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Pharmacogenetic biomarkers for secukinumab response in psoriasis patients in real-life clinical practice

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Abstract

Background: Prediction of the response to a biological treatment in psoriasis patients would allow efficient treatment allocation.

Objective: To identify polymorphisms associated with secukinumab response in psoriasis patients in a daily practice setting.

Methods: We studied 180 SNPs in patients with moderate-to-severe plaque psoriasis recruited from 15 Spanish hospitals. Treatment effectiveness was evaluated by absolute PASI ≤3 and ≤1 at 6 and 12 months. Individuals were genotyped using a custom Taqman array. Multiple logistic regression models were generated. Sensitivity, specificity and area under the curve (AUC) were analysed.

Results: A total of 173 patients were studied at 6 months, (67% achieved absolute PASI ≤ 3 and 65% PASI ≤ 1) and 162 at 12 months (75% achieved absolute PASI ≤ 3 and 64% PASI ≤ 1). Multivariable analysis showed the association of different sets of SNPs with the response to secukinumab. The model of absolute PASI≤3 at 6 months showed best values of sensitivity and specificity. Four SNPs were associated with the capability of achieving absolute PASI ≤ 3 at 6 months. rs1801274 (*FCGR2A*), rs2431697 (*miR-146a*) and rs10484554 (*HLCw6*) were identified as risk factors for failure to achieve absolute PASI≤3, while rs1051738 (*PDE4A*) was protective. AUC including these genotypes, weight of patients and history of biological therapy was 0.88 (95% CI 0.83–0.94), with a sensitivity of 48.6% and specificity of 95.7% to discriminate between both phenotypes.

Conclusion: We have identified a series of polymorphisms associated with the response to secukinumab capable of predicting the potential response/non-response to this drug in patients with plaque psoriasis.

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INTRODUCTION

Psoriasis is an immune-mediated chronic skin disease affecting 2%–3% of worldwide population. As other complex diseases, psoriasis is caused by an interaction of genetic and environmental factors. Different biologic therapies are currently available to clinicians for the treatment of plaque psoriasis, including secukinumab, a monoclonal antibody against IL-17A.[1,2] IL-17A is secreted by Th17 cells and innate immune cells and activates keratinocytes to produce proinflammatory mediators which, in turn, recruit and stimulate additional inflammatory cells establishing a positive feedback loop that perpetuates inflammatory processes. Although secukinumab treatment has been shown to exhibit high rates of efficacy, in real-world clinical practice success rates are variable.[3–7]

The high cost of biologic treatments and the impact on patients' quality of life caused by the lack of improvement in some patients warrant the identification of markers that allow treatment to be adapted to each patient through personalized medicine. Because of the polygenic nature of autoimmune diseases, the study of genetic markers, mainly single nucleotide polymorphisms (SNPs), has been proposed as a useful tool to predict the effectiveness of biological treatments in these diseases.[8] In psoriasis, different genetic variants have been associated with response to topical treatments, conventional disease-modifying anti-rheumatic drugs (cDMARDs) and biologic therapy against TNF-a or anti-IL-12/23, being the allele HLA-Cw6 the most studied.[9] Since secukinumab was approved by the FDA for plaque psoriasis, few studies have explored the usefulness of polymorphisms as biomarkers to predict its effectiveness. SUPREME Study group reported that determination of *HLA-Cw6* was unnecessary in the treatment of psoriasis with secukinumab at Weeks 24 and 72 using Psoriasis Area Severity Index [PASI] 90 as effectiveness parameter.[10,11] Later, in a study of 134 patients, no association between 5 *IL17A* SNPs and ΔPASI, PASI75 or PASI90 was identified.[12] More recently, Morelli et al described the association of several SNPs (including *HLA-Cw6*) with PASI90 and PASI100 in a cohort of 62 patients.[13] Commonly, the effectiveness of anti-psoriatic treatments is evaluated as the relative improvement from baseline PASI, reported as PASI75, PASI90 or PASI100. However, during the past few years the interest to evaluate absolute PASI as therapeutic parameter has emerged.[14]

There are two methods to detect the association of genetic variants with a specific phenotype. Genome wide associations studies (GWAS) investigate genetic variants through the whole genome while candidate-gene studies analyse a limited number of pre-specified genes. Compared to GWAS, candidate-gene studies have increased statistical power to detect differences. In this candidate-gene study, we evaluated the association of 180 SNPs of relevant genes for psoriasis, with secukinumab response in real-life clinical practice at 6 and 12 months after treatment initiation using absolute PASI ≤3 and ≤1 as effectiveness parameters.

METHODS

Subjects

This is a national, multicentre (15 dermatology centres in Spain) and cross-sectional study. Informed consent and protocol were approved by the Clinical Research Ethics Committee of Hospital Universitario de La Princesa. A total of 204 adult patients with moderate-to-severe chronic plaque psoriasis who had previously been treated or were under treatment with secukinumab in a daily practice setting, were recruited (February 2016 to March 2021). Dosage and therapeutic regimen were according to drug label (300 mg subcutaneously at Weeks 0, 1, 2, 3 and 4 and monthly thereafter). Other clinical data collected were age, sex, weight, disease duration and presence of psoriatic arthritis. Absolute PASI ≤3 and ≤1 were used as criteria to evaluate secukinumab response at 6 and 12 months.

Sample processing and genotyping

DNA was extracted from 1 mL of peripheral blood using MagNA Pure LC 2.0 (Roche, Switzerland) and quantified with nanodrop NanoDrop® ND-1000 Spectrophotometer (Wilmington, USA). We designed a custom microarray that included 180 SNPs of the genes considered relevant (Table S1). To select these, we performed an extensive bibliographic search, considering previously published data regarding psoriasis and the mechanism of action of the different drugs approved for its treatment. We also considered biological drug response in related inflammatory diseases such as psoriatic arthritis (PsA), Crohn's disease and rheumatoid arthritis. For the selection of SNPs, we prioritized those with functional significance and with a minor allele frequency of >10%. SNPs were genotyped using a QuantStudio 12 K Flex qPCR instrument with an OpenArray thermal block (Applied Biosystems, Thermofisher, USA).

Statistics

SNPs showing >5% missing genotypes were excluded as well as those individuals with more than 5% missing data. SNP filtering was performed before individual filtering.[15,16] Analysis at 12 months included only those patients with observed clinical data at that point time.

SNPassoc r package was used to test the association of every SNP with clinical response to secukinumab. Every SNP was tested to determine which logistic regression model had the best adjustment according to the type of inheritance (codominant, dominant, recessive, overdominant and additive); the optimal model was selected using the lower Akaike information criterion (AIC). Association of response to secukinumab with age, sex, PsA, disease duration and PASI at baseline (<10 vs ≥10) was analysed using univariable logistic regression. To construct the multivariable logistic regression

model, SNPs were selected using a cutoff of 0.15 of false discovery rate (FDR) q-value. Multivariable logistic regression model was performed using the stepwise (backward) selection method (STATA 14.0, StataCorpUSA). For multivariable analysis, weight of patients and previous treatment with other biologicals (0, 1, 2 or more than 3) were included as confounding variables. To assess the ability of SNPs to discriminate between responders and non-responders (according to absolute PASI), receiver operating characteristic (ROC) curve analysis was performed (STATA 14.0).

RESULTS

Patients

A total of 204 patients were genotyped, and 31 of them were excluded from the final statistical analysis because of genotyping failure. Four out of 173 patients analysed discontinued the treatment before 12 months due to effectiveness failure, 2 for pregnancy and 5 were excluded due to missing clinical data.

Thus, for the association study 173 and 162 patients were analysed at 6 and 12 months, respectively. Clinical and demographic characteristics are summarized in Table 1; 56% of recruited patients were male and 44% female with a mean age of 48.45 years, 20% had psoriatic arthritis and the average disease duration was 26 years. Around 50% were naïve for biological therapy, while around 20% were naïve for cDMARDs. Seventy-seven percent and 75% of the patients achieved absolute PASI ≤3 at 6 and 12 months of treatment, respectively, while absolute PASI ≤1 was achieved by 65% of patients at 6 months and 64% at 12 months.

Association study at 6 months after treatment

Univariable logistic regression analysis showed that weight of patients and history of other biologicals treatments were associated ($p < 0.05$, OR >1) with failure to achieve absolute PASI ≤1 or ≤3 (Table 2). PASI at baseline (<10 vs. ≥10) was associated with PASI ≤1 at 6 months with a p value <0.05 in the univariable analysis. There was no association between sex, age, history of cDMARDs, psoriatic arthritis or disease duration and the response to treatment at 6 months.

Several SNPs were identified to be associated ($p < 0.05$) with the ability to achieve absolute PASI ≤3 or ≤1 at 6 months in the univariable analysis (Tables S2 and S3, respectively). Those SNPs with an FDR value <0.15 were selected to construct a multiple regression model that also included weight of patients, PASI at baseline and history of biologicals treatments as confounding factors. Using an absolute PASI ≤3 to evaluate effectiveness treatment at 6 months, seven SNPs had an FDR <0.15 (Table S2). After multivariable analysis, four of them remained associated to the treatment response, rs1051738 (*PDE4A*) decreased the risk of failing to reach PASI ≤3, while rs12191877 (*HLACw6*), r1801274 (*FCGR2A*) and rs2431697 (*miR-146a*) were identified as risk factors of non-response as indicated by odds ratio (OR) values (Table 3). Weight and a history of biological therapy remained as risk factors of non-response (Table 3), but not baseline PASI. Next, we analysed the capability of this model to discriminate between patients who achieved PASI ≤3 and those who did not. According to the ROC analysis (AUC = 0.88, 95% confidence interval [CI] [0.83–0.94]), combination of these four SNPs along with the weight of the patient and history of biologicals had a sensitivity of 48.6% and specificity of 95.7% to discriminate between responders and non-responders (PASI ≤3). Regarding PASI ≤1 at 6 months, only two polymorphisms had an FDR corrected p value <0.15, rs2227322 (*CSF3*) and rs645544 (*SLC9A8*) (Supplementary Table 3). Multiple regression analysis showed that both polymorphisms were associated with secukinumab effectiveness independently of weight and history of biological therapy. Both polymorphisms, decreased the risk of not achieving PASI ≤1 at 6 months (Table 3). The ROC analysis of this model showed an AUC = 0.81 (95% CI 0.75–0.88), a sensitivity of 49.1% and a specificity of 82% in terms of differentiating patients that achieved absolute PASI ≤1 from those who failed.

TABLE 1 Phenotypic characteristics of patients (Baseline data).

Characteristic	Substudy at 6 months $n = 173$	Substudy at 12 months $n = 162$
Age (years), mean ± SD	48.45 ± 12.31	48.26 ± 12.47
Male, n (%)	97 (56.0)	92 (57.0)
Weight (kg), mean ± SD	83.06 ± 21.06	83.44 ± 21.22
PsA, n (%), yes	35 (20.0)	33 (20.0)
Disease duration (years), mean ± SD	26.20 ± 13.69	26.08 ± 13.24
PASI	14.6 ± 8.4	14.7 ± 8.6
Biologicals naïve, n (%), yes	92 (53.0)	85 (54.0)
cDMARDs naïve, n (%), yes	38 (21.0)	35 (22.0)

Note: Data of sex and psoriatic arthritis (PsA) are shown as percentage.

Abbreviations: cDMARDs, conventional disease-modifying antirheumatic drugs; PASI, psoriasis area and severity index.

TABLE 2 Univariable logistic regression for clinic-demographic variables.

Characteristic	OR	p value	95% CI
Absolute PASI ≤1 at 6 months			
Sex	1.2	0.54	0.64–2.29
Age	1.9	0.63	0.98–1.03
PsA	1.05	0.88	0.538–2.3
Time evolution	1.01	0.20	0.99–1.04
Weight	1.02	0.002	1.00–1.04
Baseline PASI*	0.47	0.04	0.230–0.96
Num. of biologicals			
1	2.04	0.11	0.85–4.9
2	3.32	0.01	1.33–8.25
≥3	8.58	0.00	2.69–27.41
Absolute PASI ≤3 at 6 months			
Sex	1.4	0.34	0.69–2.86
Age	0.99	0.98	0.97–1.02
PsA	0.84	0.72	0.33–2.31
Time evolution	1.01	0.40	0.98–1.04
Weight	7.83	0.01	1.72–35.54
Baseline PASI*	0.57	0.15	0.26–1.24
Num. of biologicals			
1	2.46	0.087	0.87–6.92
2	4.52	0.00	1.63–12.58
≥3	8.66	0.00	2.72–27.57
Absolute PASI ≤1 at 12 months			
Sex	0.85	0.63	0.44–1.64
Age	1.01	0.20	0.99–1.04
PsA	1.06	0.83	0.46–2.44
Time evolution	1.01	0.31	0.98–1.04
Weight	4.89	0.023	1.24–19.18
Baseline PASI*	0.61	0.19	0.29–1.28
Num. of biologicals			
1	1.47	0.39	0.60–3.63
2	2.75	0.04	1.06–7.08
≥3	21.12	0.00	4.39–101.62
Absolute PASI ≤3 at 12 months			
Sex	0.85	0.67	0.42–1.75
Age	1.00	0.89	0.97–1.03
PsA	0.99	0.98	0.40–2.42
Time evolution	1.00	0.63	0.97–1.03
Weight	7.2	0.01	1.62–32.57
Baseline PASI*	0.46	0.31	0.30–1.47
Num. of biologicals			
1	1.17	0.77	0.40–3.36
2	1.69	0.34	0.56–5.01
≥3	13.96	0.00	3.87–50.15

Note: Comparative group: Patients achieving indicated PASI *Baseline PASI (<10 vs. ≥10).
Abbreviations: CI, confidence interval; OR, odds ratio; PASI, psoriasis area and severity index; PsA, psoriatic arthritis.

Association study at 12 months after treatment

Similar to the observations at 6 months of treatment, weight of patients and history of biological treatment were associated with failure to achieve absolute PASI ≤1 or ≤3 (Table 2). No association was found between sex, age, psoriatic arthritis, history of cDMARDs, disease duration, or PASI class at baseline (<10 vs. ≥10) and response to secukinumab at 12 months.

Univariate analysis at 12 months of treatment showed, as did the analysis at 6 months, several SNPs associated ($p < 0.05$) with response to secukinumab and absolute PASI ≤3 and ≤1 (Table s4 and S5, respectively). Multivariable regression analysis showed the association of rs26528 (*IL27*) and rs12191877 (*HLACw6*) with absolute PASI ≤3 at 12 months independent of weight and history of biological therapy. The genotype TT for rs12191877 increased the risk to be classified as nonresponder, while the genotype CC for rs26528 was protective. This model had a sensitivity of 45.93%, specificity of 94.8% and an AUC of 0.85 (95% CI 0.76–0.91). Using absolute PASI ≤1 at 12 m, no SNP passed the cutoff value of FDR to construct a multivariable model (Table S5).

DISCUSSION

Since secukinumab was approved by FDA for plaque psoriasis in 2015, few studies have explored the usefulness of SNPs as biomarkers of response to treatment[10–13] In this study, we have identified different groups of SNPs whose combined analysis may be helpful to identify patients who will achieve absolute PASI ≤1 at 6 m, absolute PASI ≤3 at 6 m or absolute PASI ≤3 at 12 m in real-world clinical practice. The model for PASI ≤3 at 6 m showed the best capability to discriminate between responder and non-responder phenotypes. The genotypes AC or AA for rs1051738 (*PDE4A*) seems to be protective, while the genotypes TT for rs12191877 (*HLCw6*), AG for rs1801274 (*FCGR2*) and CT for rs2431697 (*miR-146a*) increase the risk of not achieving PASI ≤3 at 6 months. rs12191877 (*HLCw6*) was also a risk factor to not achieve PASI ≤3 at 12 months. This SNP which is in tight disequilibrium with HLA-Cw6 is associated with a better response to secukinumab using relative PASI75 to evaluate treatment efficacy.[13] Additional studies have also evaluated differences in secukinumab response between HLA-Cw6+ and HLA-Cw6- patients with negative results[11,17] However, Morelli et al found that, although rs12191877 is in tight linkage disequilibrium with HLA-Cw6, this variant was not detected in all HLA-Cw6+ patients[13] Thus, differences in allele frequency, sample size, efficacy parameters (relative PASI vs absolute PASI) or statistical analysis could be also associated with contradictory results; meta-analyses of these studies could give more reliable information. Our study shows that patient weight and the history of biological therapy are clearly risk factors, so the association with other factors is key to adjust the results for putative confounding factors. Univariate analysis showed that baseline PASI was only associated to achieve an absolute PASI ≤1 at 6 months. Those

TABLE 3 Multivariate logistic regression models.

Effectiveness	Variable	Gene	Model	Risk phenotype %Resp/%Nonresp	Odds ratio	p	[95% Conf. Interval]
Absolute PASI ≤3 at 6 months	rs1051738	*PDE4A*	A	AC/AA (33.3/5.1)	0.03	0.006	0.003–0.36
	rs12191877	*HLACw6*	R	TT (2.3/15.0)	29.80	0.012	2.09–423.9
	rs1801274	*FCGR2*	O	AG (45.3/70.0)	3.3	0.024	1.17–9.59
	rs2431697	*miR-146a*	O	CT (35.4/60.0)	6.1	0.002	1.95–19.1
	Weight				1.04	0.000	1.02–1.07
	Num. of biologicals						
	1				3.1	0.092	0.83–11.83
	2				6.9	0.009	1.63–29.86
	≥3				10.2	0.002	2.36–45.29
Absolute PASI ≤1 at 6 months	rs2227322	*CSF3*	R	GG (16.4/1.7)	0.10	0.018	0.096–0.64
	rs645544	*SLC9A8*	R	GG (22.7/5.0)	0.21	0.017	0.05–0.75
	Weight				1.02	0.007	1.01–1.04
	Num. of biologicals						
	1				2.40	0.079	0.90–6.41
	2				4.43	0.005	1.58–12.43
	≥3				9.47	0.001	2.58–34.74
Absolute PASI ≤3 at 12 months	rs26528	*IL27*	R	CC (21.5/2.4)	0.02	0.012	0.001–0.42
	rs12191877	*HLACw6*	R	TT (2.5/14.6)	27.38	0.005	2.75–254.0
	Weight				1.01	0.002	1.01–1.05
	Num. of biologicals						
	1				0.82	0.923	0.27–3.26
	2				1.96	0.324	0.55–6.23
	≥3				15.49	0.000	4.16–86.86

Note: Comparative group: Patients achieving indicated PASI (responders).

Abbreviations: A, additive; C, codominant; CI, confidence interval; D, dominant; Nonresp, non-responders to secukinumab. Inheritance model; Num. of biologicals, number of biologicals previously used; O, overdominant; OR, odds ratio; PASI, psoriasis area and severity index; R, recessive; Resp, responders to secukinumab.

patients with lower baseline PASI values showed a higher capability to achieve this effectiveness parameter. However, after correction by weight and history of biological therapy this variable was no associated to the response of treatment. Although the sensitivity of the final model for PASI ≤3 at 6 m is low, the model has a specificity higher than 90%.

Our study also shows that the presence of rs1051738 (*PDE4A*) with a log additive inheritance model is associated to achieving absolute PASI ≤3. Interestingly, this polymorphism has been described as a protein-altering variant.[18] Phosphodiesterase-4 (PDE4) is an enzyme that plays an important role in the pathogenesis of psoriasis. PDE4 degrades cyclic adenosine monophosphate (cAMP) to adenosine monophosphate (AMP), leading to the production of proinflammatory mediators. PDE-4 inhibitors work by blocking the degradation of cAMP, leading to a reduction in inflammation.[19,20]

The variant rs2431697 is an intergenic region between the pituitary-tumour transforming1 (*PTTG1*) and microRNA-146 (*miR-146a*) genes. This variant is associated with systemic lupus erythematosus susceptibility and has been associated with miR-146a expression levels.[21] Psoriasis patients carrying the C allele in this variant are less likely to respond to etanercept.[22] Similarly, we have identified a higher risk to fail with secukinumab in heterozygous patients (CT).

Here, we also identified an association between carrying the AG genotype of rs1801274 (*FCGR2A*) and higher probability of not responding to secukinumab. *FCGR2A* encodes for an immunoglobulin Fcγ receptor involved in phagocytosis and immune-complex clearance. Rheumatoid arthritis patients with this variant showed a better response to rituximab.[23] However, in psoriasis patients, rs1801274 was associated with a poor response to anti-TNF.[24]

Our data also indicate that homozygous for the alternative allele G of rs645544 (*SLC9A8*) and rs2227322 (*CSF3*) seems to have a better response to secukinumab at 6 months (absolute PASI ≤1). The SLC9A8 gene belongs to a sodium-hydrogen exchanger superfamily and is involved in mucosal protection. rs645544 (*SLC9A8*) has previously been associated with susceptibility to psoriasis,[25] and our group has described its association with achieving PASI75 at 3 months after adalimumab and infliximab treatment.[26] *CSF3* codes for Colony Stimulating Factor 3; this cytokine is produced by keratinocytes in response to IL17; and it controls production and differentiation of granulocyes.[27] SNP for *CSF3* gene (rs2227322) is 5' UTR variant and seems to be associated with granulocyte count[28]; to our knowledge, this polymorphism has not been previously described in psoriasis. We observed also that homozygous patients for the alternative allele C of

rs26528 (*IL27*) seem to have a higher capability to achieve an absolute PASI ≤3 after 12 months of treatment. rs26528 is associated with psoriasis and other immune-mediated diseases,[29] and T allele has been associated with a lower risk of premature coronary artery disease in Mexican population.[30]

It is important to remark that our data were analysed according to the inheritance model calculated for each SNP, only SNP for PDE4A had an additive effect. The inheritance model for the rest of SNPs was recessive or overdominant. Due to allele frequencies, with the number of patients in this study, more studies are necessary to confirm these data. On the other hand, multiple regression models were constructed including only those polymorphisms with a false discovery rate (FDR) value less than 0.15. While this approach may result in the exclusion of potentially important polymorphisms, it provides more confident results.

PASI is the most widely used score to evaluate disease severity. However, for low severity or residual lesions, it is unclear what is the best tool for the assessment. Recently, some data supported the role of Physician Global Assessment and body surface area (PGAxBSA) composite to evaluate the clinical response.[31] In a post hoc analysis, PGAxBSA composite score was compared with the modified (excluding head) PASI score in the assessment of disease severity and therapeutic response to a topical treatment. The authors concluded that correlation between PGAxBSA and modified PASI is higher with increasing psoriasis severity.[32] In our study, some patients had a low baseline PASI. Indeed, univariable analysis showed that PASI at baseline was associated with absolute PASI ≤1 and ≤3 at 6 months. Although this parameter was included as confounding factor in the final model, the missing PGAxBSA score is a limitation of our study.

In summary, in this study we have identified a series of polymorphisms associated with the response to secukinumab that could predict the potential response/nonresponse to this drug in patients with plaque psoriasis. Pharmacogenetic research in immune-mediated diseases such as psoriasis is increasing. However, the use of genetic markers to establish more personalized therapies has not yet reached clinical practice. One of the reasons is that the genetic profile differs between individuals from different racial and ethnic population. More studies are necessary to advance in this field.

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CONFLICT OF INTEREST STATEMENT

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The rest of the authors declare do not have conflicts of interest.

DATA AVAILABILITY STATEMENT
Data of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.