially eliminated across the intestinal wall into the lumen of the gut.

However, there still is a controversy about the oral route of hyposensitization, although a significant improvement of clinical symptoms as well as a reduction of the consumption of symptomatic medication under the sublingual therapy was shown in several clinical studies [Niekert et al. 1987; Tari et al. 1990; Feliziani et al. 1993; Sabbah et al. 1994]. Most of the studies still cannot provide consistent findings on pathologic patterns, so that until now score of symptoms and reduction of medical treatment are the best to reflect the efficacy of long term immunotherapy. A recent study on 375 patients with seasonal pollen associated allergic reactions showed an equivalent efficacy of the sublingual therapy in comparison with the subcutaneous specific immunotherapy [Corthay et al. 1996].

The present long-term study shall determine the extent of reduction of intake of different classes of symptomatic

medication under SLIT in patients with IgE-mediated allergic reactions to aeroallergens.

MATERIAL AND METHODS

182 patients treated with SLIT were documented in a two-year follow-up study. Course of therapy was documented on patients mit IgE-mediated (type 1) allergic rhinitis/conjunctivitis and/or asthma. The performance of the sublingual specific immunotherapy should last at least for 12 months. The documentation included demographic data, data referring to diagnosis including concomitant diseases, therapy of allergic diseases, the sublingual specific immunotherapy with, therapy ongoing at the time of documentation or already terminated, course of symptoms and concomitant, adverse reactions as well as physician's assessment of efficacy and tolerance.

The study included all data on ongoing specific immunotherapy on specified time of documentation as well as the documentation of already regularily or premature terminated therapy. Reasons for premature terminated therapy should be documented and adverse reactions should be specified on the adverse reaction sheets as well.

The treatment consisted of graded amounts of soluble allergen extracts of Stalmed SL®, which was graded into four vials with preparations of allergen extracts from 0.1 to 100 RI. Stalmed SL is a biological standardised allergene extract adjusted to the unit RI (relativity index), in which a soluble allergen extract with 100 RI causes a wheal with a mean diameter of 7 mm in a Prick skin test in allergic patients. The patients received increasing doses of the extract, starting with 1 drop from vial 1 and increasing by one drop daily to 10 drops on the tenth day, following the graded course up to vial 4, the drops being taken sublingually in the morning before breakfast and being kept sublingually for 1 minute and then swallowed. Maintenance therapy consisted of 10 drops dayly and was reduced to three times after 6 months of therapy. Interval dose reduction or interruption of therapy concerned seasonal pollen output and individual course of symptoms during the pollen season.

Intake of symptomatic medication was assessed in different classes of antiallergic drugs.

The statistical analysis was based on all patients included in this study. Symptoms were scored in a 5-point verbal rating scale. Intake of symptomatic medication was assessed in different classes of anti-allergic drugs. In addition intake of symptomatic medication was registered semi-quantitative in relation to medication before start of desensitisation on a 5 scale verbal rating scale as well. For this purpose the prescription rate and dosage of each drug was documented during the study. For quantification of symptomatic medication pharmacy use before treatment was documented by the doctor with dosage and number of daily application of each drug and then followed up by counting the number of prescriptions from one check-point to the other, and again control of the number of daily applications. Medication was judged to be somewhat reduced if reduction was specified at the range of about 25 % of prior use, reduced if reduction was about 50 %, and markedly reduced if 75 % or more.

A summary analysis as well as a subgroup analysis was carried out. Continuous variables were described by mean value, standard deviation, median minimum and maximum of data as well as quantiles. Frequency tables were used to summarize categorical variables. Subgroup analysis was performed for all patients with description of symptoms, symptomatic medication and course of symptomatic medication, based on moderate, severe or extremely severe symptoms before start of therapy.

As the study focussed on symptoms and medication before and during SLIT to show its safety in application, there was no further documentation of these patterns in patients who discontinued desensitisation.

All data documented in the CRF were entered by means of the SAS/FSP [1990]. A summary analysis as well as a subgroup analysis was carried out. Continuous variables were described by mean value, standard deviation, median minimum and maximum of data as well as quantiles.

RESULTS

The distribution of sex in the investigated group of patients was approximately equal. The mean age of the patients was 27.9 years with a range of 4 up to 66 years. 20 patients (11 %) were younger than 10 years, and the male patients were on an average 8.7 years younger than the female patients.

172 patients (94.5 %) suffered from rhinitis and/or conjunctivitis and for 60 patients (33 %) the diagnosis asthma was documented. For 2 resp. 23 patients there was no documentation concerning rhinitis/conjunctivitis or asthma. In patients with allergic reaction to mites/dust/moulds the diagnosis asthma was more frequently, whereas duration of complaints played no role for this.

For 159 patients duration of complaints was documented

with a mean value of 5.7 years and a range from 0 up to 30 years. The 75 %-quantile was at 7.0, but for 32 patients duration of complaints was to be > 10 years.

144 patients (79.1 %) reported seasonal complaints, 27 patients (14.8 %) suffered from symptoms throughout the year. Seasonal symptoms as well as symptoms throughout the year resp. symptoms throughout the year with seasonal aggravation were documented in 3 (1.6 %) resp. 5 (2.7 %) cases. For 3 cases no data was reported.

In 179 patients (98.4 %) diagnosis was confirmed by typical anamnesis and in 168 patients (92.3 %) by positive prick test. A positive family anamnesis was documented in 28 patients (15.4 %), a positive provocation test was reported in 19 cases (10.4 %) and a positive RAST in 9 cases (4.9 %). For one patient no data was reported.

For 63 patients (34.6 %) concomitant diseases were reported, from which 48 patients mentioned one, 11 patients complained for 2 diseases. For 2 patients 3 concomitant diseases were documented and for 1 patient 4 diseases. Concomitant diseases were mainly such of the sceletonmuscular, cardiovascular or endocrine system, such as diabetes mellitus or hyperthyreosis. The drug therapy was documented for 45 patients (24.7 %) concerning cardiovascular drugs, NSAR, antidiabetics, thyroxine and in two cases corticosteroids.

Allergen avoidance was carried out in 61 patients (33.5 %). A former specific immunotherapy was documented for 13 patients (7.1 %).

4 patients reported deviations from the recommended dosage schedule because of side effects. In one case maintenance dosage was reached after six months with maximum doses, the second case reported a short interruption because of side effects and then continued the therapy. In the third case a lower maintenance dosage was reached and in the forth-case intake failure was reported.

The number of used allergens for immunisation ranged from 1 to 7 allergens. For most of the patients the use of 2, 3 or 4 allergens was reported (39 = 21.4 %, 58 = 31.9 %, 39 = 21.4 %). For 17 patients (9.3 %) only one allergen was needed, 10 patients (5.5 %) used 5 allergens and 3 patients used 6 resp. 7 allergens. The documentation for 117 patients (64.3 %) showed used allergens for "only pollen". This class was divided in the subclass "only spring pollen" with 16 patients (8.8 %), "spring and summer pollen" with 56 patients (30.8 %) and "only summer pollen" with 45 patients (24.7 %).

Within this class 53.0 % were male. For 13 patients (7.1 %) "only mite/dust/moulds" were alleged, for 35 patients (19.2 %) "other incl. mite/dust/moulds" were documented and for 17 patients (9.3 %) "other excl. mite/dust/moulds" allergens were used. In this class two thirds (61.5 %) were female (fig. 1 and 2).

Figure 1

Figure 1: Number of used allergens

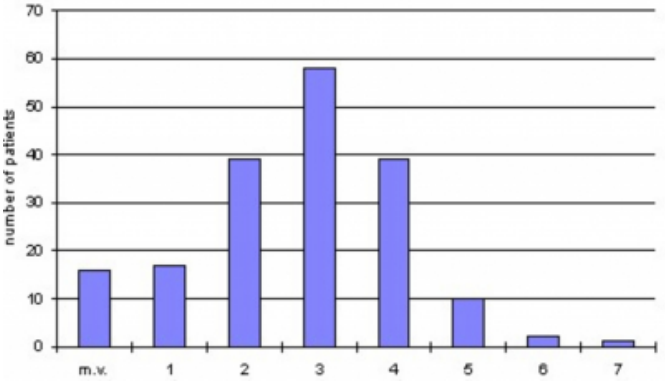
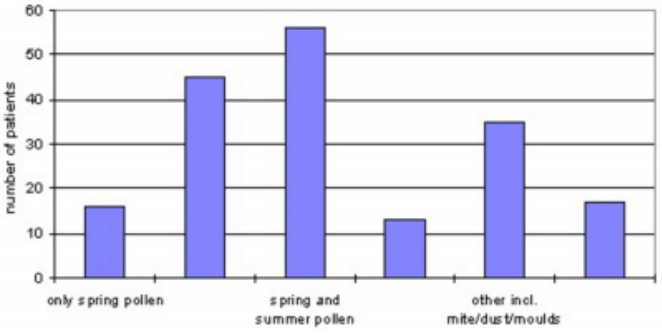


Figure 2

Figure 2: Used allergens



In accordance to the retrospective character of the study for 127 patients (69.8 %) therapy was ongoing at the time of documentation.

For 173 patients intake of symptomatic medication was documented. In the most cases local (N = 91, 63.2 %) or oral (N = 34, 23.6 %) mast cells stabilising agents and oral antihistamines (N = 66, 45.8 %) were used. Topical corticoids were used in 17 cases (11.8 %), systemic corticoids in 21 cases (14.6 %). Local antihistamines, sympathomimetics and theophylline/ xanthines were used in 12.5 %, 10.4 % and 8.3 %. Probably according to the seasonal character of pollen allergy no medication was necessary before start of therapy in 8 cases, and for 10 cases no data was available. At the time of three months, six months, one year there was a significant reduction of

medication: After one year of therapy local and oral mast cells stabilizing agents were used in 29.8 % resp. 14.0 %, oral antihistamines in 17.5 %. The intake of topical and systemic corticoids reduced to 6.1 % resp. 5.3 %, local antihistamines, sympathomimetics and theophylline/xanthines played a less role in therapy. In 5 cases no medication intake was reported. After two years of therapy intake of oral antihistamines reduced once more to 6.7 %, while the tendency of overall lower intake of symptomatic medication stabilized.

These findings correlate in general with the results of symptomatic medication for patients with 1 to 3 used allergens, most of them suffering from allergic reactions against pollen. But it is generally noticed that intake of corticosteroids is markedly reduced in comparison to the whole collective. In the subgroups of patients with 4 to 5 used allergens intake of systemic corticoids is over represented with another preponderance to oral mast cells stabilising agents. Here again a reduction of symptomatic medication after one year is seen, but intake of corticosteroids is still higher than in the whole collective.

Figure 3

Figure 3: Course of intake of symptomatic medication from patients with moderate, severe or extremely severe symptoms before start of study

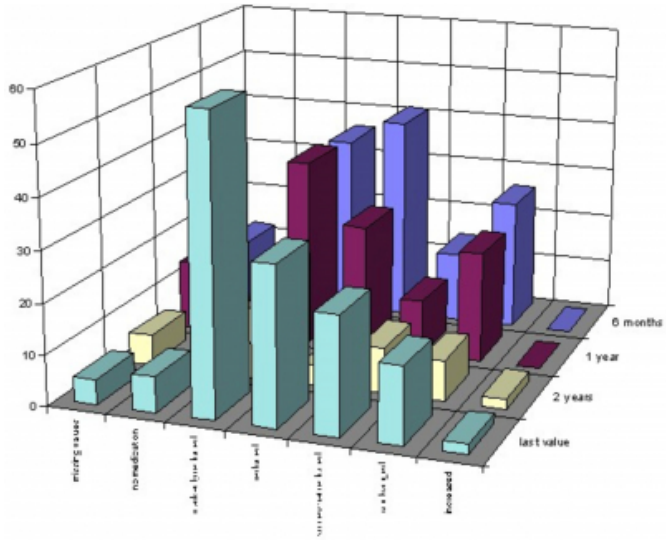


Figure 4

Figure 4: Course of intake of symptomatic medication for patients with 1 to 3 used allergens

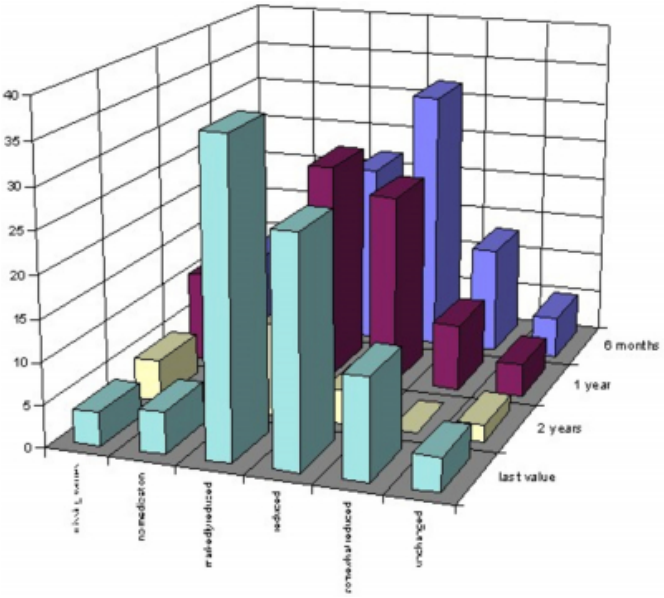
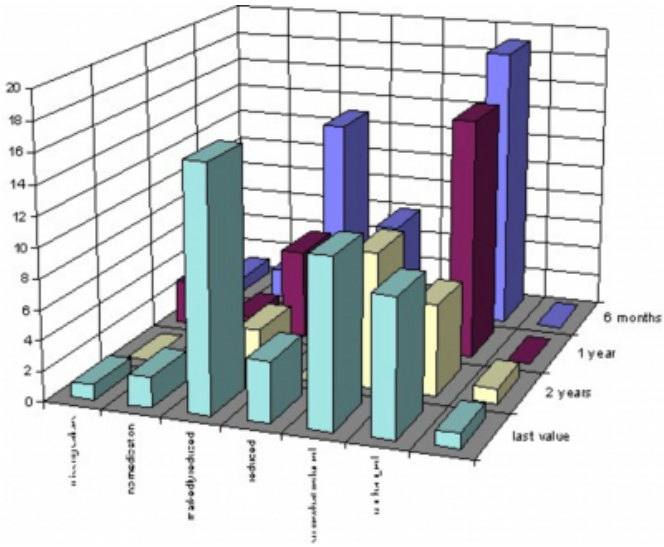


Figure 5

Figure 5: Course of intake of symptomatic medication for patients with 4 to 5 used allergens



Symptomatic medication reduced markedly within the first year, but first of all for those patients who were treated with 1 to 3 allergens. For patients treated with 4 to 5 allergens there was less efficacy of sublingual immunotherapy within the first year, but an increase of medical reduction after two years of therapy.

The group of patients which used allergens “only pollen” reflect this trend too. After six months, 33.3 % rsp. 29.0 % of 93 documented patients reduced rsp. markedly reduced

medication, after one year it was 25.0 % rsp. 35.5 % of 76 documented patients, and after two years 14.3 % of 28 documented patients reduced, 42.9 % markedly reduced 17.9 % somewhat reduced their medication, while 17.9 % remained unchanged.

The symptoms score for all subgroups of patients shows an analogous development to the course of medical intake. After one year of therapy from the still documented 114 patients only 1 showed extreme severe symptoms, 4 (3.5 %) had severe, 28 (24.6 %) moderate, 43 (37.7 %) mild and 33 (28.9 %) no symptoms. After two years of therapy from the 45 still documented patients none had extremely severe symptoms, 1 (2.2 %) had severe, 12 (26.7 %) moderate, 18 (40.0 %) mild, and 11 (24.4 %) no symptoms.

This tendency correlated with the results of the symptoms score of the subgroup "only pollen". Whereas 74 patients ((N = 100, 74.0 %) showed moderate, 22 patients (22.0 %) showed severe and 4 patients (4.0 %) showed extreme severe symptoms before start of therapy, there was a significant reduction of symptoms already after three months (N = 87) with 17.2 % no symptoms, 24.0 % mild, 41.4 % moderate, 4.6 % severe, and none of the patients with extreme severe symptoms. After one year from the 76 documented patients 32.9 % showed no symptoms, 34.2 % mild, 26.3 % moderate, 2.6 % severe symptoms, after two years from the 28 still documented patients 32.1 % showed no symptoms, 42.9 % mild and 21.4 % moderate symptoms. Severe and extremely severe symptoms were not documented.

In comparison to the “pollen group” the symptoms score for patients with used allergens “only mites/dust/moulds” or "other incl. mites/dust/moulds” developed less rapidly. Whereas 12 patients (N = 37, 32.4 %) suffered from severe and 25 patients (67.6 %) from moderate symptoms before start of therapy, the number of patients with severe symptoms reduced markedly after three months. After one year there were still 2 patients (N = 31) with severe symptoms, 7 with moderate, 14 with mild and 6 without symptoms, and after two years from the still documented patients none had severe symptoms, each 6 showed moderate or mild and 1 patient no symptoms.

Comparing the group of patients with 1 to 3 used allergens and those with 4 to 5 used allergens, the symptoms score again reduces more definitely for patients with less used allergens (fig. 6 and 7).

Figure 6

Figure 6: Course of symptoms for patients with 1 to 3 used allergens

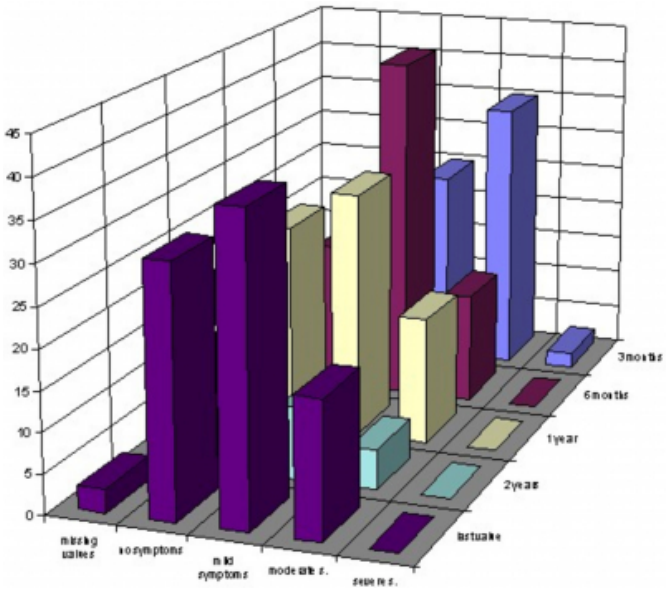
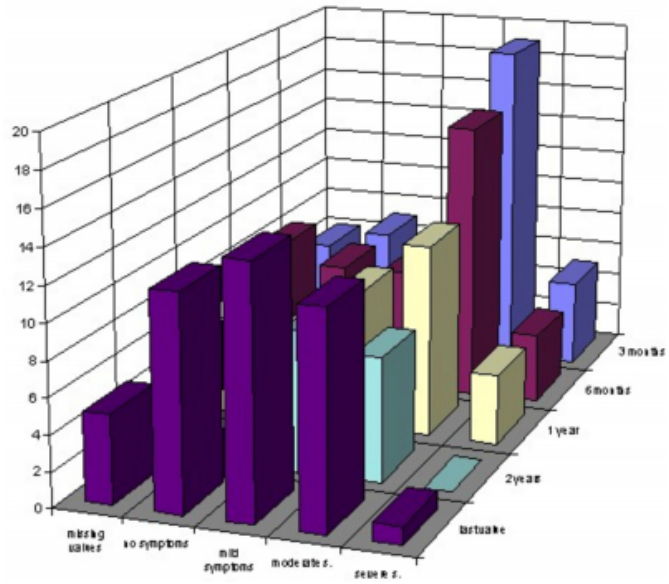


Figure 7

Figure 7: Course of symptoms for patients with 4 to 5 used allergens



Evaluation of the symptoms score as well as the symptomatic medication of patients with complaints up to 5 years in comparison to those with complaints since 8 or more years showed no differences between these two groups and no differences to the before mentioned subgroups either.

Another subgroup of 14 patients with more than 3 symptomatic medications before therapy showed reduced symptoms within the first three months and stabilization

within one year: Before start of therapy 2 patients had extremely severe, 11 severe and 1 moderate symptoms, three months later there were 1 patient with extremely severe and 3 with severe symptoms, after one year of therapy 1 patient with extremely severe and 2 with severe symptoms, 2 without and the rest with moderate or mild symptoms. This tendency correlates with the symptomatic medication in this subgroup, which demanded 58 drugs before start of therapy (N = 14), 38 drugs after three months (N = 13) and 22 drugs after one year (N = 7). In this subgroup systemic corticoids were given 11 times, topical corticoids 8 times before start of therapy, after one year there was a reduction down to 3 times each. The course of medical intake of this subgroup correlated with these findings, after one year only 2 patients reported unchanged course of intake.

54 patients (29.7 %) hat terminated the study before time of documentation. 16 patients had finished the immunisation according to the physician's instruction, half of them because of improvement, 6 patients reached the foreseen time of therapy and 1 patient each showed poor cooperation resp. contraindications were mentioned. From the 37 patients who terminated therapy not according to physician's instruction 17 refused to continue the treatment, 13 finished the specific immunotherapy because of other reasons, 9 reported improvement and 5 showed no improvement and therefore finished therapy. For one patient no data was acquired.

From the 182 documented patients 125 (68.7 %) tolerated therapy very well, 50 (27.5 %) good, 4 (2.2 %) moderate and one patient (0.5 %) bad. In 2 cases no information was available.

Reverse reactions were reported in 4 cases (2.1 %), one case with systemic side effects and 3 cases with local intolerance and systemic side effects. Adverse reactions were described as burning sensation and itching in the mouth as well as nausea, severe throat smarting and scraping. Upon passing through a too fast dosistitration one patient reported allergic symptoms like conjunctivitis, rhinitis and aggravated asthma, which longed for a reduction and adjusted dosistitration in future. Dilution of 1:10 and a slow dosistitration resulted in good tolerance. For one patient the adverse reactions were not specified.

For nearly half of the patients (N = 88, 48.4 %) the state of health was classified as “improved” by the physician, for 61 patients (33.5 %) a "highly improved” state of health was seen. "Unchanged” was documented for 27 patients (14.8 %), and in one case (0.5 %) “worsened” was documented. For 5 patients no information was available.

CONCLUSION

Immunotherapy is an established treatment of allergic diseases. Non-injective routes for immunotherapy such as the sublingual route are thought to be valuable therapeutic options for respiratory allergy and have the primary aim of minimizing the risk of adverse events and of improving the compliance of the patients. Very recent studies have demonstrated that the sublingual modality is the most promising way of mucosal immunotherapy (Passalacqua et al. 1999). However, the treatment in case of the sublingual route that is applicated without direct surveillance has to be established. In this retrospective study on patients with IgE-induced allergic disease due to airborne allergens the safety of sublingual immunotherapy was proved, and showed a striking improvement of symptoms and a distinct reduction of symptomatic antiallergic drugs as well. These results correlate well with a a reported evaluation of clinical efficacy of sublingual-swallow immunotherapy in a rush preseasonal course (Passalacqua et al. 1999), in which a significant reduction of the symptom score and drug intake score was proved true.

Most of the patients of the present study suffered from rhinitis and/or conjunctivitis, this group correlating with a higher incidence of allergic reaction to pollen, whereas the diagnosis asthma occured more frequently in the group with allergies against mite/dust/moulds and others. 20 % of the collective had complaints for more than 10 years. Clinical effects could be achieved even after six months of sublingual immunotherapy and was subsequently improved while therapy was continued up to two years. These results correlate well with other clinical trials [Andre et al., 2000), which reported eight double-blind, placebo-controlled trials carried out in France, Italy and Greece and proved the safety and efficacy of the sublingual-swallow route of immunotherapy. In these studies there, too, no severe event was reported.

In accordance to other authors and to reported results of subcutaneous immunotherapy as well clinical effects of treatment depended on the number of used allergens: using 3 or less allergens gave best results on clinical symptoms. The meaning of this observation is not yet clear. It may be supposed that patients with need for more than three allergens showed an advanced development of the disease and therefore did not respond well to specific immunotherapy.

The mechanism of specific hyposensitization is not fully understood. In accordance to research the presentation of the allergen to the lymphocytes via antigen-presenting cells, e.g. Langerhans cells and macrophages, might play an active role in immune responses to allergens (Noirey et al. 2000). In case of sensitisation the thus stimulated lymphocytes seem to develop to TH2 effector cells, while under successful hyposensitization they might develop to TH1 effector cells. It is definitely proved that the applied antigen can be absorbed by the dendritic resp. antigen presenting cells.

The World Health Organisation (Morris 1999) recognized in accordance with international experts that the so far published data concerning the efficacy and safety of the sublingual immunotherapy justify the administration of sublingual immunotherapy.

The sublingual immunotherapy allows involving other allergic patients such as children receiving injections and subjects who are not inclined to observe and comply with injection treatment. Still there has to be considered that the administration of the allergen extract is done without direct medical surveillance. This kind of therapy is only suitable for those patients, who are reliable concerning the realization of application. Dosage and application of the antigen should be thoroughly discussed and the patient kept to reduce the dosage in case of side effects, asking the physician for instructions concerning the following dosage patterns.

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