COMMENTARY

Assessing genotypes to predict therapeutic outcome in psoriasis

Therapeutic developments have profoundly changed our understanding of the pathogenesis of inflammatory skin diseases, and with it our treatment aims. In particular, the newest generation of biologics in psoriasis, namely antibodies targeting either the IL-17 or the IL-23 signalling cascade, comes with a good chance to relieve the patient completely from disease symptoms. However, diagnostic tools have not been co-developed with these therapeutic options, and our disease classification is partially old-fashioned and cuts off numerous patients from access to these new therapeutic options. Furthermore, it is currently impossible to predict which patients benefit from a given therapy as well as to stratify patients according to their risk to develop aggravating disease and/or comorbidity.

These facts demand progress in the field of inflammatory skin diseases. First, a modern classification of inflammatory skin diseases that is based on molecular events and with it immune response patterns is needed[1,2]; and second, objective biomarkers that improve our diagnostic power have to be identified. Such biomarkers can improve diagnostics,[3] mirror disease severity,[4] stratify patients according to the risk of aggravating disease course or developing comorbidities or predict therapeutic response. Numerous efforts are currently undertaken to assess the quantity of target biomarkers in serum or skin. In parallel, the potential of specific genotypes to stratify patients is investigated.

In a landmark paper published in this issue of the JEADV, Vugt and colleagues demonstrated that therapeutic response to IL-17 inhibitors is not associated with genetic variation in the IL-17 gene region.[5] Even though reporting negative data, this study underlines how important well-designed multi-centre approaches are to prove hypothesized biomarkers. As it is straight forward to investigate the target region itself for the potential to predict therapeutic response, it is also promising. In the field of melanoma and checkpoint inhibitors, levels of PDL-1 in tissue have been proposed to stratify response to PD-1 antagonists as they predict overall survival in combination with the quantity of tumour-infiltrating lymphocytes.[6] Furthermore, while parallel studies confirm there is no association of IL-17 genetic variants with response to IL-17,[7,8] there is also evidence that the genotype predicts therapeutic response in psoriasis. Namely, the PSORT registry recently published that polymorphisms in HLA-cw6 are associated with therapeutic response to ustekinumab as compared to TNF inhibitors.[9]

The study of Vugt and colleagues also illustrates how difficult it is to identify reliable biomarkers of therapeutic response. Beyond the detection method (nucleic acids or protein in serum or skin versus genotype), choosing the optimal readout is challenging. This refers both to the time point and to the chosen endpoint – is 24 weeks long enough to determine therapeutic response? Is it primary or secondary non-responders that are more interesting to investigate? Is skin severity/PASI the ideal readout or should it be a patient-related outcome or rather an indicator of inflammation/comorbidity?

This is why we need more un-biased and well-designed studies to improve our diagnostic procedure in inflammatory skin diseases. In the future, diagnostic decision-making will most likely be guided by artificial intelligence-driven image analysis as well as by molecular diagnostics. The latter will determine (a combination of) biomarkers ranging from genotype over serum factors to cutaneous determinants.[10] With time, assessment of such objective biomarkers will become more and more easy and minimally invasive. The future starts now, and it will result in true precision medicine in inflammatory skin diseases.

Conflicts of interest

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References

1 Eyerich K, Eyerich S. Immune response patterns in non-communicable inflammatory skin diseases. *J Eur Acad Dermatol Venereol* 2018; **32**: 692–703.
2 Lauffer F, Jargosch M, Krause L *et al.* Type I immune response induces keratinocyte necroptosis and is associated with interface dermatitis. *J Invest Dermatol* 2018; **138**: 1785–1794.
3 Garzorz-Stark N, Krause L, Lauffer F *et al.* A novel molecular disease classifier for psoriasis and eczema. *Exp Dermatol* 2016; **25**: 767–774.

4 Kolbinger F, Loesche C, Valentin MA *et al.* Beta-Defensin 2 is a respon-
   sive biomarker of IL-17A-driven skin pathology in patients with psoriasis.
   J Allergy Clin Immunol 2017; **139**: 923–932. e928.
5 van Vugt LJ, van den Reek JMPA, Meulewaeter E *et al.* Response to
   IL-17A inhibitors secukinumab and ixekizumab cannot be explained by
   genetic variation in the protein-coding and untranslated regions of the
   IL-17A gene: results from a multicentre study of four European psoriasis
   cohorts. *J Eur Acad Dermatol Venereol* 2020; **34**: 112–118.
6 Bence C, Hofman V, Chamorey E *et al.* Association of combined
   PD-L1 expression and tumor-infiltrating lymphocytes features with
   survival and treatment outcomes in patients with metastatic
   melanoma. *J Eur Acad Dermatol Venereol* 2019. https://doi.org/10.
   1111/jdv.16016
7 Costanzo A, Bianchi L, Flori ML *et al.* Secukinumab shows high efficacy
   irrespective of HLA-Cw6 status in patients with moderate-to-severe
   plaque-type psoriasis: SUPREME study. *Br J Dermatol* 2018; **179**:
   1072–1080.
8 Anzengruber F, Drach M, Maul JT *et al.* Therapy response was not
   altered by HLA-Cw6 status in psoriasis patients treated with secuk-
   inumab: a retrospective case series. *J Eur Acad Dermatol Venereol* 2018;
   32: e274–e276.
9 Dand N, Duckworth M, Baudry D *et al.* HLA-C*06:02 genotype is a
   predictive biomarker of biologic treatment response in psoriasis. *J Allergy
   Clin Immunol* 2019; **143**: 2120–2130.
10 Eyerich S, Metz M, Bossios A, Eyerich K. New biological treatments for
   asthma and skin allergies. *Allergy* 2019. [Epub ahead of of print]. https://
   doi.org/10.1111/all.14027