Conclusion: Our findings support the view that GLILD represents a pulmonary manifestation of a multisystemic lymphoproliferative disorder with evidence of immune dysregulation. GLILD radiological patterns should always be sought in CVID patients, even in presence of normal lung function. Specific immunological parameters (e.g. BALF lymphocyte distribution) might suggest patients personalized therapeutic approach.

1867 | Early introduction of peanut reduces peanut allergy across different risk groups: Results from pooled and causal inference analyses

Logan K[1]; Bahnson HT[2]; Beyer K[3]; Bellach J[3]; Dianne C[4]; Joanna C[1]; Du Toit G[1]; Mills EN[5]; Perkin MR[6]; Roberts G[7]; Alyssa Y[2]; Van Ree R[8]; Lack G[1]

[1]King's College London, London, United Kingdom; [2]Benaroya Research Institute, Seattle, United States; [3]Charité Universitätsmedizin Berlin, Berlin, Germany; [4]Children's Hospital at Westmead, Sydney, Australia; [5]University of Manchester, Manchester, United Kingdom; [6]St George's, University of London, London, United Kingdom; [7]University of Southampton, Southampton, United Kingdom; [8]Amsterdam University Medical Centres, Amsterdam, The Netherlands

Background: The LEAP study has shown the effectiveness of early introduction of peanut in prevention of peanut allergy (PA) among high-risk children. In the EAT study, a general population of exclusively breastfed infants, the outcome is less clear as a statistically significant reduction in PA was only present in per-protocol analyses, which can be subject to bias. Here we combine individual-level data from the LEAP and EAT RCTs and provide more robust evidence on the bias corrected, causal effect of early peanut introduction overall and amongst sub-groups of children with different risk factors for allergy.

Method: The European Union-funded iFAAM project brings together data from RCTs on the early introduction of food allergens and provides an opportunity for a pooled analysis of individual-level data. This pooled analysis combines and compares effectiveness and efficacy estimates of oral tolerance induction among a number of different risk strata and analysis methods.

Results: An intention-to-treat (ITT) analysis of pooled data showed a 75% reduction in PA prevalence among those children randomized to consume peanut from an early age. Furthermore, ITT analyses showed a significant reduction in PA across all eczema severity groups as well as in those children already sensitized to peanut at enrolment and across different ethnicities. Peanut consumption reduced the risk of PA by 98% ($p < 0.0001$) in the bias-unadjusted pooled per-protocol analysis. Implementing a causal inference analysis approach confirms the strong effect through a bias-adjusted multivariable analysis (89% average treatment effect (ATE) relative risk reduction $P < .0001$). Poor adherence (49%) in the children with no eczema at enrolment may have diluted the effectiveness of treatment in this underpowered, low risk subgroup (prevalence of PA 1%). However, a multivariable causal inference analysis approach (ATE) adjusting for non-adherence estimated a large (100%) and statistically significant ($P = .004$) reduction in PA in children without eczema.

Conclusion: We demonstrate a significant reduction in peanut allergy with early peanut introduction in a large group of pooled RCT participants. Using causal inference methods to adjust for non-adherence in per-protocol analyses, this significant reduction was demonstrated across all risk subgroups. These pooled analyses provide evidence for the effectiveness of the intervention, when it is adhered to, among all children, regardless of eczema status, peanut IgE sensitization, or ethnicity.

LB OAS 04
Skin Diseases: What is New?

1692 | Fenebrutinib in refractory chronic spontaneous urticaria

Metz M[1]; Sussman G[2]; Gagnon R[3]; Staubach P[4]; Tanus T[5]; Yang WH[6]; Lim JJ[7]; Galanter J[7]; Chinn L[7]; Chu T[7]; Teterina A[8]; Burgess T[7]; Haddon DJ[7]; Lu TT[7]; Maurer M[1]

[1]Department of Dermatology and Allergy, Charité–Universitätsmedizin Berlin, Berlin, Germany; [2]Division of Allergy and Clinical Immunology, St. Michael's Hospital and University of Toronto, Toronto, Canada; [3]Service d'Allergie et Immunologie, Département de médecine, CHU de Québec, Quebec, Canada; [4]Department of Dermatology, University Medical Center Mainz, Mainz, Germany; [5]Kern Allergy Medical Clinic Inc., Bakersfield, Ca, United States; [6]University of Ottawa Medical School & Ottawa Allergy Research Corporation, Ottawa, Canada; [7]Genentech, Inc., South San Francisco, Ca, United States; [8]Hoffmann-LaRoche, Mississauga, Canada

Background: Chronic spontaneous urticaria (CSU) is thought to be driven by FcεRI-mediated activation of mast cells via IgE autoantibodies to antigens such as TPO and IL-24 (type I autoimmunity), or IgG autoantibodies to FcεRI or IgE (type IIb autoimmunity). Fenebrutinib, a highly selective, reversible Bruton's tyrosine kinase (BTK) inhibitor, may effectively treat CSU driven by both FcεRI-mediated pathways.

Method: In this double-blind, placebo-controlled trial (NCT03137069), adults with CSU refractory to antihistamines were randomly allocated (1:1:1:1) to receive 50 mg daily (QD), 150 mg daily, 200 mg twice daily (BID) fenebrutinib or placebo for 8 weeks while maintaining stable doses of H1 antihistamines. Safety was evaluated throughout the study. The primary efficacy endpoint was the change from baseline in urticaria activity score over 7 days (UAS7) at Week 8. Other efficacy endpoints are listed in Table 1. The basophil histamine release assay (BHRA) is thought to identify CSU driven by type IIb autoimmunity. A prespecified exploratory analysis comparing fenebrutinib efficacy in BHRA-positive and BHRA-negative patients was performed.

Results: 93 patients were randomized. Change from baseline in UAS7 at Week 8 demonstrated marked improvement in the 200-mg BID

(−21.8 ± 14.8) and 150-mg groups (−17.1 ± 10.2), but not in the 50-mg group (−15.7 ± 14.3) compared to placebo (−11.3 ± 10.8). Effects across dose groups were consistent for all other efficacy endpoints (Table 1). Total numbers of adverse events (AEs) were generally balanced across groups, with no deaths or treatment-related serious AEs. Transient grade 3 elevations in ALT occurred in the 150-mg and 200-mg BID groups. BHRA-positive patients showed greater benefit from fenebrutinib treatment (50 mg: −24.1 ± 14.0; 150 mg: −20.4 ± 9.3) than BHRA-negative patients (50 mg: −9.6 ± 11.4; 150 mg: −14.3 ± 10.4) except at the 200-mg BID group where there was no difference (BHRA-positive: −22.6 ± 18.0; BHRA-negative: −23.0 ± 11.7).

Conclusion: Selective BTK inhibition with fenebrutinib diminished clinical signs and symptoms in patients with CSU refractory to antihistamines. Across all doses, even at submaximal levels of BTK inhibition, fenebrutinib improved clinical signs and symptoms in patients with type IIb CSU, a population more refractory to current treatments.

	Placebo (n = 23)	Fenebrutinib 50 mg QD (n = 23)	Fenebrutinib 150 mg QD (n = 24)	Fenebrutinib 200 mg BID (n = 23)
Primary Efficacy Endpoint				
Change from baseline to Week 8 (UAS7)				
n	20	19	22	21
Mean (SD)	−11.3 (10.8)	−15.7 (14.3)	−17.1 (10.2)	−21.8 (14.8)
Treatment difference in LS means for treatment vs. placebo*		−0.5	−6.4	−9.5
90% CI		(−6.6, 5.6)	(−12.3, −0.6)	(−15.5, −3.6)
P-value		.89	.07	.01
Other Efficacy Endpoints				
Change from baseline to Week 4 (UAS7)				
n	21	19	23	21
Mean (SD)	−9.1 (9.8)	−17.00 (14.3)	−13.8 (12.9)	−21.7 (16.2)
Treatment difference in LS means for treatment vs. placebo*		−2.8	−5.0	−10.8
90% CI		(−9.1, 3.5)	(−11.1, 1.0)	(−17.00, −4.6)
P-value		.46	.17	.005
% Well-controlled (UAS7≤6) at Week 4 (n)	17.4% (4)	43.5% (10)	37.5% (9)	60.9% (14)
Difference, treatment vs. placebo, %		26.1	20.1	43.5
P-value**		.06	.09	.003
% Well-controlled (UAS7≤6) at Week 8 (n)	21.7% (5)	34.8% (8)	45.8% (11)	56.5% (13)
Difference, treatment vs. placebo, %		13.0	24.1	34.8
P-value**		.34	.05	.02
% Achieving MID (UAS7 reduction from BL ≥ 11) at Week 8 (n)	47.8% (11)	52.2% (12)	62.5% (15)	78.3% (18)
Difference, treatment vs. placebo, %		4.3	14.7	30.4
P-value**		.77	.28	.04
Time to achieving MID (UAS7 reduction from BL ≥ 11) in Weeks				
Median	3.0	1.0	1.5	1.0
Hazard ratio, treatment vs. placebo		1.7	2.0	2.8
p-value		0.07	0.08	0.01
% Complete response (UAS7 = 0) at Week 4 (n)	4.3% (1)	8.7% (2)	12.5% (3)	34.8% (8)
Difference, treatment vs. placebo, %		4.3	8.2	30.4
P-value**		.54	.30	.01
% Complete response (UAS7 = 0) at Week 8, n	4.3% (1)	13.0% (3)	25.0% (6)	39.1% (9)
Difference, treatment vs. placebo, %		8.7	20.7	34.8
P-value**		.30	.04	.006

Continues

TABLE (Continued)

	Placebo (n = 23)	Fenebrutinib 50 mg QD (n = 23)	Fenebrutinib 150 mg QD (n = 24)	Fenebrutinib 200 mg BID (n = 23)
Exploratory Endpoints				
Change from baseline to Week 8 (UAS7) - BHRA(−)				
n	12	11	12	11
Mean (SD)	−11.3 (9.4)	−9.6 (11.4)	−14.3 (10.4)	−23.0 (11.7)
Treatment difference in LS means for treatment vs. placebo***		4.5	−3.1	−11.0
90% CI		(−3.1, 12.1)	(−10.7, 4.5)	(−18.6, −3.3)
Change from baseline to Week 8 (UAS7) - BHRA(+)				
n	8	8	10	9
Mean (SD)	−11.2 (13.3)	−24.1 (14.0)	−20.4 (9.3)	−22.6 (18.0)
Treatment difference in LS means for treatment vs. placebo*		−8.2	−11.0	−9.9
90% CI		(−17.6, 1.3)	(−19.9, −2.1)	(−18.9, −1.0)

* Least squares means and *P*-values were estimated from mixed model for repeated measurements (MMRM)
** *P*-value estimated from Cochran-Mantel-Haenszel test using non-responder imputation for patients discontinued earlier than the week under consideration
*** Least squares means for subgroups were estimated from mixed model for repeated measurements (MMRM) that included BHRA status as covariate
BL, baseline.

1792 | Peripheral blood regulatory T cells and their influencing factors on atopic dermatitis development in West Highland white terriers

Rostaher A[1]; Rodriguez-Campos S[2,3]; Fischer N[1]; Zwickl L[1]; Audergon S[1]; Urwyler A[4]; Akdis C[5,6]; Favrot C[1]

[1]*Clinic for Small Animal Internal Medicine, Dermatology Unit, Vetsuisse Faculty, Zürich, Switzerland;* [2]*Institute of Veterinary Bacteriology, Vetsuisse Faculty, University of Bern, Bern, Switzerland;* [3]*Bacteriology and Mycology Unit, Faculty of Veterinary Medicine, Norwegian University of Life Sciences, Oslo, Norway;* [4]*Cytolab, Regensdorf, Switzerland;* [5]*Swiss Institute of Allergy and Asthma Research (SIAF), Davos, Switzerland;* [6]*Christine Kühne-Center for Allergy Research and Education, Davos, Switzerland*

Background: Regulatory T (Treg) cells are involved in homeostasis of immune regulation and suppression of inflammation and T-cell polarisation and therefore may influence the early steps of the initiation of allergic diseases. The current knowledge about the function of Treg cells early in life as compared to adults is very limited in humans and dogs. The main objectives of this longitudinal study were to better explain different Treg responses in allergic versus healthy dogs and to asses the contribution of their possible influencing environmental factors.

Method: This study followed a birth cohort of West Highland white terrier dogs. Regulatory T cell phenotypes in peripheral blood were longitudinally assessed by multi-colour flow cytometer at 3 months (n = 71), 3–12 months (n = 26) and 12–36 months (n = 16) and associated with development of AD by 3 years of age. Different early-life allergenic and infectious factors were measured (endotoxins and allergens in house dust, Toxocara IgE/IgG, allergen-specific and total IgE serology, and skin microbiota). A possible association of these factors with T regulatory cell levels was assessed.

Results: Regulatory T cells ($CD4^+CD25^+Foxp3^+$ cells) in healthy dogs were significantly higher at the age of 3 months ($P = .021$) and < 1 year ($P = .028$) when compared to Treg populations in dogs that subsequently developed AD by the age of 3 years. Beyond the age of 1 year, this cell population was again significantly different between healthy and allergic dogs ($P = .053$), but the relative abundance of Treg cells was reversed. There was no difference in peripheral blood $CD4^+IL10^+$ or Helios+CD4+CD25+Foxp3+ cell percentages between healthy and allergic dogs at any of the observed time points. There was a significantly positive correlation between the relative abundance of *Lachnospiraceae* on the skin and peripheral blood Treg cells in puppies that became allergic ($r^2 = 0.57$, $p < 0.02$).

Conclusion: Low peripheral blood Treg cells during adolescence were associated with the development of atopic dermatitis later in life. These findings strongly support the concept that Treg are important players in the pathogenesis of atopic dermatitis. Further large-scale studies are needed to identify the practical value of these findings in AD diagnosis, treatment and prevention.