# Slow responder against methotrexate 50 mg intramuscular in severe psoriatic patients: A case series

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## Abstract

Methotrexate is the drug of choice used on moderate to severe psoriasis. The limited availability of oral tablet methotrexate stimulates the initiation of the protocol therapy 50 mg intramuscular methotrexate weekly in six consecutive weeks for severe psoriasis cases. There were 30 cases treated using this treatment modality. Twenty-six cases (86%) showed a good response and achieved PASI-90(Psoriasis Area Severity Index-90), four cases (13%) showed a slow response and did not achieve PASI-90. This case report collected slow response cases and identified their risk factor of slow responsiveness with this treatment modality. The comorbidity condition like metabolic syndrome, drugs induced psoriasis, continuous trauma, the side effect of methotrexate administration (ulceration), or the possibility of allergic or irritant contact dermatitis from occupation are suspected to be the risk factor for slow responders in this treatment modality.

## Introduction

Psoriasis is a chronic inflammatory disease of the skin that affects 2-3% of the world's population. Clinical manifestations of skin vary from rare to a general plaque.[1] Methotrexate is the most common drug used in moderate to severe psoriasis. Methotrexate is highly effective for long-term severe psoriasis therapy including erythrodermic psoriasis and pustular psoriasis.[2,3] The limited availability of oral tablet methotrexate stimulates the initiation of the protocol therapy of 50 mg intramuscular methotrexate weekly in six consecutive weeks for severe psoriasis cases (Figure 1). Patients must be eligible and willing to follow this therapy program by signing the informed consent. So far, there have been 30 cases that have completed 6 times methotrexate injection. There were 26 cases (86%) showing a good response and reaching PASI-90, while 4 cases (13%) showed a slow response and did not reach PASI-90. In this case report, the authors collect slow response cases and try to identify the risk factors this condition. This case report is very important, due to evaluate the effectiveness of 50 mg intramuscular methotrexate weekly therapy by analyzing the risk factors in slow response cases.

## Case Reports

The subject characteristics and the triggering factor analysis are reported in Tables 1 and 2, respectively.

## Discussion

Methotrexate is a drug that inhibits DNA (deoxyribonucleic acid) synthesis through competition with folic acid in the formation of thymidine bases, therefore, it may be useful in psoriasis patient who fails with topical therapy or phototherapy.[2,3] Methotrexate has a direct activity of inhibiting the epidermal hyperproliferation through dihydrofolate reductase resistance.[3] Methotrexate can be administered orally or parenterally. The parenteral bioavailability of methotrexate administration is higher compared to the oral ones.[4] There were 4 cases showed slow responses and did not achieve PASI-90 with 50 mg intramuscular methotrexate weekly in six consecutive weeks for severe psoriasis cases (Table 1, Figure 2). These 4 cases were differ in the risk factor or triggering factor for a psoriatic lesion (Table 2).

Comorbid conditions in the first and second patient were metabolic syndrome. Both of them had hyperglycemia. Moderate to severe psoriasis (> 10% of body surface area) is often associated with metabolic diseases, such as central obesity, diabetes, non-alcoholic fatty liver disease, dyslipidemia, metabolic syndrome and chronic kidney disease.[1] It is likely that cytokines released from either psoriatic keratinocytes or inflammatory cells in psoriatic skin might induce systemic insulin resistance, thus favoring the development of type 2 diabetes mellitus. On the other hand, it is also possible that the co-existing metabolic comorbidities might directly contribute to exacerbating psoriatic inflammation through the release of several pro-inflammatory mediators from the liver and/or visceral adipose tissues, such as increased reactive oxygen species, C-reactive protein (CRP), IL-6 (interleukin-6), and other adipokines.[1] Both patients had diabetes mellitus before the onset of psoriatic symptoms. The condition of hyperglycemia in both causes worsening of psoriasis lesions.

Although psoriasis is currently thought of as a disorder of the immune system, many environmental factors can affect the type and location of psoriatic lesions. Of the few known psoriasis triggers, drugs can aggravate psoriasis lesions even after long latent periods. Several drugs associates with worsening or development of psoriasis. The drugs that frequently affect psoriasis lesions are β-blockers, lithium, synthetic antimalarials, tetracyclines, and nonsteroidal anti-inflammatory drugs (NSAIDs); withdrawal from systemic corticosteroids also served as a trigger. Drugs are able to induce psoriasis de novo or induce lesions in previously unaffected skin and possibly aggravate psoriasis in psoriatic patients by causing flares or treatment resistance.[5]

The first patient had hypertension, hyperglycemia, and hypercholesterolemia. He has been consuming bisoprolol and sim-

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vastatin daily since 3 months ago. There are numerous reports of β-blockers inducing and exacerbating psoriasis, at times causing psoriasis vulgaris to become pustular or erythrodermic. β-2 receptors are found in keratinocytes, which can lead to decreased cyclic adenosine monophosphate (cAMP) and consequently increases intracellular calcium, thus increasing cell proliferation and suppressing cell differentiation. The latency period between drug exposure and psoriatic eruption can be varied from several days to 48 weeks; if eruptions are visible, usually patients are resistant to antipsoriatic medications before the β-blocker drugs are discontinued.[5,6] There was an improvement of skin lesions in the first patient after replacing bisoprolol with valsartan. Three patients have the similar risk factor, which is continuous trauma. The first patient is a farm laborer and often exposed to friction with the plants. The second patient gets trauma from friction on both feet of using boots shoes when working in the field. The third patient worked as a clay tile labor. He often exposed to friction or trauma in both arms and legs when making dough tile. One of the triggers for the emergence of psoriasis lesions is physical trauma. Koebner phenomenon can be demonstrated by the emergence of psoriasis lesions in healthy skin that is stimulated by trauma.[7] How physical

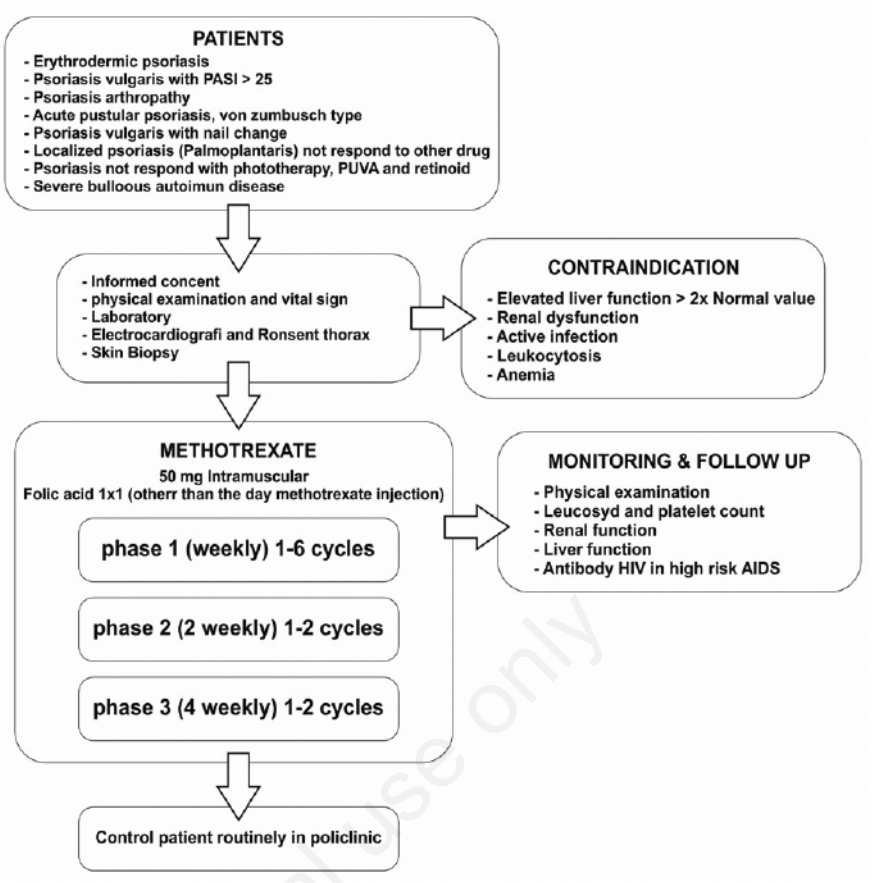


**Figure 1. The protocol for the 50 mg intramuscular methotrexate therapy.**

**Table 1. Subject characteristics.**

| | Case 1 (A) | Case 2(B) | Case 3(C) | Case 4(D) |
|---|---|---|---|---|
| Age | 67 years old | 67 years old | 42 years old | 17 years old |
| Gender | Male | male | male | female |
| Job | Farm labor | Farm labor | Clay tile labor | Student |
| Duration of psoriasis | 1 month | 2 month | 15 years | 6 month |
| First PASI | 42 | 57,2 | 39 | 47,4 |
| Clinical manifestation after 50 mg intramuscular methotrexate weekly in six consecutive weeks | On almost the entire body there is a diffuse erythema patch, with a thin scale above it (Figure 2.A1) | On almost the entire body appears erythematous plaque with a thick scale, multiple, partially confluent, edema impression limb (Figure 2.B1) | On both arms and legs, the lower abdomen, the waist appear multiple hyperpigmented plaques, with scale on top (Figure 2.C1) | On the back appears erythematous plaque with a thin squama above, on gluteus dextra visible ulcers of a diameter of 5 cm with the base of granulation tissue accompanied pus and blood, on the gluteus sinistra appear nodule eritem diameter 5 cm (Figure 2.D1) |
| PASI after six consecutive weeks | 31,8 | 37,5 | 25,8 | 8,2 |
| Achievement of PASI-90 | 2nd phase extended until the 5th cycle (Figure 2.A2) | 2nd phase extended until the 5th cycle (Figure 2.B2) | 2nd phase 2 cycle (Figure 2.C2) | 2nd phase extended until the 3th cycle after postponed 1 week. (Figure 2.D2) |
| Therapy | - Replaced bisoprolol with valsartan<br>- Low glucose diet<br>- Stop working in the field | - Use metformin<br>- Avoid friction with boots<br>- Stop working in the field | - Wear skin protector when working<br>- Replace lubricants with peanuts oil | - Levofloxacin 1x 750 mg<br>- Metronidazole 3x 500mg<br>- Incision abscess and ulcer's tampon with 1% bethadine on gluteus |

trauma can induce the emergence of psoriasis lesions, can be explained through the assumption that the non-lesion skin of a psoriasis sufferer has an increase in cellular activity compared to the skin of non-psoriasis people. This is indicated by an increase in thymidine uptake, increased percentage of S / G2 and M phases in epidermal cells, as well as increased ornithine decarboxylase activity, increased release of arachidonic acid, phospholipase A2, and calmodulin. This is supported by an increase in the population Natural killer cells (NK cells) and dermal dendritic plasmacytoid cells which explain the occurrence of hyperproliferation response that continues the emergence of psoriasiform lesions when the skin enters the regeneration phase after a trauma.[8] It can be concluded that continuous trauma can also trigger psoriatic lesion, apparently trauma is one of the risk factor in slow response in this treatment modality.

Allergy contact dermatitis also suspected of contributing to the slow response in this treatment modality. One patient in this

**Table 2. Triggering factor analysis.**

| | Case 1 | Case 2 | Case 3 | Case 4 |
|---|---|---|---|---|
| Metabolic syndrome | + | + | - | - |
| Drug-induced | + | - | - | - |
| Trauma | + | + | + | - |
| Drug adverse effect | - | - | - | + |
| Contactant | - | - | + | - |
| Infection | - | - | - | - |
| Rubbing habit | - | - | - | - |
| Smoking | - | - | - | - |
| Stress | - | - | - | - |

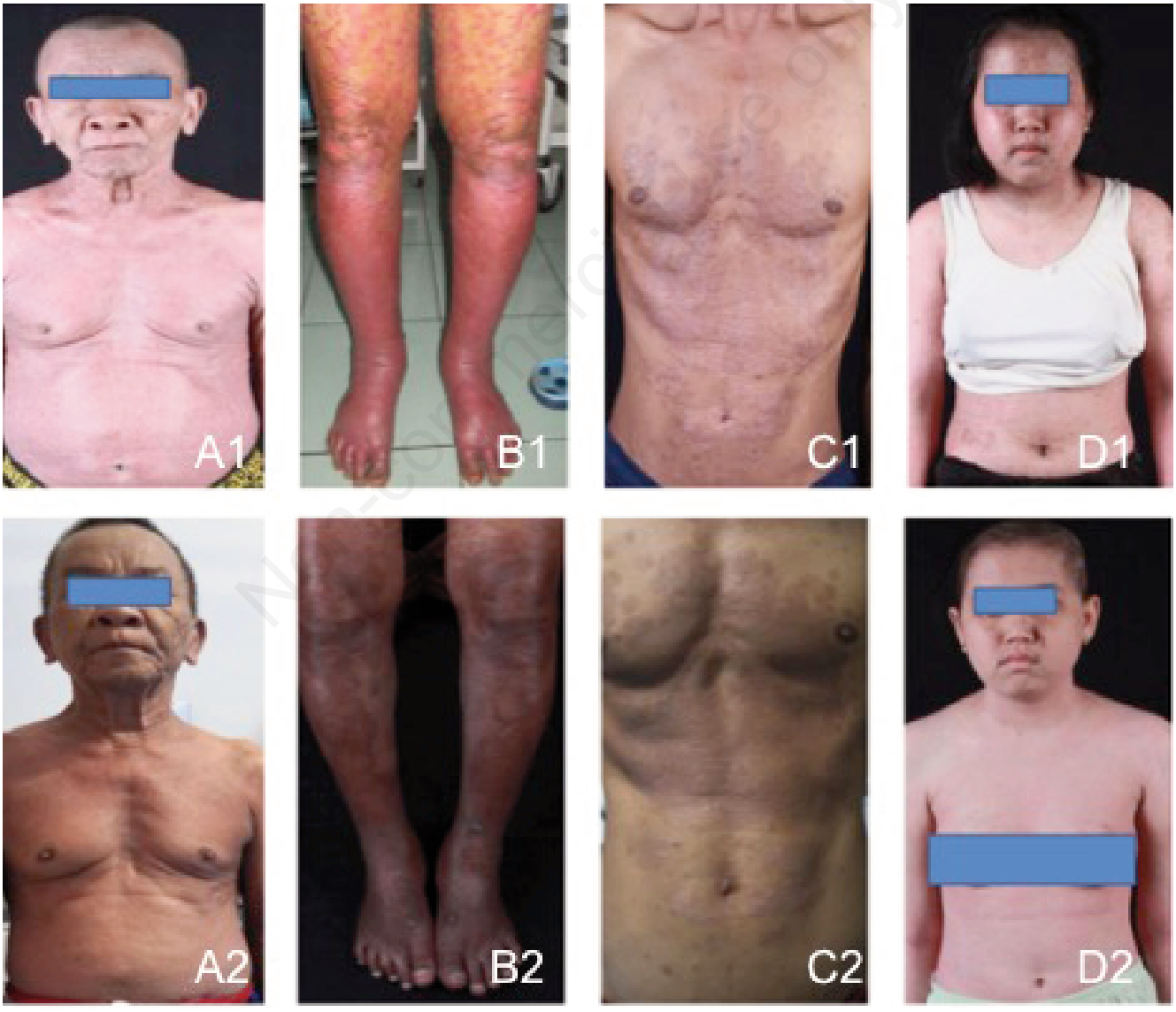


**Figure 2. (A1, B1, C1, D1) Clinical manifestation after 50 mg intramuscular methotrexate weekly in six consecutive weeks, (A2, B2, C2, D2) Clinical manifestation after achievement of PASI-90.**

report contact with clay, solar oil and kerosene as the lubricant to makes the tile. Patients are advised to wear personal protective equipment and replace lubricants with other oils. There was an improvement of skin lesions after avoiding the contactant and replaces the lubricant with peanut oil. Patients may have allergic contact dermatitis caused by solar oil or kerosene. Dermatitis reactions can be elicited by the epicutaneous challenge of common allergens or haptens in sensitized psoriatic patients (allergic contact dermatitis, ACD).[9] Local psoriatic changes can be triggered by exogenous mechanical or irritant factors. Causative occupational factors have to be distinguished from the spontaneous course of psoriasis in occupational medical evaluations.[10] Physical triggers may also be occupational. Contact allergies have also been described as trigger factors. It is essential to keep in mind that individual psoriasis patients may also suffer from allergic or irritant contact dermatitis.

Study by Mahler et al. mention that ocupational exposure (mechanical and/or irritative, rarely microtraumas or contact sensitizations) are proven as isomorphic response thus increasing the severity of skin lesions at intensely exposed site (generally hands and forearms) at work compared to longer work-free intervals (vacation, sick leave, or other reason which reduce working time).[10] It can be concluded that the possibility of allergic or irritant contact dermatitis from occupation (solar oil and kerosene) in this patient suspected to be the risk factor in slow responders in this treatment modality.

Side effects of methotrexate include aplastic anemia, leucopenia, thrombocytopenia, interstitial pneumonitis, ulcerative stomatitis, nausea, vomiting, diarrhea, weakness, fatigue, chills, fever, dizziness, decreased resistance to infection, ulceration, and gastric bleeding, sensitive and alopecia.[2] The fourth patient got skin ulcer in phase 1 of the 5th medication cycle. The ulceration and abscess appear on patients' buttocks. One of the side effects of methotrexate is the appearance of ulceration. Ulceration in this patients is caused by adverse effects of methotrexate therapy. Because of adverse effects of methotrexate, the protocol was postponed until the ulceration were improving. Ulceration of psoriatic plaques is a known adverse effect of methotrexate. Methotrexate can also trigger ulcers or make them worse.[11] Methotrexate has a side effect potential which is skin ulcers, and withdrawal of the medication may heal the ulcer lesions.[12] It can be concluded that the adverse effect of methotrexate can make the patients had a slow response to the treatment modality.

## Conclusions

Methotrexate 50 mg intramuscular weekly is an alternative therapeutic modality in severe psoriasis. It should be of concern for clinicians in comorbidity condition like metabolic syndrome, drugs induced psoriasis, continuous trauma, the side effect of methotrexate administration (ulceration), or the possibility of allergic or irritant contact dermatitis from occupation are suspected to be the risk factor for slow responders in this treatment modality. Analyzing and avoiding the causal factors can facilitate clinicians in the therapy for psoriasis patients with slow responder treatment. This case report is part of a study of the effectiveness and safety of 50 mg intramuscular methotrexate weekly therapy.

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