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Original Article

Evaluation of methotrexate and cyclosporine for severe psoriasis: A retrospective analysis from tertiary hospital in Indonesia

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Abstract

Background Psoriasis is an autoimmune disease manifested as chronic, recurrent thick red scaly plaques. Cyclosporine and methotrexate have been used as therapy for severe psoriasis since decades. This study aims to evaluate the clinical outcome of methotrexate and cyclosporine as treatment for severe psoriasis.

Methods A three-year retrospective analysis was undertaken to examine the medical records of hospitalized patients with severe psoriasis. This study evaluated outcomes such as psoriasis area and severity index (PASI) and length of hospital stay (LOS).

Results Twenty-six patients were included in the study. Mean PASI reduction was 42.8% (± 24.64), with greater reduction in cyclosporine group (mean 54.88±12.73%) than that in methotrexate group (mean 43.22±24.4%). Patients in cyclosporine group stayed longer (18.83±9.39 days) than patients in methotrexate group (11.65±5.91 days).

Conclusion Methotrexate and cyclosporine treatment are effective for severe psoriasis. However, the hospital stays for patients receiving cyclosporine treatment might be longer.

Key words
Psoriasis, methotrexate, cyclosporine, medicine, evaluation.

Introduction

Psoriasis is an autoimmune disease manifested as chronic and recurrent thick red scaly plaques on the skin. This disease is influenced by genetic susceptibility, immunological processes, and precipitating factors from the environment and is often accompanied by arthritis, cardiovascular morbidity, and psychosocial disorders.[1] The prevalence of psoriasis ranges from 0.09-11.4% of the global population. In Asia, the prevalence of psoriasis is around 0.4%. It is believed that 2-6 million Indonesians suffer from psoriasis.[1–3] Topical treatments such as calcipotriene, corticosteroids, tar, and anthralin; phototherapy with ultraviolet B (UVB) and psoralen with ultraviolet A (PUVA); systemic

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immunosuppressant drugs such as acitretin, methotrexate, and cyclosporine are available for psoriasis.[4]

Methotrexate, a folic acid antagonist, exerts an antimitotic effect on the epidermis by inhibiting DNA synthesis. Cyclosporine is a cyclic decapeptide with a strong immunosuppressive effect. Its mechanism of action in psoriasis inhibits the activation of T helper cells, and cytokines such as interleukin-2 (IL-2).[5] Cyclosporine and methotrexate have long been used to treat moderate to severe psoriasis.[6] In Indonesia, both agents are still considered as first-line systemic treatment for moderate to severe psoriasis.[7] Several clinical trials have demonstrated that methotrexate and cyclosporine are effective therapies for moderate to severe psoriasis, as well as the two drugs' potential toxicity.[4,5,8] There have also been some studies that combine the two medicines together to treat psoriasis vulgaris and nail psoriasis.[9,10] According to a recent meta-analysis, these two medications are less effective than the more effective and safer biologic agents. Biologic agents are increasingly chosen in wealthy nations, whereas conventional systemic therapy is being phased out.[11,12] The use of biologics in developing countries, such as Indonesia, is limited by its relatively high prices. As a result, conventional systemic treatment, particularly methotrexate and cyclosporine, remains the treatment of choice in clinical practice. The efficacy of these two medications on Indonesian patients must be evaluated. The purpose of this study is to assess the clinical outcomes of patients with severe psoriasis who were treated with systemic methotrexate and cyclosporine.

Methods

This retrospective study was conducted in a tertiary referral hospital of Indonesia, Dr. Soetomo General Academic Hospital in Surabaya, with the approval of the hospital ethics committee. The inclusion criteria were severe psoriasis patients hospitalized in the Dermatovenereology ward and receiving methotrexate or cyclosporine treatment during year 2016 to 2018. Demographic characteristics, psoriasis area and severity index (PASI), length of hospital stay, and therapy history were extracted from medical records. Severe psoriasis was defined as a PASI score >10.[13] Baseline PASI scores were calculated at admission and the after-treatment score was on the discharge day. PASI score reduction and length of stay (LOS) in the hospital were considered as outcomes evaluated in this study. Reduction of 75% PASI score (PASI-75) is regarded as cured target for psoriasis.[12]

Statistical analysis was performed using the Perfect Statistics Professionally Presented (PSPP) program version 3, free access statistical software. Demographic data and clinical outcomes were analyzed in descriptive manners, relationships between variables were analyzed using Pearson's correlation. Normally distributed data were compared using paired sample t-test, while Wilcoxon rank tests were used to compare the mean of not normally distributed ones.

Results

Out of 30 hospitalized patients, 26 patients treated with methotrexate and cyclosporine were included in the study. The male to female ratio was 1.7:1 and the average age was 41.08 (±16.04) years old. All the patients were categorized as severe psoriasis with an average PASI score of 39.92 (±15.88) at admission. Twenty patients received methotrexate treatment, while six patients were treated with cyclosporine **(Table 1)**. Methotrexate was administered in doses ranging from 2.5-5 mg three times a week at 12-hour intervals.

Table 1 Subject characteristic.

	Mean (±SD)
Age	41.08 (±16.04)
Gender	
Male, n (%)	17 (65.4)
Female, n (%)	9 (34.6)
Systemic treatment	
Methotrexate, n (%)	20 (66.7)
Cyclosporine, n (%)	6 (20)
Baseline PASI score	39.92 (±15.88)

*PASI: psoriasis area and severity index.

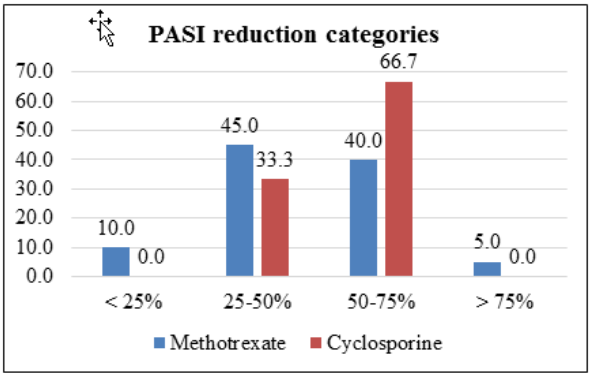

Figure 1 Psoriasis area and severity index (PASI) score reduction categories between two groups.

Cyclosporine was administered at a dosage of 50-100 mg twice daily. The baseline PASI score in the methotrexate group was 37.81 (±16.0), while in the cyclosporine group was 46.95 (±14.50). The mean percentage of PASI score reduction in both groups was 45.91 (±22.59) percent. Score of PASI decreased significantly in both groups **(Table 2)**, with 54.88±12.73 percent PASI score reduction in cyclosporine group and 43.22±24.4 percent in methotrexate group. Out of 26 patients, 5% patients treated with methotrexate achieved PASI-75. Most of Cyclosporine patients achieved 50-75% PASI score reduction **(Figure 1)**. Patients were hospitalized for 4 to 34 days, with a mean duration of 13.31 (±7.33) days. Patients treated with cyclosporine stayed longer in hospital (18.83±9.39 days) than patients in the methotrexate group (11.65±5.91 days).

Discussion

Methotrexate and cyclosporine are two systemic agents that are traditionally used to treat moderate-severe psoriasis.[10] Psoriasis severity assessment is important to decide treatments of choice. There are many options available for this purpose, according to body surface area (BSA), physician global assessment (PGA), PASI, and dermatology life quality index (DLQI).[13] PASI

Table 2 Mean psoriasis area and severity index (PASI) score in two treatment groups.

	PASI baseline (±SD)	*PASI after (±SD)*	*P value (CI 95%)*
Methotrexate	37.81 (±16.00)	17.03 (±8.29)	<0.001
Cyclosporine	46.95 (±14.50)	21.08 (±8.25)	0.003

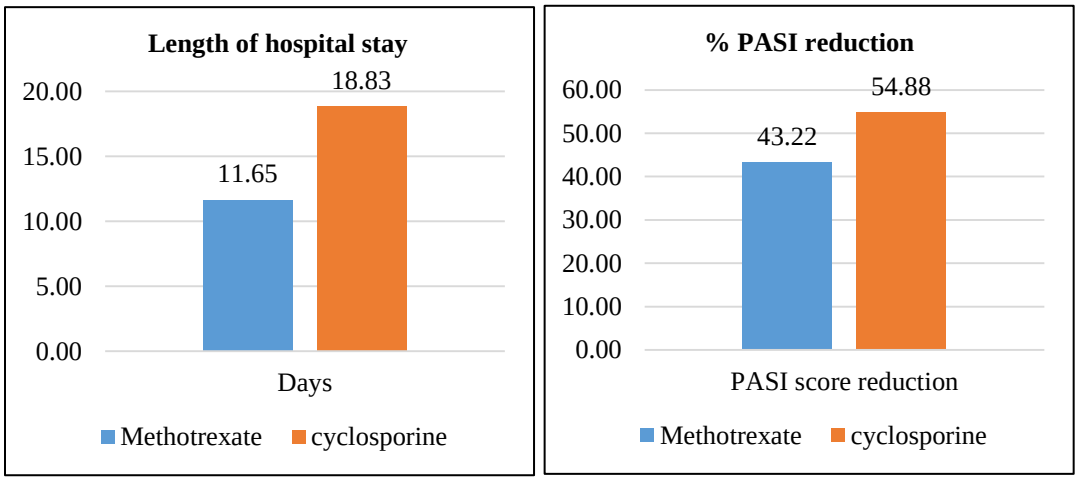

Figure 2 Length of stay in hospital and psoriasis area and severity index (PASI) score reduction among two groups.

and DLQI are the most frequently used methods of determining psoriasis severity in clinical practice, especially for systemic therapy patients.[7,13] The PASI score is used in this study to assess clinical improvement. Based on the PASI score, three severity categories are employed in clinic (mild, moderate, severe). Mild psoriasis is characterized as PASI 5, moderate as 5-10, and severe psoriasis as PASI >10.[13]

Methotrexate and cyclosporine were shown to be effective in treating severe psoriasis at an Indonesian tertiary hospital. The PASI score was significantly reduced in patients receiving cyclosporine or methotrexate in this study. Cyclosporine is more effective, however the difference is not statistically significant. A meta-analysis research found that cyclosporine was more effective than methotrexate in reaching PASI-75, although there was no statistically significant difference.[11] Heydendael's clinical trial in 2003 showed that administration of methotrexate 15 mg/week and cyclosporine 3 mg/day for 16 weeks could reduce PASI scores in 94% of patients by at least 25%. PASI-75 was achieved by 60% of subjects in the methotrexate group and 71% in the cyclosporine group.[4] Flytstrom *et al*. conducted another clinical study in 2007 that evaluated methotrexate and cyclosporine without a placebo. The mean PASI score change in the cyclosporine group was 72% and 58% in the methotrexate group, with a statistically significant difference.[8] Sandhu *et al*. found that both medications were effective for severe psoriasis. Methotrexate had superior effectiveness in this clinical trial, lowering the PASI score by 98.5% compared to 85.6% in the cyclosporine group after 12 weeks of administration.[5]

According to a meta-analysis of 48 randomized controlled trials, biological agents such as infliximab, adalimumab, ustekinumab, and etanercept are systemic therapies with the strongest evidence to be effective for moderate to severe psoriasis. These biological agents are more effective than conventional agents, such as alefacept, retinoids, fumaric acid, methotrexate, and cyclosporine.[11] Current psoriasis guidelines suggest biological therapies as therapy for individuals with moderate-to-severe psoriasis who are resistant to conventional medication or cannot tolerate it due to adverse effects.[12,14–16] The lower cost of conventional systemic therapy supports its use as the first line treatment, particularly in developing countries such as Indonesia.[7] The most crucial issue is to determine when conventional systemic therapy is no longer appropriate and when a biological agent should be used, following published worldwide consensus recommendations.[17]

The average LOS for psoriasis patients at Indonesian tertiary hospitals appears to be longer than in developed countries. Patients who received methotrexate had a lower mean LOS than those who received cyclosporine. Regardless of disease severity, the average hospital stay for uncomplicated psoriasis patients in the United States was 4.6 days. It can rise to 6.6 days in psoriasis patients with acute infections.[18] Another data from the United States said that the average LOS for psoriasis patients was 8.6 days.[19] Hospitalization is indicated for patients with moderate-to-severe psoriasis for diagnostic or treatment procedures that cannot be performed at a primary or secondary referral hospital.[20] Patients with severe psoriasis frequently have systemic diseases that necessitate treatment by other specialists. Patients with psoriasis who are hospitalized may face diminished quality of life and physiological distress, particularly in the elderly.[20] According to a qualitative research conducted by Vensel *et al*. (2016), the impairment in quality of life improved immediately after being discharged from the hospital and lasted for three months.[19]

Both methotrexate and cyclosporine have side effects to be aware of, as they occur in more than half of patients in certain studies.[6,8] Heydendael's study revealed methotrexate side effects, as 14 patients in the methotrexate group dropped out owing to an abnormally increased liver enzyme. Other reported adverse effects included nausea, particularly on the day of medication administration, muscular discomfort, weariness, and paraesthesias in the fingers.[4,5] Elevated creatinine levels are the most prevalent side effect of cyclosporine, followed by hypertension, hypertriglyceridemia, depression, and headache.[5,10] The study's limitations include the difficulty in demonstrating long-term adverse effects of methotrexate and cyclosporine after discharge since several patients skipped follow-up outpatient visits.

Conclusion

Methotrexate and cyclosporine appear to successfully reduce the clinical severity of severe psoriasis, with cyclosporine patients having a higher reduction in PASI scores but a longer length of hospital stay. It is essential to evaluate the clinical response to such therapy before transitioning to biological drugs.

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