

# A Short Assessment of Sublingual Immunotherapy

Jürgen Rakoski Dirk Wessner

Department of Dermatology and Allergology, Technical University, Munich, Germany

The WHO has recommended sublingual immunotherapy (SLIT) as the suitable treatment for allergic rhinitis in adults [1]. Our article is based on 20 double-blind, placebo-controlled studies published in peer-reviewed international journals and our own experiences with this therapy in a controlled study with patients allergic to grass pollen [2]. Eighteen studies were performed in patients with rhinitis (table 1), two studies in patients with bronchial asthma [3, 4].

## Treatment Procedures

In SLIT studies, the medicament is given in drops sublingually for 2 min and then swallowed. In 2 studies the medicament was dropped under the tongue for 2 min and then spat away. The common dose of allergen extracts is 2- to 80-fold higher in SLIT than in subcutaneous therapy. In the SLIT studies, extracts of pollens (grasses, birch, parietaria, ambrosia and olea), house dust mites and cat dander were used. The therapy doses and times of therapy are quite different. Troise et al. [10] and Purello et al. [23] treated their patients for 10 months. The total doses in the study of Purello were 12.7 µg Par j 1, Troise et al. [10] treated with a dose of 6.3 µg Par j 1. The grass studies of Clavel et al. [13], Sabbah et al. [9] and Feliziani et al. [12] were performed for 3 up to 6 months. The cumulative doses are difficult to compare, some authors described the

cumulative doses in biological units, others in micrograms of the major allergen Phl p 5.

Bagnasco et al. [5] demonstrated with radioactively marked parietaria allergen that 2% of the allergen remained associated with the oral mucosa for 20 h. The radioactivity in the plasma increased after swallowing and peaked after 2 h. The rest of the material leaves the organism very quickly.

## Immunology

In most studies in verum-treated groups, the specific IgG4 and the specific IgE increase under the therapy significantly. After a longer time of treatment the specific IgE seems to decrease. Passalacqua et al. [14] found a decrease of ICAM 1 in conjunctival fluid after exposure to allergen in the treated group.

They also reported an increase of suppressor cells in the actively treated group but not in the placebo group. Fanta et al. [6] observed a significant decrease of lymphoproliferative response to the complete grass pollen extract ( $p < 0.001$ ) and to the recombinant Phl p 1 ( $p < 0.001$ ) after treatment with verum grass pollen extract but no change of Th1/Th2 cell ratio. These data show that SLIT has an effect on the immune system in the actively treated group.

## KARGER

Fax +41 61 306 12 34  
E-Mail [karger@karger.ch](mailto:karger@karger.ch)  
[www.karger.com](http://www.karger.com)

© 2001 S. Karger AG, Basel  
1018-2438/01/1263-0185\$17.50/0

Accessible online at:  
[www.karger.com/journals/iaa](http://www.karger.com/journals/iaa)

Correspondence to: Prof. Jürgen Rakoski  
Department of Dermatology and Allergology, Technical University  
Postfach 40 18 40  
D-80718 München (Germany)  
Tel. +49 89 4140 3193, Fax +49 89 4140 3576

**Table 1.** Studies with SLIT in patients with allergic rhinitis

Author	Year	Allergen	Patient No.	Clinical scores	Challenge	IgE/IgG 4
Tari et al. [8]	1990	<i>D. pter.</i>	58	0.01	0.01	+
Sabbah et al. [9]	1994	grass	58	0.05	n.d.	n.d.
Troise et al. [10]	1995	parietaria	31	0.05	0.02	+
Quirino et al. [11]	1996	grass	20	0.02	n.d.	n.s.
Feliziani et al. [12]	1995	grass	24	0.01	n.d.	n.s.
Clavel et al. [13]	1998	grass	136	0.02	n.d.	+
Passalacqua et al. [14]	1998	mites	19	0.002	0.002	n.d.
Passalacqua and Canonica [15]	1999	parietaria	31	0.008	0.04	n.d.
Di Rienzo et al. [16]	1999	grass	36	0.01	n.d.	+
Valle et al. [17]	2000	ambrosia	33	0.04	0.0001	n.d.
Nelson et al. [18]	1992	cat	41	n.s.	n.d.	n.d.
Khinchi et al. [19]	2000	birch	58	?	n.d.	+
La Rosa et al. [20]	1995	parietaria	40	0.02	0.02	+
Vourdas et al. [21]	1998	olea	66	0.03	n.d.	n.s.
Horak et al. [22]	1998	birch	41	n.d.	0.01	n.s.
Purello et al. [23]	1999	parietaria	40	0.04	n.d.	0.05
Hirsch et al. [24]	1997	<i>D. pter.</i>	30	n.s.	n.s.	n.s.
Guez et al. [25]	2000	mites	75	n.s.	n.d.	n.s.

Clinical scores: Clinical symptoms of patients (placebo/verum) and/or use of medicaments; challenge with allergen extracts before and after treatment; IgE/IgG4 ratio: specific IgE/specific IgG4 before and after treatment.

## Clinical Data

The therapeutic effect in the rhinitis studies was measured in scores for symptoms and medicaments recorded from self-assessment of the patients on diary cards. A positive effect was seen in patients with pollen allergy and rhinitis in 11 of 13 studies. Positive results were observed in 2 of 4 studies with house dust mites. The studies of Tari et al. [8] and Passalacqua et al. [14] showed a positive therapeutic effect after treatment for 2 years. Guez et al. [25] noted no effect in the same time of therapy. The therapy with cat dander showed no benefit [18].

In seven studies the therapeutic effect was controlled with nasal challenge with the correspondent allergen extracts before and after the treatment. In six studies, a decrease in sensitivity was observed.

In the treatment of asthma by SLIT in patients allergic to house dust mites, a clinically positive effect was observed in symptom scores and reduction of use of the medicaments. Bousquet et al. [3] and Pajno et al. [4] treated patients with allergic asthma to house dust mites with sublingual swallow immunotherapy. Bousquet treated double-blind 85 patients for 2 years with a cumulative dose of 4.2 mg Der p 1 and 7.3 mg Der f 1 in the verum group [3]. The results were measured in the fre-

quency of asthma attacks and in the use of medicaments and in the reactivity to methacholine bronchial challenge. A challenge with allergen was not performed. Pajno et al. [4] treated for 2 years 24 children with asthma and allergy to house dust mites. The cumulative doses were not mentioned. The positive results in the verum group were measured in reduction of the asthma attacks and reduction of the use of antiasthmatic drugs.

## Safety

Severe side effects were not reported in the reviewed studies. André et al. [7] found no serious side effects in their review of 8 SLIT studies involving 472 adults and 218 children.

## Conclusion

SLIT has some effect on the human immune system. The positive clinical results measured in symptom and medication scores show that this therapy may be effective in rhinitis. For treatment of asthma more studies are needed.

## References

- 1 Bousquet J, Lockey RF, Mailling H-J: WHO Position paper: Allergen Immunotherapy: Therapeutic vaccines for allergic diseases. *J Allergy Clin Immunol* 1998;53(suppl 44).
- 2 Wessner DB, Wessner S, Möhrenschrager M, Rakoski J, Ring J: Efficacy and safety of sublingual immunotherapy in adults with allergic rhinoconjunctivitis: Results after 2 years of a controlled clinical trial. *Allergy* 2001;56(suppl 68): 88.
- 3 Bousquet J, Scheinmann P, Perrin-Fayolle MT, Sauvaget J, Tonnel AB, Pauli G, Caillaud D, Dubost R, Leynadler F, Vervloet D, Hermann D, Galvain S, André C: Sublingual-swallow immunotherapy (SLIT) in patients with asthma due to house-dust mites: A double-blind, placebo-controlled study. *Allergy* 1999; 54:249–260.
- 4 Pajno GB, Morabito L, Barberio G, Parmiani S: Clinical and immunologic effects of long-term sublingual immunotherapy in asthmatic children sensitized to mites: A double-blind, placebo-controlled study. *Allergy* 2000;9:842–849.
- 5 Bagnasco M, Mariani G, Passalacqua G, et al: Absorption and distribution kinetics of the major *Parietaria judaica* allergen (Par j 1) administered by noninjectable routes to healthy human beings. *J Allergy Clin Immunol* 1997;100: 121–129.
- 6 Fanta C, Bohle B, Hirt W, Siemann U, Horak F, Kraft D, Ebner H, Ebner C: Systemic immunological changes induced by administration grass pollen allergens via the oral mucosa during sublingual immunotherapy. *Int Arch Allergy Immunol* 1999;120:218–224.
- 7 André C, Vatrinet S, Galvain S, Carat F, Sicard H: Safety of sublingual-swallow immunotherapy in children and adults. *Int Arch Allergy Immunol* 2000;121:229–243.
- 8 Tari MG, Mancino M, Monti G: Efficacy of sublingual immunotherapy in patients with rhinitis and asthma due to house dust mite: A double-blind study. *Allergol Immunopathol* 1990;18:277–284.
- 9 Sabbah A, Hassoun S, Le Sellin J, André C, Sicard H: A double-blind placebo-controlled trial by the sublingual route of immunotherapy with a standardized grass pollen extract. *Allergy* 1994;49:309–313.
- 10 Troise C, Voltolini S, Canessa A, Pecora S, Negrini AC: Sublingual immunotherapy in parietaria pollen induced rhinitis: A double-blind study. *J Invest Allergol Clin Immunol* 1995;5:25–30.
- 11 Quirino T, Lernoli E, Siciliani E, Parmiani S, Milazzo F: Sublingual versus injective immunotherapy in grass pollen allergic patients: A double-blind (double dummy) study. *Clin Exp Allergy* 1996;26:1253–1261.
- 12 Feliziani V, Lamuada G, Parmiani S, Dall'Aglio PP: Safety and efficacy of sublingual rush immunotherapy with grass allergen extract: A double-blind study. *Allergol Immunopathol* 1995;23:173–178.
- 13 Clavel R, Bousquet J, André C: Clinical efficacy of sublingual-swallow immunotherapy: A double-blind, placebo-controlled trial of a standardized five-grass-pollen extract in rhinitis. *Allergy* 1998;53:629–632.
- 14 Passalacqua G, Albano M, Fregonese L, Riccio A, Pronto C, Mela GS, Canonica GW: Randomised controlled trial of local allergoid immunotherapy on allergic inflammation in mite-induced rhinoconjunctivitis. *Lancet* 1998;351: 629–632.
- 15 Passalacqua G, Canonica GW: Alternative routes for allergen-specific immunotherapy. *Invest Allergol Clin Immunol* 1999;6:81–87.
- 16 Di Rienzo V, Puccinelli P, Frati F, Parmiani S: Grass pollen specific sublingual-swallow immunotherapy in children: Open-controlled comparison among different treatment protocols. *Allergol Immunopathol (Madr)* 1999;27: 145–151.
- 17 Valle C, Bazzi S, Berra D, Sillano V, Puccinelli P, Parmiani S: Effects of sublingual immunotherapy in patients sensitised to ambrosia: An open controlled study. *Allergol Immunopathol (Madr)* 2000;28:295–300.
- 18 Nelson HS, Oppenheimer J, Vatsla GA, Bucheimer A: A double-blind placebo-controlled evaluation of sublingual immunotherapy with standardized cat extract. *J Allergy Clin Immunol* 1993;92:229–236.
- 19 Khinchi MS, Poulsen LK, Carat F, André C, Mallung HJ: Clinical efficacy of sublingual-swallow and subcutaneous immunotherapy in patients with allergic rhinoconjunctivitis due to birch pollen: A double-blind, double-dummy placebo-controlled study. *Allergy* 2000; 54(suppl 63):24.
- 20 La Rosa M, Ranno C, André C, Carat F, Tosca MA, Canonica GW: Double-blind placebo parietaria judaica extract in children with allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 1999;104:425–432.
- 21 Vourdas D, Syringou E, Potamianou P, Carat F, Batard T, André C, Papageorgiou PS: Double-blind, placebo-controlled evaluation of sublingual immunotherapy with standardized olive pollen extract in pediatric patients with allergic rhinoconjunctivitis and mild asthma due to olive pollen sensitization. *Allergy* 1998; 53:662–672.
- 22 Horak F, Stübner R, Berger UE, Marks B, Toth J, Jäger S: Immunotherapy with sublingual birch extract: A short-term double-blind placebo study. *Invest Allergol Clin Immunol* 1998;8: 165–171.
- 23 Purello-D'Ambrosio F, Gangerni S, Isola S, La Motta N, Puccinelli P, Savi E, Ricciardi L: Sublingual immunotherapy: A double-blind, placebo-controlled trial with parietaria judaica extract standardized in mass units in patients with rhinoconjunctivitis, asthma or both. *Allergy* 1999;54:968–973.
- 24 Hirsch TH, Sähn M, Leupold W: Double-blind placebo-controlled study of sublingual immunotherapy with house dust mite extract (*D. pt.*) in children. *Pediatr Allergy Immunol* 1997;8: 21–27.
- 25 Guez S, Valtrinet C, Fadel R, André C: House-dust mite sublingual-swallow immunotherapy (SLIT) in perennial rhinitis: A double-blind, placebo-controlled study. *Allergy* 2000;55: 369–375.