Original Article

CD4+CD25+FOXP3+CD127^{LOW} regulatory T cells in patients with vulgar psoriasis

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Abstract

Objective: To determine the role of regulatory cells in patients with vulgar psoriasis (VP) and to provide evidence of its possible use for diagnosis, treatment, and measurement of therapeutic effectiveness. Materials and methods: We studied 60 patients (35 women and 25 men) with VP (28 patients suffering from an advanced phase of vulgar psoriasis, 19 with remedial, and 8 with retrogressive disease phase). 42 patients suffered from VP for less than 20 years and 28 participants for 20 years and longer. Patients were also divided into three groups: with mild (10 patients), moderate (22 patients), and severe (28 patients) VP. The amount of Tregs was also examined prior to and after the narrow-band UVB phototherapy in 12 patients' vulgar psoriasis advanced phase. The group of healthy donors (HD) consisted of 22 persons. Participants' age ranged from 18 to 55 years. Results: We have shown the reduced number of CD4+CD25+Foxp3+CD127^{LOW} Tregs in peripheral blood of patients with VP (2,84±1,00% for patients with VP and 4,02±0,73% for HD), and an increase in their number over the phase transition (2,59±0,68% for advanced phase, 2,82±1,55% for remedial and 3,68±1,62% for retrogressive phase). The inverse correlation was found not only between the number of Tregs and the VP severity level (r=-0,39) but with the disease duration as well (r=-0,46). We also showed that NB-UVB phototherapy promotes the increase of Treg cells amount.

Keywords: Vulgar psoriasis, immune tolerance, regulatory T cells

Introduction

Psoriasis is a systemic inflammatory disorder [1-3] characterized by immune tolerance dysregulation and subsequent keratinocyte hyperproliferation and by epidermis thickening [4, 5]. In recent years, when studying the disease pathogenesis, scientists have paid particular attention to the role of regulatory T cells, namely the subpopulation CD4+CD25+Foxp3+CD127^{LOW} (Tregs). Regulatory T cells (Tregs) play a counterbalancing role in effector T and B lymphocytes and play an important role in immune tolerance support. In patients with autoimmune diseases, the balance between effector and regulatory cells is impaired. To provide insight into the autoimmune process pathogenesis, qualitative and quantitative analysis of regulatory T cells was carried out. It has been shown that most patients suffering from autoimmune diseases, for example, rheumatoid arthritis, systemic lupus erythematosis, type 1 diabetes, and disseminated sclerosis show a Treg cells defect [6-11]. There is a suggestion that in autoimmune diseases, both Treg dysfunction [12] and cell instability in the autoimmune inflammation focus point can develop. In addition, functional disruption of the immune balance can be exacerbated by pathogenetic T cells that become resistant to Treg-mediated suppression [13].

Treg differentiation is controlled by the FoxP3 transcription factor, an important element of Treg suppressive function [14, 15]. A decrease in Treg functional activity is correlated with a decrease in the FoxP3 level. Moreover, immunodeficiency IPEX syndrome (immune dysregulation polyendocrinopathy enteropathy X-linked syndrome) considered in the framework of the autoimmune process, is caused by the FoxP3 gene mutation [16]. FoxP3 disruption leads to an acute inflammatory response in both mice and humans [14].

$CD4^+CD25^+FoxP3^+CD127^{low}$ markers are specific to regulatory T cells. Treg expresses the low receptor level to CD127 on the cell surface [17, 18]. At the same time, CD127 expression is inversely correlated with FoxP3 expression and

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$CD25^{high}$ Treg suppressive activity [19]. Native (nTreg) $CD4^+CD25^+FoxP3^+$ develops in the thymus whereas induced Tregs can be developed in the peripheral blood from the circulating $CD4^+CD25^{low}FoxP3^-$ T cells [20].

Several studies carried out using mice as models have shown Treg's ability to inhibit both the initiation and progression of the ongoing autoimmune process [21-24]. For example, *ex vivo* grown $CD4^+CD25^+$ T cells (eTregs) have an *in vitro* suppressive ability even with the simultaneous *ex vivo* grown T effector cells.

Several studies have shown the efficiency of adoptive therapy using nTregs to treat various autoimmune diseases [23]. In particular, Kohm et al. [25] demonstrated the Treg's role in inhibiting the aggravated C57BL/6-type experimental autoimmune encephalomyelitis in mice using a MOG35-55 specific disseminated sclerosis (DS) mouse model.

A different matter is the dependence of vulgar psoriasis phases on the Treg cell level in peripheral blood. Earlier, Hairutdinov et al. [26] proved higher levels of Treg cells in peripheral blood in patients with psoriasis in the late stages compared to healthy donors. At the same time, the Treg cell level in psoriasis patients was higher in the remission phase than in healthy donors, and no significant difference was revealed between the Treg level in the late stage and during remission. Simultaneously, it was revealed that the amount of mRNA FOXP3 in the eruption sites was 10 times greater in the late stage than in the healthy donor skin.

Numerous studies have shown that Treg cells respond to drug psoriasis therapy, and the prolonged remission is associated with the Treg cell stabilization and the counter-balance between the pathogenetic memory cells and the effector cells [27]. At the end of the monoclonal antibody therapy (infliximab, etanercept, and efalizumab), patients with psoriasis show an increase in the CD4+CD25+FOXP3+ cell level both in blood and skin. The same data were shown in the adalimumab treatment [28-30]. In turn, Quaglino et al. [30] found that etanercept therapy suppresses excessive Th1/Th17 suppressive activity towards the Treg cells. Moreover, Treg cell activity stimulation may be influenced by anti-TNF mechanisms [28]. Thus, alefacept inhibits Teff cells using T cells apoptosis, due to granzymes released by NK cells. Apoptosis is triggered by Treg cells and leads to remission in turn [27]. Furuhashi et al. [15] evaluated the Treg cell blood level in patients with psoriasis before and after phototherapy. Initially, patients with PASI□90 index had a much higher Treg cell blood level than patients with lower PASI. UFB therapy has been shown to be capable of inducing Treg cell production [27]. Kubo et al. came to a similar conclusion. [31], which proved that PUVA therapy significantly increases the number of Treg cells in the blood and recovers normal Treg cells functionality in patients with psoriasis. The difference in the number of Treg cells in patients treated by different therapies can explain why some approaches to treatment (methotrexate or cyclosporin) result in short remissions, while others (alefacept and UV-B) - in longer remissions [27]. More importantly, the determination of the Treg cell level can help to predict the efficiency of a particular therapy [28, 32]. Kotb et al. [33] undertook a comparative assessment of the Treg cell level control efficiency in patients with psoriasis. The assessment was carried out against the background of different therapeutic methods: narrow-band ultraviolet phototherapy (UFB-311nm) administering adalimumab and locally administered combination of betameson and calcipotriol. Based on the results of the flow cytometry, the first treatment method showed an increase in the number of Treg cells in both peripheral blood and psoriatic areas. When adalimumab was administered, the number of Tregs remained unchanged, and the positive clinical evidence dynamics were due to a decrease in the Th17 level. Against the background of local therapy, there was both a decrease in the Th17 level and an increase in the Treg level.

Mattozzi et al. [34] described the correlation between vitamin D and Treg cells for psoriasis. The aim of the study was to identify the correlation between Treg cells circulating in blood and PASI. It has been shown that the low titer induces Th1, Th17, and Th22 activity, and vitamin D partly achieves its ability to influence immune responses due to its impact on Treg cells.

Materials and Methods

The study included 60 patients with vulgar psoriasis (35 women, 25 men) aged 18-55, being under the care of the Department of Dermatology and Venereology, Sechenov University. 28 patients were diagnosed with advanced, 19 with a remedial, and 13 with retrogressive phase. The exclusion criterion was psoriatic erythroderma, psoriatic arthritis, autoimmune diseases other than VP in the patients under study; systemic corticosteroid treatment during the previous month, as well as treatment with immunosuppressive agents (azathioprine, methotrexate) and immunoglobulins and/or monoclonal antibodies in history. PASI (Psoriasis Area and Severity Index) was calculated for each patient to determine disease severity. In 10 patients, PASI was 13.57 ± 4.32%, which corresponded to a mild severity level, in 22 patients the index was 26.42 ±2.73% which indicated moderate severity level and in 28 patients it was 41.41 ±8.11% which indicated the severe acute VP. All patients were divided into two groups, depending on the duration of the disease (42 patients with less than 20 years, 28 patients with 20 years or more).

$CD4+CD25+Foxp3+CD127^{LOW}$ Treg subpopulation level was determined for all patients. For this purpose, peripheral blood (5-10 ml) of patients with VP and healthy donors was put into tubes with K3-EDTA anticoagulant. Lymphocyte staining with appropriate antibodies was carried out using 7-Color Immunophenotyping Kit, human, produced by Miltenyi Biotec company, Germany. Cytometric analysis of $CD4+CD25+Foxp3+CD127^{LOW}$ regulatory T-lymphocytes was carried out using the MACS Quant flow cytometer (Miltenyi Biotec, Germany). Statsoft Statistica 8.0 was used

for statistical analysis. Differences at $p<0.05$ were considered statistically significant.

As the possibility to use cytometric Treg level analysis to assess the efficiency of the therapeutic potential of particular treatment tactics has been recently discussed, we have decided to show how the VP phototherapy effectiveness can be proved through the Treg level study. The study involved 12 patients with the advanced phase, whose Treg level in peripheral blood was studied before and after the UV-B-311 nm treatment session involving 15-20 procedures.

As part of the control˘group, 42 healthy donors of the same age as the patients from the main group were examined.

Results

The results of the research show that the number of regulatory CD4+CD25+Foxp3+CD127LOW T-cells (Tregs) in the blood of all examined patients with VP was low compared to healthy people. The number of Tregs in peripheral blood of patients with VP was 2.84±1.00% while 4.02±0.73% in the blood of healthy donors.

At the same time, the blood analysis of patients with VP at different stages (advanced, remedial, and retrogressive) showed that the amount of Tregs raised as the process regressed. Thus, the amount of Tregs in the advanced stage was 2, 59 ± 0.68%, the growth of Treg to 2, 82 ± 1.55% ($p = 0.001$) was noted in the remedial stage. The maximum amount of Tregs was observed in the retrogressive stage 3, 68 ± 1.62%.

In the course of the research, we also compared the number of Tregs in patients with different rapidity of recovery. The amount of Tregs was found to be inversely proportional to the disease duration. The group of patients suffering from VP for less than 20 years showed a rate of 3, 42 ± 1.11%, and the patients suffering for 20 years or more showed a rate of 2, 31 ± 0.62%. Thus, there is an inverse correlation ($r = -0.46$) between the amount of Tregs in peripheral blood and the disease duration: the longer the VP develops, the lower the Treg level.

An inverse correlation between the amount of CD4+CD25+Foxp3+CD127LOW Treg subpopulation and VP severity was also found, which was estimated with the PASI index ($r = -0.39$): the more severe the disease, the lower the Treg level in the peripheral blood of patients.

At the end of the UVB-311nm phototherapy treatment, 12 patients showed a significant increase in Treg level (2, 11 ± 0.61% before therapy and 3, 43 ± 1.02% after therapy).

Discussion

The results of the study show that the number of regulatory T cells CD4+CD25+Foxp3+ CD127^{LOW} (Tregs) in the blood of all examined patients with VP was lower compared to healthy people. A number of Tregs in peripheral blood of people with VP was 2.84±1.00% while healthy donors blood had 4.02±0.73%.

At the same time, when examining the blood of patients with VP in different phases of the disease (advanced, remedial, retrogressive), it was found that the amount of Treg increased as the disease regressed. Thus, in the advanced stage the amount of Treg was 2, 59 ± 0.68%, in the remedial stage the Treg increase up to 2, 82 ± 1.55% ($p = 0.001$) was noted. The maximum amount of Tregs was registered in the retrogressive phase - 3, 68 ± 1.62%.

In addition, in the course of the study, we compared the number of Tregs in patients with different disease duration. The amount of Tregs was found to be inversely proportional to the disease duration. In the group of patients suffering from VP for less than 20 years the indicator of Tregs was 3, 42 ± 1.11%, and in the patients suffering from VP for 20 years and more was 2, 31 ± 0.62%. Thus, an inverse correlation ($r = -0.46$) between the amount of Tregs in peripheral blood and the duration of the disease has been established: the longer the VP proceeds, the lower the Treg level.

We also found an inverse correlation between the amount of Treg subpopulation CD4+CD25+Foxp3+CD127^{LOW} and the VP severity level, which was estimated by means of the PASI index ($r = -0.39$): the more severe the disease, the lower the Treg level in peripheral blood of patients.

At the end of the UV-B-311nm phototherapy treatment session, 12 patients showed a significant increase in Treg level (2, 11 ± 0.61% prior to the therapy and 3, 43 ± 1.02% after the therapy).

In the course of the study, it wasn't revealed that the amount of Treg in the blood of patients with VP exceeds the amount of Tregs in the blood of healthy donors, which does not confirm the earlier results obtained by the Russian scientists Hayrutdinov et al. [26]. At the same time, in the carried out study, it was found that the amount of Treg in peripheral blood of patients with VP gradually increases when the advanced phase transforms into remedial and into retrogressive afterward. These data confirm the theory previously suggested by foreign scientists concerning the Treg influence on the VP phase changing [35].

The inverse correlation between disease duration and the amount of Treg concentrated in peripheral blood of patients with VP has been also proved, which is also confirmed by the researches on other autoimmune disease pathogenesis [36]. It is apparently triggered by the long-lasting autoimmune process causing regulatory mechanism depletion in the given patient category. The inverse correlation between the amount of Tregs in patients with VP and clinical pattern severity revealed in the study is the result of the activated autoimmune process which is revealed in a greater incidence of skin inflammation, development or increased amount of skin

psoriatic rashes, which is quantified by means of the PASI [index]. We have also shown the possibility to use cytometric analysis as a criterion to assess the therapy efficiency based on the example of patients treated by UV-B-311 as part of the VP therapy, which echoes the earlier study held by Kotb IS et al. [33]. All the data obtained show the key role of Tregs in the VP pathogenesis and, as a result, provide opportunities for exploring further possibilities to create immune vaccines based on autologous Tregs as an effective therapeutic method allowing to inhibit autoimmune inflammation purposefully and pointwise and minimize side effect risks at the same time.

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