745 Risk-Stratification Identifies Low-Risk Fluoroquinolone Allergies Suitable for Direct Oral Challenge

Irene Yuan, MD[1], Anna Brameli, MD[1], Matthew Krantz, MD[1], David House[2], Elizabeth Phillips, MD[3], Cosby Stone, MD, MPH[1]; [1]Vanderbilt University Medical Center, [2]University of Louisville School of Medicine, Louisville, KY, [3]Vanderbilt University.

RATIONALE: Fluoroquinolones are rarely associated with IgE-mediated reactions, and skin tests are difficult to interpret due to MRGPRX2 activation and dose-dependent non-IgE mediated mast cell degranulation. Previous studies for non-beta lactam antibiotics (e.g. sulfonamides) have used history-based risk stratification to assess for and successfully delabel low-risk patients by direct oral challenge, which forms the basis for revised practice parameter guidelines. We examined a risk-stratified approach for fluoroquinolone allergy delabeling.

METHODS: Among patients evaluated for fluoroquinolone allergy at the Vanderbilt Drug Allergy Clinic from 2015 to 2019, we retrospectively applied a modified risk-stratification approach previously validated for beta-lactams and sulfonamide antibiotics. Low-risk patients were assessed for oral challenge tolerance to the implicated fluoroquinolone.

RESULTS: Based on history, we found that 108/162 (67%) reported symptoms that place them in a "low-risk" category. Among the 108 who underwent skin testing, we found that 100% had negative skin tests, using previously published criteria. Among 77 who underwent an oral challenge to the implicated fluoroquinolone, 75/77 (97%) tolerated their challenge. Of the two symptomatic patients, one developed a fixed drug eruption selective for the implicated fluoroquinolone and the other developed a mild to moderate morbilliform drug eruption.

CONCLUSIONS: In patients labeled as fluoroquinolone allergic, a low-risk history was associated with a high (97%) likelihood of tolerating an oral challenge with the implicated fluoroquinolone. A low-risk fluoroquinolone allergy history appears to identify patients who could be safely delabeled with direct oral challenge to the implicated fluoroquinolone without preceding skin testing.

746 PEN-FAST Assessment Using Patient-Reported Reaction Histories in a Multi-Site Prospective United States Cohort

John Accarino, MD[1], Elizabeth Phillips, MD[2], Aleena Banerji[1], Allison Ramsey, MD[3], Alexei Gonzalez-Estrada, MD FAAAAI[4], Cosby Stone, MD, MPH[5], Iris Otani[6], David Khan[7], Timothy Chow, MD[8], Anne Liu, MD[9], Anna Arroyo, MD MPH[10], Andrew King, MS[1], Yuqing Zhang, DSc[11], Kimberly Blumenthal, MD;MSc[1]; [1]Massachusetts General Hospital, [2]Vanderbilt University, [3]Rochester Regional Health, [4]Mayo Clinic, [5]Vanderbilt University Medical Center, [6]UCSF Medical Center, [7]University Texas Southwestern Medical Ce, [8]University of Texas Southwestern, [9]Stanford University, [10]Stanford School of Medicine, [11]Harvard Medical School.

RATIONALE: PEN-FAST is a point-of-care tool to identify low-risk penicillin allergy patients. We aimed to validate PEN-FAST in a large multi-site US-based registry that records patient-reported allergy history.

METHODS: We considered data from the United States Drug Allergy Registry (USDAR, 01/16/2019-06/30/2023) that includes patient-reported penicillin allergy history and confirmed penicillin allergy status after testing from chart review. We assessed the association of self-reported reaction details that are PEN-FAST elements to penicillin allergy status using logistic regression. We evaluated diagnostic performance characteristics for PEN-FAST scores <3, the previously proposed low-risk cutoff.

RESULTS: Of 1,288 participants (μ age 50y [SD 18]), 80% female, 90% white) from 5 sites, 53(4.2%) had allergist-confirmed penicillin allergy. PEN-FAST scores were: 0 (45%), 1 (7%), 2 (35%), 3 (8%), 4 (4%), and 5 (1%). Compared to PEN-FAST, Odds Ratios (OR) from USDAR were consistent in direction for 'anaphylaxis or angioedema' and 'reactions within 5 years' (OR_{USDAR}=2.90 and 2.66 vs $OR_{PENFAST}$=5.64 and 4.26) but differed for 'reactions warranting hospitalization' and 'reactions with pharmacologic treatment' (OR_{USDAR}=0.19 and 0.89 vs $OR_{PENFAST}$=1.51 and 2.41). Among 1,123 (87%) receiving PEN-FAST scores<3, 96.4% were confirmed negatives, specificity capture of 87.6% of all confirmed negative participants. Among 165 (13%) with PEN-FAST scores $\geq$ 3, 7.3% were confirmed positives, representing 23% of all true positives. Overall diagnostic accuracy was 84.9%.

CONCLUSIONS: Patient-reported items that correspond to PEN-FAST clinician-derived predictors had good performance and PEN-FAST score<3 had a 96.4% negative predictive value in USDAR data. Further validation of these survey items could expand de-labeling beyond the allergy specialist.

747 Amelioration Of Mrgprb2-Mediated Anaphylactoid Drug Reactions With Briquilimab, An Anti-CD117 Antibody, Through Mast Cell Depletion In Mice Expressing Chimeric Human And Mouse CD117

Charles Chang, PhD[1], Ajay Sharma[1], Allison Ji[1], Revati Nerkar[1], Kai Martell[1], Karl Meneses[1], Hye-Sook Kwon, PhD[1], Wendy Pang, MD, PhD[1]; [1]Jasper Therapeutics.

RATIONALE: MRGPRX2, and the mouse ortholog Mrgprb2, are mast cell (MC)-specific receptors that are activated by various basic secretagogues, anesthetics, and antibiotics. MRGPRX2 is implicated in potentially life-threatening drug-induced anaphylaxis (DIA) in a subset of the population. Briquilimab is a humanized aglycosylated monoclonal antibody against CD117 that inhibits SCF-CD117 signaling and can deplete human mast cells.

METHODS: The effect of briquilimab on Mrgprb2-mediated reactions was evaluated in transgenic mice expressing chimeric CD117 consisting of extracellular human and intracellular mouse regions (hmCD117) in lieu of wild-type mouse CD117. DIA was performed with 3mg/kg compound 48/80, a classical mast cell activator. A single 25mg/kg dose of briquilimab was given to treated animals 2 weeks before challenge. Core body temperature (CBT) and clinical score were recorded for 60 minutes after challenge in procedure control wild type (n=3) without compound 48/80, briquilimab untreated (n=3), and treated hmCD117 mice (n=3). Statistical analysis of CBT changes was performed by 1-way ANOVA.

RESULTS: Briquilimab-treated animals demonstrated an average CBT after compound 48/80 challenge of 36.7$\pm$1.8°C compared to 37.3$\pm$1.1°C in control animals (P=0.76). In contrast, we measured an average CBT of 34.7$\pm$2.1°C in Briquilimab-untreated animals (P<0.05). Clinical scores peaked at 10 minutes after challenge, with untreated animals scoring 3.0$\pm$0.0 compared to 1.3$\pm$1.2 and 1.7$\pm$0.6 in control and treated animals respectively, suggesting briquilimab prevents non-IgE dependent anaphylaxis in hmCD117 mice.

CONCLUSIONS: This study provides early proof of concept that briquilimab may be a promising treatment option for IgE-independent drug-induced adverse reactions mediated by the MRGPRX2/Mrgprb2 receptors.