SCIT, WHEN AND HOW?

Giovanni Passalacqua

Allergy & Respiratory Diseases
Dept of Internal Medicine
University of Genoa

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In relation to this presentation, I declare the following, real or perceived conflicts of interest:

CONSULTANTSHIPS

ALK Abello
Almirall Prodesfarma
Altana
Anallergo
Astra Zeneca
Boehringher Ingelheim
Chiesi
GSK
Lofarma
Menarini
Merck Sharp Dohme
Novartis
Pfizer
Schering-Plough
Stallergenes
UCB Pharma
Uriach

WHO Pos Pap. Therapeutical vaccines for allergic diseases
Allergy 1998

Standards for practical allergen-specific IT
Allergy 2006

Allergen immunotherapy: A practice parameter THIRD update
JACI 2011

WORLD ALLERGY ORGANIZATION

Sub-lingual Immunotherapy: WAO Position Paper 2009

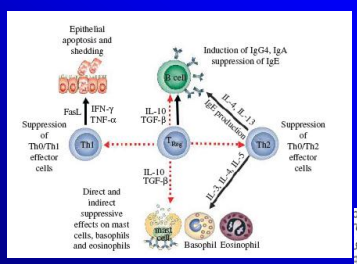
GALEN/EAACI Pocket Guide for SIT in rhinitis and asthma
Allergy 2010

ARIA UPDATE: ALLERGEN IMMUNOTHERAPY

G. Passalacqua and SR. Durham
JACI 2007

	Subcutaneous (SCIT)	Sublingual (SLIT)
Clinical efficacy: Rhinitis	Ia	Ia
Clinical Efficacy: Asthma	Ia	Ia
Clinical efficacy: children (rhinitis)	Ib	Ia
Prevention of new sensitizations	Ib	IIa
Long-term effect	Ib	IIa
Prevention of asthma	Ib*	Ib*

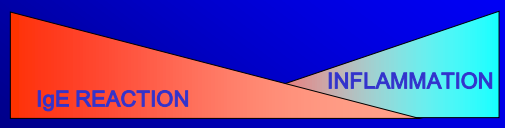
* One single randomized open study



Akdis, Allergy 2007

Mechanisms of allergen specific immunotherapy – T-cell tolerance and more

Where does IT preferentially works?



Hymenoptera Allergy
Seasonal rhinitis
Asthma
Food Allergy?
Perennial rhinitis

SIT is specific for the allergen, not for the target organ

SIT is not a last chance treatment, but should be used in association with drugs.

SIT is effective in respiratory allergy (mite, pollens, animal dander) and in hymenoptera allergy

FACTORS TO BE EVALUATED IN PRESCRIBING SIT

1. The disease must be IgE-mediated (positive skin prick test/CAP RAST)
2. The causal allergen must be clearly identified
3. Assess duration and severity of symptoms
4. Assess the efficacy of pharmacological treatment
5. Can the patient comply? (cost, lifestyle)
6. Is there a standardized vaccine
7. There are proofs of efficacy for that vaccine?

WAO Position Paper 1998

CAUSAL ROLE OF THE ALLERGEN(S):

Clinical history and exposure

SKIN TESTING

RAST ASSAY

NASAL (CONJUNCTIVAL) CHALLENGE

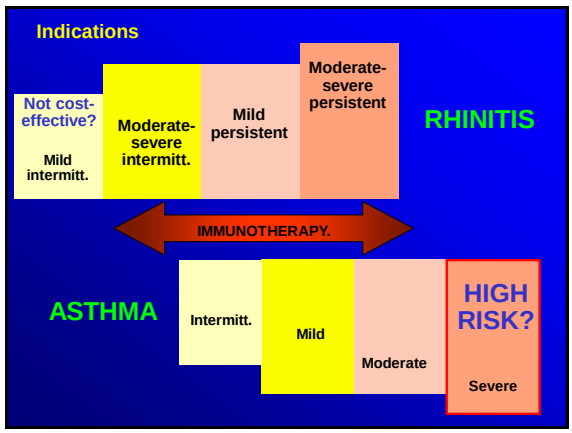
(component resolved diagnosis)

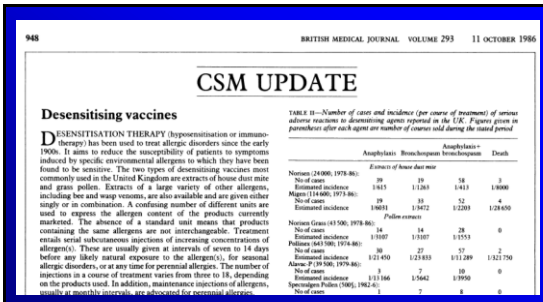
SLIT (IT in general) for the clinically relevant allergen(s)
Preferably one, but in selected cases 2 or 3 extracts.

FACTORS TO BE CONSIDERED IN PRESCRIBING IMMUNOTHERAPY

IgE-mediated mechanism
Confirmed aetiological role of the allergen
Duration of symptoms
Response to drug therapy
Expected effectiveness
Availability of standardized vaccines
Contraindications and risks
Costs
Compliance

WHO Pos Pap 1998





948 BRITISH MEDICAL JOURNAL VOLUME 293 11 OCTOBER 1986

CSM UPDATE

Desensitising vaccines

DESENSITISATION THERAPY (hyposensitisation or immunotherapy) has been used to treat allergic disorders since the early 1900s. It aims to reduce the susceptibility of patients to symptoms induced by specific environmental allergens to which they have been found to be sensitive. The two types of desensitising vaccines most commonly used in the United Kingdom are extracts of house dust mite and grass pollen. Extracts of a large variety of other allergens, including bee and wasp venoms, are also available and are given either singly or in combination. A confusing number of different units are used to express the allergen content of the products currently marketed. The absence of a standard unit means that products containing the same allergens are not interchangeable. Treatment entails serial subcutaneous injections of increasing concentrations of allergen(s). These are usually given at intervals of seven to 14 days before any likely natural exposure to the allergen(s), for seasonal allergic disorders, or at any time for perennial allergies. The number of injections in a course of treatment varies from three to 18, depending on the products used. In addition, maintenance injections of allergens, usually at monthly intervals, are advocated for perennial allergies.

TABLE II—*Number of cases and incidence (per course of treatment) of serious adverse reactions to desensitising agents reported in the UK. Figures given in parentheses after each agent are number of courses sold during the stated period*

	Anaphylaxis	Bronchospasm	Anaphylaxis+ bronchospasm	Death
Extracts of house dust mite				
Nortisen (24 000; 1978-86):				
No of cases	19	19	58	3
Estimated incidence	1/615	1/1263	1/413	1/8000
Migrex (114 600; 1973-86):				
No of cases	19	33	52	4
Estimated incidence	1/6031	1/3472	1/2203	1/28 650
Pollen extracts				
Nortisen Grass (43 500; 1978-86):				
No of cases	14	14	28	0
Estimated incidence	1/3107	1/3107	1/1553	
Pollinex (643 500; 1974-86):				
No of cases	30	27	57	2
Estimated incidence	1/21 450	1/23 833	1/11 289	1/321 750
Alutrex-P (19 500; 1979-86):				
No of cases	3	7	10	0
Estimated incidence	1/11 166	1/5642	1/1950	
Specialgen Pollen (500); 1982-6):				
No of cases	1	7	8	0

26 fatalities since 1957 certainly due to IT
11 of them since 1980

Reid MJ et al. JACI 1993

Period 1985-1989: 17 fatalities

Mean age:	**36**
Age range:	**15-77**
6 male, 11 female	
Asthma:	**77%**
Aqueous:	**15**
Build-up:	**11**

Comparison of allergen immunotherapy practice patterns in the United States and Europe

Linda Cox, MD,* and Lars Jacobsen, MSc†

Table 1. Comparison of the Differences Between US and European Allergen Extracts and Specific Immunotherapy Practice Patterns

Variable	United States	Europe
Regulatory agency	FDA	EMEA
Standardization		
Method	$ID_{50}EAL$	Nordic
Test technique	Intradermal	Percutaneous
End point	Extract dilution that produces sum of erythema of 50 mm	Extract dilution that produces a wheal equal to the histamine control
Potency determination	Comparison with CBER reference control	Compared with in-house reference
Future focus	Overall allergenicity	Major allergen content
Potency units	BAU, wt/vol, PNU, milligrams of major allergen for ragweed and cat	Varies; each company essentially has its own potency units, some provide milligrams of major allergen
Extract formulation		
Location	Prepared in physicians offices	Prepared at extract manufacturer site
No. of allergens	Multiple	Generally 1
Allergen extract types	Aqueous and glycerinated unmodified extracts, alum-precipitated depot extracts	Approximately 100% depot extract, 20% allergoid, <5% adjuvants
SLIT	Approximately 5.9% of allergists, no FDA-approved formulation	Approximately 45% of prescribed SIT, solution and tablets available, some are registered

RISK FACTORS

Based on nonfatal reactions	Based on fatal reactions
Uncontrolled asthma	**Uncontrolled asthma**
Severe asthma	**Severe asthma**
Use of betablockers	**Use of betablockers**
Rush immunotherapy	**Rush immunotherapy**
Use of new vials	**Build-up phase**
Technical errors	**Use of new vials**
	Technical errors

Estimated incidence of fatalities < 1/2.000.000 injections

Immunotherapy for Asthma

- Does SLIT work in asthma?
  - Which endpoints matter?
- Is SLIT safe in asthma?
- Mechanisms?
- Does SLIT prevent asthma or alter the natural history of asthma?

Clinical & Experimental Allergy, 1–9 doi: 10.1111/j.1365-2222.2010.03688.x

REVIEW

Specific immunotherapy in asthma: efficacy and safety

G. Passalacqua and G. W. Canonica
Allergy and Respiratory Diseases, University Of Genoa, Genoa, Italy

Clin Exp Allergy 2011

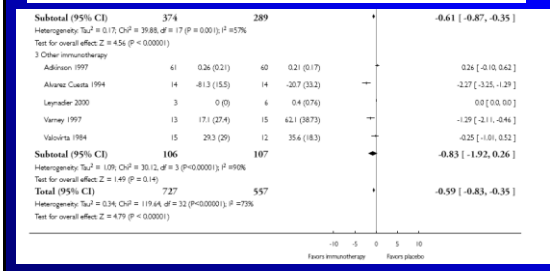
Table 2. Randomized controlled trials of slit in asthma

References	Allergen	Active/placebo*	Duration	Jadad score	Main results
Tari et al. [60]	Mite	30/28 C	18 months	4/5*	↓ asthma symptom score and total medication score; ↓ specific and non-specific bronchial reactivity
Bousquet et al. [59]	Mite	17/18 A	2 years	4/5	↓ asthma symptom score; ↑ FEV_1, PFR; ↑ QoL
Hirsch et al. [58]	Mite	13/14 C	1 year	5/5	↓ asthma symptom score; no change in bronchial reactivity
Vourdas et al. [62]	Olive	34/32 C	2 years	4/5	↓ dyspnea score; no change in medications
Pajno et al. [63]	Mite	12/12 C	2 years	5/5	↓ asthma symptom score only 2nd year; ↓ night asthma symptom and medication both years
Ippoliti et al. [61]	Mite	47/39 C	6 months	4/5	↓ asthma symptom score; ↑ FEV_1
Pajno et al. [68]	Parietaria	20/20 C	2 season	5/5	↓ inseason non-specific bronchial reactivity
Niu et al. [64]	Mite	56/54 C	6 months	4/5	↓ asthma symptom score, daytime, nighttime symptoms and medication score; no change FEV_1 and oral steroids
Lue et al. [65]	Mite	10/10 C	8 months	4/5	↓ nighttime symptoms, ↑ FEV_1 vs. baseline; no change total symptom score, medications and FEV_1 vs. placebo
Dahl et al. [56]	Grass	74/40 A	5 months	5/5	No change symptoms and medications
Pham Ti et al. [57]	Mite	55/56 C	18 months	4/5	No change symptoms, medications, FEV_1, well days
Stelmach et al. [66]	Grass	25/25 C	2 season	5/5	↓ asthma symptoms and medications
Bufe et al. [67]	Grass	126/127 C	6 months	5/5	↓ asthma symptoms; no change medications

*A, Adults; C, children. ↓, decrease/reduction; increase; FEV_1 ↑, forced expiratory volume in 1 s; PEFR, peak expiratory flow rate; QoL, quality of life.

Injection allergen immunotherapy for asthma (Review)

Abramson MJ, Puy RM, Weiner JM



Cochrane 2010

CONCLUSIONS

Based on the literature, SIT is clinically effective in asthma (decrease of symptom score and medication intake).

In general, the best results are obtained in pollen-induced asthma

SIT reduces bronchial hyperresponsiveness, that is an indirect marker of bronchial inflammation.

SIT can modify the natural course of respiratory allergy by preventing the onset of asthma

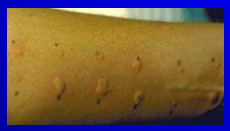
FACTORS TO BE CONSIDERED IN PRESCRIBING IMMUNOTHERAPY

IgE-mediated mechanism
Confirmed aetiological role of the allergen
Duration of symptoms
Response to drug therapy
Expected effectiveness
Availability of standardized vaccines
Contraindications and risks
Costs
Compliance

WHO Pos Pap 1998

PROBLEMS:

Aetiological diagnosis of respiratory allergies is mandatory for a correct prescription of SIT



The vast majority of patients are poly-Sensitized.

Recommendations differ among guidelines

Standards for practical allergen-specific immunotherapy.

Allergy. 2006;61 Suppl 82:1-20.

Alvarez-Cuesta E, Bousquet J, Canonica GW, Durham SR, Malling HJ, Valovirta E;

EAACI, Immunotherapy Task Force.

Allergen product.

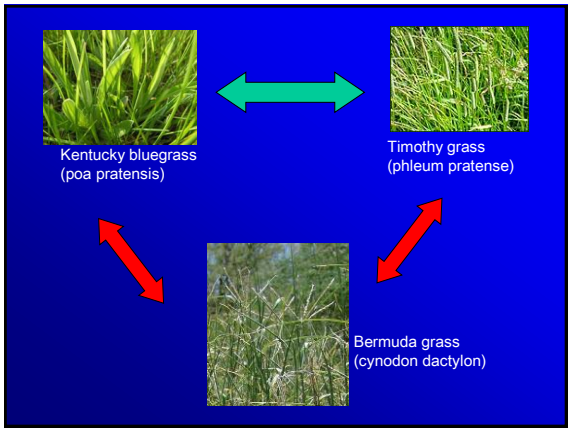
Patients with multiple allergic sensitivity may be effectively treated with several individual allergen products according to their individual sensitivities. In general this approach is limited to two or at most three allergens, which should be injected at 30-min intervals.

Mixtures of related, cross-reacting allergens, such as a mixture of individual grasses are acceptable provided regulatory demands (stability, etc.) are fulfilled. Another appropriate and widely used example is the mixture of *D. pteronyssinus* and *D. farinae* in mite allergen products.

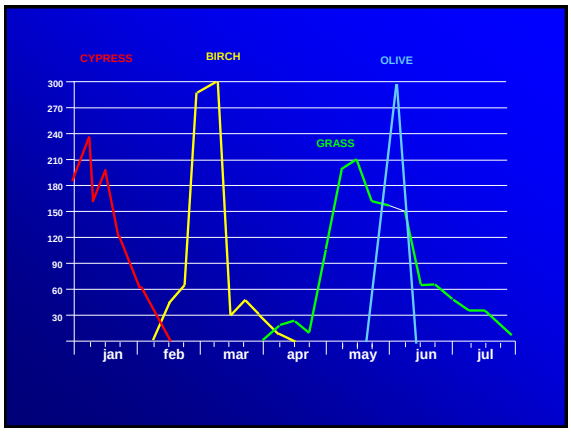
Allergen immunotherapy: A practice parameter second update

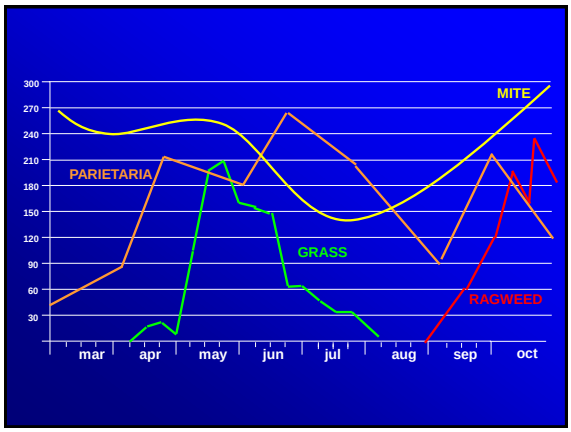
Linda Cox MD, Supplement Editor,
James T. Li MD, Harold Nelson MD
and Richard Lockey MD, Co-editors

Once the relevant allergens for each patient are identified, it is necessary to prepare a mixture that contains each of these allergens. Standardized extracts should be used, when available, and can be mixed with nonstandardized extracts.



Carya illinoensis	Pecan	
Betulaceae		Strong cross-allergenicity among Betulaceae members based on homology of group 1 and 2 allergens. Fairly strong cross-allergenicity between Betulaceae and Fagaceae members based on homology of group 1 and 2 allergens.
Betula verrucosa	Silver birch	
Alnus glutinosa	European alder	
Corylus avellana	Hazelnut (filbert)	
Carpinus betulus	Hornbeam	
Ostrya virginiana	Eastern hophornbeam	
Fagaceae		
Fagus sylatica	European beech	
Quercus alba	White oak	
Quercus rubra	Red oak	



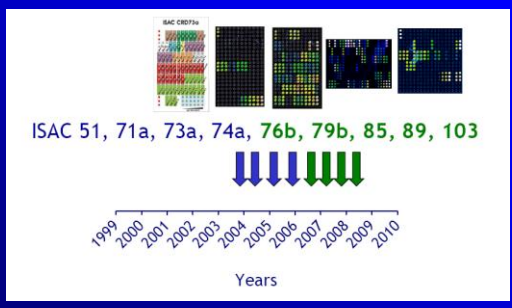


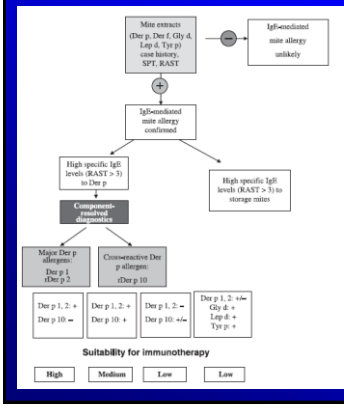
	Primary sensitization	Cross-reactivity
Pollens		
Ragweed	Amb a 1	
Mugwort	Art v 1, Art v 3	Art v 3
Parietaria	Par j 2	Par j 2
Russian thistle or saltwort	Sal k 1	
Goosefoot or Lambs quarters	Che a 1	
Plantain or Ribwort	Pla l 1	
Timothy	Phl p 1	Phl p 4
	Phl p 5	Phl p 7
	Phl p 6	Phl p 11
		Phl p 12
Bermuda grass	Cyn d 1	
Birch	Bet v 1	Bet v 1
	Bet v 6	Bet v 2
		Bet v 4
Alder	Aln g 1	Aln g 1
Oak	Que a 1	Que a 1
Olive	Ole e 1	Ole e 2
	Ole e 7	Ole e 7, Ole e 9
	Ole e 9	
Japanese cedar, Cypress	Cry j 1Z	
	Cup a 1	
Plane tree	Pla a 1	
	Pla a 2	
Latex	Hev b 1, Hev b 3, Hev b 5, Hev b 6	Hev b 5
		Hev b 6
		Hev b 8
House dust mite		Der p 1, Der p 2
pyroglyphidae		Der f 1, Der f 2
Blomia tropicalis		Blo t 5
Euroglyphus mannei		Eur m 2
Lepidoglyphys destructor		Lep d 2
Cat		Fel d 1, Fel d 4
		Fel d 2
		Fel d 4
Dog		Can f 1, Can f 2, Can f 5
		Can f 3
		Can f 5
Horse		Equ c 1
		Equ c 3
Alternaria alternata		Alt a 1, Alt a 6
		Alt a 6
Aspergillus fumigatus		Asp f 1, Asp f 2, Asp f 3 Asp f 4, Asp f 6
		Asp f 6

Sastre, Clin Exp Allergy 2010

Protein families	Characteristics	Allergens
Non-specific lipid transfer proteins	Stable to heat and digestion, causing reactions also to cooked foods. Often associated with systemic and more severe reactions in addition to oral allergy syndrome (OAS), and with allergic reactions to fruit and vegetables in southern Europe (not applicable to Par j 2 and Art v 3)	Ara h 9 Cor a 8 Pru p 3 Par j 2 Art v 3
Storage proteins	Found in seeds and serves as source material during the growth of a new plant. Often stable and heat-resistant proteins causing reactions also to cooked foods	*2S albumins* Ara h 2, 6 and 7 Ber e 1 *7S albumins* Ara h 1 Gly m 5 *11S albumins* Ara h 3 Gly m 6 Cor a 9 *Gliadins* Tri a 19
Pathogenesis-related protein family 10 proteins (PR-10)	Heat-labile proteins and cooked foods are therefore often tolerated. They are Bet v 1 homologues and often associated with local symptoms such as OAS and with allergic reactions to fruit and vegetables in northern Europe. May predispose to allergic reactions to Rosaceae fruits, hazelnut, carrot and celery	Bet v 1 Ara h 8 Gly m 4 Cor a 1 Pru p 1 Api g 1.01 Mal d 1 Act d 8 Dau c 1
Profilins	Actin-binding proteins showing great homology and cross-reactivity even between distant related species. Recognized as a minor allergen in plants and plant-related foods. Profilins are seldom associated with clinical symptoms, but may cause demonstrable or even severe reactions in a small minority of patients. Sensitization to profilin may give rise to multiple positivity when testing with plants and pollen extracts, however this has low clinical relevance in most cases	Bet v 2 Pru p 4 Hev b 8 Phl p 12

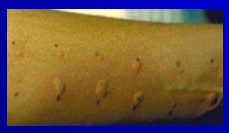
ISAC





Vrtala, Allergy 2008

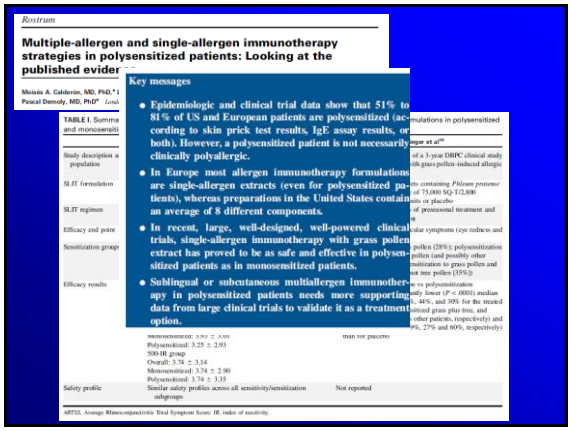
GRASS	BIRCH	PARIETARIA
Phl p 1	Bet v 1	Par j 1
Phl p 5		Par j 2
Phl p 6		
Phl p 7 (profilin)	Bet v 2 (profilin)	Par j 3 (profilin)
Phl p 12 (CBP)	Bet v 3 (CBP)	



PROBLEM:

Does SIT with a single allergen

work in polysensitized patients?

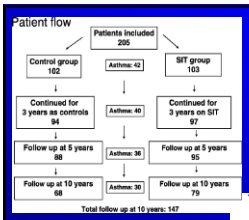


Specific immunotherapy

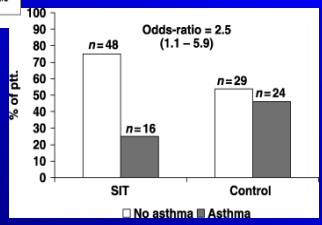
MECHANISMS OF ACTION

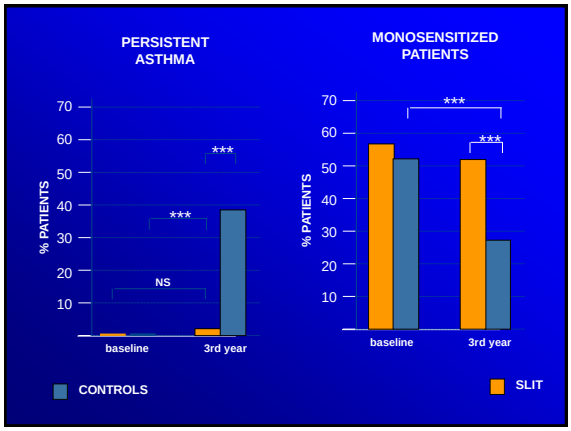
- Clinical effect
- Immunological effect
- Long-lasting efficacy
- Prevention of new sensitizations
- Prevention of asthma

Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study



Jacobssen, Allergy 2007





ADMINISTRATION
- SUBCUTANEOUS (SCIT)
- SUBLINGUAL (SLIT)
- (epicutaneous, intralymphatic)

BUILD-UP
- Standard
- Rush
- Ultra-rush
- Cluster
- No build-up (SLIT)

TIMING
- 4 wks
- 2-4 months (VIT)
- daily (SLIT)
- EOD (SLIT)

REGIMEN
- Preseasonal
- Pre-cosseasonal
- Coseasonal
- Continuous

Follow all precaution rules:

Correct site of injection
Verify dose, patient's name and batch
Inject outside vessels
Observe for at least 30 minutes
Recommend no physical exercise immediately after injection
Check vital parameters before discarding patient

HAVE AVAILABLE
Oxygen
Beta2 short acting agonist (inhaled) + spacer
Oral/injectable antihistamine
Oral/injectable corticosteroid
IM Epinephrine

Follow all precaution rules:

Correct site of injection
Verify dose, patient's name and batch
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HAVE AVAILABLE
Oxygen
Beta2 short acting agonist (inhaled) + spacer
Oral/injectable antihistamine
Oral/injectable corticosteroid
IM Epinephrine

MAIN UNMET NEEDS

- DEFINE THE OPTIMAL MAINTENANCE DOSE (AND INTERVAL) FOR ALL ALLERGENS
- STANDARDIZE CLINICAL TRIALS
- SAFETY IN PREGNANCY/LACTATION?
- AUTOIMMUNE DISORDERS?

Thank you !!!

Feel free to contact us at
canonica@unige.it
passalacqua@unige.it