COLLEGE OF PHARMACY
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Department of Pharmaceutical Sciences
Ph.D. Dissertation Defense Seminar

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Link

"Integrated Exposure-Response Analyses of Dupilumab in Pediatric, Adolescent, and Adult Patients with Atopic Dermatitis"

Presented by:

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Abstract: Atopic dermatitis is a chronic skin disease characterized by inflammation and pruritis, which affects 20 percent of children and 10 percent of adults globally. Atopic dermatitis' complex pathology includes epithelial-barrier defects, increased T_H2 immune activity, and microbiome dysbiosis. The most prominent assessments for measuring disease severity are the Eczema Area and Severity Index (EASI) and the Investigator Global Assessment (IGA), a continuous bounded outcome score assessment and a five-point ordered categorical assessment, respectively.

Dupilumab, trade name Dupixent® (Regeneron Pharmaceuticals), is a fully human monoclonal antibody that is an interleukin-4 receptor alpha antagonist, blocking interleukin-4 and interleukin-13 signaling. Dupilumab has been shown to significantly reduce measures of disease severity in moderate-to-severe atopic dermatitis after subcutaneous injections.

The objective of this work was to develop an integrated population exposure-response model, using pooled data from six clinical trials to predict the efficacy of dupilumab in adults, adolescents, and children after adjusting for confounding factors.

Indirect response models were applied to link measures of efficacy and functional dupilumab concentrations, which characterize temporal delays in drug effect. A latent variable methodology was used to apply the indirect response model for the categorical efficacy measure IGA. Final parameters in both models were well-estimated, with relative standard errors < 4% for structural parameters and < 30% for covariate effects. Numerical and graphical diagnostics were assessed at every step of the model development process. Simulation diagnostics utilized visual predictive checks (VPCs) on the final models and demonstrated the model predictability.

Based on half-life estimates of drug onset (2.0 weeks for EASI; 2.8 weeks for IGA), the full effect of dupilumab would be reached after approximately 2 months for EASI and 3 months for IGA (~ 4-5 half-lives). Drug concentrations achieving half the maximum effect (IC_{50}) were estimated as 20.3 and 27.1 mg/L for the EASI and IGA analyses, respectively. Each model had a placebo component indicating some improvement in response measures with time for patients receiving sham SC injections.

Several patient factors were assessed as potential sources of variability in efficacy response. In simulations evaluating each potential covariate in isolation, subjects with body weights ≤ 40 kg demonstrated a larger dupilumab effect relative to reference subjects with body weight of 70 kg. Higher baseline TARC was associated with higher baseline EASI score, leading to a larger predicted dupilumab EASI change from baseline in patients with higher baseline TARC.

Modeling and simulation provided an integrated assessment of dupilumab exposure-response across relevant clinical conditions and patient age groups, facilitating a comprehensive assessment of relative efficacy between adults, adolescents, and young children. For all efficacy predictions at Week 16 (EASI-75, EASI-90, IGA-0/1 and percent change from baseline in EASI score), on average, dupilumab performed better in young children than in adults and adolescents when given FDA-approved dupilumab dose regimens for moderate to severe atopic dermatitis by weight and age.

The predictive models developed in this dissertation provide conclusive evidence that may justify full extrapolation (i.e., pharmacokinetic bridging) to pediatric patients for other type 2 inflammatory diseases in scenarios in which conducting prospective, randomized, controlled trials may not be feasible. The full extrapolation method would provide direct ethical benefits to pediatric populations, such that young children would not need to be unnecessarily enrolled in clinical trials, as the exposure-response relationship of dupilumab in type 2 inflammatory diseases has already been characterized.