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Original Article

Intramuscular 50mg methotrexate injection therapy for severe psoriasis: Study on effectivity and side effect

Sunardi Radiono, Prasta Bayu Putra, Dyah Ayu Mira Oktarina

Department of Dermatology and Venereology Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada/ Dr. Sardjito Hospital, Yogyakarta, Indonesia.

Abstract

Background Psoriasis is a chronic autoimmune and inflammatory skin disease. Parenteral methotrexate has promising potential to be used as treatment choice for severe psoriasis. However, no effectivity and safety data to be used severe psoriasis. Our objective is to determine the effectivity and safety of intramuscular 50 mg methotrexate for severe psoriasis.

Methods This is a descriptive retrospective study in severe psoriasis. The data were taken from Dr. Sardjito Hospital Yogyakarta, Indonesia medical record, which fulfilled the inclusion and exclusion criteria. Subjects were previously administered with intramuscular 50 mg methotrexate injection according to the protocol. Comparative analysis is performed to determine treatment effectivity parameters consisting of psoriasis area severity index (PASI) and dermatological life quality index (DLQI) score. Side effects found in this study were analyzed descriptively.

Results 35 severe psoriasis subjects were enrolled in this study. Significant PASI and DLQI scores reduction were found during treatment protocol. PASI-75 and PASI-90 scores were achieved by 50% subject in 4th and 8th week. Severe side effect of hepatotoxicity with >2 times SGOT/SGPT upper limit level elevation was found in 2.9% subjects.

Conclusion Intramuscular 50 mg methotrexate injection can be an effective and safe treatment for severe psoriasis in a limited setting.

Key words
Intramuscular methotrexate, severe psoriasis, PASI score, DLQI score.

Introduction

Psoriasis is a chronic and inflammative autoimmune disease that mediated by T cell with polygenic predisposition and clinically manifested as erythematous papule and plaque with thick scale, pustular, or erythrodermic eruption.[1] Psoriasis severity degree can be divided based on psoriasis area severity index (PASI) into mild degree (<10), moderate degree (10-20), and severe degree (>20).[2] Severe psoriasis incidence is reported to be 17% of worldwide psoriasis.[3] Successful therapy is the main factor in reducing severity degree, maintaining remission, and improving patient's quality of life.[4,5]

Psoriasis therapy is a long-term therapy because of the its chronic disease course.[3] Methotrexate is a synthetic folic acid analog antimetabolite that has become main psoriasis conventional systemic therapy in the last decades. Methotrexate has anti-inflammative and anti-proliferative properties in the psoriasis

Address for correspondence
Dr. Dyah Ayu Mira Oktarina MD.
Faculty of Medicine, Public Health, and Nursing
Yogyakarta 55281, Indonesia.
Ph: +62811286852
Email: d.oktarina@ugm.ac.id

pathogenesis. Nuclear factor kappa B (NF-κB) inhibition that mediated by adenosine signaling pathway along with biosynthesis inhibition of purine and pirimidine become the base of methotrexate therapeutical in inflammation and hyperproliferation in psoriasis pathogenesis.[6,7]

Methotrexate has flexibility in dosing and route of administration that can be chosen based on patient condition for improving effectivity and reducing side effect risk.[8] Methotrexate can be administered orally, or parenterally from intravenous injection (IV), subcutaneous injection (SC), or intramuscular injection (IM). Parenteral methotrexate bioavaibility was reported to be more than 70% and more superior than oral methotrexate bioavaibility that was reported to be around 70%.[6,9] Therapeutical effect of methotrecate is dose dependent, which in more severe psoriasis need higher methotrexate dose. Gastrointestinal side effect that commonly found in higher dose was reported to be reduced in parenteral administration.[10] Parenteral methotrexate effectivity, safety, and tolerability study in severe psoriasis patient is still very limited.[9,11]

Oral and parenteral methotrexate are available in national formularium and covered by Indonesian national health insurance. Parenteral methotrexate is available in 2cc ampule (25 mg/mL) for intramuscular injection in tertiary health facility.[12] The oral methotrexate shortage in 2016 to 2018 because of no domestic producer and disrupted import process lead to serious problem for long term psoriasis therapy.[13]

Parenteral methotrexate has promising potential as main therapy in severe psoriasis. Its availability in Indonesian national formularium also support for the long-term psoriasis treatment. This study is designed for assessing effectivity and safety of parenteral methotrexate in severe psoriasis.

Methods

This is a descriptive retrospective study in severe psoriasis treated in Dr.Sardjito Hospital, Yogyakarta, Indonesia on July 2017 to July 2019. The datas were derived from Hospital medical record, that fulfilled the inclusion and exclusion criterias. This study was approved by Medical and Health Research Ethics Committee from Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada with reference number KE/FK/0681/EC/2019. Informed consent was obtained from all subjects in this study.

Inclusion criteria in this study consist of:

1. Psoriasis vulgaris with PASI score ≥20 or erythrodermic psoriasis that was diagnosed clinically and histopathologically.
2. Male or female with the age of <70 years old.
3. Willing to sign the research consent letter.

Exclusion criteria in this study consist of:

1. Has other autoimmune disease that was diagnosed clinically.
2. In lithium, antimalaria, cotrimoxazole, infliximab, acitretin, phototherapy, or other systemic immunosuppressive treatment beside IM 50 mg methotrexate injection in the last month.
3. In sepsis condition or active tuberculosis that was diagnosed clinically, laboratory, and radiologically.
4. In pregnancy plan, pregnant, or breastfeeding.
5. Has hypersensitivity history to methotrexate
6. Obesity with body mass index (BMI) ≥30kg/m^2.
7. Has hematology abnormality such as anemia with hemoglobin level of <10 gr/dL,

leukopenia with leukocyte level of <3000/mm^3, or trombocitopenia with thrombocyte level of 150.000/mm^3 from complete blood examination

8. Has renal or hepatology abnormality with serum glutamic-oxaloacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT), blood urea nitrogen (BUN), and creatinine levels elevation >2x from upper normal limit

Demographic data, PASI score, dermatological life quality index (DLQI) score, and histopathology data in baseline were collected from all subjects that meet the inclusion and exclusion criterias. The subjects then undergo IM 50mg methotrexate injection protocol that consist of minimum 6 weekly doses (phase I), minimum 2 two weekly doses (phase II), and minimum 2 monthly doses (phase III). Six months of maintenance phase start as the subject competed the methotrexate injection protocol. PASI and DLQI score are also collected as effectivity parameter along with side effect that found when the subject undergo the protocol and maintenance phase.

PASI score measurement is done by main examiner and co-examiner from digital photography. Bland Altman test is used to determine the agreement degree between two examiners. PASI score datas from main examiner are used in the analysis if the agreement degree test result is good. PASI-75 and 90 measurements are based on main examiner PASI score results as therapeutical effectivity parameter.

DLQI score is measured by filling DLQI questionnaire independently by subjects themselves or helped by the examiner. DLQI questionnaire that used in this study is in Indonesian language that has been validated.

Anamnesis, physical examination, and laboratory examination of routine blood test, renal function (BUN, creatinine), and hepatology (SGOT, SGPT) were performed for side effect screening of IM 50 mg methotrexate injection therapy. Mild side effect is categorized as side effect that does not made the need to protocol cessation and severe side effect is categorized as side effect that made the need to protocol cessation based on psoriasis treatment consensus of British Dermatology Society (2016).[10]

The IBM SPSS® version 24.0 for Windows was used for all analyses. Demographic data, number of cycle, PASI-75 score, PASI-90 score, and side effect of IM 50 mg methotrexate injection are presented in frequency (total and percentage), mean, and standard deviation. Comparative test based on data distribution result from Shapiro Wilk test is performed to determine the comparison of PASI and DLQI scores. Post hoc test is also performed to determine comparison the scores between each study phases.

Results

The subjects consist of psoriasis vulgaris and erythrodermic psoriasis with the baseline PASI score from 24.2 to 72 and the mean PASI score of 45.2±15.6. The Bland Altman test showed good degree of agreement. Subjects age were 15 to 68 years old with the mean of 45.91 ± 16.8 years old. The demographic data is presented in **Table 1**.

The subjects are dominated by 25% male with 22.9% farmer and 20% office employee as the main occupation. Housewife were found in 17.1% subjects as the third main occupation. Normal BMI category was found in 68.6% subjects followed by overweight (25.7%) and underweight (2%) categories.

Table 1 Demographic data of the subjects.

Characteristics	*n (%)*
Diagnosis	
Psoriasis vulgaris	16 (45.7)
Erythrodermic psoriasis	19 (54.3)
Age	
<40 years old	11 (31.4)
>40 years old	24 (68.6)
Sex	
Male	25 (71.4)
Female	10 (28.6)
Occupation	
Farmer	8 (22.9)
Office employee	7 (20.0)
Housewife	6 (17.1)
Labor	5 (14.3)
Student	5 (14.3)
Entrepreneur	3 (8.6)
Teacher	1 (2.9)
BMI (kg/m^2)	
Underweight (<18.5 kg/m2)	2 (5.7)
Normal (18.5-24.9 kg/m2)	24 (68.6)
Overweight (25-29.9 kg/m2)	9 (25.7)

BMI, body mass index.

Psoriasis length of sickness and previous therapy are presented in **Table 2**. The subjects had the length of sickness between 1 week to 25 years. Previous severe psoriasis therapies that were done by the subjects were oral methotrexate (68.57%), cyclosporine (20%), and narrow-band ultraviolet B (NBUVB) phototherapy (17.14%). There were 3 subjects (12.5%) with more than 4 grams methotrexate cumulative dose found in this study. The number of the protocol cycle, PASI-75 and 90 scores are presented in **Table 3**. There were 4 subjects that did not undergo full protocol and dropped out. The reason for protocol cessation were the oral methotrexate was already available in 5.8% subjects, moved domicile, and severe hepatotoxicity in each another 2.9% subjects. The PASI-75 and 90 scores were achieved by 50% subject in phase I and II with the pattern presented in **Figure 1**.

Table 2 Characteristics of psoriasis length of sickness and previous therapy.

Characteristics	*Mean±SD*
Psoriasis length of sickness (week)	339.71±55.07
Previous psoriasis therapy	
Oral methotrexate (n= 24)	
Length of treatment (week)	196.17±39.70
Cumulative dose (mg)	2611.67±643.51
Cyclosporine (n= 7)	
Length of treatment (week)	28.71±8.76
NBUVB phototherapy (n= 6)	
Length of treatment (cycle)	25.5±8.28
Cumulative dose (J/cm2)	3.2±14.38

NBUVB, narrow-band ultraviolet B therapy.

Table 3 Characteristic of number of the protocol cycle, PASI-75, and 90 scores.

	n (%)		
	Phase I (n=35)	*Phase II (n=34)*	*Phase III (n=31)*
Number of cycles			
On protocol	34 (97.1)	30 (85.7)	31 (100)
Extended	0 (0)	1 (2.9)	0 (0)
Cessated	1 (2.9)	3 (8.8)	0 (0)
PASI score			
PASI-75	32 (91.4)	34 (100)	31 (100)
PASI-90	17 (48.6)	25 (73.5)	30 (96.8)

PASI, Psoriasis Area and Severity Index

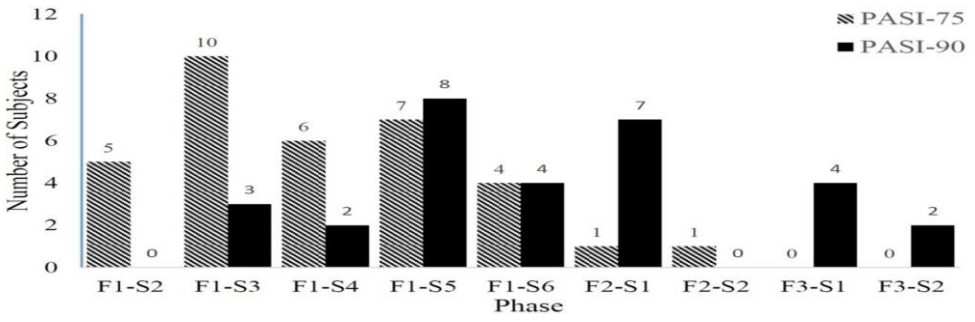

Figure 1 PASI-75 and 90 achievement patterns (F: Phase, S: Cycle).

Table 4 Intramuscular 50 mg methotrexate injection side effects.

Side Effect	*n (%)*			
	Phase I (n=35)	*Phase II (n=34)*	*Phase III (n=31)*	*Maintenance (n=31)*
Mucocutaneus				
Ulceration	1 (2.9)	1 (2.9)	0 (0)	0 (0)
Hematology				
Mild anemia	20 (57.1)	10 (29.4)	5 (16.1)	0 (0)
Gastrointestinal				
Nausea	5 (14.3)	3 (8.8)	3 (9.7)	0 (0)
Hepatotoxicity				
Mild	1 (2.9)	0 (0)	0 (0)	0 (0)
Severe	1 (2.9)	0 (0)	0 (0)	0 (0)
Secondary infection				
Gluteal abscess	1 (2.9)	1 (2.9)	0 (0)	0 (0)

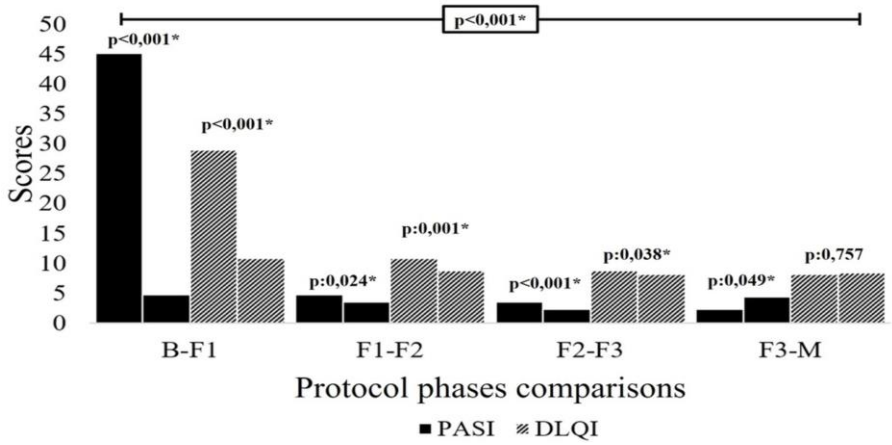

Figure 2 PASI and DLQI scores comparisons in each phase. (B: Baseline, P: Phase, M: Maintenance).

The IM 50 mg methotrexate injection therapy effectivity was determined from several parameters, such as comparison of PASI and DLQI scores in baseline, end of each protocol and maintenance phases. The data were not distributed normality using Shapiro Wilk normality test. The Friedman test and Wilcoxon post Hoc test were performed in 31 subjects to determine the PASI and DLQI scores improvement. There were 4 subjects that dropped out from this study that were not entered for comparative analysis.

The Friedman test results in PASI and DLQI scores showed statistically significant results ($p<0.05$). Based on that results can be concluded that there was at least one comparison from two measurement results that significantly different. Post Hoc test was performed to determine the comparison results in each of the study phases.

The Wilcoxon post Hoc test showed statistically significant result ($p<0.05$) in several measurements. Statistically significant PASI scores difference were found in each of phases comparisons. The DLQI scores also showed statistically significant difference in each phases comparisons except the comparison of phase III with maintenance phase. The complete presentation of PASI and DLQI scores comparison results in each phases are presented in **Figure 2**.

Side effects that found in this study are presented in table 4. Mild anemia followed with nausea were the most common side effect that

found in this study. Hepatotoxicity side effect was found in 5.8% subjects, which in 2.9% was severe and the other 2.9% was mild. Ulceration in oral mucosa was found in 1 subject in phase I and II. All of the side effects found in protocol phase were not continued to be found in maintenance phase.

Discussion

Erythrodermic psoriasis is the majority of the psoriasis type in this study. This characteristic was not in line with the psoriasis type based on the age of onset in this study that dominated by type II psoriasis (>40 years old). Based on the previous study by Parisi *et al.*, type I psoriasis was reported to have more severe degree than type II that associated with longer duration of psoriasis.[14] Erythrodermic psoriasis was found in 54.5% type I psoriasis and 54.2% type II psoriasis in this study. This characteristic showed that the earlier first age of psoriasis onset is not absolutely lead to more severe psoriasis.

Daily activity and occupation have significant role in physical trauma as external factor that can dominantly aggravate the psoriasis severity degree.[15] There were farmers (22.9%) and labors (14.3%) in the occupational characteristic that highly exposed to physical trauma. They usually worked without protective equipment such as gloves or footwear to reduce physical trauma. There was 3.2% subjects that did not achieve PASI-90 score until the end of protocol, which was a labor that could not stop from his job during the study because of economy reason. The subjects still achieve PASI-75 score in the phase I cycle 5.

The BMI level is one of factors that was previously reported to be correlated with methotrexate therapeutical effect. Takahasi *et al.* reported negative correlation between active metabolite level of methotrexate polyglutamate (MTXglu) with the BMI level, which in higher BMI level will be followed with lower methotrexate therapeutical and side effects.[16] The BMI characteristic in this study was not in line with the previous study, which in 100% and 96.8% subjects were achieved PASI-75 and 90. Side effect was not found in subjects with underweight category. Mild anemia was found in 44.4% subjects with overweight category otherwise.

There were 8.7% subjects with the methotrexate cumulative dose more than 4 grams. The liver biopsy was not performed in that subjects because from the SGOT/SGPT examination were still in normal range. The liver biopsy is the gold standard for liver fibrosis, but based on psoriasis treatment consensus from British Association of Dermatologist and Australasian, the examination is not advised to be routinely performed because it is invasive and the hepatotoxicity side effect of methotrexate is rarely found. The liver biochemical examination is advised to be performed as routine non-invasive examination and the liver biopsy is performed if the liver fibrosis is suspected regardless from the methotrexate cumulative dose.[10,17]

The IM 50 mg methotrexate injection therapy protocol in this study consist of 3 main phases that can be extended if the target is not achieved or there is still new lesion formation. In phase I there were 2.9% subjects that cessated from protocol because of severe hepatotoxicity. In Phase II there were 5.8% subjects that cessated from protocol because of the oral methotrexate was already available and moved domicile in 2,9% subjects. There were 2.9% subjects that extended until phase II cycle 6, because of there was still new lesion formation. In phase III, all of the subjects undergo the treatment according to protocol without any cessation or extension.

The PASI-75 and 90 scores in this study were achieved by 50% subjects in phase I cycle 4 (4th weeks) and phase II cycle 1 (8th weeks). These achievements are faster than the previous study by Vidal *et al.* and Warren *et al.*, which the PASI-75 scores were only achieved by 45-47% subjects in 52nd-54th weeks.[18,19] Parenteral methotrexate administration with higher dose compared to previous studies giving higher bioavaibility in this study. The higher bioavaibility lead to faster methotrexate deposition in cellular tissue and adequate therapeutical effect that shown in faster PASI-75 and 90 achievements.[6]

In line with Revicki *et al.*, the subject quality of life is improved significantly along with significant PASI score improvement during the protocol.[20] Significant difference in phase III with maintenance phase was not found, because the severity degree was not increased from mild to moderate or severe in majority of the subjects (83.9%) during the maintenance phase. DLQI score was worsen in the subjects who showed increased psoriasis severity degree.

The most common side effects found in this study were mild anemia and nausea, which were the other side effects such as oral mucosa ulceration, gluteal abscess in injection site, mild and severe hepatotoxicities only found each in 2.9% subjects. All of the side effects were only found during protocol, mainly in phase I that reduced along with lower injection frequencies in the phase II and III. The protocol cessation was only performed in subject with severe hepatotoxicity.

The pulsed dose application in methotrexate in this study is proved to showed relatively mild side effects. This result is in line with previous study, which in the longer time of methotrexate administration will be followed with higher side effect risk.[21] Hematology side effect of anemia is categorized as mild degree with haemoglobin level of 10-12 gr/dL without pancytopenia. The other side effects such as oral mucosa ulceration and gluteal abscess are included in mild side effect degree.[22] Syptomatic and wound care treatment improved the subjects side effects.

Hepatotoxicity is a rare side effect in methotrexate treatment. Severe hepatotoxicity was found in 2.9% subjects and made the protocol to be cessated in that subjects during phase I cycle 3. The subjects were female with normal BMI category and 40 mg cumulative dose. Subjects did not have history of alcohol consumption and previous liver disease. The other risk factor that can have role in that subjects is genetic factor, which in reduced folate carrier polymorphism subject was reposted to had increased methotrexate hepatotoxicity risk.[23]

Occupational factor is the confounding variable that was still could not fully controlled in this study. In 22.9% and 14.3% subjects that worked as farmers and labors were highly exposed from occupational trauma. That subjects still worked during protocol, so that the severity could be aggravated and the methotrexate effectivity could be reduced. Occupational factor control is needed for more objective results in the next study.

In conclusion, there were significant improvements of PASI and DLQI scores during treatment protocol. PASI-75 and 90 scores were achieved by at least 50% subjects in 4th and 8th weeks. The severe side effect found in this study was severe hepatotoxicity with elevated SGOT/SGPT levels >2 times of normal upper limit in 1 subject (2.9%). Control in physical trauma from occupation is needed for more objective result in the next study. The IM 50 mg methotrexate injection therapy can be used mainly for severe psoriasis treatment when the

oral methotrexate is available.

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