

RELATIONSHIP BETWEEN ETANERCEPT AND THYROID FUNCTION IN PATIENTS WITH PSORIASIS VULGARIS

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Abstract

Background and aim. Psoriasis vulgaris, a chronic inflammatory skin disease, requires a long term medication, in order to avoid relapsing episodes. TNF-alpha, one of the targeted molecule in psoriasis therapy, seems to be also involved in thyroid disorders etiopathogenesis. The aim of this study was to evaluate the relationship between anti TNF-alpha therapy and thyroid parameters: serum level of triiodothyronine (T3), free thyroxine (FT4), thyroid-stimulating hormone (TSH) and antithyroidperoxidase antibody (AbTPO) in psoriasis treated population.

Methods. The study was performed on 44 patients with psoriasis vulgaris (20 patients under antiTNF-alpha treatment (etanercept), 24 patients with no previous systemic therapy). Serum concentrations of hormones, AbAntiTPO and TNF-alpha were measured and a thyroid ultrasonographic evaluation was performed for each patient.

Results. The mean serum level of FT4 was significantly higher in patients with no systemic treatment ($p < 0.05$). The patients treated with etanercept had a significantly higher level of TNF-alpha ($p < 0.05$). No significant difference was observed for the other evaluated parameters. Also, we found a significant negative correlation between TNF-alpha and TSH levels ($r = -0.366$, $p = 0.015$).

Conclusions. We only found that the mean level of FT4 was significantly higher in patients with no systemic treatment. Also, a negative strong correlation was seen between serum level of TSH and TNF-alpha. Based on our data, comparison with other anti TNF-alpha therapies might be of interest in future studies.

Keywords: psoriasis, TNF-alpha, etanercept, thyroid

Introduction

Psoriasis vulgaris is a chronic inflammatory skin disease with a negative impact on the patients' quality of life. The prevalence in adults varies according to geographic region: 0.91% (United States) – 8.5% (Norway) [1]. The etiopathogenesis of this multifactorial disorder is not entirely elucidated, therefore a curative treatment is

not available at the moment. To avoid relapsing episodes, a long term medication is necessary. For moderate to severe forms, with poor response to traditional systemic treatment, the next step in therapy is biological agents, most of them acting as TNF-alpha antagonists. Etanercept, a soluble human fusion protein, antagonizes the interaction of TNF-alpha with its receptors, resulting in an inhibition of this proinflammatory cytokine [2].

Psoriasis is described as an immunologically mediated disease with a genetic background, which can be

Manuscript received: 12.05.2017

Accepted: 14.06.2017

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triggered by multiple factors [3]. Among these factors some endocrinological disturbances have been incriminated and the role of hormones has been investigated before [4-7].

The level of proinflammatory cytokines, including TNF-alpha, in psoriasis is increased. It seems that TNF-alpha may also play a role in the pathogenesis of thyroid disorders. Moreover, many inflammatory chronic diseases have been associated with non-thyroidal illness syndrome (NTIS) [8,9,10].

Objective

The aim of this study was to investigate the thyroid function in patients with psoriasis vulgaris and to evaluate the relationship between anti TNF-alpha therapy and thyroid parameters: serum level of triiodothyronine (T3), free thyroxine (FT4), thyroid-stimulating hormone (TSH) and antithyroidperoxidase antibody (AbTPO) in psoriasis treated patients.

Patients and methods

This was a single centre, transversal, observational study, between 2014 -2015. Forty-four adult patients (age>18 years old) with cutaneous psoriasis were included in the study and divided in two groups: 20 patients under anti TNF-alpha treatment, more precisely, etanercept ("etanercept treatment group") and 24 patients with no previous systemic therapy ("no systemic treatment group"). This study was approved by the University Ethics Committee (300/28.07.2014) and all subjects gave their written consent prior to the enrolment. All study participants were interviewed, in order to collect demographical data: age, gender, age of onset, duration of psoriasis and systemic treatment duration, if necessary. The severity of disease was assessed using PASI score (Psoriasis Area Severity Index), which takes into consideration the lesions' aspect: erythema, desquamation and induration. The clinical assessment was performed by the same physician in order to exclude any differences between evaluations. A mild form was considered under 8.5, moderate psoriasis between 8.6-20 and severe form more than 20.1. Exclusion criteria were: patients with known thyroid dysfunction

under specific therapy, concomitant medication with drugs affecting thyroid function, such as iodine, lithium, antipsychotics, antidepressants, anticonvulsants, steroids, dopamine etc., people with malignancy, age under 18 years old, women who were pregnant or lactating. Patients with other forms of psoriasis than cutaneous involvement were also excluded.

A 5 ml blood sample was collected from each person in fasting conditions. Serum concentrations of hormones, AbAntiTPO and TNF-alpha were measured using immunometric assay method, chemiluminescence assay (with normal range) for TSH (0.55-4.78 UI/ml), FT4 (0.89-1.76 ng/dl), AbAntiTPO (<35 UI/ml), TNF-alpha (<8.1 pg/ml) and electrochemiluminescence immunoassay (with normal range) for T3 (0.8-2 ng/ml). Also, a thyroid ultrasonographic evaluation was performed for each patient.

Statistical analysis

Univariate analysis was performed to assess statistical significance of between-group differences. Continuous data were tested for normality using Kolmogorov-Smirnoff Test. Based on obtained results, numerical data were analyzed using either independent samples Student t test or Mann-Whitney U test. Bonferroni adjustment was performed for multiple testing. Qualitative data were tested using Chi square test, or Fisher test according to standard application criteria. Correlations between continuous parameters were assessed using Spearman r coefficient calculus. Receiver operating characteristic (r.o.c) analysis was used to assess the liability of TNF-alpha as treatment marker, area under the curve (AUROC) and cut-off value were determined. A threshold of $p < 0.05$ was selected to establish significance.

Results

In the study we included 44 patients with psoriasis vulgaris. Twenty-four patients (14 men and 10 women) have never been treated with psoriasis specific systemic medication and 20 patients (10 men and 10 women) were taking etanercept. Clinical characteristics of the patients are summarized in Table I.

Table I. Overall and group split clinical characteristics.

Characteristics	All patients (n=44)	Etanercept treatment (n=20)	No systemic treatment (n=24)	p-value
Age (years)	45.52±16.3	44.70±15.43	46.21±17.03	0.761
Gender a				
F	45.46	50	41.67	-
M	54.54	50	58.33	
Age at onset (years)	31.14±18.75	26.3±17.4	35.17±19.24	0.11
Duration of on-going disease (years)	14.61±13	18.9±15.71	11.03±9.08	0.125
PASI	17.64±8.36	16.22±9.27	18.82±17.51	0.32
Duration of on-going treatment (years)	2.03±2.21	2.03±2.21	-	-

Data are expressed as mean±standard deviation; a: %, Z-test for proportions; *- $p < 0.05$ is considered statistically significant; PASI = Psoriasis Area and Severity Index, F – female, M – male.

In this study, no significant differences were observed in the mean level of TSH and T3 in the two groups. The mean level of FT4 was significantly higher in patients with no systemic treatment ($p < 0.05$ Table II).

Two patients (10%) from “etanercept treatment group” and 3 subjects (12.5%) from “no systemic treatment group” had positive AbAntiTPO results, though this difference was not statistically significant. Also, no significant difference was found between the mean serum levels of AbAntiTPO in the two groups. The mean serum level of TNF-alpha in patients treated with etanercept was significantly higher ($p < 0.05$, Table II).

A significant negative correlation ($r = -0.366$, $p = 0.015$) was obtained between TNF and TSH levels, as one can observe in Figure 1.

The correlation intensity level was even higher when treated group was tested separately ($r = -0.456$, $p = 0.043$). Also, treated group showed strong positive correlations between TNF-alpha with age ($r = 0.624$, $p = 0.003$) and TNF-alpha with age at onset ($r = 0.529$, $p = 0.016$), respectively. Moreover, a borderline positive correlation between etanercept treatment duration with serum level of TNF-alpha was obtained ($r = 0.392$, $p = 0.088$) (Table III).

Table II. Overall and group split laboratory parameters.

Characteristics	All patients (n=44)	Etanercept treatment (n=20)	No systemic treatment (n=24)	p-value
TSH (Ui/ml)	2.06±1.03	1.97±0.99	2.14±1.09	0.50
T3(ng/ml)	1.24±0.21	1.26±0.26	1.22±0.18	0.65
FT4(ng/ml)	1.19±0.19	1.12±0.17	1.25±0.19	0.02*
AbAntiTPO(UI/ml)	55.25±170.25	15.37±23.17	88.48±226.29	0.32
TNF-alpha(pg/ml)	72.4±92.85	141.2±97.82	15.06±25.83	<0.01*

TSH: thyroid-stimulating hormone; T3: triiodothyronine, FT4: free thyroxine; AbAntiTPO: antithyroidperoxidase antibody; TNF-alpha: tumor necrosis factor alpha. *- $p < 0.05$ is considered statistically significant.

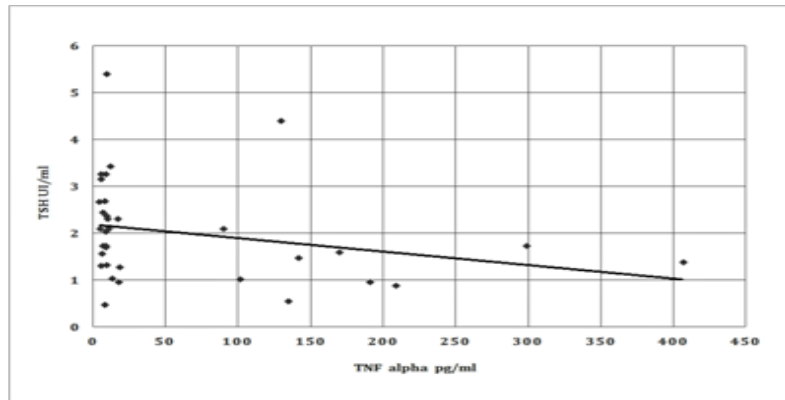


Figure 1. Correlation between serum levels of TNF-alpha and TSH in all patients.

Table III: Overall and group-split bivariate correlations between TNF-alpha and continuous parameters

Continuous parameters	Etanercept treatment (N=20)		No systemic treatment (N=24)		All patients (N=44)	
	TNF-alpha (pg/ml)		TNF-alpha (pg/ml)		TNF-alpha (pg/ml)	
	r	p	r	p	r	p
TSH (µUi/ml)	-0.456	0.043*	-0.328	0.117	-0.366	0.015
T3 (ng/ml)	0.138	0.561	0.109	0.612	0.157	0.309
FT4 (ng/ml)	0.348	0.133	0.349	0.094	-0.016	0.916
AcAntiTPO (UI/ml)	0.081	0.735	0.171	0.424	-0.037	0.809
Age(years)	0.624	0.003*	0.365	0.079	0.31	0.041*
Age at onset	0.529	0.016*	0.330	0.11	0.147	0.341
Duration of ongoing disease (years)	-0.145	0.541	0.016	0.939	0.52	0.738
Treatment duration (years)	0.392	0.088	-	-	0.392	0.088

TSH: thyroid-stimulating hormone; T3: triiodothyronine, FT4: free thyroxine; AbAntiTPO: antithyroidperoxidase antibody r- Spearman correlation coefficient; * - $p < 0.05$ - statistically significant;

Receiver operating characteristics (r.o.c) analysis revealed a significant result for TNF-alpha parameter as treatment marker (AUROC=0.877, Ci95%=0.743-0.957, $p<0.01$). For a cut-off value of >19 pg/ml, TNF-alpha presents a Sensitivity of 85% (62.1-96.8%) and a Specificity of 95.8% (78.9-99.9%) in association with the etanercept treatment (Figure 2).

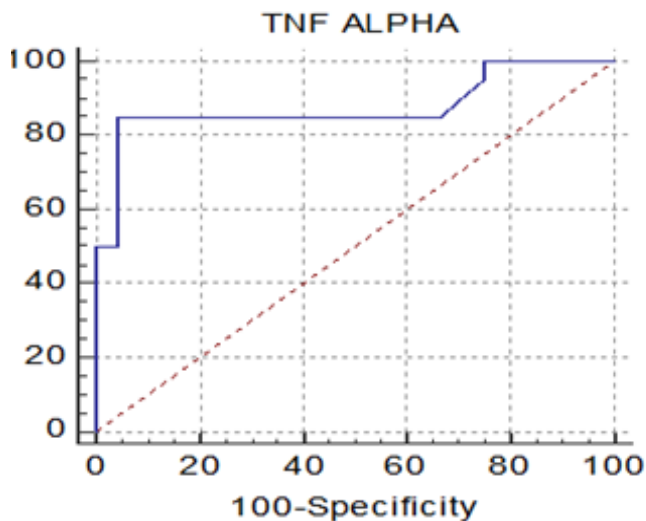


Figure 2. TNF-alpha in determination of etanercept treatment. Receiver operating characteristics curve.

When testing the correlation between duration of treatment and TSH or FT4 levels, results showed positive correlation coefficients for FT4 ($r=0.203$) and negative r values for TSH ($r=-0.297$). However, the intensity of tested correlations was weak, therefore lacking statistical significance ($p=0.331$ and $p=0.229$, respectively).

No significant association was observed between serum hormones, AbAntiTPO versus severity of psoriasis. Thus, a positive correlation coefficient was found between TSH, AbAntiTPO and severity score (PASI) ($r=0.104$; $r=0.14$), but the intensity of this correlation is weak ($p=0.502$; $p=0.36>0.05$). The correlation between T3, FT4 and severity score was found negative, with no statistical significance ($r=-0.19$, $r=-0.158$; $p=0.19$, $p=0.30$). However, a significant negative correlation was found between serum TNF-alpha level and psoriasis severity ($r=-0.366$, $p=0.015$).

Regarding the ultrasonographic assessment, 8 patients (40%) from “etanercept treatment group” had a normal aspect of thyroid gland and 12 patients (60%) from the same group had a modified structure, more precisely, the presence of micro nodules. In “no systemic treatment group” the normal ultrasonographic aspect was found in 15 patients (62.5%) and 9 subjects (37.5%) had an abnormal structure. The difference is not statistically significant ($p=0.13>0.05$). No association was found between duration of on-going disease and ultrasonographic modifications ($p=0.325>>0.05$).

Discussion

The skin can be considered a neuroendocrine organ, capable of synthesizing and releasing hormones [11]. Some of them were mentioned to play a role in psoriasis pathogenesis, due to their effects upon keratinocytes proliferation. T3 and T4 cause an increase of the Epidermal Growth Factor (EGF), which leads to epidermal hyperplasia and also stimulates the proliferation of keratinocytes [12,13].

Previous studies have shown a higher frequency of autoimmune diseases in psoriatic population [14]. Regarding the presence of thyroid disorders in psoriatic population versus healthy controls, the results are controversial. Robati RM et al. found no difference between the mean level of TSH, T3, T4 in psoriatic population compared to controls and no correlation between the level of hormones and psoriasis severity [5]. No difference has been found between psoriatic patients and controls regarding TT3 (total triiodothyronine), FT4 and TSH, but the level of free T3 and total T4 was significantly higher in patients with psoriasis in the study conducted by Arican O et al [6]. The level of FT4 was found significantly higher in patients with psoriasis, compared to controls in a study from 2009, conducted by Gul U et al [15]. In their study, LaiYC et al. concluded that patients with active disease had a lower level of TSH than patients without active psoriasis [16].

The importance of TNF-alpha activation system in patients with thyroid disorders was confirmed by Diez et al. in a study from 2002. The level of TNF-alpha was higher in patients with hypo/hyperthyroidism, compared to normal population. However, after the normalization of the thyroid function, a reduction of serum TNF-alpha level was seen only in patients with hyperthyroidism [8].

TNF-alpha is a pro-inflammatory cytokine involved in many inflammatory diseases, among them, psoriasis vulgaris. In this type of disorder, TNF-alpha is released from T helper lymphocytes in the skin, conducting to an activation of keratinocytes. This will lead to an increased production of other cytokines and chemokines with a stimulatory effect upon inflammation [17].

In our study, the mean level of TNF-alpha was higher, due to the presence of skin disease. However, only one patient had an increased level of TSH, associated with the presence of AbAntiTPO and another subject had a slightly decreased TSH with no other modification.

In the study performed by Ozawa et al., TNF-alpha was found to inhibit the effect of TSH on the thyroid gland, with a consecutive decrease in serum concentration of T3 and T4 [9].

Taking into consideration the effects of TNF-alpha upon TSH level, the literature data are controversial. In vitro studies, in cultured rat anterior pituitary cells, have shown that TNF-alpha and IL-1 decrease the level of TSH, by acting directly on the pituitary gland [18]. This effect was not found in a similar study conducted by Kennedy

et al [19]. In our study, the level of TSH was lower in patients treated with etanercept, compared with untreated patients, but the difference was not statistically significant. Moreover, a negative correlation was found between serum level of TNF-alpha and TSH. An increased level of TNF-alpha was associated with a lower serum level of TSH.

The benefits of biological treatment in patients with psoriasis are well recognized. Their effects upon thyroid function were investigated before, but not in psoriatic patients.

Raterman et al. observed the improvement of thyroid function in patients with hypothyroidism after anti TNF-alpha therapy, for rheumatoid arthritis. The level of TSH decreased significantly, with no modification of FT4 level [10]. Mention should be made regarding the high prevalence of autoimmune thyroiditis in patients with rheumatoid arthritis [20]. This association was not confirmed in patients with psoriasis by Gul U et al. in their study and was not seen in our study either [15].

The thyroid function was also evaluated in patients with inflammatory bowel disease which were taking either an anti TNF-alpha treatment, or a traditional systemic treatment [21]. Their results are comparable to ours. They also found a significant decreased level of FT4 in patients treated with anti TNF-alpha. No difference has been found regarding T3, TSH and AbAntiTPO between the two groups.

In patients with NTIS as well as in patients with psoriasis, an increased level of T4 was found, compared to controls [15]. The enzyme 5-deiodinase plays an important role in the conversion of T4 to its active form, T3. The activity of this enzyme is regulated by proinflammatory cytokines, among them TNF-alpha, which seems to have an inhibitory effect at this level [22]. Thus, the decreased level of FT4 in patients undergoing biological treatment could be explained by the blocking effect of etanercept upon TNF- α .

Etanercept is the first inhibitor of TNF-alpha approved in the treatment of psoriasis. This soluble fusion protein consists in the extracellular domains of two TNF-alpha receptors attached to the Fc portion of human IgG1. It neutralizes the activity of TNF-alpha, by preventing the interaction with its receptors [2].

In our study we measured the serum level of TNF-alpha in patients with no previous treatment and in those with etanercept therapy. Paradoxically, the mean serum level of TNF-alpha was significantly higher in treated patients, but with an improvement of skin lesions: the severity score has decreased after the treatment. A possible explanation might be that the increased TNF-alpha is not biologically active.

Data suggest that the TNF-alpha level is influenced by the treatment duration: a higher level of TNF-alpha is seen in subjects with a longer treatment period of time. However, in the literature, an increased level of TNF-alpha during etanercept treatment was associated with the

development of TNF-alpha mediated diseases, such as ankylosing spondylitis, rheumatoid arthritis, heart failure, inflammatory bowel disease, but none of those occurred in our patients [23-26]. Moreover, our data are similar with those obtained by Wu YF et al. in psoriatic patients treated with etanercept, who also presented increased level of TNF-alpha, with good response in therapy and no TNF-alpha mediated disease in association [27].

In this study the presence of thyroid nodules in the two groups of patients did not differ significantly. Thus, we couldn't establish any correlation between their development and biological treatment. To our best knowledge, there are no literature data regarding the association of psoriasis with thyroid nodules. Mention should be made regarding the geographic area where this study was performed. The region is known as iodine-deficient, which may constitute a possible confounding factor for determination of nodules development [28].

We are, however, aware of our study's limitation. The number of included patients was limited due to the amount of exclusion criteria, especially those who presented other forms, including joint involvement and other type of anti TNF-alpha treatment. Also, only psoriasis patients were included in the study, in order to see if the anti TNF-alpha therapy has an influence upon thyroid function in this population.

Conclusions

We only found that the mean level of FT4 was significantly higher in patients with no systemic treatment. Also, a negative strong correlation was seen between serum level of TSH and TNF-alpha. Based on our data and taking into consideration this particularity of etanercept (increasing the serum level of inactive TNF-alpha), the comparison with other anti TNF-alpha therapies might be of interest in future studies.

Acknowledgments

The research was funded by POSDRU grant no. 159/1.5/S/138776 grant with title: "Institutional collaborative model for the translation of biomedical research into clinical practice – TRANSCENT".

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