

OPTIMAL DOSING OF ALLERGEN IMMUNOTHERAPY : EFFICACY, SAFETY, LONG-LASTING EFFECT

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INTRODUCTION

Double-blind, placebo-controlled studies have clearly demonstrated that allergen injection immunotherapy (IT) is clinically effective for treatment of allergic rhinitis and bronchial asthma (1, 2). The clinical efficacy of IT in both conditions has recently been confirmed by means of meta-analysis techniques (4, 5). Moreover during the last few years have demonstrated that allergen immunotherapy can redirect the T lymphocyte differentiation from the Th2 towards the Th1 phenotype (5). This acquisition provides for the first time a satisfactory explanation of the model of action of IT and support its rationale of use.

Finally the long-lasting clinical efficacy after discontinuation and the preventive effect on asthma onset have been evidenced in a number of clinical trials (6). These considerations, taken together, are an encouraging basis for increasing popularity of the treatment.

The thread that underlines successful immunotherapy is the use of well characterised, standardised extracts which offer some relevant advantages (table 1) in terms of both efficacy and safety (7). However successful immunotherapy requires besides that an adequate therapeutic dose of the relevant allergen be administered to the patient for an appropriate length of time. Aim of this review is to discuss the role of the "optimal dose" defined as the dose of allergy vaccine inducing a clinical relevant effect in most patients without causing unacceptable side-effects (6), in conditioning clinical efficacy, safety and long lasting effect.

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1. Less manufacturer to manufacturer and lot to lot variation;
2. The ability to develop meaningful schedules for use of allergy extracts for diagnostic testing and for immunotherapy
3. The ability to compare skin test results from patient to patient and in the same patient over the time
4. Greater safety of immunotherapy in those patients appropriately treated with high-dose immunotherapy that is near the threshold for systemic reactions
5. Decreased risk of new IgE-specificities induction (?)

Table 1 : Advantages of Standardized Extracts.

CLINICAL EFFICACY

The rapid development of new biotechnologies offers opportunities for improved standardisation. With these new technologies, an allergen extracts can be defined by major allergen content thus improving the possibility of objective comparisons among allergen extracts and dosages. So the measurement of major allergens for standardisation is now a realistic goal which should be carefully considered (8).

Nevertheless, it is essential to remind the major allergens in allergenic products are just one of the parameter related to the biological potency and quality. The allergenic extracts are very complex mixtures of molecules characterised by various biological features like enzymatic and immunological activity (9). Consequently many operative procedures and analytical methods are required to assure the quality and standardise such products, which have been the subject of specific Guidelines released by the European

Agency for the Evaluation of Medical Products and consequently introduced in the European Pharmacopeia (10).

A further technical problem in the use of the concentration of major allergens as biological parameter of the allergenic products is the lack of availability of internationally accepted methods and reagents for their determination, with the unique exception of Der P₁ (11). As a consequence, every manufacturer has to develop internal analytical methods and standards (in-house reference preparation, IHRP) which are poorly comparable each other. Further problems arise from the use of allergoids, either polymeric (by reaction with formaldehyde or glutaraldehyde) or monomeric (by carbamylation). In fact the chemical modification of extracts almost invariably has a profound effect on the antibody binding epitopes, affecting their recognition by monoclonal antibodies used in determination procedure (12) (table 2).

In spite of these restrictions using the above mentioned parameter the WHO Position Paper (11) stated that "a maintenance dose of 5-20 µg of major allergen per injection is associated with significant clinical improvement". This evidence comes from :

➤ **The clinical results of immunotherapy controlled studies using a maintenance dose within this range:** a clinical effectiveness was demonstrated in seasonal rhinitis due to grass, birch and ragweed pollens (table 2) and in perennial allergic asthma due to dust mite (table 3) and cat dander (table 4) (13-36); in fact 12 µg of Bet v 1 was used as maintenance dose in all two studies showing clinical (22-23) and quality of life improvement (22) in birch pollenosis. In mite and cat allergic asthma a narrow range of maintenance dosages (5-11 µg of Der p 1/injection and 11-17 µg of Fel d 1/injection) proved clinically effective and capable of reducing bronchial specific hyperresponsiveness and skin reactivity (24-36). In ragweed pollenosis a wider range of maintenance dosage (4-24 µg Amb a 1/injection) was used, being the highest dosages clinically more effective (17-22). In grass pollenosis high maintenance

ADVANTAGES	DISADVANTAGES
The biological potency is related to major allergens content	In each allergenic source there are many different allergens
The measure unit is absolute (mg/mL) reagents for the determination procedure	Lack of internationally accepted
Allows comparison of allergenic products from different producers	International standards available for few allergenic sources
	The correlation with biological potency is complex in the case of allergoids

Table 2 : Use of major allergens as parameter of biological activity of allergens products.

Allergen	Major Allergen	Author (n° of reference)	Dosage (mcg)
Grass	Phl p 5	Osterballe (13)	25-41
	Phl p 6	Osterballe (13)	13-20
	Phl p 5	Varney (14)	18.6
	Dac q 5, Lol p 5	Dolz (15)	15
	Phl p 5	Walker (16)	20
Ragweed	Amb 1	Van Metre (17)	2-19
		Van Metre (18)	4-47
		Creticos (19)	12-24
		Creticos (20)	10
		Furin (21)	24
Birch	Bet v 1	Bodtger (22)	12
		Arvidsson (23)	12

Table 3 : Doses effective for allergen immunotherapy in placebo controlled studies in pollenosis.

Allergen	Major Allergen	Author (n° of reference)	Dosage (mcg)
Dermatophagoides	Der p 1	Ewan (24)	11.9
		Haugaard (25)	7
		Olsen (26)	7-10
		Pichler (27)	7
		Whan (28)	0.5-11
		Bousquet (29)	5
Cat	Fel d 1	Taylor (30)	16
		Ohman (31)	8-16
		Sundin (32)	15
		Van Metre (33)	13.8
		Alvarez Cuesta (34)	11.3
		Hedlin (35)	17.3
		Varney (36)	15

Table 4 : Doses effective for allergen immunotherapy in placebo controlled studies in dermatophagoides and cat allergy.

nance doses (13-20 µg Phl p 5/injection) were generally administered (13-16), demonstrating not only a significant reduction of drug and symptom score, but also an increased well being (16).

➤ **Several dose/response studies:** Very low doses (less than 1 µg of major allergen/injection) have been shown to be no more effective than placebo (18, 19). Creticos *et al.* in a previous study demonstrated that both symptoms and nasal response in specific challenge significantly improved in ragweed allergic subjects who had been on maintenance IT (6 mg Amb a 1/injection) when compared with untreated patients. In another double-blind prospective study of 27 ragweed allergic patients suffering from seasonal rhinitis, those patients randomized to a conventional extract of ragweed demonstrated a distinct stepwise reduction in nasal responsivity to ragweed pollen challenge as the dose of immunotherapy was increased from low dose (up to 6 mcg Amb a 1/injection) to moderate dose (12.4 µg Amb a 1/injection) to high dose (24.8 µg Amb a 1) (37). Similar dose-related findings have been demonstrated in patients with ragweed-induced asthma. Bruce *et al.* (38) used a dose of 2 µg of Amb a 1/injection and failed to demonstrate clinical improvement in asthma symptoms, rhinitis symptom and upon bronchial challenge. However Creticos *et al.* (21) showed that a maintenance dose of 10 µg of Amb a 1/injection resulted in a significant reduction in specific bronchial sensitivity to ragweed and that this was paralleled by favorable effects on clinical parameters. Haugaard *et al.* (25) used bronchial provocation to study dust mite-allergic patients. These investigators likewise demonstrated a significant dose-dependent improvement upon bronchial challenge to an extract of Der p 1 as the immunizing dose was increased from 0.7 µg to 7 µg to 21 µg Der p 1/injection. However in this study the dose/effect relationship was not linear but showed a plateau after the mid-dose (in this study 7 µg Der p 1/injection).

However in contrast with these results in other controlled studies lower dosages proved clinical efficacy. In allergic mite-asthma a maintenance dose of 3.2 Der p 1 µg induced clinical and immunologic changes which were sustained during a 5-year course of treatment, even in patient able to tolerate higher dosages (39-40) and more recently the same dosage of Der p 1 encapsulated in liposomes proved clinical effectiveness (41). In seasonal allergic rhinitis a low dose of Phl p 5 (2.1 µg/injection) of an extract calcium phosphate-adsorbed proved a clinical improvement in seasonal rhinoconjunctivitis (42) whilst birch-pollen allergy has been efficiently treated with a short course of preseasonal immunotherapy using a low maintenance dosage (1-3 µg Bet v 2) (43).

SAFETY

The frequency and severity of systemic reactions (SR) vary among studies and in clinical practice depending by many factors (table 4). Some of them are related to the extract, dosage and schedule of treatment.

■ **Extract:** Some studies reported a lower frequency of SR with the use of standardised aluminium extracts, compared with aqueous extracts (44-46), with an high proportion of late reactions (46-47). However the frequency and severity of SRs might also depend on the considered allergen. A retrospective study found that mite and grass provoked a superimposable rate of unwanted effects, but the occurrence of side side effects with grass and mite was higher than with parietaria and mixture allergens (47). More recently a standardised grass pollen extract was associated with a significantly higher number and greater severity of SRs than birch pollen immunotherapy, being the different biological potency of birch and grass-pollen extracts the most likely explanation (48).

■ **Dose scheduling:** The importance of the dose increment schedule has been clearly demonstrated by Bousquet *et al.* (49) and Hejjaoui *et al.* (50) who found rates of SRs ranging from 4% of injections during a rush protocol compared with 0.6% of injections during a semirush protocol in asthmatics patients treated with the same standardised aqueous extract of *Dermatophagoides pteronyssinus*. These results have been recently confirmed by Møllerup *et al.*, who found higher prevalence of SRs in children treated with a rush protocol (47). Moreover the prevalence of SRs is generally higher during the build-up phase of the treatment (47-50).

■ **Dosage:** In dose titration study a correlation between the dosage and the appearance of SRs has been demonstrated. Haugaard *et al.* (25), noticed a stepwise increase in SRs rate (0.56%, 3.30% and 7.10% respectively) as the immunizing dose was increased from 0.7 to 7 to 21 mcg/injection. Nevertheless in this study the higher dose regimens (7 and 21 µg /injection) were more effective as compared with 0.7 µg injection regimen. The higher reaction rate with 21 µg injection regimen lead the Authors to conclude that a maintenance dose of 7 µg Der p 1/injection was the more appropriate dose. Likewise Olaguibel *et al.* (39) noticed in a dose-titration study that 90% of patients tolerated a maintenance dose of 3.2 µg of Der p 1, but only 18% of the patients reached a maintenance dose of 16µg. In fact in combination with the development of standardised extract and more potent extracts, high dose IT has resulted in a number of side effects (51-52).

LONG-LASTING CLINICAL EFFICACY

A long-term clinical effect maintained for years after discontinuation was clearly demonstrated for grass and three pollens IT, as well as for cat dander and mite IT (table 5). In one follow-up study on grass-pollen allergic patients it was shown that patients suffering from rhinoconjunctivitis, with or without mild-to-moderate seasonal asthma consistently experienced significantly decreased symptoms during seasonal exposure 5 years after SIT discontinuation (53). A similar study with birch-pollen allergic patients showed effect after two years of SIT on asthma as well as on nasal sensitivity. This study confirms that the clinical effect persists up to six years after termination of SIT. None of the patients who initially suffered only from hay fever developed asthma during the period-study (54). Hedlin *et al.* (55) found that cat-allergic patients with mild-to-moderate asthma not only reduced their specific reactivity but also non specific hyperreactivity. The follow-up study 5 years after SIT discontinuation showed the effect was persistent with regard to exposure to cats as well as non specific hyperresponsiveness. A recently published double-blind placebo-controlled randomized long term study with grass pollen IT demonstrated that the clinical improvement achieved after a 3- to 4 years of course persisted at least 3 years after termination of SIT (56). In mite allergic subjects De Roches *et al.* (57) demonstrated a relapsing rate of 55% in patients who had received immunotherapy for a period of 12-96 months and followed up for up to 3 years. Interestingly patients who did not relapse had a decrease of skin reactivity at the end of treatment and the duration of the efficacy of SIT after its cessation depended upon the duration of the treatment. A prolonged efficacy was recently demonstrated in a long term follow-up study also in children, who, in 1989-91, underwent a 3-year course of preseasonal SIT with grass pollen extract in a double-blind placebo controlled study. On the original 28 patients Eng *et al.* (58) reassessed 23 patients in the 1997 pollen season: 13 from the former SIT group and 10 from the former placebo group. There was a significant difference in symptom score thus confirming that clinical effectiveness of SIT was still persisting. However the most intriguing results were those related to the natural course of the disease. In fact only 23% of the SIT patients still had asthma symptoms, whereas in the control group the prevalence of asthma remained 70%. Moreover the SIT group developed a significantly lower number of new sensitizations. A long-term clinical effect has been also demonstrated in pollinosis due to Parietaria. A 3 years course of SIT with parietaria allergoid achieved a clinical improvement, which persisted after discontinuation at one year evaluation (59).

Finally an open multicenter study recently demonstrated that a 3 year course of SIT with birch (12 µg Bet v 1/injection as maintenance dosage) or grass (20 µg Phl p 5/injection) standardized extracts can reduce the development of asthma in children with seasonal allergic rhino-conjunctivitis (60).

► Related to the patient

Time of onset

Asthma

- uncontrolled asthma

- FEV₁ < 70%

Drug interaction

- β -blocker therapy

- ACE-inhibitor therapy

► Related to the extract and its administration

Aqueous extract

High dose therapy

Rush immunotherapy

Methods

- incorrect technique

- errors in dosage

Table 5 : Follow-up studies with characterized, standardized allergen extracts.

Author		Patients (n°)	Length of SIT (months)	Length of SIT (years)	
Mosbech	grass	20	35	28	6
Jacobsen	birch	12	32	36	6
Hedlin	Cat	15	32	36	3
Durham	grass	20	36	36-48	3
De Roches	D. pter		40	12-96	3
Ariano	Parietaria				

Table 6 : Follow-up studies with characterized, standardized allergen extracts.

DISCUSSION

In spite some before mentioned drawbacks the range suggested by the WHO Position Paper is a good reference in terms of effectiveness and long lasting effects, though in most of the studies the rate of SR was higher than in normal practice (table 7). Moreover in these studies to an increase of the dosages corresponds a linear increase of systemic reactions, but not of the clinical efficacy. It has to be outlined that in these studies optimal doses of SIT have been identified with the maximal tolerated doses, just below the dose causing

local or SRs. In contrast other studies in which a clinical efficacy was demonstrated at lower dosages (39-43), suggest to think of optimal doses as those capable of modifying the clinical picture of the patients while giving a clear margin of good tolerance (61). The use of new adjuvants could increase the effect of lower dosages (41-43).

allergen	% of all patients	% of all injections	N° references
Grass	9.5-33	0.38 - 0.81	14- 16
Birch	16.6-23.5	0.65 - 1.31	22- 23
Mite	0 - 37	1.97 - 7.1	25 -27
Cat	18 - 40	0.14 - 1.7	32 -36

Table 7.

Besides there is the problem of the non-injective routes of immunotherapy, sublingual and local nasal, whose use in Europe is constantly growing. It is evident that we cannot transfer on these immunotherapy routes the dosing experiences acquired for injective routes, considering that the absorption and kinetics as well as bio-availability are undoubtedly different. This concept is supported by a recent immunological study where in course of grass local nasal immunotherapy a highly significant decrease of the allergen-driven proliferative response of peripheral blood T-lymphocytes, in comparison to a control group of untreated grass-allergic patients, was observed. Interestingly, the same study showed that a similar decrease of T-lymphocyte response was obtained in a third group of patients given subcutaneous immunotherapy, even though the cumulative dosage in the LNIT group was between 10 and 50 times less than in subcutaneous group (62). One possible explanation may be that the majority of allergen-specific T cells accumulate in lymph nodes draining the respiratory tract of allergic patients, so a locally introduced allergen can modify them more easily than a subcutaneous one. In fact this immunological effect has been attributed to the induction of T-cell tolerance, which may reflect the generation of allergen specific suppressor T-cells, clonal anergy, extrathymic deletion of allergen reactive Th cells and/or Th2 to Th1 switch. However long lasting clinical and immunological effects have been demonstrated only using high dosages.

In conclusion the "optimal dose" remain an unresolved question. More dose/response studies are needed to assure the clinical efficacy and above all the long lasting effect of dosages lower than those suggested by WHO Position paper. This research is particularly mandatory in "at risk" conditions, such as in children and in asthmatic patients. Finally it is advisable to overcome the lack of internationally accepted reagents and methods for the determination procedure of major

allergens in order to correctly compare extracts and treatments.

Moreover it is important to be certain that the results obtained in the controlled studies can be anticipated in the clinical application of allergen immunotherapy. One significant difference between the controlled studies and clinical practice is that the former are usually conducted with a single allergen extract, whereas, particularly in North America, clinical practice is to usually use a mixture of allergens. There is probably no harm in administering allergen extracts to which the patient is not allergic. However it has repeatedly demonstrated that allergen immunotherapy is immunologically specific (60-61). Therefore administering allergen to which the patient is not allergic is equivalent to administering additional diluent, so reducing the maintenance dose. In fact some allergen extracts contain proteases which are capable of degrading the allergenic proteins of other extracts (62).

REFERENCES

1. Norman P.-S., Winkenwerder W.-L., Lichtenstein L.-M. - Immunotherapy of hay fever with ragweed antigen E : comparison with whole pollen extract and placebo. *J Allergy* 1968;42:93-108.
2. Malling H.-J. - Allergen specific immunotherapy in allergic rhinitis. *Curr Opin Allergy Clin Immunol* 2001;1:43-6.
3. Bonifazi F., Bilò M.-B. - Efficacy of specific immunotherapy in allergic asthma : myth of reality ? *Allergy* 1997;52:698-710.
4. Abramson M.-J., Puy R.-M., Weiner J.-M. - Is allergen immunotherapy effective in asthma ? A met-analysis of randomized clinical trials. *Am J Resp Crit Care Med* 1995;151:969- 74.
5. Ross R.-N., Nelson H.-S., Finegold I. - Effectiveness of immunotherapy in the management of allergic rhinitis. An analysis of randomized, prospective, placebo-controlled blinded studies. *Clin Ther.* 2000;22:351-8.
6. Durham S.-R. - Immunologic changes associated with allergen immunotherapy. *J Allergy Clin Immunol* 1998;102:157-64.
7. Bousquet J., Lockey R.-F., Malling H.-J., editors. - WHO position paper. Allergen immunotherapy : therapeutics vaccines for allergic diseases. *Allergy* 1998;53(suppl):1-42.
8. Nelson H.-S. - The use of standardised extracts in allergen immunotherapy. *J Allergy Clin Immunol* 2000;106:41-5.
9. Ipsen H., Klysner S.-S., Larsen J.-N., Lowenstein H., Matthiesen F., Schou C., Sparholt S.-H. - Allergen extracts. In *Allergy. Principles and Practice*. Editors. Middleton E., Reed C.-E., Ellis E.-F., Adkinson N.-F. jr, Yunginger J.-W., Busse W.-W. Fourth Edition. Mosby-Year Book, Inc, St Louis, 1993;p.:529-553.
10. Committee for Proprietary Medicinal Products (CPMP). - Note for guidance on allergen products. The European Agency for the Evaluation of Medical Products 1996. CPMP/BWP/243/96.
11. Nolte H. Optimal maintenance dose immunotherapy based on major allergen content or potency labeling. (Letter) *Allergy* 1998;53:90-100.
12. Cromwell O., Weber B., Kahlert H., Fiebig H. - Standardisation in quality control of modified end-products. In : *Regulatory Control and Standardisation of Allergenic Extracts*. Ninth International Paul-Erlich Seminar, September 9-11, 1999, Langen, Germany. Editors Keurth R and Hausteine D. Git Verlag GmbH 2000; p.:93-100.
13. Osterballe O. - Immunotherapy in hay fever with two major allergens 19,25 and partially purified extract of timothy grass pollen. A controlled double blind study. *In vivo variables season.* *Allergy* 1980;35:473-89.
14. Varney V.-A., Gaga M., Frew A.-J., Aner V.-R., Kay A.-B., Durham S.-R. - Usefulness of immunotherapy in patients with severe summer hay fever uncontrolled by antiallergic drugs. *BMJ* 1991;302:530-1.

15. Dolz I., Martinez Cocera G., Bartolome J.-M., Cimarra M. - A double-blind, placebo-controlled study of immunotherapy with grass pollen extract Alutard SQ during a 3-year period with initial rush immunotherapy. *Allergy* 1996;51:489-500.
16. Walker S.-M., Pajno G.-B., Lima M.-T., Wilson D.-R., Durham S.-R. - Grass pollen immunotherapy for seasonal rhinitis and asthma: a randomized-controlled trial. *J Allergy Clin Immunol* 2000;107:87-93.
17. Van Metre T.-E., Adkinson N.-F. jr, Lichtenstein L.-M. et al. - A controlled study of the effectiveness of Rinkel method of immunotherapy for ragweed pollen hay fever. *J Allergy Clin Immunol* 1980;65:288-97.
18. Van Metre T.-E., Adkinson N.-F. jr, Amodio F.-J. et al. - A comparative study of the effectiveness of the Rinkel method and the current standard method of immunotherapy for ragweed pollen hay fever. *J Allergy Clin Immunol* 1980;66:500-13.
19. Creticos P.-S., Van Metre T.-E., Mardiney M.-R., Rosemberg G.-L., Norman P.-S., Adkinson N.-F. jr. - Dose response of IgE and IgG antibodies during ragweed immunotherapy. *J Allergy Clin Immunol* 1984;73:94-104.
20. Creticos P.-S., Reed C.-E., Norman P.-S. et al. - Ragweed immunotherapy in adult asthma. *N Eng J Med* 1996;334:501-6.
21. Furin M.-J., Norman P.-S., Creticos P.-S., Proud D., Kagey-Sobotka A., Lichtenstein L.-M., Naclerio R.-M. - Immunotherapy decreases antigen-induced eosinophil migration into the nasal cavity. *J Allergy Clin Immunol* 1998;88:27-32.
22. Bodtger L.-K., Poulsen H., Jabobi H., Malling H.-J. - The safety and efficacy of subcutaneous birch pollen immunotherapy - a one year, randomized, double-blind placebo-controlled study. *Allergy* 2002;57:297-305.
23. Arvidsson M.-B., Lowhagen O., Rak S. - Effect of 2-year placebo-controlled immunotherapy on airway symptoms and medication in patients with birch pollen allergy. *J Allergy Clin Immunol* 2002;109:777-83.
24. Ewan P.-W., Alexander M.-M., Snape C., Ind P.-W., Agrell D., Dreborg S. - Effective hyposensitization in allergic rhinitis using a potent partially purified extract of house dust mite. *Clin Allergy* 1988;18:501-8.
25. Haugaard L., Dahl R., Jacobsen L. - A controlled dose-response study of immunotherapy with standardized partially purified extract of house dust mite clinical efficacy and side effects. *J Allergy Clin Immunol* 1993;91:709-22.
26. Olsen O.-T., Larsen K.-R., Jacobsen L. - Svedsen UG. A 1-year, placebo-controlled, double-blind house dust mite immunotherapy study in asthmatics adults. *Allergy* 1997;52:853-9.
27. Pichler C.-E., Marquadrassen A., Sparholt S., Lowenstein H., Bircher A., Bishof M., Pichler W.-J. - Specific immunotherapy with Dermatophagoides pteronyssinus and D. farinae results in decreased bronchial hyperreactivity. *Allergy* 1997;52:274-83.
28. Wahn U., Scheweter C., Lind P., Lowenstein H. - Prospective study on immunologic changes induced by two different Dermatophagoides pteronyssinus extract prepared from whole mite culture and mites bodies. *J Allergy Clin Immunol* 1988;82:360-70.
29. Bousquet J., Calvajrac P., Guerin B. et al. - Immunotherapy with a standardized Dermatophagoides pteronyssinus extract. *In vivo* and *in vitro* parameter after a short course of treatment. 1985;76:734-44.
30. Taylor W.-W., Ohman J. jr, Lowell F.-C. - Immunotherapy in cat-induced asthma. Double-blind trial with evaluation of bronchial responses to cat allergen and histamine. *J Allergy Clin Immunol* 1978;61:283-7.
31. Ohman J. jr, Findlay S.-R., Leitermann K.-M. - Immunotherapy in cat-induced asthma. Double-blind trial with evaluation of *in vivo* and *in vitro* responses. *J Allergy Clin Immunol* 1984;74:230-9.
32. Sundin B., Lilja G., Graff-Lonevig V. et al. - Immunotherapy with partially purified and standardized animal dander extracts. Clinical results from a double-blind study on patients with animal dander asthma. *J Allergy Clin Immunol* 1986;77:478-87.
33. Van Metre T.-E. jr, Marsh D.-G., Adkinson N.-F. jr, et al. - Immunotherapy for cat asthma. *J Allergy Clin Immunol* 1988;82:1055-68.
34. Alvarez-Cuesta E., Cuesta-Herranz J., Puyana-Ruiz J. - Cuesta-Herranz C., Blanco-Quiros A. - Monoclonal antibody-standardized cat extract immunotherapy. Risk benefit effects from a double-blind placebo-controlled study. *J Allergy Clin Immunol* 1994;93:556-66.
35. Hedlin J.-G., Graff-Lonevig V., Heilbron H., Lilja G., Norrland K., Pegelow K., Sundin B., Lowenstein H. - Immunotherapy with cat and dog -dander extracts. *J Allergy Clin Immunol* 1991;87:955-64.
36. Varney V.-A., Edwards J., Tabbah K., Brewster H., Mavroleon G., Frew A.-J. - Clinical efficacy of specific immunotherapy to cat dander: a double blind placebo-controlled trial. *Clin Exp Allergy* 1997;27:860-7.
37. Creticos P.-S. - The consideration of immunotherapy in the treatment of allergic asthma. *Ann Allergy Asthma Immunol* 2001;87(Suppl 1):13-27.
38. Bruce A.-A., Norman P.-S., Rosenthal R.-R. et al. - The role of ragweed pollen in autumnal asthma. *J Allergy Clin Immunol* 1977;59:449-59.
39. Olaguibel J.-M., Tabar A.-I., Garcia Figueroa B.-E., Cortes C. - Immunotherapy with standardized extract of Dermatophagoides pteronyssinus in bronchial asthma: a dose titration study. *Allergy* 1997;52:168-178.
40. Olaguibel J.-M., Tabar A.-I., Garcia B.-E., Martin S., Rico P. - Long term immunotherapy with an optimal maintenance dose of a standardized Dermatophagoides extract in asthmatic patients. *J Invest Allergol Clin Immunol* 1999;9:10-6.
41. Basomba A., Tabar A.-I., de Rojas D.-H., Garcia B. et al. - Allergen vaccination with a liposome-encapsulated extract of Dermatophagoides pteronyssinus: a randomized, double blind, placebo controlled trial in asthmatic patients. *J Allergy Clin Immunol* 2002;109:943-8.
42. Leynadier F., Banoun L., Dollois B., Terrier P. et al. - Immunotherapy with a calcium phosphate-adsorbed five grass-pollen extract in seasonal rhinoconjunctivitis: a double-blind, placebo-controlled study. *Allergy* 2001; 31 : 988-96.
43. Balda B.-R., Wolf H., Baumgarten C., Klimek K. et al. - Tree-pollen allergy is efficiently treated by short term immunotherapy with seven pre-seasonal injections of molecular standardized allergens. *Allergy* 1998;53:740-8.
44. Tabar A.-I., Garcia B.-E., Rodriguez A. - Olaguibel J.-M., Muro M.-D., Quirce S. - A prospective safety-monitoring study of immunotherapy with biologically standardized extracts. *Allergy* 1993;48:450-3.
45. Osterballe O. - Side effects during immunotherapy with purified grass pollen extracts. *Allergy* 1982;37:553-62.
46. Møllerup M.-T., Hahn G.-W., Poulsen L.-K., Malling H.-J. - Safety of allergen-specific immunotherapy. Relation between dosage regimen, allergen extract, disease and systemic side effects during induction treatment. *Clin Exp Allergy* 2000;30:1423-9.
47. Ragusa R.-V., Passalacqua G., Gambardella R., Campanari S., Berbiere I., Scordamaglia A., Canonica G.-W. - Nonfatal systemic reactions to subcutaneous immunotherapy 10-year experience. *J Invest Allergol Clin Immunol* 1997;7:151-4.
48. Winther L., Malling H.-J., Mosbech H. - Allergen-specific immunotherapy in birch and grass-pollen-allergic rhinitis. Side effects. *Allergy* 2000;55:827-35.
49. Bouquet J., Hejjaoui A., Dhivert M., Clauzel A.-M., Michel F.-B. - Immunotherapy with a standardized Dermatophagoides pteronyssinus extract. III° Systemic reactions during the rush protocol in patients suffering from asthma. *J Allergy Clin Immunol* 1989;83:797-83.
50. Hejjaoui A., Dhivert M., Michel F.-B., Bousquet J. - Immunotherapy with a standardized Dermatophagoides pteronyssinus extract. IV° Systemic reactions according to the immunotherapy schedule. *J. Allergy Clin Immunol* 1990;85:473-9.
51. Turkeltaub P.-C., Campbell G., Mosimann J.-E. - Comparative safety and efficacy of short ragweed extracts differing in potency and composition in the treatment of fall hay fever. *Allergy* 1990;45:528-46.
52. Turkeltaub P.-C. - The importance of allergen dose on the safety and efficacy of immunotherapy of ragweed hayfever with standardized short ragweed extracts (SR). (abstr). *J Allergy Clin Immunol* 1986;77(part 2):211.
53. Mosbech H., Osterballe O. - Does the effect of immunotherapy last after termination of treatment? Follow-up study in patients with grass pollen rhinitis. *Allergy* 1988;43:523-9.
54. Jacobsen L., Nuchel Petersen B., Whil J.-A. et al. - Immunotherapy with partially purified and standardized tree pollen

extracts. IV° Results from a long-term (6 years) follow up study. *Allergy* 1997;52:914-20.

55. Hedlin G., Heilborn H., Lilja G. *et al.* - Long term follow up of patients treated with a three year course of cat or dog immunotherapy. *J Allergy Clin Immunol* 1995;96:879-85.

56. Durham S.-R., Walker S.-M., Varga E.-M. *et al.* - Long term clinical efficacy of grass pollen immunotherapy. *N Eng J Med* 1999;34:468-75.

57. Des Roches A., Paradis L., Knani J., Hejjoui A., Dhivert H., Chanez P., Bousquet J. - Immunotherapy with a standardized Dermatophagoides pteronyssinus extract. V° Duration of the efficacy of immunotherapy after its cessation. *Allergy* 1996;51:430-3.

58. Eng P.-A., Reinhold M., Gnehm HPE. - Long term efficacy of pre-seasonal grass pollen immunotherapy in children. *Allergy* 2002 ; 57:306-12.

59. Ariano R., Kroon A.-M., Augeri G., Canonica G.-W., Passalacqua G. - Long-term treatment with allergoid immunotherapy with Parietaria. Clinical and immunologic effects in a randomized, controlled trial. *Allergy* 1999;54:313-9.

60. Moller C., Dreborg S., Ferdousi H.-A. *et al.* - Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-Study). *J Allergy Clin Immunol* 2002;109:251-6.

61. Basomba A. - The importance of allergen dosage and treatment schedules in immunotherapy. In Reed ChE (Ed): Proceedings XII International Congress of Allergology and Clinical Immunology (Washington) 1985:335-40.

62. Giannarini L., Maggi E. - Decrease of allergen specific T-cell response induced by local nasal immunotherapy. *Clin Exp Allergy* 1998;28:404-414.



PRESS RELEASE

HORMONES MAY IMPROVE LUNG FUNCTION AND ASTHMA*

ARLINGTON HEIGHTS, Ill. (March 19, 2003) - Evidence indicates that progesterone and estrogen may improve lung function and asthma, according to a report published in this month's *Annals of Allergy, Asthma & Immunology*, the scientific journal of the American College of Allergy, Asthma and Immunology (ACAAI).

"Positive effects of estrogen and progesterone on lung function and asthma have been observed across the life span in women," said Catherine L. Haggerty, PhD, MPH, University of Pittsburgh, Graduate School of Public Health, Pittsburgh, Pa. "Studies suggest that the hormones play a role in strengthening respiratory muscle and increasing relaxation of bronchial smooth muscle, reducing the contractile response. Estrogen and progesterone also have been shown to exhibit anti-inflammatory properties."

During the premenstrual and menstrual phase when hormonal levels are low, asthmatic patients have been found to experience increased asthma episodes, increased hospitalizations for asthma and decreased pulmonary function. While taking oral contraceptives and hormone replacement therapy, some women experience improved pulmonary function and a decrease in asthma exacerbation.

"Estrogen and progesterone are highly elevated during pregnancy, reaching their greatest concentrations during the final trimester. In some women, improvements in asthma symptoms from preconception to pregnancy parallel these changes in hormonal levels, with the lowest rate of symptoms occurring during the last four weeks," Dr. Haggerty said.

According to the authors, certain subgroups of women may be more susceptible to hormone cycles.

Testosterone, estrogen and progesterone may each independently affect pulmonary function to varying degrees.

"A further understanding of the role of hormones in asthma may better predict exacerbations and direct therapeutic strategies. Such an understanding may help to improve the quality of life in women who suffer from this often debilitating disease," Dr. Haggerty said.

Women should tell their doctors if they notice a pattern of change in their asthma related to their periods, or as they approach menopause according to Joan C. Gluck, M.D., Miami, chair of ACAAI's Women's Health Committee.

"An increase in allergic symptoms can be the first sign of impending increase in asthma in pregnancy, as was recently shown. Likewise, an increase in allergy and asthma symptoms may also be an early sign of menopause. Doctors should be aware of these patterns and suggest variations in treatment relevant to hormonal changes, as well as consultation with an obstetrician-gynecologist," Dr. Gluck said.

Additional information on allergic diseases including asthma is available by calling the ACAAI toll free number at (800) 842-7777 or visiting its Web site at www.allergy.mcg.edu.

The ACAAI is a professional medical organization comprised of 4,200 qualified allergists-immunologists and related health care professionals. The College is dedicated to the clinical practice of allergy, asthma and immunology through education and research to promote the highest quality of patient care.

* From the American Academy of Allergy, Asthma and Immunology.