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Personalized and Effective Treatment Strategies for Psoriasis Patients

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Abstract Background: Psoriasis is a chronic immune-mediated inflammatory disorder with complex pathogenesis involving genetic and environmental factors. Variations in genes encoding nitric oxide synthase (NOS3) and cytochrome P450 enzymes (CYP2C9, CYP3A4) may influence both disease severity and therapeutic response to systemic immunosuppressants. Objective: This study aimed to evaluate the association of NOS3 C-786T, CYP2C9 G681A/G636A, and CYP3A4 Phe189Ser polymorphisms with the clinical characteristics and response to Cyclosporine A therapy in patients with psoriasis. Methods: Ninety-one psoriasis patients aged 14–71 years and forty-four healthy controls were examined. Clinical severity was assessed using the Psoriasis Area and Severity Index (PASI). Genotyping of NOS3, CYP2C9, and CYP3A4 polymorphisms was performed using real-time polymerase chain reaction (RT-PCR). All patients received Cyclosporine A (3–5 mg/kg/day) for 12 weeks. Treatment efficacy was determined by PASI reduction, with PASI75 considered a significant improvement. Statistical analyses were conducted using chi-square tests and odds ratios with 95% confidence intervals. Results: The NOS3 C-786T polymorphism showed a significant association with disease severity. The C/T genotype was detected in 52.7% of psoriasis patients versus 31.8% of controls ($p < 0.05$), while the T/T genotype predominated among erythrodermic forms (71.4%). CYP2C9 polymorphic variants (G681A and G636A) were found in 47.2% of patients and correlated with higher PASI values and reduced Cyclosporine A response. Patients with NOS3 C/C and CYP2C9 G/G genotypes achieved greater PASI reduction (mean 78%) compared to mutant allele carriers (52%, $p < 0.05$). CYP3A4 Phe189Ser variants were rare (9.9%), showing a nonsignificant trend toward reduced efficacy ($p = 0.08$). Conclusion: Genetic polymorphisms in NOS3, CYP2C9, and CYP3A4 influence psoriasis severity and response to Cyclosporine A therapy. The NOS3 C/C and CYP2C9 G/G genotypes are associated with milder disease and better treatment outcomes, whereas mutant alleles correspond to severe forms and decreased therapeutic response. These results highlight the clinical value of pharmacogenetic profiling to personalize immunosuppressive treatment strategies and optimize psoriasis management.

Keywords Psoriasis, NOS3, CYP2C9, CYP3A4, Cyclosporine A, Pharmacogenetics, Personalized therapy

1. Introduction

Psoriasis is among the most prevalent chronic inflammatory skin diseases, affecting 1–5% of the world's population [1]. It represents a multifactorial disorder in which immune dysregulation, vascular abnormalities, and genetic predisposition converge to produce hyperproliferation of keratinocytes and systemic inflammation [2,8]. The disease typically exhibits a bimodal age distribution, with peaks between 15–25 and 50–60 years, and shows no significant sex predilection [9]. Recent advances in molecular genetics have clarified that the susceptibility to psoriasis is determined by a complex interaction of multiple genes involved in immune signaling and xenobiotic metabolism [10,11]. In particular, nitric oxide synthase (NOS3) and cytochrome P450 enzyme families (CYP2C9, CYP3A4) play crucial roles in vascular tone regulation and drug metabolism, respectively [3–5]. Alterations in NOS3 activity affect endothelial function and inflammatory response [3,14], while CYP2C9 and CYP3A4 determine the pharmacokinetics of immunosuppressants such as Cyclosporine A and methotrexate [4,5,15]. Although numerous studies have examined cytokine polymorphisms (e.g., IL-17, IL-23, TNF-α), data on NOS3, CYP2C9, and CYP3A4 variants in psoriasis remain limited and often population-specific [4,5,16]. Considering the high clinical heterogeneity and variable drug response, understanding genetic predictors of disease course and therapy outcome is essential for personalized medicine [6,7,17,18]. Therefore, this study aimed to evaluate the distribution of NOS3 C-786T, CYP2C9 G681A/G636A, and CYP3A4 Phe189Ser polymorphisms among psoriasis patients and to determine their relationship with clinical severity and response to

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Cyclosporine A treatment.

2. Materials and Methods

A total of ninety-one patients with clinically confirmed psoriasis, aged between 14 and 71 years, were enrolled in this study. Forty-four healthy individuals without personal or family history of psoriasis or other autoimmune diseases served as a control group. All patients were diagnosed and treated at the Republican Specialized Scientific and Practical Medical Center of Dermatology and Cosmetology. The study was conducted in accordance with the principles of the Declaration of Helsinki, and informed consent was obtained from all participants.

Clinical Evaluation: The severity of psoriasis was assessed using the Psoriasis Area and Severity Index (PASI). Patients were classified according to clinical forms: papuloplaque (58.2%), guttate (14.3%), erythrodermic (11.0%), palmar-plantar (8.8%), and mixed variants (7.7%). Based on PASI scores, disease severity was defined as mild (PASI < 10), moderate (10 ≤ PASI < 20), or severe (PASI ≥ 20).

Molecular Genetic Analysis: Peripheral blood samples were collected in EDTA-containing tubes. DNA was extracted and genotyping of NOS3 (C-786T, rs2070744), CYP2C9 (G681A, rs4244285; G636A, rs4986893), and CYP3A4 (Phe189Ser, rs4987161) polymorphisms was performed by real-time polymerase chain reaction (RT-PCR) using allele-specific fluorescent probes.

Treatment and Response Evaluation: All patients received systemic therapy with Cyclosporine A at a dose of 3–5 mg/kg/day for 12 weeks, along with standard topical emollients. Clinical response was evaluated by changes in PASI after 12 weeks of treatment. A PASI reduction of ≥75% was considered a significant clinical improvement.

Statistical Analysis: Statistical processing was performed using SPSS version 22.0. The chi-square (χ^2) test was used to compare genotype frequencies between groups. Odds ratios (OR) and 95% confidence intervals (CI) were calculated to estimate the strength of associations. A p-value of <0.05 was considered statistically significant.

3. Results

The distribution of NOS3, CYP2C9, and CYP3A4 genotypes among psoriasis patients and controls is summarized below.

NOS3 (C-786T) Polymorphism: The heterozygous C/T genotype of NOS3 was observed in 52.7% of psoriasis patients, compared to 31.8% in the control group ($p < 0.05$). The homozygous T/T genotype was identified in 14.3% of patients overall, predominating among those with erythrodermic and severe plaque psoriasis (71.4% of erythrodermic cases). The C/C genotype was more frequent in mild to moderate cases and correlated with a favorable clinical course.

CYP2C9 (G681A and G636A) Polymorphisms: Polymorphic variants of CYP2C9 were detected in 47.2% of psoriasis patients. The presence of the A allele (heterozygous G/A or homozygous A/A) was significantly associated with higher PASI values ($p < 0.05$). Patients carrying the wild-type G/G genotype showed a milder disease course and better response to Cyclosporine A therapy, achieving PASI75 in 78.3% of cases versus 54.5% among A allele carriers.

CYP3A4 (Phe189Ser) Polymorphism: The Phe/Phe genotype predominated among psoriasis patients (90.1%), while the Ser variant was rare (9.9%). Carriers of the Ser allele demonstrated slightly reduced therapeutic response, though the difference did not reach statistical significance ($p = 0.08$).

Relationship between Genotypes and Therapeutic Response: After 12 weeks of Cyclosporine A therapy, a significant decrease in PASI was observed in most patients. The greatest improvement (mean PASI reduction of 78%) was noted among individuals with NOS3 C/C and CYP2C9 G/G genotypes, compared to 52% among NOS3 T/T and CYP2C9 A/A carriers. These findings indicate that genetic polymorphisms influence both disease severity and treatment outcomes.

4. Discussion

The findings of this study demonstrate that genetic variations in NOS3, CYP2C9, and CYP3A4 genes significantly contribute to the clinical heterogeneity and therapeutic response in psoriasis. Among the examined polymorphisms, NOS3 C-786T showed the most pronounced association with disease severity. The increased frequency of the T allele and T/T genotype in patients with erythrodermic psoriasis suggests that endothelial nitric oxide synthase (eNOS) dysfunction may promote microvascular inflammation and impaired dermal blood flow, thereby aggravating disease activity. These data are consistent with the results of Tervaniemi et al. [3], who demonstrated altered NOS3 expression profiles in psoriatic skin and its involvement in vascular regulation.

In addition, our findings on CYP2C9 polymorphisms indicate that the enzymatic activity of cytochrome P450 may modulate individual sensitivity to systemic immunosuppressants. The CYP2C9 G681A and G636A variants, known to reduce metabolic clearance of several drugs, were linked to more severe psoriasis and less favorable response to Cyclosporine A. Similar associations have been reported in pharmacogenetic studies of CYP2C9 polymorphisms and methotrexate metabolism [4,5]. The predominance of the wild-type CYP2C9 G/G genotype among good responders highlights its potential as a predictive biomarker for therapy selection.

Although CYP3A4 Phe189Ser polymorphism did not reach statistical significance in our cohort, the minor reduction in therapeutic response observed among Ser allele carriers may reflect altered drug metabolism pathways, as described in studies on cytochrome-mediated pharmacokinetics [6,7]. Considering that Cyclosporine A is metabolized primarily by CYP3A4, genetic screening of this gene could help optimize dosing and minimize adverse effects.

Overall, the integration of genetic data into clinical decision -making can substantially improve therapeutic efficacy and safety in psoriasis management. Our study provides the first evidence in the regional population that NOS3, CYP2C9, and CYP3A4 polymorphisms jointly influence both the course and treatment outcomes of psoriasis. These results align with the broader concept of precision dermatology and the growing importance of pharmacogenomics in chronic inflammatory diseases [2,8].

5. Conclusions

Genetic polymorphisms in NOS3, CYP2C9, and CYP3A4 are associated with variability in psoriasis severity and response to Cyclosporine A therapy. Patients with NOS3 C/C and CYP2C9 G/G genotypes exhibit a more favorable clinical course and higher therapeutic efficacy, while carriers of mutant alleles tend to develop more severe disease forms and show reduced treatment response.

These findings underscore the clinical relevance of genotyping as part of personalized psoriasis management. Incorporating molecular-genetic testing into standard dermatological practice may allow clinicians to tailor immunosuppressive therapy, predict therapeutic outcomes, and reduce adverse effects.

Author Contributions

Nazarova B.U. — conceptualization, study design, data collection, and writing of the manuscript.

Mullahanov J.B. — supervision, methodological guidance, and critical revision of the manuscript.

Mavlyanov I.R. — molecular-genetic analysis, data interpretation, and statistical validation.

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Conflict of Interest

The authors declare no conflict of interest.

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