**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 great efforts are made to develop novel therapeutic agents, 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 I/II pilot study evaluating the efficacy and safety of secukinumab for the treatment of PG (Eudra-CT 2015- 000762-65). 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 three 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 2/7 patients (28%). Further studies are needed to test the potential of anti-IL-17 treatment in combination with conventional immunosuppressants.

**A computational model suggested potential therapies for dupilumab poor responders in atopic dermatitis**

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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 biologic 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 systemic level AD pathogenesis and effects of nine biologics (dupilumab, lebrikizumab, tralokinumab, secukinumab, fazekasimab, nemolizumab, tezepelumab, GBR 830, and recombinant interleukin-17R) for patients with moderate to severe AD with a median age of 32 (25-50). Conventional immunosuppressive treatment was not allowed. The model simulation showed that 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 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-confirmed 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.