Role of Prostaglandin E-major Urinary Metabolite Levels in Identifying The Phenotype of Pachydermoperiostosis

M Ishihara1, M Oka2, Y Yoshikawa2, H Nizeki1 and K Kabashima1 1 Dermatology, Kyoto University, Kyoto, Japan, 2 Dermatology, Kitano Hospital, Tazuke Tokufuji Medical Research Institute, Osaka, Japan and 3 Dermatology, National Center for Child Health and Development, Saitama, Japan

Pachydermoperiostosis (PDP) is an autosomal recessive hereditary disease, but has three diagnostic features: digital clubbing, periostitis, and pachydermia 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 SLC20A1 have been identified. Protaglandin E2 (PGE2) is metabolized by PGD2, which mediates inflammation and NF-kappaB activation. NF-kB translocation and phosphorylation, and downstream effects, such as immune cell recruitment and activation, are thought to be involved in the pathogenesis of the disease. We evaluated for the presence of proinflammatory cytokine levels of PGE2, which are thought to contribute to the pathology. Herein, we evaluated whether PGE2 levels could correlate with PDP phenotypes.

We found that LPS-induced NF-kappaB phosphorylation and inflammatory cytokine levels were significantly elevated in patients with PDP compared to controls. However, the levels were not significantly different between patients with complete and incomplete forms of the disease. These findings suggest that LPS-induced inflammatory response may underpin its clinical efficacy are ill understood and no companion diagnostic exists to support a clinical decision-making process. Thus, we propose that LPS-induced NF-kappaB phosphorylation and cytokine levels may serve as a useful biomarker for the identification and monitoring of PDP.

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

T Miyano1, A Brownridge1, T T Statkow, B Study Group, P Consortium, C Smith and M Simpson King’s College London, London, United Kingdom

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 psoriasis patients on their first course of adalimumab. Within the BISTOP biorepository, 784 psoriasis patients had ADA data 6-16 months after starting adalimumab (discovery cohort), 232 patients had ADA data 6-12 months after starting adalimumab (early ADA cohort), and 716 patients had only clinical data available (clinical outcome cohort). We genotyped 37,419 SNPs across the genome-wide and performed HLA imputation (3). We tested these SNPs for association between genetic variation and development of ADA (logistic regression), as well as treatment failure (stopping adalimumab due to ineffectiveness [Cox proportional hazards]). We identified a novel psoriasis-associated HLA locus with strong association with ADA within the Major Histocompatibility Complex (chr06:2680928, OR 3.14, 95% CI 2.11-5.06, p=1.84x10^-9) that mapped to the close vicinity of the DPB1 and BPI genes. We also identified a novel non-HLA locus (chr11:93397208, p=1.32x10^-8) that could be also applicable for other diseases and therapies when there are reported clinical efficacies of multiple drugs.

Interleukin-17 inhibitor therapy reduces arterial intima-media thickness in severe psoriasis

A Pinto1, A Szabo2, F Reznek3, V Brodsky4, K Szalai1, N Galajda1, B Szilveszter5, E Dıs6, B Merkely7 and P Holli1 1 Department of Dermatology, Venerology and Dermatotology, Semmelweis University, Budapest, Hungary, 2 Department of Health Economics, Corvinus University, Budapest, Hungary, 3 Heart and Vascular Center, Department of Interventional Radiology, Semmelweis University, Budapest, Hungary, 4 Heart and Vascular Center, Department of Interventional Radiology, Semmelweis University, Budapest, Hungary

Psoriasis is frequently accompanied by cardiovascular diseases based on the shared immunopathologic pathway. We determined the effect of IL-17 inhibitor therapies on early-stage atherosclerosis related arterial wall inflammation described by intima-media thickness (IMT) among severe psoriatic patients. Thirty-one severe psoriatic patients were enrolled. Revascularisation procedures were not performed and patients were under immunosuppressive therapy and were treated with the IL-17A inhibitor. Ultrasound IMT was measured at different time points (after 6, 12 and 18 months) and compared with controls. We found that patients treated with the IL-17A inhibitor had a significant decrease in IMT compared to controls. These findings suggest that IL-17 inhibitor therapy may be beneficial in the treatment of psoriatic patients with cardiovascular comorbidities.

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

T Tsakok, B Study Group, P Consortium, C Smith and M Simpson King’s College London, London, United Kingdom

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