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doi.org/10.58931/cait.2024.4268

Abstract Presentation Highlights from the 2024 EAACI Annual Meeting

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Introduction

Many oral abstracts, posters and case reports were presented at The European Academy of Allergy and Clinical Immunology (EAACI) Annual Meeting which was held in June 2024 in Valencia, Spain. We have selected the following 13 articles due to their relevance to Canadian allergy and immunology clinical practice and research.

Long-term efficacy and safety of remibrutinib in patients with chronic spontaneous urticaria in the phase 3 REMIX-1 and REMIX-2 studies

Metz, M et al. (2024, June).
Presented as a late-breaking oral abstract.

Despite treatment with up-dosing of second-generation antihistamines, up to 4 times the standard dose, 75% of patients will experience no or only partial relief. Remibrutinib is a novel, highly selective oral bruton tyrosine kinase (BTK) inhibitor, which inhibits activation of human masT-cells and basophils, and the production of IgG autoantibodies against IgE or the high affinity IgE receptor. Metz M demonstrated the long-term (52-week) efficacy and safety of remibrutinib 25 mg po bid vs placebo for patients with at least 6 months of chronic spontaneous urticaria (CSU), uncontrolled on H1-antihistamines (H1-AH).[1] REMIX-1 and REMIX-2 were identically designed global, multicentre, randomized, double-blind, placebo-controlled (DBPC) Phase 3 studies. Remibrutinib demonstrated statistically significant superiority in both primary endpoints [urticaria activity score (UAS7) and the itch severity and hive severity scores (ISS7/HSS7) at week 12]. REMIX-1 included 470 adult participants, while REMIX-2 had 455 adult participants.

Key Takeaways:

1. ***Rapid Onset of Action:*** Symptom improvement was observed as early as one week after treatment initiation. Significantly more patients achieved well-controlled disease (UAS<6) with remibrutinib vs placebo at Weeks 2, 12 and 24. Approximately 30% of patients achieved complete response (UAS7=0) with remibrutinib vs 10% of those on placebo at Week 12. Patients who switched from placebo to remibrutinib at Week 24 also showed significant symptom improvement within the first week after switching.

2. ***Sustained Efficacy:*** Patients treated with remibrutinib experienced significant improvements in weekly urticaria activity scores (UAS7) through Week 52. By Week 52, almost half of the patients achieved complete relief from itch and hives (UAS7 score of 0).

3. ***Safety Profile:*** Adverse events were balanced between remibrutinib and placebo during the treatment period with a consistent safety record over the 52 weeks. Petechiae were more common in remibrutinib vs placebo, but all cases were mild-to-moderate without clinically significant platelet decreases. Newly occurring liver transaminase elevations were infrequent and balanced between the treatment and placebo groups. No serious adverse events were related to study medication.

Key Takeaways:

Remibrutinib is a new oral treatment for CSU where improvements occurred as early as Week 1, and sustained relief was noted over 52 weeks of treatment. There was overall favourable safety and tolerability with no increase in adverse events up to 52 weeks. Remibrutinib may be especially helpful in individuals with low total IgE and autoantibodies, where omalizumab is less efficacious. These results support remibrutinib's potential as a new, effective, fast-acting oral treatment option for CSU patients uncontrolled by first-line H1-antihistamines.

Dupilumab improves urticaria activity, health-related quality of life, and disease perception and severity in patients with CSU: results from the LIBERTY-CSU CUPID A study

Maurer, M (2024, June).

This study evaluated the efficacy and safety of dupilumab in patients with CSU unresponsive to H1-AH. The study design was a DBPC trial including 138 patients (70 dupilumab, 68 placebo) aged six years and older, diagnosed with CSU for over six months, and symptomatic despite standard H1-AH treatment.[2] Participants were omalizumab-naive and were excluded if they had active atopic dermatitis (AD). There was a 24-week treatment period with dupilumab vs placebo and 12 weeks of post-treatment follow-up. The primary and key secondary outcomes were the change in baseline at week 24 of UAS7 and ISS7 respectively.[2]

Key Takeaways:

1. ***Reduction in urticaria activity (efficacy):*** A higher proportion of patients treated with dupilumab achieved well-controlled urticaria (UAS7 ≤6) and urticaria-free status (UAS7 = 0) from Week 1 to Week 36.
2. ***Symptom Improvement:*** Dupilumab effectively reduced the severity of itch and hives, as measured by the Urticaria Activity Score over seven days (UAS7) and the Itch Severity Score (ISS7) at Week 24. Improvements persisted through the 12-week post-treatment follow-up, indicating sustained efficacy even after discontinuing dupilumab.
3. ***Health-Related Quality of Life:*** Patients experienced significant improvements in health-related quality of life and disease perception.
4. ***Safety/Adverse Events:*** Dupilumab was well-tolerated with a safety profile consistent with that of previous studies. Treatment-emergent adverse events (TEAEs) were similar between the dupilumab (54.3%) and placebo (58.8%) groups. Serious adverse events (SAEs) were lower in the dupilumab group (2.9%) compared to placebo (7.4%). Injection site reactions were the most common adverse events, and were generally mild and more frequent in the dupilumab group. Of note, no dupilumab-treated patients reported conjunctivitis.

Key Takeaways:

The LIBERTY-CSU CUPID A Study provides evidence supporting dupilumab as an effective and well-tolerated treatment for CSU patients unresponsive to H1-AH therapy. These findings show that dupilumab has the potential to improve disease control and quality of life for CSU patients and may be a valuable therapeutic addition for managing CSU in both adults and children. There was also sustained efficacy over the 12-week follow-up when dupilumab was discontinued.

Another presentation at EAACI 2024 reported on the "Efficacy and Safety of Therapy with Omalizumab in Children with Chronic Spontaneous Urticaria."[3] The study was a retrospective and observational analysis. It included 235 CSU patients, with a subset of 26 patients aged under 12 (range 4 to 11 years) treated with at least three omalizumab injections over an average

treatment duration of 3.4 months. Most patients (98.7%) responded to omalizumab treatment by the end of week 12. A total of 91.1% achieved a complete response (CR), indicating no symptoms of urticaria. Omalizumab was also well-tolerated among pediatric patients with no serious adverse events related to the treatment.

Key Takeaways:

This study demonstrated that omalizumab is a safe and effective treatment option for CSU in children, including those under 12 years of age. It supported the addition of omalizumab to the treatment regimen for pediatric CSU patients who do not respond adequately to antihistamines.

Patients With moderate-to-severe asthma treated with dupilumab are more likely to meet clinical remission criteria: results from the VESTIGE trial

Lugogo, NL (2024, June).

VESTIGE, a Phase 4 clinical trial, included 109 adult patients aged 21 to 70 years with uncontrolled moderate-to-severe asthma and increased Type 2 biomarkers. Patients were randomized 2:1 to receive 300 mg of dupilumab (n=72) or matched placebo (n=37) every two weeks for 24 weeks.

The VESTIGE study evaluated several key endpoints. The primary endpoint was the proportion of patients achieving clinical remission, as defined by meeting all four specified criteria, at Week 24. Additionally, the study assessed changes from baseline over time in three important measures: Fractional Exhaled Nitric Oxide (FeNO) levels, Asthma Control Questionnaire-7 (ACQ-7) scores, and pre-bronchodilator Forced Expiratory Volume in 1 second (FEV_1), to provide a more comprehensive assessment of treatment efficacy.

In this study, remission was defined by four specific criteria that patients needed to meet over a 24-week period. First, patients had to experience no severe asthma exacerbations during the entire study duration. Second, they were required to abstain from using systemic corticosteroids throughout the 24 weeks. Third, patients needed to achieve an Asthma Control Questionnaire-5 (ACQ-5) score below 1.5 at Week 24. Last, they had to demonstrate either a pre-bronchodilator percentage predicted FEV_1 greater than 80% at Week 24 or show an improvement from baseline in pre-bronchodilator FEV_1 of more than 100 mL at Week 24. The results at the 6-month mark revealed that patients receiving dupilumab were significantly more likely to meet clinical remission criteria, with 38.9% achieving remission compared to 18.9% in the placebo group.

Additional VESTIGE endpoints:

1. ***Reduction in airway inflammation:*** 56.9% of patients treated with dupilumab achieved a significant reduction in airway inflammation measured by fractional exhaled nitric oxide (FeNO) <25 parts per billion (ppb) compared to 10.8% of patients on placebo (P <0.001).
2. ***Mucus reduction:*** Dupilumab led to numerically more significant decreases in mucus plug scores and volume than placebo. The difference in mucus scores (range 0 to 20) between dupilumab and placebo was -4.9 (P<0.001).
3. ***Notable improvement in lung function:*** Patients treated with dupilumab showed numerically greater improvements in lung function from baseline compared to placebo as defined by airway volumes and airway resistance at total lung capacity.
4. ***Safety profile:*** The safety results were consistent with the known safety profile of dupilumab in moderate-to-severe asthma.

Key Takeaways:

Clinical remission has emerged as an important outcome in asthma treatment. These results affirm that dupilumab leads to significant improvements in airway inflammation, mucus plugging, and lung function, and demonstrate that patients on dupilumab are more likely to meet clinical remission criteria for moderate-to-severe asthma.

Dupilumab reduces FeNO levels and exacerbations and improves asthma control with inhaled corticosteroid withdrawal: A Phase 2 study.

Soliman, M. (2024, June).

The objective of the study was to assess the impact of withdrawing inhaled corticosteroids and long-acting beta-agonists (ICS-LABA) on exacerbations, asthma control, and fractional exhaled nitric oxide (FeNO) levels in adults treated with dupilumab who had a baseline blood eosinophil count ≥300 cells/μL, a key indicator of eosinophilic inflammation in asthma. The interventions in Phase 2a were: dupilumab 300 mg weekly and for Phase 2: dupilumab 300 mg every two weeks. Both studies lasted 12 weeks. In the last 3 weeks, patients were on no ICS-LABA.

Key Takeaways:

1. ***Exacerbation Reduction:*** In Phase 2a, there was a substantial 60% reduction in severe exacerbations compared to placebo (adjusted annualized severe exacerbation rate relative risk: 0.39, 95% CI: 0.18-0.88). In Phase 2, this reduction was even more pronounced, with a 75% decrease in severe exacerbations compared to placebo. These results provide strong evidence of the drug's effectiveness in reducing severe exacerbations (adjusted annualized severe exacerbation rate relative risk: 0.62, 95% CI: 0.22-1.76).

2. ***Asthma Control:*** By Week 12, patients treated with dupilumab showed a significant improvement in ACQ-5 scores vs placebo in both Phase 2 and 2a studies.

3. ***FeNO Levels:*** In Phase 2 and 2a studies, at Week 12, dupilumab-treated patients demonstrated a more significant decrease in FeNO levels from baseline compared to placebo.

Key Takeaways:

Dupilumab effectively reduces severe exacerbations, improves asthma control, and decreases FeNO levels, even after the withdrawal of ICS-LABA treatment, a common practice among patients. Longer term studies of ICS-LABA tapering/withdrawal are required.

Summary

Promising new therapies for adults and children are emerging for CSU, a prevalent condition with significant impacts on quality of life.

Clinical remission, a controversial term, has been increasingly adopted as a goal of therapy in many disease states. A significant proportion of moderate-to-severe asthmatics on dupilumab met predefined criteria for remission compared to placebo. The benefits of dupilumab were maintained over 12 weeks, in spite of ICS-LABA withdrawal in the latter treatment period.

Efficacy and safety of epicutaneous immunotherapy (EPIT) for peanut allergy in subjects aged 1-3 with and without atopic dermatitis in the EPITOPE study.

Scurlock, M. et al. (2023).

In a follow-up to Greenhawt et al's NEJM publication on epicutaneous immunotherapy (EPIT), Scurlock *et al.* continue the work on peanut transdermal immunotherapy. In this Phase 3, DBPC trial, 362 children aged 1–3 were treated over 1 year (in a 2:1 ratio drug: placebo) to a maximum dose of 250 mcg of peanut EPIT.[6] All children received entry peanut Double-blind, placebo-controlled food challenge (DBPCFC) with a repeat challenge at the end of 1 year of EPIT. Treatment responders fell into 2 groups. Group A, with eliciting peanut protein dose of anaphylaxis less than 10 mg; and Group B, with eliciting peanut protein doses of anaphylaxis between 10 mg and 300 mg. Unique to this publication was AD as a variable both for safety and efficacy. There were 4 times more toddlers with AD than without AD. Treatment responder rates after 12 months of EPIT were similar in the AD and non-AD group, with a slightly greater risk difference in the AD group (**Figure 1**). There was no change in SCORAD over time regardless of treatment group or AD status. There was no difference in safety in either the AD or non-AD groups.

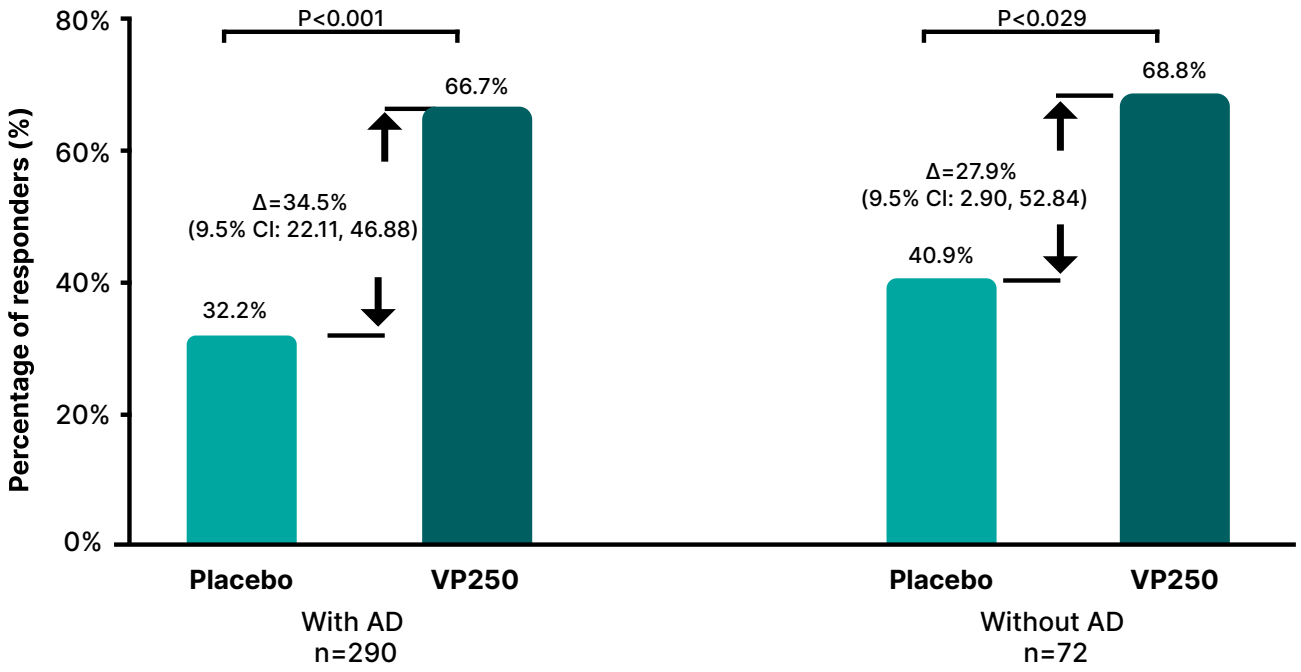

Figure 1. Treatment responder rates at month 12 DBPCFC; *adapted from Scurlock, M. et al., 2023; from abstract at EAACI Congress 2024, Valencia, Spain.*

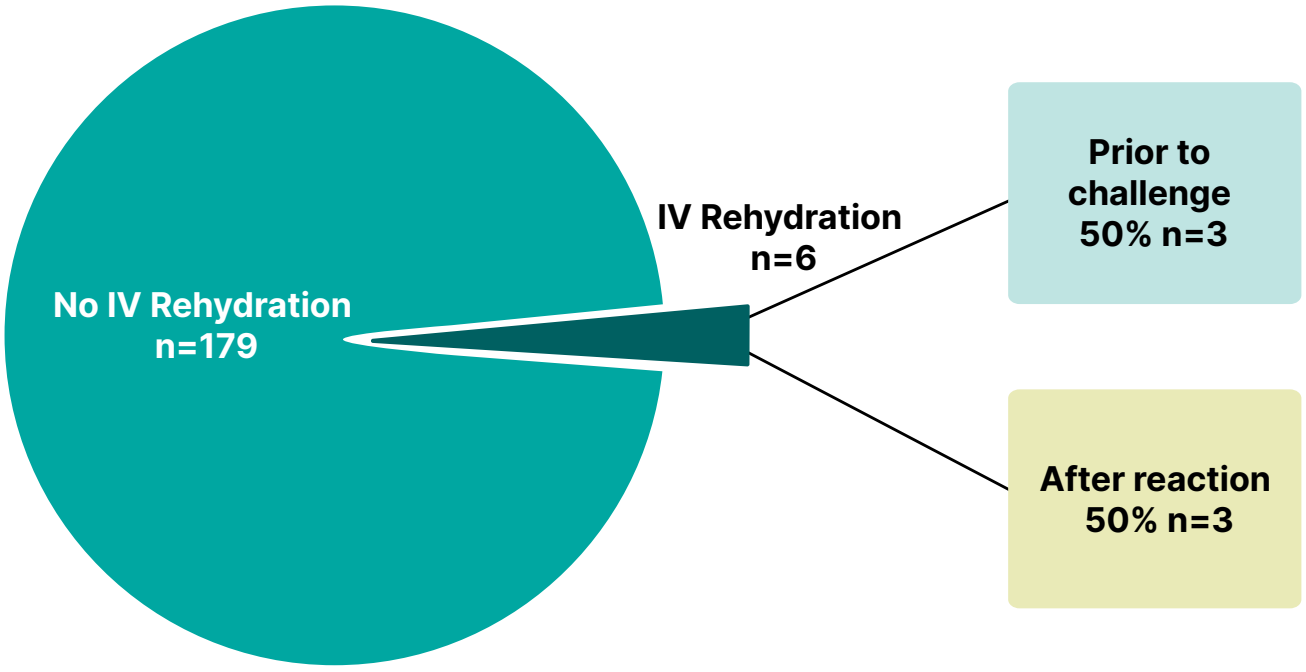

Figure 2. IV placement in patients treated with IV rehydration; *adapted from Patel, G. et al., 2023; from abstract at EAACI Congress 2024, Valencia, Spain.*

Key Takeaways:

Early peanut EPIT for toddlers is a safe and effective form of immunotherapy with peanut allergy and signifies a future alternative to oral immunotherapy (OIT). AD, a common co-morbidity in this group of early peanut allergic toddlers, was more commonly represented, but unaffected throughout the EPIT treatment program. EPIT will likely become an impactful and safe go-to form of immunotherapy for peanut-sensitized toddlers in our community.

Intravenous access is rarely necessary in food protein-induced enterocolitis syndrome oral food challenges

Patel, G et al. (2023).

In this 12-year retrospective chart review of 185 pediatric food protein-induced enterocolitis syndrome (FPIES) patients, the authors from UT Southwestern Medical Center reviewed the frequency, and utilization of intravenous (IV) access in children undergoing FPIES challenges.[7] In 44 of the patients, IV was established before their ondansetron delivery. Positive FPIES reactions occurred in 29 (16%) of patients. IV access for either ondansetron delivery (6/29) or fluids and ondansetron in (6/29) was utilized. The remaining (17/29) positive FPIES challenges were treated with oral or intramuscular (IM) ondansetron and oral fluids or no intervention at all. IV access was established in 3/6 patients before the oral challenge (OC) and 3/6 patients after symptom development (**Figure 2**). No ER transfers were needed. Variable foods were challenged. The low amount of IV usage (3%) from the initial 44/185 IV pre-OC preparation suggests that FPIES challenges in children are generally safe and can be managed without IV and need for ER transfer.

Key Takeaways:

For clinicians who diagnose and follow children with FPIES, this retrospective review on the safety of overseeing FPIES challenges without IV access is reassuring and confirms that the overwhelming majority of FPIES challenges may continue safely in the community.

Dupilumab improves histologic, symptomatic and endoscopic outcomes in children with eosinophilic esophagitis in the EoE KIDS study, regardless of history of elimination diet or concomitant food allergy

Spergel, J et al.(2024).

The KIDS study involved children with EoE aged 1–12 years, randomized to either dupilumab or placebo for 16 weeks extending to 1 year on open label dupilumab dosed by weight.[8] The primary outcome was histological changes/regression of eosinophils less than 6/hpf. Observations compared children in both groups who maintained food elimination diet or had a history of concomitant food allergy. Dosing in this pediatric EoE trial was reduced to alternate weeks in children between 15–30 kg (200 mg) and also alternate weeks between 30 to 40 kg, (300 mg) as compared to those above 40 kg, adopting the weekly adult dosing (300 mg). Dupilumab improved both groups of children with EoE, although a higher proportion of children were found with histologic remission by 52 weeks in the co-treated food elimination diet cohort (**Figure 3**).

Key Takeaways:

Having alternate week dosing regimens in the management of pediatric EoE population is highly welcomed along with the reassurances that dupilumab is effective even in those children/families who find food elimination diets prohibitive.

Pregnancy in hereditary angioedema: a single centre experience

Tan, KL. et al. Frimley Park, UK; EAACI 2024

Hormonal factors, including estrogen, have been associated with exacerbations for hereditary angioedema (HAE); however, the impact of pregnancy has not been reported on specifically as a risk factor within the HAE community. A United Kingdom Allergy Group performed a 65-year review at their immunology center in addition to a literature search to determine whether pregnancy is a trigger for HAE attacks.[9,10] Despite the small sample size, approximate 70% of patients reported their pregnancies were either “better” or “similar” to their pre-pregnancy

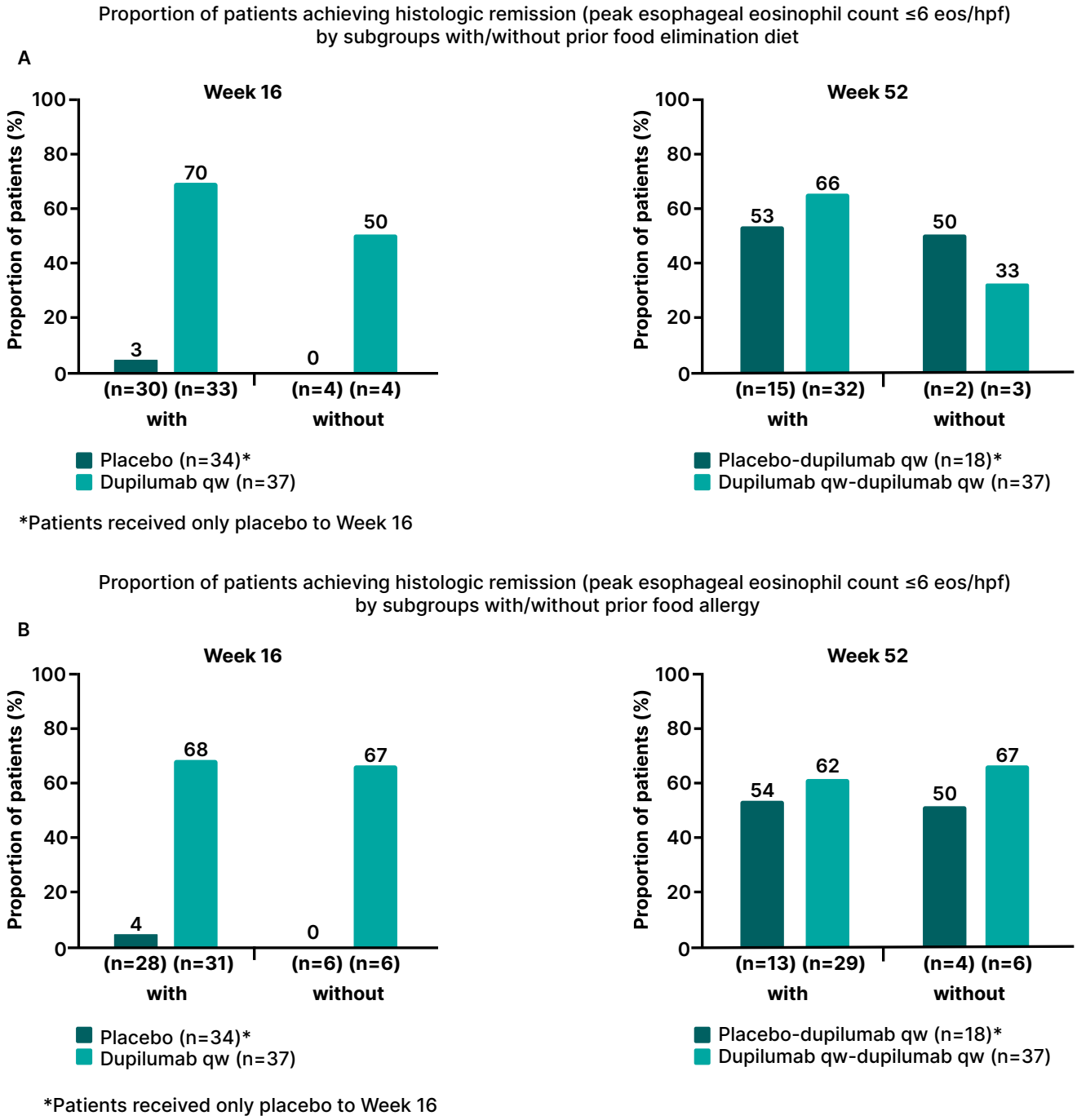

Figure 3. Improvements in achieving histologic remission (peak esophageal eosinophil count ≤6 eos/hpf) were observed in patient subgroups treated with dupilumab HE vs placebo regardless of history of **(A)** food elimination diet or **(B)** food allergy, with efficacy maintained to Week 52, and improvements observed in patients who switched from placebo to dupilmab HE at Week 16.; *adapted from Spergel, J. et al., 2024; from abstract at EAACI Congress 2024, Valencia, Spain.*

17 pregnancies  **7 patients**

Timeframe: 1957–2022

Symptoms compared to pre-pregnancy baseline	Percentage (%)
Better	53
Similar	17.6
Worse	29.4

Common affected sites: Abdomen and extremities

Figure 4. Pregnancy in hereditary angioedema: a single centre experience; *adapted from Tan, KL. et al.; from abstract at EAACI Congress 2024, Valencia, Spain.*

HAE state. Furthermore, vaginal delivery was not identified as a trigger for a HAE attack. Vaginal deliveries were pre-treated with prophylactic C1-esterase inhibitor in 1 out of every 4 deliveries; the remainder without prophylaxis or treatment. Six months post-delivery, patients stated that they had returned to their pre-pregnancy baseline of HAE activity (**Figure 4**).

Key Takeaways:

In this small but important cohort of patients with HAE, pregnancy was not found to increase the risk of HAE activity, including vaginal delivery. The hormonal changes of pregnancy do not appear to increase HAE attacks in the majority of females with HAE.

A randomized trial of penicillin skin testing versus direct challenge in pregnancy

Mustafa, SS et al., Rochester NY; EAACI, 2024

Pregnant women with a history of penicillin allergy have been increasingly evaluated for their penicillin allergy during pregnancy to increase their eligibility for amino-penicillin treatment if they are Group B streptococcus (GBS) positive at delivery. Over the last few years, an increasing number of publications have cited the safety of both skin testing (ST) and direct challenges (DC) during pregnancy. The authors of this trial randomized mothers with a history of cutaneous only, GI or unknown reactions to penicillin allergy greater than 5 years to either (A) ST followed by amino-penicillin in-office challenge or (B) DC to amino-penicillin without ST. The patients selected were considered "low risk" for true penicillin allergy. Total consulting time was measured for both groups. A total of 64 pregnant patients were evaluated at a mean age of 28 weeks and 24 weeks' gestation in the ST vs DC group, respectively. Four of 35 ST group were identified as positive; they did not proceed to amino-penicillin challenge. None of the 29 DC patients reacted to amoxicillin at 40 mg and 400 mg dosing followed by a 30-minute observational period. An average savings of 6 minutes was identified in the DC group (**Figure 5**).[11,12]

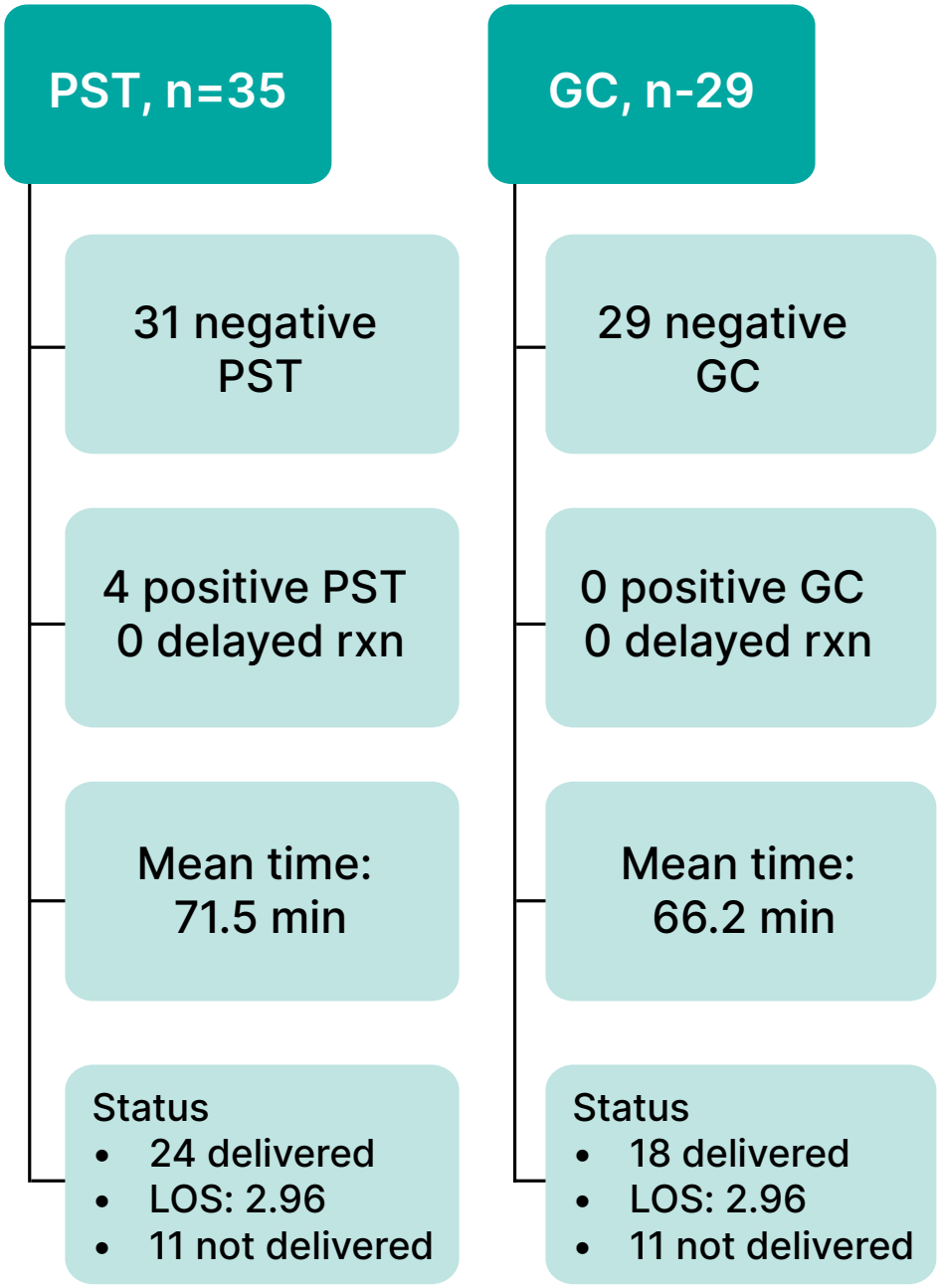

Figure 5. Penicillin skin testing and graded challenge results; *adapted from Mustafa, SS et al.; from abstract at EAACI Congress 2024, Valencia, Spain.*

Abbreviations: PST: penicillin skin testing, **GC:** graded challenge, **LOS:** length of stay

Key Takeaways:

De-labelling of penicillin allergy is increasing in the pregnancy population. Identifying pregnant patients who are low risk allowed for safe direct challenge, without skin testing. Skin testing remains an option for this population as well, followed by a DC to ensure full tolerance of amino-penicillins. The ability to ensure pregnant patients are offered complete treatment for GBS carriage through de-labelling of penicillin allergy is now a practice that community allergists should embrace to aid our obstetrical colleagues.

Sublingual immunotherapy (SLIT) for allergic rhinitis. The SQ House dust mite SLIT-tablet is effective and well-tolerated in children (5–11 years) with house dust mite allergic rhinitis/rhinoconjunctivitis – results from a global phase III clinical trial (MT-12).

An oral presentation by Dr. Antje Schuster

House dust mites (HDM) are a prominent cause of inhalant allergy and the burden of HDM allergic rhinitis (AR) is often hidden. The efficacy and safety of the HDM SLIT tablet (12 SQ HDM dose) for the treatment of HDM AR has been demonstrated in phase III clinical trials in adults and adolescents.

The objective of the study was to demonstrate efficacy and safety of the HDM SLIT tablet (12 SQ HDM dose) over 1 year of therapy vs placebo in children (5–11 years) with HDM allergic rhinitis/rhinoconjunctivitis (AR/C), with or without asthma. Subjects had high symptom and medication scores and normal lung function; 38% had concomitant asthma. A total of 52% of the children were polysensitized.

Key Takeaways:

1. Study participants showed 22% improvement in the total combined rhinitis score which combines rhinitis symptom scores and medication reduction scores vs placebo (P<0.0001).
2. The onset of effect of symptom improvement was demonstrated after only 8 weeks of therapy (P=0.011).
3. Statistically significant improvements were seen in rhinitis symptom scores, need for rhinitis medication scores, and quality of life questionnaire scores, further confirming the efficacy of the treatment.
4. 95% of subjects completed the trial.

The majority of treatment-related adverse events were transient local application site reactions that were mild or moderate in severity, and few subjects discontinued treatment due to adverse events.

The safety profile of the 12-SQ HDM dose was similar to that of the already established safety profile in adolescents and adults with HDM AR/C. The 12-SQ HDM SLIT-tablet was well-tolerated and had a favourable safety profile in children with HDM AR/C with and without asthma.

The SQ tree SLIT-tablet is effective and well-tolerated during the tree pollen season (birch homologous group) in children (5-17 years) – results from a global phase III clinical trial (TT-06)

An oral presentation by Dr. Monika Gappa

The prevalence of birch/tree pollen sensitization causing nasal and ocular symptoms increases through childhood. Pollen allergies can significantly impair quality of life. Sleep quality, daily activities (e.g., sports/outdoor activities) and school attendance can all suffer.

The SQ tree SLIT-tablet has previously been demonstrated as efficacious and safe in the TT-04 phase III trial including adults (n=574) and adolescents (n=60) with tree pollen allergy.

The objective of this study was to demonstrate efficacy and safety of the SQ tree SLIT-tablet (12 SQ-Bet dose) in children (5–17 years) with moderate-to-severe ARC-induced by pollen from birch and trees belonging to the birch homologous group.

Key takeaways:

1. 94% of 952 children aged 5–17 with moderate-to-severe tree pollen allergic rhinitis/conjunctivitis with and without asthma completed the trial.
2. There was a 22% improvement in total combined score (combining symptom score with medication reduction score) during the birch pollen season vs placebo (P=0.0004).
3. Daily symptom scores, medication scores and quality of live questionnaire scores all significantly improved, further supporting the efficacy of the SLIT-tablet.
4. The SQ tree SLIT tablet was generally well-tolerated and had a favourable safety profile in children with tree pollen AR/C with or without asthma, similar to the already established safety profile in adults.

Rilzabrutinib reduces IgG anti-thyroid peroxidase (anti-TPO), soluble mas-related G protein-coupled receptor X2 (sMRGPRX2) and eosinophils at 12 weeks in patients with chronic spontaneous urticaria

An oral presentation by Dr. Marcus Maurer

Chronic spontaneous urticaria (CSU) is a common immunologic skin disease. Bruton's tyrosine kinase (BTK), expressed in B-cells, masT-cells and other immune cells, plays a critical role in immune-mediated diseases. Rilzabrutinib (SAR444671), an oral reversible covalent BTK inhibitor, was administered for a 12-week period of the RILECSU Phase 2 study evaluating the efficacy and safety of the drug in adults with moderate-to-severe CSU not adequately controlled with antihistamines.

Key takeaways:

Serum levels of IgG anti-TPO autoantibodies, sMRGPRX2 (a masT-cell receptor), and blood eosinophils were all reduced with rilzabrutinib 400 mg TID treatment compared with placebo over 12 weeks; however, there was no change in total serum IgE levels. Reduction of these biomarkers aligned with the clinical efficacy results. The effect of various therapies on a variety of biomarkers in CSU may help clinicians better understand the cause of this common condition.

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Financial Disclosures

S.W.: None declared.
J.O.: None declared.
P.K.: Keith has been a speaker, advisory board member, or consultant for and has received honoraria from ALK, AstraZeneca, Bausch, BioCryst, Canadian Agency for Drugs and Technologies in Health, Canadian Pharmacists Association, CSL Behring, GSK, Medexus, Merck, Novartis, Sanofi Genzyme, Takeda/Shire, and Valeo; has received research grants from CSL Behring and Takeda/Shire; serves as a medical advisor (volunteer) for Hereditary Angioedema Canada, a patient organization; serves as a board member (volunteer) for the Canadian Hereditary Angioedema Network, a physician organization; and is an employee of McMaster University.

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