



Correlation of HLA-Cw6 Positivity with Clinical Characteristics and Treatment Efficacy in Korean Patients with Psoriasis

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Background: Psoriasis is a multifactorial, chronic immunological disease, in which a specific allele HLA-Cw6 is associated with various clinical manifestations. However, information regarding this genetic factor in Korean patients with psoriasis remains limited.

Objective: We aimed to explore the differences in clinical patterns and treatment responsiveness, depending on the expression of HLA-Cw6, in Korean patients with psoriasis.

Methods: We divided patients into two groups, namely HLA-Cw6-positive and HLA-Cw6-negative, based on the HLA-Cw6 allelic analysis using the single specific primer-polymerase chain reaction method. All clinical information regarding these patients was collected in a retrospective manner. Next, we evaluated the levels of serum Th17-related cytokines in 34 patients diagnosed with psoriasis using a multiplex immunoassay. Finally, we performed immunohistochemical staining of interleukin (IL)-22 and IL-31, as these cytokines showed the maximum differential expression between the HLA-Cw6 positive and negative groups.

Results: HLA-Cw6 positive and negative groups comprised of 13 and 21 patients, respectively. HLA-Cw6-positive group had more chance of having metabolic comorbidities (76.9% for HLA-Cw6-positive group; 28.6% for HLA-Cw6-negative group; $p=0.002$). Also, HLA-Cw6-positive group showed significantly higher treatment response (38.5% in positive group showed Psoriasis Area and Severity Index 90% improvement compared to 4.8% in the negative group; $p=0.012$). However, all Th17-related cytokines were not significantly different across the two groups. Furthermore, IL-22 and IL-31 immunohistochemical staining did not correlate with the serum cytokines levels.

Conclusion: HLA-Cw6 types can be associated with disease severity, comorbidities, and treatment responsiveness in Korean patients with psoriasis.

Keywords: Cytokine, HLA-C*06 antigen, Psoriasis

INTRODUCTION

Psoriasis is a multifactorial chronic immunological disease characterized by erythematous patches or plaques with silver-white scales. Environmental stimuli, such as trauma and infection, are believed to cause psoriasis in patients with genetic factors. Psoriasis can involve organs other than the skin, such as joints, and has recently been reported to be related to metabolic syndrome or cardiovascular diseases^{1,2}. Therefore, it is now recognized as a whole-body disease rather than a

simple skin disease.

Psoriasis is usually divided into early-onset, which occurs before the age of 40 years, and late-onset, which occurs after the age of 40 years³. It is thought to be a polygenic multifactorial disease that is linked to various genes, and HLA-Cw6 has been reported to be associated with early-onset psoriasis³. A study reported that HLA-Cw6 was expressed in 85.3% of early-onset patients and 14.7% of late-onset patients⁴. Some scholars have classified early-onset, frequent relapse, higher severity, and family history of psoriasis with HLA-Cw6 ex-



pression as type 1 psoriasis and late-onset, relatively good prognosis, and no family history with HLA Cw6 expression as type 2 psoriasis⁵.

Also, HLA-Cw6 positivity is known to be related to stress, obesity⁶, and guttate psoriasis⁷. In addition, patients carrying the allele are more likely to have arm, leg, and trunk involvement, along with the Koebner phenomenon⁸. Several studies involving Caucasian and Chinese patients have shown HLA-Cw6-positive patients to be more responsive to methotrexate⁹ and ustekinumab^{6,10-12}; HLA-Cw6 positivity also tends to be less frequent in high-need patients, who fail conventional therapy¹¹. However, not much had been reported previously about the status of HLA-Cw6 in Korean patients with psoriasis. Only Nam et al.¹³ reported the presence of Cw*0602 is related to the early onset age and family history.

Thus, we aimed to explore the differences in clinical patterns and treatment responsiveness depending on the expression of HLA-Cw6 in Korean patients with psoriasis.

MATERIALS AND METHODS

We evaluated the venous blood samples (5~10 ml) and lesion tissues collected from 34 patients who were diagnosed with psoriasis at their first visit to the Department of Dermatology, Ajou University Hospital, between May 2016 and March 2019. The specimens were stored at the Human Genome Resource Center (Ajou University Hospital Biobank). The patients aged more than 20 years at the time of their first visit were enrolled for the study, and those with any systemic treatment history, such as with methotrexate, cyclosporine, biologics, and narrow-band ultraviolet B (NBUBV), 6 months before the initial visit, were excluded. Clinical information of all patients, such as sex, age, disease onset age, disease duration, history of smoking and drinking, body mass index (BMI), family history of psoriasis, metabolic comorbidities, showing pruritus, existence of psoriatic arthritis and nail involvement, and Psoriasis Area and Severity Index (PASI) scores, and treatment history of psoriasis during follow-up period were collected in a retrospective manner by reviewing the electronic medical records and photos to confirm the PASI scores.

Based on their HLA-Cw6 types, the patients were divided into HLA-Cw6 positive and negative groups. HLA-Cw6 allelic analysis was conducted by DNA samples to define

such genetic type using a single specific primer polymerase chain reaction (SSPPCR) method. Allele amplification was performed using the allele-specific (297-bp) primers, forward: 5'-TACTACAACCAGAGCGAGGAGGTCG-3' and reverse: 5'-CAGCCATACATCCA-3'; meanwhile the positive control had 618 bp forward: 5'-TTGAGGATTCTC-CACTCCCCTGAGCTG-3' and reverse: 5'-TGCCTG-GCGCTTGTACTT-3' using AccuPower[®] Multiplex PCR PreMix (96 T, 20 µl; Bioneer, Daejeon, Korea). Expression of the 297 bp showed HLA-Cw6 allele specificity without differentiating between homozygote and heterozygote status. The PCR included the following steps: 10 minutes at 95°C, followed by 35 cycles of 30 seconds at 95°C, 45 seconds at 62.9°C, and 37 seconds at 72°C. A final extension step was performed for 5 minutes at 72°C.

Then, we investigated the association between the HLA-Cw6 genotype and the clinical characteristics, such as onset age, disease duration, BMI, severity of psoriasis, metabolic comorbidities, accompanying pruritus, psoriatic arthritis, nail involvement, and treatment responsiveness using PASI score improvement (initial PASI score vs. PASI score after 6 months). PASI 50 meant 50% reduction, PASI 75 implied 75% reduction, and PASI 90 indicated 90% decrease of PASI scores compared to each initial PASI score after 24 weeks. Descriptive analyses, including the chi-squared test or Fisher's exact test for categorical data and the two-sample t-test or Mann-Whitney U test for numerical data, were performed to evaluate the statistical significance of demographic data.

Also, the serum cytokine levels were measured by a multiplex immunoassay (Milliplex MAP; Millipore Corporation, Burlington, MA, USA). We particularly evaluated the initial levels of Th17-related cytokines (interleukin [IL]-17A, IL-17F, IL-21, IL-22, IL-23, tumor necrosis factor [TNF]-α, TNF-β, IL-6, IL-1β, IL-12, IL-27, interferon [IFN]-γ, IL-4, IL-5, IL-13, IL-25, IL-10, IL-28A, macrophage inflammatory protein-3 alpha [MIP3A], granulocyte monocyte-colony stimulating factor [GM-CSF], IL-15, IL-9, IL-33, IL-2, and IL-31). Differences in cytokine levels between HLA-Cw6 positive and negative groups were analyzed using the Mann-Whitney U-test to compare the median value of the data, and the range was also presented. The result was considered statistically significant when the two-tailed *p*-value was <0.05. Statistical analyses were performed using SPSS Statistics 21.0 for Windows (IBM Corp., Armonk, NY, USA). Next, we performed immunohis-

tochemical staining for IL-22 and IL-31, the two cytokines that showed maximum differential expression between the two groups, to evaluate whether a correlation existed between serum cytokine levels and tissue cytokine expressions. Paraffin-embedded tissue sections of 3- μ m thickness were processed for immunohistochemistry. The following primary antibodies were used: IL-22 (1:500, ab18499; Abcam, Cambridge, MA, USA) and IL-31 (1:100, NBP2-80396; Novus, Centennial, CO, USA). Then, the degree of immunohistochemical staining was evaluated using ordinal classification (0, negative; 1, weak; 2, moderate; 3, strong).

This study protocol was approved by the Ajou Institutional Review Board (IRB No.: AJIRB-BMR-MDB-15-341) prior to study commencement. According to Helsinki ethical principles, written informed consents were obtained from all subjects before their enrollment in the study.

RESULTS

The patients underwent HLA-Cw6 genotype analysis were divided into two groups; 13 patients in HLA-Cw6-positive group and 21 patients in HLA-Cw6-negative group. Demographic and clinical characteristics of the study population are presented in Table 1. The mean age at initial visit was 43.69 years (standard deviation, 11.28 years) in the HLA-Cw6-positive group, and 47.43 \pm 13.09 years in HLA-Cw6-negative group. The onset age was less than 40 years in 84.6% of the patients in the HLA-Cw6-positive group and in 52.4% of the patients in the HLA-Cw6-negative group. Approximately 53.8% of the patients in the HLA-Cw6-positive group and 28.6% in the HLA-Cw6-negative group had high BMI (>25 kg/m²); 23.1% of the HLA-Cw6-positive group and 14.3% of the HLA-Cw6-negative group had a family history of psoriasis. Approximately 53.8% of HLA-Cw6-positive patients had accompanying pruritus while 23.8% of the HLA-Cw6-negative group had pruritus. Less than half had accompanying psoriatic arthritis in both groups (30.8% in the positive group and 23.8% in the negative group) along with nail involvement (30.8% of the positive group and 42.9% of the negative group). Likewise, those two groups showed no statistically significant discrepancy, except for metabolic comorbidities. The HLA-Cw6-positive group had more chance of having metabolic comorbidities, such as hypertension, diabetes, dyslipidemia, and cardiovascular disease (76.9% for the positive group and

Table 1. Demographic and clinical characteristics of the study population

Characteristic	HLA-Cw6 positive (n=13)	HLA-Cw6 negative (n=21)	p-value
Sex			0.152
Male	10 (76.9)	11 (52.4)	
Female	3 (23.1)	10 (47.6)	
Age (yr)	43.69 \pm 11.28	47.43 \pm 13.09	
Onset age			0.056
Early (<40 yr)	11 (84.6)	11 (52.4)	
Late (\geq 40 yr)	2 (15.4)	10 (47.6)	
Duration			0.643
Short (<10 yr)	6 (46.2)	8 (38.1)	
Prolonged (\geq 10 yr)	7 (53.8)	13 (61.9)	
Smoking			0.456
Non-smoker	9 (69.2)	11 (52.4)	
Smoker or ex-smoker	4 (30.8)	10 (47.6)	
Alcohol			0.721
Non-drinker	5 (38.5)	11 (52.4)	
Drinker or ex-drinker	8 (61.5)	10 (47.6)	
BMI			0.094
<18.5 kg/m ²	0 (0.0)	2 (9.5)	
18.5~25 kg/m ²	6 (46.2)	13 (61.9)	
>25 kg/m ²	7 (53.8)	6 (28.6)	
Family history			0.513
Yes	3 (23.1)	3 (14.3)	
No	10 (76.9)	18 (85.7)	
Initial PASI			0.724
<10	6 (46.2)	11 (55.4)	
\geq 10	7 (53.8)	10 (47.6)	
Initial BSA			0.891
<10%	4 (30.8)	6 (28.6)	
\geq 10%	9 (69.2)	15 (71.4)	
Metabolic comorbidities			0.002
Yes	10 (76.9)	6 (28.6)	
No	3 (23.1)	15 (71.4)	
Pruritus			0.089
Yes	7 (53.8)	5 (23.8)	
No	6 (46.2)	16 (76.2)	
Psoriatic arthritis			0.655
Yes	4 (30.8)	5 (23.8)	
No	9 (69.2)	16 (76.2)	

28.6% for the negative group).

In Table 2, the frequency of metabolic comorbidities is shown in both groups; 23.1% of the HLA-Cw6-positive group and 23.8% of the HLA-Cw6-negative group had hypertension, 30.8% of the HLA-Cw6-positive patients and 9.5% of the HLA-Cw6-negative patients had diabetes mellitus and dyslipidemia, and 7.7% of the HLA-Cw6-positive patients and 9.5% of the HLA-Cw6-negative patients had accompanying cardiovascular diseases.

The treatment responsiveness to the conventional systemic therapy such as methotrexate, cyclosporine and NBUVB of both groups are listed in Table 3 and shown in Fig. 1. All the patients received conventional therapy at least a month, however the dosage and the duration varied according to their severity. The HLA-Cw6-positive group showed a significantly higher PASI index (90% improvement over negative group; $p=0.012$).

The serum Th17-related cytokine levels in patients with psoriasis were assessed with respect to each HLA-Cw6 type shown in Table 4 and in Fig. 2. In general, HLA-Cw6-positive

group showed tendency of higher levels of cytokines as seen in Fig. 2. IL-13 and IL-2 levels were found to be higher in the HLA-Cw6-negative group than in the HLA-Cw6-positive group; the levels of the other cytokines, such as IL-17F, MIP3A, IL-15, IL-22, IL-1 β , IL-33, IL-4, IL-23, IL-6, IL-25, IL-27, IL-31, TNF- α , TNF- β , and IL-28A were far higher in the HLA-Cw6-positive group. However, the levels were not significantly different between the two groups.

Even though there were no significantly different levels of serum cytokines, IL-22 and IL-31 showed relatively broad differences between HLA-Cw6 positive and negative groups. However, in the tissue IL-22 and IL-31 immunohistochemical staining conducted accordingly showed no correlation with the serum cytokine levels (relative expression level of IL-22 in dermis, 1.21 for positive group and 1.00 for negative group; $p=0.756$; relative expression level of IL-31 in dermis, 0.44 for

Table 1. Continued

Characteristic	HLA-Cw6 positive (n=13)	HLA-Cw6 negative (n=21)	p-value
Nail involvement			0.481
Yes	4 (30.8)	9 (42.9)	
No	9 (69.2)	12 (57.1)	
Treatment modalities			
MTX	11 (84.6)	14 (66.7)	0.628
CsA	4 (30.8)	6 (28.6)	0.892
NBUVB	5 (38.5)	7 (33.3)	0.523

Values are presented as number (%) or mean \pm standard deviation. BMI: body index mass, PASI: Psoriatic Area Severity Index, BSA: body surface area, MTX: methotrexate, CsA: cyclosporine, NBUVB: narrow-band ultraviolet B.

Table 2. Metabolic comorbidities

Comorbidity	HLA-Cw6 positive (n=13)	HLA-Cw6 negative (n=21)	p-value
Hypertension	3 (23.1)	5 (23.8)	0.962
Diabetes mellitus	4 (30.8)	2 (9.5)	0.121
Dyslipidemia	4 (30.8)	2 (9.5)	0.121
Cardiovascular disease	1 (7.7)	2 (9.5)	0.860

Values are presented as number (%).

Table 3. Assessment of PASI score response after 24 weeks

PASI improvement	HLA-Cw6 positive (n=13)	HLA-Cw6 negative (n=21)	p-value
After 24 wk			
PASI 50% improvement	8 (61.5)	11 (52.4)	0.601
PASI 75% improvement	7 (53.8)	5 (23.8)	0.075
PASI 90% improvement	5 (38.5)	1 (4.8)	0.012

Values are presented as number (%). PASI: Psoriasis Area and Severity Index.

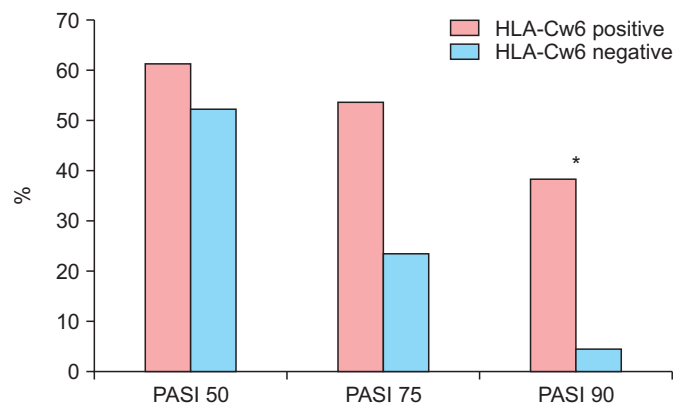


Fig. 1. PASI response after 24 weeks of treatment based on HLA-Cw6 type. After 24 weeks of treatment with methotrexate, cyclosporine, or narrow-band ultraviolet B, the probability of achieving PASI 50, 75, and 90 was high in the HLA-Cw6-positive group. Among them, the proportion of patients achieving PASI 90 differed statistically. PASI: Psoriasis Area and Severity Index. *Statistical significance ($p<0.05$).

Table 4. The serum cytokine levels in patients with psoriasis according to HLA-Cw6 types

Serum cytokine	HLA-Cw6 type		p-value
	Positive (n=13)	Negative (n=21)	
IL-17F	4.74 (0.10~8.50)	0.84 (0.01~31.32)	0.246
GM-CSF	34.32 (10.59~143.66)	30.78 (2.76~151.11)	0.727
IFN- γ	5.53 (2.97~13.04)	5.01 (2.40~20.78)	0.807
IL-10	0.27 (0.01~3.34)	0.17 (0.01~27.03)	0.972
MIP3A	25.33 (0.55~73.20)	19.96 (0.55~132.82)	0.576
IL-12P70	8.53 (1.74~34.30)	7.09 (1.23~43.53)	0.701
IL-13	261.19 (16.39~677.43)	346.13 (61.19~805.60)	0.506
IL-15	4.03 (0.66~14.76)	2.31 (0.50~27.62)	0.292
IL-17A	4.57 (2.82~8.80)	4.15 (1.60~25.98)	0.972
IL-22	31.06 (0.07~696.81)	4.69 (0.00~828.65)	0.050
IL-9	0.58 (0.10~120.06)	0.48 (0.04~120.06)	0.889
IL-1 β	3.58 (1.66~5.61)	2.77 (0.68~9.88)	0.552
IL-33	3.67 (0.03~74.81)	0.39 (0.00~94.94)	0.309
IL-2	6.86 (4.17~19.42)	7.37 (1.85~30.22)	0.506
IL-21	26.45 (0.10~81.58)	23.23 (0.07~137.20)	1.000
IL-4	4.01 (0.20~399.17)	2.12 (0.06~701.05)	0.441
IL-23	0.03 (0.00~3799.00)	0.00 (0.00~7436.00)	0.344
IL-5	7.26 (1.75~20.33)	5.97 (1.61~37.65)	0.944
IL-6	0.00 (0.00~97.02)	0.00 (0.00~170.39)	0.675
IL-25	45.89 (13.97~177.42)	28.69 (7.89~194.13)	0.309
IL-27	895.51 (249.49~1573.00)	633.22 (59.41~1791.00)	0.193
IL-31	12.43 (2.12~166.60)	5.76 (0.88~162.69)	0.096
TNF- α	37.40 (10.20~61.56)	25.33 (7.39~68.60)	0.148
TNF- β	0.10 (0.01~246.35)	0.01 (0.00~712.06)	0.181
IL-28A	0.55 (0.00~1983.00)	0.00 (0.00~4053.00)	0.529

Values are presented as median value (range). IL: interleukin, GM-CSF: granulocyte monocyte-colony stimulating factor, IFN: interferon, MIP3A: macrophage inflammatory protein-3 alpha, TNF: tumor necrosis factor.

positive group and 0.27 for negative group; $p=0.877$).

DISCUSSION

Overall, this study was able to achieve results similar to those reported by previous studies³. HLA-Cw6-positivity was shown to be associated with early-onset age, more chance of having metabolic diseases, and significantly higher treatment responses. Especially in this study, higher PASI 50, 75, and 90 were achieved in the HLA-Cw6-positive group after conventional systemic therapy with methotrexate, cyclosporine and NBUB irradiation; the treatment response was confirmed by evaluating PASI 24 weeks after treatment initiation. This is in

line with the better effect of HLA-Cw6-positive group in the methotrexate-treated patients in the other studies^{9,11,14}.

In addition to affecting the skin, psoriasis is well known to affect joints. Recently, it has been confirmed that more severe psoriasis is related with higher risk of developing metabolic and cardiovascular diseases, such as myocardial infarction, atherosclerosis, pulmonary thrombosis, stroke, hypertension, hyperlipidemia, obesity, and diabetes¹. Both obesity and psoriasis indicate an increase in C-reactive protein, IL-6, TNF- α , and leptin levels. This means that the two diseases are common systemic inflammatory diseases and this might explain the link between metabolic syndrome and psoriasis¹⁵. The relevance of psoriasis and atherosclerosis can also be explained

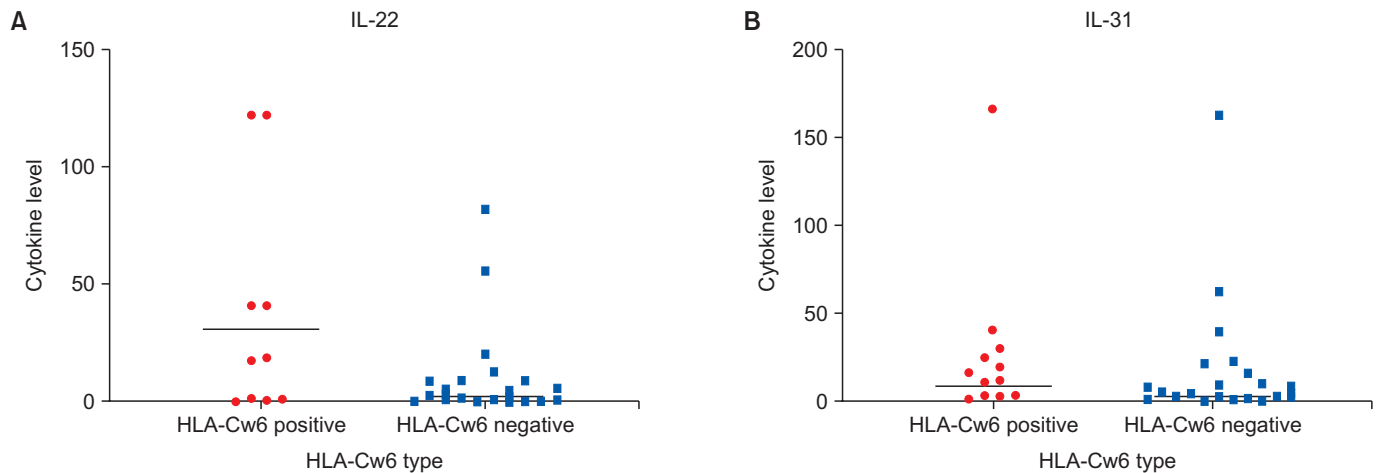


Fig. 2. The serum cytokine levels of interleukin (IL)-22 (A) and IL-31 (B) in patients with psoriasis according to HLA-Cw6 types. IL-22 and IL-31 showed the greatest differences between HLA-Cw6 positive and negative group according to Table 4. (A) The median value of IL-22 for HLA-Cw6-positive group was 31.06 (range, 0.07~696.81) and for HLA-Cw6-negative group was 4.69 (range, 0.00~828.65) respectively. (B) The median value of IL-31 for HLA-Cw6-positive group was 12.43 (range, 2.12~166.60) and for HLA-Cw6-negative group was 5.76 (range, 0.88~162.69). The black lines indicate median values and each dots represent each individuals.

by chronic inflammatory reactions of skin and vascular tissues due to functional degradation of Treg cells and excessive activation of Th1 and Th17 cells¹⁶. Other inflammatory diseases accompanying psoriasis include ulcerative colitis and Crohn's disease, which are inflammatory bowel diseases; however, they have not been identified in this study group¹⁷.

In the current study, there was no initial level of serum cytokine that showed a statistically significant difference between the groups divided based on HLA-Cw6 positivity. However, IL-22 and IL-31 showed relatively wide differences between HLA-Cw6 positive and negative group. IL-22 is a cytokine that is highly correlated with severity of the disease as it increases not only in psoriatic skin lesions but also in plasma samples of the patients¹⁸. TNF blockers are associated with an early reduction in the expression of IL-22 and its target molecules, such as IL-20 and antimicrobial peptide β -defensin 2 (BD2), in psoriatic lesions^{19,20}. A previous study had reported a significant decrease in the IL-22 level in the group with the higher therapeutic response and suggested IL-22 as a responsive marker during treatment²¹. In this study, we could not confirm the change in the IL-22 level, since the serum level after treatment was not measured; however, we could predict the possibility of a significant drop after treatment, since the initial level was high in the HLA-Cw6-positive group. We cannot still rule out the possibility of the initial high-level of IL-22 across the HLA-Cw6-positive patients being due to the

higher PASI averages in the positive group, although they were not statistically significant. Based on the results of this study, we recommended that further studies should be performed to evaluate the association of HLA-Cw6 positivity with IL-22 expression. Moreover, targeting the IL-22-IL-22R system would be a more specific therapeutic intervention for HLA-Cw6-positive patients, since it is not anticipated to induce major side effects, especially since immune cells are not responsive to IL-22¹⁹.

Besides IL-22, another cytokine that showed a wide difference was IL-31. IL-31 is known primarily to be associated with an itching sensation in inflammatory skin disorders such as atopic dermatitis and psoriasis. Recent investigations have reported serum IL-31 levels to be significantly elevated in psoriasis and chronic itch associated with psoriatic skin, owing to increased transcription of IL-31²²⁻²⁴. Narbutt et al.²³ further showed IL-31 serum levels to be significantly reduced after narrowband UVB phototherapy, coinciding with a substantial reduction in itching sensation in these patients. In this study, the *p*-value was 0.096, which was not statistically significant, although the HLA-Cw6-positive group indicated an IL-31 value higher than that in the HLA-Cw6-negative group. Following the same trend as the serum IL-31 level, patients who reported itching sensation at the time of treatment also showed higher in the HLA-Cw6-positive group (53.8%) than in the HLA-Cw6-negative group (23.8%). Thus, we were

not able to confirm the statistical significance of HLA-Cw6 positivity, although it was associated with itching sensation. Therefore, screening and management of itching would be important while treating HLA-Cw6-positive patients.

One of the limitations of this study is the small number of subjects. The rate of HLA-Cw6 positivity was low 5.66% in Koreans, which made it difficult to recruit positive patients²⁵. Disadvantage of this small number is that differences in drug responsiveness (methotrexate vs. cyclosporine) could not be identified separately through subgroup analysis. Moreover, it would have been better to reacquire serum 24 weeks after treatment to examine the change in cytokine levels, including the levels of IL-22 and IL-31. Moreover, immunohistochemical staining results may not have been accurate as some of the tissue samples were obtained several years ago. We hope to understand the relationship between these cytokines and HLA-Cw6, in depth, in future studies.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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