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

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

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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 cohort [3]. 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 a 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 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.

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Tables

Table 1. Comparison of HLA-test cohort and parent cohort[1]

	Parent cohort		HLA-C sub cohort	
	n = 333	%	n = 70	%
General Characteristics:				
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)	
Psoriasis treatment history:				
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
Comorbidities:				
Diabetes[4]	29	9	7	10
Hypertension	65	20	14	20
Concomitant PsA[5]	81	24	21	30

[1]Data 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.

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

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

[4]Diabetes. 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.

[5]See Methods on definition used for PsA.

Table 2. Clinical characteristics of the HLA-Cw6 positive and HLA-Cw6 negative cohorts[1]

	HLA-Cw6 positive		HLA-Cw6 negative	
	n = 27	%	n = 43	%
General Characteristics:				
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)	
Psoriasis treatment history:				
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
Comorbidities:				
Diabetes[4]	2	7	5	12
Hypertension	6	22	8	19
Concomitant PsA[5]	5	19	16	37

[1]Data 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.

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

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

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

[5]See 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).

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