

Efficacy of Toll-like Receptor Agonists in Allergy Immunotherapy

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Allergies

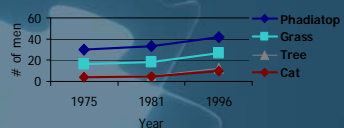
A consequence of having an immune system

6th leading cause of chronic disease

Costs the healthcare system \$18 billion annually

Increasing incidence of allergies

of men out of 50 with IgE antibodies to inhaled antigens



Year	Phadiatop	Grass	Tree	Cat
1975	~35	~15	~10	~5
1981	~38	~18	~12	~8
1996	~45	~25	~15	~10

M. Law, et al.: Changes in atopy over a quarter of a century, based on cross sectional data at three time periods. *Bmj* 2005; 330(7501): 1187-8.

Current Allergy Treatments

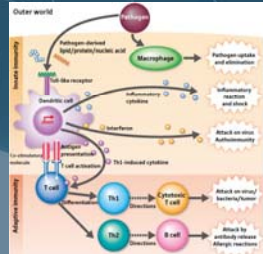
- Antihistamines (oral and inhaled)
- Inhaled Corticosteroids
- Inhaled anti-histamines
- "Allergy Shots"

Originally introduced in 1911 and is the only treatment that has been shown to alter the pathologic immune response



Immune System

- In almost all vertebrates, the immune system is composed of two portions
 1. Innate immune system
 - Sentinel defense system capable of neutralizing pathogens unaided
 - If needed, the innate immune system can activate adaptive immunity.
 2. Adaptive immune system
 - Associated with immune memory

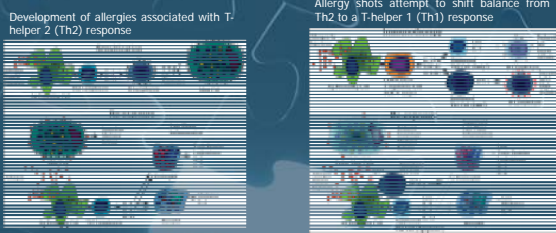


<http://www.cai.riken.go.jp/eng/group/hoist/index.html>

Allergen Specific Immunotherapy (SIT) aka "allergy shots"

Development of allergies associated with T-helper 2 (Th2) response

Allergy shots attempt to shift balance from Th2 to a T-helper 1 (Th1) response

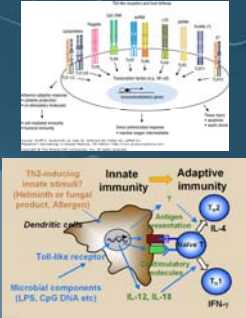


Years of shots before full efficacy can be achieved

- 30 to 50% of patients with allergic rhinitis achieve clinical tolerance
- SIT not recommended for food allergies due to high risk of anaphylaxis
- Stinging insect hypersensitivities are the most responsive to SIT

Toll-Like Receptors Linking Innate and Adaptive Immunity

- TLR originally found in *Drosophila*
- 10 TLR identified in humans
- Bind antigens via pathogen pattern recognition
- Immune response varies depending on which TLR is bound
 - Immunostimulatory or immunosuppressant
- TLR agonists can be used to selectively drive immune response and have potential application in allergy treatments.



TLR agonists in SIT

The purpose of this review is to examine clinical trials of allergy vaccines that utilize toll-like receptor agonists.

ISS: Highly Specific TLR9 Signaling
Activates innate immunity

ISS stimulates Th1, suppresses Th2

IFN- α , IFN- γ

Th1

Th2

DYNAVAX

- Currently, TLR-9 and TLR-4 agonists are being used in clinical trials on allergy therapy vaccines
- The proposed mechanism of action is similar to traditional SIT.
 - Shift from Th2 to Th1 response
- If these allergy vaccines prove effective, healthcare providers may have more options to choose from in treating allergies.

Summary of Studies

6 studies
277 Total Subjects

3 utilized TLR-9 agonists to treat Ragweed allergies (Dynavax Technologies Corp)

3 utilized TLR-4 agonists to treat grass allergies (Allergy Therapeutics Ltd)

Pollenex Quattro approved for use in Europe

Clinical trials in process...

Studies utilizing TLR agonists in SIT

Author	Title	Treatment	# of treatment group	# of control group	Vaccine schedule	Measurements	Type of study
Tulic MK 2004	Amb 1 immunostimulatory oligodeoxynucleotide conjugate immunotherapy decreases the nasal inflammatory response	Amb 1 (ragweed pollen extract) + phosphatidyl oligodeoxynucleotide immunostimulatory sequence repeating dose over 8	10	10	weekly	1) Cytokines and inflammatory cells in nasal biopsies (subset of patients) 2) Symptom log, patient diary	Double-blind randomized
Simons FER 2004	Selective immune redirection in humans with ragweed allergy by delivering Amb 1 linked to a	Same as MK Tulic study	9	10	weekly	1) Cytokines and chemokines from PBMC 2) Treatment of IgE in 20	Third party double-blind
Ortiz PS 2006	Immunotherapy with a ragweed toll-like receptor 9 agonist vaccine for allergic rhinitis	Same as MK Tulic study	14 (8 in yr 1, 2)	11 (9 in yr 1, 2)	weekly	1) Allergen levels in nasal secretions 2) IgE and IgG antibodies to Amb 1 and ragweed cytokines 3) Skin sensitivity Testing 4) Cytokines and chemokines in PBMC (ELISA, Flow cytometry, and gene chip) 5) Symptom and medication diary	Double-blind randomized
Drachenberg K 2001	A well-tolerated grass pollen-specific allergy vaccine containing a novel adjuvant, monophosphoryl lipid A, reduces allergic symptoms after only four preseasonal injections	lysine-adsorbed glutaraldehyde-modified grass pollen extract containing MPL adjuvant increasing dose over 4	11	10	weekly for 2-3 times T-4 wks before the 1st full pollen allergy	1) Symptoms via patient diary cards 2) IgE and IgG antibodies to grass pollen in patient serum 3) Inhaled skin prick tests (subset and sputum assay)	Double-blind randomized (multicenter)
Mothes M 2003	Allergen-specific immunotherapy with a monophosphoryl lipid A	same as Drachenberg study	11	9	subset of Drachenberg study	1) IgE, IgG1 to IgG4 and IgM antibodies to grass pollen in patient serum	Double-blind randomized
von Baehr V 2005	Allergoid-specific T-cell reaction as a measure of the immunological response to specific immunotherapy (SIT) with a Th1-adjuvanted allergy vaccine	lysine-adsorbed glutaraldehyde-modified pollen extract containing MPL adjuvant increasing dose over 4 injections	21	14	weekly	1) T-cell proliferation assay using PBMC from patients stimulated with vaccine components 2) Symptoms - unspecified measurement of symptoms	random assignment

Conclusions

- TLR based immunotherapy provided marked improvement in symptoms in all studies that used symptoms as a measurement of efficacy.
- TLR based immunotherapy has been shown to show measurable efficacy using as few as 4 injections. While current allergy immunotherapies require injections for years before full efficacy is achieved.
- Most of the studies used a small number of patients which limits the ability of the authors to make broad conclusions regarding the efficacy of TLR based allergy immunotherapy.
- While TLR based immunotherapy for allergies appears to be a promising new technology for allergy treatment, and TLR based allergy products are approved for use in Europe, more testing of these products needs to be done prior to FDA approval.
- Therefore, traditional SIT is still the treatment of choice for those with recalcitrant allergies.

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