A simulation study for clinical efficacy of an anti-ORAI1 antibody (DS-2741a) on atopic dermatitis using quantitative systems pharmacology (QSP) modeling for preclinical-to-clinical translation

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Introduction & Objectives

- Atopic dermatitis (AD) is a complex disorder characterized by immune-mediated skin inflammation and epidermal barrier dysfunction
- Orai1, a pore-forming subunit of calcium release-activated calcium (CRAC) channels, is essential for activation of T cells and other immune cells in AD
- A novel humanized anti-Orai1 antibody DS-2741a was developed to ameliorate AD by suppressing CRAC-mediated immune cell activation
- Clinical efficacy in AD patients is difficult to predict from preclinical studies due to lack of mouse models relevant to clinical outcome
- To overcome this translational gap, a QSP model was developed to assess the potential clinical efficacy of DS-2741a in virtual patients (VPs)
- Simulations of DS-2741a efficacy after s.c. dose were compared to dupilumab, an anti-IL-4 receptor antibody approved for AD treatment

Materials & Methods

A mechanistic QSP model of AD was developed to evaluate the potential clinical efficacy of DS-2741a

- The QSP model represents AD pathophysiology including keratinocyte, neuron and relevant immune cell and mediator dynamics, skin barrier function, clinical outcomes, and drug pharmacokinetics (PK) (Figure 1)

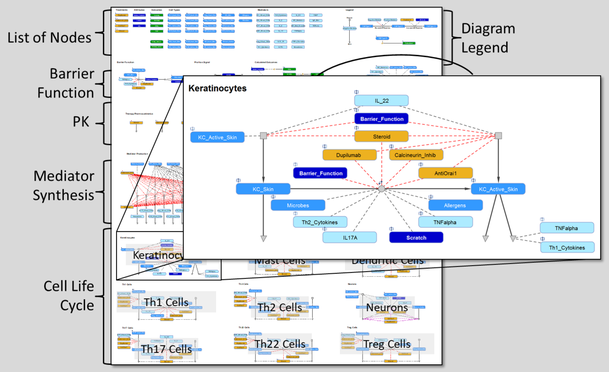

Figure 1. The AD PhysioMap™, a visual representation of the QSP model, includes key biological pathways involved in chronic AD.

- The Eczema Area and Severity Index (EASI) score, a standard clinical outcome based on redness, thickness, scratching, and lichenification, was mechanistically associated with cells, cytokines, and biological functions (Figure 2)

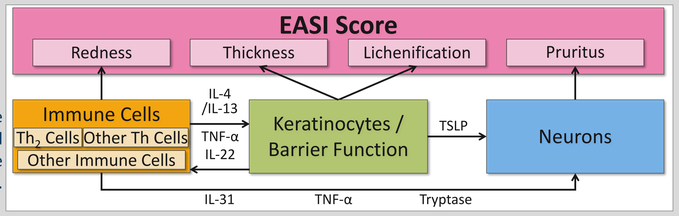

Figure 2. EASI score attributes and selected key components in the AD QSP model.

- Pre-clinical data for *in vitro* pharmacological activities of DS-2741a and predicted human PK parameters were incorporated into the QSP model
- The model was calibrated to reproduce clinical trial outcomes of current AD therapies, including dupilumab, tacrolimus, and steroids

Results: Model Qualification

The QSP model was qualified and documented according to a published Model Qualification Method[1]

- A cohort of VPs was created to span the range of EASI responses to dupilumab observed in clinical trials (Figure 3)
- A prevalence weighted virtual population (VPop) using this VP cohort reproduced the mean and distribution of EASI responses reported in Simpson 2016[2] (Figure 4)

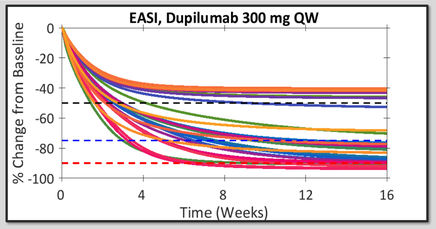

Figure 3. Simulated clinical EASI response to 300 mg dupilumab QW in the virtual patient cohort.

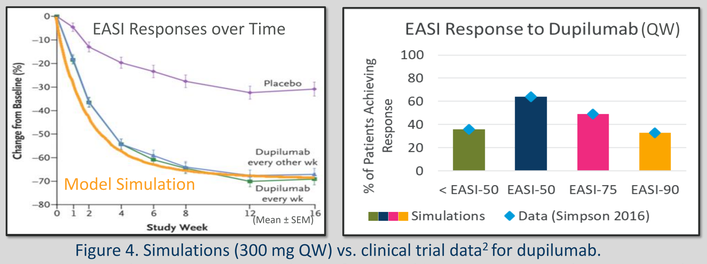

Figure 4. Simulations (300 mg QW) vs. clinical trial data[2] for dupilumab.
Left: EASI response changes over time. Right: % of VPs reaching EASI-50, -75, and -90 at 16 weeks.

- Responses to tacrolimus and steroids were also consistent with clinical data

Results: Simulations of DS-2741a Efficacy

DS-2741a is expected to be more efficacious than dupilumab

- Clinical trials of various doses of DS-2741a compared to 300 mg dupilumab QW or Q2W were simulated in the VPop (Figure 5)
- All doses of DS-2741a simulated showed superior efficacy compared to dupilumab
  - Approximately 60% of the VPs treated with DS-2741a achieved EASI-90
  - Response time was faster with DS-2741a compared to dupilumab

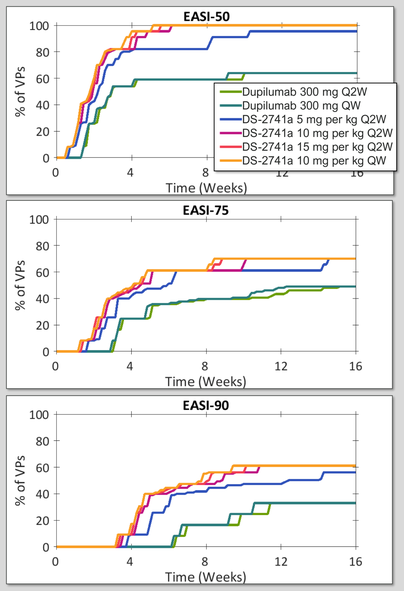

Figure 5. % of VPs achieving EASI-50 (top), -75 (middle) and -90 (bottom) over 16 weeks of simulated dupilumab or DS-2741a treatment.

Results: DS-2741a Differentiation

Relative contributions of Th2- vs non-Th2 pathways in individual VPs explain differential responses to DS-2741a compared to dupilumab

- While most VPs responded better to DS-2741a treatment than dupilumab, a few showed opposite behavior (Figure 6)

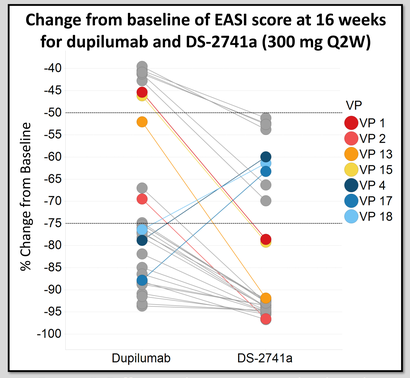

Figure 6. Differential responses to dupilumab versus DS-2741a in 31 VPs.

- VPs with stronger dupilumab responses had higher Th2-cytokines while VPs with stronger responses to DS-2741a had higher non-Th2-associated cytokine expression (Figure 7)

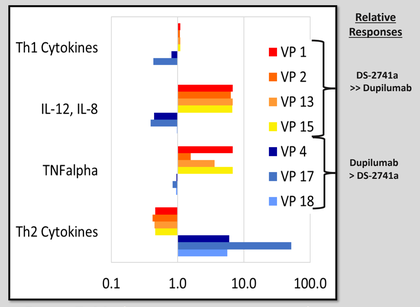

Figure 7. Mediator concentrations in skin in selected VPs (relative to a reference VP).

- Additional analysis further supported the strong contribution from non-Th2 cytokines in VPs with weak response to dupilumab (Figure 8)

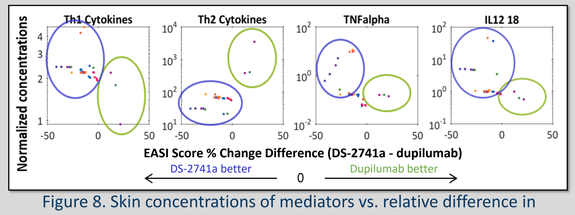

Figure 8. Skin concentrations of mediators vs. relative difference in EASI Score (DS-2741a – dupilumab) in 31 VPs.

- This is consistent with AD literature demonstrating a contribution of non-Th2 cells and cytokines to chronic AD pathophysiology[3,4,5] (Figure 9)

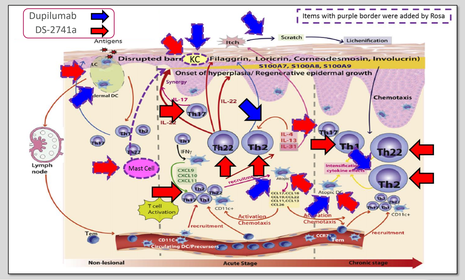

Figure 9. A schematic illustration of initiation of acute AD and progression to chronic skin lesions[5], annotated to show the cells targeted by dupilumab and DS-2741a.

Conclusions

- QSP modeling provided an early indication of the potential for DS-2741a as a novel therapeutic agent in AD
- Simulations suggest that DS-2741a could show faster response and more efficacy than dupilumab in a broad spectrum of AD patients
- QSP modeling and research was regarded in-house as an alternative investigation to preclinical animal model and was leveraged to prioritize the product toward clinical trial

References:

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