Allergy Therapeutics®
Transforming Allergy Treatment

The future of the pipeline - toward a global portfolio

Dr Murray Skinner
Chief Scientific Officer
June 2017

Overview of R&D highlights

Allergy Therapeutics®
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- Pollinex franchise continues to expand and shape the market as a more convenient treatment
- First patient recruited in pivotal PQBirch Phase III study in Europe
- US Grass MATA MPL programme proceeding as planned with safety trial advancing to dose-range finding study in H2 2017
- CTA approval in Spain for Phase I clinical study investigating safety and tolerability of Modified Mite SCIT MPL
- Positive proof of concept preclinical trial results announced with Polyvac Peanut

Development Pipeline

New technologies and markets.

Strong investment in R&D aided by growing revenue stream

R&D Scope

Three **EU** development programmes:

Seasonal SCIT

– Pollinex Quattro (PQ) product range (grass, tree and mixes)

Perennial SCIT

– Acarovac, TyroMilbe (House dust mite SCIT)

Seasonal/Perennial SLIT

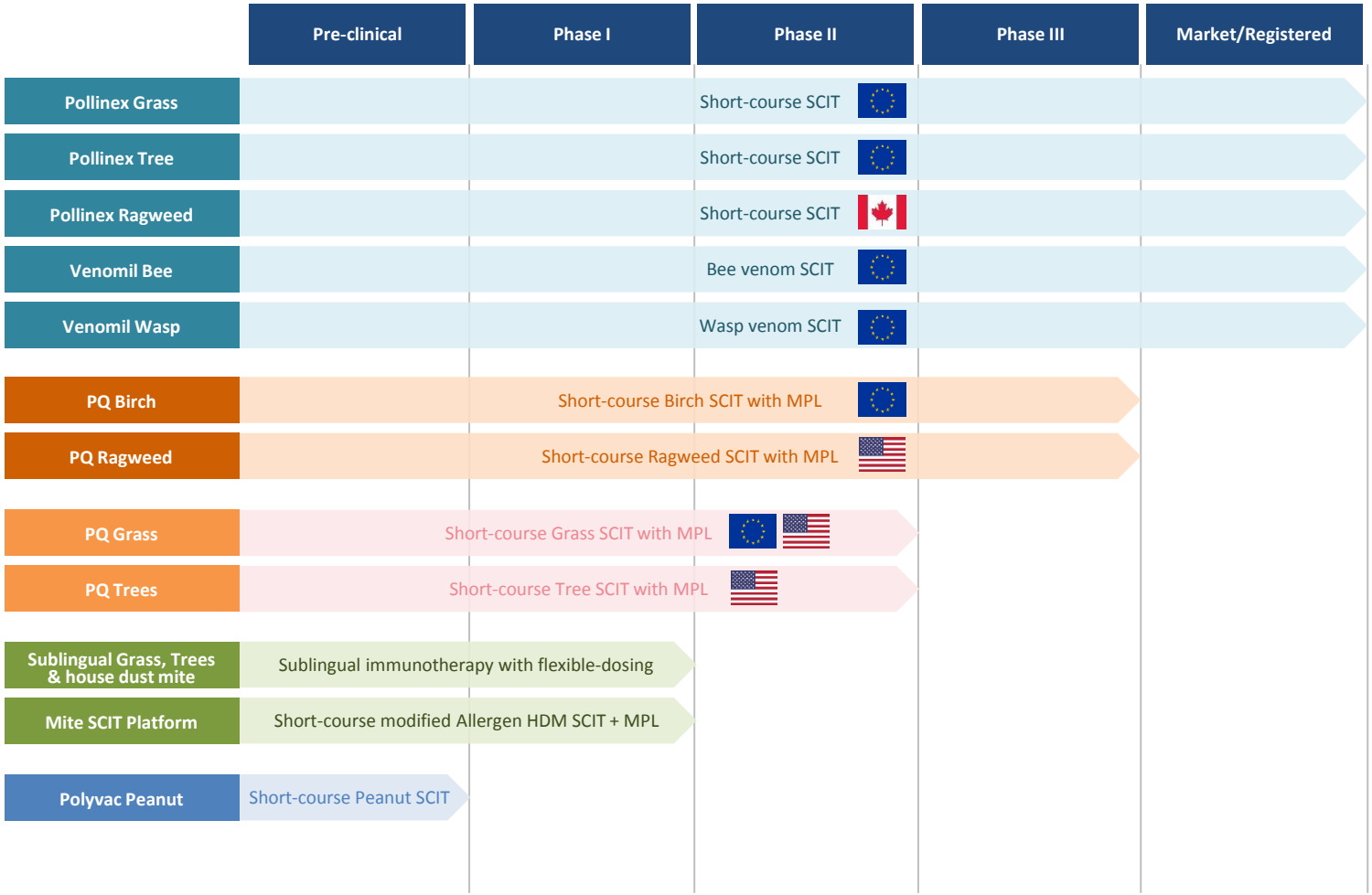
– Oralvac product range (grass, tree and house dust mite)

Global registration of PQ Grass in **EU/US**

Opportunities to support growth

- Development of adjuvant portfolio
- Food Allergy – Polyvac Peanut

Pipeline


Pre-clinical
Phase I
Phase II
Phase III
Market/Registered
Pollinex Grass
Short-course SCIT
Pollinex Tree
Short-course SCIT
Pollinex Ragweed
Short-course SCIT
Venomil Bee
Bee venom SCIT
Venomil Wasp
Wasp venom SCIT
PQ Birch
Short-course Birch SCIT with MPL
PQ Ragweed
Short-course Ragweed SCIT with MPL
PQ Grass
Short-course Grass SCIT with MPL
PQ Trees
Short-course Tree SCIT with MPL
Sublingual Grass, Trees & house dust mite
Sublingual immunotherapy with flexible-dosing
Mite SCIT Platform
Short-course modified Allergen HDM SCIT + MPL
Polyvac Peanut
Short-course Peanut SCIT

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- The TAV EU registration and US opportunity
- Next generation House dust mite SCIT
  Acarovac MPL
- Portfolio development, extension and Bencard Adjuvant Systems

TAV EU Registration

TAV German process initiated in 2008 and driven by the Paul Ehrlich Institute (PEI) based upon European legislation to enable Named Patient Product licensure

123 products originally notified across Germany

37 of 123 (30%) notified products have been removed from the process and are no longer on the market (Prof. Stefan Vieths, Vice President, Head, Division of Allergology, PEI German Allergy Congress, 2016)

All 10 Allergy Therapeutics products notified remain in the TAV licensure process

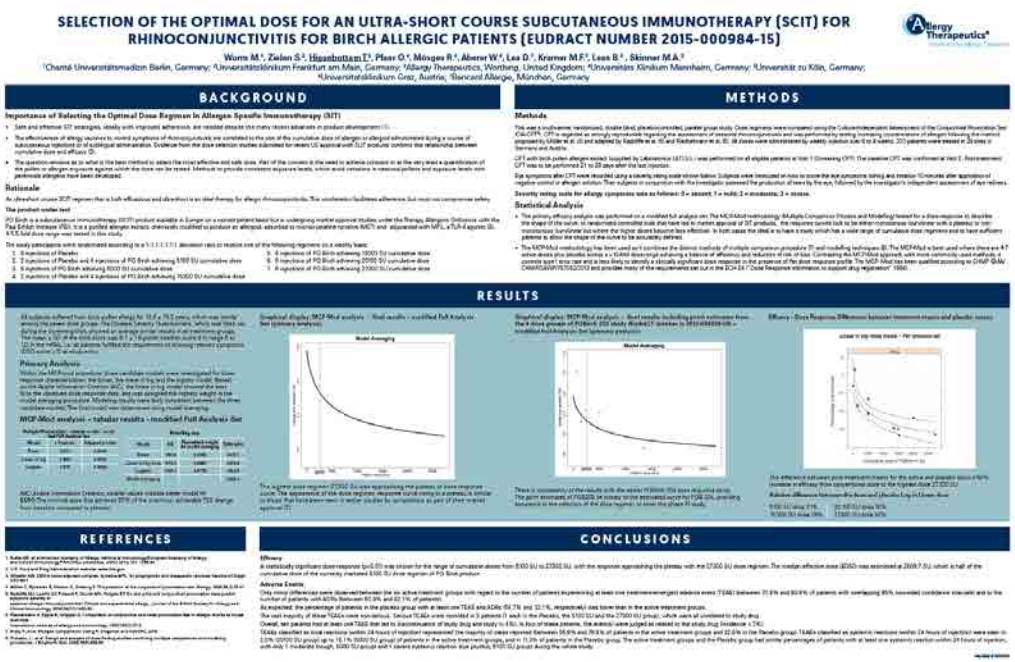
Clinical development plans submitted

TAV opportunity – main programmes

Product Range	Key Milestones
PQ	**PQ Birch/Tree** — Phase III recruitment underway Germany, Austria, Poland, Sweden
	PQ Grass — Product alignment with increased cumulative strength dose Phase II CPT Dose Finding 2017
Sublingual	**Oralvac Grass, Tree and Mite** — Phase I/II synopsis
House Dust Mite SCIT	Phase I tolerability studies

Clinical development

PQ Birch Phase II dose finding study



SELECTION OF THE OPTIMAL DOSE FOR AN ULTRA-SHORT COURSE SUBCUTANEOUS IMMUNOTHERAPY (SCIT) FOR RHINOCONJUNCTIVITIS FOR BIRCH ALLERGIC PATIENTS (EUDRACT NUMBER 2015-000984-15)

BACKGROUND

METHODS

RESULTS

REFERENCES

CONCLUSIONS

ED_{50} = 2600 SU
Commercial dose efficacious

Opportunity to increase efficacy further

Dose finding results validated by PEI enabling progression to Phase III

Phase III anticipated Sep 2017

Germany, Austria, Poland, Sweden

TAV MAA planned

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The TAV EU registration and US opportunity

Next generation House dust mite SCIT

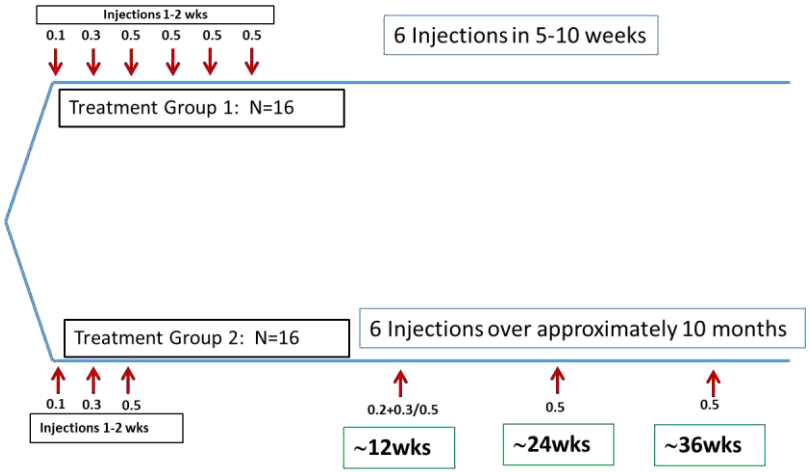
Acarovac MPL

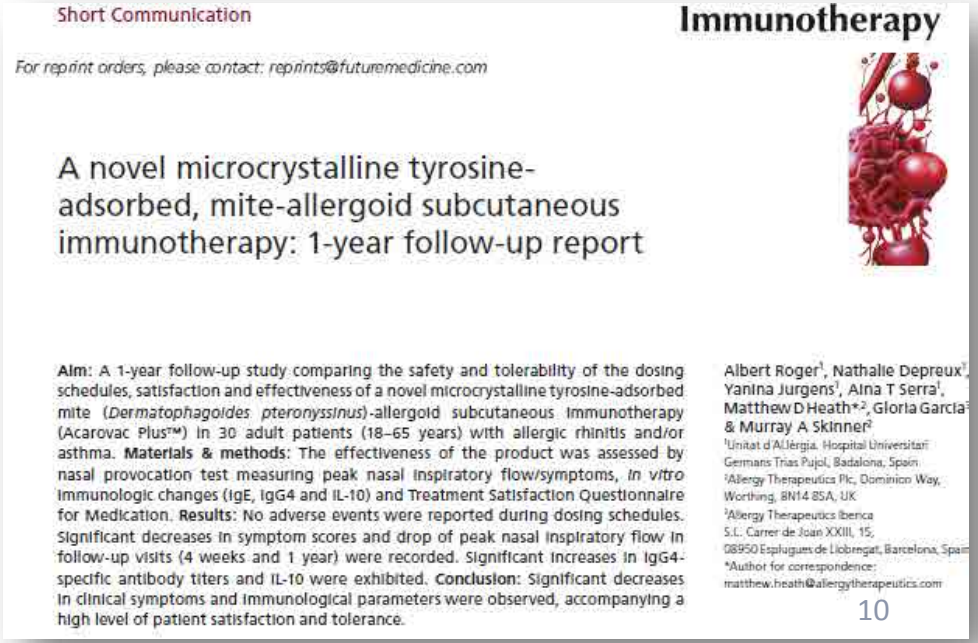
Portfolio development, extension and Bencard Adjuvant Systems

Mite-allergoid SCIT

- **Mite-allergoid SCIT** demonstrated promise for short course therapy in terms of safety and efficacy, MPL may allow further benefit in **Mite-allergoid SCIT + MPL**
- **Improve patient compliance**
- **Improve patient convenience**
- **Typical House Dust Mite SCIT > 40 injections in 3 years**
- **Mite-allergoid SCIT + MPL short course immunotherapy could revolutionise patient choice of treatment**

Mite SCIT AM101 – short course vs long course




Short Communication

Immunotherapy

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A novel microcrystalline tyrosine-adsorbed, mite-allergoid subcutaneous immunotherapy: 1-year follow-up report

Aim: A 1-year follow-up study comparing the safety and tolerability of the dosing schedules, satisfaction and effectiveness of a novel microcrystalline tyrosine-adsorbed mite (*Dermatophagoides pteronyssinus*)-allergoid subcutaneous immunotherapy (Acarovac Plus™) in 30 adult patients (18–65 years) with allergic rhinitis and/or asthma. **Materials & methods:** The effectiveness of the product was assessed by nasal provocation test measuring peak nasal inspiratory flow/symptoms, *in vitro* immunologic changes (IgE, IgG4 and IL-10) and Treatment Satisfaction Questionnaire for Medication. **Results:** No adverse events were reported during dosing schedules. Significant decreases in symptom scores and drop of peak nasal inspiratory flow in follow-up visits (4 weeks and 1 year) were recorded. Significant increases in IgG4-specific antibody titers and IL-10 were exhibited. **Conclusion:** Significant decreases in clinical symptoms and immunological parameters were observed, accompanying a high level of patient satisfaction and tolerance.

Albert Roger[1], Nathalie Depreux[2], Yanina Jurgens[1], Alna T Serra[1], Matthew D Heath*[2], Gloria Garcia[3] & Murray A Skinner[2]

[1]Unitat d'Al·lèrgia, Hospital Universitari Germans Trias Pujol, Badalona, Spain

[2]Allergy Therapeutics Plc, Dominion Way, Worthing, BN14 8SA, UK

[3]Allergy Therapeutics Iberica S.L. Carrer de Joan XXIII, 15, 08950 Esplugues de Llobregat, Barcelona, Spain

*Author for correspondence: matthew.heath@allergytherapeutics.com

The TAV EU registration and US opportunity

Next generation House dust mite SCIT

Acarovac MPL

Portfolio development, extension and Bencard Adjuvant Systems

Products for diagnosis and therapy

Continuous and new product development

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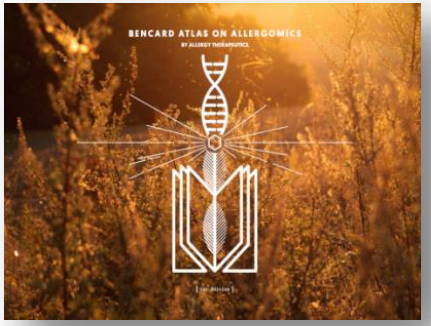
Key project themes in non-clinical developments

- Diagnostic and vaccine product characterisation
- Adjuvant characterisation

MONOCOTYLEDON POLLENS	17 Characterised	ANIMAL HAIRS	11 Characterised
DICOTYLEDON POLLENS	26 Characterised	ANIMAL FEATHERS	4 Characterised
MITES	4 Characterised	FRUIT	3 Characterised
FUNGI	2 Characterised	VEGETABLES	9 Characterised
VENOMS	12 Characterised	FLOURS AND BRANS	20 Characterised
FISH AND SHELLFISH	9 Characterised	MILK AND DAIRY	5 Characterised
NUTS	13 Characterised		



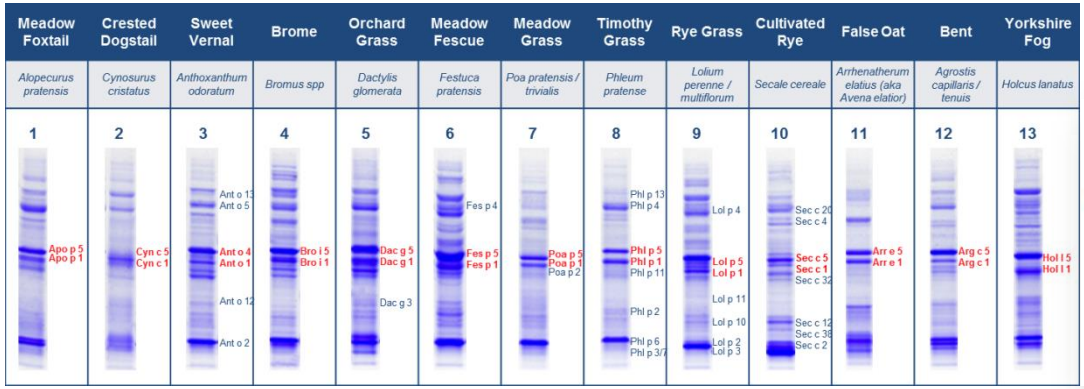

Heath et al. World Allergy Organization Journal (2015) 8:21
DOI 10.1186/s40413-015-0069-9

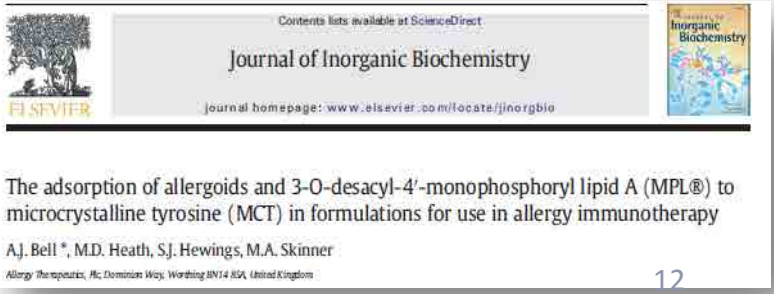
WAO journal
WORLD ALLERGY ORGANIZATION

ORIGINAL RESEARCH Open Access

Molecular, proteomic and immunological parameters of allergens provide inclusion criteria for new candidates within established grass and tree homologous groups

Matthew D Heath*, Joe Collis, Toby Batten, James W Hutchings, Nicola Swan and Murray A Skinner




Contents lists available at ScienceDirect

Journal of Inorganic Biochemistry

journal homepage: www.elsevier.com/locate/jinorgbio

The adsorption of allergoids and 3-O-desacyl-4′-monophosphoryl lipid A (MPL®) to microcrystalline tyrosine (MCT) in formulations for use in allergy immunotherapy

A.J. Bell *, M.D. Heath, S.J. Hewings, M.A. Skinner

Allergy Therapeutics, Plc, Dominion Way, Worthing BN14 8SA, United Kingdom

“The adjuvant company” MCT

First to use the depot adjuvant **microcrystalline tyrosine (MCT)** as an alternative to aluminium in allergy immunotherapy **– MCT is licenced in AGYs immunotherapy**

Alum + Allergen	→	Long-course IT: 30-50 injections
MCT + modified-allergen	→	Short course IT*: 6 injections
MCT + modified-allergen + MPL	→	Ultra short course IT**: 4 injections

*Licensed vaccines

Launch of Bencard Adjuvant Systems 2015 to develop **IP opportunities for MCT** and other patented adjuvants in **allergy/non-allergy**

BENCARD Adjuvant Systems

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Adjuvant technologies: why MCT?

EXPERT REVIEW OF CLINICAL IMMUNOLOGY, 2017
http://dx.doi.org/10.1080/1744666X.2017.1292133

Taylor & Francis
Taylor & Francis Group

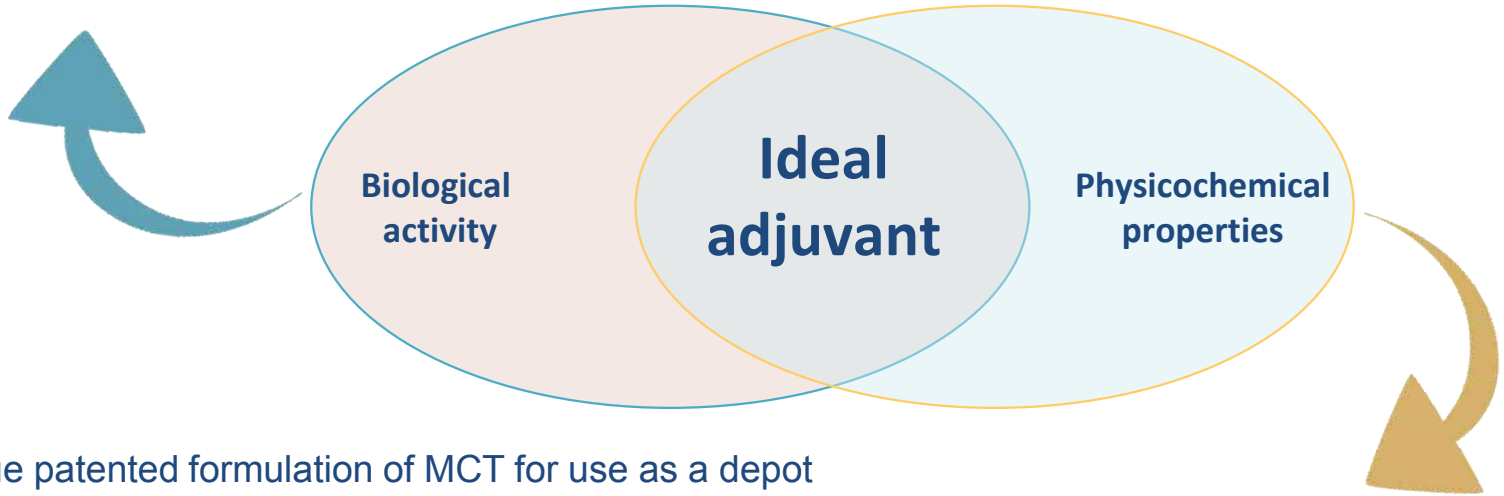
REVIEW

Clinical use of adjuvants in allergen-immunotherapy

Ludger Klimek[a], Carsten B. Schmidt-Weber[b], Matthias F. Kramer[c], Murray A. Skinner[d] and Matthew D. Heath[d]

[a]Center for Rhinology and Allergology, Wiesbaden, Germany; [b]Center of Allergy and Environment (ZAUM), Technical University and Helmholtz Center Munich, Munich, Germany; [c]Bencard Allergie GmbH, Munich, Germany; [d]Allergy Therapeutics Ltd, Worthing, UK

- Safety
- Targeted immune response
- Protective effect



- Unique patented formulation of MCT for use as a depot adjuvant to 2032 - WIPO publishes patent for "Process for Preparing Vaccine Composition"
- Characterised allergen/antigen binding capacity and stability
- Biodegradable alternative
- Proven in short course

- Particle dissolution
- Ease to make sterile
- Stability/Expiry date

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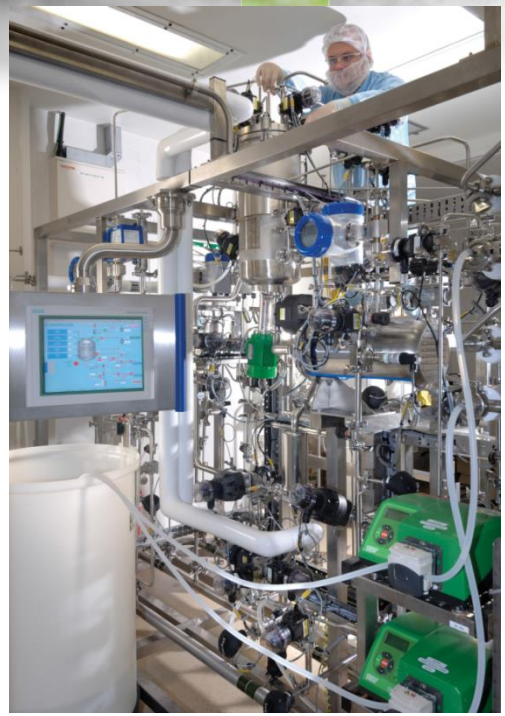
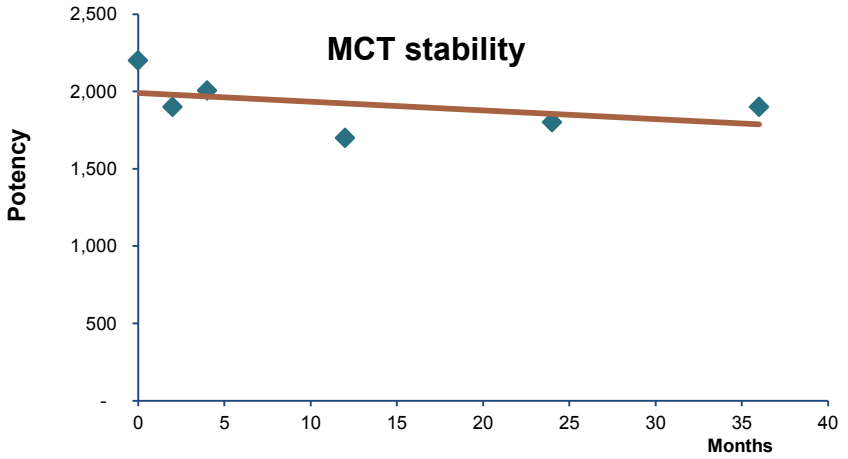
MCT – sterility and stability



Antigen-MCT formulation	Antigen content in drug substance	Antigen content in supernatant	Antigen adsorbed in MCT complex
Test Antigen 1	177 QAU/mL	≤0.1 QAU/mL	≥99%
Test Antigen 2	163 QAU/mL	≤0.1 QAU/mL	≥99%
Test Antigen 3	180 QAU/mL	≤0.1 QAU/mL	≥99%
Test Antigen 4	170 QAU/mL	≤0.1 QAU/mL	≥99%
Test Antigen 5	168 QAU/mL	≤0.1 QAU/mL	≥99%
Test Antigen 6	171 QAU/mL	≤0.1 QAU/mL	≥99%



- MCT can be manufactured as sterile
- MCT remains bound to different vaccine formulations > 99%.
- MCT is stable in different vaccine formulations

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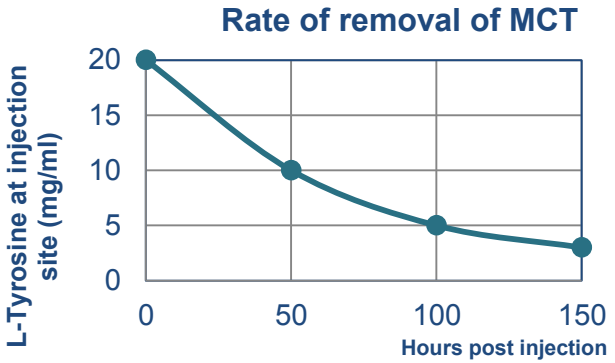
MCT is biodegradable and safe

- Extensive clinical experience in humans; 4.3 million injections
- MCT half life is 48 hours, providing sustained release of antigens for prolonged immune exposure
- Naturally metabolised and quickly removed reducing the risk of granuloma formation possible with other depots



Aluminium adjuvant could be retained at the dose site for up to **37 adult years**.

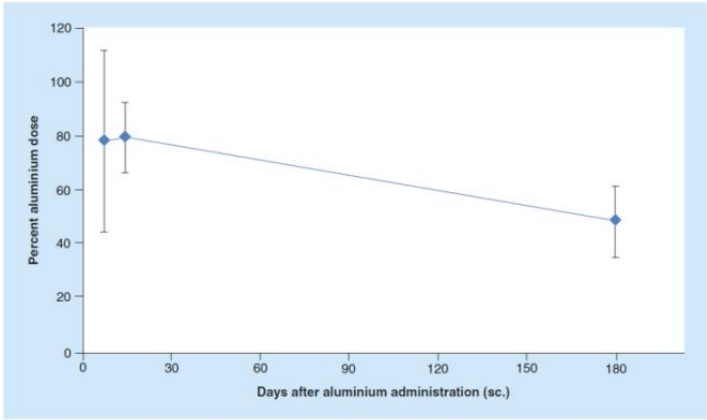


Figure 1. Mean (±standard error of mean) percent aluminium adjuvant dose associated with subcutaneous dose site.

Research Article

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Bioanalysis

Analysis of aluminium in rat following administration of allergen immunotherapy using either aluminium or microcrystalline-tyrosine-based adjuvants

Stuart A McDougall*[,1], Matthew D Heath[2], Matthias F Kramer[3] & Murray A Skinner[2]

[1]ARCINOVA, Willowburn Avenue, Alnwick, Northumberland, NE66 2JH, UK
[2]Allergy Therapeutics plc, Dominion Way, Worthing, BN14 8SA, UK
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Scope outside allergy – case study 1
MCT plus Influenza antigen candidate vaccine

Heath et al. BMC Infectious Diseases (2017) 17:232
DOI 10.1186/s12879-017-2329-5

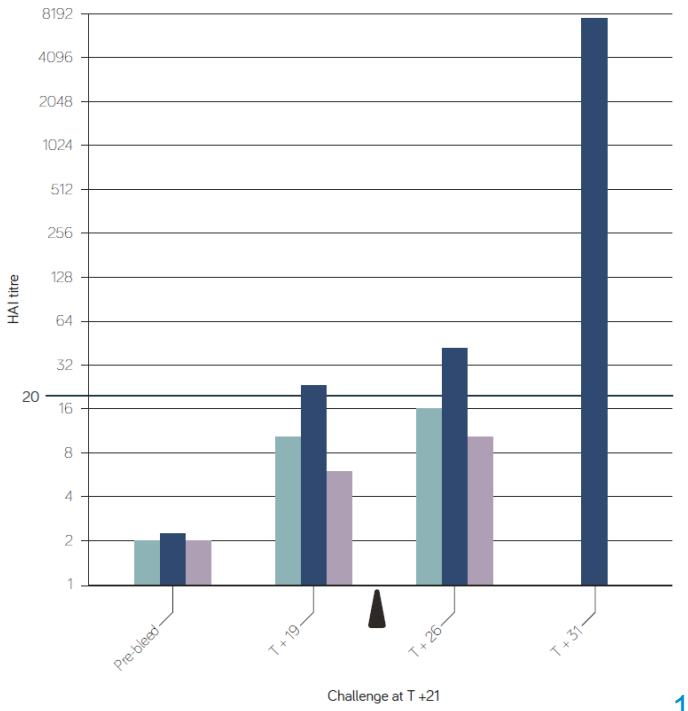
BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Comparison of a novel microcrystalline tyrosine adjuvant with aluminium hydroxide for enhancing vaccination against seasonal influenza

M. D Heath[1*], N. J. Swan[1], A. C. Marriott[2], N. J. Silman[2], B. Hallis[2], C. Prevosto[2,3], K. E. Gooch[2] and M. A. Skinner[1]

Public Health England



- **Antigen**
- **Antigen + MCT**
- **PBS Control**

MCT enhances immunity of currently available influenza vaccine

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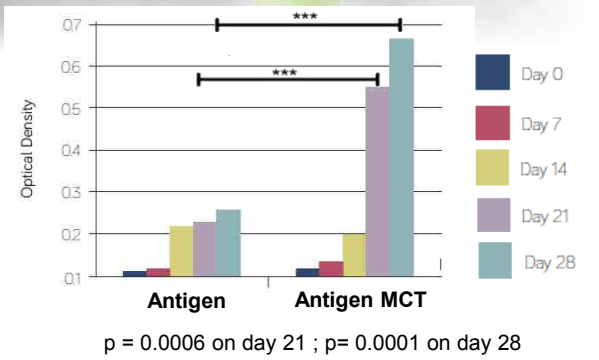
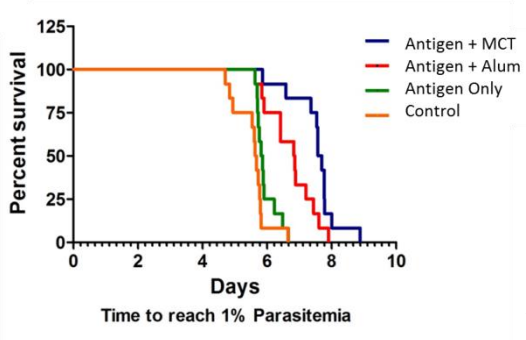
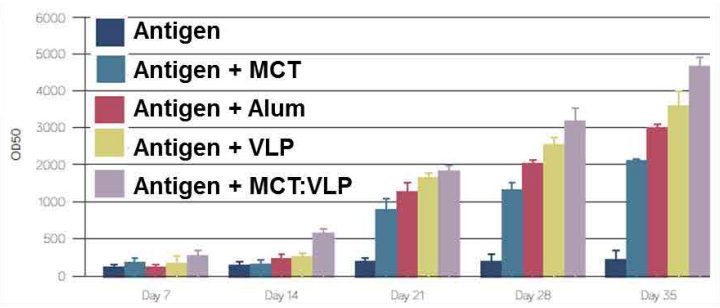
Scope outside allergy – case study 2
MCT plus malaria antigen candidate vaccines



p = 0.0006 on day 21 ; p= 0.0001 on day 28





MCT improves the immunological profile of a malaria vaccine

Survival challenge: MCT exhibits better protection for malaria than Alum

Synergistic effect of MCT:VLP observed in vaccine efficacy and protection

vaccines

MDPI

Article

Virus-Like Particle (VLP) Plus Microcrystalline Tyrosine (MCT) Adjuvants Enhance Vaccine Efficacy Improving T and B Cell Immunogenicity and Protection against *Plasmodium berghei/vivax*

Gustavo Cabral-Miranda [1,*,†], Matthew D. Heath [2], Mona O. Mohsen [1], Ariane C. Gomes [1], Paul Engeroff [3], Amy Flaxman [1], Fabiana M. S. Leoratti [3], Aadil El-Turabi [1], Arturo Reyes-Sandoval [1], Murray A. Skinner [2], Matthias F. Kramer [4] and Martin F. Bachmann [1,3,*,†]

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Strategy
The future of the AGY Pipeline

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Product Development

- PQ Birch and Trees MAA following PQ Birch Phase III
- PQ Grass – successful CPT dose finding with global Phase III
- Oralvac House Dust Mite, Grass & Trees
- Acarovac MPL – best in class short course perennial
- Best characterised allergen product portfolio (SPT, SLIT, SCIT)

Portfolio Expansion

- PQ range in the US
- Acarovac Development
- Polyvac peanut

Adjuvant Development

- MCT opportunities in allergy and non-allergy
- Revenue basis for Bencard Adjuvant Systems

Ευχαριστώ Obrigado Danke 谢谢 Grazie Merci Dakujem Thank You Gracias شكرا لك Dekuji Efharisto ありがとう

THANK YOU

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Allergy Therapeutics

New frontiers: Boosting our addressable market

PoLyVac peanut

PoLyVac
VLP

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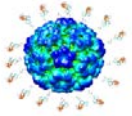
Overview of presentation

Peanut allergy: an increasing, significant health problem and growing market around the globe

Peanut allergy therapy: numerous attempts with significant limitations and recent draw backs

ATL's approach: allergy vaccination aiming for protective immunity



VLP's: an established platform adopted from vaccinology

PolyVac peanut: preclinical results

Overview of presentation

Peanut allergy: an increasing, significant health problem and growing market around the globe

Peanut allergy therapy: numerous attempts with significant limitations and recent draw backs

ATL's approach: allergy vaccination aiming for protective immunity

VLP's: an established platform adopted from vaccinology

PolyVac peanut: preclinical results

Peanut allergy: epidemiology

- The market for food allergy therapies is a multi-billion dollar opportunity
- Food allergy is very common, affecting up to 8% of young children and 3% to 6% of the entire US population, and its prevalence appears to have increased significantly over the past 15 to 20 years.
- Adverse reaction results in 200,000 emergency room visits in the US yearly
- Peanut allergy was once rare, but it is now the most common cause of fatal food-allergic reactions. The prevalence has increased steadily over the past decade, mostly in the Western world, the disease currently affecting 1–2% of children in the UK.
- A study in the Isle of Wight showed a twofold increase in reported peanut allergy and a threefold increase in sensitization, in two birth cohorts of children over a period of 7 years. A similar trend has been noticed in the USA. Sicherer et al reported a significant increase in peanut allergy in children, from 0.4% in 1997 to 0.8% in 2002 to 1.4% in 2008; this is equal to a 3.5-fold increase within a period of 11 years.

REVIEW ARTICLE

The role of dietary interventions in the prevention of IgE-mediated food allergy in children

George Du Toit[1,a], Ru-Xin Foong[1,2,a] & Gideon Lack[1]

[1]Division of Asthma, Allergy and Lung Biology, Department of Paediatric Allergy, King's College London, Guy's and St. Thomas' NHS Foundation Trust, London, UK. [2]Institute of Child Health, University College of London, London, UK.

To cite this article: Du Toit G, Foong RX, Lack G. The role of dietary interventions in the prevention of IgE-mediated food allergy in children. *Pediatr Allergy Immunol* 2017; 28: 222–228.

Food allergen immunotherapy: Current status and prospects for the future

Robert A. Wood, MD *Baltimore, Md*

(J Allergy Clin Immunol 2016;137:973-82.)

Estimating the economic burden of food-induced allergic reactions and anaphylaxis in the United States

Dipen A. Patel, PhD, David A. Holdford, PhD, Eric Edwards, BS, and Norman V. Carroll, PhD *Richmond, Va*

(J Allergy Clin Immunol 2011;128:110-5.)

Downloaded from http://adc.bmj.com/ on June 29, 2015 - Published by group.bmj.com

Review

The management of peanut allergy

Katherine Anagnostou,[1] Andrew Clark[2]


Allergy
REVIEW ARTICLE
Markers of tolerance development to food allergens
M. Ponce, S. C. Diesner, Z. Szépfalusi & T. Eiwegger
To cite this article: Ponce M, Diesner SC, Szépfalusi Z, Eiwegger T. Markers of tolerance development to food allergens. Allergy 2016; 71: 1393–1404.

Peanut allergy: epidemiology


Allergy
REVIEW ARTICLE
Markers of tolerance development to food allergens
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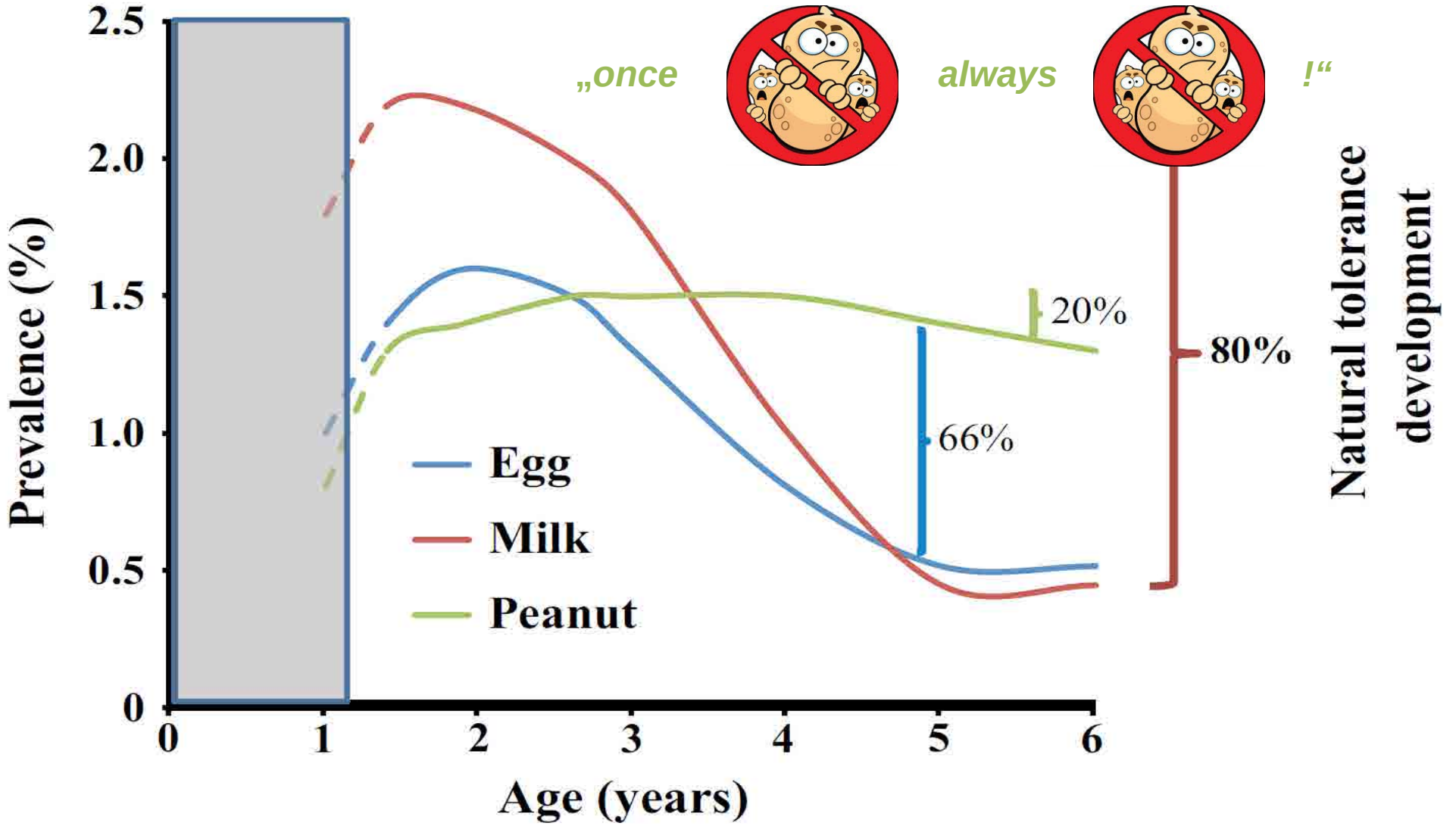
To cite this article: Ponce M, Diesner SC, Szépfalusi Z, Eiwegger T. Markers of tolerance development to food allergens. Allergy 2016; 71: 1393–1404.

Peanut allergy: epidemiology



Peanut allergy: epidemiology

Review

The management of peanut allergy

Katherine Anagnostou,[1] Andrew Clark[2]

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[2]Department of Medicine, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK

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ABSTRACT
Peanut allergy is common and can be a cause of severe, life-threatening reactions. It is rarely outgrown like other food allergies such as egg and milk. Measures aiming to reduce its prevalence via maternal avoidance during pregnancy and lactation, or delayed introduction into the diet, have failed to show any benefit. Peanut allergy has a significant effect on the quality of life of sufferers and their families due to dietary and social restrictions, but mainly stemming from fear of accidental peanut ingestion. The current management consists of strict avoidance, education and provision of emergency medication. Families find avoidance challenging as peanut is hidden in various food products. Despite the fact that food labelling has improved, with a legal obligation to declare certain food allergens (including nuts) in prepacked products, it still causes confusion and does not extend to cross-contamination. In an effort to address issues of safety at school, a lot of work has been undertaken to better care for peanut-allergic children in that environment. This includes training of school staff on how to recognise and treat allergic reactions promptly. Recent developments in the management of peanut allergy, such as immunotherapy, have shown some promise as an active form of treatment, but larger studies are required to further investigate safety and efficacy.

Summary points

- Peanut allergy is common and can cause severe, life-threatening reactions. It has a significant effect in quality of life.
- Avoidance of peanut consumption during pregnancy and lactation failed to reduce the prevalence of peanut allergy. Early introduction of peanut may actually promote tolerance and reduce the risk of peanut allergy.
- Current management consists of strict avoidance of peanut, provision of emergency medication and educating the families on how to recognise and treat allergic reactions when they occur.
- Peanut avoidance is challenging and accidental reactions are common.
- Food labelling, although improved, can still be confusing and ambiguous for peanut-allergic children and their caregivers.
- Future developments of active management of peanut allergy include peanut oral immunotherapy.

ALLERGY Net

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• CONTRIBUTIONS TO THIS SECTION WILL NOT UNDERGO PEER REVIEW, BUT WILL BE REVIEWED BY THE ASSOCIATE EDITORS •

Kiss-induced allergy to peanut

B. Wüthrich*, M. Däscher, S. Borelli

Key words: allergy; food; kiss; peanut

• In 1997, we reported in this journal on oral allergy syndrome to apple after a lover's kiss in a young woman with pollen-associated food allergy (1, 2). Her boyfriend had just eaten a fresh apple before the kiss. To the best of our knowledge, this was the first such case of "connubial" allergy to be published in the literature. Recently, we saw a patient with severe peanut allergy who experienced an allergic reaction after a kiss from his girlfriend, who had eaten peanuts 2 h before.

Food allergy transferred by love.

A 30-year-old atopic man (a medical doctor) with severe peanut allergy since childhood had developed recurrent anaphylactic reactions after ingestion of various foods (chocolate, snacks, cakes, cornflakes, and various Asian foods). The patient experienced symptoms (conjunctivitis and asthma) even when someone near him ate peanuts during a party, in a bar, or in an airplane. After a kiss from his lover, he suddenly developed swelling of his lips with an itching sensation around his mouth. His girlfriend had eaten a few peanuts 2 h before and – knowing of the life-threatening reactions of her friend to hidden peanuts – she had brushed her teeth intensively, rinsed her mouth, and chewed chewing gum. The patient's last episode of allergic reaction had happened the year before in the USA during a party after eating a spring roll made of wholemeal including soy. The patient's allergen-specific IgE (CAP FEIA, Pharmacia Diagnostics) to peanuts was class 6 (>100 kU/l), and to soy CAP class 4 (4.6 kU/l).

It is well known that accidental ingestion of hidden peanut allergens can provoke life-threatening and fatal anaphylactic reactions in peanut-allergic patients (3, 4). Only 50 µg of peanut can provoke symptoms (5). Not only hidden allergens in food but also exposure to the allergen in the kitchen when someone is preparing food, or close physical contact with or sitting beside someone who has recently eaten the allergenic food can induce allergic reactions, as was recently shown in a poster at the Symposium on Food Allergy, 11–13 March 2001 in Venice (6). In fact, Eriksson et al. reported on 11 persons, of a total of 1139 food-allergic patients who answered a questionnaire, who had allergic symptoms after kissing. The foods eliciting symptoms were apple and carrot (four cases), as well as other birch-pollen-related foods, including fish (three cases), tree nuts (two cases), and peanut (two cases). One peanut-allergic patient also reacted to milk and egg. Two cases of facial urticaria in cow's milk (CM)-allergic children after kissing have been published as an abstract (7). These were a 9-month-old infant with CM allergy who reacted whenever kissed by his sister, and a 3-month-old infant who reacted when kissed by his mother if she had just eaten cereal with milk.

In conclusion, as shown by Eriksson et al. (6), kiss-induced allergy is probably more common than the few published case histories would indicate. In consequence, kissing can constitute a severe danger for the food-allergic patient: therefore, before kissing, such patients should ask their lovers what they have just eaten.

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Correspondence

What's in a kiss: Peanut allergen transmission as a sensitizer?

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FIG 1. Binding of Ara h 1 mAb to the site of a kiss on a nitrocellulose membrane 5 minutes after ingestion of a peanut butter sandwich. A comparative kiss before ingestion of the sandwich did not bind Ara h 1 mAb *(not shown)*.

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Peanut allergen

Peanut allergen

Protein superfamily	Cupin		Prolamin			
Protein family	**Vicilin or 7S globulin**	**Legumin or 11S globulin**		**2S albumin**		**nsLTP**
Allergen	**Ara h 1**	**Ara h 3**	**Ara h 2**	**Ara h 6**	**Ara h 7**	**Ara h 9**
Isoallergen (UniProt)	Ara h 1.0101 (P43238)	Ara h 3.0101 (O82580) Ara h 3.0201 (Q9SQH7)	Ara h 2.0101 (Q6PSU2) Ara h 2.0201 (Q6PSU2)	Ara h 6.0101 (Q647G9)	Ara h 7.0101 (Q9SQH1) Ara h 7.0201 (B4XID4)	Ara h 9.0101 (B6CEX8) Ara h 9.0201 (B6CG41)
Molecular mass (kDa) and theoretical pI	monomer 63.5 kDa; pI 4.6 occurs as trimer of 180 kDa	monomer 60.0 kDa; pI 4.6 occurs as hexamer of 360 kDa	16.6 kDa; pI 5.8 18.0 kDa; pI 5.5	15.0 kDa; pI 5.5	16.4 kDa; pI 5.6 17.4 kDa; pI 7.5	9.1 kDa; pI 9.5 9.1 kDa; pI 9.3
Representative protein structure						
	Ara h 1PDB: 3S7E [34]	Ara h 3 PDB: 3C3V [47]	Ara h 6 PDB: 1W2Q [63]			Pru p 3 PDB: 2ALG [115]
Biological function	provide nourishment for the growth of the seedlings		sources of amino acids for growth of seedlings; involved in defense against pathogens			involved in defense agains pathogens and in the formation of hydro-phobic layers in plant
Prevalence of IgE binding	30-80% [17, 83]	16-57% [17, 83]	42-100% [116, 83]	86-92% [79, 116]	43% [79]	8-60%, strong association with peach allergy [84, 83]
Cross-reactivity	with other legume and tree nut vicilins and Ara h 2 and Ara h 3 [43, 11]	with other legumes and tree nut legumins and Ara h 1, 2, and 6 [43, 11]	with 2S albumins from almond and Brazil nut, and Ara h 1, 3, and 6 [11, 26]	with Ara h 1, 2, 3 [11]	not known	with peach and hazelnut nsLTPs (Pru p 3 and Cor a 8) [84]

M. Bublin, Curr Allergy Asthma Rep (2014)

Peanut allergen

Protein superfamily	**Bet v 1-like**	**Profilin**	**Glycosyl transferase GT-C**		**Scorpion toxin-like knottin**	
Protein family	**Bet v 1 family**	**Profilin**	**Oleosins**		**Plant defensins**	
Allergen	**Ara h 8**	**Ara h 5**	**Ara h 10**	**Ara h 11**	**Ara h 12**	**Ara h 13**
Isoallergen (UniProt or GenBank No.)	Ara h 8.0101 (Q6VT83) Ara h 8.0201 (B0YIU5)	Ara h 5.0101 (Q9SQI9)	Ara h 10.0101 (Q647G5) Ara h 10.0201 (Q647G4)	Ara h 11.0101 (Q45W87)	Ara h 12.0101 (EY396089)	Ara h 13.0101 (EY396019)
Molecular mass (kDa) and theoretical pI	17.0 kDa; pI 5.0	14.0 kDa; pI 4.6	17.6 kDa; pI 9.6	14.3 kDa; pI 10.1	5.2 kDa; pI 7.7	8.4 kDa; pI 7.5
Representative protein structure			no oleosin structure available			
	Ara h 8 PDB: 4M9B [92]	Ara h 5 PDB: 4ESP [87]			defensin from germinated lentil seeds PDB: 2LJ7 [117]	
Biological function	might serve as a delivery vehicle for flavonoids	regulate polymerization and depolymerization of actin monomers	structural proteins of oil bodies in seeds		antifungal, antibacterial, protease inhibitory or insect amylase inhibitory activity in plants	
Prevalence of IgE binding	relevant for birch pollen allergic patients, ca. 22-66% [17, 83]	3-24% of birch or grass pollen allergic patients [83]	not known		not known	
Cross-reactivity	with Bet v 1 and other PR-10 proteins, e.g. from soy or lentil [89, 88]	with other profilins e.g. Bet v 2 and Phl p 12 [85]	with oleosins from soy and buckwheat [99, 95]		not known	

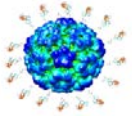
M. Bublin, Curr Allergy Asthma Rep (2014)

Overview of presentation

Peanut allergy: an increasing, significant health problem and growing market around the globe

Peanut allergy therapy: numerous attempts with significant limitations and recent draw backs

ATL's approach: allergy vaccination aiming for protective immunity



VLP's: an established platform adopted from vaccinology

PoLyVac
VLP

PolyVac peanut: preclinical results

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Review

International Archives of Allergy and Immunology

Int Arch Allergy Immunol 2014;165:179–194
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Developing Therapies for Peanut Allergy

Merima Bublin Heimo Breiteneder

Department of Pathophysiology and Allergy Research, Medical University of Vienna, Vienna, Austria

Key Words
Allergen-specific immunotherapy · Allergen-nonspecific immunotherapy · Ara h 2 · Oral immunotherapy · Peanut allergy

Abstract
Peanut allergy is an IgE-mediated, persisting immune disorder that is of major concern worldwide. Currently, no routine immunotherapy is available to treat this often severe and sometimes fatal food allergy. Traditional subcutaneous allergen immunotherapy with crude peanut extracts has proven not feasible due to the high risk of severe systemic side effects. The allergen-specific approaches under preclinical and clinical investigation comprise subcutaneous, oral, sublingual and epicutaneous immunotherapy with whole-peanut extracts as well as applications of hypoallergenic peanut allergens or T cell epitope peptides. Allergen-nonspecific approaches include monoclonal anti-IgE antibodies, TCM herbal formulations and Toll-like receptor 9-based immunotherapy. The potential of genetically engineered plants with reduced allergen levels is being explored as well as the beneficial influence of lactic acid bacteria and soybean isoflavones on peanut allergen-induced symptoms. Although the underlying mechanisms still need to be elucidated, several of these strategies hold great promise. It can be estimated that individual strategies or a combination thereof will result in a successful immunotherapy regime for peanut-allergic individuals within the next decade.

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Introduction

Peanut allergy is an IgE-mediated disease which tends to develop in early life and resolves in only 20% of peanut-allergic children when they reach school age [1]. Peanut allergy affects 0.8–3% of children and 0.6–0.8% of the adult population in the USA, Canada, UK and Australia [2–4]. So far, the only therapy for peanut allergy is the avoidance of peanuts and peanut-containing foods. Peanut allergens can induce anaphylaxis at minute doses, even in patients who have previously experienced only mild symptoms [5, 6]. Hence, the focus of peanut allergy management is to educate afflicted individuals to avoid all products that contain/may contain peanuts, to recognize early symptoms due to unintended ingestions and to administer self-injectable epinephrine when indicated [7]. However, in one study, these measures were shown to negatively affect the quality of life [8].

Clearly, therapeutic approaches that modify the immune response to peanut allergens and induce oral tolerance are needed as well as strategies that protect the patient from accidental ingestions. Such novel therapeutic approaches for peanut allergy can be generally classified as allergen-specific (table 1) and allergen-nonspecific (table 2) immunotherapies.

Allergen-Specific Immunotherapy Approaches

Allergen-specific immunotherapy involves subcutaneous injections as well as oral, sublingual or epicutaneous applications of progressively higher doses of the of-

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Table 1. Allergen-specific immunotherapy approaches for peanut allergy

Approach	Study subjects and inclusion criteria	Immunizing reagent	Effects	Publication
Subcutaneous immunotherapy	Human adults including those with anaphylaxis	Peanut extract	↑ oral tolerance and ↓ SPT; high rate of systemic reactions	1997 [15]
OIT	Children with no history of severe anaphylaxis	Peanut flour	54–84% desensitized to target maintenance doses; side effects in 47 and 81% of treated subjects; ↑ IgG4	2011 [16] and 2014 [18]
SLIT	Children [31] and adults [32] with no history of severe anaphylaxis	Liquid peanut extract	↑ oral tolerance; mild side effects; ↓ SPT; ↑ IgG4 and ↓ basophil activation	2011 [31] and 2013 [32]
EPIT	Children with no history of severe anaphylaxis	Patch containing 100 µg of peanut proteins	↑ oral tolerance in up to 67% mild side effects; ↑ IgG4	2014 [41]
Recombinant hypoallergenic peanut allergens and bacterial adjuvants	Human adults with no history of severe anaphylaxis	mAra h 1–3 plus heat/phenol-inactivated *E. coli*	↓ SPT; ↓ basophil activation; high rate of systemic reactions	2013 [52]
Recombinant hypoallergenic peanut allergens	Murine model of peanut anaphylaxis	mAra h 2	Reduced clinical symptom scores and histamine release	2001 [48]
	RBL-2H3 cells and PBMCs from 4 peanut-allergic patients	mAra h 2	Partially reduced IgE reactivity with retained T cell reactivity	2005 [45]
Peanut extract and bacterial adjuvants	Brown Norway rat model for peanut allergy	Peanut extract plus *L. casei* Shirota	Downregulation of peanut allergic response in 2 of 8 rats	2008 [69]
	Balb/c mice	Peanut extract, cholera toxin and CpG	Prevention of oral sensitization by previous subcutaneous administration of the mix	2007 [131]
	Peanut-allergic C3H/HeJ mice	Modified Ara h 1–3 plus HKLM	Reduced histamine levels, peanut-specific IgE, bronchial constriction and anaphylaxis symptoms	2003 [50]
	Peanut-allergic C3H/HeJ mice	HKE-mAra h 1–3	Reduced production of IL-4, IL-5 and IL-13 by splenocytes and long-term downregulation of peanut hypersensitivity	2003 [51]
T cell epitope-based peptide vaccines	Peanut-allergic C3H/HeJ mice	30 overlapping Ara h 2 20-mers	Reduced histamine release and anaphylaxis symptoms	2007 [81]
DNA-based vaccines	AKR/J mice	Complex of chitosan and Ara h 2-encoding DNA	Reduction of peanut-induced anaphylaxis, reduced level of IgE	1999 [86]
	AKR/J, Balb/c and C3H/HeJ mice	Plasmid DNA encoding Ara h 2	Strain-dependent induction of allergic sensitization	1999 [87]
Hypoallergenic transgenic plants	Western blot with sera from peanut-allergic patients	Seed proteins from transgenic peanut plants with silenced Ara h 2 and Ara h 6	Significant reduction of IgE-binding	2008 [96]

Peanut allergy therapy

Review

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Table 2. Allergen-nonspecific immunotherapy approaches for peanut allergy

Approach	Study subjects	Active substance	Effects	Publication (year)
Anti-IgE immunotherapy	Human adults	TNX-901	↑ oral tolerance in up to 24%; no further clinical evaluation	[112] 2003
	Human adults	Omalizumab	↑ oral tolerance; adverse reactions during oral food challenges prior to treatment	[111] 2011
Cytokine immunotherapy	C3H/HeJ mice	Liposome-encapsulated recombinant IL-12	Protection against peanut anaphylaxis; ↓ IgE, IgG1 and fecal IgA	[114] 2001
	AKR/J mice	Recombinant IL-12 or IL-21-expression plasmid	Protection against peanut anaphylaxis; ↓ total and peanut-specific IgE	[115] 2007
TLR9-based immunotherapy	TLR-9-deficient mice	Peanut proteins	Resistance to peanut-induced anaphylaxis; ↓ total and peanut-specific IgE and IgA	[127] 2013
TCM herbal therapy	C3H/HeJ mice	FAHF-1	Protection against peanut anaphylaxis; ↓ mast cell degranulation and histamine release	[119] 2001
	C3H/HeJ mice	FAHF-2	Protection from anaphylaxis lasting up to 36 weeks after treatment; ↓ peanut-specific IgE; ↑ peanut-specific IgG2a	[120] 2009
	Human adults	FAHF-2	Well-tolerated; ↓ allergen-stimulated basophil activation; ↓ percentage of circulating basophils	[123] 2011
Soybean isoflavones	C3H/HeJ mice	Dietary isoflavones genistein and daidzein	↓ anaphylactic symptoms and mast cell degranulation	[72] 2011

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Peanut allergy therapy: unmet needs

- Epicutaneous (EPIT) respectively sublingual (SLIT) applications of peanut allergen constitute alternative routes of peanut immunotherapy. Both approaches require repeated and long lasting exposures via the skin respectively the sublingual mucosa.
- Application site irritations are common phenomena in SLIT (regardeless of the allergen administered); systemic anaphylactic reactions are not excluded *
- Real life data, based on prescription data, demonstrated a 3 year adherence in SLIT of below 20% **
- A recent review on peanut SLIT described some efficacy and a good safety profile but adherence was bad (below 50% over 3 years) ***.

* *Di Bona et al. JAMA Intern Med. 2015; Vol 175:1301-9)*

** *Senna et al. JACI 2010; Vol 126: 668-9).*

*** *Burks et al. JACI 2015; Vol 135:1240-8)*

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Peanut allergy therapy: unmet needs

Epicutaneous immunotherapy for the treatment of peanut allergy in children and young adults

Stacie M. Jones, MD,[a] Scott H. Sicherer, MD,[b] A. Wesley Burks, MD,[c] Donald Y. M. Leung, MD,[d] Robert W. Lindblad, MD,[e] Peter Dawson, PhD,[e] Alice K. Henning, MS,[e] M. Cecilia Berin, PhD,[b] David Chiang, MSc,[b] Brian P. Vickery, MD,[c] Robbie D. Pesek, MD,[a] Christine B. Cho, MD,[a] Wendy F. Davidson, PhD,[f] Marshall Plaut, MD,[f] Hugh A. Sampson, MD,[b] and Robert A. Wood, MD,[g] for the Consortium of Food Allergy Research *Little Rock, Ark; New York, NY; Chapel Hill, NC; Denver, Colo; and Rockville, Bethesda, and Baltimore, Md*

(J Allergy Clin Immunol 2017;139:1242-52.)

CoFAR6 x

Consortium for Food Allergy Research 6

In October 2013, the Consortium for Food Allergy Research, or CoFAR, launched a multi-center, randomized, double-blind, placebo-controlled trial to evaluate Viaskin® Peanut in children and adults allergic to peanuts.

This trial is sponsored and funded by The National Institute of Allergy and Infectious Diseases, or NIAID, an institute of the United States National Institutes of Health and coordinated by Professor Hugh Sampson in New York. The trial is being conducted in five hospitals in the United States and includes 75 patients, both adults and children. The recruitment of CoFAR6 ended in July 2014. Subjects will be randomized to two doses of **Viaskin® Peanut** (100 µg and 250 µg) or matched placebo and will undergo a peanut protein oral food challenge at week 52. Expected to last four years, this trial will enable analysis of the effects of peanut desensitization with **Viaskin® Peanut** over an initial period of 12 months.

Key messages

- Peanut EPIT is associated with modest treatment response in children with peanut allergy after 52 weeks of blinded therapy, with a higher response noted among younger children.
- The vast majority of children treated with peanut EPIT had mild patch-site reactions; none had serious reactions, and none required epinephrine with dosing.
- Immunologic changes were associated with peanut EPIT and were similar to changes noted with other forms of immunotherapy for food allergy.

Note: „*Subjects with a history of severe anaphylaxis (previous hypotension, neurologic compromise, or mechanical ventilation) to peanut were excluded*.“

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Overview of presentation

Peanut allergy: an increasing, significant health problem and growing market around the globe

Peanut allergy therapy: numerous attempts with significant limitations and recent draw backs

ATL's approach: allergy vaccination aiming for protective immunity

VLP's: an established platform adopted from vaccinology

PolyVac peanut: preclinical results

Immunological Reviews

Daolin Tang
Rui Kang
Carolyn B. Coyne
Herbert J. Zeh
Michael T. Lotze

PAMPs and DAMPs: signal 0s that spur autophagy and immunity

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Immunological Reviews 249/2012

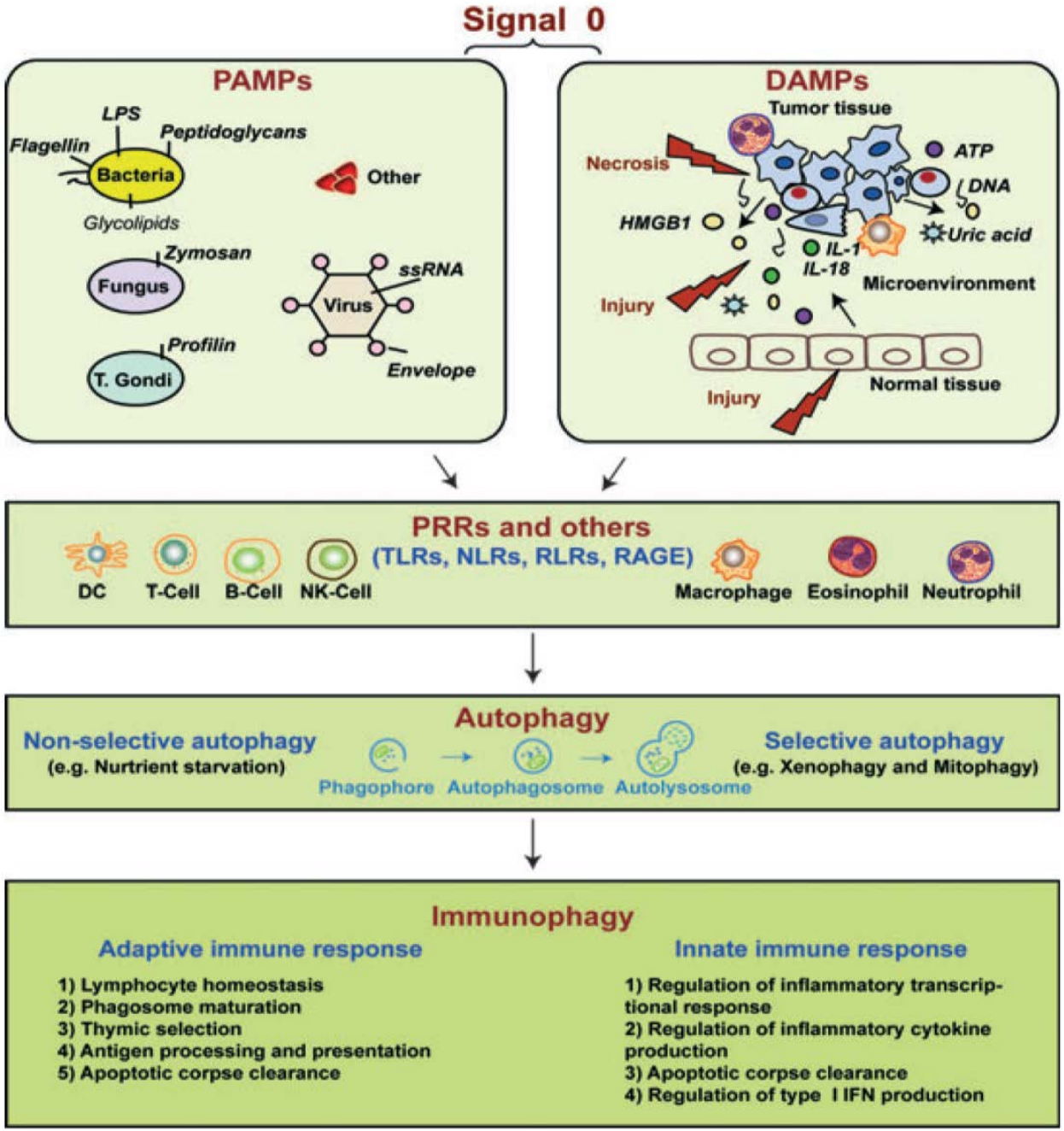
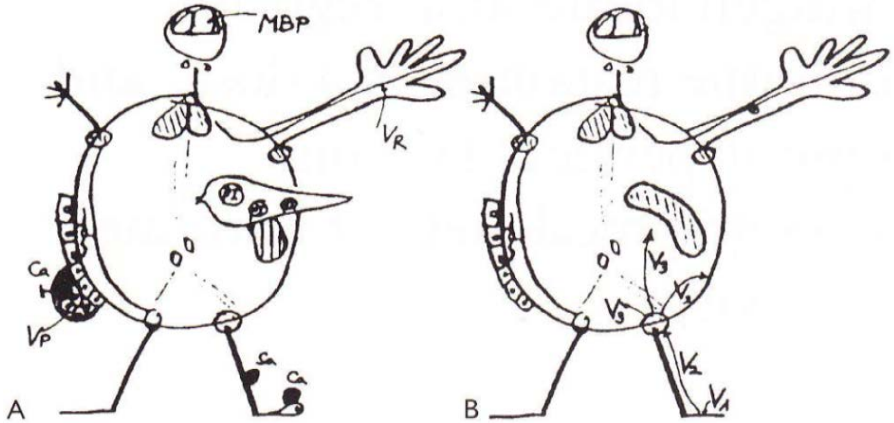


Fig. 1. Signal 0s play critical roles in autophagy and immunity. Pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) serve as signal 0s, inducing autophagy and immunophagy in the emergent immune response before the later Signal 1 (antigenic peptide and major histocompatability molecules), Signal 2 (costimulatory molecules such as CD80 and CD86), both present on the surface of DCs recruited by the signal 0s. Signal 3 represents the DC provided IL-6 family cytokine expression such as IL-12 and IL-23 which promote polarization of emergent T-cell response. Signal 4 represents the integrin expression on DCs, defining the origin of the DCs and driving specialized molecules on T-cells promoting T-cell traffic to tissues. LPS, lipopolysaccharide; HMGB1, high mobility group box 1; ATP, adenosine-5′-triphosphate; PRRs, pattern recognition receptors; TLRs, Toll-like receptors; NLRs, NOD-like receptors; RLRs, RIG-I-like receptors; RAGE, receptor for advanced glycation end products.

Rolf M. Zinkernagel
Stephan Ehl
Peter Aichele
Stephan Oehen
Thomas Kündig
Hans Hengartner

Antigen localisation regulates immune responses in a dose- and time-dependent fashion: a geographical view of immune reactivity

Immunological Reviews 156/1997



Antigen Localisation

Peripheral solid organ	Regional lymphatics	Hermatogenic spread

Antigen Dose

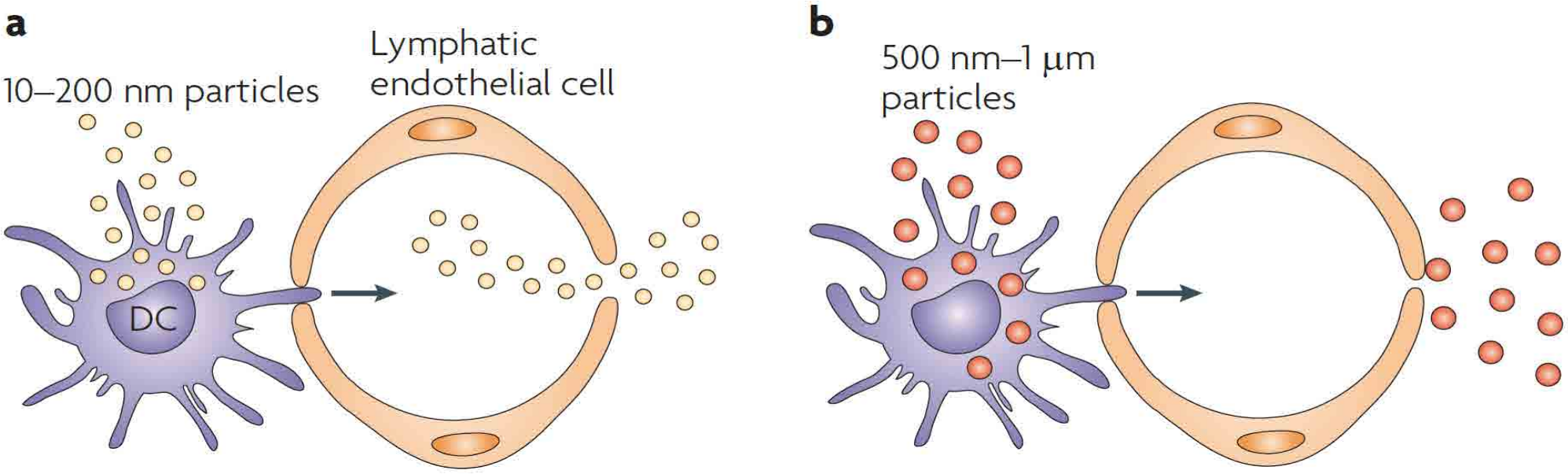
+ slow → Ignorance 2A

++ rapid → Response 2B

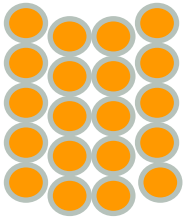
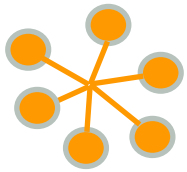
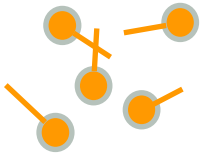
Vaccine delivery: a matter of size, geometry, kinetics and molecular patterns

Martin F. Bachmann and Gary T. Jennings

Abstract | Researchers working on the development of vaccines face an inherent dilemma: to maximize immunogenicity without compromising safety and tolerability. Early vaccines often induced long-lived protective immune responses, but tolerability was a major problem. Newer vaccines have very few side effects but can be of limited immunogenicity. One way to tackle this problem is to design vaccines that have all the properties of pathogens with the exception of causing disease. Key features of pathogens that can be mimicked by vaccine delivery systems are their size, shape and surface molecule organization. In addition, pathogen-associated molecular patterns can be used to induce innate immune responses that promote adaptive immunity. In this Review, we discuss the approaches currently being used to optimize the delivery of antigens and enhance vaccine efficacy.



lessons learned from vaccination

Organization:	high	low	absent
Antibody response	+++	++	-

T help independent type 1

SCIENCE • VOL. 262 • 26 NOVEMBER 1993

The Influence of Antigen Organization on B Cell Responsiveness

Martin F. Bachmann,* Urs Hoffmann Rohrer,* Thomas M. Kündig, Kurt Bürki,† Hans Hengartner, Rolf M. Zinkernagel‡

The influence of antigen epitope density and order on B cell induction and antibody production was assessed with the glycoprotein of vesicular stomatitis virus serotype Indiana [VSV-G (IND)]. VSV-G (IND) can be found in a highly repetitive form in the envelope of VSV-IND and in a poorly organized form on the surface of infected cells. In VSV-G (IND) transgenic mice, B cells were unresponsive to the poorly organized VSV-G (IND) present as self antigen but responded promptly to the same antigen presented in the highly organized form. Thus, antigen organization influences B cell tolerance.

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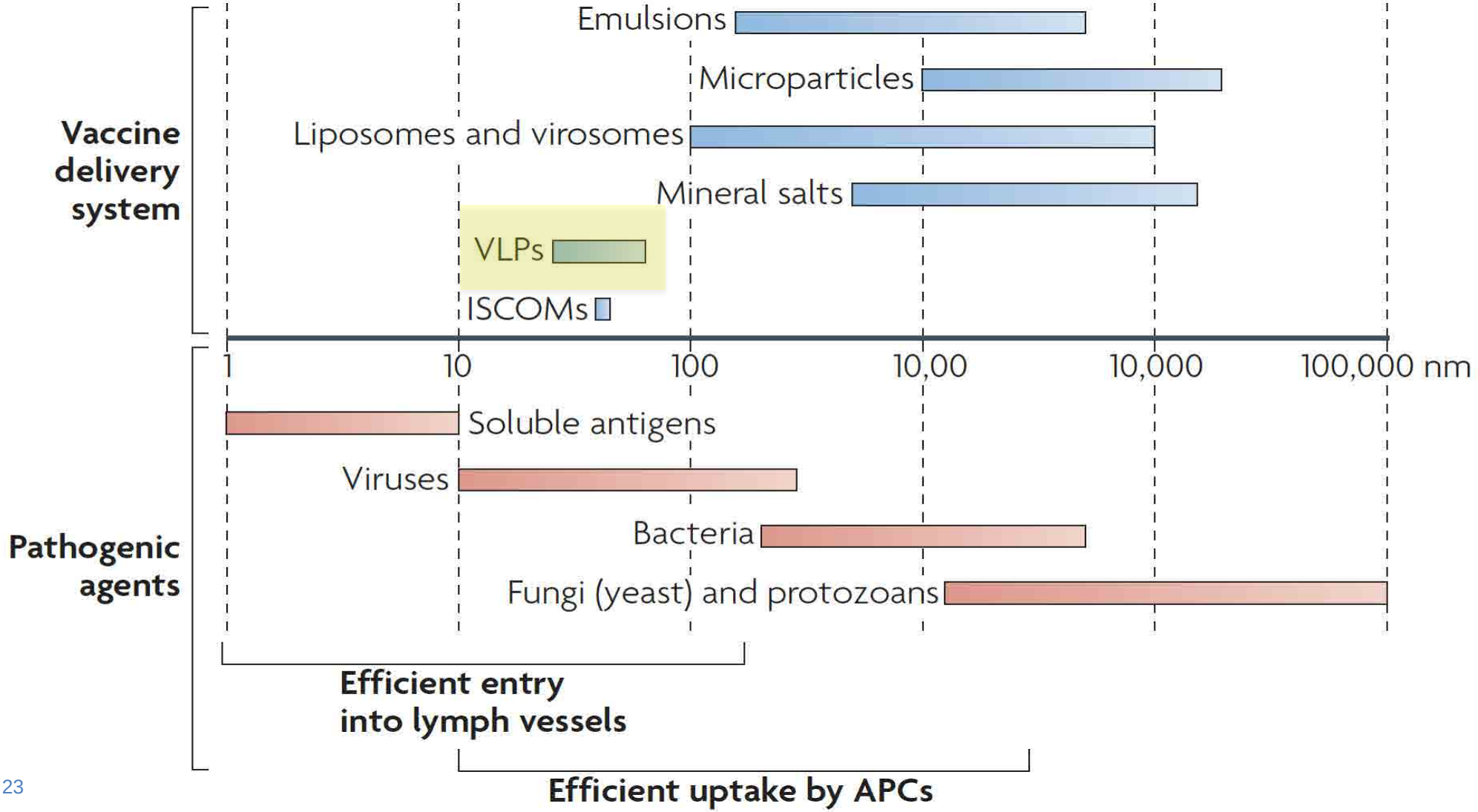
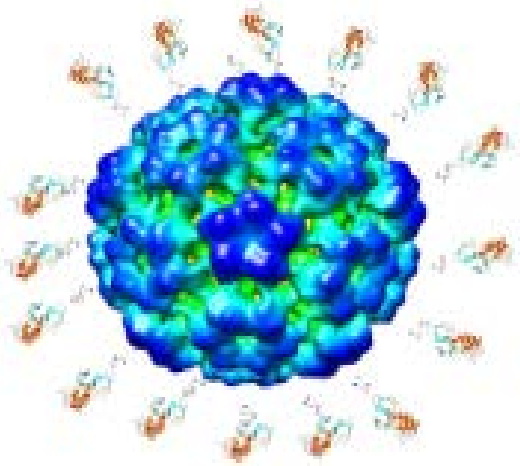
lessons learned from vaccination



Overview of presentation



Peanut allergy: an increasing, significant health problem and growing market around the globe

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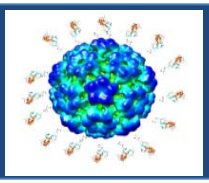
PolyVac peanut: preclinical results

VLPs



Virus-like particles: flexible platforms for vaccine development

Bryce Chackerian

Virus-like particles (VLPs) consist of viral structural proteins that, when overexpressed, spontaneously self-assemble into particles that are antigenically indistinguishable from infectious virus or subviral particles. VLPs can be considered as dense, repetitive arrays of one or more protein subunits with properties that are highly advantageous for use as stand-alone vaccines or as vaccine platforms. This review discusses the development of VLP-based platform technologies for vaccines against pathogens, as well as nontraditional targets such as self-antigens involved in chronic diseases.

Expert Rev. Vaccines 6(3), 381–390 (2007)

Key issues

- Virus-like particles (VLPs) are the basis of the highly effective human papillomavirus and hepatitis B virus vaccines.
- The dense, repetitive nature of VLPs makes them particularly effective in inducing antibody responses, often without adjuvants.
- Genetic and chemical techniques have been used to link target molecules to diverse VLP types.
- VLP-based vaccines can induce high-titer antibody and strong cytotoxic T-lymphocyte responses against target molecules.
- VLPs can also be used to induce therapeutic antibody responses against self-antigens that are involved in chronic diseases, such as arthritis, Alzheimer's and hypertension.
- Several VLP-based immunogens are currently in clinical trials.

HBV
- Energix® (GSK)
- Recombivax® (Merck)

HPV
- Gardasil® (Merck)
- Cervarix® (GSK)

VLPs

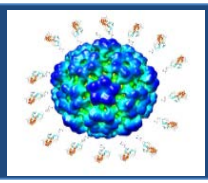


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Table 2. Selected virus-like particle-based vaccines targeting self-antigens.

Disease	Target antigen	Status	Ref.
Arthritis, encephalomyelitis and autoimmune myocarditis	IL-17	Preclinical	[40,96]
Hypertension	Angiotensin II	Phase I/II trials (Cytos)	[97]
Alzheimer's disease	Aβ	Phase I/II trials (Novartis/Cytos)	[37,61]
Rheumatoid arthritis, psoriasis and Crohn's disease	TNF-α	Preclinical	[52]
HIV infection	CCR5	Preclinical	[98,99]
Osteoporesis	TRANCE/RANKL	Preclinical	[100]
Obesity	Ghrelin	Phase I/II trials (Cytos)	[78]
Epithelial cancers	MUC1	Preclinical	[101]

Aβ: Amyloid-β peptide; CCR5: chemokine (C-C motif) receptor 5; IL: Interleukin; MUC1: Mucin 1; TRANCE/RANKL: Tumor necrosis factor-related activation-induced cytokine, also known as receptor activator of nuclear factor-κB ligand; TNF: Tumor necrosis factor.

The Use of Adjuvants for Enhancing Allergen Immunotherapy Efficacy

Julie Chesné, PhD, Carsten B. Schmidt-Weber, PhD*, Julia Esser von-Bieren, PhD

KEYWORDS

• Allergen-specific immunotherapy • Immune tolerance • Adjuvants

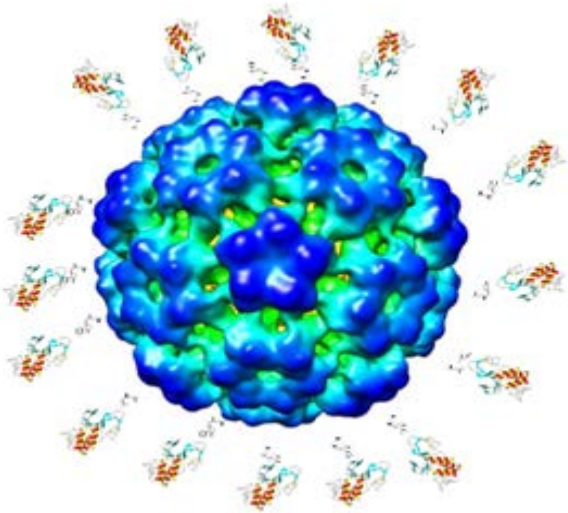
KEY POINTS

- Allergen-specific immunotherapy currently represents the only curative treatment for allergy, but its broader application requires safer and more efficacious treatment protocols.
- Adjuvants can improve the efficacy of allergen-specific immunotherapy, and a variety of promising immunomodulatory adjuvants are currently being developed.
- Innovative strategies have been proposed to simplify immunization and to achieve long-term tolerance.

Immunol Allergy Clin N Am 36 (2016) 125–145

PoLyVac

VLP



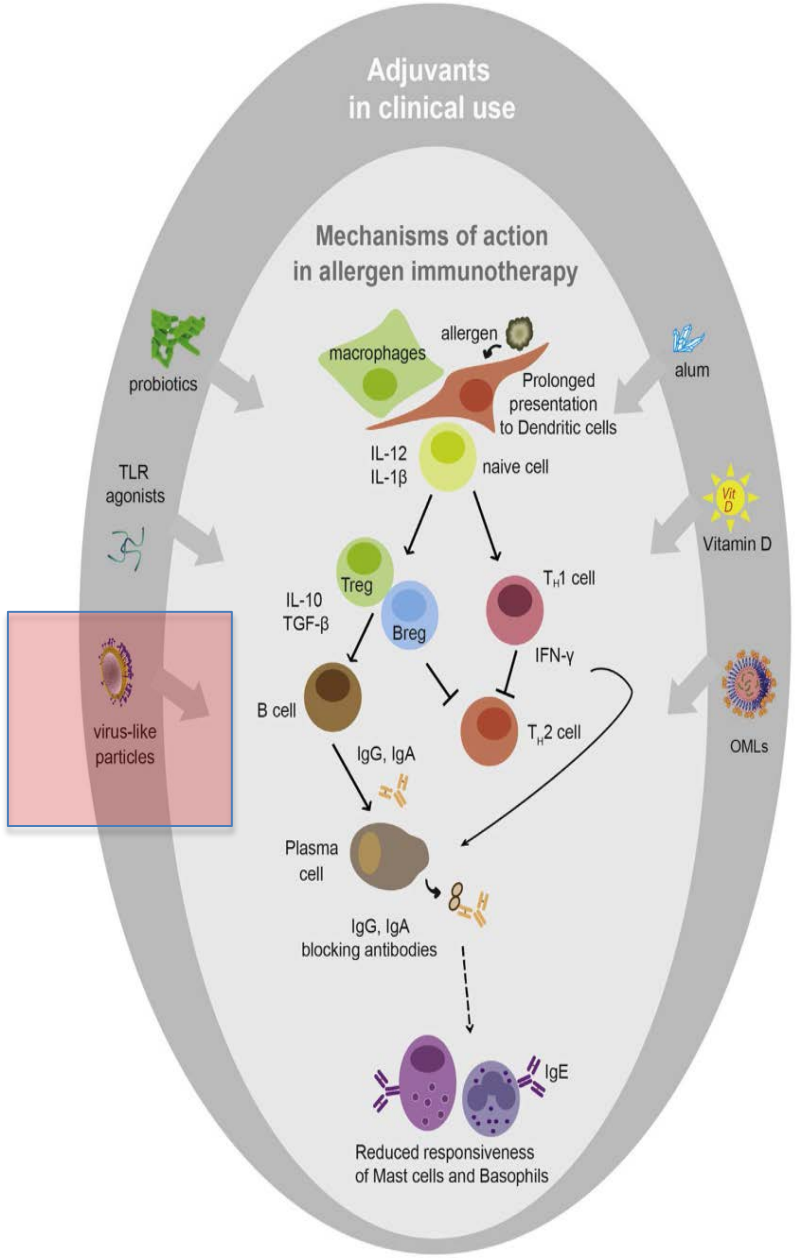
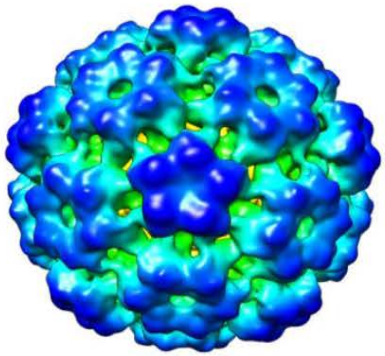
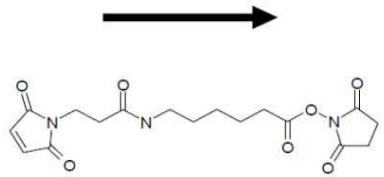


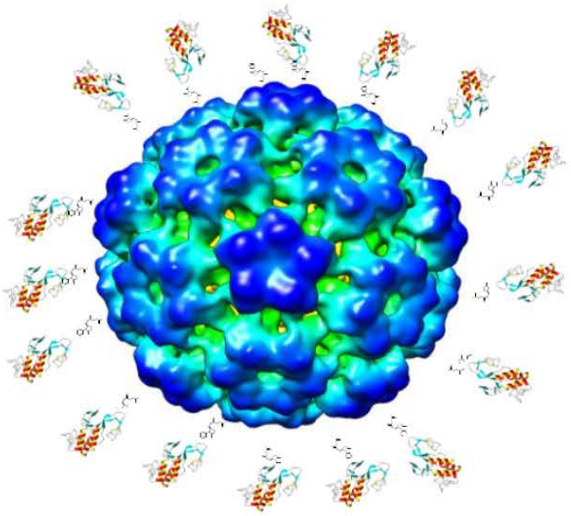
Fig. 2. Immunologic mechanisms of allergen-specific immunotherapy and the immune pontentiators or adjuvants used in clinic.

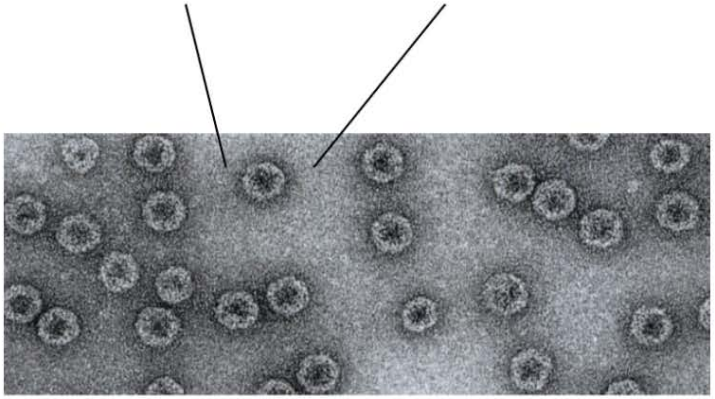
VLPs in allergy indications



allergen







diameter = 30 nm

concept: The allergen looks for the immune system like a virus and consequently induces a strong cellular and humoral immune response antagonizing the Th2 driven allergy = protective immunity.

VLP + allergen = optimized immunotherapy

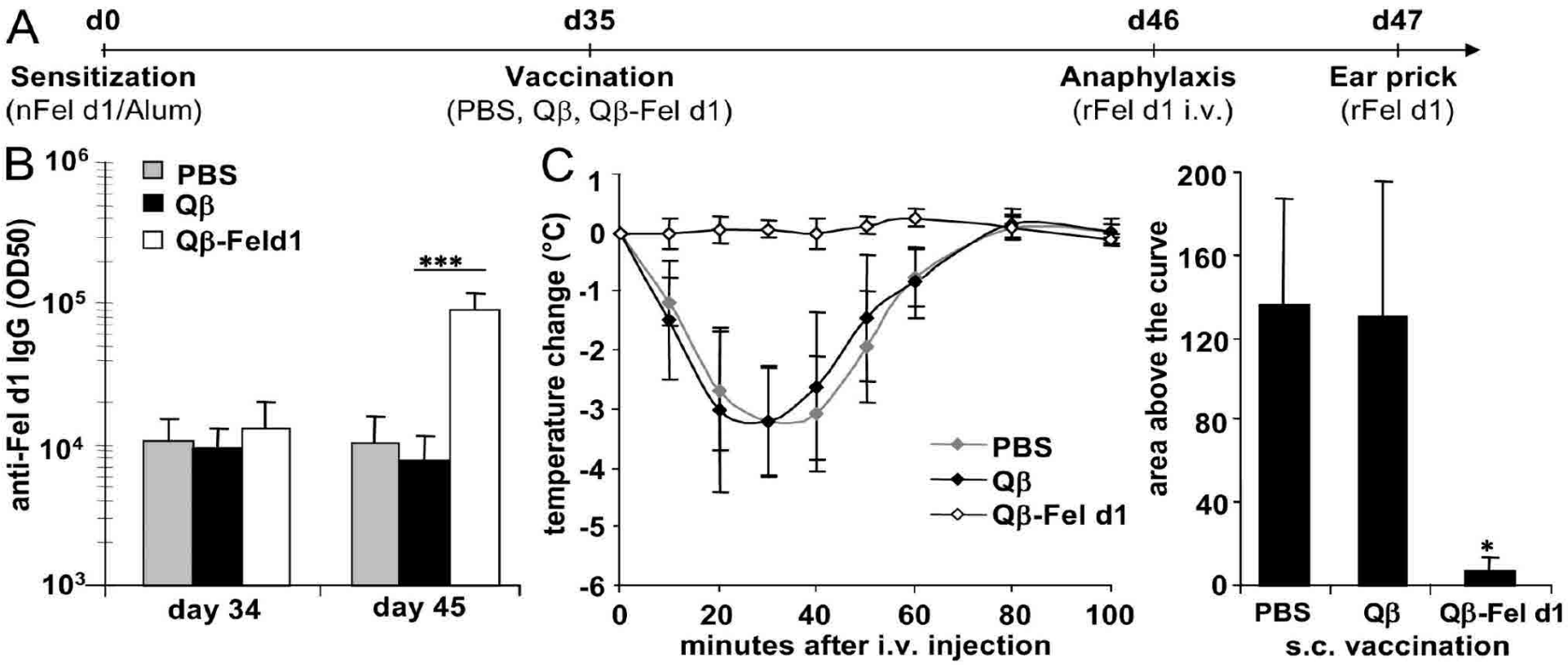
Published August 10, 2009
JEM ARTICLE

Displaying Fel d1 on virus-like particles prevents reactogenicity despite greatly enhanced immunogenicity: a novel therapy for cat allergy

Nicole Schmitz, Klaus Dietmeier, Monika Bauer, Melanie Maudrich, Stefan Utzinger, Simone Muntwiler, Philippe Saudan, and Martin F. Bachmann

Department of Immunodrugs, Cytos Biotechnology AG, 8952 Schlieren-Zürich, Switzerland

VLPs in allergy indications



highly efficacious vaccine: induction of protective immunity with one vaccination only

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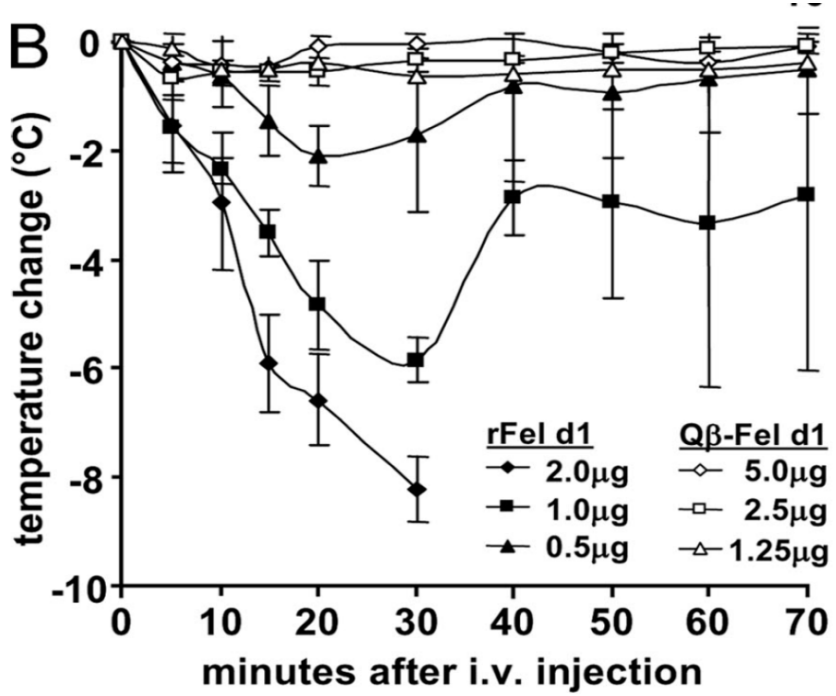
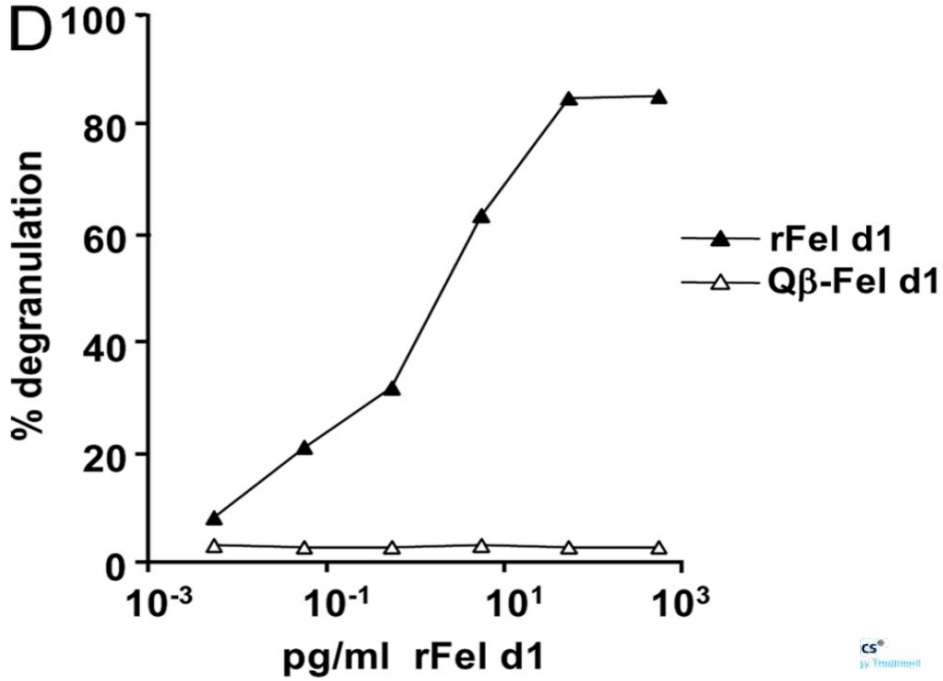
hypoallergenic vaccine:

- no anaphylaxis in allergic animals [B]
- no degranulation of human mast cells [D]





Overview of presentation

PoLyVac

VLP

Peanut allergy: an increasing, significant health problem and growing market around the globe

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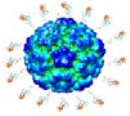
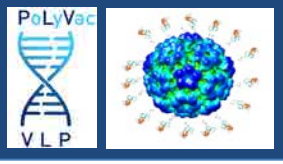


VLP's: an established platform adopted from vaccinology

PolyVac peanut: preclinical results

Allergy Therapeutics®

summary



ATL adopted the novel VLP platform for allergy indications by developing a peanut vaccine aiming for long lasting protective immunity.

This treatment will overcome current limitations of approaches aiming for avoidance or tolerance, and will open the global markets of food allergy for ATL.

acknowledgments

UNIVERSITÄT BERN

RIA Rheumatologie Immunologie Allergologie

IMMUNOLOGY BERN

Allergy Therapeutics®

Allergen Immunotherapy USA 2017 Update

Lawrence DuBuske, MD

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Washington, DC, USA

Distinguished Fellow, Past Speaker of the House of Delegates, and Past Regent,
American College of Allergy, Asthma and Immunology

Treasurer and Past President,
American Association of Certified Allergists

President,
INTERASMA- The Global Asthma Association

Fellow, American College of Physicians

Fellow, Past Chair- Practice Standards Council,
American Academy of Allergy, Asthma and Immunology

Fellow, American College of Chest Physicians

Director,
Immunology Research Institute of New England

Allergic Rhinitis in the USA

- Prevalence
- Economic Strata of Allergic Rhinitis Patients
- Insurance Coverage of Allergic Rhinitis Patients

Allergies- What's the Problem?

- Allergies are the 6th leading cause of chronic illness in the U.S. with an annual cost in excess of $18 billion.
- More than 50 million Americans suffer from allergies each year.
- Allergies are an overreaction of the immune system to substances that generally do not affect other individuals.
- These substances, or allergens, can cause sneezing, coughing, and itching.
- Allergic reactions range from merely bothersome to life-threatening.
- Some allergies are seasonal, like hay fever.
- Allergies have also been associated with chronic conditions like sinusitis and asthma.

https://www.cdc.gov/

Summary Health Statistics: National Health Interview Survey, 2015

U.S. Department of Health and Human Services • Centers for Disease Control and Prevention • National Center for Health Statistics

Allergies and Hay Fever

Morbidity: Adults (aged 18 years and over)

- **Number with diagnosed hay fever in the past 12 months: 20.0 million**
- **Percent with diagnosed hay fever in the past 12 months: 8.2%**

Prevalence of Allergic Rhinitis in the USA: Overall 7.9%

Table A-2a. Age-adjusted percentages (with standard errors) of selected respiratory diseases among adults aged 18 and over, by selected characteristics: United States, 2015

Selected characteristic	Emphysema[1]	Ever had asthma[1]	Still has asthma[1]	Hay fever[1]	Sinusitis[1]	Chronic bronchitis[1]
Total	1.3 (0.08)	12.7 (0.26)	7.6 (0.21)	7.9 (0.21)	11.7 (0.26)	3.6 (0.14)
Sex						
Male	1.5 (0.14)	11.0 (0.37)	5.4 (0.27)	6.3 (0.27)	8.5 (0.32)	2.6 (0.18)
Female	1.1 (0.09)	14.3 (0.37)	9.7 (0.33)	9.4 (0.31)	14.6 (0.40)	4.6 (0.21)
Age (years)						
18–44	0.2 (0.05)	13.5 (0.40)	7.5 (0.32)	5.9 (0.27)	8.8 (0.34)	2.2 (0.17)
45–64	1.7 (0.16)	12.7 (0.42)	8.4 (0.34)	11.1 (0.42)	15.2 (0.48)	4.8 (0.28)
65–74	3.9 (0.39)	11.1 (0.63)	6.9 (0.51)	10.0 (0.61)	16.3 (0.78)	6.0 (0.49)
75 and over	4.6 (0.50)	9.2 (0.60)	6.2 (0.51)	7.3 (0.57)	12.1 (0.73)	5.9 (0.56)

At Least 20 Million Allergic Rhinitis Patients in the USA

Table A-2b. Frequencies (in thousands) of selected respiratory diseases among adults aged 18 and over, by selected characteristics: United States, 2015

Selected characteristic	All adults aged 18 and over	Emphysema[1]	Ever had asthma[1]	Still has asthma[1]	Hay fever[1]	Sinusitis[1]	Chronic bronchitis[1]
Total	242,501	3,515	30,606	18,445	19,976	29,367	9,274
Sex							
Male	116,875	1,892	12,643	6,293	7,704	10,287	3,123
Female	125,625	1,624	17,963	12,151	12,272	19,080	6,152
Age (years)							
18–44	112,760	194	15,266	8,415	6,602	9,947	2,528
45–64	83,239	1,374	10,560	6,951	9,245	12,668	3,982
65–74	27,297	1,074	3,018	1,891	2,723	4,434	1,641
75 and over	19,204	873	1,762	1,188	1,405	2,318	1,123

Economic Status of Allergic Rhinitis Patient in the USA: Greatest Percentage in the Most Wealthy

Table A-2a. Age-adjusted percentages (with standard errors) of selected respiratory diseases among adults aged 18 and over, by selected characteristics: United States, 2015

Selected characteristic	Emphysema[1]	Ever had asthma[1]	Still has asthma[1]	Hay fever[1]	Sinusitis[1]	Chronic bronchitis[1]
Family income[8]						
Less than $35,000	2.5 (0.18)	15.3 (0.48)	10.4 (0.41)	6.7 (0.31)	11.6 (0.41)	5.7 (0.28)
$35,000 or more	1.0 (0.11)	12.0 (0.34)	6.7 (0.25)	8.7 (0.28)	12.1 (0.35)	2.9 (0.17)
$35,000–$49,999	1.3 (0.23)	12.8 (0.74)	7.4 (0.56)	6.4 (0.51)	10.5 (0.64)	3.5 (0.39)
$50,000–$74,999	1.1 (0.23)	11.9 (0.71)	6.5 (0.53)	7.6 (0.51)	12.1 (0.61)	3.5 (0.35)
$75,000–$99,999	0.8 (0.22)	11.0 (0.78)	5.3 (0.54)	7.6 (0.59)	11.6 (0.73)	2.6 (0.37)
$100,000 or more	*0.7 (0.22)	12.2 (0.56)	7.1 (0.45)	11.0 (0.53)	12.8 (0.57)	2.4 (0.31)

Economic Status of Allergic Rhinitis Patient in the USA: Greatest Frequency in the Most Wealthy and Best Insured

Table A-2b. Frequencies (in thousands) of selected respiratory diseases among adults aged 18 and over, by selected characteristics: United States, 2015

Selected characteristic	All adults aged 18 and over	Emphysema[1]	Ever had asthma[1]	Still has asthma[1]	Hay fever[1]	Sinusitis[1]	Chronic bronchitis[1]
Family income[8]							
Less than $35,000	66,342	1,880	9,913	6,780	4,530	8,031	3,958
$35,000 or more	148,656	1,334	17,881	10,040	13,542	18,709	4,345
$35,000–$49,999	25,114	372	3,178	1,853	1,633	2,706	894
$50,000–$74,999	37,018	445	4,400	2,406	2,932	4,655	1,357
$75,000–$99,999	27,607	219	3,095	1,530	2,213	3,358	724
$100,000 or more	58,917	298	7,208	4,251	6,765	7,989	1,370
Poverty status[9]							
Poor	28,022	766	4,428	3,215	1,877	2,986	1,654
Near poor	42,375	982	6,022	3,918	2,807	4,924	2,318
Not poor	159,450	1,586	18,839	10,447	14,506	20,258	4,756
Health insurance coverage[10]							
Under 65:							
Private	135,220	541	16,975	9,551	11,901	16,235	3,470
Medicaid	25,313	636	4,685	3,416	1,731	2,600	1,732
Other coverage	9,086	263	1,376	970	990	1,647	672
Uninsured	24,896	*114	2,620	1,307	1,184	2,092	629

Dramatic Change in Treatment of Allergic Rhinitis

- Shift from Physician Prescribed to Over The Counter Status of Allergy Medications in the USA
- Advent of Over The Counter Second Generation Antihistamines- 2003 to Present
- Movement of Intra-Nasal Corticosteroids to OTC status- 2013 to Present

Treatment of Allergic Rhinitis in the USA- Change from Prescription to Over The Counter Medications: Begins with Claritin

CLARITIN TO SELL OVER THE COUNTER

By MELODY PETERSEN NOV. 28, 2002

Federal regulators yesterday approved the nation's top-selling allergy drug, Claritin, as an over-the-counter medicine, a decision that will bring substantial savings for the uninsured and allow all patients to obtain the drug without a trip to the doctor.

The decision will raise costs for many allergy patients with insurance, however, because insurers will no longer cover most of the cost of Claritin.

Insured patients may also now pay more for other allergy medicines because some insurers say they plan to require copayments as high as $50 for the remaining prescription antihistamines -- Clarinex, Allegra and Zyrtec -- to prompt patients to take Claritin instead.

http://www.nytimes.com/2002/11/28/business/claritin-to-sell-over-the-counter.html

And One by One the Other 2nd Generation Antihistamines go OTC

From the WebMD Archives

Nov. 19, 2007 -- The FDA has approved over-the-counter sales of the allergy drug Zyrtec, according to McNeil Consumer Healthcare, which sells nonprescription Zyrtec.

Allegra Going Over-The-Counter

In March 2011, Allegra (fexofenadine) became non-prescription. An antihistamine, it treats runny nose, itchy nose/eyes and sneezing. All forms of Allegra are now over-the-counter, including Children's Allegra, Allegra-D 12 hour and Allegra-D 24 hour. Allegra-D also contains pseudoephedrine, which is effective for stuffy nose, sinus pressure and headache.

Xyzal OTC to be available March 2017

Xyzal OTC will soon be available without a prescription March 2017. In a growing trend in the allergy pharmaceutical market, most prescription medications are now becoming over the counter. Xyzal (generic brand name is levoceterizine) received FDA approval earlier this month for treatment for the relief of symptoms of seasonal and year round allergies.

Intra-Nasal Corticosteroids go OTC- Begins with Nasacort

February 04, 2014

OTC Nasacort Allergy 24hr Nasal Spray Now Available

OTC Nasacort Allergy 24hr Nasal Spray Now Available

Sanofi and its consumer healthcare division Chattem announced that Nasacort (triamcinolone acetonide) Allergy 24hr Nasal Spray is now available over-the-counter (OTC). Nasacort is used to relieve a range of seasonal and year-round nasal allergy symptoms, including nasal congestion, in adults and children ≥2 years of age.

Triamcinolone acetonide is a corticosteroid that has been shown to have a wide range of actions on multiple cell types and mediators involved in inflammation.

Nasacort was approved for the switch from prescription to OTC by the FDA on October 11, 2013.

It is now available in stores nationwide at the same strength of 55mcg/spray as the prescription Nasacort spray in 60- and 120-metered dose sprays

Intra-Nasal Corticosteroids go OTC- Conitnues with Flonase

Allergy & Immunology

Flonase Goes OTC

The FDA has approved over-the-counter sales for Flonase (fluticasone propionate), the nasal spray for allergies, its manufacturer said.

by John Gever, *Managing Editor, MedPage Today* July 24, 2014

The FDA has approved over-the-counter sales for Flonase (fluticasone propionate), the nasal spray for allergies, its manufacturer said.

GlaxoSmithKline, which sells Flonase Allergy Relief, said it expected to have the OTC version available for retail sale in early 2015. The dosage will be the same as in the current prescription product, the company said in a press release on Thursday. It uses a metered spray system to deliver 50 mcg of active drug per actuation.

The OTC product's label will indicate that it provides temporary relief of major nasal and eye-related allergy symptoms, including runny nose, sneezing, nasal congestion, and watery and itchy eyes, according to GlaxoSmithKline.

Intra-Nasal Corticosteroids go OTC- Then Rhinocort and Veramyst

Pharmacy Times — Practical Information for Today's Pharmacist

Rhinocort Allergy Spray Now Available OTC

FEBRUARY 17, 2016

Krystle Vermes

Rhinocort Aqua Nasal Spray with budesonide is now available OTC at all major pharmacies and retailers.

Rhinocort is designed to provide 24-hour relief from allergy symptoms, such as sneezing, runny nose, and congestion.

"For consumers who are suffering from nasal allergy symptoms, Rhinocort Allergy Spray works all day and all night to relieve their most frustrating nasal allergy symptoms of nasal congestion, sneezing, and itchy and runny nose," said Purvi Farahi, group brand director of Allergy at McNeil Consumer Healthcare, in a press release. "Rhinocort Allergy Spray expands our allergy product offerings and gives these allergy sufferers a new tool in their toolkit.

FDA Approves FLONASE® Sensimist™ Allergy Relief

02 August 2016

WARREN, N.J.

Another Rx-to-OTC Switch from GSK Consumer Healthcare to help allergy sufferers find more complete relief[1]

GSK Consumer Healthcare announced today that the U.S. Food and Drug Administration (FDA) has approved FLONASE® Sensimist™ Allergy Relief (fluticasone furoate, 27.5 mcg spray) as an over-the-counter (OTC) treatment for symptoms associated with seasonal and perennial allergies. Previously available by prescription as Veramyst®, FLONASE Sensimist is the latest Rx-to-OTC switch from GSK.

Current Status of Allergic Rhinitis Patients in the USA

- Seek Physician Care due to Failure of OTC Antihistamines and OTC Intranasal Corticosteroids
- Primary Care Physicians have little to offer- just generic versions of the OTC antihistamines and OTC Intranasal Corticosteroids
- Insurances gradually cease coverage of oral antihistamines (first)– then later…
- Insurances limit or cease coverage of intranasal corticosteroids

Limitations Placed on Insurance Coverage for Allergic Rhinitis Medications

BlueCross BlueShield
Federal Employee Program

MANAGED NOT COVERED DRUG LIST BASIC OPTION CHART

These listed drugs are not covered under Basic Option. If you use any of these Managed Not Covered Drugs, you will need to pay the full cost of the drug(s).

If you are using one of these non-covered drugs, ask your doctor for one of the covered generic or brand name options.

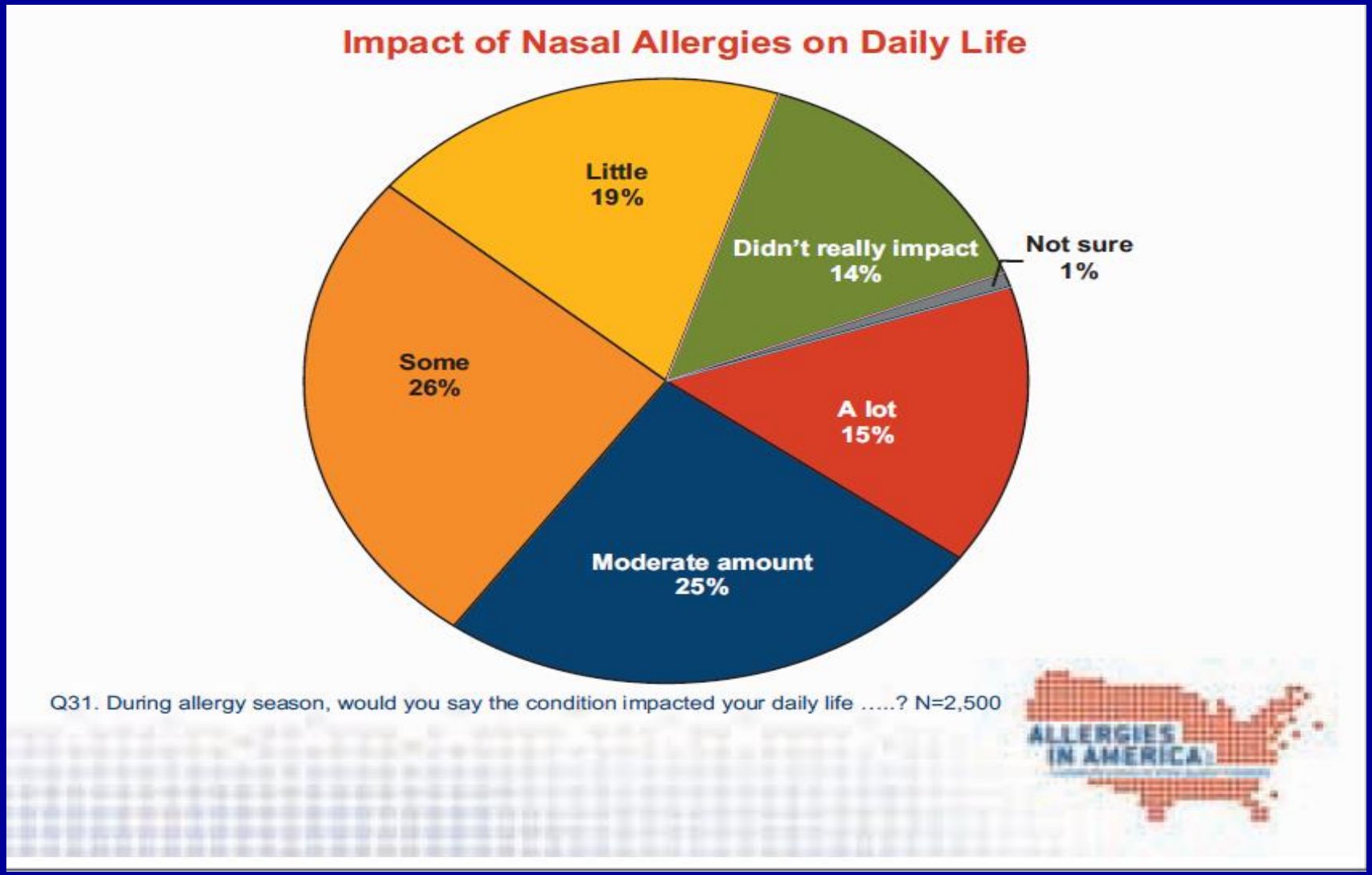
CATEGORY* DRUG CLASS	DRUGS NOT COVERED IN 2017 FOR BASIC OPTION	COVERED OPTIONS**
ALLERGIES NASAL STEROIDS	BECONASE AQ, DYMISTA, NASACORT AQ, NASONEX, OMNARIS, QNASL, RHINOCORT AQUA, VERAMYST, ZETONNA	budesonide spray, flunisolide spray, fluticasone spray, triamcinolone spray
ALLERGIES LESS SEDATING ANTIHISTAMINES	cetirizine solution, desloratadine, levocetirizine, CLARINEX, CLARINEX-D, XYZAL	montelukast, zafirlukast, ACCOLATE, SINGULAIR

Allergies in America Survey

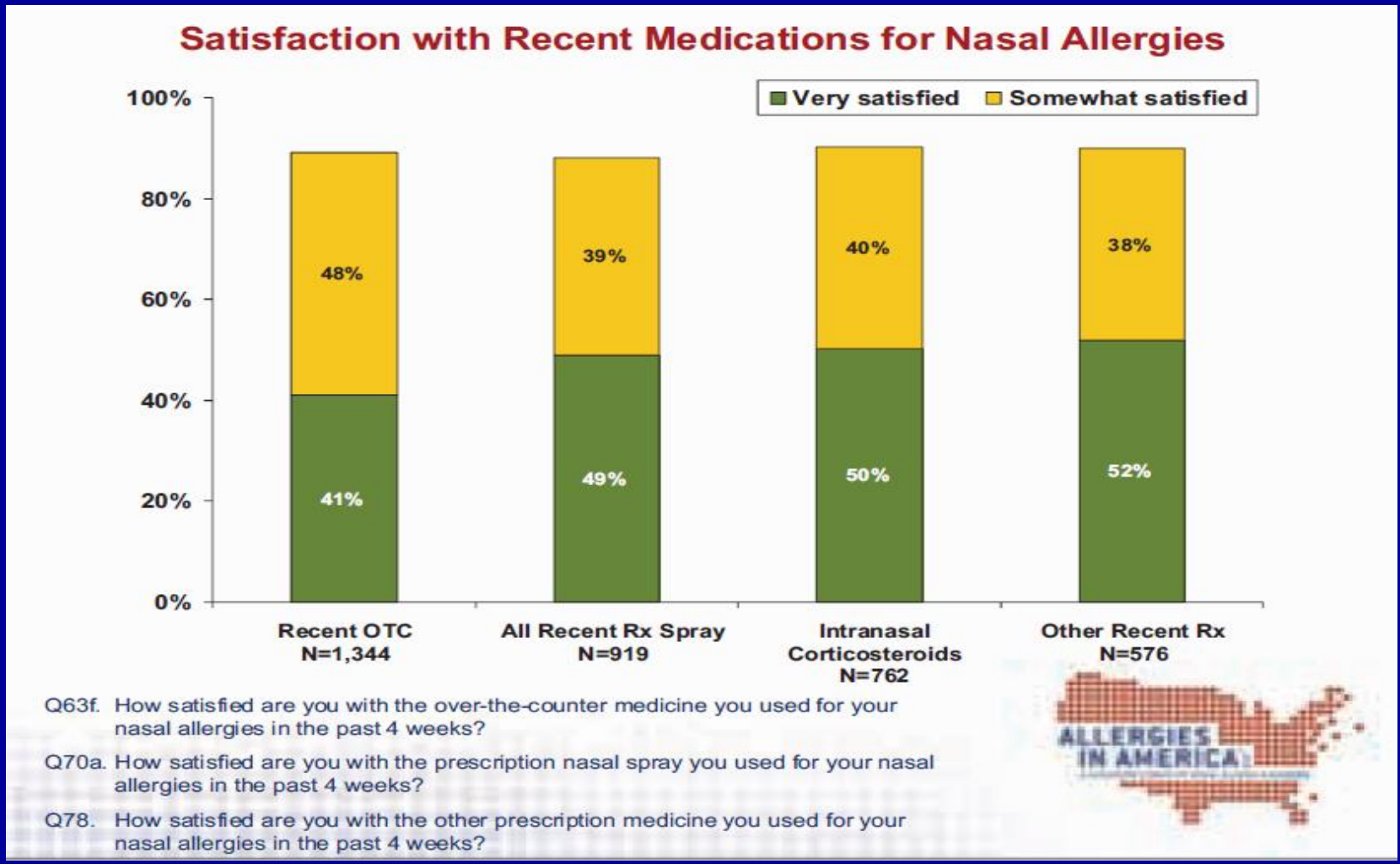
Overview

Allergies in America: A Landmark Survey of Nasal Allergy Sufferers is the largest and most comprehensive national survey of patient and health provider perspectives concerning allergic rhinitis, more commonly known as nasal allergies or "hay fever." A national probability sample of 2,500 adults, aged 18 and older, who had been diagnosed with allergic rhinitis, nasal allergies or "hay fever", and who had nasal allergy symptoms or had taken prescription medicine for allergies in the past 12 months, were interviewed by telephone about their condition and treatment. This national sample of patients with nasal allergies was obtained by systematically screening a national sample of 31,470 households in the United States to identify nasal allergy sufferers. Individual screening was conducted with a randomly selected patient (if more than one) in the household to confirm that they had been diagnosed with nasal allergies and suffered from them or been treated for them in the past 12 months. A parallel survey was conducted among 400 healthcare practitioners, including a national sample of 300 doctors in direct patient care in outpatient settings --- including 100 in Adult Primary Care specialties, 100 in Allergy, and 100 in Otolaryngology, as well as 50 Nurse Practitioners and 50 Physician Assistants --- were interviewed as part of the survey **(Figure 1).**

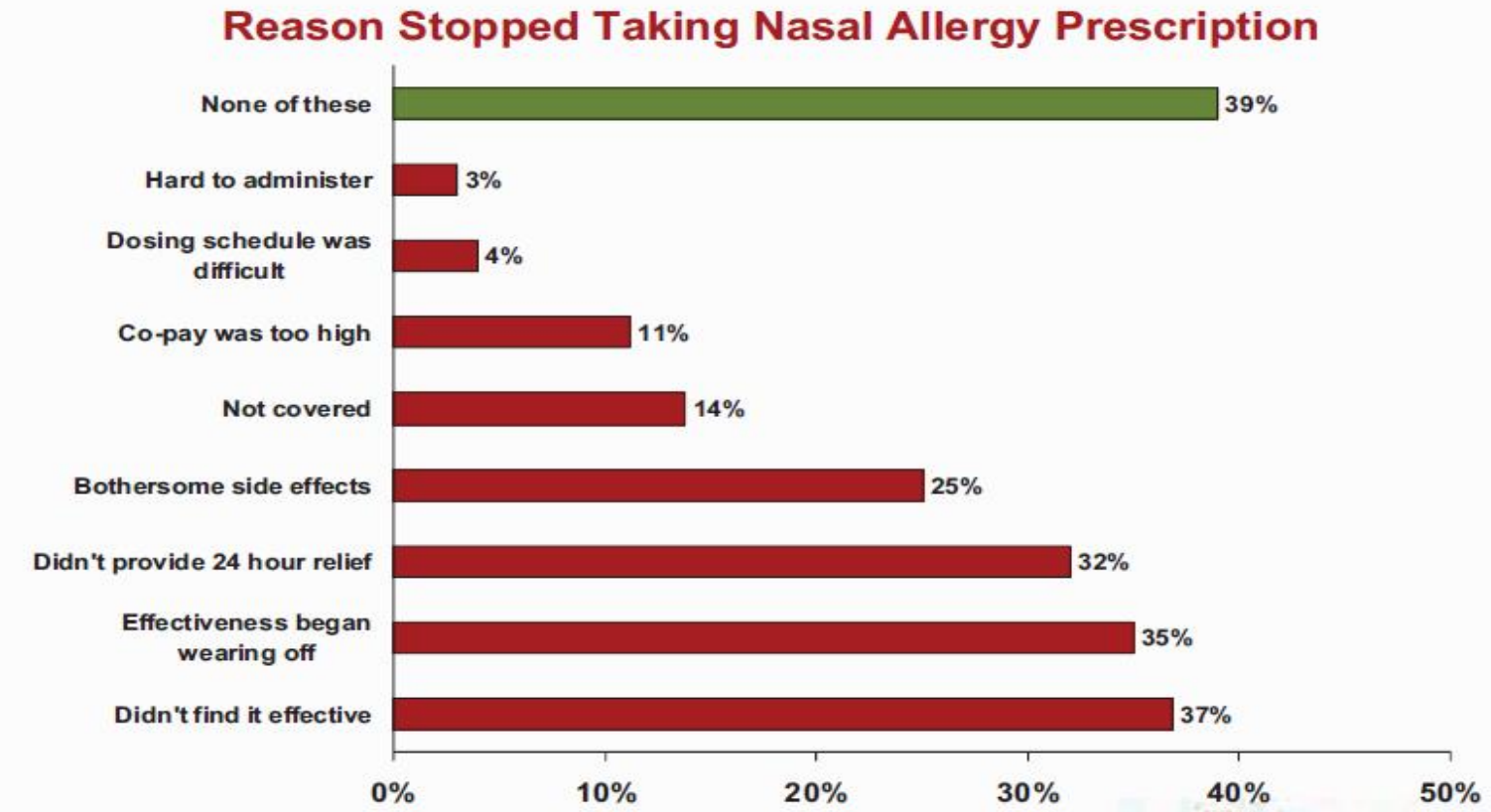
Impact of Allergic Rhinitis on Daily Life



Satisfaction with Nasal Allergy Medications



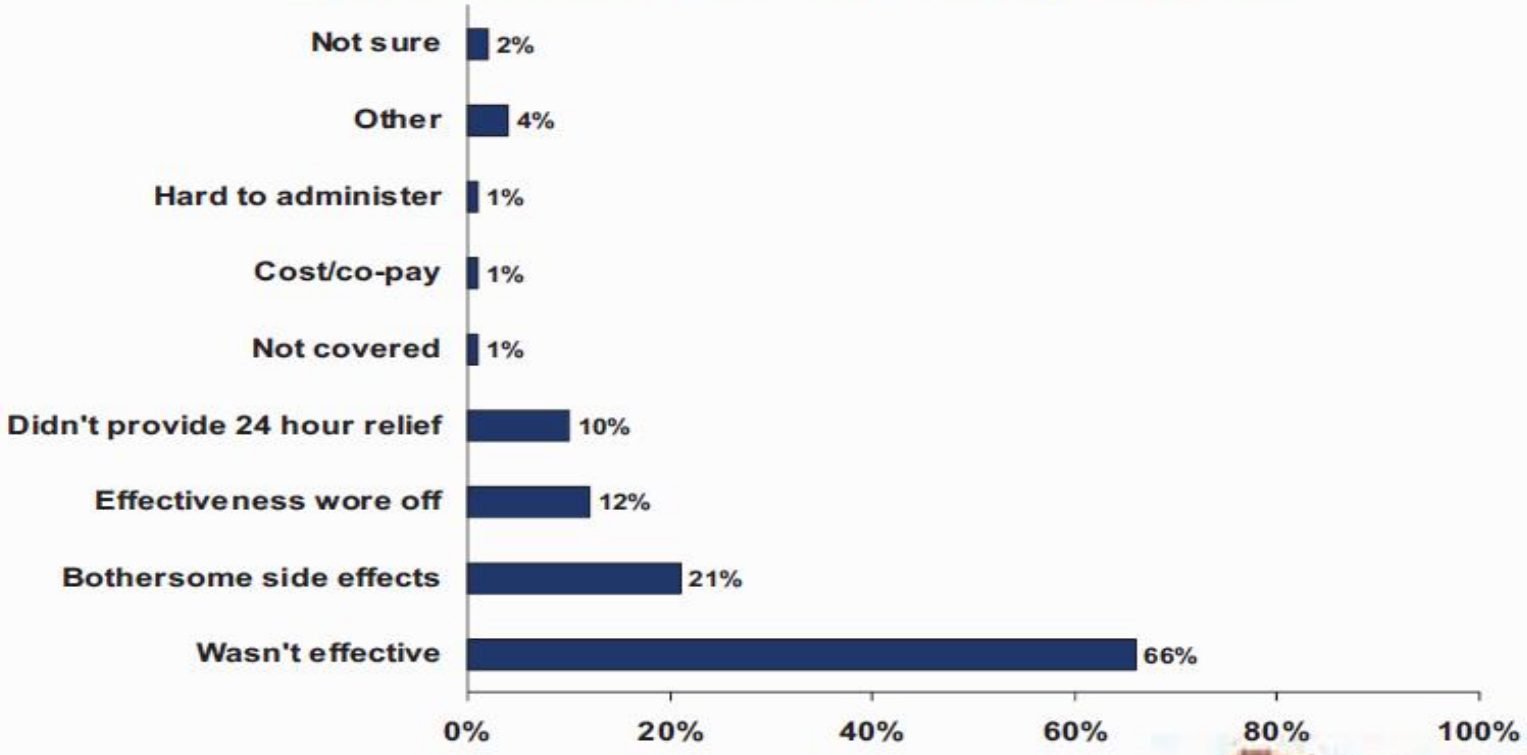
Reasons for Allergic Rhinitis Medication Discontinuation



Q94. Have you ever stopped taking a nasal allergy medicine prescribed by your doctor because …? N=2,500

ALLERGIES IN AMERICA

Dissatisfaction with Nasal Allergy Medications



The New Allergic Rhinitis Patient Referred to the Allergist

- Tried Self Medication with Over the Counter Antihistamines and Intranasal Corticosteroids
- Fail Self Medication trials then consult Primary Care Providers who prescribe the limited generic medications which are still covered by health insurances
- Referred to Allergist by Primary Care Physician due to failure of these limited medications still covered by health insurance
- Typical Referral to Allergist: for “Allergy Testing and Shots”

Allergen Immunotherapy in the United States

- Approximately 2 to 3 million Americans have received some form of allergen immunotherapy
- Approximately 100,000 to 200,000 new starts on allergen immunotherapy annually in the US
- Typical course is 3 to 5 years
- Weekly up-dosing ranges from 20 to 50 weeks in various protocols followed by bi-weekly then monthly injections
- Injections occur in health care facilities capable of treating anaphylaxis

Administration of Allergen Immunotherapy in the United States

- Three years of SCIT provides lasting benefit that can be measured at least 2 years and up to 6 years after stopping SIT. *Durham SR et al. NEJM 341: 468, 1999.*

- One year of SCIT has been shown not to provide lasting benefit. *Naclerio RM et al JACI 100: 293, 1997.*

- Two years of SCIT has been shown not to provide lasting benefit in year 3 after stopped *Scadding et al; Cox et al; JAMA, Feb 14, 2017*

- Recommendation: SIT should be administered for a minimum of 3 years after which time the treatment should be reevaluated- US Practice is 3-5 years at maintenance SCIT

Allergen Immunotherapy as Practiced by American Allergists

- Tests done for Inhalant Allergens- ie. At George Washington University we do skin prick tests for 48 inhalant allergens- tree pollens/ grass pollens/ weed pollens/ mold spores/ dust mites/ animal danders/ cockroach

- Immunotherapy vials compounded in the allergist office by trained personnel using commercial stock concentrates

Allergen Immunotherapy as Practiced by American Allergists

- Some allergists construct separate vials for each pollen/ danders/molds and dust mites-cockroach

- Some allergists use a 2 vial system:

- Vial A: tree-grass and weed pollens + animal dander
- Vial B: mold spores + dust mites + cockroach dander

Allergen Immunotherapy as Practiced by American Allergists

1) Vials are constructed from the Master Stock Vial- typically a 1:1 dilution, Total 10 ml volume
2) Vial dilutions can include 1:1; 1:10; 1:100; 1:1,000; and 1:10,000; with sometimes 1:100,000 and 1:1,000,000 used for a highly sensitized patient
3) Each diluted vial can be constructed as a 10 ml vial

Allergen Immunotherapy as Practiced by American Allergists

4) Injections begin with the most dilute vial and typically have 5 to10 incremental steps ie. beginning with 0.05 ml ending with 0.5 ml

5) If using 4 dilutions and 5 incremental steps will reach the maintenance vial in 20 weeks

6) If using 6 dilutions and 10 incremental steps will reach the maintenance vial in 60 weeks

7) All vials typically billed to insurance at $400- $600/vial

8) Injections compensated at $10 to $30 each visit depending on whether 1 injection versus 2 or more injections

George Washington University Medical Faculty Associates: SIT Schedule- 40+ steps to final maintenance concentration

MEDICAL FACULTY ASSOCIATES
Allergy & Sinus Center
2150 Pennsylvania Avenue, NW, G-400
Washington, DC 20037

TEL: (202) 741-2770/2771
FAX: (202) 741-2775

PATIENT NAME: _____ **INJECTION SITE:** _____

DOSAGE SCHEDULE: Injections should be administered every 3 – 10 days when building back up to maintenance dose. ONCE A NEW PATIENT HAS REACHED MAINTENANCE LEVEL, THEY SHOULD RECEIVE AN INJECTION ONCE A WEEK FOR TWO (2) VISITS, THEN ONCE EVERY TWO (2) WEEKS FOR TWO (2) VISITS, THEN THE PATIENT MAY ADVANCE TO A 7 – 21 DAY SCHEDULE PROVIDED THERE ARE NO ADVERSE REACTIONS. NOTE: ADJUSTMENTS MAY BE NECESSARY DUE TO PATIENT NON-COMPLIANCE/REACTIONS. Please refer to instruction sheet for adjustment instructions.

VIAL: _____	VIAL: _____	VIAL: _____	VIAL: _____	VIAL: _____	VIAL: _____	
0.05ml	0.05ml	0.05ml	0.05ml	0.05ml	0.10ml	0.35ml
0.10ml	0.10ml	0.10ml	0.10ml	0.10ml	0.15ml	0.40 ml
0.20ml	0.20ml	0.20ml	0.20ml	0.15ml	0.20ml	0.45ml
0.30ml	0.30ml	0.30ml	0.30ml	0.20ml	0.25ml	0.50ml (**)
0.40ml	0.40ml	0.40ml	0.40ml	0.25ml	0.30ml	MAINTENANCE
0.50ml	0.50ml	0.50ml	0.50ml	0.30ml		
(TO NEXT VIAL)	(TO NEXT VIAL)	(TO NEXT VIAL)	(TO NEXT VIAL)	(TO NEXT VIAL)		

** ADVISE PATIENT TO SCHEDULE OFFICE VISIT AFTER REACHING MAINTENANCE DOSE.

Date	Time	Dose	Vial # & Strength	*EPI Rinse	Cream	Initial	Time Checked	Reaction/Comments	Initial

*SEE EPI RINSE PROTOCOL

Diane Murphy, RN_____
Sandra Chacon, Allergy Specialist_____

Harnell Casmore, RMA_____
Devona Jackson, RMA_____

Created 6/2011, dmRN

George Washington University Medical Faculty Associates: SIT Vaccine Composition- Vial A

MEDICAL FACULTY ASSOCIATES
Allergy & Sinus Center
2150 Pennsylvania Avenue NW, G-400
Washington, D.C. 20037

IMMUNOTHERAPY PRESCRIPTION

VIAL: A

Patient Name:
Date of Birth:
Date:
MRN:

Daniel Ein, M.D.
Richard Nicklas, M.D.
Janine VanLancker, M.D.

Extract (stock strength) A/G (Manufacturer)	Rx Strength	&	Rx Volume
TREES			
☐ Ein Pollen Mix (40,000 pnu) Gly. (G)			
☐ Eastern 8 Tree Mix (1:20 w/v) Aq. (G)			
☐ Poplar (1:20 w/v or 56,900 pnu) Gly. (H-S)			
☐ Maple (1:20 w/v or 15,000 pnu) Aq. (G)			
☐ Oak (1:20 w/v or 25,500 pnu) Aq. (H-S)			
☐ Hickory (1:20 w/v or 24,500 pnu) Aq. (G)			
☐ Elm (1:10 w/v or 40,000 pnu) Aq. (H-S)			
☐ Birch (1:20 w/v or 12,500 pnu) Gly. (H-S)			
☐ Beech (1:20 w/v or 5,500 pnu) Gly. (H-S)			
☐ Ash (1:20 w/v or 102,500 pnu) Gly. (H-S)			
☐ Special Pollen Mix (33,000 pnu) Aq (G)			
☐ Cedar (1:20 w/v or 5,700 pnu) Gly. (H-S)			
☐ Walnut (1:20 w/v or 16,500 pnu) Aq. (H-S)			
☐ Sweet Gum (1:20 w/v or 9,500 pnu) Aq. (H-S)			
☐ Mulberry (1:10 w/v or 58,000 pnu) Gly. (H-S)			
☐ Sycamore (1:20 w/v or 23,500 pnu) Aq. (H-S)			
☐ Privet (1:20 w/v or 15,000 pnu) Gly. (H-S)			
☐ Nicklas Tree Mix (1:20 w/v or 40,000 pnu) (ALK)			
GRASSES			
☐ TBJ Grass Mix (40,000 pnu) Gly. (H-S)			
☐ Southern Grass Mix (40,000 pnu) Gly. (H-S)			
☐ Timothy (100,000 bau) Gly. (H-S)			
☐ Bermuda (10,000 bau) Gly. (H-S)			
☐ Johnson (1:20 w/v or 39,800 bau) Aq. (H-S)			
☐ Perennial Rye (10,000 bau) Gly. (G)			
☐ Bahia (1:20 w/v or 31,000 pnu) Gly. (H-S)			
☐ Sweet Vernal (10,000 bau) Gly (H-S)			
☐ Orchard (100,000 bau) Gly (H-S)			
☐ Kentucky Blue (100,000 bau) Gly (H-S)			
☐ GWU Grass Mix (10,000 pnu) (ALK)			
WEEDS			
☐ Dock/Sorrel (20,000 pnu) Aq. (H-S)			
☐ Pigweed (1:20 w/v or 29,500 pnu) Aq. (H-S)			
☐ Lambs Quarters (1:20 w/v or 35,000 pnu) Aq. (H-S)			
☐ Cocklebur (35,000 pnu) Aq. (H-S)			
☐ English Plantain (40,000 pnu) Aq. (H-S)			
☐ Ragweed (20,000 au) Gly. (H-S)			
☐ Weed Mix 2630 (40,000 pnu) Gly. (H-S)			
☐ Nicklas Weed Mix (1:20 w/v or 32,000 pnu) Gly. (ALK)			
OTHER			
☐ Feather (1:10 w/v or 1,000 pnu) Gly. (H-S)			
☐ Dog (1:10 w/v or 2,500 pnu) Gly. (H-S)			
☐ Cat (10,000 bau) Gly (H-S)			
☐ **H.S.A. SALINE**			

Physician's Signature:

BAU = Bioequivalent Allergy Unit
AU = Allergy Unit PNU = Protein Nitrogen Unit
W/V = Weight per Volume Ratio
Gly = 50% Glycerinated Aq = Aqueous

Manufacturer's Name Abbreviations:
G = Greer A = Alk Abello
H-S = Hollister-Stier

Updated 10-16-09

George Washington University Medical Faculty Associates: SIT Vaccine Composition- Vial B

MEDICAL FACULTY ASSOCIATES
Allergy & Sinus Center
2150 Pennsylvania Avenue NW, G-400
Washington, D.C. 20037

IMMUNOTHERAPY PRESCRIPTION

VIAL: B

Patient Name:
Date of Birth:
Date:
MRN:

Daniel Ein, M.D.
Richard Nicklas, M.D.
Janine VanLancker, M.D.

Extract (stock strength) A/G (Manufacturer)	Rx Strength & Rx Volume
MOLDS	
☐ Mold Mix A (40,000 pnu) Gly. (H-S)	
☐ Mold Mix B (40,000 pnu) Aq. (H-S)	
☐ Rhizopus (1:10 w/v or 8,800 pnu) Aq. (H-S)	
☐ Helminthosporium (1:10 w/v or 91,500) Aq. (H-S)	
☐ Pullararia (40,000 pnu) Aq. (H-S)	
☐ Penicillium (1:10 w/v or 41,000 pnu) Gly. (H-S)	
☐ Aspergillis (1:10 w/v or 18,500 pnu) Gly. (H-S)	
☐ Hormodendrum (1:10 w/v or 59,100 pnu) Aq. (H-S)	
☐ Alternaria (1:10 w/v or 27,000 pnu) Aq. (H-S)	
☐ Epicoccum (1:40 w/v or 20,000 pnu) (G)	
☐ Geotricum (1:20 w/v or 20,000 pnu) (G)	
☐ Mucor (1:20 w/v or 47,500 pnu) (G)	
☐ Phoma (1:40 w/v or 6,500 pnu) (G)	
☐ Stemphyllium (1:40 w/v or 30,000 pnu) (G)	
☐ Nicklas Mold Mix (1:10 w/v or 20,000 pnu) (ALK)	
OTHER	
☐ House Dust (20,000 pnu) Aq. (H-S)	
☐ Dust Mite Mix (10,000 au) Gly. (G)	
☐ Dust Mite P (10,000 au) Gly. (G)	
☐ Dust Mite F (10,000 au) Gly. (G)	
☐ Cockroach (1:10 w/v or 92,000 pnu) Aq. (H-S)	
☐ H.S.A. SALINE	

Physician's Signature:

BAU = Bioequivalent Allergy Unit
AU = Allergy Unit
PNU = Protein Nitrogen Unit
W/V = Weight per Volume Ratio
Gly = 50% Glycerinated Aq = Aqueous

Manufacturer's Abbreviations:
G = Greer A = Alk Abello
H-S = Hollister- Steir

Updated 8-23-10

GWU: New Rosch System

GWU: Immunotherapy Compounded Vaccine Production

GWU "Rosch System" In-Office Allergen Vaccine Compounding: Bottle A

Formulary Report

Account: 38[illegible]
Birthday: 12/[illegible]

Patient: [illegible]

GW Medical Faculty Associates
2300 M Street NW, Suite 200
Washington DC 20037 (202)
741-2771

Account: 3881506
Birthday: 12/23/1976

Extract: A - T, G, W, D, C

Current Treatment Plan: 7 Vial Set
Current Schedule: Dubuske - Build-up
Current Frequency: 3-10 days

Initial Vial Concentration: 1:1,000,000 w/v
Max Concentration: 1:1 w/v
Max Dose: 0.50

Antigen	Concentration	Volume
Poplar	1:20 w/v	0.25
Maple	1:20 w/v	0.2
Oak	1:20 w/v	0.25
Hickory	1:20 w/v	0.25
Elm	1:10 w/v	0.25
Birch	1:20 w/v	0.25
Beech	1:20 w/v	0.25
Ash	1:20 w/v	0.2
Cedar	1:20 w/v	0.2
Walnut	1:20 w/v	0.2
Mulberry	1:10 w/v	0.2
Timothy	100,000 bau	1.5
Bermuda	10,000 bau	0.25
Johnson	1:20 w/v	0.25
Perennial Rye	10,000 bau	0.15
Bahia	1:20 w/v	0.15
Orchard	100,000 bau	0.1
Kentucky Blue	100,000 bau	0.1
Dock/Sorrel	20,000 pnu	0.1
Pigweed	1:20 w/v	0.1
Lambs Quarter	1:20 w/v	0.15
English Plantain	40,000 pnu	0.15
Ragweed Mix	20,000 pnu	2
Dog	1:10 w/v	0.75
Cat	10,000 bau	1.75
Diluent		0
		10

Formulary Change History

2/20/2017 2:16:15PM chacons Created New Formulary

GWU "Rosch System" In-Office Allergen Vaccine Compounding: Bottle B

Formulary Report

Account: 3
Birthday: 1

GW Medical Faculty Associates
2300 M Street NW, Suite 200
Washington DC 20037 (202)
741-2771

Patient

Account: 3881506
Birthday: 12/23/1976

Extract: B-Mold,DmP,DmF,Cr

Current Treatment Plan: 7 Vial Set
Current Schedule: Dubuske - Build-up
Current Frequency: 3-10 days

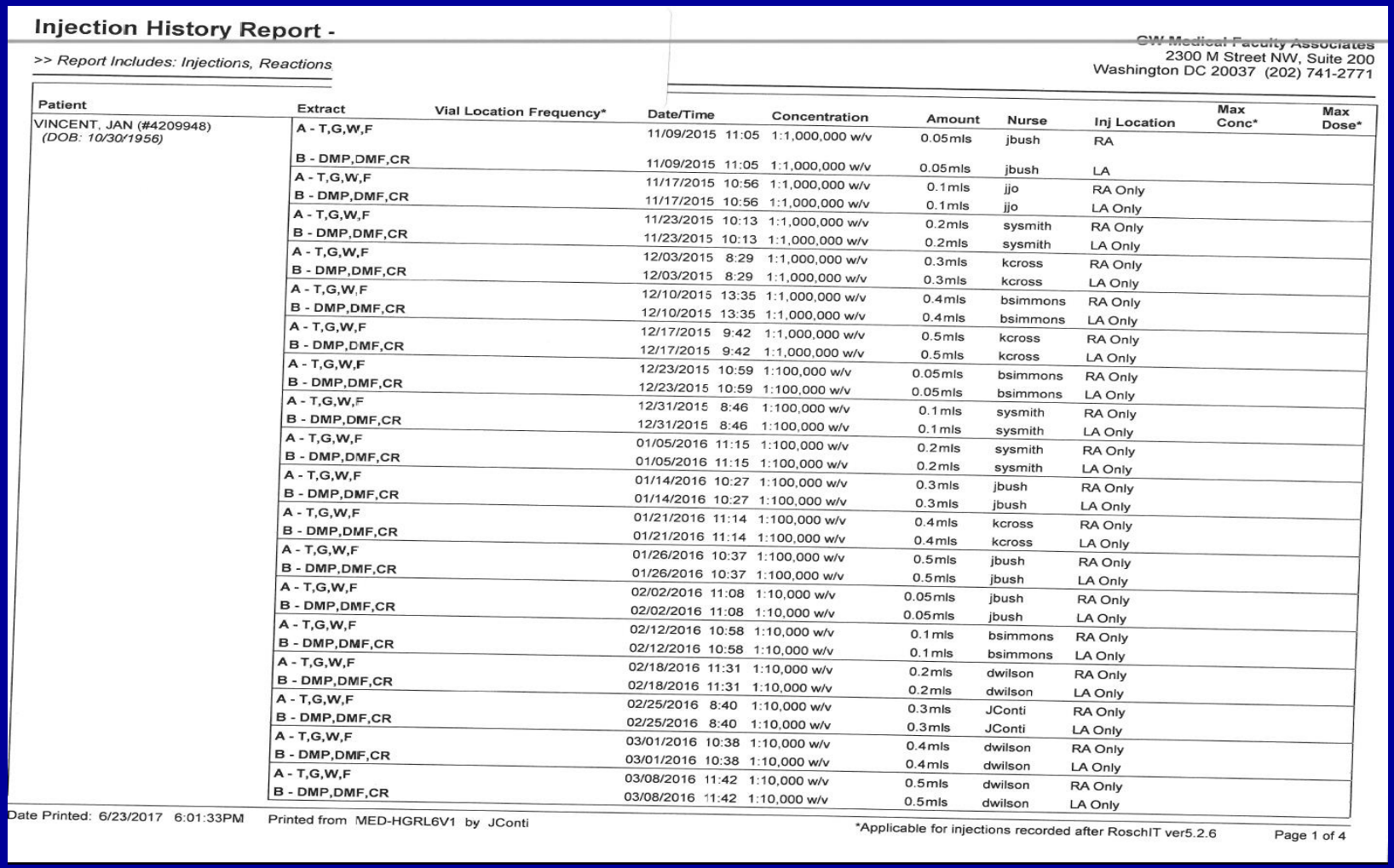
Initial Vial Concentration: 1:1,000,000 w/v
Max Concentration: 1:1 w/v
Max Dose: 0.50

Antigen	Concentration	Volume
Rhizopus	1:10 w/v	0.5
Helminthosporium	1:10 w/v	0.5
Pullararia	40,000 pnu	0.5
Penicillium	1:10 w/v	0.5
Aspergillis	1:10 w/v	0.5
Hormodendrum	1:10 w/v	0.5
Alternaria	1:10 w/v	0.5
Epicoccum	1:40 w/v	0.5
Mucor	1:20 w/v	0.5
Dust Mite Pteronyssinus	10,000 au	2.25
Dust Mite Farinae	10,000 au	2.25
Cockroach	1:10 w/v	1
Diluent		0
		10

Formulary Change History

2/20/2017 2:16:15PM chacons Created New Formulary

7 Dilution System- 46 weeks until Maintenance Final Concentration



Injection History Report -

>> Report Includes: Injections, Reactions

GW Medical Faculty Associates
2300 M Street NW, Suite 200
Washington DC 20037 (202) 741-2771

Patient	Extract	Vial Location Frequency*	Date/Time	Concentration	Amount	Nurse	Inj Location	Max Conc*	Max Dose*
VINCENT, JAN (#4209948) (DOB: 10/30/1956)	A - T,G,W,F		11/09/2015 11:05	1:1,000,000 w/v	0.05mls	jbush	RA		
	B - DMP,DMF,CR		11/09/2015 11:05	1:1,000,000 w/v	0.05mls	jbush	LA		
	A - T,G,W,F		11/17/2015 10:56	1:1,000,000 w/v	0.1mls	jjo	RA Only		
	B - DMP,DMF,CR		11/17/2015 10:56	1:1,000,000 w/v	0.1mls	jjo	LA Only		
	A - T,G,W,F		11/23/2015 10:13	1:1,000,000 w/v	0.2mls	sysmith	RA Only		
	B - DMP,DMF,CR		11/23/2015 10:13	1:1,000,000 w/v	0.2mls	sysmith	LA Only		
	A - T,G,W,F		12/03/2015 8:29	1:1,000,000 w/v	0.3mls	kcross	RA Only		
	B - DMP,DMF,CR		12/03/2015 8:29	1:1,000,000 w/v	0.3mls	kcross	LA Only		
	A - T,G,W,F		12/10/2015 13:35	1:1,000,000 w/v	0.4mls	bsimmons	RA Only		
	B - DMP,DMF,CR		12/10/2015 13:35	1:1,000,000 w/v	0.4mls	bsimmons	LA Only		
	A - T,G,W,F		12/17/2015 9:42	1:1,000,000 w/v	0.5mls	kcross	RA Only		
	B - DMP,DMF,CR		12/17/2015 9:42	1:1,000,000 w/v	0.5mls	kcross	LA Only		
	A - T,G,W,F		12/23/2015 10:59	1:100,000 w/v	0.05mls	bsimmons	RA Only		
	B - DMP,DMF,CR		12/23/2015 10:59	1:100,000 w/v	0.05mls	bsimmons	LA Only		
	A - T,G,W,F		12/31/2015 8:46	1:100,000 w/v	0.1mls	sysmith	RA Only		
	B - DMP,DMF,CR		12/31/2015 8:46	1:100,000 w/v	0.1mls	sysmith	LA Only		
	A - T,G,W,F		01/05/2016 11:15	1:100,000 w/v	0.2mls	sysmith	RA Only		
	B - DMP,DMF,CR		01/05/2016 11:15	1:100,000 w/v	0.2mls	sysmith	LA Only		
	A - T,G,W,F		01/14/2016 10:27	1:100,000 w/v	0.3mls	jbush	RA Only		
	B - DMP,DMF,CR		01/14/2016 10:27	1:100,000 w/v	0.3mls	jbush	LA Only		
	A - T,G,W,F		01/21/2016 11:14	1:100,000 w/v	0.4mls	kcross	RA Only		
	B - DMP,DMF,CR		01/21/2016 11:14	1:100,000 w/v	0.4mls	kcross	LA Only		
	A - T,G,W,F		01/26/2016 10:37	1:100,000 w/v	0.5mls	jbush	RA Only		
	B - DMP,DMF,CR		01/26/2016 10:37	1:100,000 w/v	0.5mls	jbush	LA Only		
	A - T,G,W,F		02/02/2016 11:08	1:10,000 w/v	0.05mls	jbush	RA Only		
	B - DMP,DMF,CR		02/02/2016 11:08	1:10,000 w/v	0.05mls	jbush	LA Only		
	A - T,G,W,F		02/12/2016 10:58	1:10,000 w/v	0.1mls	bsimmons	RA Only		
	B - DMP,DMF,CR		02/12/2016 10:58	1:10,000 w/v	0.1mls	bsimmons	LA Only		
	A - T,G,W,F		02/18/2016 11:31	1:10,000 w/v	0.2mls	dwilson	RA Only		
	B - DMP,DMF,CR		02/18/2016 11:31	1:10,000 w/v	0.2mls	dwilson	LA Only		
	A - T,G,W,F		02/25/2016 8:40	1:10,000 w/v	0.3mls	JConti	RA Only		
	B - DMP,DMF,CR		02/25/2016 8:40	1:10,000 w/v	0.3mls	JConti	LA Only		
	A - T,G,W,F		03/01/2016 10:38	1:10,000 w/v	0.4mls	dwilson	RA Only		
	B - DMP,DMF,CR		03/01/2016 10:38	1:10,000 w/v	0.4mls	dwilson	LA Only		
	A - T,G,W,F		03/08/2016 11:42	1:10,000 w/v	0.5mls	dwilson	RA Only		
	B - DMP,DMF,CR		03/08/2016 11:42	1:10,000 w/v	0.5mls	dwilson	LA Only		

Date Printed: 6/23/2017 6:01:33PM Printed from MED-HGRL6V1 by JConti

*Applicable for injections recorded after RoschIT ver5.2.6

Page 1 of 4

7 Dilution System- 46 weeks until Maintenance Final Concentration

Injection History Report

>> Report Includes: Injections, Reactions

GW Medical Faculty Associates
2300 M Street NW, Suite 200
Washington DC 20037 (202) 741-2771

Patient	Extract	Vial Location Frequency*	Date/Time	Concentration	Amount	Nurse	Inj Location	Max Conc*	Max Dose*
VINCENT, JAN (#4209948) (DOB: 10/30/1956)	A - T,G,W,F		03/17/2016 9:46	1:1,000 w/v	0.05mls	bsimmons	RA Only		
	B - DMP,DMF,CR		03/17/2016 9:46	1:1,000 w/v	0.05mls	bsimmons	LA Only		
	A - T,G,W,F		03/24/2016 13:37	1:1,000 w/v	0.1mls	bsimmons	RA Only		
	B - DMP,DMF,CR		03/24/2016 13:37	1:1,000 w/v	0.1mls	bsimmons	LA Only		
	A - T,G,W,F		03/29/2016 9:57	1:1,000 w/v	0.2mls	JConti	RA Only		
	B - DMP,DMF,CR		03/29/2016 9:57	1:1,000 w/v	0.2mls	JConti	LA Only		
	A - T,G,W,F		04/08/2016 9:40	1:1,000 w/v	0.3mls	bsimmons	RA Only		
	B - DMP,DMF,CR		04/08/2016 9:40	1:1,000 w/v	0.3mls	bsimmons	LA Only		
	A - T,G,W,F		04/12/2016 13:57	1:1,000 w/v	0.4mls	bsimmons	RA Only		
	B - DMP,DMF,CR		04/12/2016 13:57	1:1,000 w/v	0.4mls	bsimmons	LA Only		
	A - T,G,W,F		04/21/2016 10:48	1:1,000 w/v	0.5mls	bsimmons	RA Only		
	B - DMP,DMF,CR		04/21/2016 10:48	1:1,000 w/v	0.5mls	bsimmons	LA Only		
	A - T,G,W,F		04/28/2016 13:36	1:100 w/v	0.05mls	JConti	RA Only		
	B - DMP,DMF,CR		04/28/2016 13:36	1:100 w/v	0.05mls	JConti	LA Only		
	A - T,G,W,F		05/06/2016 10:18	1:100 w/v	0.1mls	bsimmons	RA Only		
	B - DMP,DMF,CR		05/06/2016 10:18	1:100 w/v	0.1mls	bsimmons	LA Only		
	A - T,G,W,F		05/12/2016 10:35	1:100 w/v	0.2mls	bsimmons	RA Only		
	B - DMP,DMF,CR		05/12/2016 10:35	1:100 w/v	0.2mls	bsimmons	LA Only		
	A - T,G,W,F		05/20/2016 11:34	1:100 w/v	0.3mls	sysmith	RA Only		
	B - DMP,DMF,CR		05/20/2016 11:34	1:100 w/v	0.3mls	sysmith	LA Only		
	A - T,G,W,F		05/26/2016 11:33	1:100 w/v	0.4mls	sysmith	RA Only		
	B - DMP,DMF,CR		05/26/2016 11:33	1:100 w/v	0.4mls	sysmith	LA Only		
	A - T,G,W,F		06/02/2016 13:35	1:100 w/v	0.5mls	kcross	RA Only		
	B - DMP,DMF,CR		06/02/2016 13:35	1:100 w/v	0.5mls	kcross	LA Only		
	A - T,G,W,F		06/10/2016 9:25	1:10 w/v	0.05mls	kcross	RA Only		
	B - DMP,DMF,CR		06/10/2016 9:25	1:10 w/v	0.05mls	kcross	LA Only		
	A - T,G,W,F		06/17/2016 10:55	1:10 w/v	0.1mls	kcross	RA Only		
	B - DMP,DMF,CR		06/17/2016 10:55	1:10 w/v	0.1mls	kcross	LA Only		
	A - T,G,W,F		06/24/2016 11:29	1:10 w/v	0.2mls	bsimmons	RA Only		
	B - DMP,DMF,CR		06/24/2016 11:29	1:10 w/v	0.2mls	bsimmons	LA Only		
	A - T,G,W,F Comments: .		06/29/2016 8:32	1:10 w/v	0.3mls	kcross	RA Only		
	B - DMP,DMF,CR		06/29/2016 8:32	1:10 w/v	0.3mls	kcross	LA Only		
	A - T,G,W,F		07/07/2016 9:59	1:10 w/v	0.4mls	kcross	RA Only		
	B - DMP,DMF,CR		07/07/2016 9:59	1:10 w/v	0.4mls	kcross	LA Only		

7 Dilution System- 46 weeks until Maintenance Final Concentration

Injection History Report -

>> *Report Includes: Injections, Reactions,*

GW Medical Faculty Associates
2300 M Street NW, Suite 200
Washington DC 20037 (202) 741-2771

Patient	Extract	Vial Location Frequency*	Date/Time	Concentration	Amount	Nurse	Inj Location	Max Conc*	Max Dose*
VINCENT, JAN (#4209948) *(DOB: 10/30/1956)*	A - T,G,W,F		07/15/2016 9:25	1:10 w/v	0.5mls	sysmith	RA Only		
	B - DMP,DMF,CR		07/15/2016 9:25	1:10 w/v	0.5mls	sysmith	LA Only		
	A - T,G,W,F		07/22/2016 10:16	1:1 w/v	0.05mls	kcross	RA Only		
	B - DMP,DMF,CR		07/22/2016 10:16	1:1 w/v	0.05mls	kcross	LA Only		
	A - T,G,W,F		07/28/2016 9:54	1:1 w/v	0.1mls	ssoliman	RA Only		
	B - DMP,DMF,CR		07/28/2016 9:54	1:1 w/v	0.1mls	ssoliman	LA Only		
	A - T,G,W,F		08/04/2016 10:28	1:1 w/v	0.15mls	JConti	RA Only		
	B - DMP,DMF,CR		08/04/2016 10:28	1:1 w/v	0.15mls	JConti	LA Only		
	A - T,G,W,F		08/11/2016 11:03	1:1 w/v	0.2mls	sysmith	RA Only		
	B - DMP,DMF,CR		08/11/2016 11:03	1:1 w/v	0.2mls	sysmith	LA Only		
	A - T,G,W,F		08/19/2016 10:39	1:1 w/v	0.25mls	bsimmons	RA Only		
	B - DMP,DMF,CR		08/19/2016 10:39	1:1 w/v	0.25mls	bsimmons	LA Only		
	A - T,G,W,F		08/26/2016 11:17	1:1 w/v	0.3mls	sysmith	RA Only		
	B - DMP,DMF,CR		08/26/2016 11:17	1:1 w/v	0.3mls	sysmith	LA Only		
	A - T,G,W,F		09/02/2016 10:31	1:1 w/v	0.35mls	JConti	RA Only		
	B - DMP,DMF,CR		09/02/2016 10:31	1:1 w/v	0.35mls	JConti	LA Only		
	A - T,G,W,F		09/08/2016 8:28	1:1 w/v	0.4mls	bsimmons	RA Only		
	B - DMP,DMF,CR		09/08/2016 8:28	1:1 w/v	0.4mls	bsimmons	LA Only		
	A - T,G,W,F		09/16/2016 9:52	1:1 w/v	0.45mls	bsimmons	RA Only		
	B - DMP,DMF,CR		09/16/2016 9:52	1:1 w/v	0.45mls	bsimmons	LA Only		
	A - T,G,W,F		09/23/2016 10:11	1:1 w/v	0.5mls	bsimmons	RA Only		
	B - DMP,DMF,CR		09/23/2016 10:11	1:1 w/v	0.5mls	bsimmons	LA Only		
	A - T,G,W,F		09/30/2016 9:12	1:1 w/v	0.5mls	ssoliman	RA Only		
	B - DMP,DMF,CR		09/30/2016 9:12	1:1 w/v	0.5mls	ssoliman	LA Only		
	A - T,G,W,F		10/13/2016 11:20	1:1 w/v	0.5mls	bsimmons	RA Only		
	B - DMP,DMF,CR		10/13/2016 11:20	1:1 w/v	0.5mls	bsimmons	LA Only		
	A - T,G,W,F		10/28/2016 9:11	1:1 w/v	0.5mls	sysmith	RA Only		
	B - DMP,DMF,CR		10/28/2016 9:11	1:1 w/v	0.5mls	sysmith	LA Only		

Allergen Immunotherapy in the United States

- Practitioners in the United States currently use a wide variety of formulations, prepared for individual patients *ad hoc* from commercial source allergen extract solutions.
- **Such formulations are usually based upon simple aqueous extracts, are prepared by allergists in the office or clinic, and are not commercially available as individual patient dose units.**
- As such it is difficult to standardize the level of allergen exposure between patients.
- The administered SIT may also contain allergens that are not necessarily clinically relevant to the patient.

13 Standardized Inhalant Allergen Extracts Available in the USA

- Cat Hair
- Cat Pelt
- Dust mite D. Farinae
- Dust Mite D. Pteronyssinus
- Bermuda Grass
- June Grass
- Meadow Fescue Grass
- Orchard Grass
- Redtop Grass
- Perennial Rye Grass
- Sweet Vernal Grass
- Timothy Grass
- Short Ragweed

CBER 4/30/2014 FDA website

Allergen Immunotherapy in the United States

- The drawbacks of conventional SIT in the US include:

1) variability of the pharmaceutical quality of preparations

2) variability of dose/regimen

3) long courses of treatment with a slow emergence of clinical benefit

4) efficacy and safety not supported by data for each individual regimen

5) All allergen mixes compounded in the physician office are FDA “OFF LABEL” usage of FDA approved allergen exttracts

Allergen Immunotherapy in the United States- Adherence

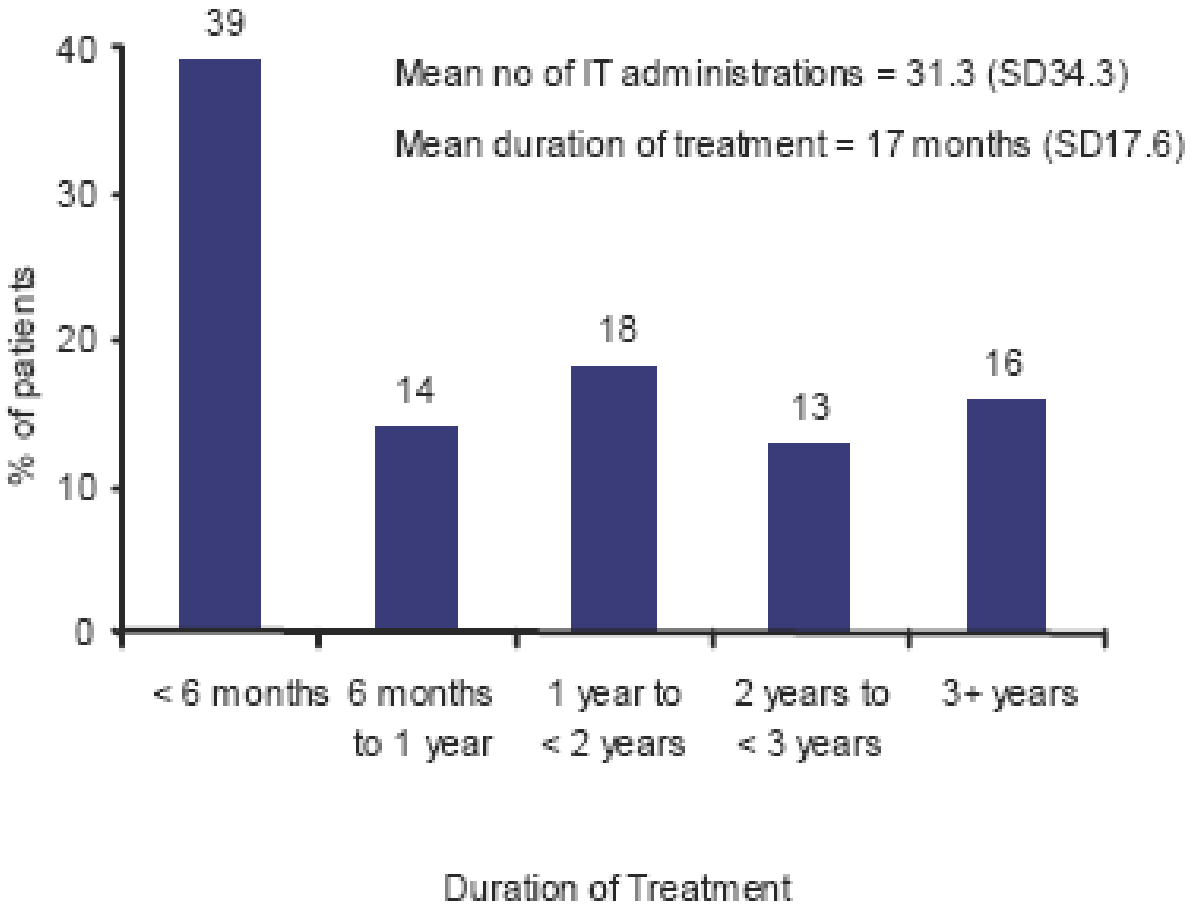
- The most considerable barrier to effective and safe treatment with conventional SIT is the large number of injections required – up to 100 per patient each year.
- This commitment limits adherence, and compliance rates above 50% are unusual after 1 year of therapy.
- In one large study, treatment compliance after the first 6 months was dramatically reduced such that only 16% of patients completed the minimum recommended 3-year duration of treatment.

Cohn JR, and Pizzi A. Determinants of patient compliance with allergen immunotherapy. *J Allergy Clin Immunol* 1993; 91:734 –737

Lower T, Henry J, Mandik L, *et al*. Compliance with allergen immunotherapy. *Ann Allergy* 1993; 70: 480–482

Hankin CS, Cox L, Lang D, et al. Allergy immunotherapy among Medicaid-enrolled children with allergic rhinitis: patterns of care, resource use and costs. 2007 JACI

Long-Term Treatment Compliance with Existing SIT in the United States: Florida Medicaid Study- Hankan, Cox, JACI 2007

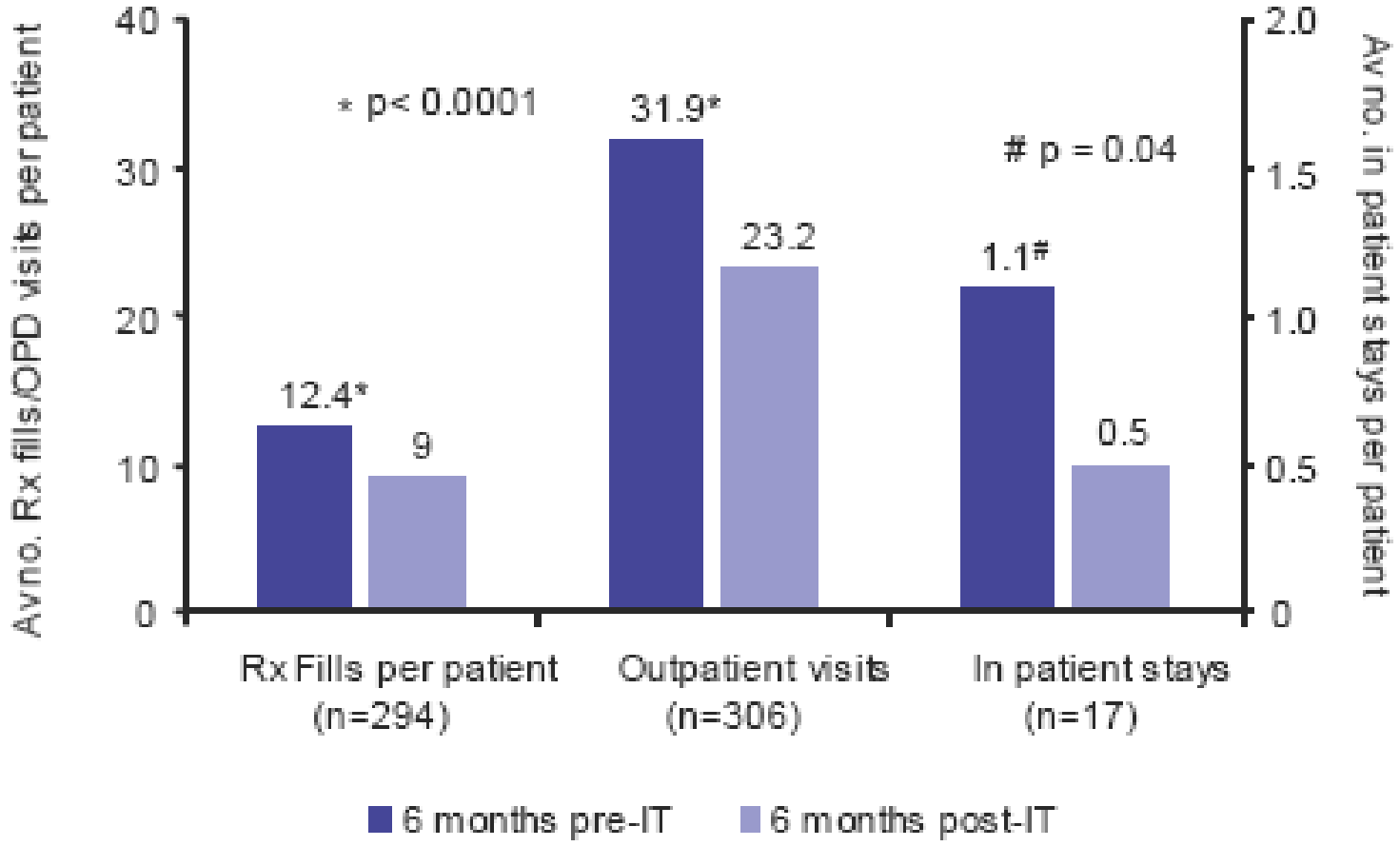


Benefits of Allergen Immunotherapy in the United States: Florida Medicaid Study

- The reduction in medical resource use associated with SIT is exemplified by the results of a study of Florida Medicaid data.
- Despite the poor compliance with SIT observed in this study with a mean duration of treatment limited to 17 months there were highly significant (27%) reductions in medication use and out-patient visits.
- These reductions translated into significant direct healthcare cost savings, equivalent to $156 in prescription drug costs per patient-year and $546 in outpatient costs per patient-year (both $p<0.01$ *vs* pre-SIT).

Hankin CS, Cox L, Lang D, et al. Allergy immunotherapy among Medicaid-enrolled children with allergic rhinitis: patterns of care, resource use and costs. 2007 ,JACI

Reduction in Medical Resource Utilization with SIT in the United States: Florida Medicaid Study- Hankin, Cox, Lang JACI 2007



Benefits of Allergen Immunotherapy in the United States

- United States guidelines propose that patients with moderate or severe allergic rhinitis and mild to moderate asthma may be managed aggressively with allergen avoidance and pharmacotherapy, but may also benefit from SIT.
- This conclusion is based on a number of SIT studies of the treatment for pollen-related allergies.
- For allergy vaccination, effects of up to 55% have been reported in small studies, although larger, more recent, and more rigorously controlled studies have show treatment effects of approximately 25% greater than placebo which compare favorably with the benefit from antihistamine or leukotriene antagonists of 5–10%.

Cox L *et al*. Allergen immunotherapy: A practice parameter second update. *J Allergy Clin Immunol* 2007; 120: Suppl 3s

Benefits of Allergen Immunotherapy in the United States

- A series of independent reviews and a meta-analysis , including the most recent update on practice parameters for allergen immunotherapy , have concluded that SIT is effective for allergic rhinitis and allergic asthma, when used appropriately.

In addition benefits of SIT include:

- Avoidance or reduction of antihistamines and synthetic steroids use
- The ability to provide long-term relief of symptoms
- Potential for the treatment of asthma
- Potential for arresting the allergic march
- Pharmacoeconomic benefits from a reduction in use of medical resource.

Abramson MJ, Puy RM, Weiner JM. Allergen immunotherapy for asthma. *Cochrane Database Syst Rev* 2003; 4: CD001186

Calderon MA, Alves B, Jacobson M, *et al.* Allergen injection immunotherapy for seasonal allergic rhinitis. *Cochrane Database Syst Rev* 2007; 1:CD001936

Cox L *et al*. Allergen immunotherapy: A practice parameter second update. *J Allergy Clin Immunol* 2007; 120: Suppl 3s

Safety Issues with current Allergen Immunotherapy in the USA

- Systemic Reactions
- Fatal Reactions

Just How Frequent Are Systemic Reactions?

- 0.51% of all injections may produce a systemic reaction
- 45% of reactions occur in patients who have had previous systemic reactions
  - Matloff SM et al. *Allergy Proceed* 1993; 14:347-350.
- 0.05% to 3.2% rate per injection for conventional
  - Stewart GE and Lockey RF. *J Allergy Clin Immunol* 1992; 90:567-78.

Risk Assessment of Allergen Immunotherapy in the United States

- Unstable asthma
- nearly all cases have had asthma
- bronchospasm is a key feature of the anaphylaxis
- highly sensitive patient during the buildup phase of SIT
- SIT administered during pollen season
- new bottle of extract used for SIT
- beta-blocker medication (do not cause adverse reactions,
- but can make them harder to manage)
- wrong dose of extract
- wrong extract

BMJ 293: 948, 1986.

Bernstein DI. AAAAI survey of SIT fatalities, 2001-2002.

Allergen Immunotherapy Risks

- Despite clinical practice guidelines, there are still severe AEs and fatalities.
- 1 death per 2 million injections.
- Fatalities due to SIT still occur in the United States, despite many improvements such as the introduction of standardized allergens.

Bernstein DI, Wanner M, Borish L, *et al.* and the Immunotherapy Committee of the American Academy of Allergy, Asthma and Immunology. Twelve year survey of fatal reactions to allergen injections and skin testing: 1990–2001. *J Allergy Clin Immunol* 2004; 113: 1129–36

Reid MJ, Lockey RF, Turkeltaub PC, Platts–Mills TAE. Survey of fatalities from skin testing and immunotherapy 1985–1989. *J Allergy Clin Immunol* 1993; 92: 615

Engler RJM, Marks SN, Garramone SM, *et al.* Anaphylaxis death after immunotherapy: root cause analysis case report. *EAACI* 2005, Poster No. 1439

Recent Changes to Allergen Immunotherapy in the USA

- FDA Review of Non-Standardized Extracts
- Removal of allergen extracts from the marketplace due to lack of adequate efficacy data
- Medicare CMS Guidelines eliminate payment for up-dosing allergen immunotherapy vials
- Private Commercial Insurances Restrict Payment for up-dosing vials
- Introduction of SLIT tablets by Merck (ALK) and Stallergenes
- Rejection of SLIT tablets by the allergists

FDA Allergen Extract Review 2011-2012- Scientific Data Review of Available Allergen Extracts in the USA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2011–N–0599]

Center for Biologics Evaluation and Research Report of Scientific and Medical Literature and Information on Non-Standardized Allergenic Extracts in the Diagnosis and Treatment of Allergic Disease; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of its report of scientific and medical literature and information concerning the use of non-standardized allergenic extracts in the diagnosis and treatment of allergic disease. The report is provided in a data file entitled ''Center for Biologics Evaluation and Research Report of Scientific and Medical Literature and Information on Non-Standardized Allergenic Extracts in the Diagnosis and Treatment of Allergic Disease.'' FDA is making this report available to provide information and obtain comments from public and private stakeholders. FDA will also seek input on the report from the Allergenic Products Advisory Committee (APAC) at a meeting to be held on October 25, 2011. FDA has not made any regulatory decisions concerning the report or the products discussed in the scientific literature and information cited. FDA will review comments and other information it receives, as part of its continued oversight of regulated products.

FDA Allergen Extract Review 2011-2012- Process of Data Collection on Allergen Extracts Began in 2004

II. Discussion

In 2004, FDA formed an internal committee to review available scientific and medical data on the safety and effectiveness of non-standardized allergenic extracts. FDA formed this committee to consider the previous evaluations performed by the external allergenics advisory review panels under 21 CFR 601.25 (Panel I or ''Original Panel'') and under 21 CFR 601.26 (Panel II or ''Reclassification Panel''). Reports of the Original and Reclassification Panels are available at *http://www.fda.gov/BiologicsBloodVaccines/Allergenics/ucm272115.htm*. The internal committee designed a data file to use in its review and to archive supporting data. The data file includes a report of information for each product, including a discussion of each product reviewed, and a list of reviewed literature associated with each product. FDA's approach to creating this data file was presented to APAC on April 7, 2005, and discussed again at the APAC meeting on September 13, 2006.

After receiving favorable feedback from the APAC on FDA's proposed methodology, FDA proceeded to collect the following information in order to facilitate its assessment of safety and effectiveness of non-standardized allergenic products.

FDA Allergen Extract Review 2011-2012- Concern About Safety and Efficacy of Non-Standardized Extracts

A. Literature Reviewed by the Allergenics Advisory Review Panels

This includes literature reviewed by the Original Panel as part of its final report in 1981 and literature reviewed by the Reclassification Panel as part of its final report in 1983.

B. Data Concerning the Effectiveness and Safety of Non-Standardized Allergenic Products That Have Become Available Since 1972

This includes published literature, available manufacturer data, and data from other external sources. FDA accumulated these data from the following sources:

1. Published Literature From 1972 to the Present

This literature was acquired by searching for articles using a PubMed and/or Institute for Scientific Information (ISI) search engine (English-language literature articles only).

FDA Allergen Extract Review 2011-2012- Concerns About Allergen Source Materials and Validity of Study Methods

2. Publicly Available Manufacturer Data

These data were obtained by reviewing information published in the literature.

3. Medwatch Data Collected for Years 1987 to 2010

These data were evaluated for safety related product trends.

4. Data From Other External Sources

These data were obtained by performing a broad Internet search (*e.g.*, Google) to check for any additional safety or effectiveness data not captured in published articles found via PubMed or ISI.

FDA collected information from published scientific and medical literature and other data sources for each extract in order to identify those studies that used acceptable alternative testing methods. FDA also collected information from studies that:

- *Provided identifiable, specific and valid nomenclature for the source materials used in the preparation of the allergenic extracts in the studies.*
- *Were performed using aqueous based extracts prepared from specifically identified source materials with correct nomenclature.*
- *Described identifiable, specific, and valid study methods.*
- *Provided objective and evaluable data.*

FDA- Movement to Pharmacy Grade Products of Allergen Vaccines

- Move to eliminate or limit non-standardized extract use
- Greater standardization of allergen vaccines
- Move towards Pharmacy grade products
- Deletions of large number of allergen vaccines which had been available for use before 2011-

Communication with Ronald Rabin of FDA June 2017 indicated at least 15 extracts were removed by the agency and many more deleted by the industry in anticipation of removal

Medicare Restrictions of Payment for Dilutions of Maintenance Vials

- No payment for dilutions
- Followed gradually by some private commercial insurers

Medicare Restriction on Billing for Allergen Immunotherapy Up-Dosing Dilution Vials

Allergen Immunotherapy (Medicare excerpts)

Billing Guidelines:

CPT procedure code 95165 is used to report multiple dose vials of non-venom antigens. Effective January 1, 2001, for CPT code 95165, a dose is now defined as a one- (1) cc aliquot from a single multidose vial. When billing code 95165, providers should report the number of units representing the number of 1 cc doses being prepared. A maximum of 10 doses per vial is allowed for Medicare billing, even if more than ten preparations are obtained from the vial. In cases where a multidose vial is diluted, Medicare should not be billed for diluted preparations in excess of the 10 doses per vial allowed under code 95165.

UnitedHealthcare®

Coverage Summary		
Allergy Testing and Allergy Immunotherapy		
Policy Number: A-004	**Products:** UnitedHealthcare Medicare Advantage Plans	**Original Approval Date:** 11/06/2007
Approved by: UnitedHeatlhcare Medicare Benefit Interpretation Committee		**Last Review Date:** 03/21/2017
Related Medicare Advantage Policy Guidelines:		
• Antigens Prepared for Sublingual Administration (NCD 110.9) • Challenge Ingestion Food Testing (NCD 110.12)	• Cytotoxic Food Tests (NCD 110.13) • Food Allergy Testing and Treatment (NCD 110.11) • Intravenous Histamine Therapy (NCD 30.6)	

2. Allergen immunotherapy to treat allergies is **covered** when:
   a. Patient is examined by a physician
   b. The physician who examines the patient, prepares the antigens and develops a plan of care and dosage regimen

United Healthcare-12 Month Supply Limit-Interpreted as Maintenance Vials and Not Up-Dosing Vials

3. Reasonable Supply of Antigen

Payment may be made for a reasonable supply of antigens that have been prepared for a particular patient if: (1) the antigens are prepared by a physician who is a doctor of medicine or osteopathy, and (2) the physician who prepared the antigens has examined the patient and has determined a plan of treatment and a dosage regimen.

Antigens must be administered in accordance with the plan of treatment and by a doctor of medicine or osteopathy or by a properly instructed person (who could be the patient) under the supervision of the doctor. The associations of allergists that CMS consulted advised that a reasonable supply of antigens is considered to be not more than a 12-month supply of antigens that has been prepared for a particular patient at any one time. The purpose of the reasonable supply limitation is to assure that the antigens retain their potency and effectiveness over the period in which they are to be administered to the patient. (See §§20.2 and 50.2.)

SLIT in the USA

- ENTs often compound their own SLIT aqueous oral extract vaccines- Greer typical supplier-all FDA OFF LABEL; generally not covered by insurance- patients self-pay
- Stallergenes: 5 Grass Mix- Oralair
- ALK:

Timothy Grass- Grastek

Short Ragweed- Ragwitek

Dust Mite- just FDA approved in March, 2017- Odactra

Cost of SLIT Tablets Retail Price ~ $350/month

Insurance Coverage usually requires “Prior Approval”

Merck's new allergy pill faces stubborn skepticism on the eve of its FDA review

by John Carroll |
Dec 11, 2013 10:31am
http://www.fiercebiotech.com/regulatory/

Tomorrow Merck ($MRK) will take its best shot at convincing a group of FDA advisers that its sublingual allergy pill Grastek deserves a place in the nation's pharmacies. But even if it wins the panel's endorsement for a formal agency approval, the pharma giant will once again find itself facing critics questioning its effectiveness and its ability to earn much money from it.

Grastek has garnered little attention and even less enthusiasm from analysts, though Merck insists that it has an innovative new approach to treating allergic rhinitis with a pill--replacing the current regimen of shots. The pharma giant in-licensed the therapy, which relies on an extract of timothy grass pollen, from ALK-abello, which sells it in Europe. And today Stallergenes, which is looking for an FDA OK for its own allergy pill, Oralair, will take the first turn in front of the FDA panel.

Merck is presenting data from a range of late-stage studies to back its application. The FDA internal review put out ahead of the panel discussion notes that at least one of the trials was not effective, but several showed a 20%-plus improvement in allergy symptoms compared to a placebo--not the shots that Merck wants to replace.

Merck's new allergy pill faces stubborn skepticism on the eve of its FDA review

That comparison to a placebo might assist in Merck's undoing if it makes it to the market. As Andrew Pollack notes in his recent *New York Times* article on the new allergy pills, Merck will likely encounter some major resistance to the pills from doctors who earn a comfortable living providing a lengthy round of injections to patients. *The Times* piece notes that shots may still outperform the pills, giving providers a chance to argue against Grastek by promising better results.

The best case scenario for Merck was made by ISI's Mark Schoenebaum, who's projecting peak sales of $350 million. That's not nearly enough to break Merck's 7-year blockbuster drought, but it could provide a boost for a beleaguered R&D division that is now undergoing a restructuring under a new research chief. Schoenebaum has also noted that the consensus estimate on peak sales is a mere $130 million, which would barely make a dent against the onslaught of generic rivals.

Merck Returns SLIT to ALK

Merck Returns Rights to Allergy Tablets Back to ALK-Abello

Jul 27, 2016
http://www.pharmtech.com/
By Randi Hernandez

Merck gave the rights to three sublingual allergy immunotherapy tablets back to Denmark-based manufacturing company ALK-Abello, according to an announcement released on July 27, 2016. The end of the partnership agreement will mean that Merck will no longer hold the rights to Grastek, Ragwitek, and an investigational SLIT tablet. The drugs seek to treat allergies to grass, ragweed, and dust mites, respectively.

ALK-Abello admitted in a press release that sales performance over the past two years has been below expectations in the United States, but believes the further development of its SLIT-tablet for the treatment of allergic asthma will be fruitful, as it has been in Europe. However, the company is now left looking for a new co-development partner in North America.

The rights to the drugs will revert to ALK-Abello in the next six months, and will be complete by early 2017. Merck committed to completing the current clinical study that is underway on the SLIT-tablet, but will slowly transition the product registration process over to ALK. Merck announced FDA acceptance of its biologics license application (BLA) for the dust mite tablet (MK-8237) in April 2016.

The return of the rights to these three therapies to ALK follows an inspection letter from FDA to the immunotherapy manufacturer that cited multiple problems with the company's aseptic manufacturing capabilities. Although many of the citations surrounded the fill/finish of a non-oral product (Pharmalgen), FDA also concluded that ALK-Abello had no written procedures surrounding how the stability of their products is tested, nor any documentation on the sampling and testing of its grass and ragweed drug product and drug substance samples. FDA estimated that the stability of the sublingual grass and ragweed tablets had not been tested since 2014.

Source: ALK-Abello

Merck shocks ALK by returning rights to allergy immunotherapies

by Nick Paul Taylor | Jul 27, 2016 5:45am

- Merck has shocked ALK-Abello and its investors by returning the rights to three sublingual allergy immunotherapy tablets. The decision, which comes partway through a clinical trial and regulatory approval process, leaves ALK without a partner in the U.S. and triggered an 18% drop in its share price.
- Merck has paid out more than DKK 700 million ($100 million) to ALK as part of the deal it struck in 2007 for the rights to the drugs, but its returns to date have been small. Faced with healthcare professionals that are reticent to shift away from existing treatment options, Merck has struggled to gain ground. In the first half of 2016, ALK earned approximately $2 million through sales royalties, R&D services and product supply under the Merck deal.

SLIT Tablets- Failure in US Market

- Excited entry to the US market- first new allergen immunotherapy products in years
- Pharmacy grade SLIT tablets face fierce resistance from US Allergists
- Failure of Merck SLIT initiative proves US is “shot-based” allergen immunotherapy marketplace

New Threats to Allergy Practice in USA

- USP Guidance
- FDA Guidance

USP GUIDELINES

- The U.S. Pharmacopeial Convention (USP) is a scientific nonprofit organization that sets standards for the identity, strength, quality, and purity of medicines, food ingredients, and dietary supplements manufactured, distributed and consumed worldwide.
- USP's drug standards are enforceable in the United States by the Food and Drug Administration, and these standards are used in more than 140 countries.
- Since its founding in 1820, USP has helped secure the quality of the American drug supply.
- Building on that legacy, USP today works with scientists, practitioners, and regulators of many nations to develop and revise standards that help protect public health worldwide.

USP GUIDELINES

- USP was created in 1820 by a group of 11 physicians who recognized an essential need for a national lexicon of drug names and formulas in the United States.
- At the time, the marketplace for drugs and medicinals was chaotic: there was little assurance of consistency or quality regarding the medicines that patients were taking.
- The first edition of the USP featured the best drugs and preparations and defined terminology that facilitated communication between the physicians who prescribed and administered medicines and the pharmacists who prepared them.

USP RESOLUTIONS

Resolution I.

- **Collaboration with the U.S. Food and Drug Administration**
- **USP will increase communication and collaboration with the U.S. Food and Drug Administration (FDA) to promote alignment with FDA's regulatory and scientific policies from the inception of the standards planning and development process. USP will work with FDA, industry, and other stakeholders throughout the process to increase understanding of the regulatory impact of such proposals.**

USP RESOLUTIONS

Resolution VII.

Quality Standards for Compounded Medicines

- **USP will continue working with stakeholders to develop and maintain practice and quality standards for sterile and non-sterile compounding.**
- **USP will increase the availability of its compounding standards, expand stakeholder engagement and education, and promote adoption of these standards by compounding professionals and regulatory authorities.**

USP 797 Update

- May 2016 Update on Revisions to USP General Chapter <797> Pharmaceutical Compounding – Sterile Preparations
- USP proposed revisions to USP General Chapter <797> and sought public comments from September 25, 2015 to January 31, 2016. During this public comment process, the USP Compounding Expert Committee received more than 8,000 comments from over 2,500 stakeholders. The Expert Committee has been reviewing the comments and met face-to-face on April 11, 2016 to discuss the comments received.

USP 797 Update

- USP expects the revision process to continue through the summer of 2016. The Expert Committee will review all of the public comments received and USP will be gathering additional information where needed.
- The USP Healthcare Quality Standards Head of Science, Shawn C. Becker, will host two roundtables to seek clarity on public comments related to allergen extracts and radiopharmaceuticals.
- These USP roundtable activities are supplemental to the compendial public comment process and the Expert Committee will use the proceedings to assist in the revision process.

USP 797 Update

- Based on the Expert Committee's evaluation of the public comments and significance of further revisions to the chapter, General Chapter <797> may be proposed for another public comment period. USP does not yet have an anticipated date for publication.

USP 797 Changes

BRIEFING

⟨797⟩ Pharmaceutical Compounding—Sterile Preparations, *USP 39* page 626. It is proposed to revise this chapter to improve clarity, respond to stakeholder input, and reflect new science. Major edits to the chapter include:

1. Reorganized existing chapter to group similar topics together, eliminate redundancies, and clarify requirements. Key procedural information is placed in boxes so that it can be easily referenced and followed.
2. Collapsed compounded sterile preparations (CSP) microbial risk categories from three to two and changed terminology. No sterile compounding is inherently "low risk" and preparation of all CSPs must be done carefully. Categories were renamed neutrally as Category 1 and 2 CSPs, which are distinguished primarily by the conditions under which they are made and the time within which they are used. Category 1 CSPs have a shorter beyond use date (BUD) and may be prepared in a segregated compounding area; Category 2 CSPs have a longer BUD and must be prepared in a cleanroom environment.

USP 797 Deletes Exceptions for Allergen Extract Compounding

~~**ALLERGEN EXTRACTS AS CSPS**~~

~~Allergen extracts as CSPs are single-dose and multiple-dose *intradermal or subcutaneous injections* that are prepared by specially trained physicians and personnel under their direct supervision. Allergen extracts as CSPs are not subject to the personnel, environmental, and storage requirements for all *CSP Microbial Contamination Risk Levels* in this chapter only when all of the following criteria are met:~~

1. ~~The compounding process involves simple transfer via sterile needles and syringes of commercial sterile allergen products and appropriate sterile added substances (e.g., glycerin, phenol in sodium chloride injection).~~
2. ~~All allergen extracts as CSPs shall contain appropriate substances in effective concentrations to prevent the growth of microorganisms. Nonpreserved allergen extracts shall comply with the appropriate CSP risk level requirements in the chapter.~~

USP 797 Deletes Exceptions for Allergen Extract Compounding

3. ~~Before beginning compounding activities, personnel perform a thorough hand-cleansing procedure by removing debris from under fingernails using a nail cleaner under running warm water followed by vigorous hand and arm washing to the elbows for at least 30 seconds with either nonantimicrobial or antimicrobial soap and water.~~
4. ~~Compounding personnel don hair covers, facial hair covers, gowns, and face masks.~~
5. ~~Compounding personnel perform antiseptic hand cleansing with an alcohol-based surgical hand scrub with persistent activity.~~
6. ~~Compounding personnel don powder-free sterile gloves that are compatible with sterile 70% isopropyl alcohol (IPA) before beginning compounding manipulations.~~
7. ~~Compounding personnel disinfect their gloves intermittently with sterile 70% IPA when preparing multiple allergen extracts as CSPs.~~
8. ~~Ampul necks and vial stoppers on packages of manufactured sterile ingredients are disinfected by careful wiping with sterile 70% IPA swabs to ensure that the critical sites are wet for at least 10 seconds and allowed to dry before they are used to compound allergen extracts as CSPs.~~
9. ~~The aseptic compounding manipulations minimize direct contact contamination (e.g., from glove fingertips, blood, nasal and oral secretions, shed skin and cosmetics, other nonsterile materials) of critical sites (e.g., needles, opened ampuls, vial stoppers).~~
10. ~~The label of each multiple-dose vial (MDV) of allergen extracts as CSPs lists the name of one specific patient and a BUD and storage temperature range that is assigned based on manufacturers' recommendations or peer-reviewed publications.~~
11. ~~Single-dose allergen extracts as CSPs shall not be stored for subsequent additional use.~~

~~Personnel who compound allergen extracts as CSPs must be aware of greater potential risk of microbial and foreign material contamination when allergen extracts as CSPs are compounded in compliance with the foregoing criteria instead of the more rigorous standards in this chapter for *CSP Microbial Contamination Risk Levels.* Although contaminated allergen extracts as CSPs can pose health risks to patients when they are injected *intradermally or subcutaneously,* these risks are substantially greater if the extract is inadvertently injected *intravenously.*~~

Allergen Immunotherapy Threats to the Allergists

- New 797 USP Guidelines will be requiring:
- isolated sterile compounding facilities
- HEPA air filtration
- laminar flow room and hood
- sterile methods: higher quality control, ongoing sterility testing of products, facility and personnel
- and more rapid lot expiration date- 28 days for all compounded products
- FDA New Guidelines will be consistent with USP Guidelines
- Current status: under review with intense push-back by the allergy community: AAAAI and ACAAI

Threats to Allergist In Office Compounding of Extracts

- USP 797 Update
- FDA Activities related to Compounding of Patient Specific Allergen Vials for Im
- New Draft Requirements which demand allergen extracts be compounded using state of the art sterility techniques
- Would eliminate in-office allergen extract compounding in almost all situations

Threats to US Allergen Immunotherapy

- American College of Allergy, Asthma and Immunology: ADVOCACY INSIDER
- UPDATE ON USP 797 AND FDA COMPOUNDING GUIDANCE

"We're working to protect your patient's access to allergy shots. And the fight isn't over."

American College of Allergy, Asthma and Immunology: ADVOCACY INSIDER

Update on USP 797 and FDA Compounding Guidance

January 9, 2017

As we start a new year, we thought this to be a good time to update you on the status of our efforts to **preserve in-office compounding of allergen extracts**. The Advocacy Council continues to be very engaged in this issue on several fronts.

Advocacy Council representatives serve on the Steering Committee that is organizing a USP Roundtable Discussion scheduled in early February on the specific issue of compounding of allergen extracts. This will be an opportunity for allergists to meet face-to-face with USP representatives related to the proposed changes to USP 797.

American College of Allergy, Asthma and Immunology: ADVOCACY INSIDER

We are also actively monitoring the Food and Drug Administration's (FDA's) release of new guidance documents. Shortly before the end of 2016, the FDA released a guidance on prescription requirements for compounded products. **This is not the guidance on *Insanitary Conditions in Compounding Pharmacies* that the allergy specialty has been concerned about.** That guidance is still pending. Rather, the year-end guidance focuses on prescription requirements for compounded drugs, addresses anticipatory compounding by pharmacies, and clarifies that in the office setting, a prescription may consist of a notation in the patient's chart.

We also continue to monitor activities in Congress that may impact compounding by allergists, as well as initiatives at the state level including activities of state Boards of Pharmacy and state legislatures. We are also continuing to stay in contact with the Federation of State Medical Boards which is studying the issue.

We feel strongly that in order to do a good job, all of these areas must continually be monitored this takes a significant number of man-hours and resources that are not part of our operating budget. Once again, we are asking you to look to the future – to the future of allergy; to the future of medicine – and support these efforts by contributing to our Defend Allergy SHots (DASH) Campaign.

USP 797- USP ROUNDTABLE February, 2017

- The latest from the USP Roundtable
- This past Thursday, Feb. 2, 2017 representatives from ACAAI and AAAAI participated in a United States Pharmacopeia (USP) roundtable on the proposed changes to USP 797 guidelines on compounding of allergen extracts in allergists offices and clinics.
- Members of the USP Roundtable Steering Committee, Drs. James Sublett, Tom Casale, Mike Nelson, and Steve Kagen attended and were joined by Drs. David Bernstein, Linda Cox, Gary Gross, Stephen Imbeau, Aidan Long, Kathleen May, and Andrew Murphy along with our legal advisors

USP 797- USP ROUNDTABLE February, 2017

- Representatives from the AAOA, AAN, AAFA, the FDA, State Federation of Medical Boards, the Allergen Extract Manufacturers Association and other stakeholders were also in attendance. The roundtable was a day long discussion with the USP staff and USP 797 Expert Panel on the potential impact of the proposed changes.
- The stated objectives for the revision of USP 797 are to assure sterility and stability. Several advances by our specialty have been made since the last Chapter 797 update.
- Our purpose was to educate the USP staff, 797 Expert Panel Chair and Vice-Chair and other roundtable members of those accomplishments.

USP 797- USP ROUNDTABLE February, 2017

- Following a presentation on Allergen Immunotherapy Vial Preparation, overviews of data and research and recent publications on sterility and the lack of infection risk from immunotherapy were presented.
- Comments related to the most recent Practice Parameter on Immunotherapy, which has been updated since the last USP 797 update, were included.
- There was also discussion on the importance of continued patient access to immunotherapy and its risk/benefits.

USP 797- USP ROUNDTABLE February, 2017

- One important factor that differentiates our compounding extracts is the use of phenol and glycerin in our vials.
- This will be considered in any decision on Beyond Use Dates The panel recognized the continuing efforts by our professional societies to assure improved safety including the College's Allergenic Extract Quiz, Annual Media Fill Test and the recently updated Allergen Immunotherapy Extract Preparation *Physician Instruction Guide*.

USP 797- USP ROUNDTABLE February, 2017

- Overall, the roundtable allowed us to fill many knowledge gaps for USP related to allergen immunotherapy.
- Continued dialogue will occur, and, after the revised draft of the Expert Panel is published, there will be another opportunity for public comments.

FDA 2016 GUIDELINES on INSANITARY CONDITIONS

- On Tuesday, June 6th, 2017, the US Food and Drug Administration (FDA) Center on Drug Evaluation and Research (CDER) Office of Compounding hosted a series of listening sessions with seven different healthcare constituencies regarding compounding practices in different settings.
- Our specialty societies participated in similar sessions held in June 2016, but it is significant to note that the Allergy/Immunology and Otolaryngology specialties were invited to a separate session from other specialties for the first time this year.

FDA 2016 GUIDELINES on INSANITARY CONDITIONS

- This allowed the discussion to focus extensively on concerns related to compounding and administration of allergen immunotherapy.
- Discussion focused on the 2016 FDA Proposed Guidance on Insanitary Conditions, which the FDA regarded as a follow-up to previous regulations and not the precursor to a set of sweeping new requirements on physical facilities.
- The FDA acknowledged that the implications on a practice such as allergen immunotherapy were not taken into account in its development

FDA 2016 GUIDELINES on INSANITARY CONDITIONS

- Specialty leaders urged an approach that would balance the potential for infectious adverse events, which the FDA admits has not been identified as a problem, with the increased threat of anaphylactic reactions possible if source extract products are not controlled for consistency and patient status in the physician's office.

USP 797 Update

- In follow up to a February, 2017 Stakeholder Roundtable on Allergen Immunotherapy, a workgroup has been formed including leadership of the USP Compounding Expert Committee, representatives from the Specialty Societies, and USP staff.
- This group met on Friday, June 2 for an update on the continuing effort to revise Chapter 797.
- Discussions included appropriate standards for training of compounding personnel and processes for ensuring sterility in the office setting.

USP 797 Update

- **The specialty societies reiterated that there is insufficient data to indicate that additional safety equipment or procedures are necessary beyond the current Chapter 797 standards.**
- ***Representatives of the USP stressed the importance of not creating an exception for any group that would appear to require insufficient safety standards compared to those applicable to other compounding settings.***

USP 797 Update

- All groups agreed to continue working together in pursuit of an approach that will allow for practitioners to continue to provide this life changing and lifesaving evidence-based treatment, while following procedures designed to ensure patient safety.

June 2017 USP Update- AAAAI

// June 2017 //

Practice Matters is brought to you by the AAAAI Office of Practice Management.

June 9, 2017

Update on USP 797 and FDA Activities Related to Compounding of Patient Specific Allergen Vials for Immunotherapy

Specialty leaders representing physicians from the American Academy of Allergy, Asthma & Immunology, American College of Allergy, Asthma & Immunology, American Academy of Otolaryngic Allergy and the American Academy of Otolaryngology – Head and Neck Surgery, along with the American Medical Association, the American Rhinologic Society and the Allergy and Asthma Network—representing patient concerns—have been actively engaged with the United States Pharmacopeia (USP) and the U.S. Food and Drug Administration (FDA) regarding proposed standards and regulations impacting in-office compounding of allergen extract for immunotherapy.

In follow up to a February 2017 Stakeholder Roundtable on Allergen Immunotherapy, a workgroup has been formed including leadership of the USP Compounding Expert Committee, representatives from the specialty societies and USP staff. This group met on Friday, June 2 for an update on the continuing effort to revise Chapter 797. Discussions included appropriate standards for training of compounding personnel and processes for ensuring sterility in the office setting. The specialty societies reiterated that there is insufficient data to indicate that additional safety equipment or procedures are necessary beyond the current Chapter 797 standards. Representatives of USP stressed the importance of not creating an exception for any group that would appear to require insufficient safety standards compared to those applicable to other compounding settings. All groups agreed to continue working together in pursuit of an approach that will allow for practitioners to continue to provide this life-changing and life-saving evidence-based treatment, while following procedures designed to ensure patient safety.

June 2017 FDA Update- AAAAI

On Tuesday, June 6 the FDA Center on Drug Evaluation and Research (CDER) Office of Compounding hosted a series of listening sessions with seven different healthcare constituencies regarding compounding practices in different settings. Our specialty societies participated in similar sessions held in June 2016, but it is significant to note that the allergy/immunology and otolaryngology specialties were invited to a separate session from other specialties for the first time this year. This allowed the discussion to focus extensively on concerns related to compounding and administration of allergen immunotherapy. Discussion focused on the 2016 FDA Proposed Guidance on Insanitary Conditions, which the FDA regarded as a follow up to previous regulations and not the precursor to a set of sweeping new requirements on physical facilities. The FDA acknowledged that the implications on a practice such as allergen immunotherapy were not taken into account in its development. Specialty leaders urged an approach that would balance the potential for infectious adverse events, which the FDA admits has not been identified as a problem, with the increased threat of anaphylactic reactions possible if source extract products are not controlled for consistency and patient status in the physician's office.

We will continue to work together and to keep our members apprised as compounding rules and standards are considered and developed.

USP and FDA

- Ongoing negotiation between allergists and USP
- FDA indicates that it will follow USP guidance
- Allergists attempt to thwart new sterility requirements proposed by USP
- Conversation with former US Congressional Representative Steve Kagen, MD- an allergist who is a liaison to USP- June 2016 : USP requirement for laminar flow hoods and enhanced sterile technique is all but certain

Summary Of US Allergen Immunotherapy Situation (1)

- High prevalence of allergic rhinitis
- Patients relatively wealthy and well insured
- Cost burden shifted to patients by moving meds to OTC status
- Patients fail OTC meds and want Allergen Immunotherapy
- Allergen Vaccines being withdrawn which do not meet current FDA standards
- Allergists compound vials of multiple antigens mixes in their office

Summary Of US Allergen Immunotherapy Situation (2)

- Medicare and Private Commercial Insurance restrict payment for up-dosing vials
- Current up-dosing methods take 6 to 12 months to reach maintenance
- Maintenance Immunotherapy should be given for 3 years
- Adherence to allergen immunotherapy regimens is as low as 15%
- Anaphylaxis remains a problem
- To manage anaphylaxis risk patients given very dilute extracts gradually up-dosed and kept 30 minutes in office after injections

Summary Of US Allergen Immunotherapy Situation (3)

- Allergists reject SLIT tablets- want in office adminsterd injectable therapy
- USP and FDA Draft Guidelines could eliminate in-office allergen extract vial compounding
- FDA expresses desire to move away from off label non-approved mixtures to “pharmacy grade medicine” allergen vaccines
- Allergy community has adopted *buy- and- bill* or *insurance- paid –physician- administered* therapies such as Xolair (omalizumab) and Nucala (mepolizumab)

Solution to the USA Allergen Immunotherapy Problem

- Pharmacy Grade Allergen Vaccines to meet FDA and USP Standards
- End of In-Office Allergen Vaccine Compounding
- Buy and Bill with Mark-Up for these new Allergen Vaccines
- Short Course Immunotherapy to enhance Adherence and Reduce Staff Cost for Administration of Prolonged Courses
- Safety Enhancement of Immunotherapy Vaccines to Near Elimination of Anaphylaxis and Fatality Risk

Short Course Pharmacy Grade SCIT Initiatives in the USA

- ImmuLogic: T cell peptides
- Circassia: T cell peptides
- Allergy Therapeutics: MATA MPL vaccines

Attempt at Pharmacy Grade Product: T Cell Reactive Peptides

- T cell reactive peptides derived from allergens
- Built on construct of the scientist Malcolm Gefter, PhD from MIT : use of T-cell peptides to induce desensitization towards an allergen
- Originally developed by the US company "ImmuLogic", with funding from Marion Merrell Dow
- Studies failed in the US in mid to late 1990s due to anaphylaxis due peptides being "too long" thereby retaining some IgE binding epitopes
- My lab involved in studying these peptides using basophil histamine release after anaphylaxis occurred

ImmuLogic Fails

Cat allergen vaccine - ImmuLogic

Alternative Names: Allervax cat vaccine

- **16 Jan 2001** Discontinued-III for Allergy in USA (Unknown route)
- **01 Dec 1997** Suspended-III for Allergy in USA (Unknown route)
- **16 Jul 1996** A clinical study has been added to the Vaccines therapeutic trials section (Pharmaceutical Approvals Monthly 1996 Jun: 50)

ImmuLogic Ousts 5 Directors, Including Company's Founder

a Wall Street Journal Staff Reporter

Updated March 6, 1997 10:11 a.m. ET

WALTHAM, Mass.-ImmuLogic Pharmaceutical Corp., under pressure from disgruntled shareholders, replaced five of eight members of its board, including founder and chairman Malcolm Gefter.

Shares of the struggling biotechnology company surged 11% on the news Wednesday, closing at $6.375, up 75 cents, in Nasdaq Stock Market trading.

ImmuLogic is developing vaccines for people allergic to cats and ragweed. But the 10-year-old company...

Biotechnology

Company Overview of Immulogic Pharmaceutical Corp.

Company Overview

As of August 1999, Immulogic Pharmaceutical Corp. went out of business. Immulogic Pharmaceutical Corp. operates as a biopharmaceutical company that develops products with a primary emphasis on the diagnosis and treatment of allergies and on the immunological treatment of addiction. The company was founded in 1997 and is based in Waltham, Massachusetts.

610 Lincoln Street Suite 300

Waltham, MA 02154 United States

Founded in **1997**

Circassia T Cell Peptide Initiative

- Work of Mark Larche to revise of T cell peptides as smaller molecules with overlapping T cell reactive epitopes to eliminate anaphylaxis
- Initial studies with Cat allergy T cell peptides promising but large Phase 3 study fails
- Dust Mite Study with T cell pepetides fails
- Early studies were done to identify effective dose by Inflammax
- ? Wrong dose versus failure of concept

Circassia Abandons the T cell Peptide Initiative

Circassia Pharmaceuticals Plc

Circassia shares volatile after abandoning anti-allergy programme

fastFT

April 18, 2017
by: Nicholas Megaw

Shares in Circassia Pharmaceuticals briefly dropped as much as 7.8 per cent on Tuesday morning and continued to trade choppily, after the British biotech group said it would end new investment in its anti-allergy treatments after a series of disappointing drug trials.

The abandonment of Circassia's allergy programme marks a disappointing reversal of fortunes for the Neil Woodford-backed company, which floated in 2014 with hopes of becoming "the next Shire" in London's biggest life-science IPO for decades.

On Tuesday the company said that trials of a new treatment for a dust mite allergy did not show a significant effect compared with a placebo.

The trial's failure followed similar issues with a new cat allergy treatment last year, which caused shares in the group to shed more than two thirds of their value.

Steve Harris, Circassia chief executive, said he believes both treatments were effective, and questioned the regulatory requirements that led to the disappointing results.

He said:

It is concerning that in two well-designed field trials, a robust placebo response has confounded our ability to demonstrate a significant treatment effect, despite positive results in earlier chamber studies. We remain convinced that the technology has biologic activity, but we also believe the difficulty in overcoming the placebo effect using the field study designs required by regulators represents a significant hurdle.

Mr Harris said Circassia will make no further investment in its allergy programmes, and will instead focus on its wider respiratory business, particularly a collaboration with FTSE 100 group AstraZeneca agreed last month.

Shares in Circassia were down 0.5 per cent at publication time, to 103p.

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Allergoids

- Modify allergen by polymerization
- Epsilon amino acid lysine reacted with glutaraldehyde to produce a polymer
- Bind ~ 80% of episilon lysines
- Long used as a means of decreasing allergenicity with maintenance of immunogenicity-
- Work of Roy Patterson at Northwestern University, Chicago, with polymerized ragweed and grass in 1970s

Professor Roy Patterson
An American Allergy Legend

A multi-institutional trial of polymerized whole ragweed for immunotherapy of ragweed allergy

Stephen G. Hendrix, M.D., Roy Patterson, M.D., C. Raymond Zeiss, M.D., Jacob J. Pruzansky, Ph.D., Irena M. Suszko, B.S., Robert C. McQueen, M.D., Raymond G. Slavin, M.D., Michael P. Miller, M.D., Philip L. Lieberman, M.D., and Albert L. Sheffer, M.D.

Chicago, Ill., St. Louis, Mo., Memphis, Tenn., and Boston, Mass.

Eighty ragweed-sensitive patients in four cities were recruited to study the safety and efficacy of partially purified, polymerized whole ragweed (PRW) as an improved form of immunotherapy. Groups of 20 patients in Chicago, Boston, Memphis, and St. Louis had blood drawn for immunologic studies before and after the 1978 and 1979 ragweed seasons and completed detailed daily symptom score sheets each day of the 1978 and 1979 ragweed pollen seasons. Beginning in March, 1979, all patients except one received 15 weekly injections of PRW totaling 50,000 protein nitrogen units (PNU) and containing about 500 μg ragweed AgE. One patient received 25,000 PNU. Symptom score indices of the posttreatment 1979 season were compared with those from the pretreatment 1978 season and also with the scores of similar groups of ragweed-sensitive patients in each city treated only with medication for symptomatic relief during the 1979 season. Local reactions to polymerized ragweed immunotherapy were minimal. No abnormalities in complete blood count, erythrocyte sedimentation rate, chest x-ray film, urinalysis, or rheumatoid factor occurred in the immunotherapy-treated groups. Total serum antibody binding of ragweed AgE increased 12-fold following immunotherapy. When compared either with their 1978 untreated group scores or when compared with scores from the untreated group in each city in 1979 (control group), the symptom score indices of the immunotherapy-treated groups in 1979 were significantly improved. PRW is efficacious in the treatment of ragweed hay fever and can be administered more safely and in higher doses with fewer injections than conventional extracts. It represents an improved form of immunotherapy.

J. ALLERGY CLIN. IMMUNOL.
DECEMBER 1980

A double-blind placebo-controlled trial of polymerized whole grass administered in an accelerated dosage schedule for immunotherapy of grass pollinosis

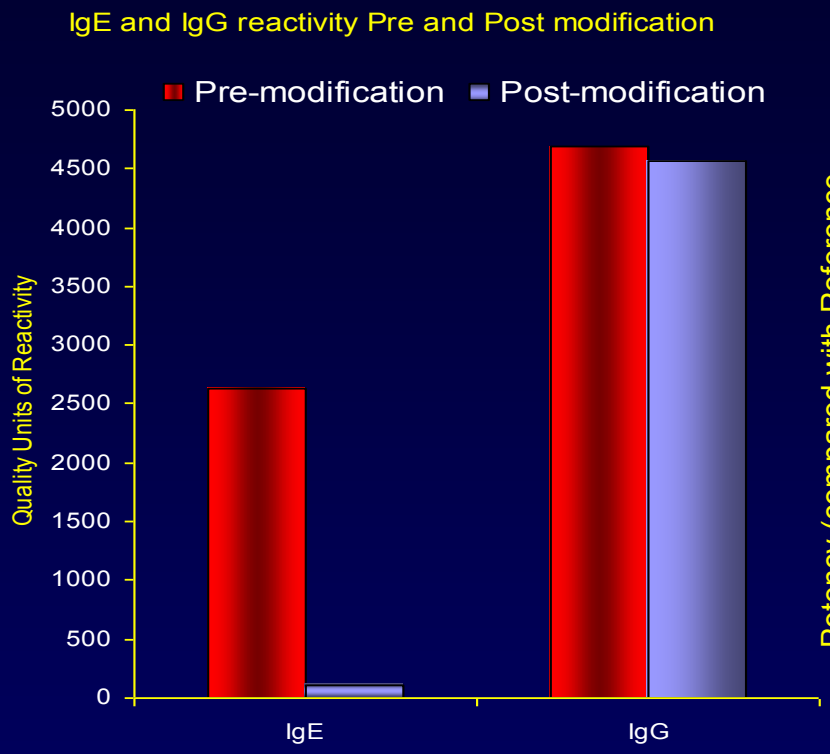
Leslie C. Grammer, M.D., Martha A. Shaughnessy, B.S., Susan M. Finkle, B.A., John J. Shaughnessy, Ph.D.,* and Roy Patterson, M.D. *Chicago, Ill., and Holland, Mich.*

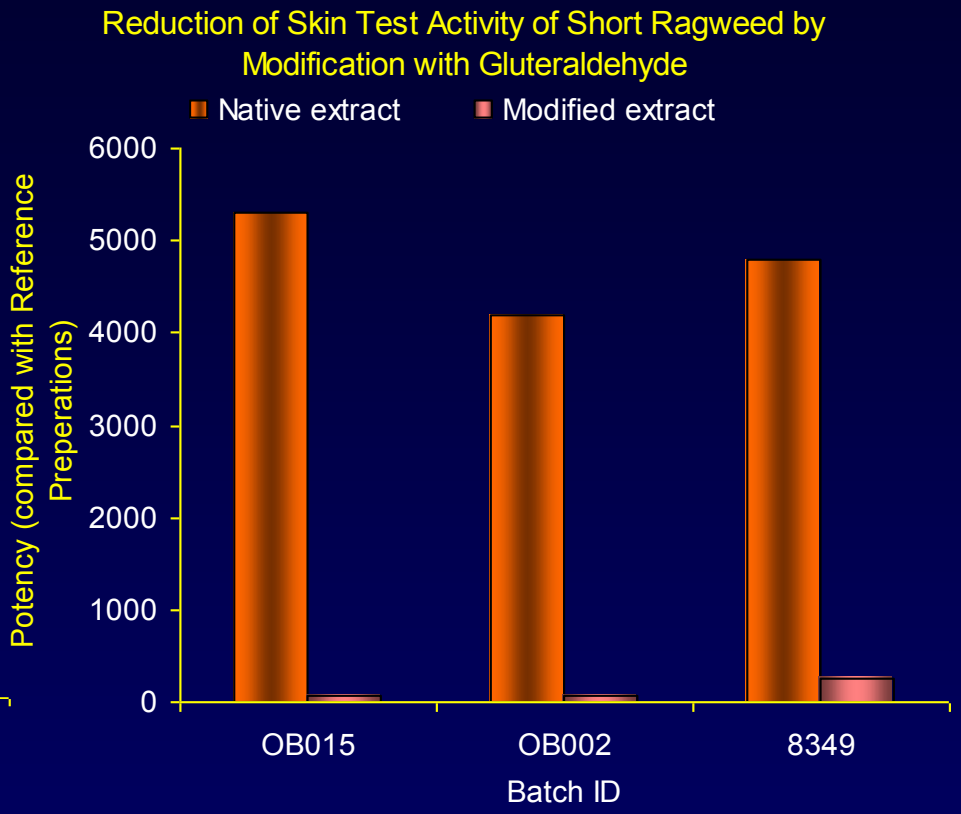
Forty-four patients were entered into a study of the efficacy and safety of individually polymerized grass (IPG) immunotherapy with an accelerated dosage schedule. Patients were paired on the basis of cutaneous end point titrations to timothy, orchard, and Bermuda grass–pollen extracts. In a double-blind manner, one patient in each pair was treated in nine weekly visits with 13 injections that totaled 24,000 PNU of each grass to which the patient had cutaneous reactivity. The other patient in each pair received caramelized glucose histamine placebo. Symptom and medication score sheets were completed by 33 patients each day of the grass season. Blocking antibody rose significantly in the IPG–treated group but was unchanged in the placebo-treated group. By Wilcoxon paired signed-rank test, the symptom medication scores in the IPG–treated group were significantly lower than those in the placebo-treated group. There were no systemic reactions and no clinically significant changes in routine laboratory tests in either group. In summation, this study demonstrates the safety, immunogenicity, and efficacy of IPG therapy in an accelerated dosage schedule for treatment of grass pollinosis. (J ALLERGY CLIN IMMUNOL 78:1180-4, 1986.)

This clinical trial was designed to evaluate safety, efficacy, and immunogenicity of an accelerated dosage schedule of IPG immunotherapy. We have previously reported successful clinical results with 12 weekly injections of IPG totaling 48,000 PNU.[3] In this trial we report similarly successful results with nine weekly visits and 13 injections of IPG totaling up to 72,000 PNU. Because patients often cite number of office visits and long therapy time as factors mitigating against immunotherapy,[10] polymerized allergens requiring fewer office visits than unmodified allergens may make immunotherapy more acceptable to patients. An accelerated dosage schedule may increase acceptability. Moreover, such an accelerated schedule may also allow the cost per patient treated to be reduced, and, in a cost-conscious age, this is desirable.

In terms of safety, there were no systemic reactions in spite of the large dose administered, up to 72,000 PNU. This was a larger dose than was received by patients in our prior study and was administered during a shorter time period of 9 weeks.[3] This is important because the major risk for patients receiving unmodified allergens is anaphylaxis, and this risk has been reported to range between 8% and 30% per patient course.[11]

Advantages of Allergoids





- Chemical modification of allergens:
- Reduced allergenic activity
  - Inactivate **IgE-binding-epitopes** (conformational)
  - Low binding to mast cell bound IgE

- Preserved immunogenity
  - Preserve **T-cell-epitopes** (sequential)
  - Stimulates T-helper cells
  - Added safety bonus
- Ideal for combination with MPL

- Reduced number of injections required to reach top dose allows short course therapy

Compared with the intact allergens, allergoid products have:

- **definitely reduced allergenicity;**
- **preserved but clear reduced immunogenicity.**

(Lund L., Henmar H., Wurtzen P.A., Lund G., Hjortskov N., Larsen J.N. Clinical and Experimental Allergy, 2007; 37:564-571)
(Henmar H., Lund G., Lund L., Peterson A., and Wurtzen P.A. Clinical and Experimental Immunology, 2008;153:316-323)

Because of IgG immune response after chemical modification of allergen usually weaker than that of unmodifed allergen it is possible to improved it using some adjuvants.

Conception of adjuvanted allergoids:

To improve efficacy (immunogenicity) of ASIT with allergoids they can be used in combination with adjuvants or immunomodulators (conjugates or complexes modified allergen and adjuvant/immunomodulator)

Allergy Therapeutics Initiative: MATA MPL

- Allergoid: allergen modified with glutaraldehyde forming polymers:

Binding of glutaraldehyde to epsilon amino lysine residues in the allergen creates large polymers which largely eliminate IgE binding allergen epitopes but retains shorter T cell binding epitopes

- Micro-Crystalline Tyrosine:

Binds to allergen and MPL via electrical forces to create a transient depot and drives Th1 responses preferentially

- Monophosphoryl Lipid A:

potent TLR4 immune adjuvant magnifies immune response in Th1 direction

MATA MPL

- Glutaraldehyde Modified Allergen Extracts and Monophosphoryl Lipid A Co adsorbed onto Micro-Crystalline L-Tyrosine (MCT)

Four Preseasonal Injections Required

- Three Rising strengths and One Repeat at Top Dose
- First allergens chosen are Grass, Tree and Ragweed Pollen

Grass MATA MPL

- Phase III Study~ 1028 subjects
- Re-analysis based on Peak Placebo Symptoms

Ultrashort-specific immunotherapy successfully treats seasonal allergic rhinoconjunctivitis to grass pollen

Lawrence M. DuBuske, M.D.; Anthony J. Frew, M.D., F.R.C.P.; Friedrich Horak, M.D.; Paul K. Keith, M.D.; Christopher J. Corrigan, M.D.; Werner Aberer, M.D.; Tom Holdich, M.B.B.S., M.F.P.M.; Karl J. Fischer von Weikersthal-Drachenberg, M.D.

Allergy & Asthma Proceedings: 10.2500/aap.2011.32.3453

G301: Multinational Grass MATA MPL Study- Largest MPL Allergen IT Study Conducted

- 4 pre-seasonal injections of Modified Grass Allergen plus MPL in Tyrosine Depot

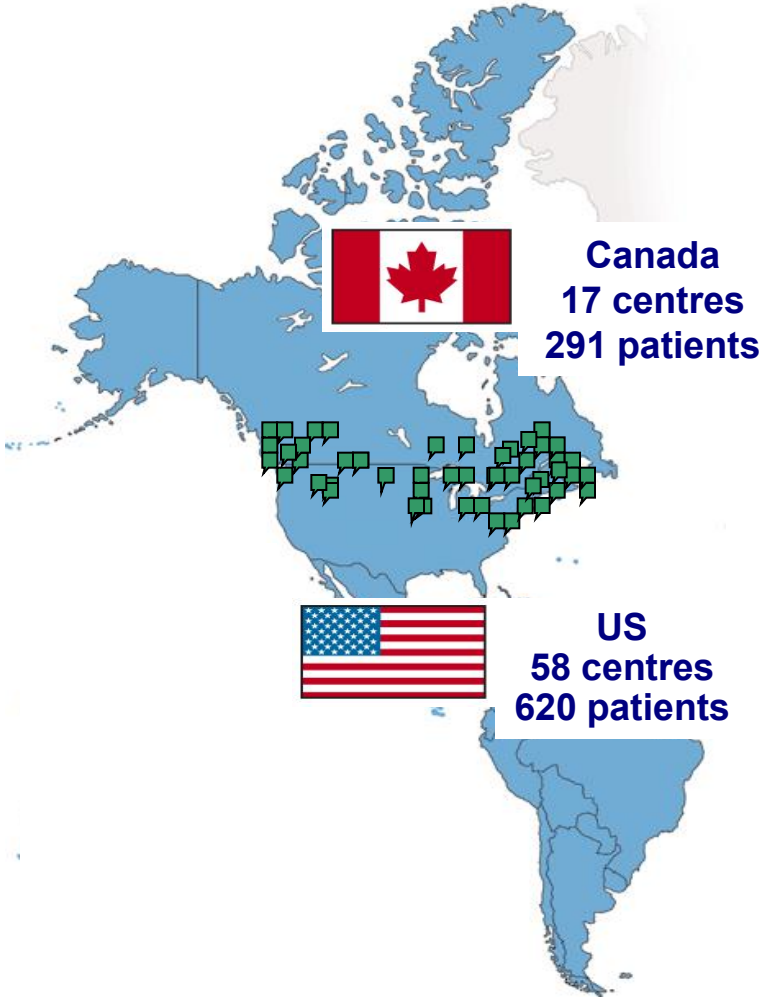
- Given grass pollen preseason in 2008

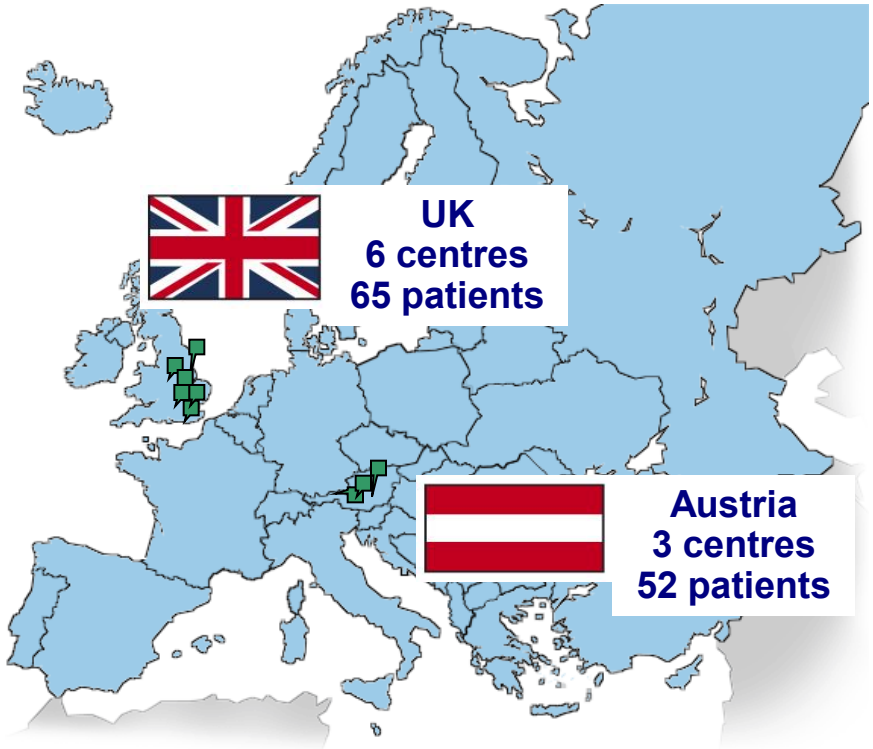
*complete records during 4 peak weeks of pollen season
L DuBuske, AAP, 2011

G301 - Pivotal Efficacy and Safety Study

Allergy Therapeutics®
Transforming Allergy Treatment

International multi-centre – 84 centres, 1028 patients





G301: Primary Study Measure

- Primary Measures
- Combined symptom + medication score (= CSMS)
  - Total symptom score (TSS) eyes and nose
  - self-reported by patients during 4 peak weeks of grass pollen season (electronic diary)

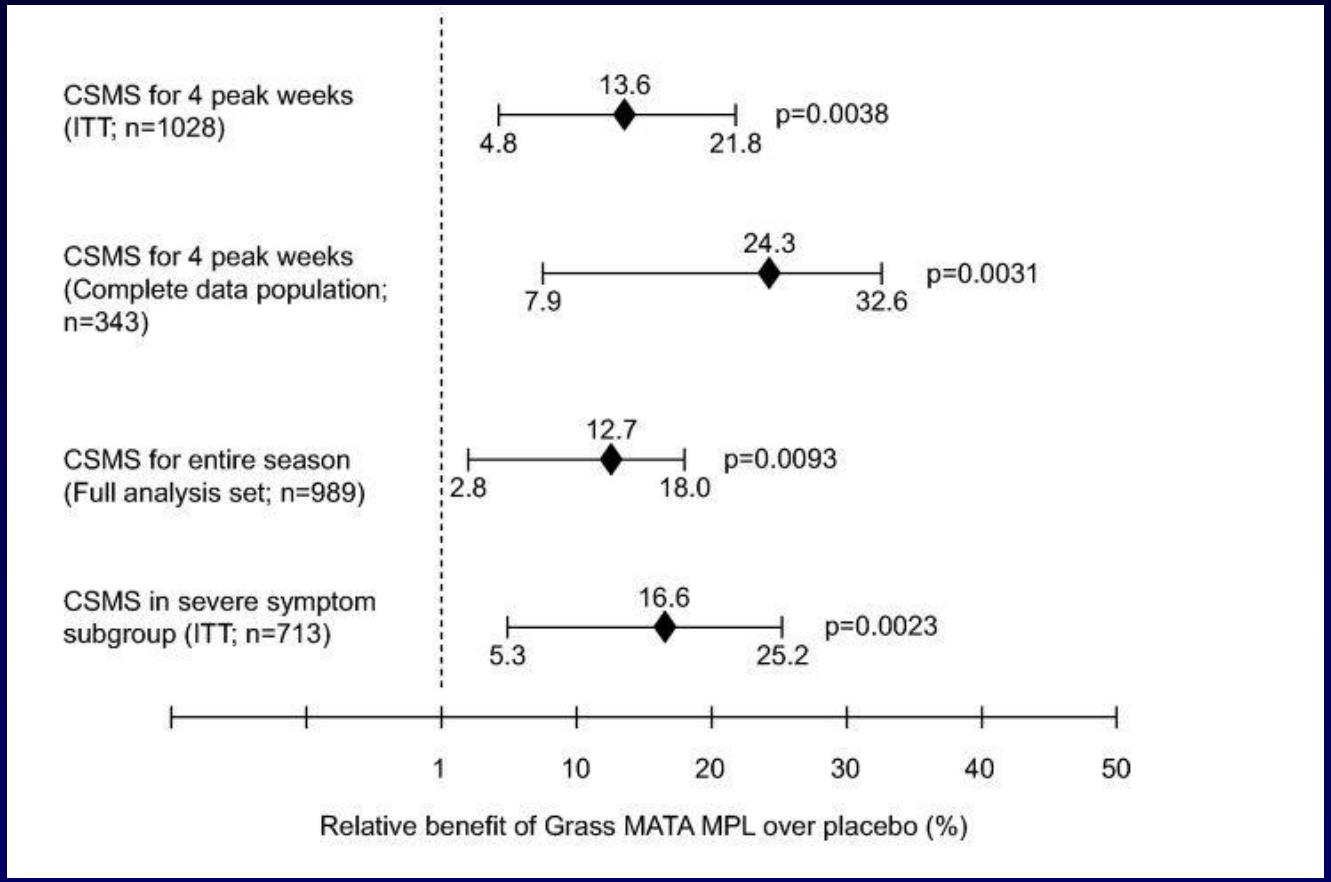
- Safety - adverse events

Compliance

	Placebo (n= 514)	Grass MATA MPL (n= 514)
Patients receiving ≥1 injection	99.8%	100%
Completed course of treatment	97.9%	95.3%
Completed study	91.4%	92.0%
Completed as planned	90.8%	90.7%
Completed visits but discontinued treatment	0.6%	1.4%

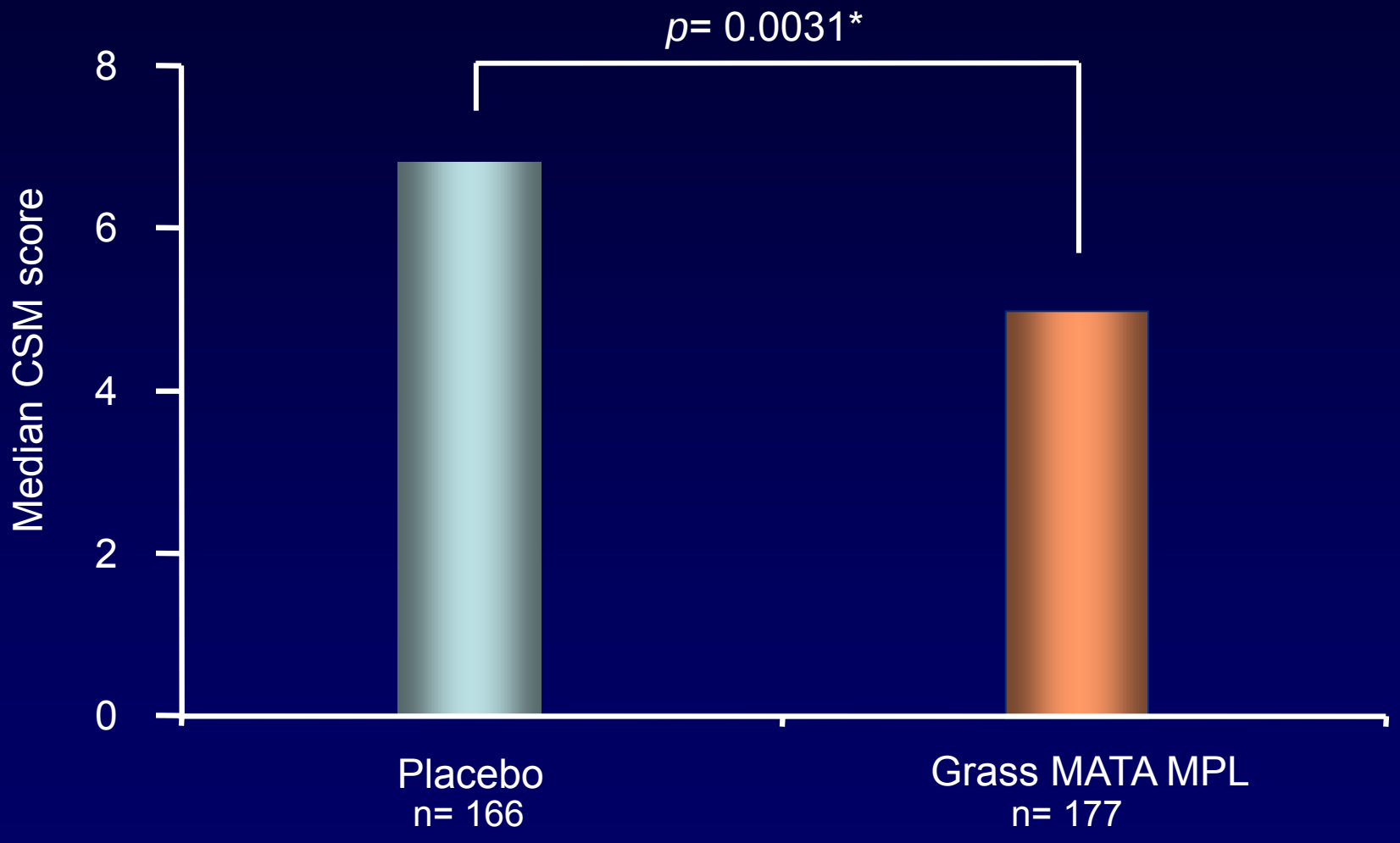
ITT population

24.3 % Benefit over Placebo



Relative benefit (%) of Grass Modified Allergen Tyrosine Adsorbate monophosphoryl lipid A (MATA MPL) over placebo during the 4 peak weeks of the pollen season and the entire pollen season and in subjects with severe symptoms (disease severity questionnaire [DSQ], ≥7 with at least one symptom category =3).
Reproduced with permission from *Allergy & Asthma Proceedings*

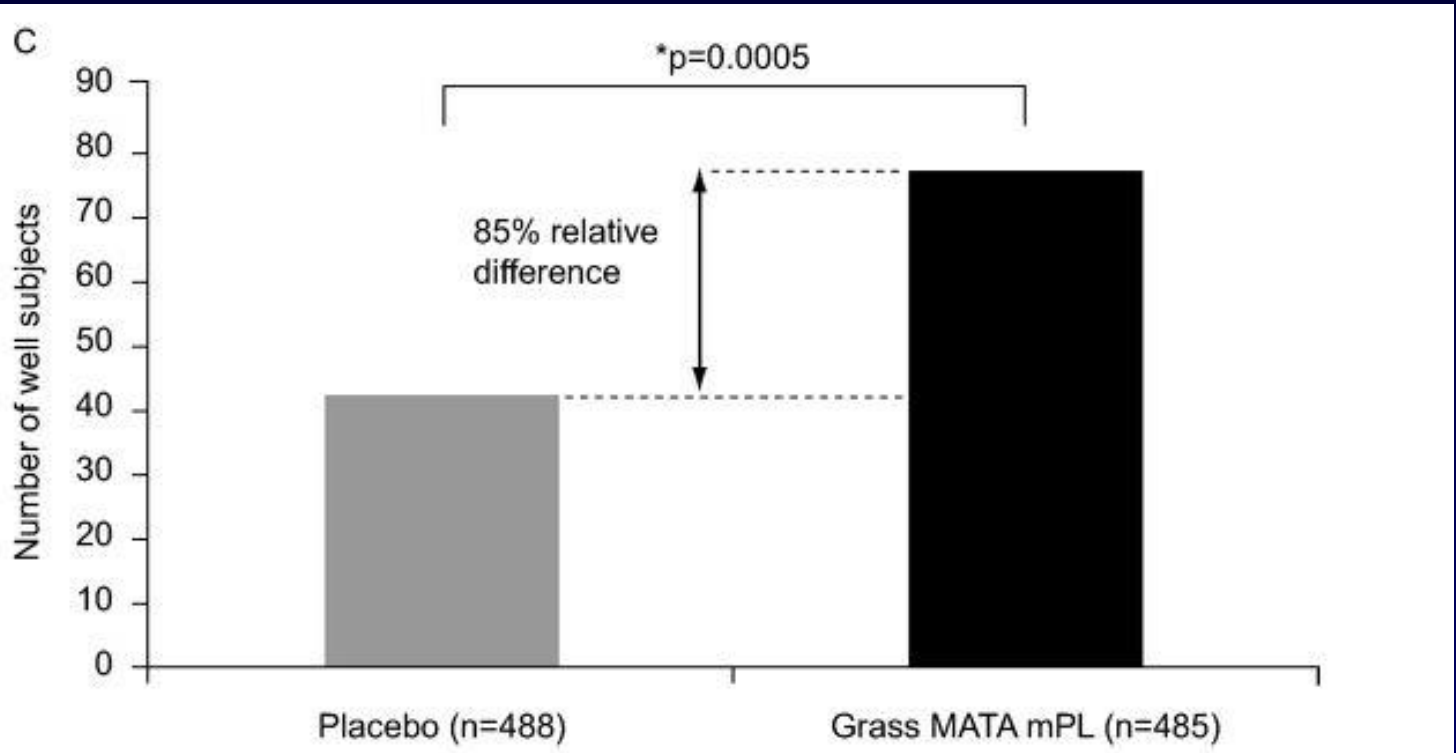
Reduction in CSMS Following Grass MATA MPL
Patients with Complete Data Set



4 peak weeks of pollen season

*Comparison of LS means

Proportion of Well Subjects Increased with Grass MATA MPL



* p value based on a Chi-Square-test with significance at the 5% level
n=number of subjects with data available

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Adverse Events: No Anaphylaxis

Table 3 **Summary of adverse events (reported in >5% of any one group) during the treatment period**

Event	Grass MATA MPL (n = 514)	Placebo (n =5 13)
Injection site conditions, (%)		
Pain	166 (32)	84 (16)
Pruritus	154 (30)	17 (3)
Swelling	129 (25)	9 (2)
Erythema	97 (19)	7 (1)
Warmth	26 (5)	2 (0)
Headache, n (%)	35 (7)	26 (5)
Nasopharyngitis, n (%)	30 (6)	31 (6)
Upper respiratory tract infection, n (%)	26 (5)	23 (4)

MATA = Modified Allergen Tyrosine Adsorbate; MPL = monophosphoryl lipid A.

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Ann Allergy Asthma Immunol 109 (2012) 342–347

Contents lists available at SciVerse ScienceDirect

Assessment of specific immunotherapy efficacy using a novel placebo score–based method

Anthony J. Frew, MD [*]; Lawrence DuBuske, MD [†]; Paul K. Keith, MD, MSc [‡]; Christopher J. Corrigan, PhD [§]; Werner Aberer, MD [¶]; and Karl J. Fischer von Weikersthal-Drachenberg, MD [‖,**]

Method: An innovative approach to the analysis of seasonal diaries - definition of peak season based on symptom/medication scores of the placebo group- G301 Study

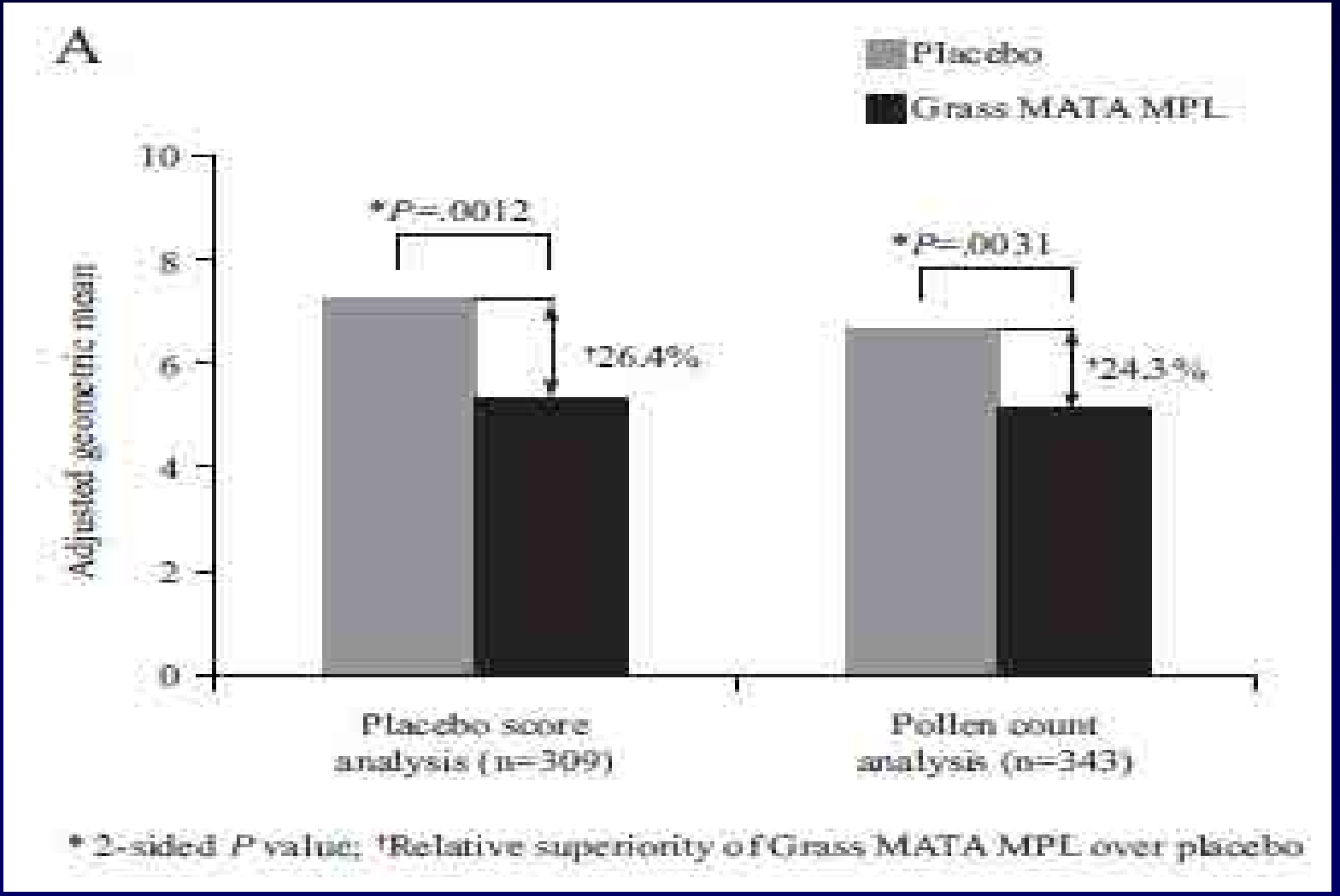
Comparison of the combined symptom/medication scores (CSMS) of the treatment groups for the primary and secondary endpoints within the 4 weeks of peak allergen load.

Definition of the 4 peak weeks:

a) based on the pollen counts collected by pollen traps.

b) based on the symptom/medication scores of the placebo group

CSMS- Complete Data Set: Difference Versus Placebo -Peak Pollen Count Versus Peak Placebo Score Analysis



JACI
Ragweed MATA MPL EEC Study

Rhinitis, sinusitis, and upper airway disease

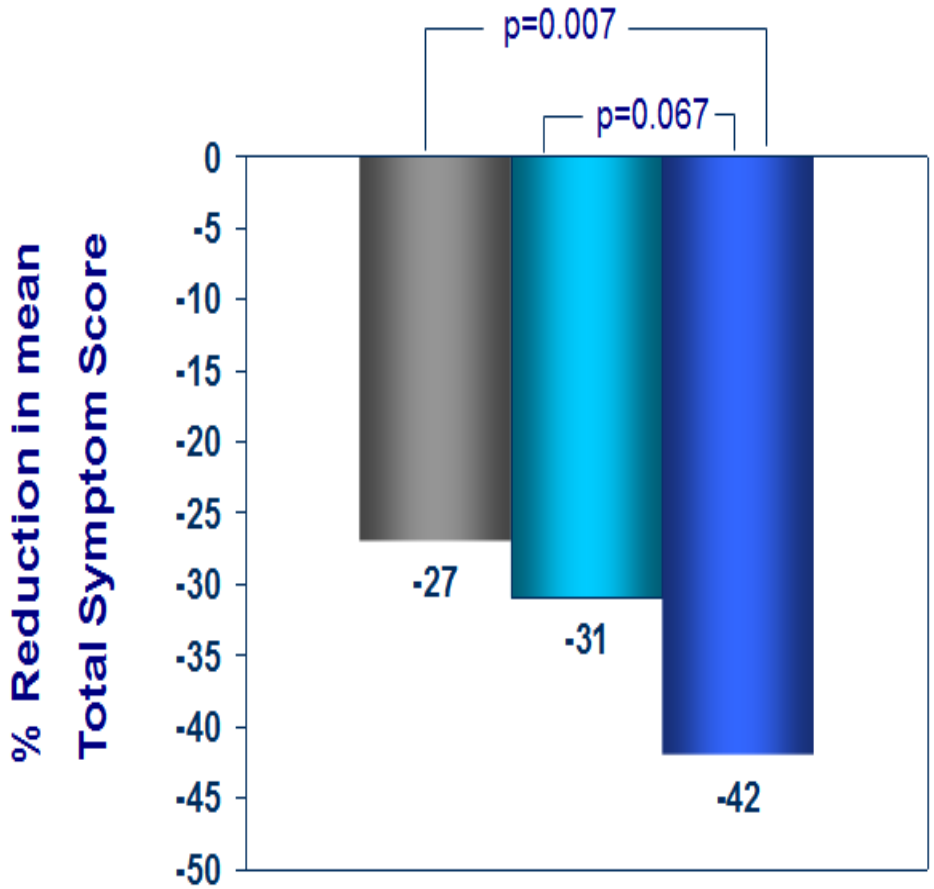
Efficacy of a short course of specific immunotherapy in patients with allergic rhinoconjunctivitis to ragweed pollen

Piyush Patel, MD,[a]* Tom Holdich, MBBS,[b] Karl J. Fischer von Weikersthal-Drachenberg, MD,[c] and Birgit Huber, PhD[c]‡ *Mississauga, Ontario, Canada, West Sussex, United Kingdom, and Munich, Germany*

Background: Specific immunotherapy acts to modify the underlying cause of allergic rhinoconjunctivitis. Addition of

symptoms in patients with seasonal allergic rhinitis and that it is well tolerated. (J Allergy Clin Immunol 2014;133:121-9.)

% Reduction in Total Symptom Scores



Study design

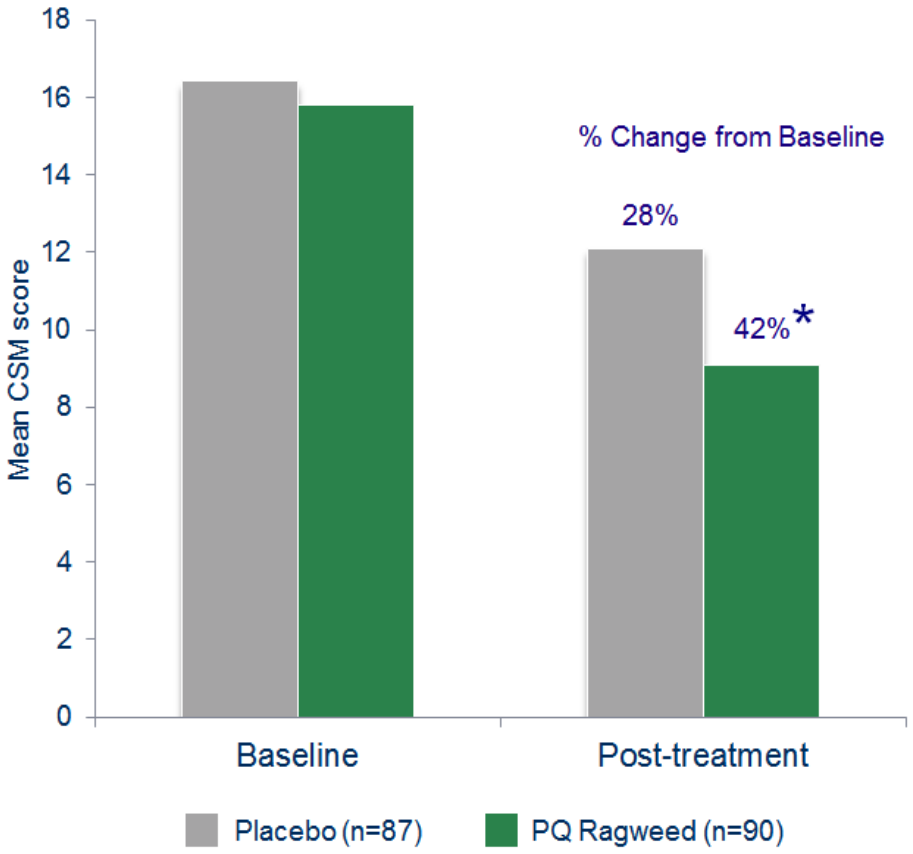
- 228 subjects
- 4 x 3h pollen challenge
- Pre & post treatment
- 4 injections – 3 weeks
- Re-challenge 3 weeks later

Placebo (n=87)

Ragweed MATA (n=35)

Ragweed MATA MPL (n=90)

% Change from Baseline in Total Symptom Scores



- Statistically significant difference in change in symptom score from baseline compared to placebo (*p<0.01)
- 48% relative superiority over placebo
- Clinically significant 42% improvement in symptoms from baseline (moderate → mild)
- No serious or severe systemic side effects

Impact of MPL in MATA Vaccine (1)

1) Change from Baseline TSS: MATA and MATA MPL versus Placebo:

Analysis based on Median TSS Change from Baseline:

Placebo: -3.54 MATA: -4.38 MATA MPL: -6.46

MATA= 23.7% > than placebo MATA MPL = 82.4% > than placebo

MATA MPL = 3.47 X effect of MATA

Impact of MPL in MATA Vaccine (2)

2) Post Treatment TSS: MATA and MATA MPL versus Placebo:

Analysis based on Median Post Treatment TSS: MATA and MATA MPL versus Placebo:

Placebo: 12.0 MATA: 11.1 MATA MPL: 8.81

Versus Placebo: MATA = -7.5% TSS reduction MATA MPL = -26.65% TSS reduction

MATA MPL = 3.57 X effect of MATA

Adverse Events

TABLE E2. Adverse reactions: ITT set

Category	Ragweed MATA MPL (n = 95)	Ragweed MATA (n = 40)	Placebo (n = 93)
Patients with no reaction, no. (%)	9 (9.5)	4 (10.0)	47 (50.5)
Patients with reaction, no. (%)	86 (90.5)	36 (90.0)	46 (49.5)
Local reaction, no. (%)	77 (81.1)	33 (82.5)	32 (34.4)
Mild, no. (%)	54 (56.8)	19 (47.5)	32 (34.4)
Moderate, no. (%)	18 (18.9)	13 (32.5)	0 (0.0)
Severe, no. (%)	5 (5.3)	1 (2.5)	0 (0.0)
Systemic reaction, no. (%)	9 (9.5)	3 (7.5)	14 (15.1)
Mild, no. (%)	8 (8.4)	3 (7.5)	13 (13.9)
Moderate, no. (%)	1 (1.1)	0 (0.0)	1 (1.1)
Severe, no. (%)	0 (0.0)	0 (0.0)	0 (0.0)

Note: Adverse reactions that occurred within 24 hours of the injection and were considered possibly, probably, or definitely related to the study medication were included in the summary. Subjects reporting more than 1 adverse reaction are only counted once (under the greatest reported severity).

(J Allergy Clin Immunol 2013; Piyush Patel, MD, Tom Holdich, MBBS,Karl J. Fischer von Weikersthal-Drachenberg, MD,and Birgit Huber, PhD
Mississauga, Ontario, Canada, West Sussex, United Kingdom, and Munich, Germany)

CONCLUSIONS

1) Ultra short-course SIT with only 4 injections of Ragweed MATA MPL over 3 weeks -efficiently reduced allergy symptoms,

   - improved quality of life,

   - and increased ragweed specific IgG, IgG1, and IgG4 levels

   in subjects with moderate-to severe SAR ascribed to ragweed pollen exposure 3 weeks after the completion of the treatment course.

2) The study did not demonstrate any safety or tolerability concerns for Ragweed MATA MPL.

(J Allergy Clin Immunol 2013; Piyush Patel, MD, Tom Holdich, MBBS,Karl J. Fischer von Weikersthal-Drachenberg, MD,and Birgit Huber, PhD Mississauga, Ontario, Canada, West Sussex, United Kingdom, and Munich, Germany)

TLR4 Activation and Allergen Immunotherapy

- Activation of TLR4 (MPL) in the presence of antigen may allow:

- rapid immunologic response
- rapid clinical improvement
- enhanced safety of IT administration