Genetic prediction of treatment response in psoriasis is still a work in progress

Foulkes, Amy; Brown, Sara

Published in:
British Journal of Dermatology

DOI:
10.1111/bjd.15691

Publication date:
2017

Document Version
Peer reviewed version

Commentary on Talamonti et al. *BJD* 2017.

Genetic prediction of treatment response in psoriasis is still a work in progress.

Amy C Foulkes

NIHR Academic Clinical Lecturer in Dermatology,

[1]Dermatopharmacology Unit, Salford Royal NHS Foundation Trust, Manchester Academic Health Science Centre, The University of Manchester

Sara J Brown

Professor of Molecular & Genetic Dermatology, Wellcome Trust Senior Research Fellow in Clinical Science and Honorary Consultant Dermatologist

[2] Skin Research Group, School of Medicine, University of Dundee

[3] Department of Dermatology, Ninewells Hospital & Medical School, Jacqui Wood Centre level 7, James Arrott Drive, Dundee DD1 9SY

Conflict of interest

ACF has received educational support to attend conferences from or acted as a consultant or speaker for Abbvie, Almirall, Eli Lilly, Leo Pharma, Novartis, Pfizer, Janssen and UCB. SJB has received honoraria for invited lectures at the American Academy of Asthma, Allergy and Immunology annual meetings.

Acknowledgement

SJB holds a Wellcome Trust Senior Research Fellowship in Clinical Science (106865/Z/15/Z).

Word count 489

The availability of biologic therapies for dermatological indications is increasing, but the targeted mechanisms and high cost necessitate careful patient selection. Treatment selected on the basis of genomic variation is already a reality for the management of advanced malignant melanoma, but in inflammatory skin disease we have yet to integrate genomic testing in to clinical practice.

In this issue of the *BJD*, Talamonti *et al.*[1] report a retrospective study of 255 patients with psoriasis treated with the anti-IL12/23 biologic ustekinumab. The authors investigated an association between HLA-Cw*06 genotype and response to ustekinumab, defined by 50% reduction in the Psoriasis Area and Severity Index (PASI 50) after 4 weeks of treatment. HLA-Cw*06 is an allele of the human leucocyte antigen (HLA) class I *HLA-Cw6* gene; it is a significant genetic determinant of psoriasis[2] and its role has therefore been investigated in treatment response. *HLA-C* genotyping is a straightforward and relatively inexpensive laboratory test. In the current study[1], 71.7% of Cw*06 positive patients reached PASI 50 at week four in comparison to 35.2% of those who were Cw*06 negative (p=<0.0001).

Other studies have shown somewhat conflicting findings when assessing HLA genotype as a predictor of treatment response in psoriasis. Talamonti *et al*. previously reported an association between the presence of HLA-Cw*06 and higher rates of response to ustekinumab in 51 patients with psoriasis[3]. A differential response was also reported by Li *et al*. [4] in a study of 332 patients who had received ustekinumab: 62% of Cw*06 positive patients versus 48% of Cw*06 negative patients reached PASI 50 after 4 weeks of therapy (p<0.05). However the Cw*06 positive patients showed only up to 10% greater efficacy, a difference that is unlikely to be sufficient rationale for using Cw*06 genotype in choice of therapy[4]. In contrast, Prieto-Perez *et al.* found no association of Cw*06 genotype with response to ustekinumab treatment in 69 psoriasis patients treated with ustekinumab[5]. These inconsistent findings are likely to result from differences in study methodology, including the ethnicity of participants and details of disease phenotype. Variation in methodology is considered to be the primary reason for a lack of replication amongst pharmacogenomic studies[6].

It is unlikely that a single immune-genetic variant would substantially predict treatment response in a complex inflammatory skin disease such as psoriasis. The study by Talamonti *et al.*[1] has contributed additional insight into the utility of *HLA-C* genotype as a biomarker to contribute to treatment selection. However, adequately powered prospective studies will be required before clinical application of pharmacogenomics can become a reality. Genotype and phenotype assessment is facilitated by the availability of ever more detailed molecular analyses and data integration. The Psoriasis Stratification to Optimise Relevant Therapy (PSORT) is one example of a stratified medicine consortium aiming to develop molecular testing to direct personalised treatment for patients[8]. Careful assessment of prospective data will be needed to integrate findings into the clinical decision-making process, to optimise the treatment of patients with psoriasis in the future.

References

1 Talamonti M, Galluzzo M, van den Reek JM *et al.* Role of HLA- C*06 in clinical response to ustekinumab: evidence from real-life in a large cohort of European patients. *Br J Dermatol* 2017.

2 Russell TJ, Schultes LM, Kuban DJ. Histocompatibility (HL-A) antigens associated with psoriasis. *N Engl J Med* 1972; **287**: 738-40.

3 Talamonti M, Botti E, Galluzzo M *et al.* Presence of HLA-Cw6 but not *LCE$_3$C_LCE3*B deletion influences clinical response to ustekinumab in psoriasis patients. *British Journal of Dermatology* 2011; **165**: e11.

4 Li K, Huang CC, Randazzo B *et al.* HLA-C*06:02 Allele and Response to IL-12/23 Inhibition: Results from the Ustekinumab Phase 3 Psoriasis Program. *The Journal of investigative dermatology* 2016; **136**: 2364-71.

5 Prieto-Perez R, Llamas-Velasco M, Cabaleiro T *et al.* Pharmacogenetics of ustekinumab in patients with moderate-to-severe plaque psoriasis. *Pharmacogenomics* 2017; **18**: 157-64.

6 Jorgensen A, Williamson P. Methodological quality of pharmacogenetic studies: Issues of concern. *Statistics in Medicine* 2008; **27**: 6547-69.

7 Warren RB, Smith CH, Yiu ZZ *et al.* Differential Drug Survival of Biologic Therapies for the Treatment of Psoriasis: A Prospective Observational Cohort Study from the British Association of Dermatologists Biologic Interventions Register (BADBIR). *The Journal of investigative dermatology* 2015; **135**: 2632-40.

8 Griffiths CE, Barnes MR, Burden AD *et al.* Establishing an Academic-Industrial Stratified Medicine Consortium: Psoriasis Stratification to Optimize Relevant Therapy. *The Journal of investigative dermatology* 2015; **135**: 2903-7.