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Investigation of +405 and –460 Polymorphisms of Vascular Endothelial Growth Factor in Psoriasis and Short-Term Responsiveness to Efalizumab Therapy

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Key Words

Psoriasis • Vascular endothelial growth factor • Efalizumab

Introduction

Psoriasis is a chronic autoimmune disorder with cutaneous manifestations. The two major pathological lesions in psoriasis are epidermal hyperproliferation with abnormal differentiation, and inflammatory infiltration in the dermal and epidermal layers [1]. Angiogenesis also plays an important role in psoriasis. Vascular endothelial growth factor (VEGF), a principal angiogenic factor, is produced by keratinocytes as well as peripheral blood mononuclear cells. VEGF is found at increased levels in psoriatic plaques compared with normal skin, and its levels are associated with the severity of the disease [2–4]. Two VEGF single nucleotide polymorphisms (SNP), at positions +405 and –460 from transcription start, have been associated with early-onset [5] and late-onset psoriasis [6], respectively, and may have significant genetic control over VEGF production in psoriasis.

Efalizumab is a humanized monoclonal IgG1 antibody that binds with high affinity to CD11a, the α subunit of LFA-1 (leukocyte function-associated antigen 1). It targets psoriasis pathogenesis at multiple levels, including the inhibition of T cell binding with endothelial cells and their migration to the site of cutaneous inflammation [7]. Given the role of VEGF in leukocyte trafficking in psoriasis and the inhibitory effect of efalizumab, we hypothesized that genetic control of VEGF production by specific SNP could influence the response of psoriasis to efalizumab therapy. We studied +405 and –460 VEGF polymorphisms in a group of psoriasis patients treated with efalizumab in order to investigate whether these polymorphisms are associated with: (1) early- or late-onset chronic plaque psoriasis and with other disease characteristics, and (2) with the response of psoriasis patients to efalizumab therapy.

Patients and Methods

Forty-four adult patients with chronic plaque psoriasis who had been or were currently being treated with efalizumab at the University Clinic of Dermatology, A. Sygros Hospital, were enrolled in the study. All of these patients had received systemic therapy prior to their treatment with efalizumab. A response to efalizumab or other systemic treatment was defined as a decrease of at least 75% in the pre-treatment Psoriasis Area and Severity Index score (PASI 75) after 3 months of therapy.

After informed consent, genomic DNA was isolated from whole blood of the patients. The research protocol was approved by the A. Sygros Hospital Institutional Review Board, and Declaration of Helsinki protocols were followed.

The +405 and –460 VEGF genotypes were studied using PCR restriction fragment length polymorphism (PCR-RFLP) as described previously [5]. Our primary objective was to compare VEGF polymorphisms in responders versus non-responders, and the secondary endpoints were to investigate whether these polymorphisms had any implications upon the age of onset, family history of psoriasis, history of guttate psoriasis and nail involvement.

Statistical Analysis

Comparisons of disease duration among genotype categories were performed using the Kruskal-Wallis test. Pairwise multiple comparisons were performed using the Mann-Whitney test. In order to examine the correlation of genotypes with categorical demographic and disease characteristics, χ^2 or Fisher's exact tests were used. All tests were two-sided, and statistical significance was set at $p < 0.05$.

Results and Discussion

Forty-four patients participated in the study [27 males (61.4%) and 17 females (38.6%); 12 (27.3%) with early-onset and 32 (72.7%) with late-onset psoriasis]. The distribution of +405 and –460 VEGF genotypes among our patients is presented in table 1. The results of our study did not indicate an association between the VEGF genotype and short-term response (at 3 months) to efalizumab (23 efalizumab responders, 21 non-responders) or other systemic therapy (tables 2, 3). Furthermore, we did not find any correlation between these genotypes and other parameters that were also studied, such as age at onset of psoriasis, disease duration, family history of psoriasis, patient history of guttate psoriasis and nail involvement (data not shown).

Psoriasis often presents therapeutical problems, since most systematic agents require prolonged usage, during which they can cause adverse events. Therefore, prognostic markers that predict therapeutic outcomes would be of significant value. In this study, we examined the role of +405 and –460 VEGF polymorphisms with regards to their association with disease characteristics and with the outcome of efalizumab treatment. Both these SNP have been associated with early-onset [5] and late-onset psoriasis [6]. Further-

Table 1. Distribution of genotypes

Polymorphism	Genotype	n	%
+405	CC	7	15.9
	CG	31	70.5
	GG	6	13.6
–460	TT	18	40.9
	CC	4	9.1
	CT	22	50.0

Table 2. Correlation between polymorphism +405 and treatment response

	CC		CG		GG		p value
	n	%	n	%	n	%	
Efalizumab	4	57.1	16	51.6	3	50.0	0.959
Ciclosporin	1	25.0	16	61.5	3	60.0	0.385
Acitretin	1	50.0	3	27.3	3	100.0	0.078
Methotrexate/ ultraviolet B	4	57.1	20	64.5	4	66.7	0.922

n = Number of responders to therapy.

Table 3. Correlation between polymorphism -460 and treatment response

	TT		CC		CT		p value
	n	%	n	%	n	%	
Efalizumab	10	55.6	2	50.0	11	50.0	0.936
Ciclosporin	7	50.0	2	100.0	11	57.9	0.407
Acitretin	1	20.0	2	100.0	4	44.4	0.156
Methotrexate/ ultraviolet B	10	55.6	4	100.0	14	63.6	0.247

n = Number of responders to therapy.

more, VEGF production by peripheral blood mononuclear cells in psoriasis is determined by genotype; -460 CC and +405 GG genotypes are 'low VEGF producers', whereas -460 TT and +405 CC genotypes are 'high VEGF producers' [8]. Finally, the VEGF -460 TT genotype has been associated with the non-response of psoriasis to acitretin treatment, while patients with the -460 TC genotype are twice as likely to respond to acitretin therapy [5, 8].

The effect of VEGF on leukocyte recruitment or efalizumab action has not been clearly established. Various adhesion molecules have been implicated in T lymphocyte binding to dermal vascular endothelium in psoriasis, but the chemotactic signals that promote subsequent movement into the adjacent dermis and overlying epidermis are poorly defined. Studies have shown enhanced expression of E-selectin, cutaneous lymphocyte antigen LFA-1, ICAM-1 (intercellular adhesion molecule-1) and other adhesion molecules in psoriatic skin [9]. Keratinocytes of patients with psoriasis show an intrinsically abnormal chemokine production profile, such as high levels of interleukin 8, monocyte chemoattractant protein 1 (MCP-1) and IFN- γ -induced protein of 10 kd (IP-10), and may thus favor the recruitment of distinct leukocyte subsets into the skin [10, 11]. In the livers of cirrhotic rats, cirrhosis progression was associated with a significant enhancement in vascular density and expression of VEGF-A, and the newly formed hepatic vasculature expressed vascular cellular adhesion molecule 1 and ICAM-1 [12]. Data from other experiments suggest that the inflammation that occurs during VEGF-induced pathological brain angiogenesis plays a contributory role in the pathological angiogenic process [13].

In this study, we have shown that +405 and -460 VEGF polymorphisms do not affect or predict the response of psoriasis to efalizumab. We also failed to show any association between these polymorphisms and age of disease onset, or the treatment response to acitretin reported by other studies. This could be due to the relatively small number of patients we studied, or to the action of other, currently unknown, factors contributing to the psoriasis phenotype and response to therapy. Further studies and large cohorts of patients are required to reach firm conclusions.

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