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Original Research Article

Dithranol treatment of plaque-type psoriasis increases serum TNF-like weak inducer of apoptosis (TWEAK)

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ABSTRACT

Purpose: TNF-like weak inducer of apoptosis (TWEAK) mediates not only apoptosis, but also inflammation, cell growth and angiogenesis. The role of TWEAK in psoriasis remains unknown. The aim of the study was to assess serum levels of TWEAK in psoriatic patients before and after topical treatment with dithranol in relation to the clinical activity of the disease.

Material and methods: Serum samples were collected from 40 patients with plaque type psoriasis before and after topical treatment with dithranol. The concentrations of serum TWEAK were measured by ELISA and next compared with 16 healthy controls. The data were analyzed with respect to Psoriasis Area and Severity Index (PASI).

Results: Baseline serum TWEAK concentrations of psoriatic patients (685 ± 166 pg/ml) were significantly greater compared to healthy controls (565 ± 110 pg/ml). Topical treatment resulted in further increase in serum TWEAK (749 ± 179 pg/ml; $p < 0.01$). In case of patients with initial serum TWEAK concentrations above the median, PASI after topical treatment was lower compared to the individuals with initial TWEAK below the median.

Conclusion: According to the study, serum Tweak was increased in psoriasis patients compared with controls. Moreover, dithranol topical treatment caused further increase in serum TWEAK. Also, a higher effectiveness of topical treatment was observed in case of patients with higher initial TWEAK concentrations. The results suggest a potential role of TWEAK in psoriasis therapy.

1. Introduction

Psoriasis is a common chronic inflammatory disorder with prevalence ranging from 0.1% to 11.0% in different populations [1]. The etiology of the disease is multifactorial and not fully known. According to recent suggestions, epidermal keratinocyte hyperproliferation and incomplete differentiation result from T-cell mediated autoimmune reaction [2,3]. The disease is characterized by the coincidence of infiltration of the dermis with multiple immune cells and increased dermal vascularity. Angioproliferation seems to play a crucial role in the early stages of the development of psoriatic lesions [4]. Laporte et al. [5] demonstrated that spontaneous keratinocyte apoptosis is decreased in lesional skin in psoriasis. They suggested that this phenomenon could play a role in the induction of psoriatic hyperplasia. Moreover, psoriatic keratinocytes are extremely resistant to apoptosis compared with normal skin-derived keratinocytes [6].

Tumor necrosis factor-like weak inducer of apoptosis (TWEAK) was first described as a member of the tumor necrosis factor (TNF) superfamily in 1997 by Chicheportich [7]. The authors reported its ability of inducing apoptosis. TWEAK is a transmembrane protein which can be cleaved to generate a smaller, active form and become a cytokine. In physiologic conditions, by binding to its receptor (fibroblast growth factor-inducible 14 – Fn14), TWEAK can participate in tissue repair and regeneration after acute injury [8]. In chronic inflammatory conditions, the TWEAK/Fn14 pathway promotes chronic inflammation [7], pathological hyperplasia and angiogenesis [9]. Girgenrath et al. [8] demonstrated that TWEAK promoted proliferation of progenitor cells and inhibited their terminal differentiation. All of these disturbances can be observed in psoriatic skin lesions.

Dithranol (anthralin) is a successful method of treatment of exacerbated plaque psoriasis. Although it is one of the oldest available therapies for psoriasis, very little data on its mechanism

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of action can be found. Recently, it has been shown to exert its therapeutic effect by inducing keratinocyte apoptosis [10].

The data on the role of serum TWEAK in psoriasis are very limited. The aim of this study was to compare serum concentrations of TWEAK in psoriatic patients and in healthy control group. We also investigated the influence of topical treatment with dithranol on serum TWEAK concentrations and their relationship with clinical disease activity measured with PASI (Psoriasis Area and Severity Index).

2. Material and methods

2.1. Patients

The study was carried out on 40 patients aged 18 to 84 with exacerbated plaque psoriasis, characterized in Table 1. The individuals with other types of psoriasis were excluded from the study. Neither topical nor systemic treatment for psoriasis had been used by the patients for a period ranging from 1 to several months. During the study all the patients were treated topically: initially with 5% salicylic acid ointment (until desquamation – a few days), followed by dithranol in three increasing concentrations (starting from 0.05%, next 0.1%, finally 0.3%) applied for 12 h. Dithranol ointment was prepared in the hospital pharmacy on 1% salicylic acid (as a preservative) and white vaseline as base. It is the standard topical treatment of psoriatic patients with mild to moderate plaque type psoriasis in the research center. The intensity of psoriasis before and after two weeks of treatment was assessed using PASI (Psoriasis Area and Severity Index) score according to Fredriksson and Pettersson [11], a useful tool for the assessment of disease severity [12]. The erythema, infiltration and desquamation were separately estimated on the head, trunk as well as upper and lower limbs. The degree of intensity of each symptom in each body part was scored from 0 to 4. The affected area of each body part was calculated as a score from 0 to 6. The score of a particular body part was obtained by multiplying the sum of severity scores by the area score and then by the constant value (0.1 for the head, 0.3 for the trunk, 0.2 for the upper limbs, and 0.4 for the lower limbs). The PASI score is the sum of the scores of the body parts and ranges from 0 to 72.

The control group consisted of 16 healthy subjects, described in Table 1.

Table 1
Patients' and controls characteristics. Significant difference in comparison to the control group is shown with: $^{***}p < 0.001$.

	Patients ($N = 40$)	Controls ($N = 16$)	p value
Age ± SD	46.7 ± 14.7 (18–84)	40.8 ± 11.3 (21–65)	*ns*
Gender			
Female	14 (35%)	6 (37.5%)	*ns*
Male	26 (65%)	10 (62.5%)	*ns*
BMI ± SD	27.2 ± 5.5 (18.6–46.5)	23.7 ± 1.7 (21.2–27.7)	$p < 0.01$
Psoriasis duration (years)	18.0 ± 12.0 (0.2–52)		
PASI			
Before treatment	10.9 ± 6.3 (2.8–27.6)		
After treatment	4.2 ± 3.4 (0.6–17.3)		
WBC	7.3 ± 1.9 (4.0–10.6)		
Hemoglobin [g/dl]	14.2 ± 1.6 (7.7–16.8)		
Serum glucose [mg/dl]	94.2 ± 14.8 (77–134)		
AlAT [IU/ml]	27.2 ± 10.1 (14–55)		
Bilirubin [mg/dl]	0.6 ± 0.3 (0.3–1.7)		
Creatinine [mg/dl]	0.8 ± 0.2 (0.5–1.3)		

The study was approved by the Bioethical Committee of the Medical University of Bialystok, Poland.

2.2. Samples collection and measurements of TWEAK

Blood was collected twice after overnight fasting: before and after two weeks of topical treatment. After centrifugation, the serum was stored at −80 °C until assayed. The concentrations of TWEAK in serum were measured using commercially available enzyme-linked immunosorbent assay (ELISA) kit: Human TWEAK instant ELISA (Bender MedSystem GmbH, Vienna, Austria, sensitivity 9.7 pg/ml) according to the manufacturer's protocol.

2.3. Statistical analysis

The data were analyzed using Statistica software. After the analysis of the distribution, Kruskal–Wallis ANOVA, Mann–Whitney and Wilcoxon tests were used; $p < 0.05$ was regarded as significant. The correlations between the variables were calculated using Spearman's test.

3. Results

We observed an over two-fold decrease in PASI following the treatment (Table 1) ($p < 0.001$). Baseline serum TWEAK concentrations (from 359 pg/ml to 984 pg/ml, median 668 pg/ml) were significantly higher than those in the healthy controls (from 329 pg/ml to 738 pg/ml, median 573) (Fig. 1). Topical treatment caused further increase in serum TWEAK ($p < 0.001$) (Fig. 1).

We observed a significant positive correlation between PASI and patients' white blood cells (WBC) count, as well as between TWEAK concentrations before and after topical treatment (Fig. 2). There were no significant correlations between serum concentration of TWEAK and the following factors: disease duration and activity, age of the patients, white blood cells count, body mass index or serum glucose (Table 1). However, lower PASI after topical treatment was observed in patients whose initial serum TWEAK concentration was higher than the median compared to the individuals with initial TWEAK lower than the median (Fig. 3). We observed no other significant differences between those two groups of patients (with higher and lower initial TWEAK concentration).

4. Discussion

In the present study we have demonstrated significantly increased serum TWEAK levels in patients with psoriasis compared

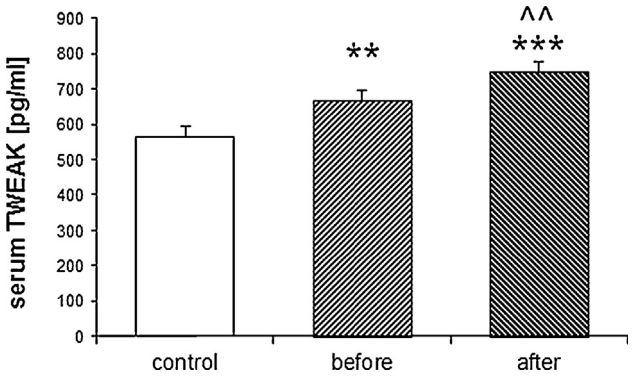

Fig. 1. Concentrations of TWEAK in serum of the control group (control) and in psoriatic patients before and after topical treatment. Data shown as mean ± SEM. Significant differences as compared to the control group are shown as: $^{**}p < 0.01$; $^{***}p < 0.001$; as compared to psoriatic patients before treatment: $^{\wedge\wedge}p < 0.01$.