A60

Occurrence of food allergen in products with precautionary labeling in Canada

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Background: The use of precautionary allergen labeling (PAL) to indicate the potential presence of priority food allergens as a result of cross-contamination is increasing [1]. These statements are often overused by industries and misunderstood by consumers and can lead allergic patients to adopt risky behaviors, resulting in potential adverse reactions [2]. The aim of this study is to quantify for the first time the risk for Canadian allergic individuals exposed to pre-packaged products that may contain allergens due to cross-contamination.
Methods: Foodstuffs with PAL have been analysed for the possible presence of milk, eggs and peanuts. Products were chosen according to a sampling plan based on the recalls done by the Canadian Food Inspection Agency (CFIA) from 1997 to 2017. Sandwich ELISA kits from r-biopharm and Morinaga were used for allergens' detection and quantification. For each food product, the allergic risk associated with its consumption will be estimated using the "consumption estimates per eating occasion" data held in the Canadian Community Health Survey (CCHS-2015). The occurrence of adventitious allergens in foods and the dose–response relationship will be estimated with a probabilistic approach like those already published in the literature [3].
Results: Three allergens have been investigated (milk = 253, eggs = 91, peanuts = 48). Considering all food product categories and the allergens together, only 17% of the products with PAL had detectable amounts of allergens. As an example, dark chocolate has the highest occurrence of milk with 88% of positive products, with a milk protein content range of 10.5–6231 ppm (mg/kg). Besides, no consistency was shown between the different lots (n = 5).
Conclusion: More data must be acquired to undergo risk assessments on the probability of occurrence of allergic reactions in Canadian allergic individuals consuming products with PALs. Allergen management guidelines linked to industry and regulation stakeholders will be proposed following the results of the risk assessments.
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OTHER ALLERGY/IMMUNOLOGY

A61

Review of the Manitoba cohort of patients with hereditary angioedema with normal C1 inhibitor

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Background: Hereditary angioedema with normal C1 inhibitor (HAE-nC1 INH) is a rare, underappreciated condition characterized by recurrent subcutaneous angioedema[1]. The underlying pathophysiology and diagnostic criteria continues to evolve. There is a significant overlap between HAE –nC1 INH and idiopathic nonhistaminergic angioedema, and this may ultimately be found to be the same condition. Characterization of cohorts suspected to have these conditions is warranted to help refine diagnosis, pathophysiology, and treatment response.
Methods: A retrospective chart review of 418 charts of patients diagnosed with angioedema was conducted. The following inclusion criteria were used: lack of response to antihistamines, steroids, and epinephrine; normal C4, C1 INH level and function; lack of urticaria or pruritus; occurrence without offending drugs; and family history. Charts meeting these criteria were reviewed for frequency and type of episodes as well as use and response to therapies.
Results: 6 patients met the above criteria. 3 underwent genetic testing and none were found to have factor XII abnormalities. None had angiopoietin 1 or plasmin testing[2]. 5 of 6 patients were successfully treated with other regimens for acute treatment of attacks (4 with C1 INH and 1 with Tranexamic acid). 4 patients have used Icatibant with good response (typically under 40 min for near full recovery); of these, 3 required Icatibant as acute treatment after other therapies were ineffective. There were 9 patients who otherwise met criteria, but due to a lack of family history were classified as having idiopathic non-histaminergic angioedema.
Conclusions: This retrospective chart review found 6 HAE-nC1 INH patients in Manitoba. 1 responded to Tranexamic acid and not C1 INH, 4 typically responded to C1 INH, and 1 responded exclusively to Icatibant. All patients—4 total—who used Icatibant responded; of the 4, 3 used Icatibant after other therapies had failed.

A62

Abstract withdrawn

A63

Lanadelumab Inhibition of plasma kallikrein activity for effective HAE prophylaxis

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Background: Hereditary angioedema (HAE) results from a mutation in the C1 esterase inhibitor (C1-INH) gene. Deficiencies in C1-INH result in uncontrolled plasma kallikrein activity, which is associated with HAE attacks. Lanadelumab binds specifically to active plasma kallikrein (Ki = 125 pM) and was efficacious in the prevention of HAE attacks in the phase 3 HELP study. Here we evaluate the dosing of lanadelumab required to achieve stable plasma kallikrein inhibition at levels sufficient to prevent HAE attacks.
Methods: Patients with type I/II HAE received placebo or lanadelumab (150 mg q4wks, 300 mg q4wks, or 300 mg q2wks) over 26 weeks in the HELP study. Blood samples were collected pre-dose and at intervals up to 26 weeks for measurement of lanadelumab and cleaved high molecular weight kininogen (cHMWK), a pharmacodynamic marker of plasma kallikrein activity.
Results: Plasma lanadelumab concentrations reached steady state at ~week 10, with a half-life of ~14 days. Compared with healthy subjects, plasma kallikrein levels were estimated based on previous reports to be elevated in HAE plasma between attacks (by 10–276 nM) and during attacks (an additional 20–186 nM). Following lanadelumab treatment, plasma kallikrein activity (cHMWK levels) decreased in a concentration-dependent manner, reaching a 44.7% reduction from baseline by week 8 with 300 mg q2wks lanadelumab, but remained elevated in the placebo group. Mean (±SE) maximum inhibition (I_{max}) was 53.7 ± 5.9%, and IC_{50} (concentration at 50% of I_{max}) was 5705 ± 13.9 ng/mL. 300 mg q2wks lanadelumab achieved steady state average plasma concentrations (29,200 ng/mL) more than fivefold above the IC_{50}. Over 26 weeks, patients receiving lanadelumab had

fewer attacks/month compared with those receiving placebo (0.31–0.48 vs 2.46 attacks/month, respectively).
Conclusions: Lanadelumab resulted in a marked suppression of kallikrein activity at drug levels approximately equimolar to the amount of protease, resulting in sufficient inhibition for effective HAE prophylaxis.

A64

Efficacy of lanadelumab in the Phase 3 HELP study: Exploratory analyses based on prior disease activity and prior use of C1-INH long term prophylaxis therapy

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Background: The HELP Study evaluated the efficacy and safety of lanadelumab for long-term prophylaxis (LTP) in patients ≥ 12 years old with HAE type I/II (NCT02586805). Here, we report lanadelumab efficacy based on a patient's prior disease activity and prior use of C1-INH LTP.
Methods: The HELP study is a phase 3, randomized, double-blind, placebo-controlled study. We performed two exploratory efficacy analyses: (1) a responder analysis comparing normalized HAE attack rates over 26 weeks of treatment to a 4–8 week run-in period prior to treatment with lanadelumab and (2) a Poisson regression model to compare the mean HAE attack rate in the lanadelumab groups to placebo by patient prior C1-INH LTP use.
Results: Over the 26-week treatment period, the percentage of patients with a ≥ 50%, ≥ 70%, and ≥ 90% reduction in investigator-confirmed HAE attacks from the run-in period, respectively, was 89.3%, 78.6% and 64.3%, [lanadelumab 150 mg q4wks (n = 28)]; 100%, 75.9%, 55.2% [lanadelumab 300 mg q4wks (n = 29)]; 100%, 88.9% and 66.7% [lanadelumab 300 mg q2wks (n = 27)] and 31.7%, 9.8% 4.9% [placebo (n = 41)], respectively. In C1-INH LTP patients (n = 60), the attack rate was significantly reduced in all lanadelumab groups versus placebo (P < 0.001); the reduction was similar in magnitude to those who did not receive prior LTP (n = 55). For the lanadelumab 150 mg q4wks, 300 mg q4wks, 300 mg q2wks and placebo groups, respectively, C1-INH LTP users reported mean monthly attack rates (3 months prior to the study) of 3.0, 2.7, 2.6 and 4.0; during run-in 3.3, 3.7, 4.6 and 4.6; and during the treatment period 0.5, 0.7, 0.5 and 2.9.
Conclusions: Treatment with lanadelumab for 26 weeks resulted in a high rate of patients who experienced a clinically meaningful reduction in investigator-confirmed HAE attacks compared to baseline run-in. Furthermore, all lanadelumab doses significantly reduced attack rates versus placebo, regardless of whether patients had received prior C1-INH LTP.

A65

Alterations in cord blood hemopoietic progenitor cell surface receptor expression precede atopy and poor lung function at 1- and 3-years in the Canadian Healthy Infant Longitudinal Development Study

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Background: Hemopoietic progenitor cells (HPC), both in the bone marrow and in peripheral tissues, differentiate towards inflammatory effector cells and, thus, can modulate central and peripheral inflammation. There is growing evidence for the involvement of hemopoietic processes in the pathogenesis of atopy and asthma from pre-conception and birth. This is the basis for the "bone marrow" hypothesis of allergic disease, arguing that a perinatal environmental challenge leads to the skewed production and mobilization of HPC, regulating central and peripheral production of cell types that perpetuate allergic responses. The objective of this study was to assess the association of cell surface receptor profiles of cord blood (CB) HPC with atopy development and lung function at 1- and 3-years in the Canadian Healthy Infant Longitudinal Development (CHILD) Study
Methods: We used six-colour flow cytometry to assess cytokine and toll-like receptor expression levels in CB HPC from infants with atopy data (defined as positive skin prick test and atopic dermatitis and wheeze) and lung function data (by lung clearance index (LCI)) at 1- and 3-years of age in CHILD.
Results: We found a significant increase in IL5R and IL17RB-expressing HPC populations in the CB of children atopic at 1-year. Conversely, GM-CSFR and ST2-expressing CB HPC were decreased in atopic children both at 1- and 3-years. The expression levels of IL17RB on the surface of CB-HPC were higher in atopics at 3-years. Finally, infants with poor lung function at 3-years exhibited higher IL5R expression on the surface of CB HPC.
Conclusion: This study provides evidence of pre-existing cellular alteration in the infants' CB progenitors at birth, which antedate development of atopy/allergic disease and potentially future asthma. Our results can contribute to novel strategies for atopic/allergic disease interception in infants before onset, and hence participate in the health and well-being of Canadian children.

A66

Efficacy and safety of lanadelumab for prevention of hereditary angioedema attacks: results from the phase 3 HELP Study

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