Efficacy and safety of tirabrutinib, highly selective Bruton’s tyrosine kinase inhibitor, for oral treatment of pemphigus: a multicenter, open-label, uncontrolled, and withdrawal study
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The identification of robust endotypes — disease subgroups of clinical relevance — is fundamental to stratified medicine. We investigate whether HLA-C*06:02 status, the major genetic determinant of pemphigus, defines a pemphigus endotype. We characterised the association between HLA-C*06:02 status and a range of demographic, environmental and clinical variables. Using two UK-based cross-sectional datasets — an observational severe pemphigus study (Biomarkers of Systemic Treatment Outcomes in Pemphigus, BSTOP; n=3,767) and a large population-based bioreource (UK Biobank, including n=5,519 individuals with pemphigus) — we assessed variation of HLA-C*06:02 with the HLA-C*06:02 allele and with no copies. We used multivariable regression analyses to account for mediation effects established a priori. We confirm previous observations that HLA-C*06:02-positive status is associated with earlier age of pemphigus onset and extended findings to reveal an association with disease expressivity in females. We also show HLA-C*06:02-negative status to be associated with characteristic clinical features (large plaque disease, odds ratio [OR] for HLA-C*06:02-0 -3.7, p=7.4×10-10, higher central adipoity [BSTOP; waist circumference difference 2.0 cm, p=8.4×10-5]; UK Biobank: 1.4 cm, p=1.5×10-5), especially in women; and a higher prevalence of other cardiometabolic comorbidities. This study reveals new findings linking HLA-C*06:02-stratification with pemphigus subgroups. HLA-C*06:02 status is therefore a candidate biomarker for the delineation of important pemphigus endotypes.

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