Eastern Allergy Conference
May 30-June 2, 2019 ~ Palm Beach, FL

All Scientific Posters will be on display in the South Ballroom Foyer, Friday, May 31 and Saturday, June 1, 2019. Authors of these posters are requested to be at their poster to discuss their work from 9:30 – 11:00 AM, both Friday and Saturday.

Not for CME Credit

Rapid Nasal Symptom Onset of Action and Ocular Symptom Relief With Olopatadine/Mometasone Combination Nasal Spray in Patients with Seasonal Allergic Rhinitis: A Pooled Analysis

Bruce Prenner, Frank Hampel, Nelumka Fernando, Cynthia F. Caracta, Sudeesh K. Tantry

Introduction: GSP301, a fixed-dose combination nasal spray containing olopatadine hydrochloride (antihistamine) and mometasone furoate (corticosteroid), was efficacious for treating seasonal allergic rhinitis (SAR) nasal and ocular symptoms, with a rapid onset of action (OOA), and was well tolerated (previously reported). Pooled analysis of OOA and ocular symptoms from 3 SAR studies are reported here.

Methods: Twice-daily (BID) treatment results were pooled from double-blind, randomized, placebo-controlled, 14-day studies (NCT02318303, NCT02631551, NCT02870205; N=2,971). SAR patients (12–65 years) were equally randomized to GSP301 (olopatadine 665µg/mometasone 25µg BID), olopatadine (665µg BID), mometasone (25µg BID), or placebo (BID). Results from once-daily treatments, evaluated only in NCT02318303, are not shown here. OOA (mean change from baseline in instantaneous Total Nasal Symptoms Scores from 15 minutes to 4 hours post-dose vs placebo) was analyzed using mixed-effect model repeated measures (MMRM; $P<0.05$=statistically significant). Average of AM and PM 12-hour reflective Total Ocular Symptom Scores (rTOSS) was also assessed.

Results: GSP301 BID OOA was observed at 15 minutes post-dose (least squares mean difference [95% CI]: -0.23 [-0.41, -0.05], $P=0.011$); at all 9 subsequent timepoints, OOA was maintained and differences were clinically meaningful and significant ($P<0.001$, all). GSP301 significantly improved rTOSS vs placebo from baseline to day 14 (-0.47 [-0.66, -0.28] $P<0.001$) and on each day (1-14; $P<0.001$, all). Treatment-emergent adverse events were low and comparable across treatments (reported elsewhere).

Conclusions: GSP301 BID provided rapid OOA of 15 minutes, statistically significant ocular symptom improvements, and was well tolerated in a pooled analysis of SAR studies conducted across different pollen seasons.

Funding: Glenmark Specialty SA

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Olopatadine/Mometasone Combination Nasal Spray for the Treatment of Seasonal Allergic Rhinitis: A Pooled Analysis of Efficacy and Safety

Gary N. Gross, Niran J. Amar, Nelumka Fernando, Cynthia F. Caracta, Sudeesh K. Tantry

Introduction: Efficacy and safety of GSP301, a fixed-dose combination nasal spray containing olopatadine hydrochloride (antihistamine) and mometasone furoate (corticosteroid), were demonstrated in 3 seasonal allergic rhinitis (SAR) natural-allergen exposure studies and an Environmental Exposure Chamber (EEC) study (previously reported). Pooled analysis of nasal symptoms and treatment-emergent adverse events (TEAEs) from these studies are presented here.

Methods: Total Nasal Symptom Scores (TNSS) from twice-daily (BID) treatments were pooled from three 14-day randomized, double-blind, placebo-controlled (RDBPC) studies (NCT02318303, NCT02631551, NCT02870205; N=2,971). SAR patients (12–65 years) were equally randomized to GSP301 (olopatadine 665µg/mometasone 25µg BID), olopatadine (665µg BID), mometasone (25µg BID), or placebo (BID). Mean change from baseline in average AM and PM 12-hour reflective and instantaneous TNSS (rTNSS, primary; iTNSS, secondary) were analyzed using mixed-effect model repeated measures ($P<0.05$=statistically significant). TEAEs were pooled from the 3 RDBPC studies plus a 14-day EEC study (NCT03444506). Results from once-daily treatments evaluated only in NCT02318303 and efficacy results from the EEC studies are not shown.

Results: GSP301 demonstrated significant and clinically meaningful improvements in average AM and PM rTNSS (least squares mean difference [95% CI]: -0.94 [-1.17, -0.70], $P<0.001$) and iTNSS (-0.91 [-1.14, -0.69], $P<0.001$) vs placebo. rTNSS and iTNSS results were similar for GSP301 vs olopatadine ($P<0.01$) and mometasone ($P\leq0.001$). TEAE rates were 13.9% (GSP301), 13.2% (olopatadine), 7.9% (mometasone) and 9.5% (placebo).

Conclusions: GSP301 BID provided statistically significant and clinically meaningful SAR nasal symptom improvements vs placebo and monotherapies and was well tolerated in a pooled analysis of studies conducted across different pollen seasons.

Funding: Glenmark Specialty SA

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Self-administration of Mepolizumab Liquid Using a Single-Use Prefilled Autoinjector

David Bernstein MD, Kenneth R. Chapman MD, Ian D. Pavord FMedSci FRCP, Richard Follows BSc, Jane H. Bentley PhD MSc, Isabelle Pouliquen PharmD, Eric Bradford MD MSc MBA

Rationale: We evaluated real-world use of mepolizumab self-administered via autoinjector (AI) by patients with severe eosinophilic asthma (SEA), or caregivers.

Methods: Patients ≥12 years, with asthma for ≥2 years and receiving mepolizumab 100mg subcutaneously (SC) every 4 weeks (Q4W) for ≥12 weeks were included. Patients not receiving mepolizumab meeting additional SEA criteria (treatment with high-dose ICS plus additional controllers plus ≥1 exacerbation requiring OCS in prior year, were included). Mepolizumab 100mg SC via AI was self-administered by patient/caregiver Q4W for ≤12 weeks. First and third doses (Week 0 and 8) were self-administered in clinic; second dose (Week 4) was self-administered at home. Patients received AIs with or without a pictogram. Endpoints were proportion of patients successfully self-administering third and second doses. Success was determined by Observer/At-home Checklists, and inspection of returned AI. Safety was evaluated.

Results: 157 (99%) patients completed the study. Almost all patients/caregivers successfully self-administered mepolizumab using either label + pictogram AI (95%) or the label AI (89%). The percentage of successful injections increased over the study. There were 12 injection failures in 11 patients (user errors). Each step on checklist was completed "easily" by ≥97%, ≥95% and ≥97% of patients/caregivers with label + pictogram AI, and by ≥89%, ≥96%, and ≥98% with label AI at Week 0, 4, and 8. 56 patients (35%) reported on-treatment AEs; 5 patients experienced drug-related AEs. Nine on-treatment serious AEs were reported by 4 patients (not considered related to treatment).

Conclusions: Patients/caregivers successfully self-administered mepolizumab 100mg SC using an AI. No new safety concerns were identified.

Funding: GlaxoSmithKline

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Self-administration of Mepolizumab Liquid Using a Single-Use Prefilled Syringe

David Bernstein MD, Eric Bradford MD MSc MBA, Leif Bjermer MD PhD, Richard Follows BSc, Jane H. Bentley MSc, Isabelle Pouliquen PharmD, Elisabeth H. Bel MD PhD

Rationale: We evaluated use of mepolizumab self-administered via prefilled syringe (PFS) by patients with severe eosinophilic asthma (SEA), or caregivers, in clinic or home.

Methods: Patients ≥12 years, with asthma for ≥2 years receiving mepolizumab 100mg subcutaneously (SC) for SEA every 4 weeks (Q4W) for ≥12 weeks were included. Patients not receiving mepolizumab meeting additional criteria of SEA (treatment with high-dose ICS plus additional controllers, plus ≥1 exacerbation requiring OCS in prior 12 months), were included. Mepolizumab 100mg SC via PFS was self-administered by patient/caregiver Q4W for ≤12 weeks. First and third doses (Weeks 0 and 8) were self-administered in clinic; second dose (Week 4) was self-administered at home. Endpoints were the proportion of patients successfully self-administering third and second doses. Success was determined by Observer/At-home Checklists, and visual inspection of returned PFS. Safety was evaluated.

Results: 56 patients/caregivers self-administered ≥1 dose; 55 patients completed the study. All patients/caregivers successfully self-administered their third and second dose. Patients/caregivers found the PFS easy/convenient to use with 75% (n=42) expressing little/no anxiety using the device at home. For patients receiving mepolizumab at screening (n=23), 96% (n=22) preferred mepolizumab via PFS at home vs. an injection administered in-clinic (4%, n=1). Post-injection, 51%–64% of patients reported pain, (generally mild). On-treatment adverse events (AEs) were low. No fatal AEs and a low incidence (4%) of anti-drug antibodies (none neutralizing) occurred.

Conclusions: Patients/caregivers successfully self-administered mepolizumab 100mg SC via PFS in clinic and at home. No new safety concerns were identified.

Funding: GlaxoSmithKline

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Perspectives on the Chronic Idiopathic/Spontaneous Urticaria Patient Journey Through Onset of Symptoms to Diagnosis

Tonya A. Winders, Howard L. Sofen, Sanaz Eftekhari, Leslie Kaufman, Stanley Goldstein

Introduction: Chronic idiopathic/spontaneous urticaria (CIU/CSU) is characterized by the spontaneous appearance of wheals and/or angioedema, and affects physical appearance and quality of life (QoL). The objective of this non-interventional qualitative study was to understand patient perspectives and key stages of the journey from symptom onset through diagnosis.

Methods: Patients in U.S. with confirmed CIU/CSU, recruited (Jun–Aug 2017) with assistance from advocacy/support groups, participated in semi-structured interviews focusing on: illness and treatment history; disease impact on personal/family life; relationship with healthcare-providers. Patients also documented disease impact in 3-day written/video diaries. A thematic analysis of interview and diary data was performed.

Results*:* Twenty-five patients (76% female) aged 23–66 who had previously, or were currently, receiving treatment(s) for CIU/CSU, participated in the study. Key stages identified in the patient journey following symptom onset were: Crisis (associated with feelings of torment, disorientation, shock); Searching for Answers (puzzlement, frustration, anxiety); Diagnosis (relief, satisfaction, fear, isolation). Predominant themes emerging from patient responses included the concept of living with their 'skinemy' (feeling their body had turned against them, loss of normalcy/identity, unpredictability); questioning 'what the heck is going on?' (unrelenting symptoms, self-medication attempts, work absenteeism); and relief/confusion at diagnosis (distress, relief, questioning of idiopathy, variability in available support and time to diagnosis).

Conclusions: Patient narratives provide insight into the impact of CIU/CSU on QoL and the emotional burden of living with CIU/CSU. These findings highlight the need for additional support services to improve patient care at symptom onset and through diagnosis.

Funding: Novartis

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Cost-Effectiveness Model for On-Demand Treatment of Hereditary Angioedema (HAE) Attacks

Christopher Tyson, PhD; Anurag Relan, MD; Philippe Adams; Angela Haynes, PharmD; Raf Magar

Introduction: HAE is a rare C1-inhibitor (C1-INH) deficiency disease involving recurrent painful episodes of severe swelling that should be promptly treated. This analysis estimated the expected cost and utility per HAE attack treated with on-demand, HAE-specific therapies to clarify expenses related to disease management.

Methods: A decision-tree model included 4 comparators (ecallantide, icatibant, plasma-derived [pd] C1-INH, and recombinant human C1-INH [rhC1-INH]) and incorporated probabilities for self-administration versus healthcare provider administration, re-dosing, and hospitalization risk. Modeled costs comprised HAE therapies and healthcare system expenses. Effectiveness considered utility during attacks (0.51), no-attack baseline (0.83), and time to attack resolution. Overall drug cost and effectiveness per attack were used to estimate cost per quality-adjusted life year (QALY). Sensitivity analyses were performed to establish cost-effectiveness ranges. A budget impact model was developed for a health plan of 1 million (M) covered lives.

Results: Costs and utility per attack were, respectively, $12,342 and 0.804 for rhC1-INH, $14,369 and 0.749 for icatibant, $13,993 and 0.759 for pdC1-INH, and $20,315 and 0.786 for ecallantide. At a mean annual attack rate of 26.9, cost per QALY was $402,769 for rhC1-INH, $475,942 for icatibant, $462,275 for pdC1-INH, and $666,153 for ecallantide. Re-dose rate was identified as a primary driver of cost-effectiveness variability. Estimated annual cost to the plan was $6.64M for rhC1INH, $7.73M for icatibant, $7.53M for pdC1-INH, and $10.93M for ecallantide.

Conclusions: This model demonstrated that rhC1-INH was the most cost-effective and ecallantide was the least cost-effective on-demand HAE treatment and cost-effectiveness was substantially impacted by re-dosing rates.

Funding: Pharming Healthcare Inc.

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Evaluation of the Risk of Ocular Effects Associated with EDS-FLU

Ellen Sher, MD; David Skoner, MD; John C. Messina PharmD, Harry J. Sacks, MD Jennifer L. Carothers, ScD, MBA; Ramy A. Mahmoud, MD, MPH

Introduction:
Increased intraocular pressure (IOP) and cataracts are known risks of systemic steroids exposure. EDS-FLU (exhalation delivery system with fluticasone) 372mcg produces higher systemic exposure than fluticasone nasal spray 400mcg, but lower systemic exposure than orally inhaled fluticasone 440mcg. Ocular effects were extensively studied in EDS-FLU trials.

Methods:
Ocular safety of EDS-FLU 186mcg and 372mcg BID in chronic rhinosinusitis with or without nasal polyps (CRSw/sNP) was assessed in two studies in CRSwNP, each 24-weeks in duration (16 double-blind [DB]+8 open-label [OL]) and placebo-controlled (N=643). Additionally, two 12- and 52-week OL studies evaluated 372mcg in CRS patients (N=898). Ophthalmologists assessed IOP and cataracts using tonometry and slit-lamp exams.

Results:
Mean change from screening in average IOP (mmHg) in right/left eyes ranged from 0.0 to -0.2. During the DB phase, 1.2%, 1.2%, and 0.4% of subjects developed increased IOP (>21), cataract, or subcapsular cataract, respectively (EDS-placebo [n=2 IOP >21; n=3 cataract; n=0 subcapsular]; 186mcg [3, 2, 1]; and, 372mcg [1, 1, 1]). All subcapsular cataracts were <grade 2. A total of 5/6 patients with increased IOP had high-normal IOP at baseline (lowest value: 17). IOP increased >6 mmHg from screening in 0.6%/0.6%, 0%/0%, and 0.6%/0% right/left eyes in EDS-placebo, EDS-FLU 186mcg, and EDS-FLU 372mcg groups, respectively. OL studies reported similar IOP changes, with 3- and 12-month cataract rates of 0.6% and 1.3% and no subcapsular cataracts.

Conclusion:
No increased risk of elevated IOP was detected with EDS-FLU, and the rate of cataract development was similar to that reported with other INS.

Funding: Optinose

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Lanadelumab 300mg Every 2 Weeks Effectively Prevented Hereditary Angioedema Attacks in the HELP Study

Aleena Banerji, Marc Riedl, Bruce Zuraw, William R. Lumry, Peng Lu, James Hao, Marcus Maurer, H. Henry Li for the HELP Study Investigators

Introduction: Lanadelumab, a highly specific, fully human monoclonal antibody targeting plasma kallikrein, demonstrated sustained and well-tolerated prophylaxis against hereditary angioedema (HAE) attacks in the phase 3 HELP Study (NCT02586805). Three dosing regimens were investigated; here we report further efficacy findings for lanadelumab 300mg every 2 weeks (q2wks).

Methods: Patients with HAE type I/II, aged ≥12 years, and with ≥1 attack/month at baseline were randomized 2:2:2:3 to lanadelumab 150mg every 4 weeks (q4wks), 300mg q4wks, 300mg q2wks, or placebo. The primary endpoint was the number of investigator-confirmed attacks over the 26-week treatment period (days 0–182). Exploratory analyses included efficacy and AE-QoL during treatment period and steady state (days 70–182; 16 weeks).

Results: Overall, 125 patients were treated, of which 27 received lanadelumab 300mg q2wks and 41 received placebo. Demographics and baseline characteristics for the lanadelumab 300mg q2wks group were comparable with the placebo group: mean (SD) age 40.3 (13.4) years, 55.6% female, 51.9% experienced ≥3 attacks/month. Compared with placebo, treatment with lanadelumab 300mg q2wks significantly reduced mean attack rate and resulted in greater proportions of attack-free patients during days 0–182 and days 70–182. Meaningful improvement in AE-QoL score was 7.2 times more likely with lanadelumab 300mg q2wks than with placebo.

Conclusion: Treatment with lanadelumab 300mg q2wks provided significant, clinically meaningful benefits to HAE patients during the 26-week treatment period, and particularly during the steady-state period, with 91.5% attack reduction versus placebo, 76.9% attack-free (versus 2.7% with placebo), and 92.5% reduction in rescue medication use versus placebo.

Funding: Takeda

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Lanadelumab exposure during steady state: Achievement of effective concentrations in patients in the HELP Study

Bruce L. Zuraw, Marco Cicardi, Joshua Jacobs, Hilary J. Longhurst, Peng Lu, Michael E. Manning, Mustafa Shennak, Daniel Soteres, Yi Wang, and Rafael H. Zaragoza-Urdaz for the HELP Study Investigators

Introduction: In the HELP Study (NCT02586805), treatment with lanadelumab (a monoclonal antibody inhibitor of plasma kallirein) 150 mg q4wks, 300 mg q4wks, or 300 mg q2wks significantly decreased attack rates over 26 weeks. We evaluated the relationship between lanadelumab exposure and efficacy during steady state (days 70-182) among the 3 dose groups.

Methods: Blood samples were collected from patients prior to dosing at weeks 0, 8, 14, and 20 for measurement of lanadelumab concentrations and cleaved high molecular weight kininogen (cHMWK) levels.

Results and Conclusions: Mean observed steady state lanadelumab concentrations in plasma increased and cHMWK levels decreased with dose and dosing frequency. These were associated with decreased attack rates. Attack rates decreased to the greatest extent in patients who received lanadelumab 300 mg q2wks (86.9% reduction vs placebo). The IC90 of lanadelumab (concentration associated with 90% of the maximum inhibitory effect on cHMWK levels) was previously determined to be 18,777 ng/mL. 88.9% of patients in the 300 mg q2wks group attained a maximum concentration at steady state ($C_{max,ss}$) ≥IC90, compared with 65.5% and 0% of patients in the 300 mg q4wks and 150 mg q4wks groups, respectively. The minimum concentration at steady state ($C_{min,ss}$) and average concentration at steady state ($C_{avg,ss}$) was ≥IC90 in 77.8% and 85.2% of patients, respectively, in the 300 mg q2wks group. Lanadelumab concentrations were maintained ≥IC90 in the majority of patients during steady state in the 300 mg q2wks group, correlating with the high extent of attack reduction observed.

Funding: Takeda

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Recombinant Human C1 Esterase Inhibitor as Rescue Therapy for Hereditary Angioedema Attacks Refractory to Other Therapies: A Case Report

Rafael Zaragoza Urdaz, Joseph R. Harper, and Angélica M. Rosado Quiñones

Introduction: Laryngeal attacks in patients with hereditary angioedema (HAE) may be potentially life-threatening, and patient quality of life is substantially negatively affected by these attacks.

Methods: A case report is presented of an adult with HAE taking prophylaxis with plasma-derived C1 esterase inhibitor (pdC1-INH) who was refractory to icatibant for breakthrough attacks but was successfully managed with recombinant human C1 esterase inhibitor (rhC1-INH).

Results: A 62-year-old Hispanic female with type I HAE whose breakthrough HAE attacks were only partially controlled by taking pdC1-INH 1500 IU intravenously every 4 days as prophylaxis. The patient would continue to experience monthly breakthrough attacks, typically abdominal, with attack severity consistently reported as an 8 (pain scale range, 1-10). Subsequently, the patient experienced a laryngeal HAE attack 1 day after she had taken a 1500-IU dose of pdC1-INH prophylaxis. Two doses of subcutaneous icatibant 30 mg, administered within 24 hours (6 hours apart), were provided as breakthrough therapy, but did not improve symptoms of the laryngeal attack. Due to the refractory nature of the laryngeal attack, the patient was prescribed 1 dose of rhC1-INH 4200 IU intravenously and the patient experienced resolution of the attack, with 50% improvement in laryngeal symptoms observed within 40 minutes post-treatment.

Conclusions: Adults with HAE who are only partially controlled on pdC1-INH prophylaxis and/or are refractory to therapies for acute treatment (eg, icatibant), including laryngeal attacks, can be successfully managed with rhC1-INH 4200 IU.

Funding: Pharming Healthcare Inc

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Recombinant C1 Esterase Inhibitor for Short-Term Prophylaxis in Patients With Hereditary Angioedema

Andrea Zanichelli, Tobias Suiter, Anna Valerieva

Introduction: Patients with hereditary angioedema (HAE) are at risk for an acute attack after medical procedures. Short-term prophylaxis may minimize this risk. This study evaluated recombinant C1 esterase inhibitor (rhC1-INH) as short-term prophylaxis.

Methods: Patients with angioedema were treated with rhC1-INH prior to medical procedures/stressful life events; HAE attacks were recorded through 2 days and >2-7 days postprocedure.

Results: Fifty-one patients (median age, 44 years [range, 17-73 years]; 62.7% female; 92.2% HAE type I) were included. A median rhC1-INH dose of 3075 IU (range, 2100-4200 IU) was administered as prophylaxis, median of 60 minutes prior, for 70 procedures (52.9% [n=37] dental [median, 60 minutes preprocedure]; 30.0% [n=21] surgical [median, 45 minutes preprocedure]; 15.7% [n=11] endoscopy [median, 30 minutes preprocedure]; and 1.4% [n=1] stressful event). Majority (n=48; 68.6%) of 70 cases had rhC1-INH administered 10-65 minutes preprocedure: 25 of 48 (52.1%) dental, 16 (33.3%) surgical, and 7 (14.6%) endoscopy. Nineteen (27.1%) cases involved patients on long-term prophylaxis (danazol/tranexamic acid). Overall, 97.1% (68/70) of cases were attack free during the 2 days postprocedure versus 23.1% of 26 procedures in a self-control (no long/short-term prophylaxis) group. For 2 attacks occurring within 2 days, rhC1-INH was administered 230 minutes and ≥24 hours preprocedure, respectively. Within 7 days postprocedure, 88.6% of 70 cases with rhC1-INH short-term prophylaxis were attack free versus 19.2% of 26 controls. No adverse events were reported.

Conclusion: Short-term prophylaxis with rhC1-INH, administered within several hours preprocedure, was efficacious and safe in adolescents/adults and reduced the risk of an HAE attack postprocedure.

Funding: Pharming Healthcare Inc

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Exploring the Patient Journey in Chronic Idiopathic/Spontaneous Urticaria: Disease Management

Stanley Goldstein, Sanaz Eftekhari, Tonya A. Winders, Leslie Kaufman, Howard L. Sofen

Introduction: The defining features of chronic idiopathic/spontaneous urticaria (CIU/CSU; spontaneous occurrence of wheals and/or angioedema) are challenging to manage and impact a patient's physical appearance, overall quality of life (QoL), and emotional wellbeing. The objective of this non-interventional qualitative study was to understand the patient's clinical journey and associated emotional burden from post-diagnosis through disease management.

Methods: Patients in U.S. with confirmed CIU/CSU, recruited (Jun–Aug 2017) with the assistance of advocacy/support groups, participated in semi-structured interviews focusing on illness and treatment history; treatment perspectives; disease impact on personal/family life; and relationship with healthcare-providers (HCPs). Patients also documented disease impact in 3-day written/video diaries. HCPs were interviewed about their views on disease management and patient care. A thematic analysis of interview and diary data was performed.

Results*:* Twenty-five patients (76% female) aged 23–66 who had previously, or were currently, receiving treatment(s) for CIU/CSU, participated in the study. Following feelings of relief/confusion at diagnosis, a range of emotions were expressed during the disease management phase, including frustration with treatment cycling, depression, anxiety, and hope. Principal themes identified in the patient journey post-diagnosis included the concept of patients experiencing their 'own personal hell' (stress, hypervigilance, emotional upheaval, and flare-ups) and feeling 'like an experiment' (trial and error, seeking alternative treatments/specialists).

Conclusions: The narratives of patients post-diagnosis with CIU/CSU provide insight into the disease management phase of the patient journey. These findings highlight a number of unmet patient needs, including the need for improved patient care and management.

Funding: Novartis.

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Interim Analysis of the Global Post Authorization Safety Study of Hyaluronidase-Facilitated Subcutaneous Immunoglobulin 10% Treatment in Patients With Primary Immunodeficiency Disease

Arye Rubinstein, Tracy Bridges, Donald McNeil, Raffi Tachdjian, H. James Wedner, Richard L. Wasserman, Heinz Leibl, Christopher J. Rabbat, Leman Yel

Introduction: HyQvia is a recombinant human hyaluronidase (rHuPH20)-facilitated subcutaneous immunoglobulin (fSCIG) 10% replacement therapy for patients with primary immunodeficiency disease (PID). To acquire long-term safety data on fSCIG and assess prescribed treatment regimens and administration in routine clinical practice, a global postauthorization safety study (PASS) is being conducted.

Methods: This is an ongoing prospective, noninterventional, open-label, uncontrolled, multicenter study initiated in the United States in November 2015 to assess local and systemic effects of fSCIG within a routine clinical setting. Patients aged ≥16 years with PID who have been prescribed and/or have started fSCIG are eligible for enrollment. Patients are followed according to standard clinical practice, and their treatment regimen is at the discretion of the treating physician. The presence of anti-rHuPH20 antibody titers is voluntarily evaluated.

Results: As of August 2017, 175 patients had been enrolled at 26 US study sites. There were no serious AEs that were deemed treatment related. Sixteen patients experienced a causally related nonserious local AE (9.1%; 0.43 events/patient-year, 0.07 events per infusion), and 25 patients experienced a causally related nonserious systemic AE (14.3%, 0.88 events/patient year, 0.14 events per infusion). Of the 113 patients with immunogenicity data, 7 had ≥1 positive binding-antibody test to rHuPH20 (titers ≥1:160); no neutralizing rHuPH20 antibodies were detected.

Conclusion: This interim analysis of prospectively collected data of fSCIG use in routine clinical practice indicates that fSCIG is well tolerated with no treatment-related SAEs and has not been associated with neutralizing anti-rHuPH20 antibodies in patients with PID.

Funding: Takeda

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Single-Use Autoinjector Functionality and Reliability for At-Home Benralizumab Administration: GRECO Trial Results

Pete Barker, Gary T. Ferguson, Jeremy Cole, Magnus Aurivillius, Paul Roussel, Ubaldo Martin

Introduction: Accessorized pre-filled syringes (APFS) are functional and reliable for delivery of benralizumab subcutaneously (SC) in the clinic or at home, as demonstrated by the GREGALE study (NCT02417961). The multicenter, open-label GRECO study (NCT02918071) was designed to assess functionality and reliability of single-use autoinjectors (AI) for at-home benralizumab administration.

Methods: Adults with severe asthma received benralizumab SC injections at the study site (Weeks 0, 4, and 8). First doses were administered by health care providers. Patients/caregivers used AI to administer the second (optional) and third doses under supervision. Patients/caregivers administered 2 benralizumab doses (Weeks 12 and 16) with AI at home. After each dose, patients/caregivers completed questionnaires concerning administration and device functioning and had study site visits within 48 hours.

Results: In total, 121 patients (mean age 48.5 years; 64% female) used 595 AI. Of 116 participants at Weeks 12 and 16, 113 (97.4%; 95% CI: 92.63–99.46) and 112 (96.6%; 95% CI: 91.41–99.05), respectively, successfully administered benralizumab at home; 108 (93.1%; 95% CI: 86.86–96.98) were successful on both occasions. Throughout the study, 10 (1.7%) unsuccessful AI administrations occurred: 8 (1.3%) because of user error, 1 (0.2%) with undetermined cause, and 1 (0.2%) caused by a manufacturing defect. No new or unexpected safety findings were observed.

Conclusions: Similar to the results for APFS in GREGALE, AI in GRECO were functional, reliable, and performed well in clinic and home settings. Nearly all patients and caregivers successfully administered benralizumab SC with AI.

Funding: AstraZeneca

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The Natural History of the Burden of Asthma in the United States by Age and Sex

Eugene R. Bleecker, Kevin Murphy, Hitesh Gandhi, Ileen Gilbert, Geoffrey Chupp

Introduction: Investigating the prevalence, control, and severity of asthma by age and sex will advance our understanding of asthma burden, morbidity, and mortality, and improve its clinical management.

Methods: The prevalence of asthma among sexes was evaluated by retrospective analysis using anonymous prescription information from IQVIA Longitudinal Access and Adjudication Data (LAAD; 7/2015-6/2018) covering ~85% of US retail prescriptions. 5,602,159 patients with an asthma diagnosis between 2015–2018 and a 2016 pharmacy claim for asthma medication were included. Patients with severe asthma (SA) were identified by treatment with approved asthma medications and dosages using GINA-based age-specific severity definitions. Exacerbations were defined by pharmacy claims for systemic steroids (ie, oral corticosteroids or steroid injections) within 12 months of the first 2016 asthma pharmacy claim. These data were used in a polynomial model to identify the percentage of patients with asthma with ≥2 annual exacerbations.

Results: For patients <~16 years of age, a greater percentage of males were treated for asthma; for those >~16 years, treatment for asthma was more prevalent in females. For patients <13 years of age, asthma exacerbations were more frequent for males. For patients >13 years, exacerbations were more prevalent in females. The difference between males and females in the percentages of patients with ≥2 exacerbations is greatest for those between 30–45 years, before declining and equalizing by ~73 years. This reduced separation in exacerbation prevalence between sexes was driven by a plateau in the proportion of females with ≥2 exacerbations, occurring at ~55 years of age, concomitant with a continued increase in the percentage of males with ≥2 exacerbations. Similar sex differences were observed for patients receiving GINA treatment Level 4/5 (SA). Exacerbations did not have a linear relationship with age; the relationship was better explained by a third order polynomial model. Age, sex, and SA status, including the interaction between age and sex, were all significantly related to exacerbations (age*sex $p<0.05$; all other variables $p<0.001$).

Conclusion: This analysis represents the largest population sample evaluated for asthma using unique methodology to investigate asthma prevalence and the natural history of asthma exacerbations across patient lifespans. The ages at which sex differences in asthma prevalence and exacerbations begin and end suggest that hormonal factors during puberty and/or menopause may affect systemic immunity, airway smooth muscle, or vascular biology; these factors may be important for understanding asthma over the full range of the patient lifespans.

Funding: AstraZeneca

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Real-World Biologic Medication Use in a Diverse Population of US, Specialist-Treated Adults with Severe Asthma: Results of CHRONICLE Study

Wendy C. Moore, Warner Carr, Bradley E. Chipps, Dennis K. Ledford, Njira Lugogo, Reynold A. Panettieri, Jr., Weily Soong, Jennifer Trevor, Laura Belton, Frank Trudo, Christopher S. Ambrose

Introduction: Several biologic therapies are now available in the United States for treatment of severe asthma (SA). However, few data reflect real-world use of individual biologic therapies by patients with SA treated by US subspecialists.

Methods: The CHRONICLE Study is an ongoing, non-interventional, observational study of US adults with SA treated by a diverse sample of US allergists/immunologists or pulmonologists. Protocol-eligible patients are adults receiving biologic treatments and/or long-term systemic corticosteroids (SCS), as well as those receiving high-dosage inhaled corticosteroids (HD ICS) with additional controllers and uncontrolled per ATS/ERS criteria. For enrolled patients, sites reported details of any biologic therapy use within 12 months prior to enrollment, including start dates prior to the 12-month period. Use of individual biologic medications were summarized by time period for overall use, as well as initiations or terminations of a specific product. Biologic switches and concomitant use of anti-IgE and anti–IL-5/anti–IL-5Rα biologic therapies were also summarized.

Results: Between 2/27/18 and 9/15/18, 65 sites evaluated 810 eligible patients; 60% (n=488) were receiving biologic therapy. Of enrolled patients, 273 had data regarding current or prior use of biologic therapies available for analysis. Of eligible and enrolled patients, 8% and 10% of those receiving biologic therapy were receiving concomitant long-term SCS therapy, respectively. Anti-IgE (omalizumab) therapy was the most prevalent biologic treatment, with anti–IL-5/anti–IL-5Rα most prevalent among biologic therapy initiations since December 2017. Concomitant use of omalizumab and anti–IL-5/anti–IL-5Rα biologic therapies was reported for 8 patients (3% of biologic therapy recipients). Nineteen biologic therapy switches were reported for 18 patients (7%): 14 were between anti–IL-5 and anti–IL-5Rα, and five were inter-class (between anti-IgE and anti–IL-5/anti–IL-5Rα). The most common switch was from mepolizumab to benralizumab (n=11). The most commonly reported reasons for switching biologic treatments were asthma symptom worsening (n=7), medication was never effective (n=5), and medication effectiveness waned and is now ineffective (n=5).

Conclusions: In this sample of 273 United States patients with SA treated with biologic therapies by US subspecialists, the most prevalent biologic therapy was omalizumab. However, anti–IL-5/anti–IL-5Rα biologic treatments were predominant in those initiating therapy since December 2017. Switching most commonly occurred among anti–IL-5/anti–IL-5Rα agents. Concomitant use of >1 biologic treatment occurs rarely. A limitation of these data is that sites were only required to report biologic therapy use that was ongoing in the 12 months prior to enrollment.

Funding: AstraZeneca

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Tezepelumab treatment effect on annualized rate of exacerbations by baseline biomarkers in uncontrolled severe asthma patients: Phase 2b PATHWAY study

Jonathan Corren, Esther Garcia Gil, Jane R. Parnes, Tuyet-Hang Pham, and Janet M. Griffiths

Introduction: Thymic stromal lymphopoietin (TSLP) is an epithelial cell-derived cytokine produced in response to environmental and mechanical triggers, activating multiple cell types and downstream inflammatory pathways associated with asthma. Tezepelumab is a human monoclonal antibody (IgG2λ) that selectively blocks TSLP from interacting with its receptor complex.[1,2] In the Phase 2b PATHWAY study (NCT02054130), tezepelumab demonstrated an acceptable safety profile and improvement in clinical outcomes versus placebo in patients with severe, uncontrolled asthma, independent of blood eosinophil (bEOS) count.[1] We evaluated the relationship between type 2 (T2) inflammation-associated biomarkers and cytokines at baseline and tezepelumab-associated reduction of annualized asthma exacerbation rate (AAER) in the PATHWAY study population.

Methods: Patients aged 18–75 years with severe, uncontrolled asthma were randomly assigned 1:1:1:1 to subcutaneous tezepelumab (70 mg every 4 weeks [Q4W], 210 mg Q4W, 280 mg Q2W), or placebo. Randomization was stratified by bEOS count to ensure approximately equal enrollment of patients across treatment arms with bEOS counts ≥250 and <250 cells/μL. Fraction of exhaled nitric oxide (FeNO), bEOS, interleukin-5 (IL-5), IL-13, immunoglobulin E (IgE), periostin, and thymus and activation-regulated chemokine (TARC) were measured at baseline. Baseline biomarker categories were defined using standard clinically used cutoffs (where available) or medians. Results are reported for the pooled tezepelumab cohorts and tezepelumab 210 mg Q4W, which was selected as the dose for Phase 3 studies.

Results: In total, 550 adults were randomized to tezepelumab or placebo (intent-to-treat population). At Week 52, AAER was reduced from baseline by 66% in the pooled tezepelumab cohorts, versus placebo. Reductions from baseline in AAER were observed at Week 52, irrespective of baseline biomarker cutoffs applied, ranging from 55–83% in the pooled tezepelumab cohorts, versus placebo. Similar reductions in AAER were observed in the tezepelumab 210 mg Q4W cohort, compared to placebo.

Conclusions: In the PATHWAY study, tezepelumab treatment reduced exacerbations in patients with severe uncontrolled asthma irrespective of the level of baseline inflammation, as measured by FeNO, bEOS, IL-5, IL-13, IgE, periostin or TARC. These results provide additional evidence that tezepelumab is able to reduce exacerbations in patients with asthma, regardless of whether they have high or low T2 inflammation status.

Funding: AstraZeneca

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Two-Year Integrated Efficacy and Safety Analysis of Benralizumab SIROCCO, CALIMA, ZONDA, and BORA Trials in Severe Asthma

J. Mark FitzGerald, Eugene R. Bleecker, Arnaud Bourdin, William W. Busse, Gary T. Ferguson, Laura Brooks, Peter Barker, Ubaldo Martin

Introduction: Benralizumab reduces exacerbations, improves lung function, and decreases oral corticosteroid (OCS) use for patients with severe, uncontrolled eosinophilic asthma, as evidenced by results from the Phase III SIROCCO (48 weeks; NCT01928771), CALIMA (56 weeks; NCT01914757), and ZONDA (OCS-sparing trial; 28 weeks; NCT02075255) trials. After completing SIROCCO, CALIMA, or ZONDA, patients could continue in BORA (NCT02258542), an ongoing, long-term safety and efficacy trial. The adult cohort of BORA (56-week treatment with follow up at Week 68) is completed, and 56-week treatment data are available for adolescents (end of treatment at 108 weeks). We analyzed 2-year integrated efficacy and safety results for patients who initiated benralizumab treatment in SIROCCO or CALIMA and continued in BORA. We also assessed data for patients in the ZONDA trial who continued in BORA (≤1.5 years of benralizumab treatment).

Methods: Patients received medium- or high-dosage inhaled corticosteroids/long-acting β_2-agonists at study initiation and benralizumab 30 mg every 4 weeks (Q4W) or every 8 weeks (Q8W, first three doses Q4W). The SIROCCO/CALIMA full analysis set (FAS) included patients who completed SIROCCO or CALIMA, received ≥1 dose of study treatment in BORA, and did not continue into another trial. Data from patients who initiated treatment in ZONDA were analyzed separately because of trial design differences.

Results: The SIROCCO/CALIMA FAS for the integrated analysis included 1,030/1,655 total patients randomized to benralizumab Q4W or Q8W in SIROCCO/CALIMA. During the integrated period, mean benralizumab exposure was 24.2 and 24.7 months, respectively, for benralizumab Q4W (n=518) and Q8W (n=512) groups. Reductions in exacerbation frequency observed during SIROCCO/CALIMA were maintained, as were improvements in prebronchodilator FEV_1, ACQ-6 scores, and AQLQ+12 scores. Improvements in OCS reductions observed in ZONDA were maintained. In the SIROCCO/CALIMA FAS and ZONDA groups, rates of all treatment-emergent adverse events (TEAEs) and serious AEs were similar between the BORA extension and SIROCCO/CALIMA and ZONDA study periods. Risk of infection did not increase over time with benralizumab, and the malignancy rate was low.

Conclusion: Reduced exacerbation rates, as well as improved pulmonary function, asthma control, and health-related quality of life, were sustained through 2 years in this integrated analysis of patients in SIROCCO and CALIMA who progressed to BORA. Long-term treatment with benralizumab was well-tolerated, with no new or unexpected safety findings. These results and associated safety data build on the 1-year BORA results and further support the long-term use of benralizumab.

Funding: AstraZeneca

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Tolerability and Onboarding Experience With Subcutaneous Human Immune Globulin 20% (Ig20Gly) Infused at High Rates and Volumes in Pediatric Patients With Primary Immunodeficiency

Kenneth Paris, Iftikhar Hussain, Sudhir Gupta, Ping Wang, Heinz Leibl, Barbara McCoy, Leman Yel

Introduction: Ig20Gly was efficacious and well tolerated in the phase 2/3 North American study in primary immunodeficiency disease (PID). This post hoc analysis assessed safety and onboarding experience with Ig20Gly infused at high rates and volumes in pediatric patients.

Methods: The analysis included patients aged 2–<16 years with PID who received weekly Ig20Gly infusions at volumes ≤60 mL/site and rates ≤60 mL/h/site for ~1.3 years in the North American study (NCT01218438). Adverse events (AEs), tolerability, and infusion parameters were assessed by age group (2–<5y [n=1], 5–<12y [n=14], and 12–<16y [n=6]).

Results: Median infusion rates and volumes/site were higher in patients aged 12–<16 years (50 mL/h/site; 42.7 mL/site) versus younger patients (5–<12y [30 mL/h/site; 19.5 mL/site]; 2–<5y [15 mL/h/site; 14.5 mL/site]). Five patients (5–<12y [n=2]; 12–<16 y [n=3]) used infusion rates ≥60 mL/h/site for ≥2 infusions; this rate was first reached at a median of 4th infusion. Maximum infusion rates were not tried in the majority of patients given smaller dose volumes in pediatric patients. Low rates of causally related AEs were seen in all pediatric-age groups (AEs/infusion: 0 [2–<5y]; 0.033 [5–<12y]; 0.022 [12–<16y]); none were serious or severe. Larger infusion volumes and faster infusion rates were not associated with an increase in causally related local AEs; the proportion of patients with ≥1 causally related local AE decreased over time.

Conclusions: Ig20Gly, infused at high rates and volumes, was well tolerated in pediatric patients with PID across age groups.

Funding: Takeda

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Ig20Gly Tolerability and Infusion Characteristics Across Age Groups in Patients With Primary Immunodeficiency Disease

Kenneth Paris, Daniel Suez, Sudhir Gupta, Iftikhar Hussain, Mark Stein, Ping Wang, Barbara McCoy, Leman Yel

Introduction: Subcutaneous immune globulin 20% (Ig20Gly) was well tolerated in the phase 2/3 North American study in patients with primary immunodeficiency disease (PID). Here, we analyze the safety, tolerability, and infusion parameters by age groups.

Methods: Patients aged ≥2 years with PID received weekly Ig20Gly infusions at volumes ≤60 mL/site and rates ≤60 mL/h/site for ~1.3 years in the North American study (NCT01218438). Adverse events (AEs), tolerability, and infusion parameters were assessed in 74 patients (2–<5y [n=1], 5–<12y [n=14], 12–<16y [n=6], 16–<65y [n=44], ≥65 y [n=9]).

Results: Overall, 71.6% (53/74) of patients achieved a maximum infusion rate ≥60 mL/h/site. Median maximum infusion rates and volumes/site were higher in adults (16–<65y [60 mL/h/site; 45.3 mL/site]; ≥65 y [60 mL/h/site; 39 mL/site]) and adolescents aged 12–<16 years (50 mL/h/site; 42.7 mL/site) versus children (5–<12y [30 mL/h/site; 19.5 mL/site]; 2–<5y [15 mL/h/site; 14.5 mL/site]). Percentages of infusions associated with causally related AEs were low among all pediatric age groups (0% [2–<5y]; 3.3% [5–<12y]; 2.2% [12–<16y]) and in adults including elderly patients (3.1% [16–<65y]; 2.0% [≥65y]); there were no serious or severe causally related AEs. Ig20Gly infusions were well tolerated by all age groups; >99% of infusions were administered without an infusion rate reduction, interruption, or discontinuation due to AEs.

Conclusion: Ig20Gly, infused at relatively high rates and volumes, was well tolerated in patients of all ages with PID.

Funding: Takeda

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Identification of Peanut-Allergic Participants for Oral Immunotherapy With AR101 Using Clinical Reaction History and Immunologic Markers Without Oral Food Challenge – A Comparison Between RAMSES and PALISADE Trials

Ellen Sher, MD, Alan Goldsobel, MD, Noelle M. Griffin, PhD, Kari R. Brown, MD, Brian P. Vickery, MD

Introduction: RAMSES, a phase 3, multicenter, randomized, double-blind, placebo-controlled, real-world safety study of AR101 (an investigational oral biologic drug used in oral immunotherapy), used readily available clinical data to identify eligible subjects. We compared baseline characteristics of RAMSES subjects with those from PALISADE, a phase 3 trial of AR101, which utilized clinical data and a screening double-blind, placebo-controlled food challenge (DBPCFC) to determine eligibility.

Methods: RAMSES enrolled subjects aged 4-17-years-old in North America with a physician-confirmed diagnosis of peanut allergy, skin prick test (SPT) mean peanut wheal diameter ≥8mm, and peanut-specific IgE (psIgE) ≥14kU$_A$/L. PALISADE enrolled subjects based on clinical history, SPT mean peanut wheal diameter ≥3mm and/or psIgE ≥0.35kU$_A$/L, and at screening DBPCFC results (dose-limiting symptoms ≤100mg peanut protein). Summary statistics for baseline characteristics are compared between RAMSES and PALISADE subjects 4-17-years-old.

Results: Subjects in both studies (RAMSES N=505; PALISADE, N=496) were predominantly male (63.4%; 57.3%) and Caucasian (78.2%; 78.4%) with a median age of 9-years (both trials). Atopic comorbid disease frequencies were comparable between trials: allergic rhinitis (74.5%; 71.8%), atopic dermatitis (59.2%; 62.1%), other food allergies (52.7%; 65.5%), and asthma (49.5%; 52.8%). PsIgE (median [IQR]: 93.5kU$_A$/L [42.8, 201.0]; 71.3kU$_A$/L [19.7, 202.0]) and SPT wheal diameter (median 13.5mm [10.5, 19.0]; 11.0mm [9.0, 15.0]) were similar.

Conclusions: Baseline characteristics appeared similar in RAMSES and PALISADE subjects, despite RAMSES requiring more stringent clinical history but not requiring a DBPCFC. This suggests that it is feasible to identify potential AR101-eligible peanut-allergic individuals with the use of readily available clinical data, which aligns with routine clinical practice.

Funding: Aimmune

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Longer-Term Safety and Efficacy Measures of AR101 Oral Immunotherapy for Peanut Allergy: Results from a Phase 3 Follow-On Study

Ellen Sher, MD, Wayne G. Shreffler, MD, Noelle M. Griffin, PhD, Rezi Zawadzki, DrPH, Stacie M. Jones, MD

Introduction: Of subjects who completed the phase 3 study of the experimental treatment AR101 for peanut allergy (PALISADE), 76% of AR101-treated vs 5.4% of placebo-treated subjects tolerated ≥600mg of peanut protein at exit double-blind, placebo-controlled food challenge (DBPCFC). Adverse events (AEs) were mostly mild-to-moderate in severity. Ability to tolerate doses >1000mg and safety beyond the first 6 months of AR101 therapeutic dosing (300mg/day) have not been established. PALISADE follow-on study initial findings (ARC004) are reported.

Methods: PALISADE completers (AR101-treated subjects had to tolerate ≥300mg peanut protein at exit DBPCFC) were eligible to enter ARC004 and continue AR101 therapeutic dosing (300mg/day) for 6 months before the next DBPCFC, which included an additional 2000mg challenge dose. AEs/discontinuations were recorded and compared to the prior 6-month therapeutic dosing period.

Results: 117/316 AR101-treated PALISADE subjects (37%) enrolled in the continued therapeutic dose regimen; remainder were assigned to other dosing regimens (not included in this analysis). 109/117 subjects (85%) completed the DBPCFC. AEs, regardless of causality, were similar during both therapeutic dosing periods (PALISADE 88% vs follow-on 81.2%). Three subjects (2.6%) discontinued due to AEs: 2 were treatment-related (1 EoE, 1 mild systemic reaction). Median tolerated dose was 1000mg; 49% of subjects tolerated the highest challenge dose of 2000mg. Of subjects who tolerated <1000mg at PALISADE exit, 69% (27/39) could tolerate a higher challenge dose at ARC004 exit.

Conclusions: 300mg daily AR101 was well-tolerated in ARC004 (study ongoing); most subjects could tolerate higher challenge amounts (1000mg and 2000mg) of peanut protein after continuing therapeutic dose for 6 additional months.

Funding: Aimmune

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Stability of eosinophil classifications over time using common cut-points

Bradley Chipps, William Calhoun, Ahmar Iqbal, Cecile Holweg, Tmirah Haselkorn, Ming Yang, Jonathan Corren

Introduction: Blood eosinophil levels are advocated to aid decisions regarding biologic asthma therapies. Historical measurements have been suggested to suffice for treatment decisions, making the variation over time of practical interest. This analysis examined the stability of eosinophil levels based on common cut-points over periods up to 1 year.

Methods: Post-hoc analyses of placebo arm data from LUTE/VERSE (Phase IIb) and LAVOLTA I/II (Phase III) studies of lebrikizumab using patient data assessed monthly at ≥5 timepoints. The proportion of time a patient was classified in the same eosinophil category (<150, 150-299, ≥300 cells/µL) over a year was calculated.

Results: Of 813 included patients, 751 (92.4%) patients had ≥5 eosinophil measures. Eosinophil classification stability (eg, ≥80% of time at same level classification) was lower among patients with baseline eosinophil levels 150-299 cells/µL (20.5%) compared with levels <150 cells/µL (44.7%) or ≥300 cells/µL (46.4%). Stability decreased as the minimum proportion of time a patient maintained in the same classification increased (<150 cells/µl: 75%, 30%; 150-299 cells/µl: 71%, 7%; ≥300 cells/µl: 80%, 35% for maintaining in the same category 60% or 90% of the time, respectively). Efficacy and safety aspects were not evaluated in this analysis.

Conclusions: Stability of eosinophil classification over time using common thresholds, shows that the proportion of patients maintaining the same levels decreases as the minimum proportion of time being stable increases, indicating that eosinophil levels are variable over the studies 1-year timeframe. This should be taken into account when eosinophil levels are used for patient care.

Funding: Genentech

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Effect of reslizumab exposure on efficacy outcomes in a pharmacokinetic–pharmacodynamic (PK–PD) analysis of weight-based intravenous (IV) dosing

Julie Passarell, David Jaworowicz, Jill Fiedler-Kelly, Elizabeth Ludwig, Douglas A. Marsteller, Margaret Garin, Laura Rabinovich-Guilatt

Introduction: IV reslizumab is approved for the treatment of adult patients with severe, inadequately controlled eosinophilic asthma. A population PK model using pooled data from clinical studies indicated weight-based IV reslizumab 3.0mg/kg dosing resulted in numerically comparable steady-state exposures across a >4-fold range of body weight. Exposure-response analysis of key efficacy endpoints was performed subsequent to PK analysis.

Methods: Exposure–response models were developed to understand the relationships between reslizumab exposures and blood eosinophil (EOS) levels, FEV_1 and Asthma Control Questionnaire scores (ACQ-7). These models were based on population PK data from four Phase (P) 1, two P2, and two P3 randomized, placebo-controlled studies of weight-based IV reslizumab, including a P3 52-week placebo-controlled study of IV reslizumab 3.0mg/kg.

Results: Findings from population PK model-based simulations demonstrated comparable median steady-state exposures following once-monthly IV reslizumab 3.0mg/kg, including trough exposures, across a wide range of body weights (33.9–156 kg). The magnitude and duration of peripheral blood EOS reductions increased with increasing reslizumab concentrations. Minimal fluctuations in suppressed blood EOS between 3.0mg/kg doses suggest saturation of blood IL-5 pathway inhibition throughout the dosing interval. A sigmoid Emax time-course described the placebo response in the FEV_1 and ACQ-7 models. The reslizumab effect imposed on the placebo maximum response time-course models indicated linear improvement of FEV_1 and ACQ-7 scores with increasing reslizumab exposure ($p=0.001$ and $p\leq0.0001$, respectively).

Conclusions: Weight-based IV dosing leads to consistent steady-state reslizumab exposure across a wide range of body weights, with subsequent beneficial exposure-related effects on EOS, FEV_1 and ACQ-7.

Funding: Teva

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Dupilumab Improves Outcomes of Concurrent Asthma and Chronic Sino-Nasal Conditions in Patients With Atopic Dermatitis—a Pooled Analysis of Four Phase 3 Studies (LIBERTY AD SOLO 1 & 2, CHRONOS, and CAFÉ)

M. Boguniewicz, D. Thaçi, P. Lio, A.B. Rossi, L. Eckert, A. Gadkari, B. Shumel, X. He, Z. Chen, M. Ardeleanu

Rationale: Dupilumab, a fully human anti-interleukin (IL)-4 receptor α monoclonal antibody, inhibits signaling of IL-4 and IL-13, key drivers of type 2-mediated inflammation. In the US, dupilumab is approved for treatment of patients 12 or older with inadequately controlled moderate-to-severe AD or as add-on maintenance treatment in patients with moderate-to-severe asthma (eosinophilic phenotype or with oral corticosteroid dependent asthma). We assessed dupilumab's efficacy in adults with concurrent AD, asthma, and chronic nasal/paranasal sinus conditions (N/PNS) from 4 phase 3 trials: LIBERTY AD SOLO 1 & 2 (NCT02277743, NCT02277769), CHRONOS (NCT02260986), and CAFÉ (NCT02755649).

Methods: Data were pooled from patients with moderate-to-severe AD, asthma requiring treatment plus baseline Asthma Control Questionnaire (ACQ-5) score ≥ 0.5, and N/PNS (12.7% of study patients). Patients received subcutaneous dupilumab 300 mg every 2 weeks (q2w; n=95), weekly (qw; n=102), or placebo (n=114). Outcomes assessed at Week 16 included ACQ-5 (asthma), 22-item Sino-Nasal Outcome Test (SNOT-22, N/PNS), and Eczema Area and Severity Index (EASI) and peak pruritus Numerical Rating Scale (NRS) for AD.

Results: Dupilumab q2w/qw vs placebo improved scores (least squares mean reduction from baseline) on the ACQ-5 (0.53/0.66 vs 0.24; *P*=0.0242/0.0007), SNOT-22 (12.27/13.39 vs 6.47; *P*=0.0110/0.0017), EASI (77.7%/75.3% vs 35.5%; *P*<0.0001), and peak pruritus NRS (46.1%/50.7% vs 24%; *P*<0.0001). Injection-site reactions and conjunctivitis were more common in dupilumab-treated than placebo-treated patients.

Conclusions: This subgroup analysis shows that dupilumab-treated AD patients with asthma and N/PNS experienced clinically and statistically significant improvement in all 3 diseases.

Funding: Sanofi/Regeneron

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Dupilumab Improves Lung Function and Reduces Severe Exacerbation Rate in Patients with Uncontrolled, Moderate-to-Severe Asthma With or Without Comorbid Allergic Rhinitis: Results from the Phase 3 LIBERTY ASTHMA QUEST Study

William W. Busse, Jorge F. Maspero, Nicola. A. Hanania, J. Mark FitzGerald, Linda B. Ford, Megan S. Rice, Paul Rowe, Heribert Staudinger, Nikhil Amin, Marcella Ruddy, Neil M. H. Graham, Ariel Teper

Introduction: Dupilumab, a fully human monoclonal antibody, blocks the shared receptor component for interleukin (IL)-4 and IL-13, key drivers of type 2 inflammation. In the phase 3 LIBERTY ASTHMA QUEST study (NCT02414854), add-on dupilumab 200/300 mg every 2 weeks (q2w), vs placebo, significantly reduced severe asthma exacerbations, improved pre-bronchodilator FEV_1, and improved quality-of-life measures in patients with uncontrolled, moderate-to-severe asthma. This post-hoc analysis assessed the effect of dupilumab in patients with or without comorbid allergic rhinitis (AR).

Methods: The effect of add-on dupilumab 200mg/300mg or matched placebo q2w on the annualized rate of severe exacerbations and FEV_1 was assessed in asthma patients with (1,207/1,902) and without (695/1,902) a self-reported medical history of comorbid AR.

Results: Baseline characteristics of patients with and without AR were generally similar. The annualized rate of severe exacerbations was reduced (vs placebo) with dupilumab 200mg q2w (relative risk with AR: 0.606 [95%CI, 0.451–0.814]; *P*=0.0009; without AR: 0.406 [95%CI, 0.273–0.605]; *P*<0.0001) with similar results for 300mg q2w. FEV_1 was improved at Week 12 with dupilumab 200mg (LS mean difference vs placebo with AR: 0.14L [95%CI, 0.07–0.21]; *P*<0.0001; without AR: 0.13L [95%CI, 0.05–0.21]; *P*=0.0025) and sustained to Week 52 (both with/without AR: *P*<0.0001), with similar results at Week 52 for 300mg q2w. Overall, the most common adverse event in dupilumab-treated patients (vs placebo) was injection-site reactions (15%/18% vs 5%/10%).

Conclusions*:* Dupilumab significantly improved FEV_1 and reduced annual severe exacerbation rates in patients with uncontrolled asthma, with and without comorbid AR.

Funding: Sanofi/Regeneron

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Conjunctivitis Adverse Events in Dupilumab Clinical Trials

Elena Rizova, Marius Ardeleanu, Zhen Chen, Stefan Plaum, Ana B. Rossi, Mandeep Kaur, Bolanle Akinlade

Introduction: Dupilumab, a human anti-IL-4Rα mAb, is approved in the USA for patients aged 12 and older with inadequately controlled moderate-to-severe atopic dermatitis (AD). We reviewed incidence, severity, and resolution of conjunctivitis in patients from dupilumab clinical trials in AD, asthma, chronic rhinosinusitis with nasal polyposis (CRSwNP), and eosinophilic esophagitis (EoE).

Methods: "Conjunctivitis" comprised MedDRA Preferred Terms conjunctivitis, conjunctivitis allergic, conjunctivitis bacterial, conjunctivitis viral, adenoviral conjunctivitis, and atopic keratoconjunctivitis. Randomized, double-blind, placebo-controlled trials in adults with moderate-to-severe AD: 1. primary safety pool (R668-AD-1021, LIBERTY AD SOLO 1/SOLO 2; 2. LIBERTY AD SOLO-CONTINUE; 3. LIBERTY AD CHRONOS; 4. LIBERTY AD CAFÉ. Moderate-to-severe asthma: 5. DRI12544; 6. LIBERTY ASTHMA QUEST; 7. LIBERTY ASTHMA VENTURE; CRSwNP: 8. ACT12340; EoE: 9. R668-EE-1324.

Results: Conjunctivitis rates, as % patients with ≥1 event (hazard ratio [95% CI]), were: primary safety pool: dupilumab 300 mg every 2 weeks (q2w)/weekly (qw)/combined 9.3% (4.43 [2.30–8.51])/7.9% (3.80 [1.95–7.40])/8.6% (4.13 [2.21–7.72]), vs placebo 2.1%; CHRONOS: q2w+topical corticosteroids (TCS)/qw+TCS/combined 13.6% (1.76 [0.93–3.33])/19.4% (2.51 [1.57–3.99])/17.9% (2.31 [1.47–3.63]), vs placebo+TCS 7.9%; CAFÉ: q2w+TCS/qw+TCS/combined 28.0% (2.69 [1.38–5.26])/16.4% (1.47 [0.71–3.06])/22.1% (2.06 [1.09–3.88]), vs placebo 11.1%. Conjunctivitis incidence in SOLO-CONTINUE, asthma, and CRSwNP trials was low and similar among groups. No conjunctivitis was reported in the EoE trial.

Conclusions: Conjunctivitis was more frequent in dupilumab-treated vs placebo patients in AD trials, except for SOLO-CONTINUE. Conjunctivitis rates in the asthma/CRSwNP/EoE trials were very low and similar among treatment groups. Most cases were mild/moderate, and resolved/resolving by end of treatment.

Funding: Sanofi/Regeneron

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Dupilumab Reduces Severe Exacerbations and Improves Lung Function Regardless of Baseline Bronchodilator Reversibility in Patients With Uncontrolled Moderate-to-Severe Asthma Enrolled in the LIBERTY ASTHMA QUEST Study

Ian D. Pavord, Mario Castro, Klaus F. Rabe, Nicola A. Hanania, Alberto Papi, J. Mark FitzGerald, Megan S. Rice, Paul Rowe, Nikhil Amin, Heribert W. Staudinger, Neil M.H. Graham, Ariel Teper

Introduction: Dupilumab, a fully human monoclonal antibody, blocks the shared receptor component for interleukin (IL)-4 and IL-13, key drivers of type 2 inflammation. In the phase 3 LIBERTY ASTHMA QUEST study (NCT02414854), add-on dupilumab 200 mg or 300 mg every 2 weeks (q2w), vs placebo, significantly reduced severe asthma exacerbations, improved pre-bronchodilator FEV_1, and improved quality-of-life measures in patients with uncontrolled, moderate-to-severe asthma. This post-hoc analysis assessed the effect of dupilumab by baseline bronchodilator reversibility.

Methods: All patients had baseline bronchodilator reversibility ≥12% and ≥200mL in FEV_1 following β_2-agonist administration. The population median (20.89%) was used to divide bronchodilator FEV_1 into reversibility-high (RH) and -low (RL) subgroups. Severe exacerbations during the 52-week treatment period, change from baseline in pre-and post-bronchodilator FEV_1, and pre-bronchodilator $FEF_{25–75\%}$ at Weeks 12 and 52 were assessed.

Results: Dupilumab 200/300 mg q2w vs placebo reduced severe exacerbations in RL (−41.9%/−58.5%;*P*=0.002/*P*<0.0001) and RH subgroups (−52.6%/−26.8%;*P*<0.0001/*P*=0.06). In both subgroups, dupilumab q2w vs placebo improved both pre-and post-bronchodilator FEV_1 (ranges 0.07−0.28L and 0.07−0.27L, respectively; *P*≤0.05 for all) at Weeks 12 and 52. In both subgroups, dupilumab q2w vs placebo improved $FEF_{25–75\%}$ at Weeks 12 and 52 (range 0.10−0.25L/s; *P*<0.05 for all), except for a non-significant Week 12 improvement for the RL subgroup (0.07L/s; *P*=0.12). The most frequent adverse event in dupilumab-treated patients (vs placebo) was injection-site reactions (15%/18% vs 5%/10%).

Conclusions: Dupilumab reduced severe exacerbations and improved lung function in uncontrolled, moderate-to-severe asthma patients with low- and high-baseline post-bronchodilator FEV_1 reversibility.

Funding: Sanofi/Regeneron

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Dupilumab Improves Upper and Lower Airway Outcome Measures in Patients With Severe Chronic Rhinosinusitis With Nasal Polyps and Comorbid Asthma: Pooled Results From the SINUS-24 and SINUS-52 Phase 3 Studies

Tanya M. Laidlaw, Seong Cho, Jorge F. Maspero, G. Walter Canonica, Lawrence Sher, Claus Bachert, Joseph K. Han, Xuezhou Mao, Mei Zhang, Naimish Patel, Neil M.H. Graham, Heribert Staudinger, Leda P. Mannent, Nikhil Amin

Introduction: Chronic rhinosinusitis with nasal polyps (CRSwNP) is a type 2 inflammatory disease with a high symptom burden. CRSwNP and type 2 asthma are frequent comorbidities sharing the same inflammatory pathophysiology. Dupilumab, a human mAb, blocks the shared receptor component for IL-4/IL-13, key drivers of type 2 inflammation. Dupilumab efficacy and safety were evaluated in patients with severe CRSwNP in 2 double-blind, placebo-controlled, phase 3 studies, SINUS-24 (NCT02912468) and SINUS-52 (NCT02898454). We report dupilumab effect vs placebo on upper/lower airway outcome measures in patients with comorbid asthma from the pooled population of these studies.

Methods: SINUS-24 patients were randomized 1:1 to 24 weeks of subcutaneous dupilumab 300mg or placebo every 2 weeks (q2w). SINUS-52 patients were randomized 1:1:1 to 52 weeks of dupilumab 300mg q2w; 24 weeks of dupilumab 300mg q2w then 28 weeks every 4 weeks; or 52 weeks of placebo q2w.

Results: 428/724 patients reported a history of asthma. Dupilumab 300mg q2w improved (least-squares mean difference from baseline at Week 24 vs placebo): forced expiratory volume in 1 second (0.21L); 6-item Asthma Control Questionnaire score (−0.82); 22-item Sino-Nasal Outcome Test score (−21.42); nasal peak inspiratory flow (46.15L/minute); nasal polyp score (−2.04); nasal congestion score (−1.04); and Lund–Mackay CT score (−6.43); P<0.0001 for all. Adverse events (in ≥5% patients) were nasopharyngitis, nasal polyps, headache, injection-site erythema, asthma, and epistaxis, all occurring more frequently with placebo.

Conclusions: Dupilumab improved upper/lower airway outcome measures in patients with severe CRSwNP with comorbid asthma in the SINUS-24/SINUS-52 population and was well tolerated.

Funded: Sanofi/Regeneron

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Dupilumab Improved Asthma Control and Health-Related Quality of Life in Patients With Oral-Corticosteroid-Dependent Severe Asthma in the Phase 3 LIBERTY ASTHMA VENTURE Study

Linda B. Ford, Klaus F. Rabe, Robert N. Wolfe, Santiago Quirce, Megan S. Rice, Paul Rowe, Siddhesh Kamat, Nikhil Amin, Neil M.H. Graham, Ariel Teper, Asif Khan

Introduction: Dupilumab, a fully human monoclonal antibody, blocks the shared receptor component for interleukin (IL)-4 and IL-13, key drivers of type 2 inflammation. In the phase 3 LIBERTY ASTHMA VENTURE study (NCT02528214), add-on dupilumab 300mg q2w vs placebo reduced oral corticosteroid (OCS) maintenance dose and rate of severe asthma exacerbations and improved pre-bronchodilator FEV_1 in patients with OCS-dependent severe asthma. This pre-specified analysis assessed the effect of dupilumab on asthma control (AC) and health-related quality of life (HRQoL) in these patients.

Methods: AC was assessed by 5-item Asthma Control Questionnaire (ACQ-5), where higher scores (range 0─6) indicate decline. HRQoL was assessed by Asthma Quality of Life Questionnaire (AQLQ), where higher scores (range 1─7) indicate improvement. Changes from baseline were analyzed using mixed-effect models with repeated measures.

Results: In the dupilumab and placebo groups, mean baseline ACQ-5 scores were 2.42 and 2.58, and AQLQ scores 4.38 and 4.31. With dupilumab, ACQ-5 rapidly improved (Week 2, LS mean change from baseline: ─0.57, *P*=0.002 vs placebo), further improved at Week 12 (─1.01, *P*=0.001 vs placebo), and stabilized through Week 24 (─1.05, *P*=0.002 vs placebo). LS mean improvements from baseline in AQLQ of 0.76 and 0.89 were observed at Week 12 (*P*=0.14 vs placebo) and Week 24 (*P*=0.008 vs placebo). The most frequent treatment-emergent adverse event in dupilumab-treated patients (vs placebo) was eosinophilia (14% vs 1%); injection-site reactions also occurred (9% vs 4%).

Conclusions: Dupilumab vs placebo significantly improved AC and HRQoL in patients with OCS-dependent severe asthma. Dupilumab was generally well tolerated.

Funding: Sanofi/Regeneron

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Dupilumab in Moderate-to-Severe Atopic Dermatitis With or Without Comorbid Allergic Rhinitis: Pooled Analysis of 2 Randomized Phase 3 Trials (LIBERTY AD SOLO 1 & 2)

Diamant Thaçi, Thomas Bieber, Neil M.H. Graham, Bolanle Akinlade, Laurent Eckert, Abhijit Gadkari

Introduction: Dupilumab, a fully human anti-IL-4Rα mAb, inhibits signaling of IL-4 and IL-13, key drivers of type 2/Th2 immune diseases. Dupilumab is approved for patients aged 12 years and older in the USA with inadequately controlled moderate-to-severe atopic dermatitis (AD). We report efficacy and safety of dupilumab in adults with moderate-to-severe AD with/without patient-reported comorbid allergic rhinitis (AR) in two pooled phase 3 monotherapy trials (LIBERTY AD SOLO 1&2: NCT02277743; NCT02277769).

Methods: Patients were randomized (1:1:1) to subcutaneous dupilumab 300mg every 2 weeks (q2w; n=457) or weekly (qw; n=462), or placebo (n=460) for 16 weeks. Endpoints included proportion of patients with Investigator's Global Assessment (IGA) 0/1, ≥75% improvement in Eczema Area and Severity Index (EASI-75), and peak pruritus Numerical Rating Scale improvement ≥4 (NRS≥4).

Results: Baseline characteristics were consistent across groups and between patients with (dupilumab q2w, n=224/qw, n=244, placebo, n=224) or without comorbid AR. At Week 16, more patients with comorbid AR receiving dupilumab 300mg q2w/qw achieved IGA 0/1 (32.6%/36.1% vs 9.4%), EASI-75 (45.5%/48.0% vs 12.5%), and NRS ≥4 (39.2%/35.9% vs 10.8%) versus placebo (p<0.0001 for all). Patients without comorbid AR showed similar results. Treatment groups (dupilumab q2w/qw, placebo) had similar rates of adverse events (69%/67%, 69%). Injection-site reactions and conjunctivitis were more frequent in dupilumab-treated patients.

Conclusions: This subgroup analysis shows that dupilumab-treated patients with or without comorbid AR have comparable/significant improvement in AD signs and symptoms. Future studies in AD patients with symptomatic comorbid AR will help assess the potential benefit of dupilumab in both conditions.

Funding: Sanofi/Regeneron

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Clinically Meaningful Responses in Moderate-to-Severe Atopic Dermatitis Patients Treated With Dupilumab

Marjolein de Bruin-Weller, Laurent Eckert, Eric L. Simpson, Michael J. Cork, Marius Ardeleanu, Zhen Chen, Brad Shumel, Ana Rossi, Neil M.H. Graham, Abhijit Gadkari

Introduction: Dupilumab, a fully human anti-IL-4Rα mAb, is approved in the USA for patients aged ≥12 years with inadequately controlled moderate-to-severe atopic dermatitis (AD). Here we determine the proportion of moderate-to-severe AD patients treated with dupilumab who achieved a clinically meaningful response in at least 1 of the 3 major AD domains (signs, symptoms, and quality of life [QoL]), across four phase 3 trials: LIBERTY AD SOLO 1 & 2 (NCT02277743, NCT02277769), CHRONOS (NCT02260986), CAFÉ (NCT02755649).

Methods: Patients received subcutaneous dupilumab 300mg weekly (qw)/every 2 weeks (q2w) or placebo qw monotherapy for 16 weeks (SOLO 1&2), or plus concomitant topical corticosteroids (TCS) for 16 weeks (CAFÉ) or 52 weeks (CHRONOS). Clinically meaningful response was defined based on improvement from baseline: ≥50% in Eczema Area and Severity Index (EASI-50), or ≥3-point in Peak Pruritus Numerical Rating Scale (NRS), or ≥4-point in Dermatology Life Quality Index (DLQI).

Results: Dupilumab resulted in significantly higher proportions of patients achieving ≥1 clinically meaningful response after 16 weeks of treatment compared to placebo (SOLO 1&2 [qw/q2w vs placebo]: 70.1%/76.6% vs 35.0%) or placebo+TCS (CHRONOS [qw/q2w+TCS vs placebo+TCS]: 83.4%/84.0% vs 52.7%; CAFÈ [qw/q2w+TCS vs placebo+TCS]: 91.8%/95.3% vs 61.1%), and after 52 weeks (CHRONOS [qw/q2w+TCS vs PBO+TCS]: 72.1%/79.2% vs 36.2%); *P*<0.0001 for all.

Conclusions: Across multiple phase 3 trials, the majority of AD patients treated with dupilumab experienced clinically meaningful improvement in at least one of signs, symptoms, and QoL as measured by the proportion of patients achieving EASI-50, NRS≥3, or DLQI≥4 at Weeks 16 and 52.

Funded: Sanofi/Regeneron

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Recom Dupilumab in Adolescents With Moderate-to-Severe Atopic Dermatitis and a History of Asthma or Allergic Rhinitis: Subgroup Analysis From a Randomized Phase 3 Trial

Mark Boguniewicz, Amy S. Paller, Lawrence Sher, Elaine C. Siegfried, Paola Mina-Osorio, Randy Prescilla, Zhen Chen, Ashish Bansal

Introduction: Dupilumab is a fully human monoclonal antibody that inhibits signaling of interleukin (IL)-4 and IL-13 involved in type 2 diseases including atopic dermatitis (AD), asthma, and allergic rhinitis (AR). In the USA, dupilumab is approved for patients aged ≥12 years with inadequately controlled, moderate-to-severe AD or as add-on maintenance treatment in patients ≥12 years with moderate-to-severe asthma with an eosinophilic phenotype or with oral corticosteroid-dependent asthma. The impact of history of asthma or AR on dupilumab efficacy in adolescents with moderate-to-severe AD is reported.

Methods: This is a post-hoc analysis of a double-blind, placebo-controlled, phase 3 trial (NCT03054428) in patients aged ≥12 to <18 years with moderate-to-severe AD inadequately controlled with topical therapies randomized 1:1:1 to 16-week dupilumab 300mg every 4 weeks (q4w), dupilumab 200/300mg every 2 weeks (q2w), placebo q2w.

Results: Of 251 randomized patients, >50% had asthma (57%/62%/64%) or AR (60%/72%/67%) history in the q4w/q2w/placebo groups, respectively. At Week 16, regardless of comorbidities, more dupilumab vs placebo patients achieved: Investigator's Global Assessment score 0/1 (with asthma 14.6%/23.5%/3.7%, without asthma 22.2%/25.8%/0%, with AR 22.0%/25.4%/3.5%, without AR 11.8%/21.7%/0%); ≥75% improvement from baseline in Eczema Area and Severity Index (with asthma 37.5%/41.2%/9.3%, without asthma 38.9%/41.9%/6.5%, with AR 36.0%/44.1%/8.8%, without AR 41.2%/34.8%/7.1%); ≥4-point improvement from baseline in Peak Pruritus Numerical Rating Scale (with asthma 29.8%/35.3%/5.6%, without asthma 22.2%/38.7%/3.3%, with AR 26.5%/37.3%/5.4%, without AR 26.5%/34.8%/3.6%).

Conclusions: Dupilumab improved signs and symptoms in adolescents with moderate-to-severe AD regardless of asthma or AR history, suggesting that coexisting atopic diseases did not impact dupilumab efficacy.

Funded: Sanofi/Regeneron

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Clinical Experience With Subcutaneous C1-Esterase Inhibitor Prophylactic Therapy in Pregnant Patients With Hereditary Angioedema

Nayla Mumneh, Huamin Henry Li, John Dang, Joseph Chiao

Introduction Subcutaneous C1-esterase inhibitor (C1-INH [SC]) is indicated as routine prophylaxis to prevent hereditary angioedema (HAE) attacks in adolescents and adults. Current HAE guidelines recommend
C1-INH as on-demand treatment or prophylaxis for women during pregnancy. We report on the real-world experience of 2 patients receiving C1-INH (SC) during pregnancy. These cases add to the clinical evidence of C1-INH (SC) efficacy and safety in pregnant patients.

Methods
Patient 1: A 38-year-old female treated with intravenous (IV) C1-INH prophylaxis during her first pregnancy in 2016. She experienced no attacks but developed access issues and required a port. She was switched to C1-INH (SC) in July 2017 and had the port removed. She became pregnant again in June 2018 and continued C1-INH (SC) throughout pregnancy.

Patient 2: A 28-year-old female with a history of severe abdominal attacks as well as throat and facial swelling. During the first 5 months of pregnancy, she was managed with on-demand C1-INH (IV) alone. In the 6th month, she was switched to C1-INH (SC) prophylactic therapy.

Results Patient 1 had no attacks during pregnancy. Patient 2 had no attacks until labor, when she had an abdominal attack treated with C1-INH (IV). Both patients delivered healthy babies with no congenital abnormalities reported.

Conclusions C1-INH (SC) was effective in pregnant patients, with no treatment-related adverse events or complications. C1-INH (SC) may facilitate continuity of HAE management before, during, and after pregnancy.

Funding: CSL Behring

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Clinical Experience With Subcutaneous C1-Esterase Inhibitor Prophylactic Therapy in Pediatric Patients With Hereditary Angioedema

Courtney Blair, Huamin Henry Li

Introduction Subcutaneous C1- inhibitor (C1-INH [SC]) is indicated as routine prophylaxis to prevent hereditary angioedema (HAE) attacks in adolescents and adults. Patients <12 years old are generally underrepresented in HAE clinical trials. Here, we present 2 case reports documenting the use of C1-INH (SC) in children <12 years old.

Methods
Patient 1: Male patient diagnosed with HAE at age 8; no family history of HAE. He had a combination of peripheral, abdominal, and disfiguring facial attacks. He had 2-3 angioedema attacks per month, each associated with ER visit and frequent intravenous (IV) C1-INH infusion. Obesity hindered IV access at home for on-demand and prophylactic treatments. At age 10 (July 2018), he was started on C1-INH (SC).

Patient 2: Male patient (mother has HAE) presented at age 7 with facial angioedema attack.
He had at least 7-8 subsequent attacks, 2 of which required ER visits treated with on-demand C1-INH (IV). He also experienced many milder, untreated angioedema attacks. Light physical activity, anxiety, physical trauma, and viral upper respiratory tract infections were triggers. Mother had significant anxiety associated with caregiver burden. At age 9 (November 2018), he was started on C1-INH (SC).

Results Since starting C1-INH (SC), Patient 1 experienced mild attacks occurring approximately every 2 months with no ER visits; Patient 2 has had no attacks. Both patients have resumed normal activities, with no missed school days due to HAE.

Conclusions Prophylaxis with C1-INH (SC) can reduce attack frequency, decrease use of on-demand medication, and improve quality of life in pediatric patients with HAE.

Funded: CSL Behring

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Long-term Safety of Subcutaneous C1-Esterase Inhibitor in the Prophylactic Treatment of Hereditary Angioedema

H. Henry Li, Timothy Craig, Joseph Chiao, Ingo Pragst, and Ellen Bonagua, on behalf of the COMPACT Investigators

Introduction Subcutaneous C1-inhibitor (C1-INH [SC]) is indicated as routine prophylaxis to prevent attacks in patients with hereditary angioedema (HAE). We present data on the long-term safety of C1-INH (SC) from an open-label extension (OLE) of the phase III COMPACT trial.

Methods Patients aged ≥6 years with ≥4 attacks over 2 consecutive months before enrollment self-administered C1-INH (SC) 40 IU/kg or 60 IU/kg twice weekly for 52 to 140 weeks. Safety endpoints included treatment-related serious adverse events (SAEs), AEs leading to premature discontinuation, AEs of special interest (thromboembolism, anaphylaxis), solicited AEs (injection-site reactions [ISRs]), hospitalizations for HAE, and clinically significant laboratory abnormalities.

Results Of 126 patients randomized, 110 completed the study (discontinuations: 4, pregnancy; 4, AEs; 8, patient decision). The AE rate (1811 events/18,699 injections) was not dose related (40 IU/kg vs 60 IU/kg: 11.3 vs 8.5 AEs/patient-years of exposure). None of the 12 SAEs were assessed as treatment related. One unrelated serious HAE attack resulted in hospitalization, but did not lead to discontinuation. No related thromboembolic events or cases of anaphylaxis were reported. ISRs were the most common AEs, accounting for 99% of treatment-related AEs, and were reported more frequently with the 40 IU/kg dose (0.08 vs 0.06 events per injection); 99% were mild and all events resolved. No patients had neutralizing anti-C1-INH antibodies at baseline or postbaseline visits.

Conclusions
C1-INH (SC) has a favorable long-term safety profile in the prophylactic treatment of HAE, with no
dose-dependent safety concerns. No cases of anaphylaxis and no related thromboembolic events were reported during C1-INH (SC) treatment.

Funding: CSL Behring

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Wixela™ Inhub™ Dry Powder Inhaler: In Vitro Performance Compared with Advair Diskus® and Inhalation Profiles in Patients with Asthma or Chronic Obstructive Pulmonary Disease

Andrew Cooper, Claire Newcomb, Jonathan K. Ward, Richard Allan, Roisin Wallace

Introduction: Wixela™ Inhub™ is a fluticasone propionate/salmeterol dry powder inhaler developed as a generic equivalent of Advair Diskus®. Objectives were to explore inhalation profiles of patients with asthma or chronic obstructive pulmonary disease (COPD) using Inhub and evaluate in vitro dose delivery with Inhub versus Diskus.

Methods: Inhalation profiles were recorded 3 times in each patient with asthma or severe COPD with an empty Inhub. The primary end point was peak inspiratory flow rate (PIFR). Emitted dose (ED) and dose impactor-sized mass (ISM) were measured at flow rates ranging from 30 to 90 L min^{-1}.

Results: For Inhub, mean PIFR was lowest for children with asthma aged 4 to 7 years (50.6 L min^{-1}) and highest for adults with asthma (74.8 L min^{-1}). Adults with severe COPD had mean PIFR 69.5 L min^{-1} with Inhub. All subjects generated a PIFR >30 L min^{-1}. ED and ISM from Inhub showed low flow dependency across the patient-relevant flow rate range of 30 to 90 L min^{-1} with comparable in vitro performance to Diskus for all strengths and flow rates. Mean ED from Inhub was within 96% to 111% of that from Diskus. Mean ISM from Inhub was within 90% to 112% of that from Diskus.

Conclusions: Comparable performance of Inhub to Diskus demonstrated that Wixela Inhub is a generic equivalent to Advair Diskus across all patient groups, including pediatric
asthma and severe COPD.

Funded: Mylan

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Pulmonary Therapeutic Bioequivalence of Wixela™ Inhub™ and Advair Diskus® in Adults with Asthma

Dik Ng, Edward M. Kerwin, Martha V. White, S. David Miller, Scott Haughie

Introduction: Wixela™ Inhub™ (fluticasone propionate/salmeterol [FP/S]) is a dry powder inhaler developed as a generic equivalent to Advair Diskus®. This study tested the pulmonary bioequivalence of Wixela Inhub (test [T]) and Advair Diskus (reference [R]) following oral inhalation.

Methods: This study in patients with mild-to-moderate asthma used forced expiratory volume in 1 second (FEV_1) to compare therapeutic effects of FP/S (100/50 µg) following twice-daily inhalation via T and R. The bronchodilator component was evaluated using the change from baseline (CFB) in FEV_1 (FEV_1 area under the effect curve over 12 hours [$AUC_{0\text{-}12}$]), measured after the first dose on Day 1. The anti-inflammatory component was assessed using CFB in trough FEV_1, measured on day 29, 12 hours after 28 days of twice-daily dosing. To demonstrate assay sensitivity, T and R treatments had to show significant superiority over placebo (P<0.05). To demonstrate bioequivalence, 90% confidence intervals for the T/R ratios of mean FEV_1 $AUC_{0\text{-}12}$ and trough FEV_1 had to fall within the prespecified interval (0.80-1.25).

Results: Compared with placebo, T and R significantly increased Day 1 FEV_1 $AUC_{0\text{-}12}$ and Day 29 trough FEV_1 (all P<0.0001), demonstrating assay sensitivity. Least squares mean T/R ratios for Day 1 FEV_1 $AUC_{0\text{-}12}$ and day 29 trough FEV_1 indicated bioequivalence for both end points. FP/S was similarly well-tolerated when administered via T or R.

Conclusions: Wixela Inhub demonstrated pulmonary bioequivalence to Advair Diskus, representing a generic product that is therapeutically equivalent to Advair Diskus in treating asthma and chronic obstructive pulmonary disease.

Funded: Mylan

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Equivalent Systemic Exposure to Fluticasone Propionate/Salmeterol Following Single Inhaled Doses of Advair Diskus® and Wixela™ Inhub™: Results of 3 Pharmacokinetic Equivalence Studies

Jonathan K. Ward, Nolan Wood, Richard Allan, Scott Haughie

Introduction: Wixela™ Inhub™ is a fluticasone propionate/salmeterol (FP/S) dry powder inhaler developed as a generic equivalent of Advair Diskus®. Our objective was to confirm the pharmacokinetic bioequivalence of FP/S following single doses of Wixela Inhub (test [T]) and Advair Diskus (reference [R]).

Methods: Three studies (one in each of 100/50, 250/50 and 500/50 dose strength products) in healthy adults compared systemic exposure of a single-dose of FP/S following oral inhalation using T and R. Primary end points were area under the plasma concentration time curve from 0 to last measurable plasma drug concentration ($AUC_{0\text{-}t}$) and the maximum observed plasma drug concentration (C_{max}) for FP and S. Bioequivalence acceptance criteria specified that the 90% confidence intervals (CIs) of the geometric mean T/R ratios for $AUC_{0\text{-}t}$ and C_{max} be between 0.80 and 1.25 for FP and S.

Results: Plasma concentration versus time data for T and R were comparable in each study. Estimated $AUC_{0\text{-}t}$ and C_{max} geometric mean T/R ratios (and 90% CIs) for FP and S were within the prespecified ranges for all dose strengths, indicating bioequivalence for FP and S components. FP/S at all doses was similarly well-tolerated when using T and R.

Conclusions: Wixela Inhub demonstrated pharmacokinetic bioequivalence to Advair Diskus at all dose strengths, providing direct evidence for equivalent systemic safety and indirect evidence for equivalent pulmonary deposition.

Funded: Mylan

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Usability and Robustness of the Wixela™ Inhub™ Dry Powder Inhaler

Richard Allan, Claire Newcomb, Kelly Canham, Roisin Wallace, Jonathan K. Ward

Introduction: Wixela™ Inhub™ is a fluticasone propionate/salmeterol (FP/S) dry powder inhaler developed as a generic equivalent of Advair Diskus®. Studies were designed to evaluate the usability and robustness of Inhub when used by representative patients.

Methods: To assess usability, patients with asthma or chronic obstructive pulmonary disease were asked to use an empty Diskus or Inhub inhaler without instruction. Subjects, including those with reduced dexterity, performed 3 tasks to examine intuitive and learned device usability and orientation. Device robustness was evaluated separately; subjects received 3 weeks of twice-daily Wixela Inhub 250/50 µg, after which in vitro tests were conducted of the unused drug in the inhaler. The device was considered robust if commercial specifications for Wixela Inhub were met, with no issues with device functionality.

Results: Of 110 subjects, 91% performed "at-home use" steps correctly, and 91% used the Inhub in the intended orientation; 9 of 10 who used it in a different orientation still achieved a peak inspiratory flow rate ≥30 L/min and a total inhaled volume ≥1 L, confirming they would have received a dose. In the device robustness study, all devices were functional and pharmaceutical performance of FP and S were preserved following 3 weeks of regular use. No new safety concerns were identified.

Conclusions: Patients successfully used the Inhub with no safety issues. Regardless of the Inhub orientation during inhalation, subjects should receive the intended dose. The outpatient study confirmed the robustness of the Inhub, including maintenance of product performance during and after use.

Funded: Mylan

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Type 2 Helper T-Cell (Th2) Effects of Crisaborole Ointment, 2%, Versus 3 Topical Corticosteroids (TCSs) With a Range of Potencies: An Ex Vivo Human Skin Model Study

Karl Nocka, William C. Ports, Bonnie Vlahos, Chuanbo Zang, Gabriel Berstein, Steven R. Feldman, Marc Brown, Alison Caserta, Jessica Neil

Introduction: The Th2 pathway plays a central role in the pathophysiology of atopic dermatitis (AD). Crisaborole ointment is a nonsteroidal phosphodiesterase 4 inhibitor for the treatment of mild-to-moderate AD. An ex vivo human skin model was used to compare the suppressive effects of crisaborole with topical corticosteroids (TCSs) of varying potencies (hydrocortisone cream, 1% [HC; lowest], hydrocortisone butyrate cream, 0.1% [HB; lower-medium], and betamethasone valerate cream, 0.1% [BV; medium]) on T-cell and Th2 cytokine activation.

Methods: Test articles were applied topically to human skin explants from 4 healthy (ie, non-AD) donors (5 replicates each) 16 hours before Th2 activation via proprietary Th2 stimulation cocktail. To determine the effect of test article application on the Th2-mediated inflammatory state of the tissue, gene expression was measured via quantitative PCR of RNA isolated 24 hours after stimulation for 4 AD-associated biomarkers (interleukin [IL]-13, IL-31, interferon [INF]-γ, and matrix metalloprotease 12 [MMP12]).

Results: Mean percentage inhibitions with crisaborole versus HC, HB, and BV respectively were 77.7% versus 90.2%, 84.7%, and 96.3% for IL-13, 75.9% versus 72.2%, 83.7%, and 89.4% for IL-31, 63.9% versus 72.3%, 52.2%, and 72.0% for IFN-γ, and 91.5% versus 73.6%, 85.9%, and 87.6% for MMP12.

Conclusions: Topical application of crisaborole or any of the 3 TCSs resulted in a significant reduction (>50%) in activity of all 4 AD-associated biomarkers. There were no differences in biomarker expression between crisaborole and the 3 TCSs except for a numerically greater reduction in MMP12 for crisaborole than with HC.

Funded: Pfizer Inc.

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Demographics and Baseline Disease Characteristics of Early Responders to Crisaborole Ointment, 2%, for Atopic Dermatitis (AD)

Linda F. Stein Gold, Liza Takiya, Chuanbo Zang, Paul Sanders, Steven R. Feldman

Introduction: Crisaborole ointment is a nonsteroidal phosphodiesterase 4 inhibitor for the treatment of mild-to-moderate AD. Efficacy and safety of crisaborole were established in phase 3 trials (NCT02118766, NCT02118792). This post hoc analysis identifies baseline characteristics associated with early (day 8) response—Investigator's Static Global Assessment (ISGA) success (clear [0]/almost clear [1] with ≥2-point improvement) or ISGA clear/almost clear.

Methods: Patients ≥2 years were randomized to crisaborole (N=1016) or vehicle (N=506) for 28 days. Subgroups included sex, age, race, ethnicity, percentage of treatable body surface area (%BSA; mild [<16%] vs moderate/severe [≥16%]), prior AD treatment, disease duration (≤ vs > median [6.45 years]), history of asthma/allergy, concurrent antihistamine use, and baseline ISGA (mild vs moderate).

Results: Early ISGA success was more likely for age <12 years (odds ratio, 1.826 [95% CI, 1.240-2.691]; *P*=0.0023), white (1.507 [1.037-2.190]; *P*=0.0316), no prior AD treatment (1.543 [1.067-2.237]; *P*=0.0213), disease duration ≤6.45 years (1.463 [1.027-2.084]; *P*=0.0349), no concurrent antihistamine use (1.779 [1.112-2.825]; *P*=0.0148), or moderate baseline ISGA (2.079 [1.399-3.086]; *P*=0.0003). Early ISGA clear/almost clear response was more likely for age <12 years (1.474 [1.116-1.947]; *P*=0.0063), white (1.569 [1.188-2.073]; *P*=0.0015), mild %BSA (1.953 [1.458-2.618]; *P*<0.0001), no prior AD treatment (1.342 [1.022-1.764]; *P*=0.0338), disease duration ≤6.45 years (1.614 [1.235-2.108]; *P*=0.0005), no concurrent antihistamine use (1.938 [1.385-2.717]; *P*=0.0001), or mild baseline ISGA (5.628 [4.224-7.499]; *P*<0.0001). No significant differences were observed between remaining subgroups.

Conclusions: Factors associated with early response with crisaborole were consistent between the 2 ISGA outcomes, except for baseline ISGA.

Funded: Pfizer Inc.

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Pruritus Outcomes With Crisaborole Ointment, 2%, by Baseline Atopic Dermatitis (AD) Severity

Gil Yosipovitch, Melissa Olivadoti, Mizuho Kalabis, Chuanbo Zang, Bonnie Vlahos, Paul Sanders, Daniela E. Myers, Andrew G. Bushmakin, Joseph C. Cappelleri, Linda F. Stein Gold

Introduction: Crisaborole ointment is a nonsteroidal phosphodiesterase 4 inhibitor for the treatment of mild-to-moderate AD. In phase 3 trials (NCT02118766, NCT02118792) crisaborole demonstrated efficacy and safety, with clinically relevant improvement in pruritus, assessed by Severity of Pruritus Scale (SPS; 0 [no itching] to 3 [bothersome itching/scratching that disturbs sleep]). This pooled, post hoc analysis of phase 3 trials assessed SPS outcomes for mild and moderate baseline Investigator's Static Global Assessment (ISGA).

Methods: Patients ≥2 years were randomized to crisaborole (N=1016) or vehicle (N=506) for 28 days. Proportions of patients achieving SPS success (weekly average SPS ≤1 with ≥1-point improvement), ≥1-point improvement in weekly average SPS, and time to success/improvement in daily average SPS were assessed (only patients with average baseline and postbaseline assessments included).

Results: For crisaborole versus vehicle, mean baseline SPS was 1.60 (n=297) versus 1.57 (n=138) for mild and 1.96 (n=465) versus 1.89 (n=230) for moderate. Differences were observed from week 1 (W1) through W4 for SPS success for mild (W1: 17.5% vs 8.7%, *P*=0.0068; W4: 37.4% vs 25.0%, *P*=0.0094) and moderate (W1: 19.1% vs 10.0%, *P*=0.0007; W4: 34.8% vs 18.4%, *P*<0.0001) and for ≥1-point SPS improvement for mild (W1: 25.9% vs 14.5%, *P*=0.0036; W4: 42.7% vs 28.1%, *P*=0.0032) and moderate (W1: 32.7% vs 20.4%, *P*=0.0004; W4:4 45.9% vs 31.4%, *P*=0.0003). Times to success/improvement were shorter for crisaborole than vehicle regardless of baseline ISGA.

Conclusions: Patients with mild or moderate AD treated with crisaborole versus vehicle experienced significant improvement in pruritus outcomes through W4.

Funded: Pfizer Inc.

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Improvement in Investigator's Static Global Assessment (ISGA) With Crisaborole Ointment, 2%, by Baseline Atopic Dermatitis (AD) Severity

Lawrence Eichenfield, Melissa Olivadoti, Mizuho Kalabis, Chuanbo Zang, Bonnie Vlahos, Paul Sanders, Amy Paller

Introduction: Crisaborole ointment is a nonsteroidal phosphodiesterase 4 inhibitor for the treatment of mild-to-moderate AD. In phase 3 trials (NCT02118766, NCT02118792), crisaborole was well tolerated and demonstrated efficacy versus vehicle in Investigator's Static Global Assessment (ISGA) success (clear [0]/almost clear [1] with ≥2-grade improvement). This pooled, post hoc analysis of the phase 3 trials assessed ISGA outcomes for mild and moderate baseline ISGA.

Methods: Patients ≥2 years were randomized to crisaborole (N=1016) or vehicle (N=506) for 28 days. Proportions of patients and time to achieving ISGA success, ISGA
clear/almost clear, or ≥1-grade ISGA improvement were analyzed.

Results: Higher proportions achieved ISGA success with crisaborole versus vehicle at day 8 (D8) for mild (9.5% vs 4.1%, *P*=0.0111) and moderate (17.9% vs 6.1%, *P*<0.0001), and continued through D29 for moderate (36.7% vs 22.3%, *P*<0.0001), but not mild (24.9% vs 21.2%, *P*=0.3470). Differences were observed for ISGA clear/almost clear for mild (D8 55.2% vs 29.7%, *P*<0.0001; D29: 71.4% vs 56.7%, *P*=0.0024) and moderate (D8: 17.9% vs 6.1%, *P*<0.0001; D29: 36.7% vs 22.3%, *P*<0.0001), and for ≥1-grade ISGA improvement for mild (D8: 55.2% vs 29.7%, *P*<0.0001; D29: 71.4% vs 56.7%, *P*=0.0024) and moderate (D8: 60.4% vs 43.4%, *P*<0.0001; D29: 68.7% vs 52.1%, *P*<0.0001). Time to each ISGA outcome was shorter for crisaborole versus vehicle regardless of baseline ISGA.

Conclusions: Crisaborole produced significant improvement in ISGA endpoints versus vehicle that were observable at the first postbaseline assessment (D8) for patients with mild or moderate baseline ISGA.

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Acute Ischemic Colitis Secondary to Idiopathic Anaphylaxis

Deborah L. Lee, MD; Evelyn Konsur, MD; Julie Sterbank, DO

Purpose: Idiopathic anaphylaxis (IA) is a systemic hypersensitivity response without an identifiable precipitating exposure. We present a case in which IA was diagnosed after a patient had idiopathic anaphylactic shock complicated by acute ischemic colitis.
Methods: Case report

Results: A 42-year-old woman with seasonal allergies presented for evaluation of twenty years of progressively frequent and severe episodes of angioedema, sensation of throat closing, nausea, vomiting, and abdominal cramping. Symptoms occurred two to three hours after ingestion of foods, although no specific food trigger could be identified. Symptoms resolved with oral diphenhydramine. The most recent episode occurred hours after ingestion of fried chicken and was associated with hypotension, angioedema, severe abdominal cramping, and hematochezia. During the hospital admission, diagnostic colonoscopy and confirmatory biopsy revealed acute ischemic colitis from the hepatic flexure to the recto-sigmoid colon. Evaluations for allergic, immunologic (radioallergosorbent testing, alpha-1,3-galactose IgE, complement and Cl esterase inhibitor function, tryptase, immunoglobulin concentrations), and infectious etiologies of her anaphylactic shock were negative. She was prescribed intramuscular epinephrine and treated with oral loratadine and montelukast. She had no further episodes of IA over twelve months of treatment.

Conclusion: To our knowledge, this is the first reported case of ischemic colitis secondary to an episode of idiopathic anaphylaxis. The complications of shock in idiopathic anaphylaxis may be life threatening. The unpredictable nature of IA compounds its severity and poses a serious factor affecting quality of life.

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Successful use of mepolizumab in a patient with chronic eosinophilic pneumonia

Warit Jithpratuck MD, Panida Sriaroon MD, Vinny O Samuel MD

Summary: Chronic eosinophilic pneumonia (CEP) often poses a diagnostic challenge due to its overlapping presentations with other eosinophilic lung diseases. Patients with CEP typically present with gradual onset of cough and progressive shortness of breath over several months. Our patient presented with a 4-month history of cough and respiratory symptoms and had peripheral blood and bronchoalveolar lavage (BAL) eosinophilia. Chest radiographs revealed extensive infiltrations. Her CEP diagnosis was made after other causes of eosinophilic lung disease were excluded. She had a relapse while tapering her steroid. Mepolizumab treatment led to excellent clinical response.
CEP should be considered in the differential diagnosis of patients presenting with respiratory symptoms with thick cast sputum production, elevated peripheral eosinophilia and IgE level. Most patients require a prolonged course of systemic corticosteroids and relapse is common. Mepolizumab can be considered an adjunct therapy in CEP patients who have frequent relapses or are steroid-dependent.

Patient Presentation and Testing: A 20-year-old female with history of asthma, environmental allergies, and eosinophilic esophagitis presented with productive cough and progressive shortness of breath for 4 months associated with thick cast sputum production. Oral antibiotics, inhaled corticosteroids and bronchodilator failed to improve symptoms. White blood cell count (25,000/mm3), absolute eosinophil count (10,750/mm3 [43%]), and IgE level (1,122 IU/mL) were elevated. CT chest showed bilateral multifocal opacities, predominantly in the upper lobes. Her sputum cast revealed dense eosinophils and numerous Charcot-Leyden crystals. The diagnosis CEP was made following negative evaluation for drug allergies, infections, hypereosinophilic syndrome, allergic bronchopulmonary aspergillosis, and eosinophilic granulomatosis with polyangiitis.

Diagnosis, Treatment and Patient Outcomes: Prednisone was started for possible CEP. Her respiratory symptoms, lung function test and AEC improved dramatically within 1 week of prednisone. She required prolong course of prednisone due to relapse of her respiratory symptoms while tapering steroid. Her AEC remained high at 1,560/mm3 with a new chest CT finding of a new area of impaction in the bronchus with distal bronchiectasis. Mepolizumab was considered due to persistent eosinophilia.
Within one month of treatment, her respiratory symptoms, lung function and AEC improved. Over the next year of mepolizumab treatment, her respiratory symptoms remained stable, with no exacerbation or prednisone use.

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Monozygotic Twins with Multiple Tree Nut Allergies Documented by Skin Prick Test; It's Not All About Genetics

Evelyn Konsur, MD, David McGarry, DO, Tyler Greenlee, OMS-IV, Robert Hostoffer, DO

Introduction: Tree nut (TN) allergies have a prevalence of up to 4.3% in the US and have been shown to cause anaphylaxis in up to 40% of cases. Having one TN allergy increases the risk of developing another TN allergy. TN allergies are important to identify and be able to prevent adverse outcomes for patients.

Objective: To present the first case of monozygotic (MZ) twin boys of Mediterranean descent who were found to have multiple TN allergies on SPT after they presented for evaluation after allergic reactions to a TN at different times in childhood.

Methods: Case report. Skin testing was standardly performed.

Results: At 14 months old, Twin A, presented after ingestion of a pistachio. Shortly after exposure, he developed labored breathing and perioral erythema. He presented to the emergency department (ED) and received oral diphenhydramine. SPT demonstrated reactions to multiple TNs: almond, cashew, English walnut, pecan, black walnut, hazelnut, and pistachio. At the time of this evaluation, Twin B also had TN SPT conducted with negative results. At 5 years old, Twin B, presented after ingesting cashews and developed respiratory symptoms and urticaria. In the ED, the patient was given intramuscular epinephrine and intravenous diphenhydramine for anaphylaxis. He was found to have reactions to cashew, black walnut, hazelnut and pistachio on SPT.

Conclusion: There is minimal data evaluating the genetic, exposure, and cultural factors contributing to TN allergies. Genetics do not play a singular role in TN hypersensitivity but exposure, timing and cultural considerations contribute as well.

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A Rare Presentation of a Common Problem or an Under Recognized Association of Conditions; A Case of Allergic Fungal Dacryocystitis

Jacob T. Maddux, M.D., Matthew A. Rank, M.D., John C. Lewis, M.D.

Introduction: The pathophysiology of Dacryocystitis, an inflammatory condition of the nasolacrimal sac, follows a complex pathway that includes an uncomplicated, traditional IgE-mediated hypersensitivity reaction, eosinophilic mediated inflammation and fungal colonization triggering a significant immunologic reaction culminating in an aggressive inflammatory response. Many conditions, including allergic bronchopulmonary aspergillosis (ABPA) and allergic fungal sinusitis (AFS) share similar pathophysiologic mechanisms, however, are rarely see in association. Herein, we describe a case of allergic fungal dacryocystitis (AFD) associated with ABPA, eosinophilic otitis media and AFS.

Case: The patient was referred for poorly controlled AFD. She was first treated with bilateral open dacryocystorhinostomy and tapered oral steroids. Pathology revealed thick, green, tenacious material in both lacrimal sacs consistent with fungal dacryocystitis. Additional history revealed chronic serous otitis requiring multiple T tubes and a longstanding history of allergies. She has a history of asthma with a total serum IgE of 2,483. Allergy testing demonstrated the strongest reaction to Aspergillus fumigatus. She was again treated surgically and given lacrimal sac irrigations with Decadron postoperatively. Control of her symptoms was maintained with low dose prednisone and Itraconazole, as well as, typical allergic rhinosinusitis and asthma treatment.

Discussion: Considering the proposed shared pathophysiologic mechanisms underlying AFD, AFS and ABPA, and the proximity of the nasolacrimal duct to the nasal/sinus tissues, it is curious that these conditions do not present as a group more frequently. Is this a failure to recognize one or more of these conditions or that this constellation of findings is indeed rare?

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Assessment of a Symptom-based Coding Algorithm for Identification of ED Anaphylaxis Patients

Lauren S. Harper, MD, Mollie L. Alpern, MD, James T. Li, MD PhD, John B. Hagan, MD, Ronna L. Campbell, MD PhD

Introduction: Administrative data allows researchers access to larger and more varied populations than can be studied with prospective research. But in the case of conditions like anaphylaxis which are commonly underdiagnosed, accuracy of case identification must be carefully assessed. A symptom-based International Classification of Disease (ICD) anaphylaxis identification algorithm was previously described but not validated against expert review. We sought to validate that algorithm with expert review and to determine whether accuracy could be improved with additional codes.

Methods: Patients were identified using ICD-9 codes (January 2013-September 2015) and ICD-10 codes (October 2015-September 2017) including: 1) specific anaphylaxis codes; 2) anaphylaxis symptom codes; and 3) allergy codes. Diagnostic accuracy of these codes was assessed by comparison to expert review by one of two allergist-immunologists and/or an allergy-immunology fellow. Percentages with 95% confidence intervals (CIs) were calculated based on sample weighting.

Results: 2154 patients were identified and 779 patient records were reviewed. Experts classified 31% of visits as anaphylaxis. Among these, 47% were identified with anaphylaxis specific codes, 5% with the symptom-based coding algorithm, and 48% by individual allergic codes. The sensitivity and specificity of the anaphylaxis-specific codes were 47% (95%CI, 43-51) and 88% (95%CI, 86-90), respectively. Adding the symptom-based algorithm, improved sensitivity slightly (52% [95%CI, 48-56]) but reduced specificity (69% [95%CI, 67-71]).

Conclusions: Anaphylaxis specific codes failed to identify over 50% of anaphylaxis cases. Addition of a symptom-based coding algorithm did not improve accuracy of anaphylaxis identification. Further studies are needed to identify optimal ED anaphylaxis identification strategies.