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Herpes zoster, acute cardiovascular events and the role of zoster vaccination

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Herpes zoster is common, may have serious consequences and an effective vaccine is available. Emerging data suggests that there may be an increased risk of acute cardiovascular events following zoster. However, the majority of existing data are limited by residual confounding. No study has assessed the risk of acute myocardial infarction shortly after herpes zoster or the role of zoster vaccination in the association between zoster and acute cardiovascular events. Our objective was to quantify the effect of zoster on the short-term risk of acute cardiovascular events and to assess whether zoster vaccination might modify this effect. The self-controlled case series method was used to estimate rates of stroke and acute myocardial infarction in defined periods after herpes zoster compared to other time periods, within individuals. Participants were Medicare beneficiaries aged 65 or older with zoster and either a stroke (n=42,954) or myocardial infarction (n=24,237) between January 2006 and December 2011. Age-adjusted incidence ratios for stroke and myocardial infarction during pre-defined periods up to 12 months after zoster relative to unexposed time periods were calculated using conditional Poisson regression. We observed a marked increase in the rate of acute cardiovascular events in the first week after zoster: a 2.4-fold increased stroke rate (IR 2.37, 95% CI 2.17-2.59) and a 1.7-fold increased MI rate (IR 1.68, 95% CI 1.47-1.92), followed by a gradual resolution over six months. The incidence ratio for stroke was reduced among zoster vaccinees during the first four weeks after zoster but no significant effect modification was observed. Stroke and MI rates are transiently increased after exposure to zoster and zoster vaccination may lessen the effect of zoster on stroke. These findings greatly enhance our understanding of the temporality and magnitude of the effect of zoster on acute cardiovascular events and highlight a potential role for zoster vaccination in reducing incident stroke after zoster.

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Expression ability of *RNAIII* gene encoding δ-toxin in *Staphylococcus aureus* isolated from infant skin is associated with atopic dermatitis development

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Atopic dermatitis (AD) is reportedly associated with colonization by *S. aureus* in the affected skin. We previously reported that δ-toxin released by *S. aureus* induced rapid and robust mast cell (MC) degranulation *in vitro*. In addition, colonization of the mouse lesional skin with *S. aureus* resulted in severe allergic skin inflammation, which was dependent on δ-toxin released by the bacteria and the presence of MCs in the skin. About 60% of AD patients reportedly develop the eruption in the first year of life. In a birth cohort that recruited 270 mother-child pairs, we found that 6-month old infants with *S. aureus* colonization on their cheek developed AD more frequently at 1 year old than the bacteria negative 6-month infants with higher AD odds ratio (odds ratio 4.203, *p=0.008*). To further clarify the virulency of δ-toxin in AD development, we examined *RNAIII* expression in *S. aureus* (n=132) strains isolated from 270 infant cheeks by qPCR. *RNAIII*, a regulatory RNA that is induced by the agr quorum-sensing of *S. aureus*, encodes δ-toxin. The expression of *RNAIII* in *S. aureus* isolated from 6-month old infants was associated characteristically with AD disease development at 1 year old. Other exotoxins, SEs and TSST-1, were not associated with AD disease development. *RNAIII* does not express constitutively, but is induced by agr quorum-sensing. This induction is mediated by a cell density-dependent signal transduction system, which controls a variety of the physiological behavior in bacteria. Therefore, we also examined *RNAIII* expression of *S. aureus* in the lesional and non-lesional skin of patients with AD. *RNAIII* expression was elevated only in the lesional skin but not in non-lesional skin of AD. These studies provide a mechanistic link between δ-toxin of *S. aureus* and AD, suggesting that δ-toxin may become a promising new preventive and therapeutic target in AD.

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Baseline Expression of T Cell Receptor Gamma-V Gene Family is Associated with High Levels of Response to Ixekizumab Treatment in Psoriasis

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A goal for new medical therapies is personalizing treatment by identifying those individual patients most likely to achieve the greatest benefit prior to clinical exposure such as through the use of a biomarker. To identify biomarkers that may predict future response to a therapy, we performed a hypothesis generating experiment comparing clinical outcomes in psoriasis to baseline mRNA expression using samples from a phase 2 study of ixekizumab, an anti-IL-17A monoclonal antibody. In a randomized, double-blind, placebo controlled trial, patients with chronic, moderate to severe plaque psoriasis were randomized to receive subcutaneous injections of ixekizumab at 150 mg (n=28), 75 mg (n=29), 25 mg (n=30), 10 mg (n=28) or placebo (n=27) at Weeks 0, 2, 4, 8, 12 and 16. mRNA levels from whole blood samples were evaluated using Affymetrix HG-U133 Plus 2 whole genome microarrays. Magnet bead isolation using a TRGV framework monoclonal antibody was used to isolate TRGV-positive cells. TRGV genes were analyzed by qPCR from patient samples along with controls. Clinical responses were measured using the psoriasis area and severity index (PASI). In the 75 mg and 150 mg groups at week 16, we observed significant differences in baseline mRNA expression of TRGV in patients achieving a PASI 90 or PASI 100 compared to those that did not (p=0.007 and p=0.003, respectively). These results were confirmed using qPCR. These results suggest that the level of mRNA expression for TRGV at baseline may help predict clinical response to ixekizumab treatment. Furthermore, while inflammation and epidermal hyperplasia in psoriasis are thought to be controlled by Th17-derived cytokines, with IL-17A having a central role in the disease, these data suggest that innate lymphoid cells expressing TRGV may also have a role in the immune pathogenesis of psoriasis.

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A comprehensive omics assessment of etanercept therapy for psoriasis

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Pharmacogenomics holds promise for biomarker discovery and mechanistic insight into the personalisation of therapies for psoriasis. We present a pharmacogenomic characterisation of 10 psoriasis patients receiving etanercept therapy. We performed analysis of the genome through genome-wide association study, transcriptome through RNA sequencing and metabolome through three validated technologies. Participants underwent detailed phenotyping and were assessed for response to therapy using the Psoriasis Area and Severity Index (PASI). Blood, skin biopsies (lesional and non-lesional) and urine samples were collected at three time points. RNA sequencing was conducted on RNA extracted from paired lesional and non-lesional skin samples (n = 60) and on total RNA and miRNA extracted from blood samples (n = 30). Metabolomic assessment was carried out on serum and urine samples. Differential expression between responders and non-responders at 12 weeks of therapy identified 118 transcripts from analysis of lesional sample data and identified 295 transcripts from analysis of lesional and non-lesional sample data ($p < 0.05$, corrected for multiple testing). Comparison of lesional and non-lesional skin sample data reflects many known mediators of the immune-inflammatory processes that characterise psoriasis. Hierarchical clustering of differentially expressed genes also identified novel genes that appeared to show co-regulation with known psoriasis genes, offering new insights into mechanisms of disease and drug response. Metabolomic assessment demonstrated clustering of metabolite profiles from urine and serum samples across multiple technologies. Psoriasis is a model disease for the development of pharmacogenomic markers of treatment response. We have identified pathways that may play a role in dictating therapeutic response in psoriasis.

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Risk of Death in Bullous Pemphigoid: a Retrospective Database Study in Finland

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The aim of this study was to investigate, firstly, the standardized mortality ratio (SMR) of bullous pemphigoid (BP) patients in Finland, and secondly, the concomitant comorbidities and medications. This was a retrospective, cross-sectional database study of the records of all BP cases diagnosed at the Department of Dermatology at Oulu University Hospital, Finland, between 1985 and 2012. We found 198 immunologically confirmed BP cases with the mean age of 77.5 years: 51.5% females and 48.5% males. The 1-year mortality was 16.7% and the SMR 7.56 (95% CI 4.98-10.14). The most common comorbidities were cardiovascular diseases (76.3%) and neurodegenerative diseases (40.9%). Polypharmacy was common, and it was significantly associated with increased mortality. The first line treatments used were oral prednisolone (62.6%), topical corticosteroid alone (29.8%), and tetracycline (7.6%). To compare the effect of treatment on mortality we divided BP patients into three groups. Group 1 (100 patients) was treated solely with oral prednisolone (together with topical corticosteroids), group 2 (40 patients) with topical corticosteroids with or without oral tetracycline, and group 3 (26 patients) with oral prednisolone and adjuvant immunosuppressant: azathioprine and/or methotrexate. Group 1 had the lowest 1-year survival. Groups 2 and 3 seemed to have similar prognosis, and were combined in the statistical analysis due to the small number of cases. When group 1 was compared with the combined groups 2 and 3, the patients in group 1 had 2.3-fold increased risk of death within one year after the diagnosis (HR=2.3, 95%CI 1.0-5.4, p=0.053). When the result was adjusted for age and sex, HR was 2.2 (95% CI 0.9-5.1, p=0.073). In conclusion, BP patients have elevated mortality compared with general population of the same age, and it can be partly caused by the medications used to treat BP.

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Cancer in neurofibromatosis 1

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Neurofibromatosis Type 1 (NF1) is well known to cause cancer, primarily malignant peripheral nerve sheath tumors and intracranial gliomas. Based on these findings, NF1 can be called cancer syndrome. We present data to suggest a broader, more general cancer predisposition for NF1. The population-based Finnish NF1 cohort contained 1,404 patients with NF1 diagnosis verified from their medical records from 1987 to 2011. Total number of person years was 19075.2, with median follow up of 13.6 years. The NF1 cohort was cross-referenced with the Finnish Cancer Registry to correlate new cancer events and all deaths 1987-2012, and estimate standardized incidence ratios (SIR) and standardized mortality ratios (SMR). Survival was considered in terms of cancer type, age, gender and diagnosis year. These results suggest that NF1 syndrome is associated with a high risk of developing a variety of cancers and dying from them. The study revealed novel findings: 1) The early age of onset, female gender excess and high mortality; 2) excessive, early and aggressive breast cancer and excessive carcinomas of selected other types; 3) an excess of NF1 patients with two to three sequential cancers of different varieties. The material presented here gives new ways of considering NF1 germinal and somatic mutations as contributory to human cancer in general. These new considerations are likely to be important far beyond the NF1 syndrome itself. The results also show that NF1 is a life threatening disease and the patients require lifelong follow-up.

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Quantification of risk factors for postherpetic neuralgia in a cohort of herpes zoster patients

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Herpes zoster commonly causes disabling neuropathic pain called postherpetic neuralgia. We aimed to investigate risk factors for postherpetic neuralgia. Using primary care data from the Clinical Practice Research Datalink, we fitted multivariable logistic regression models to investigate potential risk factors for postherpetic neuralgia (defined as pain ≥90 days after zoster, based on diagnostic and/or prescription codes), including demographic characteristics, co-morbidities, and characteristics of the acute zoster episode. We also assessed whether their effects were modified by antiviral use. Of 119,413 zoster patients, 6,956 (5.8%) developed postherpetic neuralgia. Postherpetic neuralgia risk rose steeply with age, most sharply between 50-79 years (adjusted odds ratio for a 10-year increase, 1.71, 99% confidence interval 1.63-1.78). Postherpetic neuralgia risk was higher in women (6.3% vs 5.1% in men:OR=1.19, 1.10-1.28); and those with severely immunosuppressive conditions, including leukaemia (14.4%: 2.07, 1.08-3.96) and lymphoma (12.1%: 2.45, 1.53-3.93); autoimmune conditions, including rheumatoid arthritis (9.1%: 1.21, 0.99-1.46); and other comorbidities including asthma and diabetes. Ex-smokers also had an increased risk (7.1%: OR vs never-smokers =1.14, 1.05-1.24) as did underweight individuals (8.7%: OR vs healthy weight=1.25, 1.01-1.54). Antiviral use was not associated with postherpetic neuralgia (OR=1.04, 0.97-1.11). However the increased risk associated with severe immunosuppression appeared less pronounced in patients given antivirals. Postherpetic neuralgia risk increased with age and among those with severe immunosuppression, who remain contraindicated for zoster vaccination.

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Prospective controlled studies on the routine use of a novel multivariant ELISA for the diagnosis of autoimmune bullous diseases

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The value of a novel multivariant ELISA (that allows the simultaneous testing for autoantibodies against BP180 NC16A, BP230, collagen type VII, desmoglein 1 and 3, and envoplakin) in the routine diagnosis of autoimmune bullous diseases (AIBD) has been probed in two prospective studies. In the multicenter study, consecutive sera from AIBD patients with positive direct IF microscopy (n=204) and in a single center study, consecutive sera from patients with suspicion of AIBD (n=289) were compared with the conventional multistep approach including IF microscopy of various substrates and immunoblotting of cellular extracts. In both studies, a high agreement was found between the multivariant ELISA and the conventional approach with 41 (20.1%) and 22 (7.6%) sera being discrepant in the multicenter and single center study, respectively. The highest agreement was found in patients with pemphigus (n=73 and n=11) with only 1(1.4% and 8.3%) discrepant serum in each cohort. 17 (47.3%) and 13 (56.5%) of the divergent results in the pemphigoid disorders were attributed to the lack of target antigens (e.g. p200 antigen, laminin 332, BP180 ectodomain) and the restriction to IgG reactivity in the multivariant ELISA. In summary, the multivariant ELISA is a novel and practical single-step tool that allows the rapid diagnosis of pemphigus diseases and the great majority of pemphigoid disorders. **Antalya, Turkey (S. Uzun); Belgrade, Serbia (L. Medenica); Bern, Switzerland (M. Horn); Poznan, Poland (M. Dmochowski); Rome, Italy (G. DiZenzo); Sofia, Bulgaria (K. Drenovska, S. Vassileva); Sydney, Australia (D. Murrell); Tel Aviv, Israel (E. Sprecher); Thessaloniki, Greece (A. Patsatsi); Warsaw, Poland (C. Kowalewski)*

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Gross cystic disease fluid protein 15 as a potential marker for decreased sweating in atopic dermatitis

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It has been well known that eccrine sweating is dysregulated and reduced in patients with atopic dermatitis (AD). Gross cystic disease fluid protein 15 (GCDFP15) is expressed in normal exocrine organs, such as sweat, salivary and lacrimal glands. We have reported by using proteome analysis that the amounts of GCDFP15 are decreased in *stratum corneum* (SC) samples from AD patients (JACI, 2014). The aim of this study was to evaluate GCDFP15 production by eccrine glands with SC samples and to assess sweating in AD. SC samples were obtained from 51 healthy controls (HC) and 51 AD individuals, and proteins were extracted by our previously reported procedure. Sweat samples were from 18 HC and 12 AD subjects. GCDFP15 in SC and sweat was quantified by ELISA. The amounts of GCDFP15 in the SC extracts were significantly lower in AD than HC ($P < 0.0001$). The sweat samples from AD patients also had lower levels of GCDFP15 concentration ($P < 0.05$). The eccrine sweat apparatus consists of eccrine gland secretory coil, dermal duct, and acrosyringium. Immunohistochemistry showed positive GCDFP15 staining in the eccrine gland secretory cells and the ductal and acrosyringial lumen in normal skin, but AD lacked clear staining. To identify GCDFP15-producing cells, double immunofluorescence staining for GCDFP15 and S100 protein was performed in frozen sections. The results showed that GCDFP15 was co-expressed with S100 protein, suggesting that the clear cell of eccrine glands produces GCDFP15. To address the mechanism underlying the decreased eccrine sweating in AD patients, we examined the expression of cholinergic receptor M3 (CHRM3), a receptor for acetylcholine-induced sweating, in eccrine sweat glands. The expression of CHRM3 was depressed in AD, suggesting contribution to the low sweating. In conclusion, this study showed that the SC of AD patients contained a low amount of GCDFP15 due to both low sweating and low GCDFP15 concentration in the sweat. GCDFP15 in SC could be a possible marker of eccrine sweating for AD.

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Elongated microparticle penetration profiling reveals potential for enhanced transepidermal drug delivery in distict body sites despite differences in strata composition

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Elongated microparticles are a recently developed technology to enhance topical drug delivery. Topical treatment is an attractive management approach for treating skin lesions. Unfortunately, many potentially therapeutic drugs have poor skin penetration profiles. We have developed and patented a novel platform for field- or lesion-directed drug delivery based on high-aspect ratio microparticles that were engineered to only penetrate the stratum corneum and viable epidermis. These microparticles are applied by massaging the material, with the active ingredient, into the skin. In these studies we utilize clinical reflectance confocal microscopy to show elongated microparticle penetration profiles in healthy skin, palm and in skin with dense hair coverage. We also compare chemokine profiles of elongated microparticle treated volunteer skin using our microbiopsy skin microsampling technology. Our results show that the primary barrier to elongated microparticle penetration is the dermal network of collagen and elastin. Mouse and volunteer data support the hypothesis that elongated microparticle treatment induces erythema but does not induce the typical inflammatory responses seen in chemical irritant exposure, i.e. sodium lauryl sulfate. Together, these data support the use of elongate microparticles to enhance delivery through the viable epidermis in a minimally invasive manner.

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Serum IL-17A at baseline correlates with clinical response to tofacitinib and etanercept in moderate to severe psoriasis

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Psoriasis is an inflammatory skin disease with systemic involvement. This study aimed to evaluate correlations between effects on circulating cytokines and chemokines and clinical efficacy in psoriasis patients (pts) treated with tofacitinib or etanercept. Tofacitinib is an oral JAK inhibitor that is being investigated for psoriasis. Etanercept is a TNFa blocker used in the treatment of psoriasis. Serum concentrations of IL-17A, IL-17AF, E-Selectin, IL-8, IP-10, MIG, MIP-1b, MIP-3b and TARC were determined at Week 0, 4 and 12 in pts with moderate to severe psoriasis treated with placebo (n=60), tofacitinib 5mg PO BID (n=184), tofacitinib 10mg PO BID (n=189) or etanercept 50mg SC BIW (n=190). IL-17A and IL-17AF were measured by Singulex Erenna immunoassays, while the other analytes were measured in one custom multiplex assay from Meso-Scale Discovery. Only IL-17A showed clear correlation with clinical response. Serum IL-17A decreased by 57.1% in pts achieving a PASI75 response at w12, but decreased only by 15.9% in non-responders. Although etanercept and tofacitinib 10mg had the same PASI75 response rate, the decrease in IL-17A was somewhat greater with etanercept (64.1% etanercept vs 53.6% tofacitinib 10mg, p=0.0045), which may suggest a different contribution of IL-17A reduction to the clinical efficacy of the two drugs. Serum levels of IL-17A at w0 showed moderate correlation with disease severity with Spearman correlation coefficient of 0.43. In PASI75 responders IL-17A at w12 was comparable between the two treatments (0.24-0.27pg/ml), but IL-17A at w0 was higher in the etanercept (0.76pg/ml) than in the tofacitinib cohort (0.56–0.59pg/ml). In contrast, in pts who did not achieve PASI75, IL-17A was higher in the tofacitinib (0.65–0.77pg/ml w0, 0.61–0.62pg/ml w12) than in the etanercept cohort (0.53pg/ml w0, 0.37pg/ml w12). These observations suggest that serum IL-17A w0 may be predictive of clinical response to treatment w12 with these agents.

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The Effect of Prednisolone Treatment on the Expression of Glucocorticoid Receptors GRalpha and GRbeta in Bullous Pemphigoid

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Bullous pemphigoid (BP) is the most common autoimmune blistering disease. The first line treatments of BP are topical and/or systemic glucocorticoids (GC). The actions of GCs are mediated by glucocorticoid receptor (GR). GR exists in many isoforms, of which GRalpha and GRbeta are the most important. Here we have analysed the expression levels of GRalpha and GRbeta in BP, and also investigated whether the expression of GR isoforms is altered during prednisolone treatment. The expression level of GR isoform mRNAs in peripheral blood mononuclear cells (PBMC) isolated from BP patients and controls were quantitated using qPCR. GRalpha was present in all 16 BP and 17 control samples, the expression of GRbeta was detected in 13 BP and 12 control samples. Western blot analysis of PBMC lysates showed the presence of GRalpha in all patient and control samples, whereas GRbeta was detected only in few samples. In addition, the expression of GRalpha and GRbeta was confirmed by immunohistochemical staining of lesional skin biopsies of BP samples and flow cytometric analysis of PBMC. To analyze the effect of prednisolone on the expression of GR isoforms in BP, GR isoform mRNA levels were measured from PBMC samples taken on days 5, 14 and 60 after the initiation of prednisolone. On days 5 and 14 no constant changes in the expression of GR isoforms were detected, but on day 60, the expression of GRalpha was increased in majority of BP patients and GRbeta was decreased more than half of the BP patients. In summary, we report that patients with BP express both GR isoforms and that the expression is altered during systemic glucocorticoid treatment. GRbeta expression varied significantly and was not suitable as a clinical marker of GC sensitivity in BP patients.