Increased plasma lipocalin-2 levels correlate with disease severity and may be a marker of acute inflammatory response in patients with psoriasis

Chuyen Thi Hong Nguyen, Oanh Phan Tram Nguyen
Department of Dermatology, University of Medicine and Pharmacy at Ho Chi Minh City, Vietnam

Abstract

More than a skin disease, psoriasis is also considered a systemic disorder. Lipocalin-2, an adipokine, may be a link between psoriasis and systemic inflammation. We conducted this study to measure the plasma level of lipocalin-2 and investigate its relationship with the clinical manifestations in patients with psoriasis. We assessed 62 patients with psoriasis and 31 healthy controls. Their demographic information and clinical characteristics were determined by physical examination and review of the recorded medical history. Plasma lipocalin-2 levels were measured using an enzyme-linked immunosorbent assay. Plasma lipocalin-2 concentration was significantly higher in patients with psoriasis than in the control group (P<0.001). Patients with acute psoriatic subgroups, including psoriatic erythroderma and pustular psoriasis, had significantly higher plasma lipocalin-2 levels than those with the chronic plaque type. In addition, plasma lipocalin-2 concentration positively correlates with the disease severity index, including the psoriasis area severity index, body surface area, high-sensitivity C-reactive protein, nail psoriasis severity index, and pustular severity index. In patients with psoriasis, increased plasma lipocalin-2 levels correlated with severity and indicated an active disease state. These findings suggest that lipocalin-2 may play an important role in determining the pathogenesis of acute psoriasis and may serve as a valuable clinical biomarker of this disease.

Introduction

Psoriasis is a common immune-mediated disease that affects approximately 2-3% of the population. It mainly affects the skin and joints and increases the comorbidities that lead to many mental problems.\(^1\) The relation of the TNF-α – IL-23 – Th17 – IL-17 axis to the pathogenesis of psoriasis has been proven in the recent decade.\(^2\) Therefore, psoriasis is not only a skin disease but is also a systemic inflammatory condition. Diabetes and metabolic syndrome are the two main comorbidities of psoriasis. Compared to the normal population, patients with psoriasis have twice the risk of developing metabolic syndrome, which is present in approximately 20–50%.\(^3\) The proportion of obesity in psoriatic patients was higher than in the normal population,\(^4\) and the body mass index (BMI) has been positively correlated with the risk of developing psoriasis.\(^5\) Psoriasis and its comorbidities are linked by a chronic inflammatory condition that increases cytokine production, which leads to metabolic disorders, atherosclerosis, and myocardial infarction.\(^6,7\) Adipokines, which are produced by white fat tissue, have been implicated as one of the connections of the complex pathogenesis between psoriasis and obesity as well as metabolic syndrome. These proteins have crucial functions in the metabolism of carbohydrates and lipids and the development of insulin resistance and atherosclerosis.\(^8\) Some adipokines, including leptin, adiponectin, resistin, and visfatin, have been reported to increase in psoriasis and may participate in its pathogenesis.\(^9,5\)

Lipocalin-2 is an adipokine that has recently gained attention because of its role in the pathogenesis of psoriasis. It stimulates neutrophils to release pro-inflammatory cytokines, including IL-6, IL-8, TNF-α, and IL-1α, via the 24p3R receptor on the cell surfaces.\(^10,11\) Recent studies have found a high lipocalin-2 expression in psoriatic lesions and keratinocytes, with lipocalin-2 being produced by neutrophils. Previous studies have also reported an increased level of lipocalin-2 in patients with psoriasis vulgaris compared to normal controls, showing a positive correlation between lipocalin-2 levels and the psoriasis area severity index (PASI),\(^3,11-14\) and pruritus.\(^15\) Another study found high expressions of lipocalin-2 in the affected tissues compared to normal skin.\(^16\)

The role of lipocalin-2 in the pathogenesis of psoriasis is not fully understood. Previous reports have only focused on the correlation between lipocalin-2 and metabolic syndrome characteristics in psoriasis vulgaris.\(^9,11,14\) However, the changes in its levels in different types of psoriasis, including psoriatic arthritis, psoriatic erythroderma, and pustular psoriasis, were not investigated. The pathogenesis of psoriasis in different concepts may lead to a specific approach.\(^17\) Therefore, we performed this study to measure the level of lipocalin-2 in different types of psoriasis and investigate the correlation of its level and clinical and laboratory characteristics of psoriatic patients.
Materials and methods

Study population

This study was conducted at the Ho Chi Minh City Hospital of Dermatology-Venereology, Vietnam, between November 2019 and July 2020. A total of 62 patients diagnosed with psoriasis and 31 healthy volunteers without a personal or family history of psoriasis or inflammatory disorders were enrolled in the study. We excluded patients with psoriasis treated with systemic anti-inflammatory or immunosuppressive agents within 6 months prior to the study, pregnant patients, lactating patients, and patients with other acute and chronic diseases known to be associated with increased plasma lipocalin-2 levels (infection, renal disease, lupus nephritis, severe pancreatitis, autoimmune diseases, cancer, and immunodeficiency). All participants signed an informed consent form after fully understanding the benefits and risks of this study.

After qualified physicians performed physical examination to confirm the diagnosis of psoriasis, a complete medical history (general health, age, sex, occupation at presentation, course and duration of disease, and family history), clinical examinations, and laboratory tests were obtained from each patient. Three subgroups of psoriasis were collected in a 1:1:1 ratio (psoriatic erythroderma: psoriasis vulgaris: pustular psoriasis). Among them, patients whose symptoms met the Classification Criteria for Psoriatic Arthritis were classified as having psoriatic arthritis. The severity of skin disease was determined using the PASI and BSA. For generalized pustular psoriasis, the severity was evaluated according to a previous report. Nail abnormalities were recorded, and the severity of the affected nails was evaluated using the nail psoriasis severity index (NAPSI) score.

Blood sample preparation

Up to 3 mL of peripheral blood samples were obtained from patients and healthy subjects and stored in plasma separator test tubes with ethylenediaminetetraacetic acid. The blood samples were then analyzed at the Medic Medical Center (Ho Chi Minh City, Vietnam) within 2 h of collection, and the plasma lipocalin-2 level was quantitatively detected using a human NGAL enzyme-linked immunosorbent assay kit (KIT 036 RUO, BioPorto Diagnostics, Denmark). Blood samples from the patients were collected and paired with routine analyses at the first visit.

Statistical analyses

All collected data were coded and analyzed using a standard software (R version 3.6.3 for Mac OS). Qualitative data are described as frequencies and percentages (%). Quantitative data with normal distributions are described using mean and standard error of the mean (SEM), while those with non-normal distributions are described as median and interquartile range.

The chi-square test was applied for the comparison of non-numerical data. For normally distributed data, Student’s t-test and ANOVA were used to determine the statistical significance of the difference between two or more study group means. The Mann-Whitney and Kruskal-Wallis tests were used to compare two or more groups with non-normal distributions. The Spearman correlation test was used to study the correlation between quantitative parameters. All statistical tests were two-sided, and a P-value <0.05 was considered significant in all statistical tests.

Results

Plasma lipocalin-2 concentrations in psoriasis

Selected demographic, clinical, and laboratory characteristics of patients with psoriasis and healthy controls are summarized in Table 1. There were no statistically significant differences between the two groups with respect to sex, age, and BMI.

The median value of plasma lipocalin-2 level in psoriatic patients was 263.6 ng/mL (interquartile range 207.7–384.1 ng/mL). It was significantly higher than in controls (median 125.8 ng/mL, interquartile range 95.7–165.5 ng/mL; p<0.0001) (Figure 1). Moreover, all subgroups of psoriasis also showed significantly upregulated lipocalin-2 levels in comparison to the control groups. In particular, patients with acute psoriasis, including psoriatic erythroderma.
and pustular psoriasis, had significantly higher plasma lipocalin-2 levels than those with the chronic plaque type (Table 2). These data suggest that lipocalin-2 may be a good marker of the acute inflammatory response in psoriasis.

**Plasma lipocalin-2 levels and clinical and laboratory features**

In this study, plasma lipocalin-2 levels did not correlate with the demographic characteristics, including age, age of onset, and duration of disease, in patients with psoriasis (Table 3). Despite being an adipokine, we did not detect any relationship between the plasma lipocalin-2 levels and the different metabolic parameters in patients with psoriasis, including BMI, waist circumference, and metabolic syndrome status (Tables 3 and 4). This finding indicates that lipocalin-2 may not play its role as an adipokine but participates in other pathways in the complex pathogenesis of this disease as an inflammatory protein.

**Plasma lipocalin-2 levels in correlation with severity markers**

**Skin**

Regarding the markers of skin severity, lipocalin-2 levels positively correlated with BSA and PASI in the subgroup of psoriatic erythroderma and psoriasis vulgaris and the severity score of generalized pustular psoriasis in the subgroup of pustular psoriasis (Table 3).

Table 1. Clinical manifestation of studied groups.

| Characteristics                          | Patients with psoriasis (n = 62) | Control subjects (n = 31) | P value |
|----------------------------------------|--------------------------------|--------------------------|---------|
| Sex, n (%)                             |                                |                          | 1.000†  |
| Male                                   | 35 (56.4)                      | 17 (54.8)                |         |
| Female                                 | 27 (43.6)                      | 14 (45.2)                |         |
| Age, years                             |                                |                          |         |
| ≤40 yrs old                            | 48 (77.4)                      | 31 (100)                 | 0.945$  |
| ≥40 yrs old                            | 14 (22.6)                      |                          |         |
| Age of onset, n (%)                    |                                |                          |         |
| ≤10 years                              | 40 (64.5)                      | 20 (64.5)                | 0.921†  |
| <10 years                              | 22 (35.5)                      |                          |         |
| Duration of disease, n (%)             |                                |                          |         |
| BMI (kg/m²)                            | 21.5±3.4                       | 21.5±2.8                 | 0.472‡  |
| BMI Categories, n (%)                  |                                |                          |         |
| Underweight                            | 13 (21.0)                      | 7 (25.0)                 |         |
| Normal weight                          | 30 (48.4)                      | 13 (41.9)                |         |
| Overweight                             | 8 (12.9)                       | 6 (21.4)                 |         |
| Obese                                  | 11 (17.7)                      | 2 (7.1)                  |         |
| Waist circumference (cm)               | 80.5±9.6                       | 77.2±8.8                 | 0.115†  |
| Metabolic syndrome, yes (%)            | 12 (19.4%)                     | 4 (13.3%)                | 0.751†  |
| Subgroups of psoriasis, n (%)          |                                |                          |         |
| Psoriasis vulgaris                     | 21 (33.9)                      |                          |         |
| Pustular psoriasis                     | 20 (32.2)                      |                          |         |
| Psoriatic erythroderma                 | 21 (33.9)                      |                          |         |
| Psoriatic arthritis                    | 16 (25.8)                      |                          |         |
| Nail psoriasis, yes (%)                | 41 (66.1)                      |                          |         |
| Severity of disease: BSA               |                                |                          |         |
| Psoriasis vulgaris                     | 19.0 (10.0-54.0)               |                          |         |
| Psoriatic erythroderma                 | 96.0 (97.0-99.0)               |                          |         |
| Pustular psoriasis                     | 58.5 (35.5-81.5)               |                          |         |
| Severity of disease: PASI              |                                |                          |         |
| Psoriasis vulgaris                     | 13.0 (5.8-21.7)                |                          |         |
| Psoriatic erythroderma                 | 44.4 (34.5-49.8)               |                          |         |
| Severity score of GPP                  | 10.4±2.8                       |                          |         |
| NAPS1                                  |                                |                          |         |
| Psoriasis vulgaris                     | 50.1±21.9                      |                          |         |
| Psoriatic erythroderma                 | 77.8±31.4                      |                          |         |
| Pustular psoriasis                     | 60.1±21.0                      |                          |         |
| Psoriasis arthritis, n (%)             |                                |                          |         |
| Only peripheral joints                 | 4 (6.5)                        |                          |         |
| Both axial and peripheral joints       | 12 (19.3)                      |                          |         |
| No                                     | 46 (74.2)                      |                          |         |
| Topical treatment, yes (%)             | 38 (61.3)                      |                          |         |
| hs-CRP, mg/L                           | 18.8 (4.6-101.1)               | 0.6 (0.4-1.1)            | <0.001**|

Data were described using mean (± standard error of the mean) for normal distribution and median (interquartile range) for non-normal distribution. Differences between patients and controls was analyzed by using †Chi-square, ‡Mann-Whitney, §T-Test, and ¶ Fisher’s Exact Test. BMI: Body Mass Index, BSA: Body Surface Area, GPP: Generalized Pustular Psoriasis, hs-CRP: high sensitivity C-Reactive Protein, NAPS1: Nail Psoriasis Severity Index, PASI: Psoriasis Area Severity Index. *Statistically significance (p<0.05).
Nail involvement
As nails are known to be highly impaired in patients with psoriasis, we detected a significant positive association (p=0.044, Table 3) upon analysis of the relationship between lipocalin-2 levels and the nail psoriasis severity index (NAPSI). However, there was no statistical difference in the lipocalin-2 concentrations between patients with and without nail lesions (p>0.05, Table 4).

Joint involvement
Although plasma lipocalin-2 levels in patients with psoriatic arthritis were found to be significantly higher than those in the control group (p<0.0001, Table 2), no significant increase in plasma lipocalin-2 levels was observed in patients with both axial and peripheral joint involvement compared with patients with only peripheral joint involvement and patients without joint involvement (p>0.05, Table 4).

Laboratory findings
High-sensitivity C-reactive protein (hs-CRP) is a sensitive marker of systemic inflammation in psoriasis (20). In our study, both the plasma hs-CRP and lipocalin-2 levels in patients with psoriasis were significantly higher compared to that of healthy controls (Table 1 and Figure 1). Furthermore, a significant positive correlation between lipocalin-2 levels and hs-CRP levels was detected (p<0.0001, Table 3).

Discussion
To emphasize the importance of our findings, we propose three points for discussion.

Plasma lipocalin-2 plasma levels were significantly increased in patients with psoriasis compared to those in the control groups
This finding is consistent with other previous studies, but our data particularly pointed out that patients with acute psoriasis, including psoriatic erythroderma and pustular psoriasis, had significantly higher plasma lipocalin-2 levels than those with the chronic plaque type. The pathways involved in acute inflammatory conditions and the chronic type in psoriasis vulgaris may be different, though the majority of the process have not been understood. The main cells that actively participate in these responses include keratinocytes and neutrophils. Keratinocytes produce chemokines and lipocalin-2, which recruit neutrophils to migrate into the lesional area and produce oxidation stimulation and various cytokines and peptides, including lipocalin-2. Lipocalin-2 regulates the function of neutrophils, including activation, migration, and infiltration, and stimulates neutrophils to produce pro-inflammatory cytokines, such as IL-6, IL-8, IL-1a, and TNF-α, via specific 24p3R on these cell surfaces. Therefore, neutrophil dysfunction may lead to severe diseases.

Both IL-17 and TNF-α are important cytokines in the pathogenesis of psoriasis. The expression of lipocalin-2 has been shown to be enhanced by IL-17A stimula-

Table 2. Plasma lipocalin-2 in subgroups of psoriasis.

|                      | Controls n = 31 | Psoriasis vulgaris n = 21 | Psoriatic erythroderma n = 21 | Pustular psoriasis n = 20 | Psoriatic arthritis n = 16 |
|----------------------|----------------|--------------------------|-----------------------------|---------------------------|---------------------------|
| Lipocalin-2 (ng/mL)  | 125.8          | 203.9                    | 381.7                       | 257.9                     | 338.4                     |
|                      | (95.7-165.5)   | (165.0-237.9)            | (297.7-500.0)               | (236.4-365.8)             | (226.3-479.7)             |
| p (vs. controls)     | <0.0001*       | <0.0001*                 | <0.0001*                    | <0.0001*                  | <0.0001*                  |
| p (vs. PV)           | 0.001*         | 0.001*                   | 0.001*                      |                           |                           |

Data were presented as median (range) and its range is 25-75th percentiles. Statistically analysis is done using Mann-Whitney test. *Statistically significance (p<0.05). PV: Psoriasis vulgaris.

Table 3. Spearman correlation between lipocalin-2 level and different variables.

|                                | Plasam lipocalin-2 (ng/mL) | Correlation (r) | p     |
|--------------------------------|---------------------------|-----------------|-------|
| Age (year)                     | 0.880                     | 0.538           |       |
| BMI (kg/m²)                    | 0.023                     | 0.859           |       |
| Waist circumference (cm)       | 0.164                     | 0.202           |       |
| Age of onset (year)            | 0.146                     | 0.257           |       |
| Duration of disease (year)     | -0.121                    | 0.349           |       |
| BSA (%)                        | 0.578                     | <0.001*         |       |
| PASI                           | 0.607                     | <0.001*         |       |
| Severity score of GPP↑         | 0.668                     | 0.002*          |       |
| NAPSI                          | 0.316                     | 0.044*          |       |
| hs-CRP (mg/L)                  | 0.424                     | <0.001*         |       |

BMI: Body Mass Index, BSA: Body Surface Area, GPP: Generalized Pustular Psoriasis, hs-CRP: high sensitivity C-Reactive Protein, NAPSI: Nail Psoriasis Severity Index, PASI: Psoriasis Area Severity Index. *Statistically significance (p<0.05).

Table 4. Comparison of plasma lipocalin-2 levels according to the clinical variables.

|                                | Plasma lipocalin-2 (ng/mL) | p     |
|--------------------------------|---------------------------|-------|
| BMI Categories                  |                           |       |
| Underweight                    | 297.7 (214.4-380.3)        | 0.311*|
| Normal weight                  | 249.4 (201.4-378.6)        |       |
| Overweight                     | 221.8 (199.9-279.6)        |       |
| Obese                          | 294.3 (249.7-440.8)        |       |
| Metabolic syndrome             |                           |       |
| Yes                            | 296.3 (227.7-500.2)        | 0.345*|
| No                             | 254.3 (206.2-380.3)        |       |
| Nail psoriasis                 |                           |       |
| Yes                            | 274.9 (207.4-462.1)        | 0.294*|
| No                             | q244.5 (2119.3-310.7)      |       |
| Psoriatic arthritis            |                           |       |
| Only peripheral joints         | 297.4 (212.7-412.6)        | 0.628*|
| Both axial and peripheral joints| 338.4 (256.9-497.8)        |       |
| No                             | 242.0 (204.5-363.4)        |       |

BMI: Body Mass Index, BSA: Body Surface Area, GPP: Generalized Pustular Psoriasis, hs-CRP: high sensitivity C-Reactive Protein. *Statistically significance (p<0.05).

Data were presented as median (range) and its range is 25-75th percentiles. Differences between two or more groups were tested by Kruskal-Wallis test and Mann-Whitney test. P values <0.05 is statistically significant.
tion.²⁴ It may also trigger inflammation in psoriasis by enhancing the Th17 pathway,²⁵ causing the production of Th17 cytokines (IL-17A, IL-17F, IL-22, IL-23p19, and IL-23p40), which then leads to an inflammatory response.²⁵ The neutralization of this peptide showed a decrease in epidermal proliferation, inflammation, and neutrophil infiltration in psoriatic lesions in an imiquimod-induced psoriasis model.²³ As the lesions faded over time, the expression of lipocalin-2 decreased, highlighting its correlation with disease progression.²⁶ This finding suggests that lipocalin-2 may participate in the pathogenesis of psoriasis through the regulation of neutrophil function during the acute immune response. As such, it may be a potential treatment target in the future.²³ Another report found a correlation between lipocalin-2 levels and TNF-α in patients with psoriasis.³¹ Lipocalin-2 can be produced from the local skin tissue and a wide range of cells, including neutrophils, macrophages, adipocytes, and epidermal cells.¹⁰,¹¹,²³

**Lipocalin-2 may have a pathogenic role in the acute types of psoriasis**

Lipocalin-2 may take part in the inflammatory response by stimulating and causing the migration of neutrophils and activating the Th17 pathway.²³,²² To date, there have been no reports of lipocalin-2 levels in pustular psoriasis. In a recent report, the author found high lipocalin-2 expression in the lesions of patients with palmoplantar pustular psoriasis, and IL-1β was the active cytokine stimulating the expression of lipocalin-2.²⁷ IL-1β has been proven to be the main cytokine that drives the acute response in pustular psoriasis.¹⁷ Therefore, increased lipocalin-2 in the plasma may be mediated by the IL-1β pathway, leading to neutrophil infiltration and formation of the typical pustules in pustular psoriasis.

In erythrodermic psoriasis, the inflammatory pathway is mediated by a large amount of IFN type I from pyruvate dehydrogenase complexes, which is different from the traditional TNF-IL-23-Th17 pathway in psoriasis vulgaris.²⁸ The overexpression of antimicrobial peptides in the lesion may activate the immune response,²⁸ with lipocalin-2 being one of the highly expressed antimicrobial peptides in the lesions.²⁹ Therefore, we assumed that lipocalin-2 plays a crucial role in the pathogenesis of this acute systemic type of psoriasis.

**Plasma lipocalin-2 positively correlates with disease severity**

In contrast to previous reports on the role of lipocalin-2 in metabolic syndrome,³⁰ insulin resistance, and diabetes,³¹ we did not detect any relationship between the plasma lipocalin-2 levels and the different metabolic parameters, including BMI, waist circumference, and metabolic syndrome status. However, we noticed a positive correlation between the peptide levels and severity indices, including PASI, BSA, NAPSI, pustular severity index, and hs-CRP. Lipocalin-2 is an acute phase protein that makes it a potential biomarker for the early diagnosis,³² follow-up, prognostication of several inflammatory diseases, including lupus nephritis, severe pancreatitis, colitis, acute renal disease; and the assessment of the severity of chronic renal disease.¹⁰ Therefore, our results are in line with other reports that lipocalin-2 is one of the most important pro-inflammatory cytokines that may drive the inflammatory response in the active phase of psoriasis.

We should point out that there was a limitation in our present study because we substituted circulating lipocalin-2 levels instead of their expression within the affected tissue. Further studies including a large number of patients will be required to validate the possible contributions and underlying mechanisms of different immunologic pathways in psoriasis pathogenesis.

**Conclusions**

Increased plasma lipocalin-2 levels in patients with psoriasis correlate with severity and particularly indicate an active disease state. In the current study, we assumed that lipocalin-2 may play an important role in the pathogenesis of acute psoriasis and may serve as a valuable clinical biomarker of disease severity. Further investigation is needed to provide more insight into the pathogenesis of psoriasis.

**References**

1. Sewon Kang, Masayuki Amagai, Anna L. Bruckner, et al. Psoriasis. Fitzpatrick’s Dermatology. 1. 9th ed. United States: Mc Graw Hill Education; 2019. p. 457-97.
2. Lunde CW, Poulin Y, Vender R, et al. Interleukin 17A: toward a new understanding of psoriasis pathogenesis. J Am Acad Dermatol 2014;71:141-50.
3. Gisondi P, Fostini AC, Fossa I, et al. Psoriasis and the metabolic syndrome. Clin Dermatol 2018;36:21-8.
4. Coimbra S., Catarino C., Santos-Silva A. The triad psoriasis-obesity-adipokine profile. J Eur Acad Dermatol Venereol 2016;30:1876-85.
5. Boehncke WH, Boehncke S, Tobin AM, Kirby B. The ‘psoriatic march’: a concept of how severe psoriasis may drive cardiovascular comorbidity. Experim Dermatol 2011;20:303-7.
6. Padhi T, Garima. Metabolic syndrome and skin: psoriasis and beyond. Indian J Dermatol 2013;58:299-305.
7. Ouchi N, Parker JL, Lugus JJ, Walsh K. Adipokines in inflammation and metabolic disease. Nat Rev Immunol 2011;11:85-97.
8. Bai F, Zheng W, Dong Y, et al. Serum levels of adipokines and cytokines in psoriasis patients: a systematic review and meta-analysis. Oncotarget 2018;9:1266-78.
9. Romani J, Caixas A, Ceperuelo-Mallafre V, et al. Circulating levels of lipocalin-2 and retinol-binding protein-4 are increased in psoriatic patients and correlated with baseline PASI. Arch Dermatol Res 2013;305:105-12.
10. Abella V, Scoetece M, Conde J, et al. The potential of lipocalin-2/NGAL as biomarker for inflammatory and metabolic diseases. Biomarkers 2015;20:565-71.
11. Kamata M, Tada Y, Tasuta A, et al. Serum lipocalin-2 levels are increased in patients with psoriasis. Clin Exp Dermatol 2012;37:296-9.
12. Ataseven A, Kesli R, Kurtipek GS, Ozturk P. Assessment of lipocalin-2, clusterin, soluble tumor necrosis factor receptor-1, interleukin-6, homocysteine, and uric acid levels in patients with psoriasis. Dis Markers 2014;2014:541709.
13. Gul FC, Cicek D, Kaman D, et al. Changes of serum lipocalin-2 and retinol binding protein-4 levels in patients with psoriasis and Behcet’s disease. Eur J Dermatol 2015;25:195-7.
14. Baran A, Swiderska M, Mysliwiec H, Flisiak I. Effect of psoriasis activity and topical treatment on serum lipocalin-2 levels. J Dermatol Treat 2017;28:136-40.
15. Aizawa N, Ishiuij Y, Tominaga M, et al. Relationship between the Degrees of Itch and Serum Lipocalin-2 Levels in Patients with Psoriasis. J Immunol Res 2019;2019:8171373.
16. El-Hadidi H, Samir N, Shaker OG, Otib S. Estimation of tissue and serum lipocalin-2 in psoriasis vulgaris and its relation to metabolic syndrome. Arch Dermatol Res 2014;306:239-45.
17. Conrad C, Gilliet M. Psoriasis: from Pathogenesis to Targeted Therapies. Clin Rev Allergy Immunol 2018;54:102-13.
18. Chakraborty S, Kaur S, Guha S, Batra
SK. The multifaceted roles of neutrophil gelatinase associated lipocalin (NGAL) in inflammation and cancer. Biochim Biophys Acta 2012;1826:129-69.

19. Fujita H, Terui T, Hayama K, et al. Japanese guidelines for the management and treatment of generalized pustular psoriasis: The new pathogenesis and treatment of GPP. J Dermatol 2018;45:1235-70.

20. Beygi S, Lajevardi V, Abedini R. C-reactive protein in psoriasis: a review of the literature. J Eur Acad Dermatol Venereol 2014;28:700-11.

21. Chiang CC, Cheng WJ, Korinek M, et al. Neutrophils in Psoriasis. Front Immunol 2019;10:2376.

22. Schroll A, Eller K, Feistritzer C, et al. Lipocalin-2 ameliorates granulocyte functionality. Eur J Immunol 2012;42:3346-57.

23. Shao S, Cao T, Jin L, et al. Increased Lipocalin-2 Contributes to the Pathogenesis of Psoriasis by Modulating Neutrophil Chemotaxis and Cytokine Secretion. J Invest Dermatol 2016;136:1418-28.

24. Ferreira MC, Whibley N, Mamo AJ, et al. Interleukin-17-induced protein lipocalin 2 is dispensable for immunity to oral candidiasis. Infect Immun 2014;82:1030-5.

25. Hau CS, Kanda N, Tada Y, et al. Lipocalin-2 exacerbates psoriasiform skin inflammation by augmenting T-helper 17 response. J Dermatol 2016;43:785-94.

26. Mallbris L, O’Brien KP, Hulthen A, et al. Neutrophil gelatinase-associated lipocalin is a marker for dysregulated keratinocyte differentiation in human skin. Exp Dermatol 2002;11:584-91.

27. Wolk K, Frambach Y, Jacobi A, et al. Increased levels of lipocalin 2 in palmoplantar pustular psoriasis. J Dermatol Sci 2018;90:68-74.

28. Kabashima K. Langerhans Cells and Dermal Dendritic Cells. Immunology of the Skin. Japan: Springer; 2016. p. 47-8.

29. Morizane S, Gallo RL. Antimicrobial peptides in the pathogenesis of psoriasis. J Dermatol 2012;39:225-30.

30. Yan QW, Yang Q, Mody N, et al. The adipokine lipocalin 2 is regulated by obesity and promotes insulin resistance. Diabetes 2007;56:2533-40.

31. Wang Y. Small lipid-binding proteins in regulating endothelial and vascular functions: focusing on adipocyte fatty acid binding protein and lipocalin-2. Br J Pharmacol 2012;165:603-21.

32. Sultan S, Pascucci M, Ahmad S, et al. LIPOCALIN-2 is a major acute-phase protein in a rat and mouse model of sterile abscess. Shock (Augusta, Ga) 2012;37:191-6.
Long term efficacy, safety, and tolerability of tildrakizumab in epileptic patient with psoriasis and eczema

Nicoletta Bernardini, Nevena Skroza, Giovanni Rossi, Alessandra Mambri, Ersilia Tolino, Federica Marraffa, Martina Caviglia, Antonio Di Guardo, Salvatore Volpe, Ilaria Proietti, Concetta Potenza

Department of Medico-surgical Sciences and Biotechnologies, Sapienza University of Rome, Polo Pontino, Italy

Abstract

Psoriasis is a chronic inflammatory disease which mostly affects skin. Tildrakizumab is a specific anti-interleukin-23p19 monoclonal antibody approved for the treatment of plaque psoriasis in adults. Herein, we report about a patient who came to our attention for a moderate-to-severe plaque psoriasis, involving primarily upper limbs, elbow, abdomen and knees (PASI 18 – DLQI 22). His medical history was relevant for epilepsy controlled pharmacologically. In addition, an eczematous and edematous appearance of the tibial area was detected; the histologic findings did not contradict the diagnostic hypothesis of subacute spongiotic dermatitis. The patient was treated with Tildrakizumab. After 12 weeks the clinical lesions improved significantly, and the eczematous component disappeared in the tibial area bilaterally. The clinical improvement was maintained even after one year of therapy with Tildrakizumab. Indeed, eczematous areas and edematous lesions not attributable to psoriatic disease were detected on clinical examination. The morphologic findings described did not contradict the diagnostic hypothesis of subacute spongiotic dermatitis. The patient had previously been treated with cyclosporine, acitretin and systemic steroids, which proved ineffective.

Case Report

Herein, we describe the case of a 45-year-old man with moderate-to-severe plaque psoriasis. He had a history of cortical dysplasia, cerebellar vermis atrophy, corpus callosum dysplasia and mono-lateral microgyria determining prominent progressive spastic ataxia, sensory motor axonal neuropathy mild intellectual disability and frequent epileptic events controlled pharmacologically.

The patient came to our attention for a moderate-to-severe plaque psoriasis, involving primarily upper limbs, elbow, abdomen and knees (PASI 18 – DLQI 22). He referred itching, burning and skin tightness. On skin examination skin dryness, cracking, scaling, flaking, redness and bleeding were detectable. In addition, skin lesions not attributable to psoriatic disease were detected on clinical examination. Indeed, eczematous areas and edematous appearance of the tibial areas with hyperpigmented reddish-brown spots were detected. For this reason, an incisional biopsy on tibial area was performed before starting therapy. Histological examination showed a mild and focal orthokeratosis hyperkeratosis, hyper granulosis, spongiotic vesicles with neutrophilic granulocytic infiltrate and sporadic images of lymphocytic exocytosis. Moreover, an inflammatory lymphocytic infiltrate circumscribed the ectatic vessels of the superficial dermis. The morphologic findings described did not contradict the diagnostic hypothesis of subacute spongiotic dermatitis.

Considering this clinical information, we started treatment with Tildrakizumab 100 mg every 12 weeks in March 2020. After 12 weeks the clinical lesions improved significantly, and the eczematous component disappeared in the tibial area bilaterally. The clinical improvement was maintained even after one year of therapy with Tildrakizumab as showed in Figure 1.

Introduction

Psoriasis is a chronic inflammatory disease which mostly affects skin, but may also affect the joints and different organ systems. Its severity can vary depending on numerous genetic and environmental factors. The IL-23 and the downstream T-helper cell 17 (Th17) pathway are key drivers of psoriasis pathogenesis. The treatment of psoriasis has undergone a revolution with the advent of biologic therapies that target specific components of the immune system. Tildrakizumab is a specific anti-interleukin-23p19 monoclonal antibody approved in US and Europe for the treatment of moderate-to-severe chronic plaque psoriasis, which binds specifically to the p19 protein subunit of the cytokine 23 (IL-23) inhibiting its interaction with the specific IL-23 receptor.

The promising results of phase one studies I terms of efficacy of Tildrakizumab (Kopp et al.) have been confirmed by double-blind randomized phase III trials (reSURFACE1 ad reSURFACE2); the rate of severe infections, malignancies, skin cancers, major cardiovascular events, and drug-related hypersensitivity reactions was low.

Key words: Psoriasis, Eczema, Tildrakizumab.

Contributions: NB, NS: conception and study design. GR, AM, ET and IP: writing-original draft. MC, ADG, FM, SV: writing-review ad editing. CP: supervision.

Conflict of interest: The authors declare no potential conflict of interest.

Funding: None.

Informed consent statement: The patient has given written informed consent to the publication of his case details.

Availability of data and material: Data and materials are available by the authors.

Received for publication: 22 December 2021. Accepted for publication: 16 September 2022.

This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License (CC BY-NC 4.0).

Correspondence: Nicoletta Bernardini, Dermatology Unit “Daniele Innocenzi”, “A. Fiorini” Hospital, Via Firenze, 1, 04019, Terracina (LT), Italy. Tel.: +39.0773.708811. E-mail: nicoletta.bernardini@libero.it

©Copyright: the Author(s), 2022 Licensee PAGEPress, Italy Dermatology Reports 2022; 14:9447 doi:10.4081/dr.2022.9447

Publisher’s note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publishers, the editors and the reviewers. Any product that may be evaluated in this article or claim that may be made by its manufacturer is not guaranteed or endorsed by the publisher.
Discussions

As demonstrated elsewhere, tildrakizumab showed excellent results in the control of psoriasis in the short term, with an excellent safety profile. The promising results of the clinical trials have been confirmed even in a real-life setting.8

Consistently with the literature, our case confirms the long-lasting durability of the therapeutic effects of tildrakizumab. This sustained response over time has been related to inhibition of IL-23, which acts upstream in the IL-23/Th17 pathway.9

Tildrakizumab is a valid therapeutic choice in special population including patients with IBD, cardiovascular disease, metabolic syndrome, advanced age, and history of malignancy; however, there are no reports about its safety in epileptic patients. In our case, neurological adverse events did not verify. Furthermore, there is a growing body of evidence about the involvement of inflammatory mediators-released by brain cells and peripheral immune cells in both the origin of individual seizures and the epileptogenic process, which include the IL23-Th17 axis.10

In addition, our patient had a histologically demonstrated eczematous component. Historically, psoriasis and eczema were considered as opposite diseases, especially regarding their pathophysiology, psoriasis being Th17 dominant and eczema being Th2 dominant. However, it is now recognized that these entities can co-exist.11 In our case, it is interesting to note that tildrakizumab managed to control both the psoriatic and eczematous components. Moreover, there are anecdotal reports of IL12/23 inhibitors in atopic dermatitis with good outcomes, highlighting that the impact of anti-IL-12/IL-23p40 therapy in eczematous diseases is still unclarified.12

Conclusions

Our case highlights that tildrakizumab is a promising drug for the biological treatment of plaque psoriasis in the moderate or severe stage and confirms its safety and efficacy even in special populations and the complex settings offered by the real-life practice.

References

1. AlQassimi S, AlBrashdi S, Galadari H, Hashim MJ. Global burden of psoriasis - comparison of regional and global epidemiology, 1990 to 2017. Int J Dermatol 2020;59:566-71.
2. Rendon A, Schäkel K. Psoriasis Pathogenesis and Treatment. Int J Mol Sci 2019;20:1475.
3. Sivamani RK, Goodarzi H, Garcia MS, et al. Biologic therapies in the treatment of psoriasis: a comprehensive evidence-based basic science and clinical review and a practical guide to tuberculosis monitoring. Clin Rev Allergy Immunol 2013;44:121-40.
4. Reich K, Warren RB, Iversen L, et al. Long-term efficacy and safety of tildrakizumab for moderate-to-severe psoriasis: pooled analyses of two randomised phase III clinical trials (reSURFACE 1 and reSURFACE 2) through 148 weeks. Br J Dermatol 2020;182:605-17.
5. Tildrakizumab, Summary of Product Characteristics.
6. Kopp T, Riedl E, Bangert C, et al. Clinical improvement in psoriasis with specific targeting of interleukin-23. Nature 2015;521:222-6.
7. Reich K, Papp KA, Blauvelt A, et al. Tildrakizumab versus placebo or etanercept for chronic plaque psoriasis (reSURFACE 1 and reSURFACE 2): results from two randomised controlled, phase 3 trials. Lancet 2017;390:276-88.
8. Drerup KA, Seemann C, Gerdes S, Mrowietz U. Effective and Safe Treatment of Psoriatic Disease with the Anti-IL-23p19 Biologic Tildrakizumab: Results of a Real-World Prospective Cohort Study in Nonselected Patients. Dermatology 2021;1-5.
9. Di Cesare A, Di Meglio P, Nestle FO. The IL-23/Th17 axis in the immunopathogenesis of psoriasis. J Invest Dermatol 2009;129:1339-50.
10. Mao LY, Ding J, Peng WF, et al. Interictal interleukin-17A levels are elevated and correlate with seizure severity of epilepsy patients. Epilepsia 2013;54:e142-5.
11. Barry K, Zancanaro P, Casseres R, et al. Concomitant atopic dermatitis and psoriasis - a retrospective review. J Dermatol Treat 2021;32:716-20.
12. Husein-ElAhmed H, Steinhoff M. Effectiveness of ustekinumab in patients with atopic dermatitis: analysis of real-world evidence. J Dermatolog Treat 2021;1-6.