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Original Article

The correlation between histopatology severity score, expression of JAK1 and expression of STAT3 in psoriasis vulgaris

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Abstract

Background Psoriasis vulgaris diagnosis and severity are currently considered as less objective. Histopathological scoring using Trozak's score is a quantitative assessment which is considered to represent the disease's process. Janus Kinase (JAK) 1 and Signal Transducer and Activator of Transcription (STAT) 3 examinations in psoriasis vulgaris is also currently considered to represent the diseases' process and severity.

Objective To analyze the correlation between JAK1 and STAT3 expression with the severity of psoriasis vulgaris as determined by the Trozak score on paraffin block with psoriasis vulgaris features.

Methods This was retrospective cross-sectional study on 37 paraffin blocks with psoriasis vulgaris features at the Department of Dermatology and Venereology and Pathology Anatomy of RSUD Dr. Soetomo Surabaya. The results of the biopsy in the form of paraffin blocks were re-cut, stained with Hematoxylin & Eosin (HE), anti-JAK1, and anti-STAT3 antibodies. Psoriasis vulgaris severity was determined histopathologically by Trozak score. Immunohistochemical score was calculated from the total score of fluorescent cells after staining with anti-JAK1 and anti-STAT3 antibodies. Correlation analysis was performed with Spearman test, with $p<0.05$ considered significant.

Results Thirty-seven biopsies were from 21 (56.76%) female patients and 16 (42.2%) male patients were collected, with the highest incidence found in the 45-60 years age group (43.2%). No significant correlation was found between the increase in JAK1 and STAT3 scores with an increase in Trozak scores on paraffin block with psoriasis vulgaris features.

Conclusion No significant correlation between Trozak score, JAK1, and STAT3 were found on paraffin blocks with psoriasis vulgaris features.

Key words
Psoriasis vulgaris; Severity; Trozak, JAK1; STAT3.

Introduction

Psoriasis vulgaris is a chronic, recurrent, multifactorial inflammatory disease associated with a combination of genetic, environmental, and immunological factors with characteristics of impaired epidermal growth and differentiation accompanied by increased risks of arthritis, cardiovascular morbidity, and other systemic inflammatory disorders.[1-5] The worldwide psoriasis vulgaris prevalence is estimated at 0.1-

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3% in various populations, while in Asia it is reported as 0.05-0.47%.[4,6]

Psoriasis Assessment Severity Index (PASI) is considered to reflect the clinical severity of psoriasis but still has limitations due to its high variability, although it is used as the basis for selecting therapy and to estimate the patient's prognosis.[7-9] Paul *et al.* (2010) who conducted an evidence-based study reported that there was not enough evaluation regarding PASI validation.[10]

Histopathological examination is considered as the gold standard in psoriasis vulgaris diagnosis, but it is still considered subjective. Trozak score was developed in 1994 to assess psoriasis vulgaris severity based on quantitative histopathological findings, but it is still considered unable to describe psoriasis vulgaris severity.[2,11] A study on Janus Kinase (JAK) and Signal Transducer and Activator of Transcription (STAT) pathways reported that these two pathways, which are considered important in the Interleukin (IL)-17/IL-23 axis, are thought to represent psoriasis severity more objectively.[12] Study regarding JAK1 and STAT3 expressions in histopathological specimens of psoriasis vulgaris has not been conducted in Indonesia. This study aimed specifically to evaluate JAK1 and STAT3 expressions in histopathological specimens of psoriasis vulgaris.

Methods

Study Design This was an analytic observational study with a retrospective cross-sectional design to determine the correlation between Trozak scores with JAK1 and STAT3 expressions in paraffin block with psoriasis vulgaris features at the Anatomical Pathology Laboratory, RSUD Dr. Soetomo Surabaya.

Study population and sample The study population was all paraffin blocks with features in accordance with psoriasis vulgaris obtained from biopsy of psoriasis vulgaris patients at the Dermatology and Venereology Outpatient Clinic of RSUD Dr. Soetomo, Surabaya in January 2016-December 2020 period. The study sample was all paraffin blocks with features in accordance to psoriasis vulgaris that met the criteria for sample acceptance.

The sample acceptance criteria are as follows:

1. Paraffin block with psoriasis vulgaris features from Anatomical Pathology Laboratory of RSUD Dr. Soetomo Surabaya.

2. Paraffin blocks taken from psoriasis vulgaris patients in January 2016-December 2020 period.

3. Undamaged paraffin block with psoriasis vulgaris.

4. Paraffin block with psoriasis vulgaris that were still available for cutting and re-staining for hematoxylin and eosin (H&E) and immunohistochemical examination.

The sample rejection criteria are as follows:

1. Paraffin block with psoriasis vulgaris features with incomplete electric medical record (EMR) data at the Dermatology and Venereology Outpatient Clinic of RSUD Dr. Soetomo, Surabaya.

2. Paraffin block with psoriasis vulgaris features which also reflect the features of other dermatoses.

Study Procedure Basic data recording was conducted by researchers in the form of data from paraffin block with psoriasis vulgaris features, patient identity, EMR, slide number,

and diagnosis at the Anatomical Pathology Laboratory of RSUD Dr. Soetomo, Surabaya, who was registered in January 2016-December 2020 period. The data from paraffin block data with psoriasis vulgaris features was matched with the EMR which was recorded at the Dermatology and Venereology Outpatient Clinic of RSUD Dr. Soetomo, Surabaya. The paraffin blocks were sorted according to the month and year of sampling, starting from January 2020 to December 2016. The 5-year period was determined based on the standard operating procedure for storing paraffin blocks at the Anatomical Pathology Laboratory of RSUD Dr. Soetomo, Surabaya and to avoid the large number of paraffin blocks that had been damaged due to storage. Histopathological and immunohistochemical examinations were conducted at the Anatomical Pathology Laboratory of RSUD Dr. Soetomo, Surabaya, starting from the newest sample until 37 slides were collected. Paraffin blocks with good H&E staining was examined for their histopathological features (Psoriasis Histopathologic Scores (PHS) assessment) and then cut for immunohistochemical (IHC) examination (Immunoreactive Score (IRS) assessment). Paraffin blocks with poor H&E staining were re-cut for H&E staining before histopathological examination and then were cut for IHC examination (IRS assessment).

Psoriasis Histopathologic Scores use numerical values assigned to each of psoriasis vulgaris microscopic criteria. The criteria observed were regular lengthening of rete ridge (score 1), club-shaped rete ridge (score 2), elongation and edema of dermal papilla (score 1), perivascular mononuclear infiltrate in upper papillary dermis (score 1), loss of stratum granulosum (score 1 for focal, score 2 for total), parakeratosis (score 1 for focal, score 2 for total), suprapapillary plate thinning (score 2), mitoses above stratum basalis (score 2), Munro's microabscess (score 3), and Spongioform Kogoj pustules (score 3). The total score is added up with a maximum total score of 19.

Immunoreactive Score was obtained by multiplying the percentage of the number of positive cells by the staining intensity, with a maximum value of 12. Percentage of positive cells was assigned a value of 0 (no positive cells), 1 (<10% of positive cells), 2 (10- 50% of positive cells), 3 (51-80% of positive cells), and 4 (>80% of positive cells). Staining intensity was assigned a value of 0 (no positive cells), 1 (mild intensity), 2 (moderate intensity), and 3 (strong intensity).

Data Analysis Data in the form of IRS JAK1 scores, IRS STAT3 scores, andTrozak scores were collected in data collection sheets. The study results were analyzed using the Spearman correlation test and displayed in narratives and tables.

Ethical Clearance This study was approved by the Health Research Ethics Committee of RSUD Dr. Soetomo with reference number: 0663/LOE/301.4.2/X/2021.

Results

There are a total of 137 paraffin blocks with descriptions consistent with psoriasis vulgaris obtained from a biopsy of psoriasis vulgaris patients at the Dermatology and Venereology Outpatient Unit of RSUD Dr. Soetomo Surabaya in the period January 2016-December 2020. Thirty paraffin blocks that met the research inclusion criteria were included as samples for miracles.

Demographic Data of Research Sample **Table 1** illustrates the patient demographic data assessed by age, gender, severity based on PASI, and history of previous treatment. Female

Table 1 Sample demography.

Characteristics	*n*	*%age*
Age		
<15 years	3	8.1
15 – 24 years	3	8.1
25 – 44 years	10	27.0
45 – 60 years	16	43.2
> 60 years	5	13.5
Mean age	42.65	
Sex		
Male	16	42.20
Female	21	56.76
Severity Score (PASI)		
Mild (<3)	2	5.4
Moderate (3-10)	8	21.6
Severe (>10)	23	62.2
No data	4	10.8
Previous Treatment		
Desoximetasone cream	37	100.0
MTX and desoximetasone cream	37	100.0
	4	10.8

Table 2 Histopathological parameter data in the research sample.

Criteria	*n*	*%age*
Rete ridges lengthening	3	8.1
Club shaped rete ridges	1	2.7
Elongation and edema of the papillary dermis	5	13.5
Perivascular and peridermal infiltrates in the upper dermis	11	29.7
Loss of granular layer	26	70.3
Parakeratosis	32	86.5
Suprapapillary plate thinning	1	2.7
Mitosis above the stratum basalis	4	10.8
Munro microabscess	7	18.9
Spongiform pustules	0	0

sample was prevalent than male (56.76%). The mean age of the sample was 42.65 years, where the youngest sample was 4 years and the oldest sample was 69 years. The most prevalent age category was 45-60 years (43.2%). PASI data were only obtained in 33 patients, with the majority of patients had severe PASI (62.2%). All patients had been treated with 0.025% desoximetasone cream, four patients (10.8%) had previously been treated with 0.025% desoximetasone cream and methotrexate (MTX).

The distribution of psoriasis vulgaris histopathology **Table 2** describes the distribution of each histopathological parameter in the study sample which consisted of 10 histopathological parameters of psoriasis vulgaris from 37 paraffin block samples with psoriasis vulgaris features. It was found that parakeratosis and loss of granular layer were the most common histopathological features of psoriasis vulgaris in 32 (86.5%) and 26 (70.3%) cases, respectively.

Table 3 Trozak Score Distribution

Trozak Score	*n*	*%age*
1	3	9.09
2	6	18.18
3	7	21.21
4	8	24.24
5	2	6.06
6	6	18.18
7	0	0.00
8	0	0.00
9	1	3.03

Trozak score distribution **Table 3** illustrates Trozak scores distribution in 37 samples of paraffin blocks with psoriasis vulgaris features. Trozak score has a maximum value of 19, that is, if all microscopic criteria are found with maximum level. In this study, the highest Trozak score was 9 in one case (3.03%), and the lowest score was 1 in three cases (9.09%).

Distribution of JAK1 and STAT3 expression **Table 4** illustrates the distribution of JAK1 and STAT3 expressions as assessed from IRS scores. Only two paraffin blocks showed no JAK1

Table 4 *Distribution of JAK1 and STAT3 expression*

JAK1/STAT3	n	%age
JAK1		
Negative	2	6.1
Mild	6	18.2
Moderate	15	45.5
Strong	10	30.3
STAT3		
Negative	23	69.7
Mild	9	27.3
Moderate	1	3.0
Strong	0	0.0

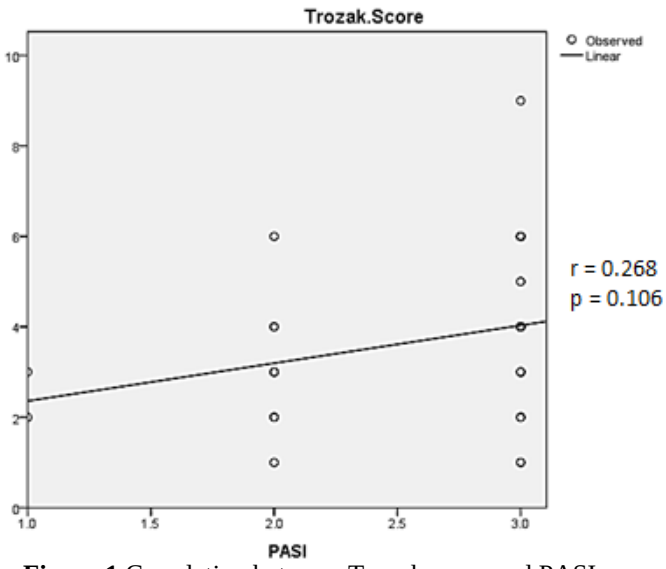

Figure 1 Correlation between Trozak score and PASI.

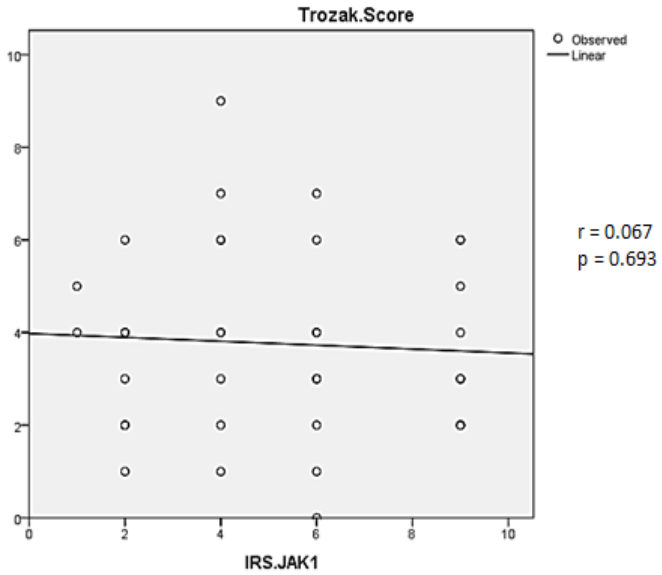

Figure 2 Correlation between Trozak score and JAK1 Expression.

expression. The majority of paraffin blocks showed a moderate IRS JAK1 score with 15 paraffin blocks (45.5%). In contrast, the majority of paraffin blocks showed no STAT3 expression with 23 paraffin blocks (69.7%). In paraffin blocks that showed STAT3 expression, most paraffin blocks had mild IRS STAT3 scores with 9 blocks (27.3%).

Correlation of PASI with Trozak score A correlation test was conducted between PASI and Trozak scores on 33 paraffin blocks containing PASI data. The results of the test are depicted in **Figure 1**. There was no correlation between PASI and the Trozak score, which was tested using the Spearman correlation test ($p < 0.05$).

Correlation of JAK 1 expression with Trozak score The results of correlation analysis test between JAK1 expression and Trozak score are depicted in **Figure 2**. There was no correlation between JAK1 expression and Trozak score, which was tested using the Spearman correlation test ($p < 0.05$).

Correlation of STAT3 expression with Trozak score The results of correlation analysis test between STAT3 expression and Trozak score are depicted in **Figure 3**. There was no correlation between STAT3 expression and Trozak's score, which was tested using Spearman correlation test ($p < 0.05$).

Correlation of JAK1 and STAT3 Expressions The results of correlation analysis test between JAK1 and STAT3 expressions are depicted in **Figure 4**. There was no correlation between JAK1 and STAT3 expressions, which was tested using the Spearman correlation test ($p < 0.05$).

Discussion

The sex distribution of the sample in this study was dominated by female patients (56.76%). Based on the age group, 45-60 years age group was the most prevalent group (43.24%). The incidence of psoriasis was reported equally in male and female and could appear at any age.[4,13] Several previous studies reported bimodal age onset, with the first peak occurring at 15-20 years of age and the second peak occurring at 55-60 years.[14] Psoriasis onset at 10 years old individuals was reported to be rare.[4] The majority of the samples in this study were

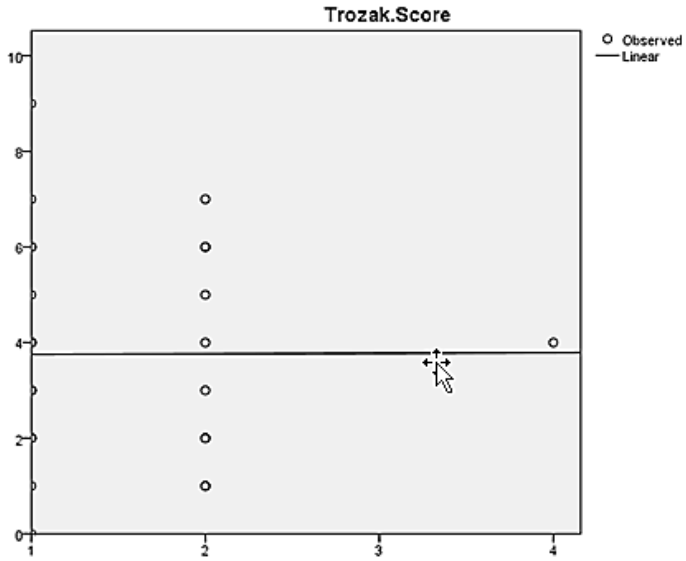

Figure 3 Correlation between Trozak score and STAT3 expression.

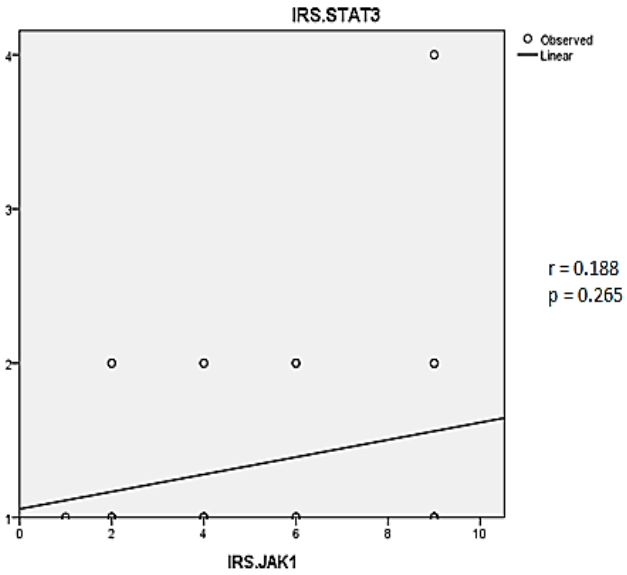

Figure 4 Correlation between JAK1 and STAT3 Expressions.

included in severe PASI category (45.45%). This could be because the current study was conducted in a tertiary referral hospital where most of the patients presented with a more severe clinical course, and biopsies were performed on patients who were newly diagnosed in nonclassical or refractory cases. Patients with a clinical diagnosis of psoriasis vulgaris which has not been confirmed histopathologically also generally have just received topical steroid therapy and have not received systemic psoriasis therapy, where MTX was generally given at our hospital.

Histopathological features Parakeratosis and loss of the granular layer were the most common features (87.9% and 72.7% of cases, respectively) in our study. Chau *et al.* (2017) examined 51 paraffin blocks with a diagnosis of psoriasis vulgaris in California, where they reported loss of granular layer and club-shaped rete ridges as the most frequent features found in their study with 49.96% of cases each.[15] Kim BY *et al.* (2015) studied 98 paraffin blocks with various types of psoriasis in South Korea and reported that inflammatory cell infiltrates, vascular dilatation, granular layer loss, and parakeratosis were the most common features found in 99%, 97%, 96%, and 93% of paraffin blocks, respectively.[8]

All histopathological features of psoriasis vulgaris are rarely seen in one histopathological section of psoriasis vulgaris.[11] The presence of several nonclassical features does not exclude the diagnosis of psoriasis vulgaris.[15] Histopathological examination is still the gold standard tool for psoriasis vulgaris diagnosis. In the absence of well-formed Munro microabscesses and Kogoj pustules, confirmatory evidence of psoriasis vulgaris could be established by other epidermal features such as parakeratosis, hyperkeratosis, spongiosis, papillomatosis, absence or thinning of the granular layer, and dilated and tortuous capillaries in the dermis.[2]

Correlation between PASI and Trozak score Correlation analysis between PASI and Trozak score with Spearman correlation test in this study found no significant correlation between PASI and Trozak score with (p=0.106). This was in line with a study from Kim *et al.* (2015) who examined the correlation of

histopathological scores with psoriasis type and the severity of each biopsy lesion in that study as measured by PSI scores on 98 paraffin blocks with various types of psoriasis in South Korea. Kim *et al.* reported that histopathological scores could reflect psoriasis type based on morphology, but it could not reflect psoriasis lesion severity as measured by clinical PSI. This might be due to more subjective clinical judgments or different clinical grading techniques.[8] The finding in this study was not in line with a study from Eysteinsdóttir *et al*. (2017) who examined the correlation between Trozak score, PASI, and DLQI in 21 biopsy slides of patients with chronic plaque psoriasis vulgaris. They reported that there was a significant correlation between Trozak score and PASI.[16] This could be due to the discontinue of all treatment for one month prior to lesion biopsy in this study.

The discrepancies between the results of the study and previous studies might be due to differences in clinical severity determination techniques, differences in techniques for determining histopathological score severity, differences in assessment time for each slide, variations in each histopathological finding of the psoriasis vulgaris itself, the histopathological slides examined did not reflect the Trozak score because it was only taken from one histopathological specimen, the total number of patients who had received topical treatment at the time of the biopsy that could affect the PASI and histopathological features, the biopsy was performed by different examiners, and the PASI data differed from the one at the time of biopsy. In addition, this study was a retrospective study of existing data. PASI determination in this study was conducted by several doctors, therefore the subjectivity of the assessors could be very different. Larger sections or biopsies of multiple lesions in one patient need to be studied to show a more representative Trozak score to reflect the severity index.[11] This was also a retrospective study using pre-stored paraffin blocks, therefore there was a possibility of partial destruction of paraffin blocks during storage, which affected slide preparation during re-cutting process.

Correlation test between JAK1 and STAT3 expressions Correlation test between JAK1 and STAT3 expressions with Trozak score using Spearman correlation test in this study found no significant relationship correlation between JAK1 and STAT3 expressions with Trozak score. There was also no significant correlation between JAK1 expression and STAT3. The results of this study were not in line with a study from Farag *et al.* (2019) in 26 psoriasis vulgaris patients that were compared with 26 non-psoriasis vulgaris patients. They reported a significant correlation between JAK1 H-score of dermal lesions and psoriasis severity ($p = 0.01$), STAT3 H-score of dermal lesions with severe psoriasis ($p=0.001$), and JAK1 H-score of epidermal lesions and STAT3 H-score ($r= 0.44$, $p= 0.03$).[3] This could be due to the fact that their study examined the correlation between histopathological scores and JAK1 and STAT3 expression in the epidermis and dermis, whereas in this study there was no difference between JAK1 and STAT3 in the epidermis or dermis. The difference could also be due to the difference in the number of samples of this study with previous studies and the previous study was a prospective study, therefore there the possibility of tissue damage could be minimized.

JAK1 has a pro-inflammatory role in psoriasis vulgaris pathogenesis which is associated with STAT3 activation. JAK1 binds to JAK2, JAK3, or TYK2 and transduces signals from IFN-α, IFN-γ, IL6 and IL-10 receptors. STAT3 is mainly activated by JAK1, JAK2, and TYK2. STAT3 is involved in the induction and differentiation of Th-17 cells through IL-23-

induced JAK2/TYK2 pair activation. STAT3 was also associated with Th17 cell differentiation and keratinocyte proliferation via IL-6-induced JAK1/JAK2 or JAK1/TYK2 signalling. IL-17 activates STAT 3 indirectly through a process that induces the production of IL-19 and IL-36 by keratinocytes leading to epidermal hyperplasia.[17]

STAT3 was identified as a major IL-6-mediated cell mediator. STAT3 activation occurs not only downstream of all members of the IL-6 cytokine family, but also a large number of other cytokines, growth factors, and oncogenes, including cytokines that play a role in psoriasis vulgaris such as IL-21, IL-22, IL-23, IL- 26, and IL-29. STAT3 also plays a role in Th-17 expansion which plays a role in psoriasis vulgaris pathogenesis.[18] Andres *et al.* (2013) in their study reported that different signalling pathways could integrate and lead to the regulation of STAT3 transcriptional activity.[19] Fridman *et al.* (2011) reported in their study that JAK1/JAK2 inhibition with INCB018424 topical agent could reduce STAT3 expression, edema, lymphocyte infiltration, keratinocyte proliferation, and inhibit tissue inflammation caused by IL-23 or intradermal TSLP.[20] Administration of STAT3-inhibiting agents could also provide clinical improvement in some known STAT3-mediated disorders, and previous literature stated that STAT3 inhibitors were also used for malignancy.[21]

There was also no correlation between Trozak score and JAK1 and STAT3 expressions in this study. JAK1 was reported to be associated with Munro microabscess formation, parakeratosis, and Kojog's pustules, which are indicators of severe psoriasis and have a high score in determining the Trozak score.[3] The lack of association between JAK1 expression and Trozak score in this study could be due to the fact overall histopathological findings are rarely found in one biopsy slide, variations in each histopathological finding of psoriasis vulgaris itself, and the paraffin block used is a paraffin block that has been stored, re-cut, and immunohistochemically stained, therefore the slide quality might be reduced. The limited number of samples, the fact that all patients had received topical therapy with desoximetasone cream 0.025% could affect JAK1 value and histopathological feature due to its ability to affect the response and activity of T cells, which are known to play a role in psoriasis vulgaris pathogenesis.[22]

The absence of a significant correlation between the Trozak score and STAT3 could be due to the factors that influence the determination of JAK1 score and STAT3 activation which is not only influenced by JAK1. This finding could also be supported by the absence of a significant correlation between JAK1 and STAT3 in this study. STAT3 is also activated by several other cytokines and growth factors that are upregulated in psoriasis such as IL-6, IL-21, IL-22, IL-26, and IL-29.[18] STAT3 has been shown to play a role in psoriasis-associated IL-23 signalling pathway of other factors such as IL-17 and IL-16.[19] Patients who have received previous treatment could also affect STAT3 expression. The majority of patients were treated with topical desoximethasone, which has a suppressive effect on IL-6 and also known to play a role in STAT3 expression.[22] This might also explain the absence of significant correlation between JAK1 and STAT33 in this study.[22] STAT3 also affects the formation of parakeratosis, Munro's microabscess, and Kojog's pustules which affect the assessment of the Trozak Score.[18]

Conclusion

There is no significant correlation between Trozak score and JAK1, Trozak score and

STAT3, and JAK1 and STAT3 expression on paraffin block with psoriasis vulgaris features at the Anatomical Pathology Laboratory of RSUD Dr. Soetomo Surabaya. It is necessary to conduct a study with a prospective design that is expected to provide a more subjective assessment of PASI or PSI and a more uniform location for sampling psoriasis vulgaris lesions with multiple lesion locations in order to better describe the Trozak score that is more representative of the severity of the disease at the time of biopsy. In addition, it is necessary to conduct a prospective study that could provide a better description of the histopathological features of H&E staining, JAK1 expression, and STAT3 from the new paraffin block. A prospective study comparing the expression of JAK1 and STAT3 in psoriasis vulgaris lesions compared with controls could also be conducted. Finally, a prospective study to determine the correlation between the entire JAK family, STAT family, and other cytokines that are known to play a role in the pathogenesis of psoriasis vulgaris at one time could be conducted to describe the overall effect of the JAK/STAT signaling pathway on psoriasis vulgaris.

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