020 Clinico-pathological and molecular characterization of autosomal recessive epidermolysis bullosa simplex due to EXPH5 (exophilin-5) mutations

T. Rother (1), J. Machado-Canosa (2), T. McGrath (3, 4) & T. Machado-Canosa (1)

1 St John’s Institute of Dermatology, London, United Kingdom; 2 Great Ormond Street Hospital for Sick Children, London, United Kingdom

Epidermolysis bullosa simplex (EBS) is a heterogeneous disorder caused by mutations in at least 9 genes. Eight of the 9 genes have been implicated in autosomal recessive subtypes, including EXPH5 (encoding exophilin-5, a Rab27B effecter protein, also known as SLC24-2). Thus far, 7 cases of this form of EBS have been reported in 4 different families from Iran, Germany, the UK, and Pakistan, with 6 different homozygous or compound heterozygous mutations identified (4 indel; 2 nonsense). Here, we report 3 further cases (sister, 2 brothers) and review the global clinical, skin and molecular pathology of this subtype of EBS. Clinically, the children (British Pakistani; aged 12, 10 and 1 year) all had trauma-induced generalized skin blistering from birth, with small crusts at the sites of previous blisters and areas of post-inflammatory hyper- and hypo-pigmentation mainly on the trunk, limbs, face and buttocks; mucosal were not involved. Skin biopsy from 1 individual showed ultrastructural evidence of keratin filament clumping with filament cytoplasmic vesicles. Sanger sequencing of genomic DNA demonstrated homozygosity for a new mutation, c.448delA (p.Met149Ser*), in exon 6 of EXPH5; all children homozygous, parents heterozygous. Based on this pedigree, and the previous reports, we conclude that this new subtype of EBS is associated with generalized blistering that typically improves with age; skin pathology demonstrating keratin filament aggregation, reduced/existent exophilin-5 immunostaining, and varying degrees of increased intracellular and cell-cell vesicles; and, molecular pathology revealing bi-allelic loss-of-function mutations in EXPH5 (all in exon 6). Nevertheless, precisely how exophilin-5, a protein involved in vesicle transport, disrupts intermediate filament integrity akin to some keratin 3/4 mutations remains to be determined.

021 WITHDRAWN

023 Efficacy and tolerability of biologic therapies for psoriasis: network meta-analysis

Z.K. Jabbar-Lopez (1), Z. Zia (1), C.H. Smith (2) and B.A. Association of Dermatologists

1 Biologics Guideline Development Group, 2 Dermatology Centre, The University of Manchester, Manchester, United Kingdom; 3 St John’s Institute of Dermatology, London, United Kingdom; 4 Centre for Biostatistics, University of Manchester, Manchester, United Kingdom

Multiple biologic treatments are available for psoriasis but their relative efficacy and tolerability is unclear due to the limited number of head-to-head randomised clinical trials (RCTs). We conducted a systematic review to examine the efficacy and tolerability of biologic therapies for psoriasis. We searched databases for RCTs comparing etanercept, infliximab, adalimumab, ustekinumab and secukinumab (SEC) to each other or placebo or methotrexate. Pairwise random-effects meta-analyses and a network meta-analysis (NMA) were performed to derive a relative ranking of treatments. Key outcomes were: Clear/near-clear and Partially cleared Dermatology Life Quality Index (DLQI) at 16 weeks (tolerability); Study quality, heterogeneity and inconsistency were evaluated. Outcomes were jointly ranked using hierarchical cluster analysis. Direct comparisons from 42 RCTs (19,017 participants) were included. All included biologics were efficacious compared with placebo at 3-4 months. SEC had an 86% chance of being best in terms of clear/near-clear. UST had a 38% chance of being best in terms of mean improvement in DLQI. UST had a 38% chance of being best in terms of tolerability. A head-to-head comparison of SEC and UST (48 per 1000 [95% CI 44 to 233]) would more people would achieve clear/near-clear with SEC at 3-4 months, equating to a number needed to treat of 7 (95% CI 3-23). Overall, joint rankings of efficacy/tolerability suggest SEC has the best performance at 3-4 months. The key limitation is the lack of longer-term head-to-head RCT data available, restricting our analyses to short-term outcomes. Results need to be considered alongside real-world long-term safety and effectiveness data.

024 Psoriasis Stratification to Optimise Relevant Therapy (PSORT): Clinical and demographic predictors of biologic response for psoriasis

R. Warren (1), D. Burden (2), B. Tomenson (1), M. Soliman (1), E. Reilly (1), C. Griffiths (1) and C.H. Smith (1)

1 T. Dermatology Centre, The University of Manchester, Manchester, United Kingdom; 2 University of Glasgow, Glasgow, University of Manchester; 3 St John’s Institute of Dermatology, London, United Kingdom; and 4 Centre for Biostatistics, University of Manchester, Manchester, United Kingdom

Psoriasis Stratification to Optimise Relevant Therapy (PSORT) is a large stratified medicine development programme whose goal is to identify differential predictors of biologic response when treating psoriasis. We assessed baseline demographic and/or disease specific characteristics for their ability to predict response to adalimumab, etanercept and ustekinumab. Biologic naive patients (n=2042) registered with The British Association of Dermatologists Biologic In- formation Register were included. Univariate analysis was used to identify baseline predictors of improvement in psoriasis area severity index by 90% or more (PASI 90). Predictors with p<0.2 were included in a multivariate logistic regression, and interactions between treatment and predictor tested. Logistic model was fitted for each biologic. In total, 2042 patients were still on their first biologic and had PASI follow up data at 6 months (+/2); 1197 adalimumab, 501 etanercept and 344 ustekinumab. Univariate analysis showed that BMI > 30 (p=0.037), hypertension (p=0.002) and lower baseline PASI score (p=0.001) were predictors for not achieving PASI 90. These variables remained significant after logistic regression; and smoking (now or ever) was also significantly associated (odds ratio 0.74, 95% CI 0.59 to 0.93, p=0.009). Psoriasis phenotype such as plaque size or thickness, duration of disease, or treatment failure were not significant predictors of response. For adalimumab, a significant interaction was found for etanercept over adalimumab for small plaque psoriasis (p=0.021) suggesting that the superiority of adalimumab over etanercept is greater for patients without ulcer or plaque disease. Data from this national registry suggest that demographic and disease phenotype alone may not be enough to allow stratification of biologic therapy and integration of omics data should be explored.