University of Dundee

HLA-Cw6-positive patients with psoriasis show improved response to methotrexate treatment

West, J.; Ogston, S.; Berg, J.; Palmer, C.; Fleming, C.; Kumar, V.

Published in:
Clinical and Experimental Dermatology

DOI:
[10.1111/ced.13100](https://doi.org/10.1111/ced.13100)

Publication date:
2017

Document Version
Peer reviewed version

[Link to publication in Discovery Research Portal](#)

Citation for published version (APA):

West, J., Ogston, S., Berg, J., Palmer, C., Fleming, C., Kumar, V., & Foerster, J. (2017). HLA-Cw6-positive patients with psoriasis show improved response to methotrexate treatment. *Clinical and Experimental Dermatology*, 42(6), 651-655. <https://doi.org/10.1111/ced.13100>

General rights

Copyright and moral rights for the publications made accessible in Discovery Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from Discovery Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain.
- You may freely distribute the URL identifying the publication in the public portal.

Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

HLA-Cw6+ psoriasis patients show improved response to methotrexate treatment

Jonathan West¹, Simon Ogston¹, Jonathan Berg¹, Colin Palmer¹, Colin
Fleming², Vinod Kumar³, John Foerster^{1,2,&}

¹University of Dundee, College of Medicine, Dentistry, and Nursing, Dundee,
Scotland, ²Department of Dermatology and Photobiology, and ³Department of
Rheumatology

&Corresponding author: j.foerster@dundee.ac.uk, Ninewells Hospital, Dundee,
DD1 9SY

key words: methotrexate, psoriasis, pharmacogenomics

manuscript word count: 932; 2 tables, 1 figure

The authors declare no conflicts of interest

financial disclosures: none declared by the authors

running head:

This is the peer reviewed version of the following article: 'HLA-Cw6-positive patients with psoriasis show improved response to methotrexate treatment', *Clinical and Experimental Dermatology*, which has been published in final form at <http://doi.org/10.1111/ced.13100>. This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Self-Archiving.

Abstract

It is well documented that HLA-Cw6+ (type 1) psoriasis patients have increased severity and reduced age of onset of psoriasis. However, not much is known about any differential response of this genetic subgroup to various treatments. We set out to determine if there was any genetic association of the HLA-Cw6 allele with the first-line systemic treatment commonly used in psoriasis, methotrexate. A cohort of patients from Tayside, Scotland was recruited through a novel generic consenting process (GoShare), extensively phenotyped, and analysed for an association of their HLA-Cw6 genotype status with treatment outcomes. HLA-Cw6+ patients showed notably improved response to methotrexate ($p = 0.05$), and further analysis demonstrates an even greater response in a sub-cohort of the HLA-Cw6+ patients without concomitant psoriatic arthritis ($p = 0.01$). HLA-Cw6+ patients also exhibited fewer treatment limiting adverse events. In addition to these findings, the methodology and primary clinical outcome phenotype, which we validate here, will greatly facilitate replication of the present results in independent cohorts.

Introduction

Pharmacogenomics for genetic diseases has been identified as a future area of knowledge growth ¹ but data have been sparse. For a common genetic disease, psoriasis, and a very common treatment, methotrexate, few pertinent data have been published ².

One limitation for population-based pharmacogenomics has been availability of good phenotypic data and limitations around patient consent. To address these limitations, we have recently established a novel generic approach to consenting entitled GoShare (www.goshare.org.uk) whereby patients consent to use of residual blood samples taken in routine practice for research. This allows rapid and inexpensive establishment of patient cohorts.

Apart from cohort assembly, description of phenotypes with low selection and reporting bias is another limitation in pharmacogenomics approaches. In this regard electronic capture available in Tayside allows for near-complete phenotype collection regarding medical treatments and outcomes in a population size of 450000. These resources have allowed the recent in-depth phenotyping of the largest population-based cohort of psoriasis patients treated with methotrexate to date ³.

We here report the first GoShare consented sub-cohort of the Tayside methotrexate treatment cohort ³ and report efficacy and safety outcomes for methotrexate treatment based on HLA-Cw6 status, which identifies two established genetic psoriasis subgroups and is also genetically associated with psoriasis arthritis ⁴.

Report

Establishment of a cohort of MTX-treated psoriasis patients for genetic analysis. Detailed methods are supplied in the Supplement. The overall clinical characteristics of the HLA-test cohort and parent cohort are very similar (Table 1). Furthermore, the overall treatment outcome over a period of ten years shows similar rates of MTX discontinuation for both lack of efficacy and treatment limiting AEs in both the HLA-test and the parent cohorts (Fig 1a). Finally, the spectrum of treatment limiting AEs in the HLA-test cohort is largely in line with the parent cohort (Table S2). We conclude that sampling bias introduced by GoShare cohort building is minimal and that results obtained by genotyping of the HLA-test cohort are likely to be representative of the parent cohort.

Clinical characteristics of the cohort by HLA-C genotype. The clinical characteristics of the HLA-Cw6 genotyped cohort are shown in Table 2. As expected, the HLA-Cw6 positive cohort exhibits a lower median age of onset of disease, consistent with “type 1 psoriasis”⁵. However, both subgroups differ in the prevalence of concurrent psoriatic arthritis wherefore this potential confounder was addressed in further analysis (see below).

Improved response to methotrexate treatment in HLA-Cw6+ patients. We previously validated the outcome “treatment duration beyond 12 months” as a proxy for treatment efficacy in the parent cohort³. We were able to verify the same in the HLA-test cohort (Fig S1). The outcome “on treatment > 1 year” was therefore analysed stratified by HLA-C status. As shown in Fig 1b, four-fifths of treatment episodes for the HLA-Cw6 positive group were carried on beyond 12

months, compared with only two-thirds of treatment episodes for the HLA-Cw6 negative group ($p = 0.05$). As evident from the figure, both lack of efficacy and limiting adverse effects occur with higher frequency in the HLA-Cw6-negative subgroup and contribute to the overall poorer response to treatment.

HLA-Cw6-status is highly predictive of response to MTX treatment in psoriasis patients without concomitant arthritis. Since the prevalence of patients with arthritis was unevenly distributed between the HLA-Cw6+ and HLA-Cw6- cohorts, treatment outcome in both subgroups was analysed after eliminating patients with concomitant psoriatic arthritis. The results are shown in Fig 1b (lower panels). Strikingly, despite the resultant smaller cohort size, the treatment outcomes were even more significantly affected by HLA-Cw6 status with regard to the number of patients reaching treatment duration of 1 year. Thus, 80% of HLA-Cw6+ patients reach 1 year of treatment compared to 51% of HLA-Cw6- patients ($p = 0.01$, exact test mid p value).

As an independent treatment outcome, the effect of methotrexate in those patients, who do achieve one year of treatment duration, on the usage of psoriasis – targeted topical treatments was also analysed, as shown in Fig 1c. There was a greater reduction in prescriptions made out for HLA-Cw6+ patients after methotrexate treatment. Again, this effect was more pronounced, and highly statistically significant in the arthritis-free subgroup. These data indicate that – not only do more HLA-Cw6+ patients show an overall response to methotrexate but, in addition, those who do respond, appear to achieve better disease control.

Discussion

The current data show that the response of psoriasis patients to treatment with methotrexate appears to be influenced by genetic subtype. HLA-Cw6 positive patients (largely overlapping with type 1 psoriasis) have a better chance of responding, and fewer appear to develop adverse effects than HLA-Cw6 negative patients. Although the size of our sample is the principle limitation of our findings, the sample still is significantly larger than that recently reported to substantiate a genetic association of HLA-Cw6 status with response to ustekinumab treatment in psoriasis ⁶. In general, pharmacodynamic studies on the effect of HLA-Cw6 status on treatment response in psoriasis are scarce. A recent medium-size study did not find any effect on the response to anti-TNF treatment ⁷.

The large observed effect size (threefold reduction in primary lack of efficacy among HLA-Cw6+ patients) would certainly appear large enough to warrant replication studies. To that end, the inexpensive methodology (single SNP genotyping) and the validated, and widely available primary clinical phenotype endpoint we here provide (“on treatment > 1 year”) should prove very useful in real-world cohorts where formal outcomes such as PASI are rarely available.

It is unclear why the effect of HLA-Cw6 status should be more pronounced in patients without concomitant arthritis. Certainly, the effect could be spurious, given the moderate sample size. Alternatively, the presence of systemic inflammatory arthritis itself may well affect not only psoriasis severity but also response to treatment. In that regard, the response rate to

methotrexate has recently been shown to be associated to another genetic marker (KIR2DS4 alleles) in rheumatoid arthritis ⁸. The genetic association of HLA-Cw6 with the response of psoriasis arthritis as such to methotrexate has not been reported to date.

In addition to genetic psoriasis subgroups, genetic heterogeneity in genes regulating methotrexate metabolism may affect treatment outcome in psoriasis, as has been shown in rheumatoid arthritis ^{9, 10}. Although MTX-related genes variants have not been shown to be predictive of clinical outcomes in a previous study ¹¹, regulatory SNPs for these and other genes remain to be tested. We were unable to address these issues here, as our sample size precluded multiple testing.

The ability to rapidly assemble cohorts for association studies using a generic consenting approach in conjunction with complete phenotype access through the availability of electronic database (detailed in ³) offers considerable potential to advance pharmacogenomics research, especially under real-world conditions, complementing data on methotrexate efficacy gathered in clinical trials ¹².

In conclusion, we here report that HLA-Cw6+ (type 1) subgroup of psoriasis patients exhibit a significantly better response to methotrexate treatment. If confirmed in larger replication cohorts, this may lead to validation of an inexpensive predictive blood test helpful for clinical decision making.

Acknowledgements

We thank all patients for providing samples for this study. In addition we would like to acknowledge the services of the health informatics center at Dundee University and the Tayside tissue bank. No external funding was supplied.

Tables

Table 1. Comparison of HLA-test cohort and parent cohort¹

	Parent cohort		HLA-C sub cohort	
	n = 333	%	n = 70	%
<i>General Characteristics:</i>				
Female	195	59	41	59
Age at onset of disease < 41 (years)	200	60	41	59
Median age at start MTX (range) ²	48 (9 - 85)		49 (16 - 77)	
Median disease duration prior to MTX (range)	12.5 (0 - 23)		13 (0 - 23)	
<i>Psoriasis treatment history:</i>				
Prior UVB	263	79	56	80
Prior PUVA	189	57	38	54
Prior Topical treatments ³	323	97	70	100
Prior Acitretin	47	14	12	17
<i>Comorbidities:</i>				
Diabetes ⁴	29	9	7	10
Hypertension	65	20	14	20
Concomitant PsA ⁵	81	24	21	30

¹Data shown summarise clinical profile accessible through electronic data mining as detailed in Methods. Abbreviations: MTX - methotrexate; UVB - ultraviolet B; PUVA - psoralen combined with ultraviolet A; PsA - psoriatic arthritis.

²Five of the total cohort and one of the HLA sub-cohort were started on MTX treatment under 18 years of age.

³Topicals include agents containing steroids, calcipotriol, coal tar, dithranol, retinoids, salicylic acid but no emollients.

⁴Diabetes. From the 29 diabetes patients in the parent cohort the diagnosis were: 27 type 2 diabetes, 1 type 1 diabetes and 1 patient with impaired glucose tolerance. All of the 7 patients in the HLA-cohort were diagnosed with type 2 diabetes.

⁵See Methods on definition used for PsA.

Table 2. Clinical characteristics of the HLA-Cw6 positive and HLA-Cw6 negative cohorts¹

	HLA-Cw6 positive		HLA-Cw6 negative	
	n = 27	%	n = 43	%
<i>General Characteristics:</i>				
Female	18	67	23	53
Age at onset of disease < 41 (years)	18	67	23	53
Median age at start MTX (range) ²	44 (16 - 77)		51 (24 - 76)	
Median disease duration prior to MTX (range)	14 (0 - 21)		11 (0 - 23)	
<i>Psoriasis treatment history:</i>				
Prior UVB	24	89	32	74
Prior PUVA	18	67	20	47
Prior Topical treatments ³	27	100	43	100
Prior Acitretin	5	19	7	16
<i>Comorbidities:</i>				
Diabetes ⁴	2	7	5	12
Hypertension	6	22	8	19
Concomitant PsA ⁵	5	19	16	37

¹Data shown summarise clinical profile accessible through electronic data mining as detailed in Methods. Abbreviations: MTX - methotrexate; UVB - ultraviolet B; PUVA - psoralen combined with ultraviolet A; PsA - psoriatic arthritis.

²One of the patients in the HLA-Cw6 negative patients was initiated on methotrexate therapy below 18 years of age.

³Topicals include agents containing steroids, calcipotriol, coal tar, dithranol, retinoids, salicylic acid but no emollients.

⁴All of the seven patients with diabetes had a diagnosis of type 2 diabetes.

⁵See Methods on definition used for PsA.

Legend to Figure

Figure 1 - A. Data show the percentage of patients discontinued due to lack of efficacy (left) and treatment limiting AEs (right) over a treatment period of 10 years. B. The number of patients on continued treatment and those discontinued due to either lack of efficacy or MTX related toxicity at 12 months of treatment for HLA-Cw6 positive patients (left) and HLA-Cw6 negative patients (right). “Toxicity” - any treatment limiting adverse effect. Upper panels show all patients, and lower panels those without concomitant psoriatic arthritis, as indicated. C. The percentage of patients who achieved a reduction in the number of psoriasis specific prescriptions after one year of successful MTX treatment among the whole HLA-test cohort (left) and psoriasis patients without concomitant psoriatic arthritis (right), respectively. * $p < 0.05$ (exact test mid-p value).

References

1. Lee JW, Aminkeng F, Bhavsar AP, et al. The emerging era of pharmacogenomics: current successes, future potential, and challenges. *Clin Genet*. 2014 Jul;86(1):21-8. PubMed PMID: 24684508. Pubmed Central PMCID: 4233969.
2. Warren RB, Chalmers RJ, Griffiths CE, Menter A. Methotrexate for psoriasis in the era of biological therapy. *Clinical and experimental dermatology*. 2008 Aug;33(5):551-4. PubMed PMID: 18801095.
3. West J, Ogston S, Palmer C, et al. Methotrexate in psoriasis under real world conditions: long-term efficacy and tolerability. *Br J Dermatol*. 2016 Feb 6. PubMed PMID: 26852010.
4. Sokolik R, Gebura K, Iwaszko M, et al. Significance of association of HLA-C and HLA-E with psoriatic arthritis. *Human immunology*. 2014 Dec;75(12):1188-91. PubMed PMID: 25454626.
5. Gudjonsson JE, Karason A, Runarsdottir EH, et al. Distinct clinical differences between HLA-Cw*0602 positive and negative psoriasis patients--an analysis of 1019 HLA-C- and HLA-B-typed patients. *The Journal of investigative dermatology*. 2006 Apr;126(4):740-5. PubMed PMID: 16439971.
6. Talamonti M, Botti E, Galluzzo M, et al. Pharmacogenetics of psoriasis: HLA-Cw6 but not LCE3B/3C deletion nor TNFAIP3 polymorphism predisposes to clinical response to interleukin 12/23 blocker ustekinumab. *Br J Dermatol*. 2013 Aug;169(2):458-63. PubMed PMID: 23521149.
7. Ryan C, Kelleher J, Fagan MF, et al. Genetic markers of treatment response to tumour necrosis factor-alpha inhibitors in the treatment of psoriasis. *Clinical and experimental dermatology*. 2014 Jun;39(4):519-24. PubMed PMID: 24758522.
8. Majorczyk E, Pawlik A, Gendosz D, Kusnierczyk P. Presence of the full-length KIR2DS4 gene reduces the chance of rheumatoid arthritis patients to respond to methotrexate treatment. *BMC musculoskeletal disorders*. 2014;15:256. PubMed PMID: 25069714. Pubmed Central PMCID: 4118653.
9. Moya P, Salazar J, Arranz MJ, et al. Methotrexate pharmacokinetic genetic variants are associated with outcome in rheumatoid arthritis patients. *Pharmacogenomics*. 2016 Jan;17(1):25-9. PubMed PMID: 26652611.
10. Ghodke-Puranik Y, Puranik AS, Shintre P, et al. Folate metabolic pathway single nucleotide polymorphisms: a predictive pharmacogenetic marker of methotrexate response in Indian (Asian) patients with rheumatoid arthritis. *Pharmacogenomics*. 2015 Dec;16(18):2019-34. PubMed PMID: 26616421.
11. Warren RB, Smith RL, Campalani E, et al. Outcomes of methotrexate therapy for psoriasis and relationship to genetic polymorphisms. *The British journal of dermatology*. 2009 Feb;160(2):438-41. PubMed PMID: 19016697. Pubmed Central PMCID: 2680291.
12. West J, Ogston S, Foerster J. Safety and Efficacy of Methotrexate in Psoriasis: A Meta-Analysis of Published Trials. *PloS one*. 2016;11(5):e0153740. PubMed PMID: 27168193. Pubmed Central PMCID: 4864230.