ORIGINAL ARTICLE

Bali Medical Journal (*Bali MedJ)* 2022, Volume 11, Number 1: 328-333
P-ISSN.2089-1180, E-ISSN: 2302-2914

Clinical improvement of patients with moderate-to-severe psoriasis treated with methotrexate at Dr. Soetomo General Hospital, Surabaya, Indonesia

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Received: 2022-01-26
Accepted: 2022-04-05
Published: 2022-04-21

ABSTRACT

Background: Psoriasis is a complex, chronic disease with increasing global incidence. Studies on the effectiveness of psoriasis therapy in Indonesia are limited. This study aimed to evaluate the patient's clinical improvement with moderate-to-severe psoriasis vulgaris using the Psoriasis Area and Severity Index with ≥75% score reduction (PASI75).
Methods: This is a retrospective study involving patients diagnosed with psoriasis vulgaris who visited the Dermatology and Venereology Outpatient Clinic in Dr. Soetomo General Hospital between January 2016 and December 2018. The electronic medical record obtained data on demographic characteristics, the number of visits, psoriasis at initial (PASI) score before and after treatment, type and dose of treatment, and comorbidities. Data were analyzed using SPSS version 23 for Windows.
Results: Overall, 54 patients with psoriasis vulgaris were included. Almost all subjects were adults (≥18 years old) and presented with severe PASI (PASI score > 10) (96.3%). The majority of the subjects (64.8%) successfully achieved PASI75. Most subjects received methotrexate (72.2%); the most frequent dosage was 15 mg/week (61.5%). A significant association was found between methotrexate treatment and a larger improvement in PASI scores (p=0.001).
Conclusion: moderate-to-severe psoriasis therapy in terms of PASI75 achieved a satisfactory success rate of 64.8%, and the improvement of PASI score was significantly better in patients who received methotrexate. Further studies in Indonesia are needed to explore the effectiveness of psoriasis therapy and its factors.

Keywords: Clinical Improvement, Methotrexate, Psoriasis, PASI.
Cite This Article: Hendaria, M.P., Hidayati, A.N., Ervianti, E., Listiawan, M.Y., Damayanti., Citrashanty, I., Anggraeni, S., Umborowati, M.A., Utomo, B., Prakoeswa, C.R.S. 2022. Clinical improvement of patients with moderate-to-severe psoriasis treated with methotrexate at Dr. Soetomo General Hospital, Surabaya, Indonesia. *Bali Medical Journal* 11(1): 328-333.
DOI: 10.15562/bmj.v11i1.3417

INTRODUCTION

Psoriasis is a complex, multifactorial disease; its pathogenesis is not fully understood and is thought to be related to genetic predisposition, autoimmune disease, and environmental factors such as infection, stress, and trauma.[1,2] The prevalence of psoriasis in adults and children is estimated to be 0.15%–11.43% and 0.1%–1.37%, respectively, with increasing global incidence.[3,4] A retrospective study by Gayatri et al. at the Dermatology and Venereology Outpatient Clinic in Dr. Soetomo General Hospital, Surabaya, Indonesia, in 2010–2011, found that the predilection of psoriasis seems to be similar in males and females. Psoriasis affects all age groups; it is most prevalent in patients aged 15–40 years old and rarely found in children younger than 10 years old.[5]

Anti-psoriatic agents, both topical and systemic, are widely available. It is important to consider the affected area and the severity of the psoriasis lesion when choosing a therapeutic regimen.[1,6] Topical agents for psoriasis include topical corticosteroid, vitamin D analog, tazarotene, and calcineurin inhibitor.[1,7] In contrast, the common systemic psoriasis agents are cyclosporine A, methotrexate, acitretin fumarate, acid esters, hydroxyurea, 6-thioguanine, mycophenolate mofetil, sulfasalazine, apremilast, and tofacitinib.[1]

The severity of psoriasis vulgaris can be assessed based on several parameters, which include the Body Surface Area (BSA) affected by the lesion, the Psoriasis Area and Severity Index (PASI), systemic symptoms, and the Dermatology Life Quality Index (DLQI).[8] Psoriasis vulgaris is categorized as follows: mild if BSA ≤ 3%, PASI < 5, or DLQI < 5; moderate if BSA > 3% but ≤ 10%, PASI = 5–10, or DLQI = 5–10; and severe if BSA > 10%, PASI > 5, DLQI > 10, or with comorbidities, recalcitrant psoriasis, or psoriasis that is difficult to treat, such as psoriasis affecting the nail or scalp and palmoplantar psoriasis. Treatment is considered successful if a 75% reduction in PASI initial score (PASI75) is achieved and unsuccessful if PASI50 is not attained; PASI50–PASI75 with DLQI < 5

is considered successful, while that with DLQI > 5 is considered unsuccessful.[8]

Studies on the effectiveness of psoriasis therapy in Indonesia are limited. Based on those mentioned above, this study aimed to evaluate the clinical improvement of patients with psoriasis vulgaris using PASI75 at the Dermatology and Venereology Outpatient Clinic in Dr. Soetomo General Hospital Surabaya, Indonesia, between January 2016 and December 2018.

MATERIAL AND METHODS

Study Design and Sample

This retrospective study was conducted at the Dermatology and Venereology Outpatient Clinic in Dr. Soetomo General Hospital, Surabaya, Indonesia, from April to May 2020. This study involved patients diagnosed with psoriasis vulgaris who visited the Dermatology and Venereology Outpatient Clinic in Dr. Soetomo General Hospital, Surabaya, Indonesia, between January 2016 and December 2018. Inclusion criteria in this study were new patients with a diagnosis of psoriasis vulgaris, both male and women, who came for treatment to the Dermatology and Venereology Outpatient Clinic in Dr. Soetomo General Hospital between January 2016–December 2018 and had PASI scores recorded at the beginning and end, an old patient with a diagnosis of psoriasis vulgaris who had exacerbations who come for treatment to Dermatology and Venereology Outpatient Clinic in Dr. Soetomo General Hospital between January 2016–December 2018 and has a PASI score of beginning and end of treatment, and in patients with a diagnosis of psoriasis vulgaris both male and women in the Dermatology and Venereology Inpatient Unit, Dr. Soetomo General Hospital, Surabaya, Indonesia between January 2016–December 2018 and have PASI scores that are disabled at the start and end of treatment. Exclusion criteria for this study were patients with a diagnosis of psoriasis vulgaris, both male and women, who came for treatment to the Dermatology and Venereology Outpatient Clinic, Dr. Soetomo General Hospital, Surabaya, Indonesia for January between 2016–December 2018, without having a PASI score recorded in beginning and end of treatment and in patients with a diagnosis of psoriasis vulgaris both male and women in Dermatology and Venereology Inpatient Unit, Dr. Soetomo General Hospital, Surabaya, Indonesia between January 2016–December 2018 without having a defective PASI score at the start and end treatment. New patients with a diagnosis of psoriasis vulgaris and old patients with a diagnosis of psoriasis vulgaris with exacerbations who come to the Dermatology and Venereology Outpatient Clinic, as well as patients with a diagnosis of psoriasis vulgaris who received inpatient therapy in Dermatology and Venereology Inpatient Unit will be given an initial condition assessment using PASI to determine the severity of the disease. PASI, namely mild, can assess the severity of the disease (PASI <5), moderate (PASI 5-10), and

severe (PASI > 10). The therapy given to psoriasis vulgaris is based on disease severity. Methotrexate was given to the patient with moderate-severe psoriasis vulgaris with the dosage of 2.5 mg/week-25 mg/week based on the severity of clinical manifestations.

Data Collection

Patients with records of PASI scores at the initial visit and after treatment were included. Total sampling was used for data collection. Data on demographic characteristics, number of visits, PASI score before and after treatment, type and dose of therapy, and comorbidities were obtained from electronic medical records.

Statistical Analysis

The SPSS statistical software version 23 was used for data analysis. The demographics and clinical characteristics were descriptively presented. At the same time, the factors associated with PASI improvement were analyzed using an independent T-test or Mann–Whitney and Pearson or Spearman correlation test as an alternative.

RESULTS

This study involved 54 patients with psoriasis vulgaris. Table 1 presents the characteristics of the subjects. The proportion of males and females was the same. Almost all subjects were adults (≥18 years old). The majority of the subjects were private employees, housewives, and civil servants or military members. About half of the subjects had ideal nutritional status. The most prevalent predilection sites of the lesion were the upper and lower extremities and trunk. The most common triggers for flares were tooth infection and stress. No subject had a known history of psoriasis. The majority of the subjects had biopsy results indicative of psoriasis. The most common comorbidity was type 2 diabetes mellitus (T2DM), followed by dyslipidemia, obesity, spondylarthritis/arthropathy, hypertensive heart disease (HHD), and depression (Table 1).

Table 2 presents the severity of psoriasis based on the PASI scores. Almost all subjects presented with severe psoriasis at the initial visit (PASI score > 10). After treatment, almost half of the subjects had moderate psoriasis (PASI = 5–10), and a quarter of them remained with a severe degree. The majority of the subjects (64.8%) successfully achieved PASI75.

Table 3 presents the distribution of treatment modalities among the subjects. Most of the subjects received combined topical and systemic therapy. The most common topical agents prescribed were dexamethasone cream, mometasone furoate cream, Vaseline Album, and urea. The most frequently used systemic therapies were cetirizine, folic acid, and methotrexate. Of all the subjects who received methotrexate, the majority received a 15 mg/week dosage.

Table 4 presents the association between sex, duration of disease, number of visits, methotrexate therapy, and PASI score improvement. A significant association was found between methotrexate treatment and a larger improvement in PASI scores (p-value = 0.001). However, there were no significant relationships between sex and number of visits as well as PASI score improvement.

DISCUSSION

In this study, the proportion of males and females was the same. This finding is supported by most studies that found a balanced proportion of sex in patients with psoriasis.[9] Most of the subjects in this study were adults; this is supported by many previous studies that reported a

Table 1. **Baseline characteristics of subjects.**

Characteristics	Period			Total n (%)
	2016 n (%)	2017 n (%)	2018 n (%)	
Sex				
Male	0 (0.0)	5 (38.5)	22 (55.0)	27 (50.0)
Female	1 (100.0)	8 (61.5)	18 (45.0)	27 (50.0)
Age				
< 18 years old	0 (0.0)	1 (7.7)	0 (0.0)	1 (1.9)
≥ 18 years old	1 (100.0)	12 (92.3)	40 (100)	53 (98.1)
Occupation				
Housewive	0 (0.0)	5 (38.5)	11 (27.5)	16 (29.6)
A civil servant or military members	0 (0.0)	1 (7.7)	9 (22.5)	10 (18.5)
Private employee	1 (100.0)	6 (46.2)	16 (40.0)	23 (42.6)
Student	0 (0.0)	1 (7.7)	0 (0.0)	1 (1.9)
Self-employed/entrepreneur	0 (0.0)	0 (0.0)	4 (10.0)	4 (7.4)
Body Mass Index (BMI)				
<18.5 kg/m^2	0 (0.0)	3 (23.1)	0 (0.0)	3 (5.6)
18.5-22.9 kg/m^2	0 (0.0)	5 (38.5)	23 (57.5)	28 (51.9)
≥ 23.0 kg/m^2	1 (100.0)	5 (38.5)	17 (42.5)	23 (42.6)
Predilection Site				
Scalp	0 (0.0)	2 (15.4)	5 (12.5)	7 (13.0)
Upper extremity	1 (100.0)	12 (92.3)	37 (92.5)	50 (92.6)
Lower extremity	1 (100.0)	13 (100)	36 (90.0)	50 (92.6)
Trunk	1 (100.0)	13 (100)	35 (87.5)	49 (90.7)
Triggers				
Tooth infection	0 (0.0)	3 (14.9)	17 (26.4)	20 (37.0)
Ear, nose, and throat infection	0 (0.0)	5 (11.9)	4 (6.9)	9 (16.7)
Stress	1 (100.0)	4 (34.3)	13 (40.3)	18 (33.3)
Low compliance	0 (0.0)	1 (1.5)	4 (3.4)	5 (9.3)
Unknown	0 (0.0)	0 (0.0)	2 (30.0)	2 (3.7)
Family history of psoriasis				
Present	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
None	1 (100.0)	13 (100.0)	40 (100)	54 (100)
Biopsy result				
Aligned with psoriasis	0 (0.0)	5 (38.5)	26 (65.0)	31 (57.4)
Not aligned	0 (0.0)	5 (38.5)	4 (10.0)	9 (16.7)
None	1 (100.0)	3 (23.1)	10 (25.0)	14 (25.9)
Comorbidity				
Type 2 DM	1 (33.3)	5 (41.6)	10 (25.6)	16 (29.6)
Hypertensive Heart Disease	0 (0.0)	2 (16.7)	1 (2.6)	3 (5.6)
Dyslipidemia	1 (33.3)	1 (8.3)	4 (10.3)	6 (11.1)
Obesity	1 (33.3)	1 (8.3)	2 (5.1)	4 (7.4)
Spondylarthritis/Arthropathy	0 (0.0)	1 (8.3)	3 (7.7)	4 (7.4)
Depression	1 (33.3)	0 (0.0)	0 (0.0)	1 (1.9)

Table 2. **The severity of psoriasis is based on the PASI score.**

Variable	Period						Total n (%)	
	2016 n (%)		2017 n (%)		2018 n (%)			
	Before	After	Before	After	Before	After	Before	After
Severity								
Mild (PASI < 5)	0 (0)	0 (0)	0 (0.0)	3 (25)	0 (0.0)	11 (28.2)	0 (0)	14 (25.9)
Moderate (PASI 5-10)	0 (0)	2 (66.7)	0 (0.0)	8 (66.7)	2 (5.0)	16 (41.0)	2 (3.7)	26 (48.1)
Severe (PASI > 10)	3 (100)	1 (33.3)	12 (100.0)	1 (8.3)	37 (94.9)	12 (30.8)	52 (96.3)	14 (25.9)
PASI75								
Achieved	2 (66.7)		11 (91.7)		22 (56.4)		35 (64.8)	
Not achieved	1 (33.3)		1 (8.3)		17 (43.6)		19 (35.2)	

higher prevalence of the disease among the adult population. A study in Germany in 2007 stated that the prevalence of psoriasis rises with increasing age. Several studies showed that the average age of onset for psoriasis is 33 years old and that 75% of the cases occur before the age of 46.[9] The most common predilection sites of the lesion in this study were the upper and lower extremities and trunk. The well-known predilection sites for psoriasis vulgaris are the extensor side of the extremities, especially the knee and elbow, as well as the scalp, lumbosacral region, buttocks, and genitalia.[1]

The most prevalent triggers for psoriasis flare in this study were stress and tooth infection, as well as ear, nose, and throat infections. Many studies reported that psoriasis could be triggered by various endogen and exogen factors, such as skin aggression, infection (streptococcus infection, periodontitis, and tonsilitis), alcohol and smoking, stress, drugs (lithium, beta-blocker, antimalaria, ACE inhibitor, NSAID, IFN-α and IFN-γ, imiquimod, and gemfibrozil), hormonal changes, and allergy.[1,9,10] All subjects in this study have no known family history of psoriasis. This finding was different from that of previous studies that reported significant percentages of family history in patients with psoriasis, which were 17.5%, 45.9%, 40.7%, 28.6%, 23.1%, and 23.1% in a study in Egypt, Italy, Spain, Maghreb, China, and Malaysia, respectively.[11] The inheritance factor of psoriasis is best described as multifactorial. The concordance rate of psoriasis between monozygotic twins ranged from 35% to 73%.

Interestingly, the number decreases as the location becomes closer to the equator. This finding indicates that ultraviolet exposure might interact with genetic factors in psoriasis.[1] In this study, the absence of a family history of psoriasis might be caused by many undetected cases in the patient's family or the influence of social and cultural factor that causes individuals to report psoriasis symptoms hesitantly. A small proportion of the subjects had the histopathological result that was not aligned with the psoriasis image. This is the result of psoriasis diagnosis primarily based on clinical examination. The histopathological examination has more role in diagnosing atypical or questionable cases.[12] Half of the subjects did not obtain biopsy results because the results were still in process, the patients declined to do the biopsy, or the biopsy was not performed as a previous biopsy had already been taken within the last 30 days.

T2DM and dyslipidemia were the most prevalent comorbidities among all the subjects, followed by obesity, spondylarthritis/arthropathy, HHD, and depression. Psoriasis has been associated with various comorbidities.[13] The classic ones are psoriatic arthritis, inflammatory bowel disease (IBD), psychiatric disorders, and uveitis. Most patients with psoriatic arthritis suffer from psoriasis vulgaris. Conversely, the prevalence of psoriatic arthritis in patients with psoriasis reached 6%–42%. Compared to the normal population, patients with Chron's disease (CD) have a seven-fold higher risk of psoriasis, while patients with psoriasis have a 2.9-fold higher risk of CD.[13] This may be caused by similar genetic susceptibilities shared between psoriasis and IBD. The physical, emotional, and social effects of psoriasis on quality of life are similar or can be worse than other chronic diseases. Psoriasis is linked with low self-esteem and a high prevalence of anxiety and depression (30% and 60%, respectively).[13]

Psoriasis has also been linked with increasing comorbidities, such as metabolic syndrome, nonalcoholic fatty liver disease, lymphoma and another neoplasm, obstructive sleep apnea, and chronic obstructive pulmonary disease.[13] A previous population study has proven that the association between psoriasis and metabolic syndrome becomes stronger as the severity of psoriasis increases.[13] In addition, the relationship between obesity, hypertriglyceridemia, and hyperglycemia also becomes stronger as the severity of psoriasis increases, independent of metabolic syndrome. Moreover, several studies showed that cardiovascular comorbidities were more prevalent in patients with psoriasis. In a cohort study involving patients with psoriasis treated with systemic therapy and patients without psoriasis, a hazard ratio of 1.53 was found after adjustment with age, sex, diabetes, hypertension, dyslipidemia, and smoking. In psoriasis, chronic inflammation accompanied by Th1 and Th17 production triggers systemic inflammation.[14] Pro-inflammation cytokines, such as TNF-α and IL-6, can stimulate the hypothalamus–hypophysis axis, which is related to central obesity, hypertension, and insulin resistance.[14] Therefore, psoriasis can worsen obesity, diabetes, thrombosis, and atherosclerosis. Inversely, those conditions characterized by the production of inflammatory molecules, such as IL-6, TNF-α, plasminogen activation inhibitor, and several adipokines (leptin and resistin), induced chronic pro-inflammation condition, contributing to the onset and/or worsening of psoriasis. Several systemic drugs consumed by patients with psoriasis can also worsen comorbidities. Cyclosporine is nephrotoxic and can potentially cause hypertension and dyslipidemia.[13,14]

Initially, almost all subjects presented with severe psoriasis. After treatment, almost half improved to moderate psoriasis, and a quarter improved to mild psoriasis. The success rate of PASI75 in this study was 64.8%. The therapeutic target of psoriasis is based on several outcomes that include the severity of skin lesions and the impact on quality of life. In Europe, the percentage of PASI score reduction is the standard measure representing the effectiveness of therapy. Today, PASI75 is the basis of the primary outcome in almost all psoriasis clinical trials. However, the ultimate goal of treatment is the complete recovery or nearly complete recovery of all skin lesions and 90% or more improvement of PASI score (PASI90), which today is considered a more relevant outcome, especially in severe psoriasis. Patients without improvement of at least 50% from the initial PASI score are called non-responders. The therapeutic target is usually evaluated between weeks 12 and 16, near the completion of induction therapy.[15]

The success of psoriasis therapy is affected by many factors, including lesion severity, genetic factors (e.g., the mutation in the PSORSI gene), environmental factors such as smoking, infection history (especially streptococcus), drug choice, metabolic disease comorbidities,

Table 3. Treatment modalities and types.

Variable	Period			Total n (%)
	2016 n (%)	2017 n (%)	2018 n (%)	
Treatment modality				
Combination of topical and systemic	3 (100.0)	12 (100)	35 (89.7)	50 (92.6)
Combination of topical, systemic, and phototherapy	0 (0.0)	0 (0.0)	4 (10.3)	4 (7.4)
Topical therapy				
Vaseline album	0 (0.0)	6 (50.0)	24 (61.5)	30 (55.6)
Urea 10% cream	1 (33.3)	9 (75.0)	19 (48.7)	29 (53.7)
Hydrocortisone cream	0 (0.0)	1 (8.3)	5 (12.8)	6 (11.1)
Mometasone furoate cream	1 (33.3)	9 (75.0)	28 (71.8)	38 (70.4)
Desoximetasone cream	3 (100.0)	12 (100)	36 (92.3)	51 (94.4)
Clobetasol proprionate cream	0 (0.0)	1 (8.3)	1 (2.6)	2 (3.7)
Desonide lotion	0 (0.0)	2 (16.7)	11 (28.2)	13 (24.1)
Systemic therapy				
Methotrexate	2 (66.7)	8 (66.7)	29 (74.4)	39 (72.2)
Cyclosporine	0 (0.0)	1 (8.3)	0 (0.0)	1 (1.9)
Folic acid	3 (100.0)	11 (91.7)	32 (82.1)	46 (85.2)
CTM	0 (0.0)	0 (0.0)	2 (5.1)	2 (3.7)
Loratadine	0 (0.0)	0 (0.0)	14 (35.9)	14 (25.9)
Cetirizine	2 (66.7)	12 (100.0)	35 (89.7)	49 (90.7)
MTX dosage per week				
2.5 mg	0 (0.0)	0 (0.0)	3 (10.3)	3 (7.7)
5 mg	1 (50.0)	0 (0.0)	1 (3.4)	2 (5.1)
7.5 mg	0 (0.0)	0 (0.0)	1 (3.3)	1 (2.6)
10 mg	0 (0.0)	0 (0.0)	3 (10.3)	3 (2.6)
12.5 mg	0 (0.0)	2 (25.0)	3 (10.3)	5 (12.8)
15 mg	1 (50.0)	6 (75.0)	17 (58.6)	24 (61.5)
25 mg	0 (0.0)	0 (0.0)	1 (3.4)	1 (2.6)

Table 4. Factors related to PASI improvement.

Variable	PASI score improvement	p	r
Sex			
Male	21.0 (3.0; 30.0)	0.258[a]	N/A
Female	16.0 (-8.8; 28.0)		
Methotrexate therapy			
No	12.0 (-8.8; 26.5)	0.001*[a]	N/A
Yes	23.6 (5.0; 30.0)		
Number of visits		0.476[b]	0.100

[a]Mann-Whitney Test; [b]Spearman Test; *p-value<0.05 is considered significant.

socioeconomic status, the presence of psychopathology, physician-patient relationships, the accessibility of therapy, lifestyle, physical activity, diet pattern, and genetic polymorphism related to therapy response.[16]

The difference in treatment outcomes between gender has not been well studied. There was no significant difference in PASI score improvement between gender. This finding is supported by Hernández-Fernández CP et al., who reported no differences in the effectiveness of systemic psoriasis therapy, in terms of drug survival, between males and females.[14] However, Maul JT et al. found that women in the nonbiological systemic therapy group showed better treatment response compared with men in terms of PASI response, PASI75, and PASI ≤ 3 over 12 months and superior treatment outcome in the biologic therapy group in terms of PASI ≤ 3 at 3 and 6 months.[17] In contrast, Højgaard et al. described better TNF-α inhibitor (TNFI) outcomes among male patients with psoriasis regarding TNFI persistence and treatment response.[18]

Interestingly, in this study, the improvement of PASI score was significantly higher in patients who received methotrexate than in those who received other systemic therapy. A meta-analysis by Mason et al. found better drug survival at 1 year for methotrexate (50%) compared to cyclosporine (23.0%) and acitretin (42.0%) but worse PASI75 percentage in methotrexate (53.0%–59.0%) compared to fumaric acid esters (76.0%).[19] Similarly, a systematic review by Winden et al. reported that, in older adults over 65 years old, the percentage of PASI75 is 49% in methotrexate users, 46.0%–52.6% in cyclosporin users, and 27%–47.8% in acitretin users.[20]

Side effects and clinical response toward moderate-to-severe psoriasis treatment vary among individuals. This variability can be explained by the genetic differences between individuals in single-nucleotide protein (SNP). Generally, SNP is located at key genes related to psoriasis pathogenesis or the mechanism of action of drugs used to treat psoriasis.[21,22] Several pharmacogenetic studies have searched for SNP that can predict the response to methotrexate. The presence of SNP on efflux transporter ATP-binding cassette subfamily C member 1 (rs35592, rs2238476, and rs28364006) and ATP-

binding cassette subfamily G member 2 (rs17731538 and rs13120400) is related to a better response to methotrexate therapy in psoriasis. A significant difference in the frequency of genotype HLA C:06:02 and rs3761548 (FOXP3) was also found in patients who respond and do not respond to methotrexate in a Tamil South Indian population. The presence of one repetition of triplet 28-b (allele heterozygote 3R/2R, allele heterozygote 3R/2R) on thymidylate synthase 50' untranslated region was more prevalent in patients who do not respond to methotrexate.[23]

CONCLUSION

In conclusion, the success rate of moderate-to-severe psoriasis therapy in PASI75 at The Dermatology and Venereology Outpatient Clinic in Dr. Soetomo General Hospital, Indonesia, from 2016 to 2018, achieved a satisfactory rate of 64.8%. The improvement of PASI score was significantly better in patients who received methotrexate. Further studies in Indonesia are needed to explore the effectiveness of psoriasis therapy and its factors. The limitation of this study was the incompleteness in recording PASI in the patient's medical record so that the success of therapy cannot be assessed.

ACKNOWLEDGMENT

The authors thank the Universitas Airlangga/Dr. Soetomo General Academic Teaching Hospital for supporting this research.

ETHICAL CLEARANCE

This study was obtained ethical clearance and approved by Clinical Research Unit from the Ethics Committee of Dr.Soetomo General Academic Teaching Hospital Surabaya (1979/KEPK/IV/2020).

CONFLICTS OF INTEREST

The authors declare that there is no have a potential conflict of interest.

SOURCE OF FUNDING

None.

AUTHOR CONTRIBUTIONS

All authors contribute to the study from the conceptual framework, data acquisition, data analysis until reporting the study results through publication.

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