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Serum vascular endothelial growth factor and sublingual immunotherapy

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Key words: allergic rhinitis; sublingual immunotherapy; vascular endothelial growth factor.

Allergic rhinitis (AR) is characterized by an inflammatory reaction, sustained by Th2 polarization (1). In this regard, angiogenesis is a complex and multifaceted process including endothelial cell proliferation and migration, recruitment of pericytes, and a maturation process (2). This sequence is tightly integrated and mediated by a balance between pro-angiogenic factors, including vascular endothelial growth factor (VEGF), angiopoietins, angiogenins, and a range of chemokines, and

anti-angiogenic factors, such as endostatin and constatin. Anyway, the most necessary and sufficient angiogenic protein is VEGF.

Vascular endothelial growth factor has been implicated as a driver not only of airway angiogenesis but also of enhanced allergic sensitization, upregulated Th2 inflammatory response, mucus gland hyperplasia, induction of metalloproteinase, chemotaxis for monocytes and eosinophils, airway edema, and airway hyperreactivity (3). Recently, it has been shown that VEGF is over-expressed in the nasal mucosa of patients with seasonal AR (4) and might be associated with the link between rhinitis and asthma (5). Sublingual immunotherapy (SLIT) is the unique causal treatment for AR affecting immune response (6).

Thus, the aim of this preliminary study was to evaluate serum VEGF levels in a cohort of AR patients, enrolled outside pollen season, and treated with a preseasonal course (3 months) of SLIT (Anallergo, Florence, Italy) and compared with healthy controls.

Forty patients (19 males and 21 females, mean age 38.86 years), with pollen allergy, and 15 normal subjects (eight males and seven females, mean age 43 years) were evaluated. Patients' blood samples for assessing VEGF serum levels were collected before initiating SLIT (baseline), after 3 month preseasonal SLIT course, and three months after.

The study was conducted with the approval of the local Ethics Committee and performed with the written informed consent of all participants.

The human VEGF Immunoassay (R&D Systems, Milan, Italy) was performed according to the Manufacturer's Instructions and expressed as $\mu\text{g/ml}$. The Wilcoxon test and Pearson's test were used for statistical analyses. The package 'S-PLUS' (MathSoft Corp, Rome, Italy) was used for all analyses.

Vascular endothelial growth factor serum levels were 532.09 pg/ml (± 262.6 SD) in normal subjects. In allergic patients, VEGF serum levels were 159.92 pg/ml (± 408.29 SD) at baseline and were significantly lower than in normal subjects ($P = 0$) as reported in Fig. 1. At the end of preseasonal SLIT course, i.e. after 3 months, VEGF serum levels significantly increased to 373.10 pg/ml (± 264.98 SD) in comparison with baseline levels. After 3 months, VEGF further increased to 404.65 pg/ml (± 206.99 SD), but without significant difference with the previous one. Finally, there was a significant correlation between times ($P = 0.0005$).

The findings of this preliminary study are surprising for two main reasons: firstly VEGF serum levels are significantly lower in AR patients than in normals. It is completely conflicting with previous studies (4, 5). However, these studies were conducted in symptomatic patients as exposed to pollens, whereas our patients were symptomless as they were initially studied outside the pollen season.

Secondly, SLIT induced an increase of VEGF serum levels. It may appear a paradox as VEGF may be considered a marker of allergic inflammation as it was reported to be over-expressed during acute phase of pollen AR. However, it is well known that SLIT is able to reduce the severity of allergic symptoms and the use of rescue medications down-regulating Th2-mediated inflammation (6).

A possible hypothesized explanation of this aberrant phenomenon might be that the VEGF over-expression mainly occurs at the level of the target organ, such as the nose, where it is effectively and significantly increased. Thus, this local 'capture' might justify the low 'peripheral' VEGF levels in basal conditions. Moreover, VEGF serum levels might reduce at nasal levels and consequently increase in the serum after SLIT.

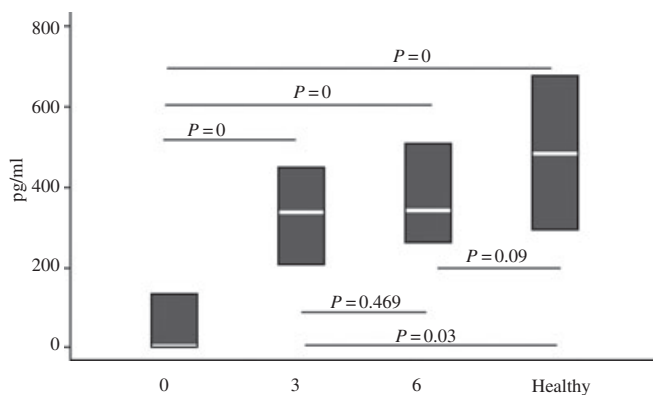


Figure 1. VEGF serum levels in patients with pollen AR evaluated before (0), after a 3-month preseasonal SLIT course (3), and after 3 months (6), and in healthy subjects.

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Contact allergy to topical antifungal agents

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Key words: ciclopiroxolamine; clinical epidemiology; contact allergy; imidazoles; nystatin; patch testing; topical antifungals.

Topical antifungal agents (AF) are used to treat superficial fungal infections such as dermatophytoses, candidiasis and pityriasis versicolor. The polyene derivative nystatin is only active against yeasts, while azole and morpholine AF show a broad spectrum of activity against dermatophytes, yeasts and moulds. Contact allergy (CA) has been reported after use of AF (1–5). Croconazole in particular has been found to be an important sensitizing agent in East Asia (4, 5). In contrast, other azole AF are regarded as (very) infrequent sensitizers. Most studies on CA to AF, however, comprise sporadic case reports; systematic patch test studies based on a large clinical population are currently lacking. This study reports the results of patch tests with AF applied to patients attending the clinics of the Information Network of Departments of Dermatology (IVDK, <http://www.ivdk.org>; accessed 2 April 2008) (6), a CA surveillance network in Germany, Austria and Switzerland.

From May 2001 to April 2002, 20 departments of dermatology – members of the German Contact Dermatitis Research Group (DKG) and the IVDK (6), see footnote – performed a study to evaluate CA frequency to five topical AF (Table 1). Standardized patch test allergens were supplied by Hermal/Trolab (Reinbeck, Germany). Patients' own AF products were additionally analyzed, provided these had been patch tested as well. The diagnosis of CA was based on the D3 readings. Patch test reactions scored '+', '++' or '+++[†]' were considered to be positive.

[†]The following centres contributed data to the following analysis (in alphabetical order): Augsburg (A. Ludwig), Dortmund (C. Pirker, P.J. Frosch, R. Herbst), Dresden (G. Richter, R. Aschoff), Essen (U. Hillen), Graz (B. Kränke, W. Aberer), Göttingen (J. Geier, Th. Fuchs), Halle (D. Lübke, G. Gaber), Hamburg (M. Kiehn, R. Weißbecher), Heidelberg (M. Hartmann, U. Jappe), Homburg/Saar (P. Koch), Jena (A. Bauer, M. Kaatz, S. Schlie-mann-Willers), Kiel (J. Brasch), Krefeld (A. Wallerand, M. Lilie, S. Wassilew), Marburg (H. Löffler, I. Effendy), München Schwabing (M. Agathos), München TU (J. Rakoski), Nürnberg (I. Müller), Osnabrück (H. Dickel, H.J. Schwanitz (+), N. Schürer, S.M. John), Tübingen (G. Lischka, M. Röcken), Ulm, BWK (H. Pillekamp)

Topical antifungals are rare contact sensitizers.

Altogether 1254 patients (median age 49 years, interquartile range: 36–64; 35.9% male) were patch tested with the AF series. In 10 centres, ≤ 10% of all patients were tested with the study battery, i.e. in a more aimed fashion, whereas in the remaining 10 centres the proportion ranged from 11 to 22%. Positive reactions were altogether rare, with ciclopiroxolamine yielding the highest number of positive ($n = 4$) and doubtful ($n = 13$) reactions as well (Table 1). Among patients tested positively to AF [$n = 12$ [0.94%; 95% confidence interval (CI): 0.49–1.63]] no concomitant positive patch test reaction was observed among the AF, even among the chemically related azoles. AF brand products brought in by the patient were tested in 41 cases, yielding the following results in 35 patients tested with one or more product(s) containing the target AF – all positive reactions but one were caused by creams (O/W emulsions; positive reactions to other ingredients of these were not observed):

- clotrimazole ($n = 17$), two positive reactions, only one concordantly with the standardized patch test substance;
- nystatin ($n = 9$), one patient with two (strong) positive reactions in absence of a positive reaction to the commercial allergen;
- ciclopiroxolamine ($n = 8$, all negative);
- ketoconazole ($n = 6$), two positive reactions – one of these, however, to a 1 : 10 diluted, ketoconazole-containing shampoo – without positive reactions to the commercial allergen.

Products containing other AF such as bifonazole, miconazole, econazole, terbinafine, etc. had occasionally been tested (without yielding positive results) on these and the other six patients.

This work evaluated CA in an extensive series of patients patch tested to important AF agents at numerous IVDK centres. Our findings confirm the weak sensitizing capacity of the tested AF, as reported previously (1–4), although a more aimed use of the test series, i.e. just in the supposedly few patients with