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Review article

Different methods of local allergen-specific immunotherapy

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In the treatment of allergic disorders, specific immunotherapy (SIT) occupies a central role as the only currently available causal method of treatment. The concept of "local immunotherapy" includes all non-subcutaneous forms of SIT, which are used to treat allergic disorders such as rhinitis and asthma. Nasal, bronchial, oral and sublingual administration of allergen extracts is regarded as local immunotherapy (LIT). Attempts were made very early to produce tolerance to certain allergens by the oral route. Dakin reported in1829 that North American Indians regularly chewed small amounts of leaves of the "poison ivy" (*Rhus toxicodendron*) in order to prevent or weaken the severe dermatitides that occur after contact with this plant (Dakin, 1829 quoted after (1)). In 1900, 11 years before the first work on subcutaneous immunotherapy, Curtis published an article about the efficacy of oral allergen-specific immunotherapy (OIT) in hay fever (2). This was followed five years later by other reports about the success of OIT in cow's milk allergy (3). In the 1920s and 1930s, too, reports of positive experiences with this method appeared again and again. However, a negative, multicentre comparative study of ragweed pollinosis (4) (in which, interestingly, good results were reported in children!) severely limited the use of OIT in adults in the Anglo-Saxon countries. In the early 1950s, Schuppli in Basel, Switzerland took up OIT again. His positive results in children ensured that this method soon became widespread (5–12). New methods of local application were sought, because various studies in recent years showed that OIT is clearly inferior to allergen-specific subcutaneous (injected) immunotherapy (SIT) with regard to both clinical and immunological efficacy.

From a clinical aspect however, there is a whole series of arguments to explain the preference for LIT compared to injected IT.

Poor compliance can limit the applicability of injected SIT (13). Because LIT can be carried out at home by the patient and the injections in the doctor's office are no longer necessary, greater compliance is ascribed to LIT than to SIT. However, more precise studies of this subject are lacking, so the effective compliance of LIT patients is not known. Severe systemic side-effects restrict the broad use of SIT, although the risk in hay fever patients is lower compared to asthma patients (14, 15). When SIT is carried out correctly, severe systemic side-effects in patients with allergic rhinitis, who are treated with potent extracts, occur in about 5% of all the SIT injections (16). Based on the published data, on the other hand, systemic side-effects appear to occur only very rarely with LIT.

The rapid development of molecular biology and progress not only in general allergen characterization but also in the production of large quantities of recombinant allergens have reawakened interest in recent years in local immunotherapy (LIT), both in science and among the producers of allergen extracts. At present there appears to be a trend away from oral towards sublingual allergen-specific IT (SLIT).

Immunological basis of local immunotherapy

Experimental evidence for the local administration of allergen extracts to the mucous membranes of the respiratory tract is based on the model of local induction of tolerance (17–20). The concept of oral

and sublingual IT derives from animal studies, which show that tolerance can be produced by taking in antigen orally (21–23). Hypothetically, the effect of sublingual IT can be explained by several mechanisms. The oral mucosa is especially rich in dendritic cells, which are known to demonstrate strong MHC class II molecule expression (24). These dendritic cells can absorb and process allergens and antigens and also activate autologous native T lymphocytes (25). Animal models in which induction of tolerance in the oral mucosa was investigated show that the dendritic cells of the oral mucosa can act as antigen-presenting cells, and that the clonal anergy of specific T cells is one of the mechanisms by which tolerance can be induced through the oral mucosa (26, 27). In addition, dendritic cells produce IL-12, which favors the development of Th1 cells compared to that of Th2 cells (28, 29).

Three important aspects are emphasised below through detailed descriptions, to give a better understanding of the immunological reactions after oral administration of an allergen:

the absorption of an allergen through the intact mucosa;

the resulting induced mucosa-associated immune reaction;

the possibility of influencing existing sensitization by oral administration of an allergen.

Absorption of an allergen through the intact mucosa

Since the observations of Herbst in 1834, it has been known that corpuscular elements such as starch grains, pollens and spores can be absorbed through the intact mucosa under physiological conditions (12, 30, 31). Besides these corpuscular elements, macromolecules and proteins are absorbed in biologically and immunologically active forms (32–38). It is important to emphasize that macromolecules of a certain, allergologically relevant size can pass the mucosa much more easily in atopic subjects than in healthy persons (39–42). It is thus certain that under physiological circumstances allergens also can be absorbed in an immunologically active form and in substantial quantities through the mucosa. The degree of permeability is influenced by both exogenous (infections, medications, e.g. acetylsalicylic acid, nonsteroidal anti-inflammatory drugs (NSAID) and others) and endogenous factors (atopic disposition, immunological reactions such as formation of a complex between allergen and serum IgA) (43). These characteristics, described for the intestinal mucosa, apply also by extension to other mucous membranes, for instance to the oral and nasal mucosa or the mucous membranes of the respiratory and urogenital tract.

Mucosa-associated immune reactions

The submucosa contains scattered collections of lymphatic tissue of T and B lymphocytes, which are concentrated in the intestine in Peyer's plaques and belong together with other immunoreactive cells to the MALT (mucosa-associated lymphoid tissue). The abbreviation GALT (gut-associated lymphoid tissue) is also used in connection with the digestive tract. Active exchange of lymphocytes takes place in this nonencapsulated lymphatic tissue, with migration especially into the submucosa of other mucous membranes (44–47). An immune reaction can spread into other MALT sites by means of migration of locally activated T cells without antigen getting into the circulation and without changes of immunological parameters being detectable in the serum (48–50). However, local administration of antigen appears to lead to an immune reaction in the entire MALT only if as many Peyer's plaques or similar structures (e.g. in the respiratory tract) are included by the antigen contact (51). This could explain, for instance, why nasal IT has a local effect on the symptoms of rhinitis but is unable to influence asthma symptoms (52), and why the sublingual application form followed by spitting out the extract (so-called sublingual-spit method) gives less satisfactory results than sublingual hyposensitization followed by swallowing of the allergen extract (sublingual-swallow method).

Influence on existing sensitization of oral administration of an allergen

Wells and Osborne observed in 1911 that guinea pigs could no longer be sensitized parenterally to zein (a maize protein) if they were fed with maize beforehand (32). Some time later, Sulzberger (53) and Chase (54) showed that animals could no longer be sensitized epicutaneously if the antigen was given orally beforehand. This proves that specific tolerance can be induced orally. It would be desirable to exploit this possibility of inducing tolerance with local IT. However, since LIT is performed in an already sensitized body, those observations showing that existing sensitization can be weakened or even made to disappear by oral administration of the allergen are important (49, 55). It is important that, unlike parenteral administration, oral administration of an antigen is more likely to suppress the specific humoral immune response. This would explain why changes in the serum immunoglobulins are generally not observed with OIT, and in particular there is no rise in so-called blocking IgG (56). The degree of tolerance achieved by oral administration of an antigen is not only genetic but also determined by numerous other complex interactions (57, 58), where age, the current permeability of the intestinal mucosa, the dose of allergen, the allergen quality, the form of administration, and the intervals between allergen doses, play a crucial part (59–65).

On the basis of more recent research results, allergen-

specific subcutaneous immunotherapy appears to cause a shift of the immune response of the activated T cells from a T helper type 2 cytokine profile (interleukin-4 and interleukin-5) to a T helper type 1 cytokine profile (interleukin-2 and interferon-γ) (66). In contrast, local mechanisms such as the production of specific secretory IgA antibodies and the production of specific T suppressor cells play an important part in LIT (67). Although many changes during immunotherapy can be explained by these mechanisms, by no means all of the questions about the mode of action of immunotherapy have been answered yet. Indisputably, the progress in molecular biology in recent years will allow new treatment strategies in mucosa-associated forms of allergy, which will go far beyond what has been achieved so far.

Allergen extracts, preparations and duration of treatment with LIT

All of the studies considered had to meet the following criteria:

(a) Placebo-controlled, double-blind study design (DBPC studies).

(b) Defined allergen extracts and dosages.

(c) Appropriate treatment protocols and statistics with sufficiently large numbers of patients (>7 patients per group).

(d) Publication in peer-reviewed journals in English.

(e) Symptom/medication score present.

Pollen extracts (birch, grasses, pellitory (*Parietaria*) and ragweed (*Ambrosia*)) were used in most LIT studies. House dust mites and cat extracts have been investigated less well until now. The extracts are derived from different manufacturers and are standardized with different methods. Validation of the extract quality was not carried out, but it can be assumed that the manufacturers have followed the international guidelines for allergen standardization and manufacture (68).

Both aqueous and powdered extracts are used in local and bronchial IT. Besides nonmodified extracts, allergoids are also employed. Both aqueous extracts and gastric acid-resistant capsules are used in oral IT. In contrast, aqueous extracts were used exclusively in all sublingual studies. Because the potency of the extracts was given in the manufacturer's arbitrary units in most studies, a direct comparison of dosage is not possible.

Many of the studies cited here were performed only over a short period, a few weeks to a few months, pre- or co-seasonally. The treatment period was over one year in only five studies. The duration of treatment was not included in assessing clinical efficacy, although it was shown with injected IT that the success of treatment depends on the duration of the IT (14). The degree of clinical success was dependent on the duration of the IT in only one oral IT study (69). However, it is important to emphasize here too, that when an extract is ineffective in a short-term study, clinically relevant efficacy does not automatically follow when it is given for a prolonged period.

Nasal immunotherapy

Method and clinical efficacy

Nasal IT can be given both preseasonally and perennially. The allergens are self-administered by the patient, either in powder form or as an aqueous extract (solution). During administration of the allergen, the patient exhales or vocalises in order to avoid bronchial deposition of allergen. The extracts are taken daily or on alternate days during the induction phase and then weekly during the maintenance phase.

The clinical efficacy of nasal IT was assessed on the basis of 17 studies (70–87). Sixteen of 17 studies show statistically significant clinical efficacy. Overall, 419 patients were treated in these 17 studies, and 22 patients in the "no-effect" study (83). The patients were reviewed after two years in only one study. No long-term effect was found after stopping the nasal IT, so that nasal IT can be recommended currently only as preseasonal prophylactic treatment for pollen-induced rhinitis (85).

Safety

No severe systemic side-effects occurred in the evaluated studies. However, the majority of the patients had local (nasal) symptoms such as itching, sneezing and irritation. Nasal IT can induce asthmatic symptoms. In one study, three patients had to be excluded from the active group because of bronchospasm (79). However, local side-effects occurred with the same frequency in patients who received either histamine placebo or allergen (71). Critics have accused nasal IT of inducing local symptoms for a prolonged period (both during the dose increase phase and during the pollen season). However, this seems to be of subordinate importance, because the higher symptom scores in the actively treated patient group do not lead to a higher medication score, which shows that the patients accept these relatively mild symptoms and do not resort to medications more because of them (80). In summary, the local side-effects induced by the nasal IT were mild and of short duration.

Paraclinical effects

In vivo A reduction in the nasal provocation test was found in many studies (70, 73, 76–83). The skin test reactions do not appear to be influenced by nasal IT (70, 76, 77, 80, 81, 83).

In vitro In most of the studies, there were no relevant

changes in the allergen-specific IgE and/or IgG levels in the serum, while in one study there was a marked rise in allergen-specific IgG and IgA in the serum and nasal secretion (70). In another study, there were stable serum sICAM-1 levels in the actively treated group compared to increased sICAM-1 levels in the placebo group during the pollen season, a significant reduction in the ICAM-1 positive cells and a reduction in the eosinophil count after nasal provocation (78). However, these changes were not accompanied by any changes in the serum IgE, IgG or ECP.

Conclusion: nasal immunotherapy

Nasal immunotherapy reduced the symptoms and/or medication consumption significantly in patients with allergic rhinitis in 16 of 17 DBPC studies. Clinical efficacy was found for the following allergens: grasses (70, 74, 81, 83, 86), ragweed (71, 72, 75, 84), *Parietaria* (76, 78, 79, 85), birch (80, 82) and house dust mites in two studies (77, 87). The efficacy and safety were investigated in pediatric patients also in only one study (83). The side-effects do not appear to represent a relevant problem in nasal immunotherapy and can be brought under control well with local measures or antihistamine prophylaxis. The patients were reviewed after two years in only one study. No long-term effect was found after stopping the nasal IT, so that nasal IT can currently be recommended only as preseasonal prophylactic treatment for pollen-induced rhinitis (85).

Bronchial immunotherapy

Clinical efficacy

The clinical efficacy of bronchial immunotherapy was investigated in two studies using mite allergens (88, 89). Clinical efficacy with continuous improvement of the symptom and medication score was recorded during a 24-month treatment period in one study (88).

Safety

Bronchospasm was induced in the majority of patients in both studies. In most cases, the immediate fall in lung function was to less than 85% of the pre-therapeutic baseline level, but in a few patients a delayed asthmatic reaction (to less than 75% of the pre-therapeutic baseline level) was induced. No other systemic reactions occurred with bronchial IT.

Paraclinical effects

In vivo In the only study that showed a clinical effect, no significant difference in methacholine sensitivity was observed between the active and the placebo group. On the other hand, there was a significant improvement in bronchial allergen tolerance in the actively treated group (89). In contrast, the skin test reactions remained unchanged.

In vitro There was a significant rise in total IgG, IgG1 and IgG4, but no change in allergen-specific IgE and lymphocyte subpopulations during the therapy in one study (89) while these parameters were unchanged in the other study (88).

Conclusion: bronchial immunotherapy

Bronchial IT has been insufficiently documented for clinical use. There is a substantial risk of severe immediate and delayed side-effects.

Oral immunotherapy

Clinical efficacy

The efficacy of oral IT was evaluated using nine studies (69, 90–97). Five of these studies showed no efficacy. A reduction in the symptom/medication scores was observed in four studies (birch, ragweed (two studies), house dust mite) (69, 91, 96, 97). In a study using microencapsulated gastric acid-resistant ragweed extract, a significant reduction in the symptom and medication scores was obtained in 19 of 21 patients who tolerated the highest allergen dose (>20 µg Amb a1) (96). In another study, the only significant difference between the treated and untreated group was a reduction in the ocular symptoms in the treated group (94). Because no differences were found in this study with regard to nasal symptoms and medication use, the usefulness of oral IT must therefore be regarded as low with regard to complexity, cost and patient inconvenience (very high allergen doses had to be used). In contrast to birch pollen (92), a study with grass pollen in gastric acid-resistant capsules demonstrated no efficacy (93). The reason for the ineffectiveness of oral IT with grass pollen cannot be due to differences in the breakdown of these allergens, since both allergens are broken down very rapidly in the duodenum (99). In the only study which showed a significant improvement in symptoms after two years, a five times higher dose of an aqueous house dust mite extract was used than in subcutaneous IT for three years in children (69). The positive effects of a prolonged duration of treatment were apparent in the continuous improvement in the symptom and medication scores. There were no changes in the rhinitis symptoms during the first year of treatment while the rhinitis scores improved significantly in the second and third years. The asthma symptoms improved only in the third year. Ninety-four patients were treated in the "negative" and 86 patients in the "positive" studies.

Safety

Oral administration of high allergen doses can induce systemic side-effects, which can be severe. Eight cases with rhinitis and one case with asthma were documented in a study of 22 patients. However, the incidence was the same as in the placebo group (90). Five cases of urticaria were observed in another study involving 24 patients (93), and in another study with 18 patients there was one case of urticaria (94). In another oral IT study with cat allergens, two patients had severe side-effects, which were, however, probably not due to the treatment (95). Mild gastrointestinal side-effects occurred in one study in which very high doses were used that were 10 times the dose used in subcutaneous IT (94).

Paraclinical effects

In vivo In most studies, no changes were found in the nasal provocation tests and skin test reactions. However, there was a reduction in the nasal provocation test in one study (92), and two other studies found an improvement in the conjunctival provocation test (69, 94).

In vitro A significant rise in allergen-specific IgE was observed only one month after the start of the oral IT, along with a weakening of the seasonal rise in IgE. In addition, the allergen-specific IgG (but not the IgA) increased in the actively treated group. A rise in IgG1 and IgG4 was also observed during the treatment in a study with mite allergens (69) and in two studies with ragweed (96, 97). However, this could not be confirmed in other studies (91, 93–95).

Conclusion: oral immunotherapy

Oral IT has been insufficiently documented for routine clinical use. Clinical efficacy (significant reduction in symptoms) was found in only three of nine studies, and this was for high-dose birch allergens in gastric acid-resistant capsules, house dust mites after treatment for at least one year, and ragweed.

Sublingual immunotherapy

Clinical efficacy

Sublingual immunotherapy (SLIT) can be given in two different ways; either strictly sublingually, where the extract is held in the mouth for absorption through the oral mucous membranes and is then spat out (sublingual-spit), or combined sublingual/oral administration, where the extract is swallowed after a certain time in the mouth (sublingual-swallow). Evidence of efficacy is ascribed only to the sublingual-swallow method in the current WHO position paper on specific immunotherapy (98).

Sublingual IT is carried out either preseasonally, co-seasonally or perennially. The patients take the allergen extracts at home, as aqueous solutions, either daily or every two days in the induction phase, and one to three times a week during the maintenance treatment.

In three studies with the sublingual-spit method clinical efficacy was found for cat allergens (100), grasses (101) and for house dust mites in asthmatic children (102).

Efficacy was recorded for sublingual IT with the sublingual-swallow method for extracts of house dust mites (103–106), grass pollen (107–109), *Parietaria* (110, 111), birch pollen (112) and olive pollen (children with rhinoconjunctivitis and mild asthma (113)). A total of 421 patients were treated with these allergens in 14 studies.

Safety

No systemic side-effects have been reported so far in adults, and in most of the studies no differences were found between the actively treated group and the placebo group regarding the frequency of systemic side-effects. The most frequently occurring side-effects are local with itching in the throat, nose and oral region, followed by gastrointestinal symptoms (nausea, vomiting, abdominal pain). In a study including children (rhinitis and asthma, n allergen-treated = 30) there were 32 episodes of systemic side-effects (three patients with urticaria, 11 patients with asthma (three of them severe), and four patients with diarrhoea) (103). In another study in children, generalized urticaria occurred in one patient (109). In a recently published meta-analysis of the safety of sublingual-swallow immunotherapy there were no severe adverse events or even anaphylactic reactions in the eight examined DBPC studies. There was an equal incidence of mild local side-effects in adults and children (114).

Paraclinical effects

In vivo In one study, there was a significant reduction in the skin test sensitivity and a marked improvement in the nasal provocation test (103). However, there were no changes in the methacholine and bronchial allergen provocation test. In three other studies, a significant improvement was found in the conjunctival (104, 111) and in the nasal (110) provocation test, while in other studies no changes were found in the investigated parameters (101, 107).

In vitro The allergen-specific IgE antibodies did not appear to be influenced by sublingual IT in a few earlier studies (103, 110, 113), while more recent studies found a significant rise in allergen-specific IgE both alone (106) and together with IgG4 antibodies (105). Allergen-specific IgG antibodies increased

significantly in one study (103) but they remained the same in another study (110). A significant rise in the IgG subclasses was observed for IgG1 (103), IgG4 (103, 108, 110, 111) and for the IgG4/IgG1 ratio (103), while in another study there was no change in the IgG4 antibodies (113).

Conclusion: sublingual immunotherapy

With sublingual immunotherapy, the symptom and medication scores were improved in all 14 DBPC studies ($n=421$) for birch pollen (one study), grass pollen (four studies), olive pollen (one study), *Parietaria* (two studies), house dust mites (*D. pteronyssinus* and *D. farinae*; five studies) and cat allergens (one study). The dosages were five to 500 times higher than in subcutaneous IT and the clinical efficacy was equal to that of subcutaneous IT. Four studies ($n=124$) were conducted exclusively in children and systemic side-effects occurred more frequently in these studies (102, 103, 111, 113). Overall, however, in the meta-analysis by André et al. of eight DBPC studies involving 218 children and 472 adults, there were similar rates of exclusively mild adverse reactions in children and adults (114).

The WHO working group on allergic rhinitis (ARIA: Allergic Rhinitis and its Impact on Asthma) has given the studies of the efficacy of sublingual immunotherapy in the treatment of seasonal and perennial rhinitis in adults and seasonal allergic rhinitis in children the highest "A" grade according to the criteria of evidence-based medicine. However, this applies only for high-dose sublingual-swallow immunotherapy in which the dose is at least 50–100 times higher in comparison to the subcutaneous form of administration. The indications for sublingual IT then correspond to those for the subcutaneous form (115).

Efficacy of local allergen-specific IT compared to subcutaneous IT

There are a few open studies which have compared local with subcutaneous IT (101, 110, 116–123). In one of these open studies, local nasal IT was compared with subcutaneous IT for 24 months. While nasal IT did not achieve a reduction in symptoms, subcutaneous IT was effective (121). In two other studies, the efficacy of bronchial IT was compared to subcutaneous IT (119, 120). One of the studies showed that bronchial IT had a greater effect on the reduction in bronchial hyperreactivity than injected IT (120) while the other study gave the opposite result. Oral and subcutaneous IT was compared in three studies. In two of these studies, oral IT in children was markedly inferior to subcutaneous IT (116, 117) while in another study (also in children) the effect was about the same (118). In a house dust mite study, the efficacy of subcutaneous IT was markedly greater than that of sublingual IT (101), while in another open study, which compared subcutaneous with sublingual IT in patients allergic to *Alternaria tenuis*, better results were obtained with sublingual IT (60% improvement in the subjective symptom scores (sublingual) *vs* 45% improvement (subcutaneous)) (122). In a recently published DB study, which compared the efficacy of sublingual and injected IT, there was a 50% reduction in the total symptom and medication scores compared to the preseasonal grass pollen monitoring phase for both patient groups (116, 123). Unfortunately, this study was not placebo-controlled so that independently of the fact that the pollen season was about the same in both years, it is doubtful whether the clinical reduction in symptoms can be attributed to the treatment. Another study, which investigated initial parenterally injected IT followed by placebo or oral IT showed that the actively treated patients had significantly reduced rhinitis symptom scores but no reduction in medication use (117). However, another similar study was unable to confirm the efficacy of oral "grass pollen boosters" (118).

Because only one comparative study with a DBPC double-dummy protocol has been conducted so far, objective comparison of these two forms of therapy is difficult (124). In this DBPC double-dummy comparative study, the only one so far, 89 patients were treated either with sublingual-swallow IT (SLIT) or with subcutaneous IT (SCIT) for two years with a birch pollen extract. After two years, 14 patients in the SLIT group, 19 patients in the SCIT group and 15 patients in the placebo group completed the study. In the two actively treated groups, a significant reduction in the symptom and medication scores was found and there were no significant differences between the SLIT and SCIT groups. In the SLIT group, 200 times higher doses of birch allergen were used than in the SCIT group. In the SCIT group there were two severe systemic reactions (anaphylactic shock and generalized urticaria), while only mild local reactions were observed in the SLIT group. The authors conclude that SLIT should be preferred because of the better side-effect profile together with equal clinical efficacy. However, before SLIT can be recommended generally as the gold standard of SIT, the following points must still be consdidered: long-term efficacy, preventive efficacy, patient compliance, costs and patient selection.

Long-term efficacy

The long-term efficacy of local IT has not been studied hitherto. However, since long-term efficacy and preventive aspects are the main aims of injected IT (14), the possible advantages of local IT, which, like subcutaneous SIT, has to be given for several years, must be

investigated. Until studies of long-term efficacy and the preventive effect of SLIT have been completed, these questions cannot be answered securely.

Conclusions

The diagnosis and treatment of allergic diseases (125), including local IT, should remain in the hands of the allergologist. Evaluation of the diagnostic tests, advising patients about allergen elimination, prevention and prophylactic measures and determining when IT is indicated requires the experience of a specialist (14). General uncritical use of local IT without allergological supervision is not approved, because the effects and side-effects and also the compliance and the long-term efficacy are less well documented for local IT than for subcutaneous IT. Non-indicated use of local IT results in poorer patient management with treatment failures, which in turn discredits the reputation of the other therapeutic measures in allergic disorders. Only the specialist who has been extensively trained in all treatment methods should therefore undertake regular follow-up and therapeutic measures.

Bronchial and oral IT are currently recommended only in controlled studies because of the insufficient documentation of the clinical efficacy and the severe side-effects.

Local nasal IT effects have been documented in adults with allergic rhinitis caused by pollen allergy (grass, birch, *Parietaria* and ragweed pollen). The efficacy in house dust mites was documented in two studies. Potential candidates for nasal IT are recruited from such patients, whose symptoms cannot be controlled adequately by medical treatment, who have had systemic side-effects on subcutaneous IT and either show poor compliance or have declined subcutaneous IT. However, the risk of inducing asthma during nasal IT remains a relative contraindication to this form of treatment which is used by the patient himself without supervision by a doctor. The patients must therefore be informed carefully about the risks and emergency treatment in the case of systemic side-effects.

Sublingual IT has been documented for birch, grass, olive, *Parietaria*, house dust mite and cat allergens in 14 DBPC studies (allergen-treated $n=421$), mainly in patients with rhinitis and mild asthma. The available data are not yet adequate at present especially for patients with perennial asthma. The WHO ARIA working group classifies the high-dose sublingual-swallow immunotherapy, with a dose at least 50–100 times higher compared to subcutaneous administration, as the highest degree of evidence "A" for the treatment of seasonal and perennial rhinitis in adults and seasonal allergic rhinitis in children. The indications for SLIT follow those for SCIT, supplemented by patients who have a fear of injections or those with severe side-effects on subcutaneous therapy. Further studies with standardized sublingual extracts to document the long-term efficacy and the efficacy and tolerability of this therapy in asthma patients and/or children with perennial allergies are necessary in order to establish the position of this promising form of therapy.

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