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Influence of PUVA and UVB Radiation on Expression of ICAM-1 and VCAM-1 Molecules in Psoriasis Vulgaris

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ABSTRACT

The expression of adhesion molecules Intercellular adhesion molecule-1 (ICAM-1) and Vascular cell adhesion molecule-1 (VCAM-1) is increased in lesional and in non-lesional skin of psoriatic patients, and play role in pathogenesis of the disease. PUVA and UVB therapy are important treatments of psoriasis vulgaris. It has been demonstrated that UVA and UVB therapies reduce expression of these molecules. In this investigation, phototherapy was used to treat psoriatic patients. The expression of these molecules was examined by immunohistochemical method in lesional and non-lesional skin of 10 patients with psoriasis vulgaris before and after treatment. Results showed increased expression of ICAM-1 molecules in keratinocytes, in perivascular infiltrate – lymphocytes, and in endothelial cells. The expression of VCAM-1 molecules was also increased, although with less intensity than ICAM-1. After therapy, the expression of the adhesion molecules decreased together with a marked improvement of the disease. In conclusion, study demonstrated that phototherapy improves psoriasis vulgaris probably through mechanisms acting on the adhesions molecules. Adverse reactions due to intense or long lasting UVA (PUVA) and UVB therapies are immunosuppression and damage of DNA which can lead to development of non-melanocytic skin tumors like basal cell carcinoma and squamous cell carcinoma, as well as melanoma.

Key words: psoriasis, UV treatment, ICAM-1, VCAM-1

Introduction

Intercellular adhesion molecule-1 (ICAM-1) and Vascular cell adhesion molecule-1 (VCAM-1) play an important role in the pathogenesis of psoriasis vulgaris^{1–3}. Adhesion molecules belong to three families of proteins: the immunoglobulin superfamily, selectin and integrin family. ICAM-1 on endothelial cells is connected to Lymphocyte Functional Associated Antigen-1 (LFA-1) as its ligand on lymphocytes which is important for the influx of lymphocytes in perivascular infiltrate and for the proliferation of keratinocytes.

Phototherapy with ultraviolet rays is a mainstay in treatment of psoriasis. Today we use UVB or oral methoxsalen followed by UV-radiation (PUVA) therapies in treatment of psoriasis vulgaris. Bath-PUVA and Re-PUVA,

i. e. a combination of PUVA therapy and oral retinoids are also possible. Contraindications for PUVA therapy are liver and kidney disease, cataract, systemic lupus erythematosus, porphyries, malignant tumors, pregnancy, xeroderma pigmentosum¹. UVB or selective ultraviolet radiation (SUN) is provided 3–4 times a week through a period of 3–4 weeks. Narrow band UVB with frequency of 311 nm is used which is less erythemalogenic and less carcinogenic than PUVA. Contraindications are photodermatoses, lupus erythematosus, dysplastic naevus syndrome, xeroderma pigmentosum. The aim of this study was to investigate the influence of PUVA or UVB radiation on ICAM-1 and VCAM-1 adhesion molecules in patients suffering from psoriasis vulgaris.

Materials and Methods

We examined 10 patients with psoriasis vulgaris. In our investigation, we made comparison of the expression of ICAM-1 and VCAM-1 adhesion molecules in lesional and non-lesional skin of 10 psoriatic patients before and after UV therapy. All of patients were observed and treated at the Department of dermatovenereology. Study was approved by the ethical commission of the Clinical Hospital Centre, and all patients were given informal consent. The diagnosis of psoriasis vulgaris was made on clinical examination. After excisional biopsy, fresh frozen sections of the skin underwent procedure as described below. We used kit of labelled streptavidin biotin (LSAB) reagents, DAKOLSAB+kit alkaline phosphatase universal K678 for immunohistochemical staining of ICAM-1 and VCAM-1 molecules. Cryostat sections were cut from snap frozen tissue blocks and air dried for 2–24 hours. Dried sections were ready for immediate processing, or they were wrapped air-tight and stored frozen at -20°C or lower. If stored frozen, sections should have been brought to room temperature before unwrapping. Tissue sections were fixed with acetone for 10 minutes. Alternatively, fixation could have been performed after sectioning and air drying, prior to frozen storage. Sections were air-dried after fixation. Slides were submerged in buffer bath for 5 minutes and then staining procedure started.

Staining procedure

Incubation lasted 60 minutes with primary antibody or negative control reagents. The specimens were gently rinsed with wash solution from a wash bottle and placed in fresh butter bath. Excess buffer was immediately tapped of and slides were wiped as before. Then yellow drops from Bottle 2 were applied in sufficient amount to cover specimen and incubated for 30 minutes. Slides were wiped as before. Then red drops from Bottle 3 (Streptavidin) were applied in sufficient amount to cover specimen, and incubated for 30 minutes. After that the substrate-chromogen solution was prepared, and slides were rinsed as before.

Substrate chromogen solution

Slides were wiped as before. After that substrate-chromogen solution was applied in sufficient amount to cover specimen, and incubated for 10 minutes. Slides were gently rinsed with distilled water from wash bottle.

Counter stain

Specimens were covered with hematoxylin. Alternatively, slides were placed in a bath of hematoxylin, and incubated for 2–5 minutes, depending on the strength of the hematoxylin used, and gently rinsed with distilled water from a wash bottle. Then they were dipped 10 times into wash bath filled with ammonia water, and placed in distilled or deionized water for 2 minutes.

Mounting

Specimens were mounted and cover-slipped with an aqueous-based mounting medium or a non-aqueous, permanent mounting medium. Recommendation was to use a xylene substitute such as Histoclear for cleaning the slides when preparing slides for permanent mounting media. This procedure helped to eliminate the reduction of staining of xylene. We interpreted the stain with Olympus microscope and examined fuchsia-colored end-product at the site of the target antigen. We used simple way of arithmetic median for statistic analysis, and average percentage of cell expressing adhesion receptors for ICAM-1 and VCAM-1 molecules, in standard manner like other authors^{2,3,4,5, 6}.

Results

General characteristics of patients are shown in Table 1. We detected ICAM-1 molecules on endothelial cells, perivascular infiltrate and keratinocytes. VCAM-1 molecules were also detected, but with less intensity especially in non-lesional skin. Our results are summarized in Table 1. Positive immunohistochemical staining of ICAM-1 and VCAM-1 molecules are shown in Table 1. We excluded negative stain or +/- stain. Results showed strong positivity of VCAM-1 and ICAM-1 molecules in lesional skin in 10 cases (100%). In nonlesional skin, ICAM-1 molecules were positive in 8 cases (80%), and VCAM-1 molecules were positive in 6 cases (60%) of psoriatic skin, before UV treatment. After UVB and PUVA therapies, ICAM-1 molecules were positive in 8 cases (80%) and VCAM-1 molecules were positive in 9 cases (90%), in lesional skin.

Discussion and Conclusion

According to our results, ICAM-1 and VCAM-1 molecules are highly expressed in lesional skin of patient with

TABLE 1
EXPRESSION OF ADHESION MOLECULES ICAM-1 AND VCAM-1 IN LESIONAL AND NON-LESIONAL SKIN OF PSORIATIC PATIENTS BEFORE AND AFTER UVB AND PUVA THERAPIES IN ABSOLUTE NUMBERS AND PERCENTAGES

Topic	Absolute value	Percentage (%)
ICAM-1 lesional skin in psoriatic patients	10	100
ICAM-1 non-lesional skin in psoriatic patients	8	80
ICAM-1 lesional skin in psoriatic patients after UVB and Puva th.	8	80
VCAM-1 lesional skin in psoriatic patients	10	100
VCAM-1 non-lesional skin in psoriatic patients	6	60
VCAM-1 lesional skin after UVB and PUVA th.	9	90

psoriasis vulgaris. ICAM-1 molecules are also expressed in non-lesional skin, while VCAM-1 molecules are expressed with less intensity. We clearly demonstrated that these adhesion molecules can play an important role in the pathogenesis of psoriasis vulgaris. Some authors found an increased serum concentration of soluble ICAM-1 (sICAM-1) molecules in patients with psoriasis vulgaris. They correlated it with the severity of the disease (PASI score)^{7,12,13}, while others did not find an increased level of sICAM-1 molecules after UVB and PUVA therapies^{8,9}. It was also demonstrated that sICAM-1 and sTNF-R1 molecules were elevated in skin with psoriatic characteristics in comparison to healthy skin¹¹.

In our investigation we did not compare sICAM-1 levels in patients, but only ICAM-1 molecule in the skin. It is proven that ICAM-1 and E-selectin molecules are highly expressed on endothelial cells in lesional skin in patients with psoriasis¹⁰. VCAM-1 expression is weaker than the expression of ICAM-1 in non-lesional skin. Results were similar in our investigation. IL-4 could be up-regulated by UVB treatment and could selectively stimulate VCAM-1 expression¹⁰. That is the reason why there is higher expression of VCAM-1 molecules after UVB treatment. UVB treatment decreased the adhesive interaction between peripheral blood mononuclear cells and endothelial cells¹⁰. It has been demonstrated that UVB radiation therapy reduces T cell infiltration and disease severity (PASI score) in a period of few weeks. After treatment of 6 MED with UVB, ICAM-1 staining was reduced on endothelial cells in lesional skin in patients with psoriasis¹⁰. PUVA treatment reduced the dermal infiltrate, but not ICAM-1 molecules that were expressed on endothelial cells in examined patients. According to our results, the expression of ICAM-1 and VCAM-1 diminished after UVB and PUVA therapies in lesional skin of patients suffering from psoriasis vulgaris. The reason for that was the influence of phototherapy on the immunological process and on the adhesion molecules ICAM-1 and VCAM-1, which are important in progression and re-

gression of the disease. Other authors reported decrease of ICAM-1 molecules in lesional skin of patients with psoriasis after 4 weeks of local therapy with calcitriol¹⁴. UVB and PUVA therapies have many benefits for patients suffering from psoriasis vulgaris, and are accepted well from patients, but there are some side effects of this therapy so careful examination is needed during the therapy. Simple side effects include burning or erythema of the skin after few exposures, but chronic actinic dermatitis can also develop¹⁵. The most serious side effect is the development of skin cancers after UVB and PUVA therapies which include non-melanoma cancers like basal cell carcinoma and squamous cell carcinoma in treated patients, as well as melanoma^{22,23,24,25}. UVB therapy increases the risk of non melanoma skin cancer in lower percentage than PUVA¹⁶. PUVA increases the risk for development of squamous cell carcinoma and basal cell carcinoma in lower percentage in psoriatic patients¹⁷. The most severe side effect of PUVA therapy is the development of malignant melanoma²⁰.

In conclusion, we could confirm that PUVA and UVB therapies are effective for patients suffering from psoriasis vulgaris. We followed the results of these therapies by clinical appearance and by change in intensity of immunohistochemical staining of the adhesion molecules ICAM-1 and VCAM-1 in lesional skin and with slightly lower intensity in nonlesional skin. This shows that they play an important role in pathogenesis of psoriasis vulgaris. Today there is a targeted therapy like monoclonal antibodies against LFA-1 (Efalizumab) which connects ICAM-1 molecules and has promising results in therapy of psoriasis vulgaris²¹. Careful monitoring of those patients is necessary especially if therapy lasts for longer period of time because it can lead to the development of non-melanoma as well as melanoma skin cancers^{18,19}. Our results were obtained on a small group of patients, so the action of phototherapy on ICAM-1 and VCAM-1 molecules needs further investigation.

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UTJECAJ UVA I UVB ZRAČENJA NA ISPOLJAVANJE ICAM-1 I VCAM-1 MOLEKULA U VULGARNOJ PSORIJAZI

S A Ž E T A K

Ispoljavanje adhezijskih molekula ICAM-1 i VCAM-1 je povišena u promijenjenoj koži i nepromijenjenoj koži bolesnika s psorijazom, te mogu imati ulogu etiopatogenezi psorijaze. UVA ili PUVA, te UVB se koriste kao terapija u psorijazi. Poznato je da ta terapija smanjuje ispoljavanje molekula ICAM-1 i VCAM-1. U ovom istraživanju pokazali smo utjecaj te terapije na našoj Klinici za kožne i spolne bolesti, gdje smo istraživali ispoljavanje tih molekula imunohistokemijskim bojenjem kože bolesnika prije terapije njihove promijenjene kože. Rezultati su pokazali pojačanu ekspresiju ICAM-1 na keratinocitima, u perivaskularnom infiltratu-limfocitima i endotelnim stanicama, a isto se pokazalo za VCAM-1, iako manjeg intenziteta. Poslije terapije smanjenje ispoljavanja obih molekula bilo je nazočno u preparatima kože kao i kliničko poboljšanje. U zaključku možemo reći da fototerapija (UVA i UVB) zrakama poboljšava psorijazu i možda u tome ulogu igraju i adhezijske molekule. Neželjene reakcije fototerapije tijekom dugogodišnje primjene UVA (PUVA) i UVB su imunosupresija i oštećenje DNA, koje može dovesti do nastanka tumora poput bazalioma i spinalioma, te melanoma.