Evidence Table 10. Control of Factors Affecting Asthma: Immunotherapy

Abbreviations used in table:

A. artemisiifolia	**Ambrosia artemisiifolia**
Amb a 1	**Ambrosia artemisiifolia**
BPT	**bronchial provocation test**
Der f	**Dermatophagoides farinae**
Der p	**Dermatophagoides pteronyssinus**
IgE	**immunoglobulin E**
IQR	**interquartile range**
SIT	**specific immunotherapy**

indicates primary outcome

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Citation/Sponsor	Study Design	Purpose/Objective	Study N (Number Evaluable)	Population Characteristics	Asthma Severity at Baseline (if reported)	Treatment	Dose	Duration of Active Treatment; Duration of Postintervention/Off-Treatment Followup	Taper/Decrease Steroids	Lung Function	Exacerbations/ Symptoms	Other
Johnstone & Dutton. The value of hyposensitization therapy for bronchial asthma in children–a 14-year study. Pediatrics 1968;42(5):793–801.	Prospective, randomized comparative study	To compare the reported numbers of asthma attacks, numbers of days wheezing, and several other items of clinical interest	210 (131 who had reached 16th birthday)	Age 20% <1 yr, 23% 1–3 yr, 30% 3–6 yr, 21% older than 6 yr Gender 67% male, 33% female Ethnicity Not reported	Perennial bronchial asthma	Arm 1 Extracts of all inhalable allergens to which children reacted Arm 2 Extracts of all inhalable allergens to which children reacted Arm 3 Mixtures of individual allergens to which children reacted (highest tolerated dose) (n=67 in treated groups combined) Arm 4 Placebo (n=64 reached age 16)	0.10 mL of 1/10,000,000 dilution, increased weekly to 0.50 mL; given every 28 days. 0.10 mL of 1/500,000 dilution, increased weekly to 0.50 mL; increased through 3 dilutions to 0.50 of 1/5,000 dilution reached. Same as Arm 2; highest dose tolerated with constitution reaction to injections was maximum dose given. Buffered saline per "injection schedule."	Maximum of 14 years; some children reached age 16 before 14 years.			66% of the 1/5,000 group and 78% of the highest tolerated dose group were symptom-free in their 16th year.	By age 16, 22.2% of P and 71.6% of treated groups had outgrown their asthma. Loss of asthma was not related to gender, age of onset, or severity of symptoms when first seen. Previous history of hay fever increased the likelihood of asthma persisting into adolescence.
Olsen et al. A 1-year, placebo-controlled, double-blind house-dust-mite immunotherapy study in asthmatic adults. Allergy 1997;52(8):853–859.	Randomized, double-blind, placebo-controlled trial (randomization stratified by age, gender, and severity of asthma)	To evaluate the safety and efficacy of allergen-specific immunotherapy in patients suffering from bronchial asthma due to house-dust mites	31 (23)	Age 18–64 yr, mean = 34.3 yr Gender Not reported Ethnicity Not reported Weight 52–89 kg/mean = 73.1 kg Height 158–191 cm, mean = 178 cm	Clinical history indicating asthma due to house-dust mites Positive skin prick test with allergen extracts of house-dust mites Significant level of specific IgE antibodies to Der p and Der f in sera Positive bronchial provocation test with Der p and Der f	Arm 1 Specific immunotherapy with extracts of Der p or Der f (SIT) (n=21; n=17 completers) NOTE: Results are not presented for the 2 extract groups separately. Arm 2 Placebo (P) (n=10; 6 completers)	Single-dose updosing with weekly injections of 100, 1,000, 10,000, and 1,000,000 SQ-U/mL. Maintenance dose of 100,000 SQ-U/mL (~7 mcg Der p1 or ~10 mcg Der f1) reached after 15 weeks. Injections of histamine dihydrochloride in aluminum hydroxide solution; updosing performed with weekly injections on same schedule as for Arm 1.	1 year after 4-week run-in period.	SIT showed decrease ($p<0.01$) in use of inhaled beta$_2$-agonists (46%) and inhaled steroids (38%) with no change in P.	FEV_1/FVC ratio increased for SIT (86.5 to 87.5) and decreased for P (77.6 to 76.7); difference between groups after treatment but not before ($p<0.05$). Bronchial sensitivity decreased to Der p and Der f ($p=0.022$ and 0.039, respectively) in SIT with no change in P.	Symptom scores decreased for SIT ($p<0.001$) with no change for P. Among SIT, 82% classified treatment effect as good or very good vs. in P where all patients classified effect as none or slight ($p=0.0022$).	No one developed systemic side-effects during updosing or maintenance dosing. No change in skin-prick tests for either group. Total and specific IgE to Der p and Der f show only minor fluctuations with no differences within or between groups.

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Gonzalez et al. Immunotherapy with an extract of Olea europaea quantified in mass units. J Investig Allergol Clin Immunol 2002;12(4):263–271.	Randomized, open, controlled parallel groups trial Study conducted in Southern Spain	To evaluate the tolerance, safety, and efficacy of specific immunotherapy in monosensitized patients to olive	46 (46)	Age Median 13 in active group and 24 in control group Gender 37% male, 63% female Ethnicity Not reported	20.9% mild asthma, 44.2% moderate asthma, 25.6% severe asthma Clinical history of rhinitis and/or asthma caused by sensitization to *Olea europaea* with ≥2 years of evolution Positive skin-prick test to Olea and specific IgE to that allergen class 2 or higher	Arm 1 Active treatment: preseasonal immunotherapy from September to April (A) (n=23) Arm 2 Control group (C) (n=23)	Hypersensitizing dose of *Olea europaea* extract preseasonally to maintenance dose 3.8 times higher than conventional treatment (75 BU corresponding to 45 mcg Ole e 1). Symptomatic treatment only.	(8 months preseason) administered twice with 2-week interval and then every 21 days until start of pollen season.	(within-group comparisons) Decrease in A in use of beta$_2$-agonists ($p<0.01$) and antihistamines ($p<0.05$), but not in C ($p>0.10$).		(within-group comparisons) Decrease in nasal symptoms in A ($p<0.05$) but not C ($p=0.84$). Decrease in pulmonary symptoms in A ($p<0.03$) but not in C ($p>0.14$). Comparison between groups in severity of disease favored A ($p<0.001$). No difference in conjunctival sensitivity for A or C, but higher tolerance in A when maintenance dose reached ($p<0.05$) that was not kept at end of study. Cutaneous sensitivity of C vs. A was 13.4 times higher after second 14-day dose after reaching maintenance and 4.4 times higher after pollen season ($p<0.01$).	Differences in evolution ($p<0.05$) for IgE and IgG$_1$ and for IgG$_4$ ($p<0.001$) for A. 15 AE in A in 7 patients during build-up phase with treatment required in 8 cases. Systemic reactions on 4 occasions in 2 patients, 3 mild and 1 moderate.
Pifferi et al. Benefits of immunotherapy with a standardized Dermatophagoides pteronyssinus extract in asthmatic children: a three-year prospective study. Allergy 2002;57(9):785–790.	Randomized, placebo-controlled trial	To verify the benefits of specific immunotherapy in children with asthma during a 3-year period	29 (25)	Age 6–14 yr, mean = 10.6 yr Gender 55% male, 45% female Ethnicity Not reported	At least 5 episodes of doctor-diagnosed asthma in past 12 months Mean = 8.3 exacerbations/year Monosensitization to house-dust mites confirmed by skin-prick test No previous treatment with specific immunotherapy Salbutamol use, mean = 44.8 days/yr; systemic steroid use, mean = 23.4 days/yr FVC mean = 2.5 L FVC % pred. mean = 99.9 FEV$_1$ mean = 2.1 L FEV$_1$ % pred. mean = 91.9	Arm 1 Purified standardized allergenic extract of D pt (SIT) (n=15; n=15 completers) Arm 2 Control group (n=14; n=10 completers)	Dosing schedule in accord with EEACI. Dose increased from 1 U, concentration 10 U/mL (volume 0.1) each week to maximum tolerated dose. Maintenance dose 800 U, concentration 1,000 U/mL every 4–6 weeks.	3 years; 1-year run-in period	Reduced salbutamol and systemic steroids intake in SIT vs. controls ($p<0.01$).	*Final comparison between SIT and controls was not significant for FVC, FEV$_1$, and FEF$_{25-75}$. Likelihood of nonimprovement of bronchial reactivity of SIT was one third that of controls (RR 0.3, 95% CI 0.11 to 0.87).	Number of exacerbations decreased among SIT vs. controls after 1st year ($p<0.01$) and remained at end of 3-year period ($p<0.01$). Occurrence of new sensitizations was lower in SIT vs. controls (0% vs. 33%; $p=0.01$).	All subjects reached suggested dose for maintenance phase. No major local or systemic side-effects were reported during treatment period.

Citation	Study Design	Purpose/Objective	Study N (Number Excluded)	Population Characteristics	Asthma Severity at Baseline (if reported)	Treatment	Dose	Duration of Active Treatment; Duration of Post-intervention/Off-Treatment Follow-up	Topical/Decrease Steroids	Lung Function	Exacerbations/ Symptoms	Other
Maestrelli et al. Effect of specific immunotherapy added to pharmacologic treatment and allergen avoidance in asthmatic patients allergic to house dust mite. J Allergy Clin Immunol 2004;113(4):643–649. (Regione Veneto, Giunta Regionale, Ricerca Sanitaria Finalizzata, Venezia; ALK-Abelló, S.P.A., Lainate, Milano, Italy)	Multicenter, randomized, double-blind, placebo-controlled trial (11 centers)	To investigate whether specific immunotherapy is associated with clinical improvement and a significant reduction in antiasthma medication use	95 (72)	**Age** Mean = 21.6 yr, 32% <16 yr **Gender** 65% male, 35% female **Ethnicity** Not reported	(Characteristics of those who completed the study) 51% mild, 49% moderate asthma Duration of bronchial asthma >1 year Confirmed sensitization to house-dust mite Absence of concomitant sensitization to perennial allergens other than house-dust mite 49% taking inhaled steroids 26% allergy to grass pollen Bedroom-mite allergens: 58% >2 mcg/g Der p1 24% >2 mcg/g Der f1 Morning PEF % pred. mean = 98.4 FEV1 % pred. mean = 96.1	**Arm 1** Specific immunotherapy (SIT) (n=49; n=41 completers) **Arm 2** Placebo (P) (n=46; n=31 completers)	Subcutaneous injection of 0.1 mL of a 0.1 BU/mL concentration increased weekly to target maintenance dose of 7 BU in adults and 6 BU in children; maintenance therapy consisted of 6 mcg/mL Der 1 + Der 2 given every 3 weeks. Aluminum hydroxide solution; histamine (10 mg/mL) added to half of the placebo vials during 1st and 2nd years of treatment.	3 years after observation and stabilization for 1 year. Salbutamol (MDI 100 mcg/actuation) used as bronchodilator; beclomethasone dipropionate (MDI 250 mcg/actuation) used as regular anti-inflammatory agent.	No change in average use of inhaled steroids and bronchodilators in the 2 groups.	*Morning and evening PEF improved in SIT (p<0.001) but did not change in P. Average increase in SIT group between 1.6% and 4.7% in morning PEF and between 2.5% and 5.5% for evening PEF during autumn months of last year of study. No difference in FEV_1 or in PD_{20} FEV_1 between the groups at any visit.	SIT was associated with decrease in skin sensitivity to house-dust-mite extract (p<0.05), whereas there was a trend toward increasing skin reaction to the allergen in P. Median asthma symptom scores in both groups showed nonsignficant decrease during study.	88% of SIT and 94% of P received target maintenance dose.
Mirone et al. Efficacy and safety of subcutaneous immunotherapy with a biologically standardized extract of Ambrosia artemisiifolia pollen: a double-blind, placebo-controlled study. Clin Exp Allergy 2004;34(9):1408–1414.	Multicenter, randomized, double-blind, placebo-controlled trial	To evaluate the safety and efficacy of specific injective immunotherapy to *Ambrosia* in European patients	32 (23 Phase I; 22 Phase II)	**Age** 23–60 yr, mean = 36.8 yr **Gender** 56% male, 44% female **Ethnicity** Not reported	Clinical history of rhinoconjunctivitis (68.8%) and/or asthma (40.6%) in late summer Skin test positive to *Ambrosia artemisiifolia* extract with specific IgE None with severe asthma	**Arm 1** Amb a 1 (A) (n=16; n=11 completed Phase I and Phase II) **Arm 2** Placebo (P) (n=16; n=12 and n=11 completed Phase I and Phase II)	Extract of *A. artemisiifolia* pollen absorbed onto aluminum hydroxide and suspended in phenolated (0.4% w/v) saline solution. Weekly dose increased from 0.09 to 9 mcg/mL Amb a 1.	12 months (3 build-up phases of active treatment followed by maintenance phase); months 12–24, A continued maintenance and P began active therapy. Oral antihistamine, antihistamine eye drops, antihistamine nasal spray, $beta_2$-agonist, and oral cortisone allowed as rescue drugs.			Scores for symptoms (p=0.02) and drugs (p=0.0068) decreased in A after first year with no change for P. Days with asthmatic symptoms (p=0.003), rhinitis symptoms (p=0.05), and intake of drugs (p=0.0058) decreased in A after first year with no change for P. Number of days with rhinitis and with asthma lower in A vs. P (p=0.048 and =<0.0001) after 1 year.	Decrease in skin reactivity for A after 1 year (12.2-fold, p=0.0001) and after 2 years (12.4-fold, p<0.0001) with no difference between 1st and 2nd year of therapy (p=0.47). No change in P after 1st year and decrease (4.8-fold, p=0.0022) after 12 months of active treatment.

Citation (Sponsor	Study Design	Purpose/Objective	Study N (Number Evaluable)	Population Characteristics	Asthma Severity at Baseline (if reported)	Treatment	Dose	Duration of Active Treatment, Duration of Post-Intervention/Off-Treatment Follow-up	Taper/Decrease Steroids	Lung Function	Exacerbations/ Symptoms	Other
Ameal et al. Double-blind and placebo-controlled study to assess efficacy and safety of a modified allergen extract of Dermatophagoides pteronyssinus in allergic asthma. Allergy 2005;60(9):1178–1183. (Laboratorios LETI, S.L; the University of Málaga; the Allergy Department of the Hospital of 'Carlos Haya' of Málaga, Spain)	Randomized, double-blind, placebo-controlled trial	To evaluate the clinical efficacy and safety of a depigmented, polymerized vaccine-containing *D. pteronyssinus*	63 (45)	Age 14–48 yr, mean = 23 yr Gender 47% male, 53% female Ethnicity Not reported	Mild-to-moderate asthma Rhinoconjunctivitis because of sensitization to *D. pteronyssinus* Clinical history suggestive of house-dust-mite allergy Positive skin tests using standardized extract and negative to other common aeroallergens Positive specific bronchial provocation test (BPT) Detectable specific immunoglobulin E (IgE) to dust mite	Arm 1 Modified allergen extract of D. pteronyssinus (E) (n=32; n=29 completers) Arm 2 Placebo (n=31; n=26 completers)	Both groups received pharmacological treatment, if needed, consisting of oral ebastine, salbutamol, and budesonide.	12 months	E had 56% decrease in medication scores vs. 11.4% decrease in P. After 12 months E had a 68% decrease of medication over P.	*Change in $PD_{20}FEV_1$ at 12 months was greater for E (median 4.27 HEP, IQR 1.74 to 8.45) vs. P (–0.05 HEP, IQR –1.17 to 5.19) (p=0.0004). At 12 months E needed a median of 4.5 times more extract to achieve the value of 10 HEP whereas P did not change from baseline.	E showed decrease in symptom scores from baseline (p=0.0001) vs. no change in P (p=0.73). At 12 months E had a 78% decrease of symptoms over P. At 12 months E showed improved asthma quality of life scores vs. P (p=0.0025).	Two local reactions with diameter between 5 and 10 cm in E and 3 reactions in P.
Roberts et al. Grass pollen immunotherapy as an effective therapy for childhood seasonal allergic asthma. J Allergy Clin Immunol 2006;117(2):263–268. (ALK-Abelló; Special Trustees, St. Mary's Hospital, London)	Randomized, double-blind, placebo-controlled study	To examine the clinical efficacy and safety of specific immunotherapy in children with seasonal allergic asthma and to measure changes in specific allergen reactivity and airway inflammation	39 (35)	Age 3–16 yr, mean = 9.9 yr Gender 71% male, 29% female Ethnicity White/English/Scottish/Welsh, 74% Black African/Caribbean/Other, 9% Indian subcontinent, 15% White other, 3%	Summer asthma: 86% moderate symptoms, 14% severe symptoms Summer rhinoconjunctivitis: 8.6% mild symptoms, 82.9% moderate symptoms, 8.6% severe symptoms Clinical history of grass pollen-induced asthma requiring ≥200 mcg inhaled beclomethasone (or equivalent) daily; median 400 mcg Positive skin-prick test response Specific IgE level >0.7 IU/mL Positive conjunctival provocation test result 40% atopic dermatitis, 6% symptoms on exposure to tree pollen, 20% symptoms on exposure to house-dust mite	Arm 1 Specific immuno-therapy (SIT) (n=18) Arm 2 Placebo (P) (n=17)	Alutard SQ *P pratense* corresponding to 20 mcg of major allergen (Phl p 5) with placebo containing histamine to maintain binding. Placebo identical in color and viscosity.	Two pollen seasons. All subjects allowed to use rescue medications for symptoms of hay fever and asthma during grass pollen season; treated in a step-up/step-down manner according to clinical symptoms.	No difference in reduction in total corticosteroid score (p=0.16) or use of inhaled bronchodilators (p=0.38) between SIT and P.	No difference in highest standardized exhaled nitric oxide (FE_{NO}) in SIT (median 1.77, IQR 1.56 to 2.13) and P (median 1.99, IQR 1.44 to 2.50).	*Reduction in asthma symptom-medication score in SIT vs. P (median 0.5, IQR 0.1 to 0.9 for SIT vs. median 1.0, IQR 0.4 to 2.0 for P; p=0.04). After 1st and 2nd pollen seasons, difference in cutaneous (p=0.003 and p<0.001, respectively) and conjunctival (p=0.002 and p=0.03, respectively) allergen reactivity favored SIT.	72% of SIT and 41% of P reported treatment-related AE.