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HLA-Cw6 homozygosity in plaque psoriasis is associated with streptococcal throat infections and pronounced improvement after tonsillectomy: A prospective case series

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Abstract

Background—Carriage of the HLA-Cw*0602 allele is associated with a particular set of clinical features and treatment responses in psoriasis. Tonsillectomy can improve psoriasis.

Objectives—To evaluate whether HLA-Cw*0602 predicts a favourable outcome after tonsillectomy of psoriasis patients.

Methods—This prospective case series followed 28 tonsillectomized patients with plaque psoriasis for 24 months. The Psoriasis Area and Severity Index (PASI), the Psoriasis Disability Index (PDI) and the Psoriasis Life Stress Inventory (PLSI) were used for assessment. Tonsils were swabbed for bacteria and patients genotyped for HLA-Cw*0602.

Results—After tonsillectomy, HLA-Cw*0602 homozygotes showed significantly more improvement, compared with heterozygous and HLA-Cw*0602 negative patients. Thus, PASI was reduced by 82% in the homozygous patients compared with 42% and 31% respectively ($P < .001$), PDI improved by 87% compared with 38% and 41% respectively ($P < .001$) and PLSI was 82% reduced compared with 60% and 54% respectively ($P < .001$). The homozygotes had more often

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None of the data have been previously reported or are under consideration for publication elsewhere.

psoriasis onset associated with a throat infection ($P = .007$) and an increased frequency of streptococcal throat infections per lifetime ($P = .038$).

Limitations—Few patients were included and some data was retrospective.

Conclusions—Homozygous HLA-Cw*0602 carriage in plaque psoriasis may predict a favourable outcome after tonsillectomy.

Keywords

Chronic plaque psoriasis; HLA-Cw*0602; sore throat; streptococcal throat infection; tonsillectomy; Psoriasis Disability Index; Psoriasis Life Stress Inventory

INTRODUCTION

Psoriasis is a common T lymphocyte mediated skin disease caused by a combination of genetic and environmental factors[1] with over 60 genetic susceptibility loci now reported to be associated with psoriasis.[2,3] HLA-Cw*0602 is the major psoriasis susceptibility allele[4] and over 60% of psoriasis patients carry one or two copies of HLA-Cw*0602, while the frequency in the general population is only 10-15%.[4] Although various environmental factors have been reported to influence psoriasis, throat infections with β-haemolytic streptococci have most convincingly been associated with both initiation and exacerbation of psoriasis.[5-7] It has been proposed that T cells, primed by streptococcal antigens in the palatine tonsils, may migrate to the skin where they may react to antigens that share sequence homology with streptococcal proteins.[8-10] A number of studies have shown partial or complete remission of psoriasis after tonsillectomy,[11-13] and we have recently conducted a prospective, randomized, and controlled study indicating that tonsillectomy can lead to a marked clinical improvement of chronic plaque psoriasis.[14]

Carriage of the HLA-Cw*0602 allele has been associated with a particular set of clinical features in psoriasis.[15] HLA-Cw*0602 positive patients usually have a younger onset age,[16,17] a more severe psoriasis course,[18] guttate or eruptive plaque psoriasis phenotypes,[15,19] more frequent streptococcal throat carriage or infections,[18,20] and streptococcal-associated psoriasis exacerbation.[18] We therefore wanted to evaluate whether psoriasis patients carrying the HLA-Cw*0602 allele, with a history of sore throat-induced onset or exacerbation of psoriasis, responded more favourably to tonsillectomy than HLA-Cw*0602 negative patients.

MATERIALS AND METHODS

Study design

This was a prospective case series study with a 24-month follow-up period. The research was approved by the National Bioethics Committee of Iceland (VSNb2006090015/ 03-15), the Data Protection Authority of Iceland and conducted in accordance with the 1964 Declaration of Helsinki and its later amendments. Data were collected within the departments of Otolaryngology-Head and Neck Surgery, Dermatology and Immunology at

Landspitali-The National University Hospital of Iceland, Reykjavik, Iceland from November 2007 to January 2011.

Subjects and follow-up

Twenty-eight patients with chronic plaque psoriasis were included in the study and a signed informed consent was obtained from each participant before initiation of participation. Fifteen patients participated in our previous study,[14] and an additional 13 patients who fulfilled the inclusions criteria were recruited. Inclusion criteria included: a) Age at least 18 years; b) Dermatologist-diagnosed moderate-to-severe plaque psoriasis; c) History of psoriasis exacerbation in association with sore throats and/or streptococcal throat infections, as recalled by the patients; d) No other health issues that could pose a risk for patients undergoing tonsillectomy and anaesthesia, including heart and lung diseases, alcohol and substance abuse and bleeding disorders; e) Consent to have tonsillectomy.

Demographic data and psoriasis features were collected at study entry. Included patients were followed for 24 month, starting 2 months after tonsillectomy. Psoriasis severity was assessed by the Psoriasis Area and Severity Index (PASI score)[21] at study entry and at 2, 6, 12, 18 and 24 months. The participants were evaluated by the same observer throughout the study period and the clinical evaluation was carried out before patients were typed for HLA-Cw*0602 carriage.

The Psoriasis Disability Index (PDI)[22] was used to assess health-related quality of life (HRQoL). The PDI is a validated psoriasis-specific questionnaire that includes 15 questions concerning functional disability due to psoriasis in the preceding month. The score is rated on a four-point scale and the total score, which can range from 0 to 45, is calculated by summing the scores to each question. For assessment of stress related to having to cope with psoriasis on a daily bases the Psoriasis Life Stress Inventory (PLSI)[23] was used. The PLSI is a 15-item scale that rates the level of stress experienced over the previous month. The PLSI score is calculated from a 4-point scale, ranging from 0 to 45, by summation. The higher the PDI and PLSI score, the greater impairment in quality of life. Both these questionnaires were completed by the patients at study entry and at 12 and 24 months and both have previously been translated into Icelandic using the translation-back-translation procedure and validated by the Nordic Quality of Life study.[24]

HLA-Cw*0602 genotyping

All participating patients were genotyped for HLA-Cw*0602 after the 24-month clinical follow-up period. DNA was prepared from peripheral blood mononuclear cells and HLA-Cw*0602 was determined by PCR amplification by genotyping 7 SNPs in exons 2 and 3 of the *HLA-C* gene, as previously described.[4]

Bacterial culture and typing

After removal of the tonsils, bacterial throat swabs were taken, both from the tonsil surface as from deep within the tonsil crypts. Typing of the bacteria was performed by culture on sheep blood agar. Subspecies of *Streptococcus* were identified with a Streptex kit (Thermo Fisher Scientific, Remel, Lenexa, KS, USA).

Statistical analysis

Data were tested for normality using the Kolmogorov-Smirnov test. Categorical variables were compared with Fisher's exact test and statistical significance was defined by $P \leq .05$ on two-tailed tests. The effects of HLA-Cw*0602 genotype and improvement after tonsillectomy (determined by change in PASI, PDI and PLSI over 24 months) were modelled using linear regression and analysed on an intention-to-treat basis with missing values being replace with the last nonmissing assessment (last observation carried forward). Three different models were tested, dominant (either one or two HLA-Cw*0602 alleles effects phenotype), recessive (two HLA-Cw*0602 alleles required to effect phenotype) and additive (phenotype changes sequentially with each HLA-Cw*0602 allele), where the recessive model was used for calculations. The linear model assumptions were checked by visual analysis of residual plot. Data analyses were performed using R software, version 2.10 (The R foundation, Austria).

RESULTS

The study cohort consisted of 28 patients (6 men and 22 women) with chronic plaque psoriasis and a history of psoriasis exacerbation associated with sore throat and/or streptococcal throat infection. (Table I). All patients reported an early onset psoriasis (type I psoriasis)[16] and the onset was attributed to streptococcal pharyngitis in 11 (39%) patients. There were no differences between the groups at baseline, although the homozygous HLA-Cw*0602 carriers had a slightly higher baseline PASI, PDI and PLSI scores compared with the heterozygous and HLA-Cw*0602 negative groups. Four (14%) patients were HLA-Cw*0602 homozygotes, 17 (61%) heterozygotes, and 7 (25%) were HLA-Cw*0602 negative. Twenty-five patients finished the 24-month follow-up. Two patients in the heterozygous group discontinued the study after 12 and 18 months of follow-up and 1 patient in the HLA-Cw*0602 negative group discontinued after 18 months.

HLA-Cw*0602 homozygosity is associated with streptococcal throat infections

The HLA-Cw*0602 homozygous patients reported significantly more often that their psoriasis onset had been triggered by a throat infection, compared with HLA-Cw*0602 heterozygotes and non-carriers (100% vs. 29%, $P = .007$) (Table II). In concordance with this, cultures from tonsil swabs, which had been taken after removal of the tonsils, revealed that 75% of the homozygous patients were carriers of group A, C, G streptococci or *Streptococcus anginosus* at the time of the surgery, compared with 65% of the heterozygous patients and 43% of the HLA-Cw*0602 negative patients. Furthermore, HLA-Cw*0602 homozygotes reported a significantly higher frequency of streptococcal throat infections per lifetime than the heterozygotes and non-carriers (3.5 times vs 1.4 and 1.1 times respectively, $P = .038$). The homozygous patients were all smokers, and they all had a family history of psoriasis (Table II). There were no significant differences between homozygous, heterozygous and HLA Cw*0602 negative patients concerning age at psoriasis onset, body mass index, psoriasis nail changes, arthritis involvement, and stress and alcohol-associated psoriasis exacerbation (data not shown).

HLA-Cw*0602 homozygosity is associated with pronounced improvement after tonsillectomy

There was an association between the degree of clinical improvement after tonsillectomy and carriage of HLA-Cw*0602 (Figure 1). Thus, patients who were homozygous HLA-Cw*0602 carriers showed significantly more clinical improvement than the heterozygous and the HLA-Cw*0602 negative patients at all time points (Table III). The homozygous patients had a mean 82% PASI reduction, during the 24-month follow-up, compared with 42% for the heterozygous, and 31% for the HLA-Cw*0602 negatives ($P < .001$ for overall change by linear regression). All four homozygotes achieved PASI 75 by month 6 and PASI 90 by month 12. This was accompanied by a markedly improved health-related quality of life **(**PDI) and psoriasis-related stress (PLSI). Again, the homozygous patients fared best, reporting a mean PDI and PLSI reduction of 87% and 82% compared to 38% and 60% for the heterozygous patients, and 41% and 54% for the HLA-Cw*0602 negative patients ($P < .001$ for overall change by linear regression).

The use of psoriasis treatments was monitored throughout the 24-month follow-up period (Table IV). There was a significant decrease in the use of psoriasis treatments after tonsillectomy. Before tonsillectomy 75% (n = 21) of patients used some form of treatment for psoriasis (topicals, phototherapy or systemic therapy), but after tonsillectomy only 32% (n = 9) of patients required treatment ($P = .003$).

DISCUSSION

HLA-Cw*0602 is the major psoriasis susceptibility allele, located in the PSORS1 locus.[4] Given that HLA-Cw*0602 carriage has been associated with a higher frequency of streptococcal throat carriage/infections[18,20] and streptococcal-associated psoriasis exacerbation,[18] we typed our study cohort for HLA-Cw*0602 and found an association between the magnitude of improvement after tonsillectomy and HLA-Cw*0602 carriage status. Patients who were homozygotes showed significantly more improvement than the HLA-Cw*0602 heterozygous and non-carriers. Thus, all HLA-Cw*0602 homozygotes reached PASI 75 by month 6 and approached PASI 90 by month 12. These improvements are comparable to results seen by recently introduced biologics.[25] Their health-related quality of life also improved markedly (almost 90% reduction in PDI score) after the surgery and they experienced 82% less stress related to having psoriasis.

The carriage of HLA-Cw*0602 has been associated with a particular set of clinical features in psoriasis patients,[15] such as guttate or eruptive plaque psoriasis phenotypes,[15,19] and more frequent streptococcal throat carriage or infections.[18,20] Furthermore, an increasing body of evidence has emerged suggesting that different psoriasis genotypes might predict different treatment responses.[26] Thus, two recent studies showed that carriage of HLA-Cw*0602 predicts a better response to the interleukin-12/23 inhibitor ustekinumab[27,28] and etanercept has also been shown to be more effective in early-onset psoriasis compared to late-onset psoriasis.[29]

The mechanism whereby HLA-Cw*0602 predisposes to psoriasis remains to be elucidated. However, our data and those of others[9,30-33] are consistent with the hypothesis that CD8+ T

lymphocytes infiltrating lesional epidermis recognize autoantigens presented in the context of HLA-Cw6 expressed on the surface of epidermal cells.[10] Thus HLA-Cw*0602 may play a direct role in the pathogenesis of psoriasis.[34] Our data and those of an earlier study[20] indicate that HLA-Cw*0602 carriage may impact the bacterial colonization of the tonsils. The tonsils are a major site for streptococcal carriage, and streptococcal throat infections are associated with onset and exacerbation of psoriasis[6,7,10,11] Throat swabs taken from both the surface and from deep within tonsil crypts revealed a high level of streptococcal throat carriage in our patients. Combined carrier frequency of Lancefield groups A, C or G *Streptococcus* or *Streptococcus anginosus* was almost 70% in homozygous and heterozygous HLA-Cw*0602 patients compared with 43% of non-carriers. *S. anginosus* can cause pharyngitis, is sometimes β-haemolytic and carries a typeable Lancefield group antigen, A, C, G or F.[35] The genetic background of psoriasis is thus associated with both asymptomatic and symptomatic streptococcal throat infections compared to age and sex matched controls,[7,36] and streptococcal tonsillitis has long been associated with flares of guttate psoriasis,[5,37,38] as well as exacerbation of plaque psoriasis.[6,7,39] It should be noted that the participants included in the current study all had a history of psoriasis exacerbation in association with sore throat, which applies to approximately 40 percent of patients with plaque psoriasis in Iceland.[40]

Smoking is an important environmental risk factor for many chronic diseases, including several autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus.[41,42] Although there is a strong link between palmoplantar pustulosis (PPP) and smoking, with up to 80% of patients being smokers or ex-smokers,[43] smoking is also a risk factor for the development of psoriasis.[44] Interestingly, smoking was significantly more common in our homozygous HLA-Cw*0602 patients compared to the heterozygous and HLA-Cw*0602 negative patients ($P = .013$). Smoking increases oxidative damage and promotes heightened inflammatory state and may modify expression of several psoriasis-associated genes, including the HLA genes.[45] Homozygous HLA-Cw*0602 individuals have about a 2.5-fold increased risk for psoriasis compared with HLA-Cw*0602 heterozygotes[46] and a recent study reported that HLA-Cw*0602 positive smokers have a further increased risk of developing psoriasis compared with non-smoking HLA-Cw*0602 carriers, suggesting that smoking might trigger psoriasis in some genetically predisposed individuals.[47]

In this study, the need for psoriasis treatment decreased significantly after tonsillectomy. Although all groups required less treatment after the procedure, this was not significant for the homozygous HLA-Cw*0602 group. However, since the homozygous group only included 4 patients, it is difficult to draw concrete conclusions. The only patient that received systemic treatment before tonsillectomy was homozygous for HLA-Cw*0602. He improved considerably after the tonsillectomy but was restarted on systemic therapy after 12 months of follow-up because of psoriatic arthritis symptoms. The other 3 homozygotes did not require any psoriasis treatment during the 24-month follow-up. Thus, available data do not indicate that improvement of psoriasis after the tonsillectomy can be attributed to additional psoriasis treatment. Furthermore, we have previously shown that tonsillectomized patients with plaque psoriasis use less treatment and improve significantly more compared to matched controls.[14]

Taken together, our findings indicate that HLA-Cw*0602 homozygosity can be regarded as a predictor of favourable outcomes after tonsillectomy of patients with plaque psoriasis and a history of streptococcal-associated psoriasis exacerbation. Profiling psoriasis patients with respect to disease history and genotype can help identify psoriasis patients who could benefit the most from tonsillectomy. Although our patients were only followed for 24 months, we have observed that the improvement after tonsillectomy remains largely unchanged for at least 5 years after tonsillectomy (unpublished data). However, in view of the relatively few patients genotyped for HLA-Cw*0602, our findings need to be expanded with more HLA-C typed patients.

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List of abbreviations

HLA-Cw*0602	The allele for HLA-Cw6
HLA-Cw6	Human leukocyte antigen Cw6
PASI	Psoriasis Area and Severity Index
PASI 75	At least 75% improvement in PASI
PASI 90	At least 90% improvement in PASI
PCR	Polymerase chain reaction
PDI	Psoriasis Disability Index
PLSI	Psoriasis Life Stress Inventory
PSORS1	Psoriasis susceptibility locus 1
SD	Standard deviation
SNPs	Single-nucleotide polymorphisms

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Capsule summary

- Tonsillectomy can improve psoriasis, yet the patient group likely to benefit the most is poorly defined.
- We show that homozygous HLA-Cw*0602 carriage is associated with a particularly favourable outcome after tonsillectomy in patients with streptococcal-associated psoriasis exacerbation.
- Profiling psoriasis patients can identify patients who could benefit the most from tonsillectomy.

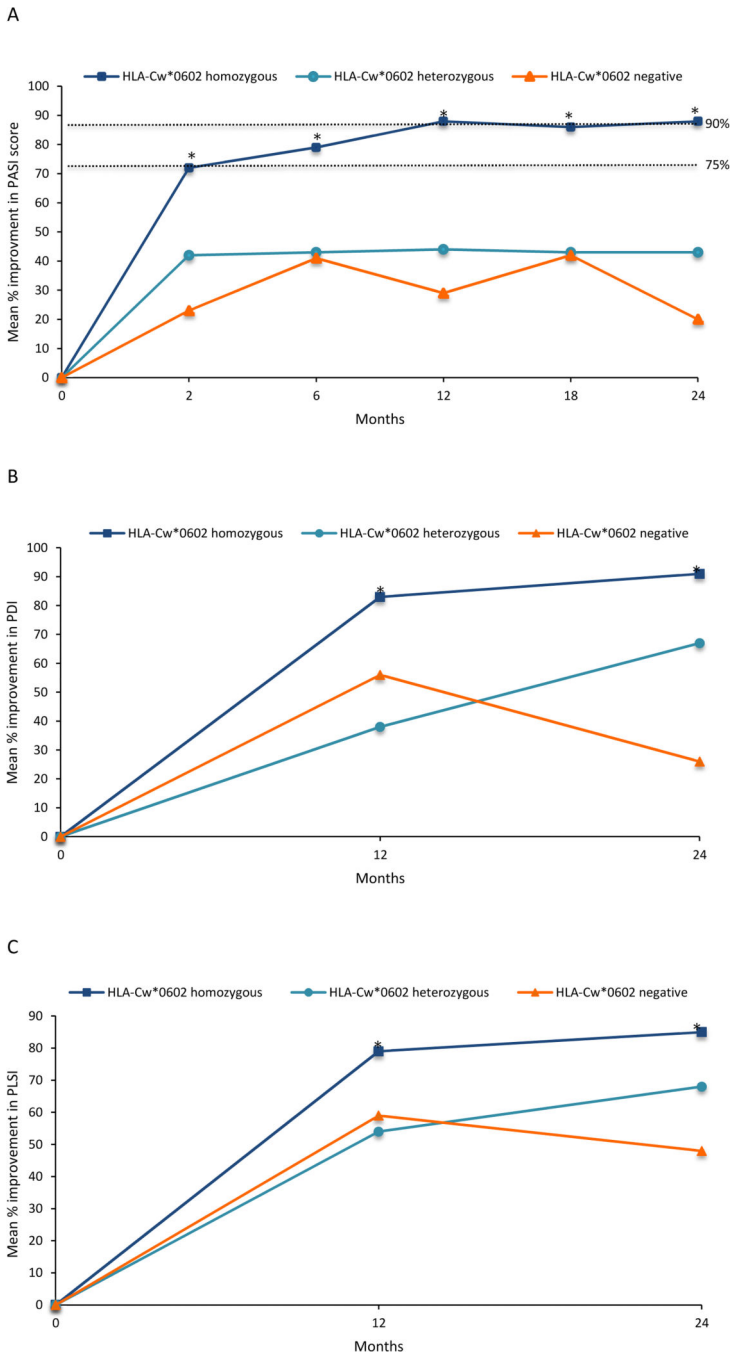

Figure 1.

Tonsillectomy efficacy outcomes through month 24. Panel A shows the mean percentage reduction of Psoriasis Area Severity Index (PASI) score. Point lines denote 75% and 90% reduction from baseline PASI score (PASI 75 and PASI 90 respectively). Panel B shows the mean percentage improvement in Psoriasis Disability Index scores. Panel C shows the mean percentage improvement in Psoriasis Life Stress Inventory (PLSI). *denotes statistical

significance, where HLA-Cw*0602 homozygous patients are compared to heterozygous and HLA-Cw*0602 negative patients.

Table I

Demographic information and disease characteristics of the 28 participating psoriasis patients

	HLA-Cw*0602		
	Homozygous (n=4)	**Heterozygous (n=17)**	**Negative (n=7)**
Men, *n* (%)	0	5 (29)	1 (14)
Age, mean years ± SD	32.5 ± 5.9	33.2 ± 11.8	35.1 ± 6.0
Body mass index (kg/m^2) ± SD	24.0 ± 1.5	25.6 ± 4.9	23.6 ± 3.4
Age at psoriasis onset, mean years ± SD	14.3 ± 6.9	13.9 ± 6.5	16 ± 7.3
Psoriasis duration, mean years ± SD	18.3 ± 10.1	19.3 ± 9.3	19.1 ± 8.6
Psoriatic arthritis, *n* (%)	1 (25)	4 (24)	1 (14)
Initial PASI score, mean ± SD	13.5 ± 1.7	12.3 ± 4.9	9.9 ± 3.2
Initial PDI score, mean ± SD	13.3 ± 2.8	12.4 ± 7.2	10.4 ± 6.4
Initial PLSI score, mean ± SD	14.0 ± 1.9	12.0 ± 5.1	12.3 ± 5.5

PASI, Psoriasis Area and Severity Index. PDI, Psoriasis Disability Index. PLSI, Psoriasis Life Stress Inventory.

Table II

HLA-C genotypes and clinical features of the 28 participating psoriasis patients

	HLA-Cw*0602			
	Homozygous	**Heterozygous**	**Negative**	***P* value***
Number, *n* (%)	4 (14)	17 (61)	7 (25)	
Sore throat-induced psoriasis onset,† *n* (%)	4 (100)	5 (29)	2 (29)	.007**
Sore throat per year,† mean *n* ± SD	5.3 ± 3.5	3.9 ± 2.9	6.9 ± 3.6	.768
Strep-throat per lifetime,‡ mean *n* ± SD	3.5 ± 2.1	1.4 ± 1.5	1.1 ± 0.6	.038**
Streptococcal carriage,§ *n* (%)	3 (75)	11 (65)	3 (43)	.527
Cigarette Smoking, *n* (%)	4 (100)	5 (29)	3 (43)	.013**
Psoriasis family history, *n* (%)	4 (100)	14 (82)	5 (71)	.314

*HLA-Cw*0602 homozygous patients compared to heterozygous and HLA-Cw*0602 negative patients.

†As recalled by the patients.

**Statistically significant.

‡Streptococcal throat infections diagnosed by a physician, throat culture or strep test (rapid antigen detection test).

§Cultured at the time of the tonsillectomy.

Table III

Effects of tonsillectomy in relation to HLA-Cw*0602 carriage during the 24-month follow-up

	HLA-Cw*0602			
	Homozygous (n=4)	**Heterozygous (n=17)**	**Negative (n=7)**	***P* value***
Mean PASI improvement %	82	42	31	< .001
Month 2	72	42	23	< .001
Month 6	79	43	41	< .001
Month 12	88	44	29	< .001
Month 18	86	43	42	< .001
Month 24	88	43	20	< .001
Mean PDI improvement %	87	38	41	< .001
Month 12	83	38	56	.004
Month 24	91	67	26	.005
Mean PLSI improvement %	82	60	54	< .001
Month 12	79	54	59	.03
Month 24	85	68	48	.04

*HLA-Cw*0602 homozygous patients compared to heterozygous and HLA-Cw*0602 negative patients. PASI, Psoriasis Area and Severity Index. PDI, Psoriasis Disability Index. PLSI, Psoriasis Life Stress Inventory.

Table IV

Use of psoriasis treatments before and after tonsillectomy of the 28 participating patients

	HLA-Cw*0602		
Treatment	**Homozygous (n=4)**	**Heterozygous (n=17)**	**Negative (n=7)**
Before tonsillectomy			
Topical therapy,* *n* (%)	0	7 (41)	4 (57)
Phototherapy,† *n* (%)	2 (50)	5 (29)	2 (29)
Systemic therapy, *n* (%)	1‡ (25)	0	0
After Tonsillectomy			
Topical therapy,* *n* (%)	0	3 (18)	2 (29)
Phototherapy,† *n* (%)	0	3 (18)	0
Systemic therapy, *n* (%)	1‡ (25)	0	0

*Corticosteroid creams, vitamin D analog creams or combination of both.

†With or without topical psoriasis treatment.

‡This patient was treated with methotrexate before tonsillectomy. His rheumatologist initiated methotrexate treatment again for reasons of psoriatic arthritis after 12 months of study follow-up.