Evaluation of Efficacy and Side Effects of Impairement Liver Function in Psoriasis Vulgaris Patients Treated with Methotrexate in Dr. Soetomo General Academic Hospital Surabaya: A Retrospective Study

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RESEARCH ARTICLE

Evaluation of Efficacy and Side Effects of Impairement Liver Function in Psoriasis Vulgaris Patients Treated with Methotrexate in Dr. Soetomo General Academic Hospital Surabaya: A Retrospective Study

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ABSTRACT:

Background: Psoriasis is a chronic inflammatory skin disease that involves several factors, genetic, immunity defects, hormones, and environmental factors. Psoriasis vulgaris is often characterized by a thick, erythematous, well-defined, rough, layered, silvery white plaque. Methotrexate is a first-line systemic therapy in the management of psoriasis vulgaris. This drug effective to reduce the severity of the disease by at least 50% in more than 75% of patients. Unfortunately, methotrexate also has the potential to cause adverse effects, this drug is considered one of the main causes of increased liver enzymes in psoriasis patients for several years so special consideration is needed when prescribing methotrexate to patients. Therefore, periodic evaluation during the use of this drug is needed to find out the side effects that can be caused. **Purpose:** The aim was to to evaluate PASI, SGOT and SGPT score of psoriasis vulgaris patients who received methotrexate therapy at Dermatology and Venerology Outpatient and Inpatient Clinic Dr. Soetomo General Academic Hospital Surabaya. **Methods:** This was a observational analytical study with retrospective data through one shot case study pre-experimental study approach, but was conducted pre and post treatment that aimed to evaluate PASI, SGOT and SGPT score of psoriasis vulgaris patients who received methotrexate therapy at Dermatology and Venerology Outpatient and Inpatient Clinic Dr. Soetomo General Academic Hospital Surabaya for the period January 2018-December 2020. **Results:** The results of this study were 51 psoriasis patients who received methotrexate that include in inclusion criteria. The number of male patients was more than women, 30(58,8%) for men and 21(41.2%) for women. There was a statistically significant difference in the reduction in PASI score of psoriasis vulgaris patients before and after methotrexate therapy (p = 0.001). However, the results of statistical analysis SGOT score of psoriasis vulgaris patients before methotrexate therapy were no different than after receiving methotrexate therapy (p = 0.286). In contrast, the results of statistical analysis SGPT score of psoriasis vulgaris patients after receiving methotrexate therapy increased significantly compared to before receiving methotrexate therapy (p = 0.001). **Conclusion:** there was significant decrease in PASI scores and significant increase in SGPT scores before and after receiving methorexate therapy. However, for SGOT scores statistically there was no significant difference before and after receiving methorexate therapy.

KEYWORDS: Psoriasis vulgaris, Methotrexate, PASI, SGOT, SGPT.

INTRODUCTION:

Psoriasis is a chronic inflammatory skin disease that involves several factors, genetic, immunity defects, hormones, and environmental factors. Psoriasis vulgaris is often characterized by a thick, erythematous, well-defined, rough, layered, silvery white plaque.[1] Psoriasis vulgaris, also called plaque type psoriasis, is the most common type, occurring in about 90% of

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patients. The prevalence of psoriasis patients in Indonesia varies. Data in Dermatology and Venerology Outpatient Clinic Dr. Soetomo General Academic Hospital Surabaya showed that in 2013, there were 0.46% new cases of psoriasis vulgaris from a total of 5,454 new visiting patients.[2] Appropriate, safe, and effective therapy is indispensable for psoriasis vulgaris patients. Psoriasis therapy options include topical therapy, phototherapy, systemic, and biological agents. Systemic therapy are prescribed for severe and widespread psoriasis.[3] This drug effective to reduce the severity of the disease by at least 50% in more than 75% of patients.[3] Methotrexate is an antifolate that competively binds to dihydrofolate reductase (DHFR) which inhibits precursors of DNA and RNA and inhibits cell replication. It is an important drug in treatment of an acute lymphoblastic leukemia (ALL), choriocarcinoma, related trophoblastic tumors and psoriasis.[4] Methotrexate competitively and reversibly inhibits dihydrofolate reductase (DHFR), an enzyme that participates in the tetrahydrofolate synthesis.[5] Methotrexate goes about as anti-proliferative and a mitigating specialist against the cells causing psoriasis vulgaris inflammation.[6] Unfortunately, methotrexate also has the potential to cause adverse effects, this drug is considered one of the main causes of increased liver enzymes in psoriasis patients for several years so special consideration is needed when prescribing methotrexate to patients.[7] The liver has an enormous task of maintaining the body's metabolic homeostasis. This includes, the processing of dietary amino acids, carbohydrates, lipids, and vitamins; synthesis of serum proteins; and detoxification and excretion into bile of endogenous waste products and pollutant xenobiotics.[8] The liver is the principle organ of metabolism and excretion is subject to a number of diseases which may be classed as liver cirrhosis (cell destruction and increase in fibrous tissue), acute chronic hepatitis (non inflammatory condition) jaundice a yellow fever discoloration of the skin and eyes caused by bile in the blob is the symptom of blockage of the bile duct or disease within the tissue of the liver itself.[9] Therefore, periodic evaluation during the use of this drug is needed to find out the side effects that can be caused.

METHODS:

This study was observational analytical study with retrospective data through one shot case study pre-experimental study approach, but was conducted pre and post treatment that aimed to evaluate PASI, SGOT and SGPT score of psoriasis vulgaris patients who received methotrexate therapy at Dermatology and Venerology Outpatient and Inpatient Clinic Dr. Soetomo General Academic Hospital Surabaya for the period January 2018 - December 2020, using secondary data in the form of medical record data. This study has received ethical approval from the Hospital Ethics Committee RSUD Dr. Soetomo Surabaya (0684/LOE/301.4.2/XI/2021). The inclusion criteria were all patients recorded in the medical record with a diagnosis of psoriasis vulgaris, while the exclusion criteria were patients without psoriasis vulgaris, patients who stop undergoing methotrexate therapy and there was no follow-up 2 consecutive cycles, and patients who undergo laboratory examination of liver function tests other than in the clinical pathology laboratory of Dr. Soetomo Hospital.

RESULT:

This study obtained of 315 patients of psoriasis vulgaris, both new and old patients who were treated at Dermatology and Venerology Outpatient and Inpatient Clinic Dr. Soetomo General Academic Hospital Surabaya for the period January 2018 - December 2020. Psoriasis vulgaris patients who received methotrexate therapy were 132 patients. There were a total of 51 psoriasis vulgaris patients who met the study inclusion criteria.

Table 1: Distribution of psoriasis vulgaris patients receiving methotrexate therapy

Variable	Total (n=51)
Gender, *n* (%)	
Male	30 (58.8)
Female	21 (41.2)
Age range, *n* (%)	40.96 (15-72)
Age category (Kemenkes RI, 2009)	
0-5 years old	0 (0)
5-11 years old	0 (0)
12-16 years old	2 (3.92)
17-25 years old	11 (21.56)
26-35 years old	8 (15.69)
36-45 years old	5 (9.80)
46-55 years old	16 (31.38)
56-65 years old	8 (15.69)
>65 years old	1 (1.96)
PASI scores, *n* (%)	
Mild (<5)	0 (0)
Moderate (5-10)	2 (3.9)
Severe (>10)	49 (96.1)

The results showed that the number of male patients was higher than female which are 30 (58.8%) in male and 21 (41.2%) in female. The average age was 40.96 years with the youngest age being 15 years and the oldest age being 72 years old. Distribution of severity degrees based on initial PASI scores before receiving methotrexate therapy were 2 patients (3.9%) experienced moderate severity and 49 patients (96.1%) experienced severe severity.

Table 2: Evaluation of PASI scores initials, follow-up 1, and follow-up 2 of psoriasis vulgaris patients before and after receiving methotrexate therapy.

	n	*Mean* ± SD	*p value all*
SGOT Initials	51	23.39 ± 8.98	0.286*
SGOT *Follow-up* 1	51	25.33 ± 9.72	
SGOT *Follow-up* 2	51	23.49 ± 70.1	

*Friedman Test , **Wilcoxon test declared siqnificant p value < 0.05

Statistical analysis were showed p value = 0.001 which showed that there was a statistically meaningful difference in the decrease in PASI scores before and after receiving methotrexate therapy in follow-up 1 and 2. Then a post hoc test was conducted that showed that a significant decrease in PASI scores was obtained at initials vs follow-up 1 vs follow-up 2.

Table 3. Evaluation of SGOT values initials, follow-up 1, and follow-up 2 of psoriasis vulgaris patients before and after receiving methotrexate therapy.

	n	*Mean* ± SD	*p value all*	*p value* PASI Initials vs PASI *Follow-up* 1	*p value* PASI Initials vs PASI *Follow-up 2*	*p value* PASI *Follow-up* 1 vs PASI *Follow-up 2*
PASI Initials	51	20.32 ± 7.49	0.001*	0.001**	0.001**	0.001**
PASI *Follow-up* 1	51	12.56 ± 5.82				
PASI *Follow-up 2*	51	7.96 ± 5.24				

*Anova Test same subject , **Pairwise Comparasion declared siqnificant p value < 0.05

Statistical analysis were showed p value = 0.286 which showed that there was no statistically meaningful difference in the increase in SGOT values before and after receiving methotrexate therapy in follow-up 1 and 2. Then a post hoc test was conducted that showed that there was no significant increase in SGOT value at the initials vs follow-up 1 vs follow-up 2.

Table 4. Evaluation of SGPT values initials, follow-up 1, and follow-up 2 of psoriasis vulgaris patients before and after receiving methotrexate therapy.

	n	*Mean* ± SD	*p value all*	*p value* SGPT Initials vs SGPT *Follow-up* 1	*p value* SGPT Initials vs SGPT *Follow-up 2*	*p value* SGPT *Follow-up* 1 vs SGPT *Follow-up 2*
SGPT Initials	51	30.33 ± 13.95	0.001*	0.003**	0.219**	1.000**
SGPT *Follow-up* 1	51	35,65 ± 20.31				
SGPT *Follow-up 2*	51	30.33 ± 13.95				

*Anova Test same subject , **Pairwise Comparasion declared siqnificant p value < 0.05

Statistical analysis were showed p value = 0.001 which showed that there was a statistically meaningful difference to the increase in SGPT values before and after receiving methotrexate therapy in follow-up 1 and 2. Then a post hoc test was conducted that showed that a significant increase in the value of SGPT at the initials vs follow-up 1 while at the SGPT value initials vs follow-up 2 and SGPT follow-up 1 vs follow-up 2 did not get a significant increase.

DISCUSSION:

The results of this study showed that total 315 psoriasis vulgaris patients, both new and old patients who were treated in the Outpatient and Inpatient Clinic Dr. Soetomo General Academic Hospital Surabaya for the period January 2018 - December 2020. The number of psoriasis vulgaris patients who received methotrexate therapy were 51 patients who met the criteria for research inclusion. The gender distribution of psoriasis vulgaris who were treated in the Outpatient and Inpatient Clinic Dr. Soetomo General Academic Hospital Surabaya for the period January 2018-December 2020 showed that female patients was higher than men, 164(52.1%) in women and 151(47.9%) in men. But, the gender distribution of psoriasis vulgaris patients who received methotrexate therapy showed that male patients was higher than women, namely 30 (58.8%) in men and 21(41.2%) in women.

Data from Outpatient Clinic Dr. Soetomo General Academic Hospital Surabaya in 2013 showed the distribution of gender was male 10 patients (62.5%) and women 6 patients (37.5%).[2] Men and women have an equally large prevalence, but recent studies have shown that psoriasis is slightly more common in men than women.[10] The prevalence of psoriasis in men and women has an equally large prevalence, but it is found to be slightly more common in men. This can be because the clinical manifestations of psoriasis in men are often more severe so that male patients are more often to come for treatment to the hospital. Men also tend to have a higher risk of obesity and metabolic disease than women, and the influence of smoking and consuming alcohol which is likely to be higher in male patients can be a triggering factor for psoriasis.[11]

Distribution severity of psoriasis vulgaris patients before receiving methotrexate therapy were 2 patients (3.9%) experienced moderate severity and 49 patients (96.1%) experienced severe severity. This retrospective study showed that there were 29 patients who experienced a decrease in PASI scores after receiving methotrexate therapy. Statistical analysis were showed p value = 0.001 which showed that there was a statistically significant difference in the decrease in PASI scores before and after receiving methotrexate therapy. This is in accordance with research by Cabello and colleagues on 218 psoriasis vulgaris patients with moderate to severe severity, methotrexate was shown to help lower PASI scores significantly.[12] Methotrexate has been approved as a recommended first-line systemic therapy in moderate to severe degrees of psoriasis vulgaris.[13] In light of the therapeutic condition and response to treatment, its dosage and frequency of use can be

determined.[14] Methotrexate has a cell cycle specific action-kills cells in S phase; primarily inhibits DNA Synthesis, but also affects RNA and protein synthesis. It is an anti-metabolite and antifolate drug used in treatment of psoriasis.[15]

This retrospective study research showed that there were 2 patients who experienced an increase in SGOT scores after receiving methotrexate therapy. The most common side effects of methotrexate are gastrointestinal manifestations such as nausea, vomiting, stomatitis, loss of appetite and hepatotoxicity effects.[16] But, in this study statistical analysis were showed p value = 0.286 which showed that there was no statistically meaningful difference in the increase in SGOT scores before and after receiving methotrexate therapy. This is in accordance with a study that reporting 68.2% of psoriasis vulgaris patients observed had normal SGOT levels after receiving methotrexate therapy, and only 18.2% of patients experienced elevated levels of SGOT. From 45.5% of patients experienced an increase in SGOT but still within normal limits.[1] Liver is the largest glandular and major organ for metabolism. The liver reacts with different types of responses to injury in response to variety of metabolic, toxic, microbial, circulation and neoplastic insults. Hepatic injury leads to disturbances in transport function of hepatocytes resulting in leakage of plasma membrane thereby causing an increased enzyme level in serum.[17] Enzymes SGOT and SGPT are associated with the parenchyma of liver cells, the difference is that SGPT is found more in the liver whereas SGOT is found in the liver, heart muscle, skeletal muscle, kidneys, brain, and red blood cells. Therefore, SGPT is a more specific indicator of liver inflammation than SGOT. Enzymes SGOT can increase in diseases that can affect other organs, such as myocardial infarction, acute pancreatitis, acute hemolytic anemia, severe burns, acute kidney disease, musculoskeletal disease, and trauma.[18] This is in accordance with this retrospective study because it does not mean statistically the value of SGOT which shows that SGOT may not be a specific indicator in assessing liver inflammation compared to SGPT.

This retrospective study research showed that there were 12 patients who experienced an increase in SGPT scores after receiving methotrexate therapy. Statistical analysis were showed p value = 0.001 which shows that there is a statistically meaningful difference in the increase in SGPT scores before and after receiving methotrexate therapy. It is explained in the study that liver injury is most often assessed through liver enzymes, namely SGPT which increases in 7.5-26% of all patients treated with MTX depending on the cut-off rate used.[19] Increased SGPT during methotrexate therapy supports a multifactorial background of liver toxicity. A study identified SGPT elevations found before the start of MTX therapy as the strongest predictors for SGPT elevation during MTX therapy. Elevation of SGPT values prior to the start of MTX therapy was found in 20 of 84 patients (24%), and all experienced repeated increases in SGPT during MTX therapy.[20] Enzyme SGPT is mainly found in the hepatocyte cytoplasm, and increases during liver damage involving the cytoplasm. Therefore, methotrexate may have injured the hepatocyte cytoplasm resulting in a significant increase in SGPT activity.[21] Liver toxicity is a major health problem of worldwide proportions. The hepatoprotective activity is confirmed by decreasing the activity of serum enzymes, SGOT, SGPT, Bilirubin, Cholesterol, while it significantly increased the reduced protein levels in dose dependant manner.[22] A combination of methotrexate with biologics works synergistically leads to an improvement in their clinical efficacy, methotrexate tolerability and also suppresses the immunogenicity of these agents and increasing their serum drug levels.[23]

From this retrospective study we can concluded there was significant decrease in PASI scores and significant increase in SGPT scores before and after receiving methorexate therapy. However, for SGOT scores statistically there was no significant difference before and after receiving methorexate therapy.

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