https://doi.org/10.31925/farmacia.2023.6.12 **ORIGINAL ARTICLE**

CHALLENGING CORRELATIONS BETWEEN PSORIASIS SEVERITY AND TNF-α LEVELS IN HARD-TO-TREAT AREAS

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Abstract

The current study highlights the important role of tumour necrosis factor-α (TNF-α) in the development of psoriasis and suggests that an assessment of serum TNF-α levels might be useful as a predictor of psoriasis severity. Furthermore, these results could answer the dilemma raised by this article itself, more precisely the cause of the severity of special sites. We evaluated a group of 47 patients for the possible link between the severity according to Psoriasis Area and Severity Index (PASI), Psoriasis Scalp Severity Index (PSSI), Nail Psoriasis Severity Index (NAPSI), or Erythema, Scaling, Induration, Fissuring Scale (ESIF) scores and pro-inflammatory cytokines profile in difficult-to-treat areas. The severity of the disease was assessed using PASI and other scores dedicated to these special sites. The correlation between the PASI score and serum TNF-α was evaluated. Serum TNF-α levels are significantly increased in patients with severe psoriasis, which is correlated with the PASI score, and are within limits as long as the PASI score is lower, regardless of the severity of the difficult-to-treat areas. Deciphering the cause of the severity of special sites might change the therapeutic approach in order to personalise therapy according to the cytokine profile and increase access to biological therapies with significant benefits for the patient.

Rezumat

Studiul evidențiază rolul important al factorului de necroză tumoral-α (TNF-α) în dezvoltarea psoriazisului și sugerează că determinarea nivelului seric de TNF-α ar putea fi utizată ca un predictor al severității psoriazisului. Mai mult, rezultatele acestui studiu ar putea răspunde dilemei ridicate de acest articol în sine, mai exact determinarea cauzei gravității zonelor speciale. Am evaluat un grup de 47 de pacienți pentru posibila legătură între severitate utilizând scorurile PASI, PSSI, NAPSI sau ESIF și profilul citokinelor proinflamatorii în zonele speciale. Severitatea bolii a fost evaluată folosind PASI și alte scoruri dedicate acestor zone speciale. A fost evaluată corelația dintre scorul PASI și nivelul seric al TNF-α. Nivelele serice ale TNF-α sunt semnificativ crescute la pacienții cu psoriazis sever, acesta corelându-se cu scorul PASI și se află în limite normale atâta timp cât scorul PASI este mai scăzut, indiferent de severitatea afectării zonelor speciale. Descifrarea cauzei severității zonelor speciale ar putea schimba abordarea terapeutică pentru a personaliza terapia în funcție de profilul de citokine și a crește accesul la terapii biologice cu beneficii semnificative pentru pacient.

Keywords: psoriasis, TNF-α, hard-to-treat areas, biologics

Introduction

Psoriasis is a chronic immune-mediated inflammatory skin disease that can also affect the joints, having a significant impact on quality of life. It is often associated with various comorbidities (psoriatic arthritis, cardiovascular diseases, metabolic syndrome, inflammatory bowel disease, depression and anxiety) that negatively impact the natural history and the prognosis of the disease.

Its pathogenesis is a complex interaction among genetic, immunological and environmental components. While the understanding of the pathogenesis of psoriasis has been improving, it seems that TNF-α, interleukin (IL)-12, IL-23 and IL-17 are playing a critical role. Therefore, psoriasis is a chronic inflammatory disease driven by a complex interplay between the immune system and keratinocytes. Initially, psoriasis was considered a keratinocyte proliferation and differentiation disorder, but later the disease was better defined as an immune dysregulation. The T-helper type 1 (Th1)/Th2

concept was introduced as an explanation for the aggravation of psoriasis after interferon-γ treatment. Following the discovery of a new subset of T cells, the Th17 cells, the Th1/Th2 paradigm was revised. These cells seem to play a central role as they produce IL-17 and IL-22 with significant downstream proinflammatory effects on the skin, contributing to the development of psoriatic lesions. These findings have led to the integration of the IL-23/Th17 axis into the revised concept of psoriasis and have already been translated into newer therapeutic strategies in clinical practice [1].

A personalised treatment plan is becoming a necessity in order to establish the best strategy. The discovery of the Th17 pathway has improved the treatment and prognosis of psoriasis, and IL-17 family polymorphisms have been correlated with disease severity and response to treatment [2].

It has been established that Th17 cells, through IL-17, can contribute to the maintenance of the inflammatory process. The pathogenic Th17 phenotype has been described in many diseases and is associated with high severity in inflammatory experimental models. However, it is not clear if this pathogenic phenotype is present in the skin and peripheral blood, as well as its possible association with psoriasis' severity. In lesional skin, there is a high infiltration of pathogenic Th17 cells, with a correlation between their density and the PASI score [3]. Likewise, in peripheral blood, there is a pool of Th17 cells that can acquire pathogenic features, and, similarly with the skin lesions, the percentage of pathogenic Th17 cells correlates with disease severity [4].

Moreover, there is some disagreement concerning the correlation between serum levels of TNF-α, IL12/23p40 and IL-17 and disease severity (according to the PASI score). Serum levels of TNF-α, IL-12/23p40 and IL-17 may potentially be elevated due to skin, joint, or nail disease, while PASI is an indicator only for skin involvement. For patients with concomitant joint and/or nail disease, it is still uncertain whether the differences found in serum levels of TNF-α, IL-12/23p40 and IL-17 can be explained solely by the presence of cutaneous psoriasis, psoriatic arthritis, nail psoriasis, or a combination of factors [4].

Nevertheless, different studies have shown that serum levels of TNF-α, IL-12, IL-23 and IL-17 don't seem to correlate with disease severity in untreated patients. In particular, serum levels of TNF-α were significantly higher in psoriatic patients compared to controls, in contrast to IL-12/23p40 and IL-17 levels. According to multiple studies, especially those regarding TNF-α, skin findings don't reflect peripheral blood findings and *vice versa*. Serum concentrations of cytokines may be altered by several processes, such as the production, tissue deposition, degradation and elimination of these molecules. It is likely that changes of cytokine serum levels in psoriatic patients may not be the cause, but the consequence of the disease. It is possible that there are other sources outside the skin lesions that contribute to the production of these cytokines; this theory may provide a potential mechanism linking psoriasis with its extracutaneous comorbidities. It is still unclear what the real correlation is between serum levels of various inflammatory molecules and the PASI score, and whether the serum levels of these cytokines may be used as an objective parameter for measuring psoriasis activity and clinical severity [4–6].

Psoriasis pathogenesis involves a crucial interplay between T cells and dermal dendritic cells (DCs). Dermal DC release IL-12 and IL-23, which will promote Th1, Th17 and Th22 responses, producing epidermal hyperproliferation and alteration of epidermal differentiation. Traditionally, CD4+ T cells have been classically separated into two dominant effector cell populations: Th1 and Th2. Th1-type CD4+ T cells producing high levels of IFN-γ and TNF-α are important players in triggering psoriasis. TNF-α is an important proinflammatory cytokine in acute and chronic inflammation, has anti-tumour activity and helps defend against infections. It is produced by many cells, including macrophages, monocytes, lymphocytes and keratinocytes, and induces CD4 cell proliferation and the production of various chemokines and cytokines, such as IL-1, but also promotes apoptosis in various cell types. Serum levels of TNF-α may correlate with disease activity, and TNF-α inhibitors have been shown to be effective in the treatment of psoriasis [7].

The current study aims to determine the cause of the difficulty in treating these special areas. The challenge may come from the histological characteristics of the scalp, the palms, the soles or the nails in comparison with more common areas like the trunk. There is limited information regarding the specificity of the pro-inflammatory cytokine profile in these difficult-to-treat areas, questioning the existence of a possible link between the reactivity of these areas to biological therapies and a specific Th cell subtype.

Materials and Methods

The aim of this study was to evaluate serum levels of TNF-α in psoriatic patients and also to assess the possible correlation between serum levels of TNF-α and disease severity.

A group of 47 patients were evaluated for the possible link between disease severity according to PASI, PSSI, NAPSI, or ESIF scores and pro-inflammatory cytokine profiles in difficult-to-treat areas.

Only the patients with chronic plaque psoriasis were included. Those who received any topical or systemic treatment within the previous 3 months were excluded from the study, as were those with other diseases that could influence the serum levels of TNF-α. The disease

severity was assessed using the PASI score and other special area scores.

Serum TNF-α levels were measured using the Quantikine® Human TNF-α Immunoassay. The correlation between the PASI score and serum TNF-α was evaluated. The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Roma Medical Centre for Diagnosis and Treatment, Bucharest, Romania. All subjects gave their informed consent in accordance with the requirements of the Institutional Ethical Committee.

Results and Discussion

Out of a total of 47 patients, 42.5% (20 patients) were classified as having a severe form of psoriasis with a median PASI of 16.09 (Table I).

Table I

Distribution of patients according to the degree of severity

	Moderate psoriasis	Severe psoriasis
Number of patients	27	20
Mean PASI	7.83	16.09

This data is consistent with the ones obtained from clinical trials and clinical practice, respectively. 62% of them (29 patients) had at least one difficult-to-treat area, distributed as follows: 5 patients with nail lesions, 13 patients with palmoplantar lesions, and 11 patients with significant scalp involvement. Regardless of the value of severity scores (PASI or special area scores), all 29 patients were classified as having severe psoriasis with a DLQI greater than 10.

There is limited information in the literature about the special site severity scores (such as NAPSI, ESIF and PSSI) compared to other severity scores more commonly used in clinical trials and current clinical practice (such as PASI). The information regarding the maximum value of each score and the minimum value required for classifying it as a severe form of psoriasis is compiled in Figure 1. Interestingly, in a severe form of psoriasis, the cumulative score represents 20% (NAPSI score) and 33%, respectively (ESIF or PSSI scores), of the maximum score of the area involved.

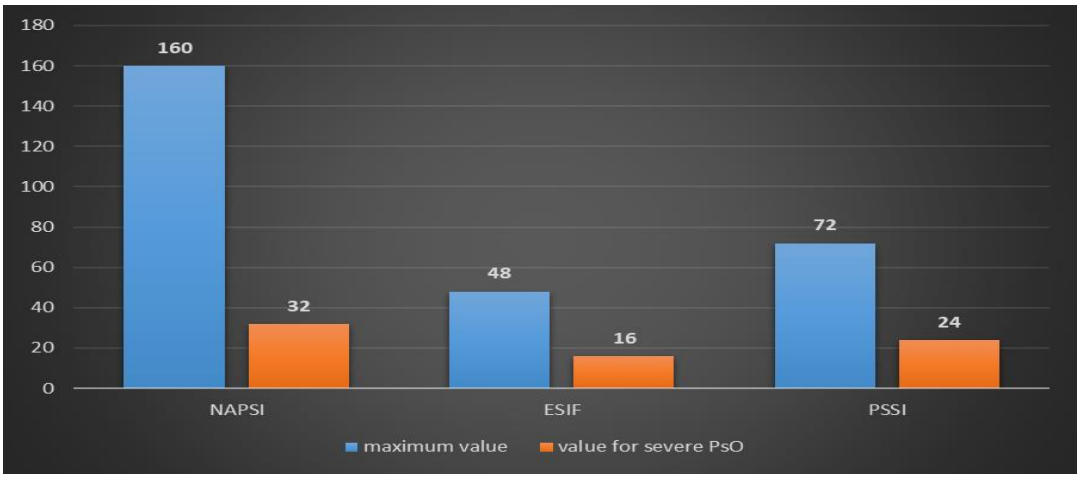

Figure 1.

Severity scores for difficult-to-treat areas: maximum value possible and the minimum value required for a severe form

By using the PASI score, more than 60% of patients with involvement in difficult-to-treat areas could be classified as having moderate psoriasis. This misjudgement can significantly impact patients' management and even block access to biological therapy. More specifically, all patients with palmoplantar involvement would be classified as having a moderate form of psoriasis according to the PASI score, although various studies support the idea that this difficult-to-treat area is associated with a significant impact on quality of life, always disproportionately compared to the affected area. These patients were also classified as having severe psoriasis based on the DLQI score that was greater than 10 (Table II).

Regardless of the degree of severity and the presence or absence of involvement in a difficult-to-treat area, the TNF-α level was measured in all patients. The results raised some concerns that should be addressed in further studies. Severe psoriasis, including those with involvement in difficult-to-treat areas, was associated with increased levels of TNF-α, while moderate psoriasis, especially those with involvement in difficult-to-treat areas, was associated with normal levels of TNF-α (Table III).

Table II

Stratification of patients with difficult-to-treat areas according to PASI

Area severity score	Patients with hard-to-treat affected areas	Number of patients	Mean PASI	Severity of hard-to-treat areas
NAPSI	5	3	12.2	severe
		2	7.1	severe
ESIF	13	13	6.9	severe
PSSI	11	9	11.65	severe
		2	7.1	severe

Table III

Association of TNF-α levels with moderate and severe forms of psoriasis

The disease severity according to PASI score	Number of patients	TNF-α levels	Severity of hard-to-treat areas	Number of patients
Moderate Psoriasis	27	Normal levels of TNF-α	severe	17
Severe Psoriasis	20	High levels of TNF-α	severe	12

In recent years, various studies have shown that IL-17-producing T cells represent a new lineage of effector CD4 T cells, the Th17 cells. Later, IL-23 was shown to mediate the expansion of IL-17-producing cells, and the finding led to the discovery of Th17 cells. The concept of Th17 cells as a distinct subset of T cells was further strengthened by the delineation of their unique differentiation pathway. Like Th1 and Th2 cells, Th17 cells produce a group of distinctive cytokines. Th17 cells do not produce IFN-γ or IL-4; instead, they produce IL-17 and express the IL-23 receptor (IL23R). Although IL-23 was originally shown to be important for the proliferation of Th17 cells, compelling scientific evidence suggests that IL-23 alone was not sufficient for the initiation of Th17 differentiation in naïve T cells as they did not express IL-23R. A concomitant presence of transforming growth factor-b (TGF-b) and at least one proinflammatory cytokine, such as IL-6, IL-1b, IL-23, or IL-21, was necessary for the differentiation of naïve T cells to Th17 cells. After induction by TGF-b and proinflammatory cytokines, differentiating and differentiated Th17 cells upregulate the expressions of IL-23R and IL-1R1, which may mediate or maintain the final lineage specification or induce the proliferation of precommitted Th17 cells. There is evidence that IL-23 had little effect on fully differentiated Th1 or Th2 cells, and the Th1 or Th2 development apparatus inhibited the development of Th17 cells. Mature Th17 cells were resistant to suppression by Th1 or Th2 cytokines. These studies suggest that the differentiation of CD4+ T cells to Th17 cells starts at a point that precedes commitment to the Th1 or Th2 lineages [1, 8, 9].

The systemic and local activity of IL-17 and Th17 seems to be an important part of the development of the autoimmune reaction. The ability to induce pro-inflammatory function in cells outside the immune system, *e.g.*, synovial cells, is one of the factors leading to chronic inflammation. Disturbances in the balance between Th17 lymphocytes and regulatory cells are described in the majority of autoimmune diseases. The correlation between disease activity and concentration of IL-17 or percentage of Th17 in peripheral blood or other body fluids could be an additional laboratory parameter used in clinical prognosis and monitoring the clinical course of the disease [10]. Th1 cells have long been considered to be major effectors in multiple autoimmune diseases, while Th2 cells have been known to be involved in atopy and asthma. More recently, Th17 cells have been implicated as culprits in a plethora of autoimmune and other inflammatory diseases. An imbalance between Th17 and Treg cell function may be central to some of these diseases. Although there is abundant evidence that Th17 cells have important roles in a variety of inflammatory conditions, there is considerable controversy as to whether the key cytokines produced by these cells are essential in these diseases [11].

Kagami *et al.* demonstrated that circulating Th1, Th17 and Th22 cells were increased in psoriasis patients while plasmatic levels of Th17 and Th1 cells decreased after TNF-α antagonist therapy. CD4+ Th17 cells were present in higher numbers in psoriatic lesions than in healthy skin and decreased after treatment. IL-17 can also be produced by CD8+ T cells, called type 17 cytotoxic T cells (Tc17). Tc17 cells are characterised by sharing some, but not all, phenotypic and molecular features with both Th17 and Th1 cells. Studies have shown that Tc17 cells derived from psoriasis-inflamed skin tissue produce IL-17, IL-21 and IL-22 (Th17-related cytokines), as well as TNF-α and IFN-γ (Th1-related cytokines).

In patients with psoriasis, researchers recently identified a unique subset of T lymphocytes called Th22 that are characterized by the secretion of IL-22, IL-10 and TNF-α, but not IFN-γ, IL-4, or IL-17. Some studies have shown that cutaneous dendritic cells, particularly Langerhans cells, can induce the differentiation of distinct IL-22-producing Th22 cells from naïve T cells and peripheral T cells with the help of IL-6 and

TNF-α. Additionally, further studies showed that Th22 cells were increased in psoriatic lesions and, like Th17 cells, showed an epidermal homing characteristic. Th22-producing IL-22 amplified TNF-α-induced signals, leading to a proinflammatory microenvironment during skin immune reactions. These findings imply that Th22 may also contribute significantly to the pathogenesis of psoriasis [12–14].

TNF-α is a crucial cytokine in the inflammatory process of psoriasis and is produced by cells of both the innate and adaptive immune systems. Circulating levels of TNF-α, IFN-γ and IL-17A are directly correlated with the severity of psoriasis. Biological therapy has been shown to reduce TNF-α levels in most studies. Anti-TNF-α therapies block the free soluble fraction and the membrane fraction of this cytokine. Anti-TNF has been shown to act more rapidly on Th17 populations than on Th1 populations, and the inhibition of the Th1 population appears to have a stronger correlation with clinical improvement [15–16].

TNF can be produced by various cells, including keratinocytes and Th1 and Th17 cells. Keratinocytes have both TNF-α and IL-17 receptors and can produce inflammatory products upon stimulation. TNF and IL-17 signalling share a common pathway, such as activation of NFκB. Previous studies suggest that TNF-a may serve as an indirect activator of the Th17 response through activating effects on myeloid dendritic cells. Additionally, in a recent study, TNF and IL-1 were shown to further increase Th17 cell differentiation in the presence of TGF-β and IL-6. Chiricozzi *et al*. investigated the complex interplay between IL-17 and TNF-α in psoriasis and indicated that they enhanced each other's effect, both dependently and synergistically. Their combined activity contributed to many of the key inflammatory pathways in psoriasis. Consistent with these findings, several studies have shown that treatment with TNF-α antagonists suppressed synergistic TNF-α/IL-17 gene transcripts to a greater extent than TNF-α "single-regulated" gene products. The clinical response to TNF-α antagonists was correlated with an early reduction of IL-23 and IL-17A, followed by a tardive decrease in Th1-associated genes [17-20].

Blockade of TNF-α leads to an initial reduction of the chemokine CCL20, which preferentially recruits TH17 cells into inflamed tissue, coinciding with the loss of IL-17 and diminution of dermal and epidermal T-cells. In addition, it leads to normalisation of DC numbers and reduction of IL-23 cytokine expression, followed by normalised keratinocyte differentiation, histological improvement and clinical response. TNF-α maintains a pro-inflammatory environment that primes pathogenic TH17 T-cells by inducing IL-23, maintaining them at the site of inflammation, and sustaining TH17 cytokine production. Although TNF-α might contribute to increased IL-17 production by TH17 cells, IL-23 directly governs TH17 cytokine production, both by critically participating in TH17 cell polarisation and by stimulating the production of IL-17 by differentiated TH17 cells. IL-17 may act synergistically with TNF-α to further potentiate the expression of multiple pro-inflammatory mediators known to play a role in psoriasis, such as IL-8, beta-defensins, S100A proteins, IL-19 and CCL20 [21, 22].

The greatest challenge in establishing disease severity, therapeutic choice and monitoring effectiveness are "difficult-to-treat" areas, especially in the absence of significant involvement of the body surface elsewhere. The location and morphological features of scalp, nail, palmoplantar and genital psoriasis can often lead to ineffective topical treatment and often require systemic treatment. In spite of the small surface area that is commonly affected by psoriatic lesions in such areas, patients have increased physical impairment and emotional distress. The quality of life (QoL) of patients with psoriasis affecting fewer common areas may be disproportionately impacted by the affected area. Patients with scalp psoriasis have reported greater disease burden and pruritus severity than those with psoriasis localised to other areas. Nail psoriasis can lead to substantial functional impairment in manual dexterity as well as pain, discomfort and psychological stress, resulting in decreased QoL and work productivity [23]. Patients with palmoplantar psoriasis have reported worse health-related quality of life than those without. The locations and morphologic features of scalp, nail, palmoplantar and genital psoriasis can often lead to ineffective treatment with topical therapies and often require systemic treatment [24].

Severity assessment in patients with several affected areas and at least one difficult-to-treat area may be an issue regarding health insurance. The existence of country-specific therapeutic protocols limits the use of newer systemic therapy (biologics, small molecules) for severe psoriasis, only to be done according to PASI, Physician's Global Assessment (PGA), Body Surface Area (BSA) and Dermatology Life Quality Index (DLQI) scores. The existence of scores dedicated to special areas (PSSI, NAPSI and ESIF) allows a more accurate calculation of the disease severity in these areas, but the dilemma remains whether or not to assess the overall severity of the disease by integrating these special area scores into already existing scores. The limitation of current severity scores is that they don't fully assess the impact of disease on patients' quality of life, and therefore many of them do not receive adequate care.

For example, in a patient with psoriasis that involves two areas (scalp and trunk), the scalp presents erythema, induration and exfoliation involving an area of over 70%, while the trunk lesions involve up to 10%, with the highest grade of severity (grade 4) regarding erythema, induration and scaling. The PASI score for this patient is 8, meaning a moderate form of psoriasis, but if the PSSI score were used instead, obtaining a score of 60 points, the patient would be

classified as having a severe form of psoriasis. These findings can significantly influence therapeutic options and the choice of an effective treatment for both areas involved. For a more accurate diagnosis and severity assessment, one of the solutions could be to classify the disease according to the highest calculated score, whether it is PASI, PSSI, NAPSI, or ESIF. The severity assessment would be made according to the specific scores of the special areas, and then the patients would be classified as having severe psoriasis with all the implications arising from this position (choosing the right treatment according to the involvement of a difficult-to-treat area, establishing the therapeutic goal, evaluating the success or failure of the therapy). The challenge of this new possible classification could be the subsequent monitoring of the effectiveness of the treatment [24].

The current study highlights the important role of TNF-α in psoriasis pathogenesis and suggests that TNF-α serum level assessment might be useful for clinical evaluation of severity. Thereby, TNF-α serum levels are within limits as long as the disease is not classified as severe according to the PASI score, regardless of the severity of the special sites. At the same time, TNF-α serum levels are significantly increased in patients with a severe form of psoriasis, according to the PASI score.

Various studies have shown that high levels of TNF-α correlate with the clinical severity of psoriasis and concluded that measurement of serum TNF-α levels can be an objective parameter for assessing disease severity [6, 25-29]. Further investigations are needed to clarify the pathogenic role and clinical significance of TNF-α, and they may provide important clues to help develop new therapeutic strategies.

Furthermore, these results could help uncover the cause of the severity of certain areas. Thus, it could be a mixture of several factors, such as different particular anatomical structures with specific characteristics that possess a lower response to treatment; a correlation between the significant impact on the quality of life and severe forms of psoriasis involving more common affected areas; or the specificity of the proinflammatory cytokine profile, such as increased serum levels of IL-17, in these difficult-to-treat areas that could influence the response to biological therapies. The role of IL-17 in the pathophysiology of psoriasis is now world-wide recognised, and some studies have shown a significant positive correlation between IL-17 serum and scale concentrations and psoriasis severity, indicating that IL-17 could be used as a biomarker of disease severity [5, 6, 30-32].

Conclusions

A better understanding of psoriasis severity may change the approach to the patient with involvement of difficult-to-treat areas in order to obtain personalised therapy according to the pro-inflammatory cytokine profile, further increasing access to biological therapies with significant benefits for the patient.

Conflict of interest

The authors declare no conflict of interest.

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