

Allergy Immunotherapy Literature Update

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Harold S. Nelson, MD
Professor of Medicine
National Jewish Health and
University of Colorado Denver School of
Medicine



Disclosure: Harold S. Nelson MD

Below I have disclosed relevant commercial associations that might pose a conflict of interest

- **Consultant Arrangements:**
ALK
- **Stock/Other Equity Ownership:**
None
- **Patent Licensing Arrangements:**
None
- **Grants/Research Support:**
None
- **Speakers' Bureau:**
None

Learning Objective

After participating in this session the attendee should be updated on some recent publications in the field of allergy immunotherapy and be able to apply them to their practice.

Mining Data from the German Health Care Systems

Pharmacy data from German health care systems suggested that AIT:

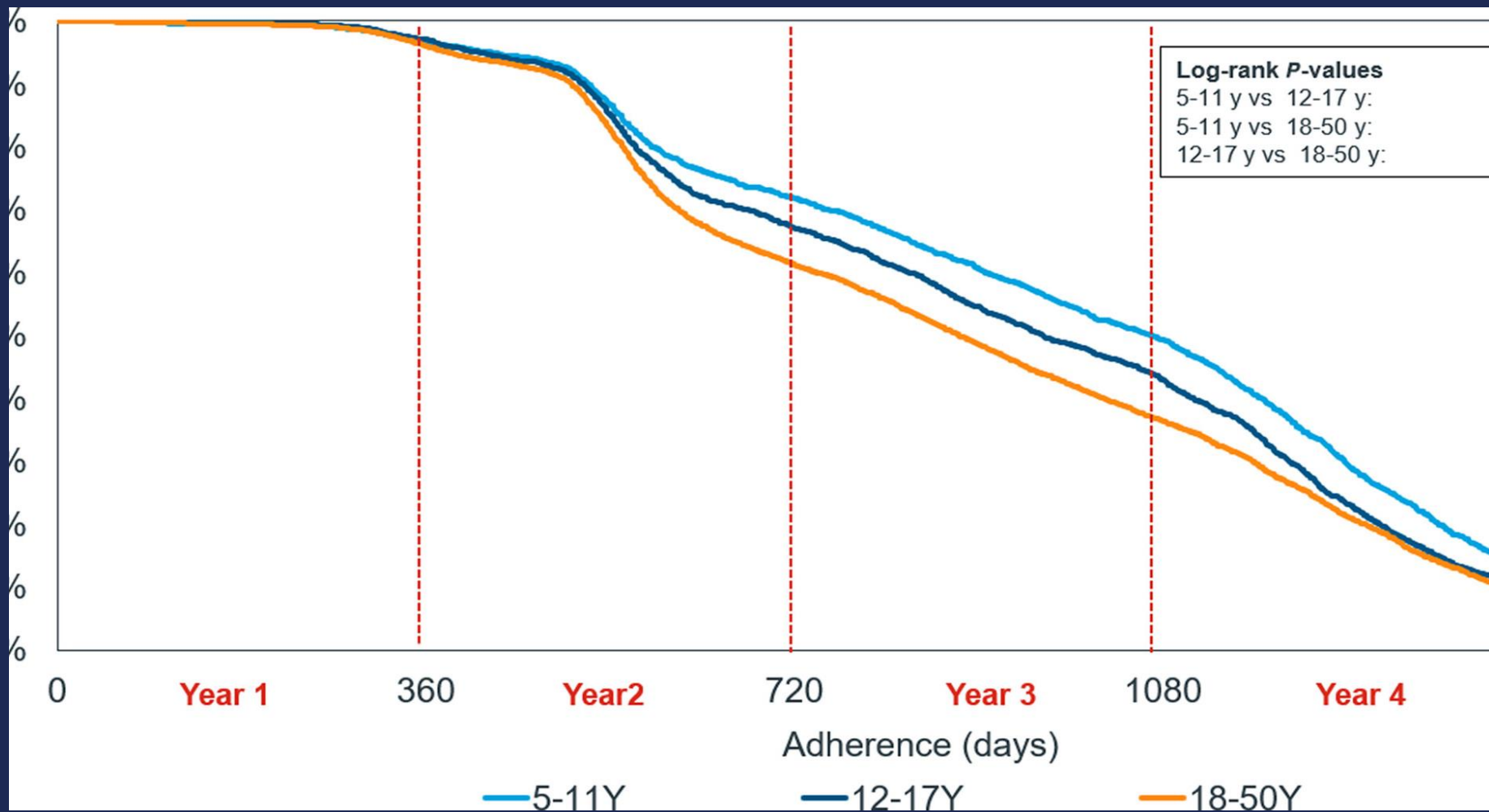
- reduced medication requirements for existing allergic rhinitis and asthma.
- reduced the development of asthma
- reduced the progression to increased severity in newly developed asthma

Real-world Evidence of Subcutaneous Allergoid Immunotherapy in House Dust Mite-induced Allergic Rhinitis and Asthma

M Jutel, et al. Allergy 2020;75:2050-2058

- Used a database covering 60% of German prescriptions.
- AR and BA defined by medication use during September-January (no seasonal aeroallergens)
- Analysis on data 2008 to 2017 with initiation of AIT 2010 to 2014. (3-7 years follow-up on AIT)
- Treatment an allergoid containing all 3 major and 4 intermediate mite allergens.

Adherence to Mite-SCIT by Age



Real-world Evidence of Subcutaneous Allergoid Immunotherapy in House Dust Mite-induced Allergic Rhinitis and Asthma

- 2,350 patients received HDM allergoid and 64,740 served as controls.
- In patients receiving HDM allergoid, compared to controls:
 - Allergic rhinitis medication reduced by 59.7% ($p < 0.001$)
 - asthma medication reduced by 10.8% ($p < 0.015$)
 - The probability of developing asthma was reduced (OR 0.81) ($p = 0.008$)

Real-world Evidence of Subcutaneous Allergoid Immunotherapy in House Dust Mite-induced Allergic Rhinitis and Asthma

Conclusions

HDM allergoid SCIT with adherence of only 63.8% the end of the 2nd year and 38.6% at the end of the 3rd year, significantly reduced medication for allergic rhinitis and asthma and reduced the likelihood of developing asthma (OR 0.81).

The Moderating Role of Allergy Immunotherapy in Asthma Progression: Results of a Population-based Cohort Study

J Schmitt, et al. Allergy 2020;75:596-602;

- Data from a large statutory health insurance in Saxony included diagnoses, prescriptions, age and gender.
- Subjects ≥ 12 years continuously insured 1 January 2005 to 31 December 2014.
- No asthma 2005-2006. (8 year follow-up)
- Incident asthma defined by both physician diagnosis and asthma medication ≥ 2 times

The Moderating Role of Allergy Immunotherapy in Asthma Progression: Results of a Population-based Cohort Study

- Progression of newly developed asthma the primary outcome.
- Progression defined by:
 - escalation from GINA stage I to III (PRN SABA to low dose ICS plus LABA) or
 - stage III to IV (Low dose ICS plus LABA to medium/high dose ICS plus LABA)
 - stage 2 rarely used.
- 4,111 with incident asthma exposed to AIT, 35,056 not exposed, no adjustment for duration of AIT

J Schmitt, et al. *Allergy* 2020;75:596-602

Association Between AIT Exposure and Asthma Progression

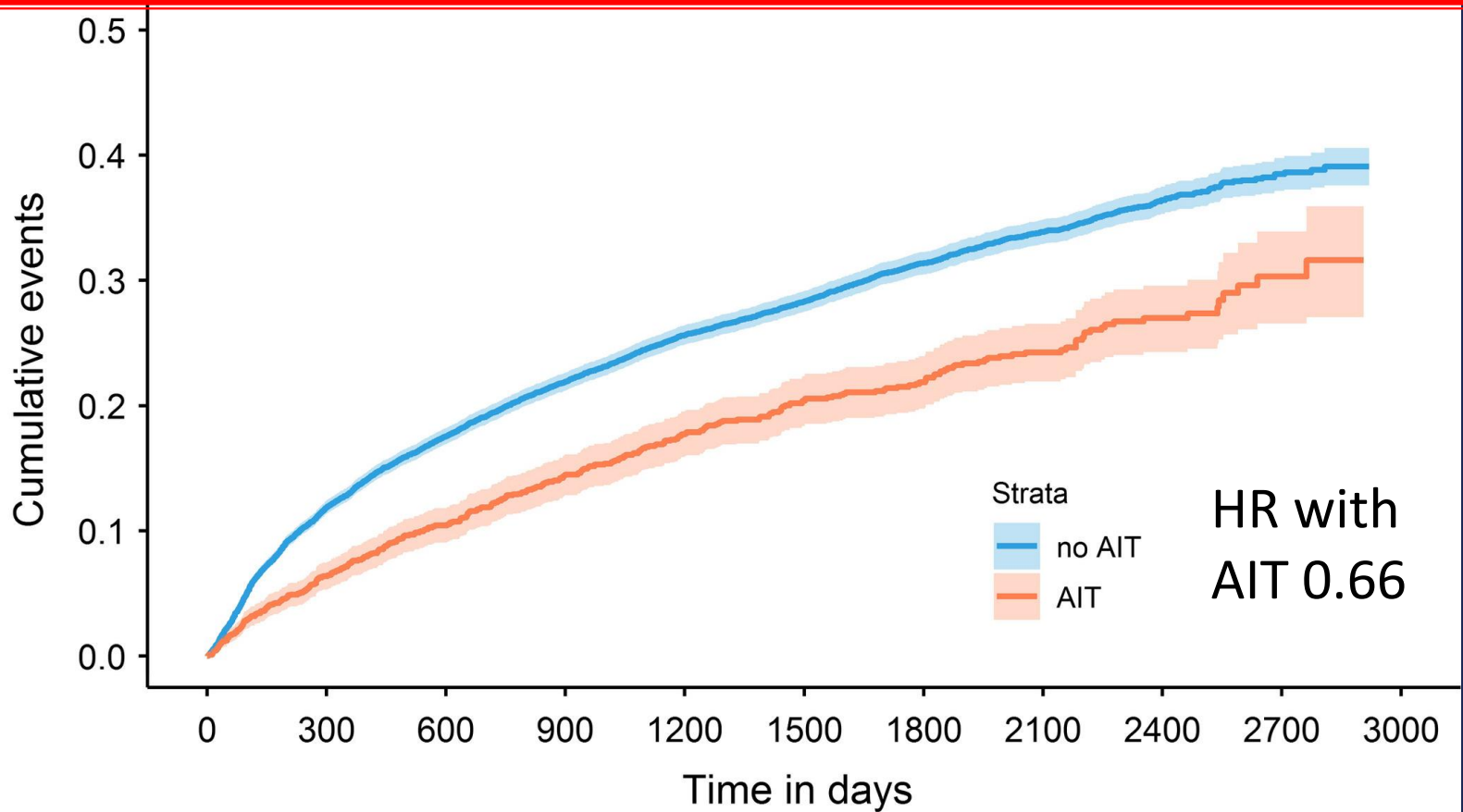
- Progression GINA step 1 to step 3 (prn SABA to low-dose ICS + LABA): Hazard Ratio AIT vs None

	All	Adolescents	Young Adults	Older Adults
AIT	0.87 (95% CI .80-.95)	0.72 (95% CI .58-.88)	0.89 (95% CI .80-.98)	1.09 (NS)

- Progression GINA step 3 to step 4 (low dose ICS + LABA to High-dose ICS + LABA) Hazard Ratio

	All	Adolescents	Young Adults	Older Adults
AIT	0.65 (95% CI .60-.74)	0.76 (95% CI .58-.99)	0.63 (95% CI .56-.72)	0.72 (95% CI .56-.94)

GINA Step 3 to 4 in Incident Asthma



Strata	Time in days												
	0	300	600	900	1200	1500	1800	2100	2400	2700	3000		
no AIT	14 646	11 847	10 005	8300	6688	5235	3736	2535	1416	446	0		
AIT	2022	1750	1539	1320	1099	858	638	429	249	82	0		

The Moderating Role of Allergy Immunotherapy in Asthma Progression: Results of a Population-based Cohort Study Conclusions

Records from a large German health care provider suggest that in individuals with onset of asthma after age 12 years AIT prevents the progression to more severe disease.

Intralymphatic Immunotherapy Improves Grass Pollen Allergic Rhinoconjunctivitis: A Three-year Randomized, Placebo- controlled Trial

SH Skaarup, et al. J Allergy Clin Immunol 2020;

- 36 patients with grass pollen induced rhinoconjunctivitis were randomized to:
 - 3 intralymphatic injections at 4 week intervals plus a booster before the 2nd grass pollen season..
 - 3 IL injections plus a placebo injection before the 2nd grass pollen season.
 - 3 placebo injections plus a placebo booster.

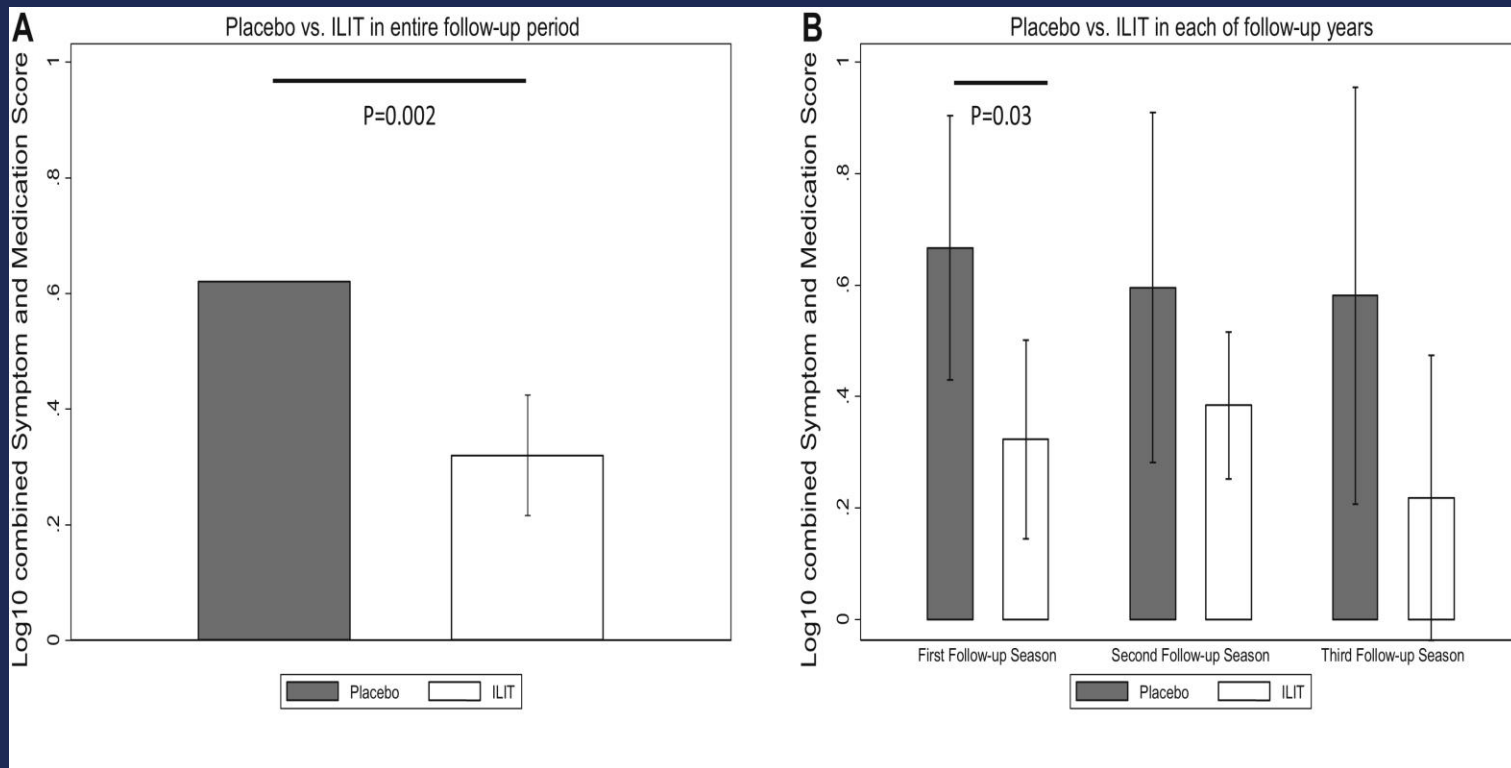
Intralymphatic Immunotherapy Improves Grass Pollen Allergic Rhinoconjunctivitis

- Patients were followed for 3 grass pollen seasons.
- Recorded symptom and medication scores (cSMS) during GPS.

Intralymphatic Immunotherapy Improves Grass Pollen Allergic Rhinoconjunctivitis

- There was no benefit noted from the booster injection so all active treatment was combined.
- When all observations on each subjects were reduced to a single median cSMS, for all 3 years the reduction with active treatment, compared to placebo, was 48% ($p=0.002$).
- By season, only the reduction (51.4%) the first year was statistically significant.

Log 10 Combined Symptom and Medication Scores Mean of 3 -year and Individual Year Comparisons



Intralymphatic Immunotherapy Improves Grass Pollen Allergic Rhinoconjunctivitis Summary

- Three intralymphatic injections at 4-week intervals produced, overall, a 48% reduction versus placebo in symptoms over 3 grass pollen seasons.

Efficacy of Epinephrine and Diphenhydramine Rinses in Decreasing Local Reactions to Subcutaneous Aeroallergen Immunotherapy

SS Mustafa, K Vadamalai, T Bingemann, A Ramsey. Allergy, Asthma
Proceedings (in press)

- Patients receiving SCIT & experiencing “bothersome local symptoms” despite premedication with antihistamines were enrolled in the study.
- Randomized to receive next 3 monthly SCIT injections from syringes pre-rinsed with epinephrine, diphenhydramine or saline prior to filling with allergen extract.

Efficacy of Epinephrine and Diphenhydramine Rinses in Decreasing Local Reactions to Subcutaneous Aeroallergen Immunotherapy

- 70/74 patients completed the study
- At the 1st visit epinephrine rinse significantly reduced local reactions ($p < 0.001$) compared to diphenhydramine (DPH) and placebo.
- For those reporting consistent improvement or not (41 subjects) epinephrine was superior to DPH and placebo for the 3 visits ($p = 0.001$)

Efficacy of Epinephrine and Diphenhydramine Rinses in Decreasing Local Reactions to Subcutaneous Aeroallergen Immunotherapy

Local Reaction: Medial (mm) Interquartile Range (mm)

Schedule	30 Minutes	2 Hours	4 Hours	6 Hours
Saline Wash	22.5 (8-40)	52.5 (28-69)	50 (27-75)	49 (21-72)
Epi Wash	0 (0-10)	20.5 (0-57)	22.5 (0-44)	29.5 (21-43)
% Reduction	100%	61%	55%	39.8%
P value	P=0.004	P=0.02	P=0.001	P=0.004

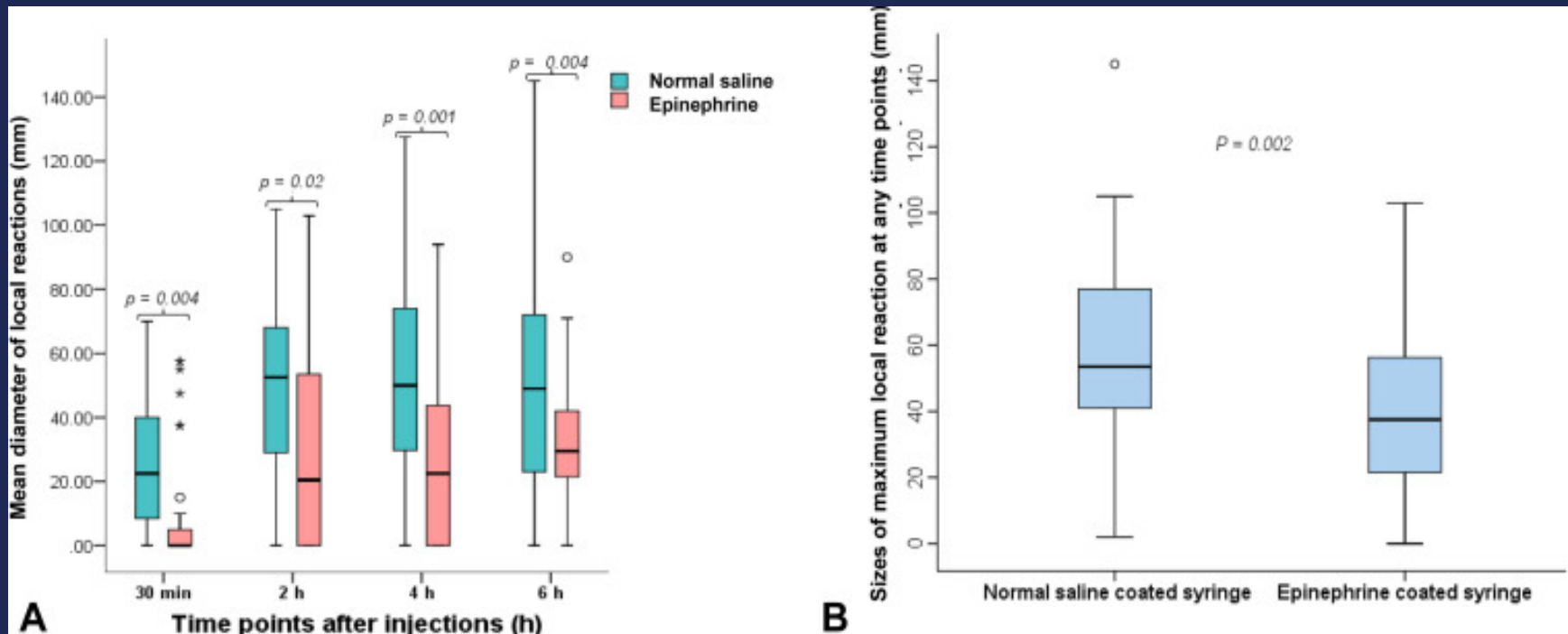
Epinephrine-coated syringe for SCIT Reduced Local Reactions: A Randomized, Double-blind, Placebo-controlled trial

S Sapsaprang, et al. J Allergy Clin Immunol Pract 2020;8:1465-7

- 17 children > 6 years, on maintenance SCIT, with local reactions ≥ 25 mm occurring $\geq 20\%$ of injections over previous 5 months despite premedication.
- Randomly assigned to receive injection from syringe coated with 0.2 ml epinephrine (1 mg/mL) or saline and treatment crossed-over for next injection.
- Patient continued premedication. Patient and physician blinded to treatment.

Epinephrine-coated syringe for SCIT

Reduced Local Reactions



Size of local reactions (30 minutes to 6 hours)

Maximum size of local reactions at any time

Epinephrine Rinsing to Reduce Large Local Reactions: Summary

- Two double-blind studies were conducted of rinsing the syringe with epinephrine before loading with allergen extract in patients who had large or bothersome local reactions to previous injections.
- In both studies epinephrine reduced subsequent local reactions compared to placebo.

Immunization of Cats against Fel d 1

Results in reduced Allergic symptoms of Owners

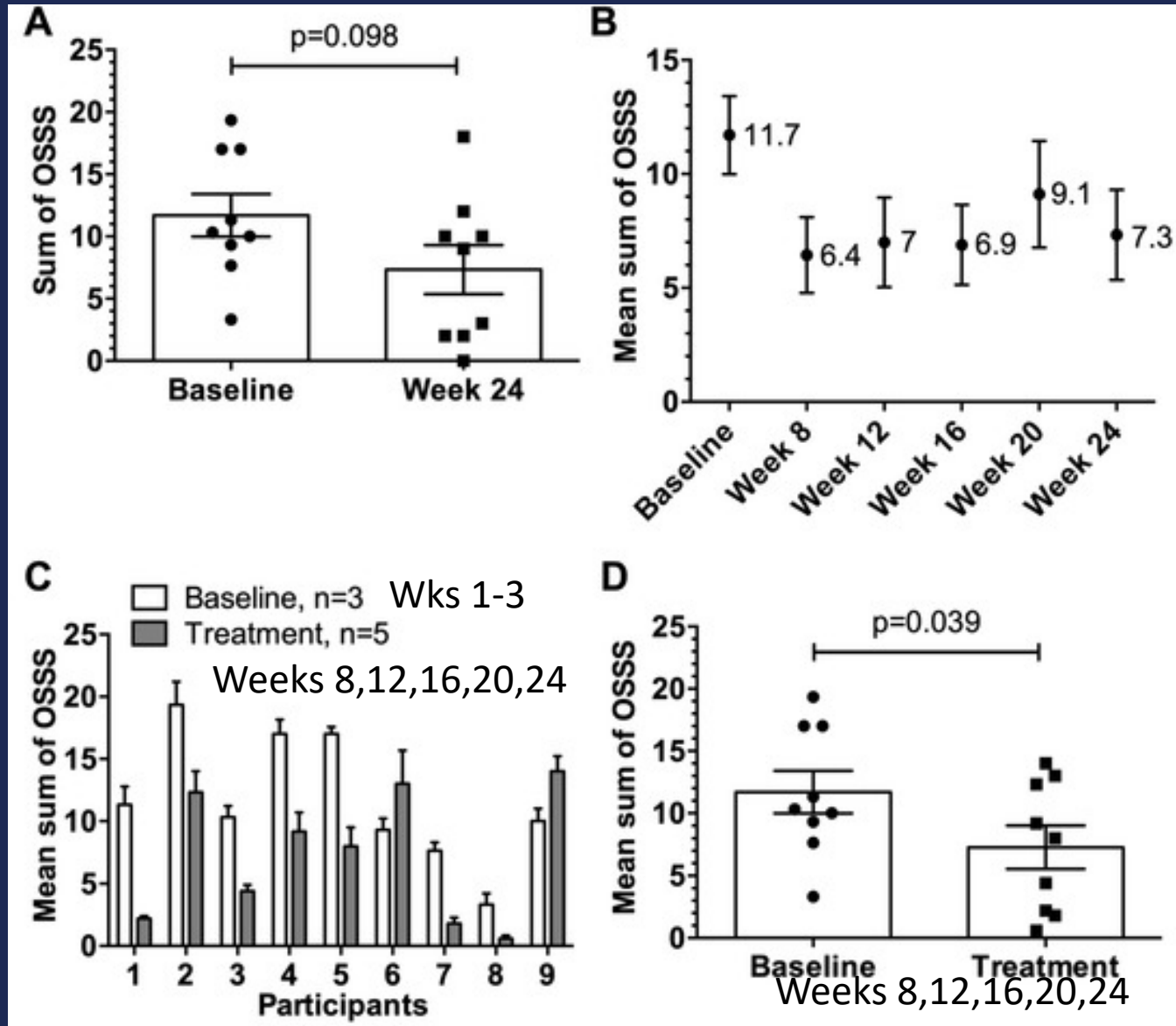
F Thoms, et al. Viruses 2020;12:288 DOI10.3390/v12030288

- 13 cats belonging to 10 cat-allergic individuals were immunized with 100 μ g Fel d 1 in virus-like particles from cucumber mosaic virus in study weeks 4, 7, and 10.
- Cat owners were assessed periodically for duration they tolerated petting their cats and levels of symptoms developed.
- Nasal symptoms were assessed weekly throughout 4 weeks baseline and 25 weeks of cat treatment

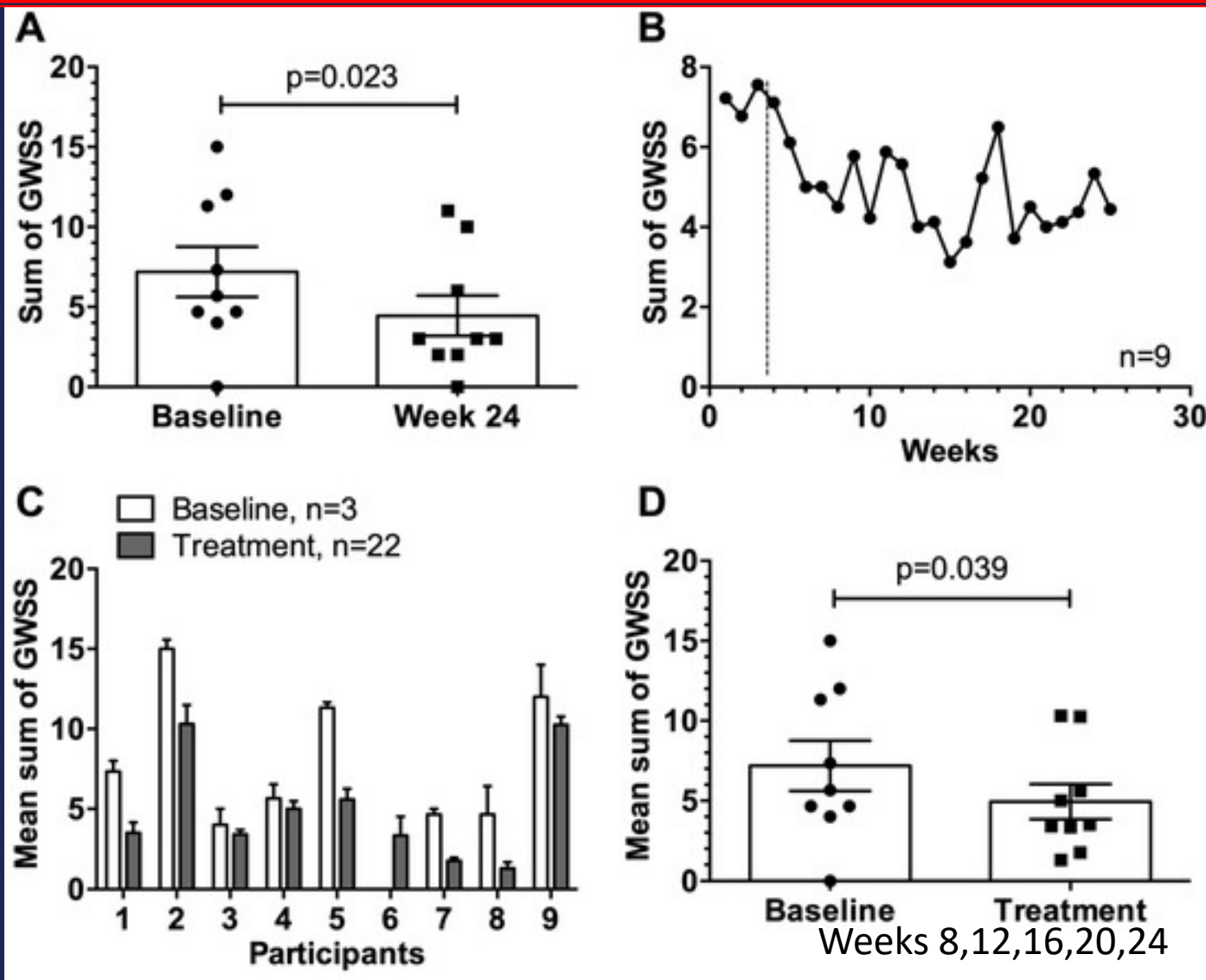
Immunization of Cats against Fel d 1 Results in reduced Allergic symptoms of Owners

- Ocular/nasal symptoms during petting: Mean change baseline to week 24 (11.7 to 7.3) N.S.
- Petting time: Mean change baseline to 24 weeks (16.9 to 27.7 minutes) $p=0.02$
- Weekly Symptom Score: Mean change from baseline to week 24 (7.2 to 4.4) $p=0.023$.
- There was a significant increase in anti-Fel d 1 IgG antibodies in all cats ($p=0.001$)

Organ-specific Symptoms Scores following Petting the Cat



Weekly Symptom Scores



Immunization of Cats against Fel d 1

Results in reduced Allergic symptoms of Owners

Conclusions

- Cats with cat-allergic owners received 3 injections of Fel d 1 in VLPs at weeks 4, 7 and 10.
- 8/9 owners had improvement in weekly nasal symptom scores beginning by week 8.
- At 24 weeks the owners tolerated a significantly longer time petting the cat.

Keep the Cat, Change the Care Pathway: A Transformational Approach to Managing Fel d 1, The Major Cat Allergen

- Polyclonal antibodies against Fel d 1 block basophil activation.
- Chickens were immunized with Fel d 1 producing anti-Fel d 1 –IgY in chicken serum and egg yolks.
- Cats were fed dry food (ad lib throughout the day) with added egg yolks from immunized or control chickens for 10 weeks.
- Active Fel d 1 was measured in the cat saliva 5 hours after feeding and in cat hair and dander by brushing.

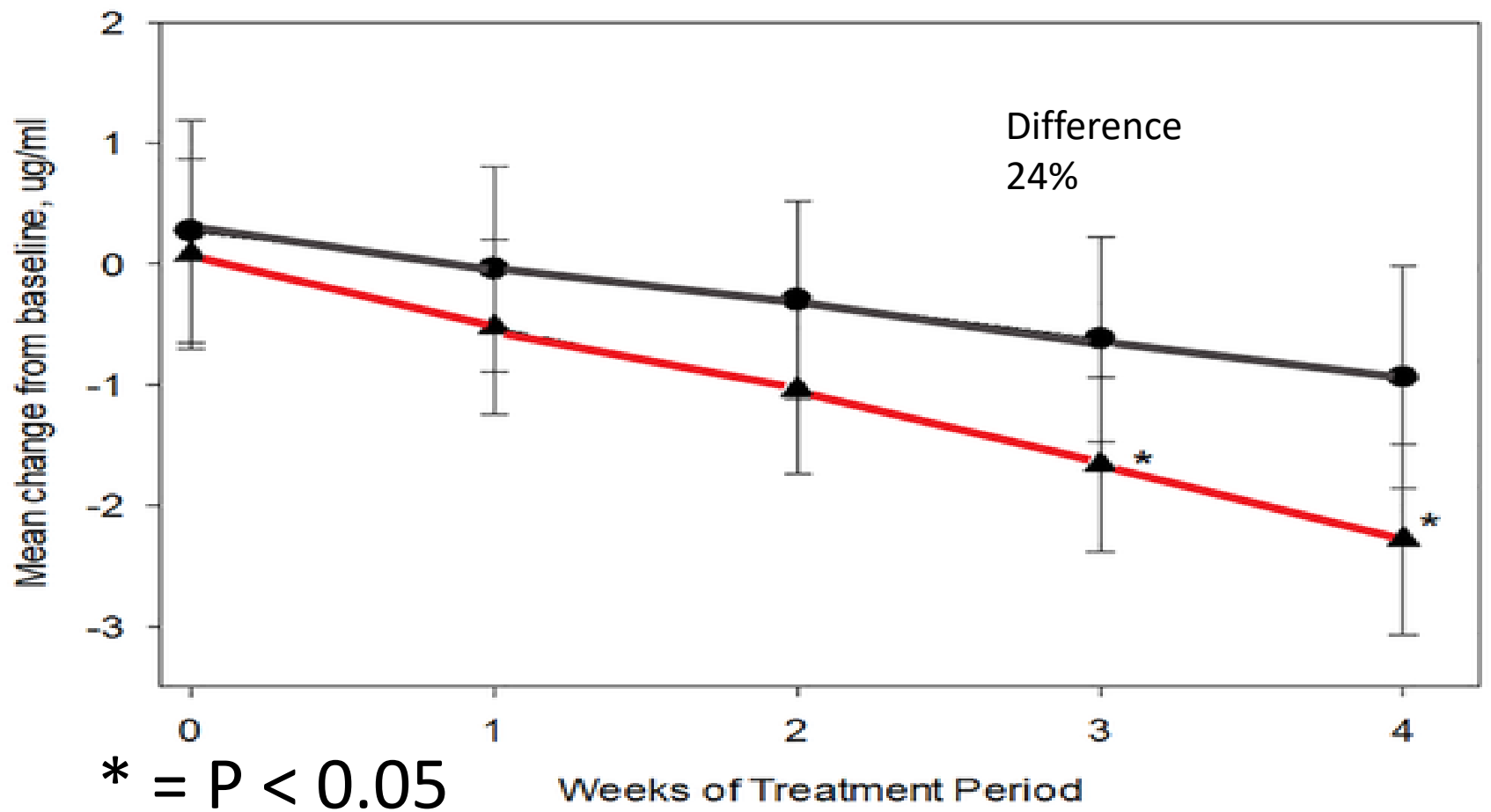
Keep the Cat, Change the Care Pathway: A Transformational Approach to Managing Fel d 1

1, The Major Cat Allergen: Conclusions

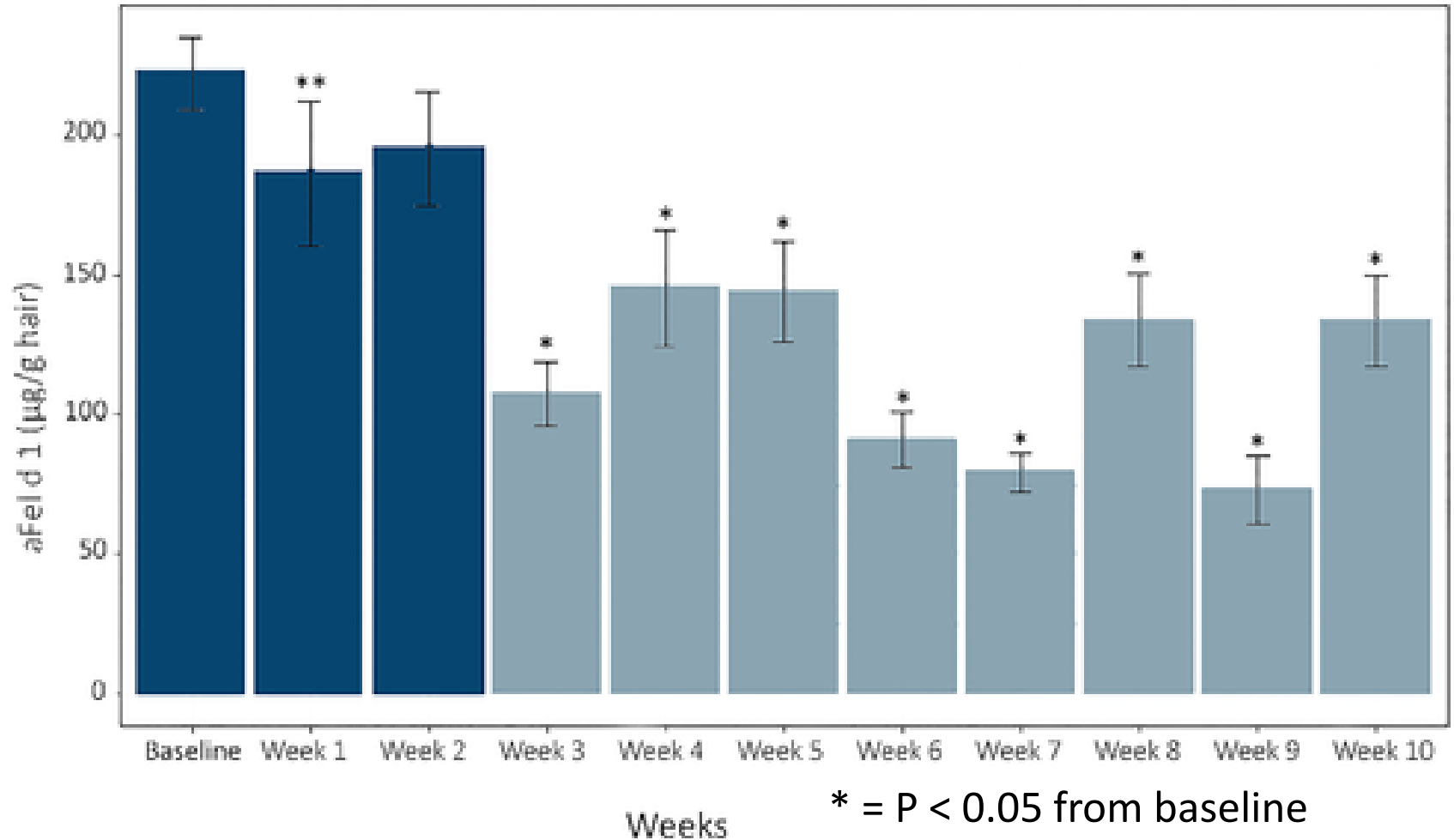
- Feeding cats eggs containing anti-Fel d 1 antibodies:
 - Reduced salivary active Fel d 1 by 24% over 4 weeks.
 - Reduced active Fel d 1 deposited on cat fur by an average of 47% over 10 weeks.
 - Reduction of Fel d 1 on fur was greatest in cats with the highest baseline levels.
- “In-home” trials have been completed but results are not yet published.

Reduction in Salivary Active Fel d 1 Levels

Black – Control Diet Red-Test Diet



Active Fel d 1 Levels ($\mu\text{g}/\text{gram}$ of hair)



Keep the Cat, Change the Care Pathway: A Transformational Approach to Managing

Conclusions: Fel d 1, The Major Cat

- Cats fed a diet containing yolks from chickens immunized with Fel d 1:
 - Had decreased Fel d 1 in their saliva
 - After 10 weeks had an average reduction of Fel d 1 in hair (belly, shoulders, & sides) of 47%
 - Unpublished studies showed decreased symptoms on intimate exposure to cats.

Literature Review 2021

Allergy Immunotherapy:

Take Home Messages Takeaways

- Data from German Health Care Agencies suggest AIT decreases development of asthma in patients with AR as well as progression of asthma to higher GINA treatment levels.
- 3 intralymphatic injections decreased AR symptoms over a 3 year period.

Literature Review 2020

Take Home Messages

Allergy Immunotherapy:

Takeaways

- Pre-rinsing the syringe with epinephrine reduced large local reactions
- Immunizing cats with Fel d 1, reducing their release of Fel d 1, and improved symptoms in owners, particularly when petting the cat.
- Cat release of Fel d 1 can also be reduced by feeding cats egg yolks containing anti-Fel d 1 antibodies.