Clinical and Life Quality Improvement, and IL-17 Serum Level in Psoriasis Patients Treated with Metothrexate Injection: A Pilot Study in 15 Severe Psoriasis Cases

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Abstract: Psoriasis is an autoimmune T cell mediated chronic skin disorder which is difficult to treat. Conventional therapy using oral methotrexate in severe cases often showed unsatisfying result. Our department was developing methotrexate injection protocol for severe cases to improve patient treatment and life quality and for achieving quick remission. Objective: This pilot study was aimed to observe efficacy of methotrexate injection 50mg/week for 6 consecutive weeks. Method: Study subjects were severe psoriasis patients that unresponsive to any conventional therapies. PASI score and DLQI score improvement and serum IL-17 level at the end of study were measured. Result: PASI-100 was achieved by 12 subjects (80%) at the end of sixth weeks. DLQI score were significantly different ($p<0.001$) after sixth injection and subjects serum IL-17 level were not significantly different with healthy peoples at the end of study. Conclusion: Methotrexate injection 50mg/week for 6 consecutive weeks initiation can be considered as an effective treatment for severe psoriasis. Further studies with larger samples and longer observation period are needed to determine long term efficacy, side effects, and protocol guideline policy.

1 INTRODUCTION

Psoriasis is an autoimmune T cell mediated chronic skin disorder with polygenic predisposition and clinical manifestation such as papule and erythematous plaque with thick scale, pustular, or erythroderma (Gudjonsson *et al.*, 2012). Psoriasis pathogenesis is run by IL-23/Th17 axis, in which IL-23 is Th17 cell activator, and IL-17 is the prime secreted cytokine. Recent study also reported that IL-23 and IL-17 can be used to assess psoriasis remission (Chiricozzi, 2014; Karczewski *et al.*, 2016).

Psoriasis often need long term therapy and difficult to treat. Conventional therapeutic modalities that can be used for psoriasis treatment consist of topical agent, systemic, and phototherapy. Topical corticosteroid, vitamin D analogues, tazaroten, and calcineurin inhibitor can be used as topical therapy. Cyclosporine, methotrexate, acitretin, fumaric acid esther, hydroxyurea, mychophenolate mofetil, and sulfasalazine can be used as systemic therapy. Phototherapy modality consist of Narrowband Ultraviolet B (NB-UVB), Broadband Ultraviolet B (BB-UVB), and Psoralen with Ultraviolet A (PUVA) (Gudjonsson *et al.*, 2012).

Methotrexate is the prime choice for systemic conventional therapy in psoriasis treatment that has anti-proliferative effect by inhibition of DNA synthesis giving anti-inflammatory and immunosuppression effect (Puig, 2014; Yélamos & Puig, 2015) Mild to severe psoriasis and psoriasis that unresponsive to topical therapy and phototherapy are the indications of methotrexate administration. Methotrexate as single psoriasis drug need 1-8 weeks to achieve therapeutic effects. High dose methotrexate (15-25 mg/week) is more effective than

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low dose (7,5-15 mg/week) (Dogra & Mahajan, 2013). The usual adverse effects of methotrexate such as nausea, vomitus, bone marrow depression, folic acid deficiency, and hepatotoxicity have been reported. Cumulative dose more than 3 gram increasing the hepatotoxicity risk (Pathirana *et al.*, 2009).

In severe psoriasis cases, the conventional therapy using oral metothrexate often showed unsatisfying results with low clinical and life quality improvement (Gudjonsson *et al.*, 2012). Due to the the disease severity and socio-economic limitation, our department tried to develop methotrexate injection protocol. The protocol is using methrotrexate injection 50mg/week for 6 consecutive weeks in phase I, followed by two 50mg methotrexate injection per two weeks in phase II and two 50mg methotrexate injection per month for phase III. This is the pilot study that observe efficacy of methotrexate injection 50mg/week for 6 consecutive weeks (phase I) in the treatment of severe psoriasis from the clinical and life quality improvement and serum IL-17. The result of this study can be used as baseline data for further study for determining efficacy, side effects, and protocol guideline policy in severe psoriasis cases.

2 METHODS

The study was conducted in Dermatology and Venereology Clinic and Ward Dr. Sardjito General Hospital, and Dermatology and Venereology Department Faculty of Medicine Gadjah Mada University. All procedures were performed after ethical clearance gained from Medical and Health Research Ethics Committee of Faculty of Medicine, Gadjah Mada University. Our study subjects population were severe psoriasis patients that treated regularly in Dr. Sardjito Hospital Yogyakarta during September to December 2017 period and previously unresponsive to any conventional psoriais therapies.

Selected subjects in this study were erythroderma psoriatica or psoriasis vulgaris patients with PASI score more than 25, who previously unresponsive to conventional therapies. Patients with other autoimmune disease, immunodeficiency, pregnancy and lactation, obesity with BMI>30kg/m^2, severe anemia, in combination therapy with other immunosuppressive drugs, renal failure, elevated lived transaminase enzyme, hepatitis, or cirrhosis were excluded from this study. Patients were informed about the protocol, asked for consent and recruited as study subjects if they signed the informed consent form. Methotrexate 50 mg/week for 6 consecutive weeks was administered via intramuscular injection.

Psoriasis disease severity and remission were assessed using Psoriasis Area and Severity Index (PASI) score at the beginning of the therapy (baseline) and one week after each of methotrexate injection until 6th injection. Patient's life quality was assessed using Dermatological Life Quality Index (DLQI) score at the beginning of the therapy (baseline) and one week after 6th methotrexate injection. Blood samples from the subjects were taken at one week after the 6th injection and from healthy peoples without autoimmune disease or systemic infection, to measure IL-17A serum level using Komabiotech® human IL-17A ELISA kit. The data were analyzed using IBM SPSS® version 24 comparative and correlation test, with the p value <0.05 was considered as significant result.

3 RESULT

During September to December 2017 there were 15 severe psoriasis patients that undergo methotrexate injection therapy in Dermatology and Venereology Clinic and Ward unit Dr. Sardjito General Hospital Yogyakarta. Mean subject's age was 46 ± 3,98 years old, which is range from 18 to 66 years old and consist of 12 men and 3 women. From the occupation, most of the subjects were farmer and labor (**Table 1**). The baseline PASI score and DLQI score were significantly decreased after 6th injection, and there was no significant serum IL-17 level difference found between subjects and healthy peoples at the end of therapy (**Table 2**).

In this study 87% subjects achieved PASI-75 at the end of therapy, which was achieved mostly after the third injection. The PASI-100 was achieved mostly after the fourth injection and at the end of therapy was achieved by 80% subjects. There were 13% and 20% non responsive subjects that improved clinically, but didn't achieved PASI-75 and PASI-100 respectively at the end of study (**Chart 1**). From statistic analysis test result, there was significant linear correlation between PASI score improvement (ΔPASI score) and DLQI score improvement (ΔDLQI score) with strong correlation power (r= 0.641, p= 0.01) (**Chart 2**).

Table 1. Subject characteristics

Characteristics		Total (%)	Mean
Sex	Male	12 (80%)	
	Female	3 (20%)	
Age	<40 years old	4 (27%)	46 ± 3,98
	40-60 years old	8 (53%)	
	>60 years old	3 (20%)	
Job	Farmer	5 (33%)	
	Labor	4 (27%)	
	Student	2 (13%)	
	Housewife	2 (13%)	
	Office work	1 (6,7%)	
	Teacher	1 (6,7%)	
Diagnosis	Erythroderma Psoriatica	9 (60%)	
	Psoriasis Vulgaris	6 (40%)	

Table 2. PASI scores, DLQI scores, & serum IL-17 levels data

Measurement	Period	Mean	p Value
PASI Score	Baseline	51,56 ± 4,41	0.001[1]
	Post 1st Injection	32,1 ±3,04	
	Post 2nd Injection	18,52 ± 2,38	
	Post 3rd Injection	9,6 ± 1,8	
	Post 4th Injection	3,92 ± 1,56	
	Post 5th Injection	2,14 ± 1,27	
	Post 6th Injection	1,36 ± 1,08	
DLQI Score	Baseline	27.6 ± 0,66	0.001[1]
	Post 6th Injection	5,27 ± 0,78	
Serum IL-17 Level	Healthy Peoples	7,75 ± 0,41	0.070[2]
	Subjects (Post 6th Injection)	9,68 ± 0,79	

[1] *p* value is obtained from Wilcoxon comparative test
[2] *p* value is obtained from Mann Whitney comparative test

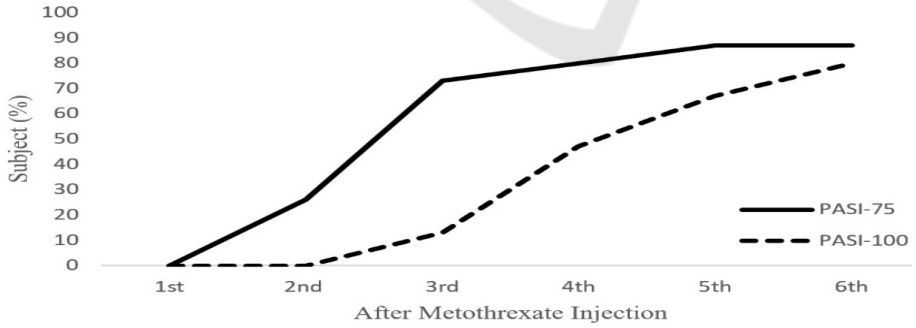

Chart 1. Subject PASI-75, PASI-100

(ΔPASI score) and DLQI score improvement (ΔDLQI score) with strong correlation power (r= 0.641, p= 0.01) (**Chart 2**).

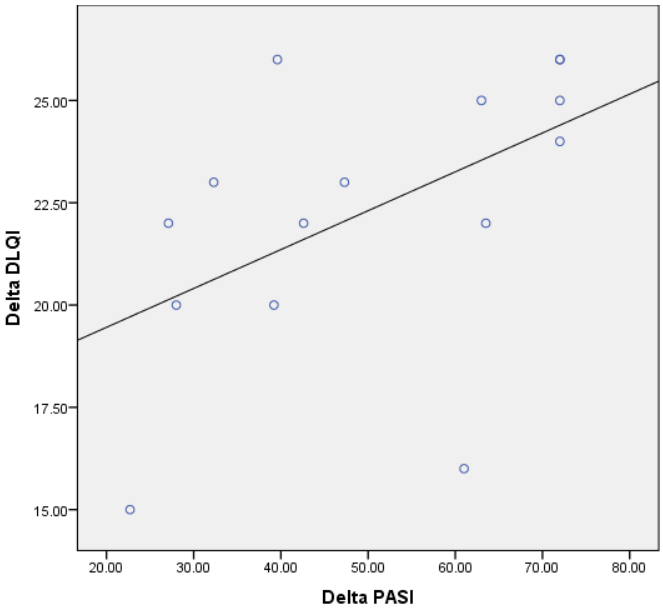

Chart 2. ΔPASI score & ΔDLQI score correlation

[1] *p value* is obtained from Spearman correlation test
[2] correlation coefficient (r) is obtained from Spearman correlation test
*ΔPASI & ΔDLQI Score obtained from difference between baseline and post 6th injection score

4 DISCUSSION

Methotrexate is the prime choice for systemic conventional therapy in patient with extensive, refractory, or severe psoriasis. Methotrexate monotherapy in psoriasis treatment show various responses depend on the administered dose (Dogra & Mahajan, 2013). When low dose is used (7,5-15mg/week), PASI-75 response is achieved by 24% patients at 12th week. When higher dose is used (15-25mg/week), PASI-75 response is achieved by 42-60% patients at 16th week (Cabello *et al.*, 2017). In this study the earliest PASI-75 and PASI-100 responses was achieved at 2nd week by 26% subjects and at 3rd week by 13% subjects respectively by using 50mg/week methotrexate dose. These findings are in line with previous studies that higher dose of methotrexate could induce quicker remission in study subjects.

IL-17 is a cytokine that has role in psoriasis pathogenesis and host defence against pathogens such as bacteria and fungal. IL-17 cytokine has 6 subunits that consist of IL-17 (A-F) and 5 receptor subunits that consist of IL-17R (A-E). IL-17A cytokine subunit and IL-17RA and IL-17RC receptor subunits are the subunits that have major role in psoriasis pathogenesis (AbuHilal *et al.*, 2016)

The importance of IL-17 in the pathogenesis can be used to assess psoriasis remission (Karczewski *et al.*, 2016). In this study we found that the subject's serum IL-17 level after 6th injection had no significant difference with the healthy peoples and we assumed the remission was achieved. However, IL-17 serum level in study subjects was still higher than in healthy peoples.

Dermatological life quality index score is the most often used tool for assessing patient life quality due to its reliability and applicability. Revicki et al (2008) study on moderate to severe plaque psoriasis reported that PASI score improvement had correlation with DLQI score improvement (Revicki *et al.*, 2008). The same results had been found in this study, in which the PASI score and DLQI score improvement significantly correlated. Significant difference also can be found between baseline and after 6th injection in DLQI score and PASI score as well.

In this study we also found that the earliest PASI-75 and PASI-100 responses were achieved by all <40 years and >60 years old subjects and some of 40-60 years old subjects. All of non responsive subjects derived from 40-60 years old subjects showed PASI score improvement, however they did not achieved PASI-75 and PASI-100 responses after 6 consecutive weeks of 50mg/week methotrexate injection. Daily

activity, job, and environmental exposure might have role in this condition, as the subject's job majority are farmers and labors that usually work without protective equipment, which can triggering new lesions formation or aggravating the old lesions (Mahler *et al.*, 2014).

5 CONCLUSION

This study reported that methotrexate injection protocol 50mg/week for 6 consecutive weeks initiation can be considered as an effective treatment for severe psoriasis. Most of the subjects had achieved full remission and significantly improved quality of life at the end of protocol. Both clinical and life quality improvement were significantly correlated each other in this study. Further studies with larger samples and longer observation period are needed to determine long term efficacy, side effects, and protocol guideline policy.

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