043  
Role of Prostaglandin E-maj or Urinary Metabolite Levels in Identifying The Phenotype of Pachydermoperiostosis
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Pachydermoperiostosis (PDP) is an autosomal recessive hereditary disease, but has three diagnostic features: digital clubbing, periostitis, and pachydermis including cutis verticis gyrata (CVG). CVG is a condition in which folds of the hypertrophic scalp skin create a cerebriform appearance. The phenotypic spectrum of PDP has been categorized to the complete and incomplete form depending on presence or absence of CVG, respectively. Two causative genes: HPGD and SLCO2A1 have been identified. Prostaglandin E2 (PGE2) is metabolised from PGE-MUM and has a major efficacy and is understood and no companion diagnostic exists to guide prescription. We performed in-depth immunomonitoring of 67 psoriasis patients, before and during adalimumab therapy to identify immune biomarkers of response. Clinical response was assessed using PASI75. The model simulation reproduced clinical efficacy of the biologics, with root mean square errors of the mean EASI and EASI-75 between the simulated and actual clinical trials 2.1 (out of 72 – the max EASI) and 7.4%, respectively. We then simulated the clinical efficacy of existing and hypothetical therapies 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 simulation can also be applicable for other diseases and therapies when there are reported clinical efficacies of multiple drugs.

044  
Safety and efficacy of anti-IL-17 (Secukinumab) for the treatment of pyoderma gangrenosum
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Pyoderma gangrenosum (PG) is a severe autoinflammatory disease causing relapsing, painful ulcers of the skin. Typically, wounds are surrounded by a highly inflammatory margin and any mechanical manipulation promotes further inflammation. Treatment of PG is difficult and generally ineffective, such as high-dose corticosteroids or cyclosporine.

As neutrophil granulocytes dominate the inflammatory infiltrate in PG lesions, IL-17 might be a central regulator of PG pathogenesis. To test this hypothesis we performed an investigator initiated phase II pilot study evaluating the safety and efficacy of secukinumab for the treatment of PG (Euxtra-CT: 2015-00076-65). In total seven patients were included. All patients received 300mg secukinumab every week from week 0 – 4, followed by 300mg every 4 weeks until week 16 (2 patients) or 300mg secukinumab every two weeks until week 16 (5 patients). Concomitant immunosuppressive treatment was not allowed. The primary endpoint was the change of 5 point scale physician's global assessment (PGA) at week 16. Secondary endpoints included change of ulcer surface size, inflammatory serum parameters and dermatological life quality index (DLQI). Four patients received secukinumab treatment until week 16, whereas the other patients dropped out earlier due to worsening of PG. Mean PGA was 3.3 at baseline and 2.8 at week 16. All patients reported a reduction of pain during treatment. Three patients receiving secukinumab every 2 weeks continued treatment until week 12. Of these, two had a marked decrease of ulcer size, inflammatory serum parameters and DLQI. No new safety signals were observed. Thus, treatment with secukinumab monotherapy resulted in improvement of PGA in 27 patients (82%). Further studies are needed to test the potential of anti-IL-17 treatment in combination with conventional immunosuppressants.

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NF-kB phosphorylation in type-2 dendritic cells at baseline is a blood predictive biomarker of clinical response to adalimumab in psoriasis
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Biological therapies have transformed the management of psoriasis, but clinical response is variable and there is an urgent clinical need to identify predictive biomarkers. Whilst newer biologics have been licensed, the anti-TNF drugs add additional information in the decision-making of patients in psoriasis, given its effectiveness, well-established safety profile and, with the advent of biologics, significantly reduced costs. Nevertheless, the cellular and molecular mechanisms underpinning its clinical efficacy are ill understood and no companion diagnostic exists to guide prescription. We investigated the in vivo NF-kB phosphorylation in type-2 dendritic cells (DC) before and during adalimumab therapy to identify immune biomarkers of response. Clinical response was assessed using PASI 75. The model simulation reproduced clinical efficacy of the biologics, with root mean square errors of the mean EASI and EASI-75 between the simulated and actual clinical trials 2.1 (out of 72 – the max EASI) and 7.4%, respectively. We then simulated the clinical efficacy of existing and hypothetical therapies 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 simulation can also be applicable for other diseases and therapies when there are reported clinical efficacies of multiple drugs.

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A computational model suggested potential therapies for dupilumab poor responders in atopic dermatitis
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Targeted biologic therapies can elicit an undesirable host immune response characterised by an upregulation of anti-antibody antibodies (ADA), an important cause of treatment failure. The most widely used biological across immune-mediated diseases is the TNF inhibitor adalimumab. This genome-wide association study aimed to identify genetic predictors of developing ADA in a cohort of anti-IL-17a treatment of anti-antibody antibodies (ADA), an important cause of treatment failure. We genotyped 440 SNPs genome-wide and performed HLA imputation. 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]). The model simulation reproduced published clinical efficacy of the biologics, with root mean square errors of the mean EASI and EASI-75 between the simulated and actual clinical trials 2.1 (out of 72 – the max EASI) and 7.4%, respectively. We then simulated the clinical efficacy of existing and hypothetical therapies 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 simulation can also be applicable for other diseases and therapies when there are reported clinical efficacies of multiple drugs.