Safety and efficacy of anti-IL-17 (Secukinumab) for the treatment of pyoderma gangrenosum

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Atopic dermatitis (AD) is the most common inflammatory skin disease, whose pathogenesis involves heterogeneous immunological dysregulations. Several biologics have demonstrated good efficacy in clinical trials of AD treatment, but with a substantial proportion of patients being identified as poor responders. Dupilumab, the only AD-specific biologics so far, has shown 44%-69% of responder rates based on EASI-75. To investigate promising therapies in dupilumab poor responders, we developed a computational model that describes systems-level AD pathogenesis and effects of nine biologics (dupilumab, lebrikizumab, tralokinumab, secukinumab, ifakizumab, nemolizumab, tezepelumab, GBR 830, and recombinant interleukin-13). The model simulates the biological processes underlying AD pathogenesis with root mean square errors of the mean EASI and EASI-75 between the simulated and actual clinical trials being 2.1 (out of 72 – the max EASI) and 7.4%, respectively. We then simulated the clinical efficacy of existing and hypothetical treatments on virtual dupilumab poor responders. The simulation results showed that virtual dupilumab poor responders did not respond to the nine existing biologics (EASI-75 ≤ 25%), but they responded to simultaneous inhibition of IL-13 and IL-22 (EASI-75: 22%). Hence, we identified the simultaneous inhibition of IL-13 and IL-22 as a potential therapy for dupilumab poor responders. The model will serve as a computational platform for model-informed drug development for precision medicine, as it allows to evaluate the validity of potential drug targets, including combinations of multiple targets, in stratified patients. Similar mathematical models and simulations can also be applicable for other diseases and therapies when there are reported clinical efficacies of multiple drugs.

The anti-drug antibody response is associated with amino acid variation within the HLA-DRB1 peptide-binding groove

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Targeted biologic therapies can elicit an undesirable host immune response characterised by the development of anti-drug antibodies (ADA), an important cause of treatment failure. The most widely used biologics across immune-mediated diseases is the TNF inhibitor adalimumab. This genome-wide association study aimed to identify genetic predictors of developing ADA in psoriatic arthritis patients on their first course of adalimumab. Within the BISTOP biorepository, 784 psoriatic patients had ADA data 6-36 months after starting adalimumab (discovery cohort), 232 patients had ADA data <6 months after starting adalimumab (early ADA cohort), and 716 patients had only clinical data available (clinical outcome cohort). We genotyped 1,671,634 SNPs genome-wide and performed HLA imputation (1). We tested for association between genetic variation and development of ADA (logistic regression), as well as treatment failure (stopping adalimumab due to ineffectiveness (Cos proportional hazards)). Two loci were significantly associated with ADA within the Major Histocompatibility Complex (rs9268628, OR 3.44, 95% CI 2.21-5.6, p = 4.93 x10^-8) that mapped to the pres-