# Efficacy and Safety of Methotrexate Administered by Oral and Subcutaneous Routes in Patients with Severe Psoriasis

Mehwish Amin[1], Kulsoom Farhat[1], Aisha Akhtar[2] and Sakina Sadiq Malik[2]

[1]*Department of Pharmacology, Army Medical College, Rawalpindi, Pakistan*
[2]*Department of Dermatology, Pak Emirates Military Hospital, Rawalpindi, Pakistan*

## ABSTRACT

**Objective:** To compare the efficacy and safety of oral and subcutaneous (SC) routes of methotrexate (MTX) administration in patients with severe psoriasis in terms of the time taken to attain a Physician Global Assessment (PGA) score of 0 or 1.

**Study Design:** Single-blinded randomised controlled trial.

**Place and Duration of the Study:** Department of Pharmacology and Therapeutics, Army Medical College, in collaboration with Departments of Dermatology and Pathology, Pak Emirates Military Hospital, Rawalpindi, Pakistan, from January 2024 to January 2025.

**Methodology:** Patients of either gender aged between 18 and 65 years, diagnosed with severe psoriasis (PGA score of 4), were included. Patients were randomised by the lottery method into two equal groups, with 30 patients in each group. Group 1 (G-1) received oral MTX (10 to 25mg) once a week for 4 weeks, and Group 2 (G-2) received SC MTX (10 to 25mg) once a week for 4 weeks. Efficacy and safety were compared between the two groups at 0 and 4 weeks. The Chi-square and t-test were used for comparison among the groups.

**Results:** A total of 60 patients with a median (IQR) age of 42.0 (27.0) years; 51 (85%) were males and 9 (15%) were females. The pre-treatment PGA score was 4, while after treatment, 14 (23.3%) patients had a score of 0, 23 (38.3%) had a score of 1, 17 (28.3%) had a score of 2, and 06 (10%) had a score of 3. Both groups showed effective improvement after the treatment, with statistically significant findings ($p < 0.001$). The SC route in the G-2 showed a greater reduction in the PGA score compared to the oral route in the G-1. Correspondingly, the SC route of medicine is comparatively safer than the oral route by reporting less episodes of diarrhoea (76.7% *vs.* 3.3%) and vomiting (26.7% *vs.* 6.7%).

**Conclusion:** The SC route of MTX administration is safer and more effective than the oral route in patients with severe psoriasis.

**Key Words:** *Efficacy and safety of methotrexate, Methotrexate, Oral route, Psoriasis, Subcutaneous route*.

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## INTRODUCTION

Psoriasis is a prevalent chronic inflammatory disorder, with global incidence varying from 0.27% to 11.4%.[1] It is a persistent, inflammatory, and proliferative dermatological condition influenced significantly by both hereditary and environmental factors.[2] The defining lesions are red, scaly, well-defined, indurated plaques, predominantly located on the extensor surfaces and the scalp. The aim of treatment is to achieve rapid remission of symptoms, decrease the incidence of relapse, and enhance the quality of life.[3]

*Correspondence to: Dr. Mehwish Amin, Department of Pharmacology, Army Medical College, Rawalpindi, Pakistan*
*E-mail: mehwishlaeeq8@gmail.com*
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Methotrexate (MTX) continues to be an effective, cost-efficient, and widely utilised systemic therapy for moderate to severe psoriasis, even in the current era of biologic.[4] The significance of MTX in psoriasis therapy is paramount, particularly in underdeveloped nations, where most patients lack health insurance and must bear the costs independently. A Physician Global Assessment (PGA) score of 4 signifies severe psoriasis. The mechanism of action by which MTX is effective in psoriasis is attributed to the reduction of T lymphocyte and monocyte proliferation, leading to an anti-inflammatory and immunosuppressive impact.[5]

Current guidelines favour the oral route of MTX administration over the subcutaneous (SC) route due to its convenience and ease of use.[6] Most physicians prescribe a single weekly oral dose, which usually starts at a low dose to reduce adverse effects and is then gradually increased to achieve efficacy.[7] The parenteral method is favoured in cases of insufficient clinical response or to avoid excessive gastrointestinal side effects to oral MTX.[8] Oral absorption of MTX is rapid yet unpredictable, with a bioavailability ranging from 30% to 70%. The SC route is preferred when a high dosage of medication is necessary to

achieve therapeutic objectives in individuals with severe psoriasis.[9] SC injection of MTX may also lead to a faster response compared with the oral route.

SC MTX has been associated with better patient adherence to therapy and higher patient satisfaction.[10] To date, no such study has been conducted in the Pakistani population to determine the preferred route of MTX administration in patients with severe psoriasis. This study aimed to compare the efficacy and safety of both routes of MTX administration and to determine which route should be preferred in severe psoriasis, in terms of the time required to attain recovery as assessed by the Physician Global Assessment (PGA) score.

## METHODOLOGY

It was a single-blinded randomised controlled trial (RCT) conducted in the Department of Pharmacology and Therapeutics, Army Medical College in collaboration with the Departments of Dermatology and Pathology, Pak Emirates Military Hospital, Rawalpindi, Pakistan, from January 2024 to January 2025. Ethical approval was obtained from the Ethical Committee of Pak Emirates Military Hospital, Rawalpindi, Pakistan (Approval No. A/28/ERC/19/2024; dated: 3 January 2024). This RCT was designed according to the CONSORT guidelines. Figure 1 shows the CONSORT diagram of the study population. This RCT was registered at the Iranian clinical trial registry (ID: IRCT20231010059674N1).

The sample size of 60 was calculated using the WHO sample size calculator, considering a 4% prevalence of psoriasis and a 95% confidence interval with a 5% margin of error.[5] Patients were randomised by the lottery method into two equal groups, with 30 patients in each group. Group-1 (G-1) received oral MTX (10 mg up to 25 mg) once a week for four weeks, while Group-2 (G-2) received SC MTX (10 mg up to 25 mg) once a week for four weeks.

Patients of either gender aged between 18 and 65 years, having severe psoriasis (PGA score of 4), were included. Patients with any major respiratory, cardiac, gastrointestinal, hepatic, or renal illness, pregnant or lactating women, and participants unwilling for monthly follow-up were excluded. After obtaining informed consent, eligible patients were randomly recruited to one of the therapeutic regimens. Coding was performed, and the treating dermatologist selected the route of administration according to the code selected through the lottery method by the patient. Both groups received the same dose of MTX, starting from 10 mg up to 25 mg weekly, but administered through different routes (either oral or SC). Patients were photographed when willing.

Detailed personal and medical histories, along with demographic data, were obtained using a pre-designed proforma. Laboratory investigations, including haemoglobin level, complete blood counts, liver function tests (LFTs), renal function tests (RFTs), serum alanine transaminase (ALT), serum alkaline phosphatase levels, urea, and creatinine levels, were performed at baseline (0 week) and at 4 weeks. Monthly follow-up for 2 months was conducted. Efficacy was evaluated by comparing the PGA score before and after four weeks of treatment,[8] while patient safety was assessed by monitoring considering adverse effects, such as episodes of vomiting and diarrhoea, along with laboratory investigations.[9,10] As the patients were admitted in the ward for four weeks, there was no loss to follow-up, and MTX was administered according to the prescribed dose and duration, taking into consideration the adverse effects and PGA scores of the patients.

IBM SPSS version 26 was used for data analysis. Quantitative data were analysed using the paired t-test or the Wilcoxon signed-rank test for pre- and post-treatment analysis, and the independent t-test for normally distributed data or the Mann-Whitney U test for non-normally distributed data was applied for intergroup analysis. To determine whether the distribution of PGA scores differs significantly among the four scores (0-4), the Chi-square ($\chi 2$) test was used. Pairwise differences between the groups across PGA score categories (0, 1, 2, and 3) were analysed using the Chi-square test. A p-value of $\leq 0.05$ was considered significant (95% CI).

## RESULTS

A total of 60 patients with a median (IQR) age of 42 (27) years and weight 60 (18) kg were recruited. Of which, fifty-one (85%) were male and 15% (9/60) were females. Out of the 60 patients, 24 (40%) had vomiting, and 10 (16.7%) had diarrhoea.

Efficacy was assessed by comparing the PGA score before and after (4 weeks) the treatment. Before the treatment, patients had severe psoriasis, with PGA score of 4, while after the treatment, 14 (23.3%) patients had a score of 0, 23 (38.3%) had a score of 1, 17 (28.3%) had a score of 2, and 06 (10%) had a score of 3, as mentioned in Table I. Both groups showed effective improvement after the treatment, with statistically significant findings ($p < 0.001$); however, the SC route in the G-2 showed more reduction in the PGA score (13 patients had a score of 0, 16 had a score of 1, 1 had a score of 1, while nobody had a score 3) compared to the oral route in the G-1 (1 patient had a score of 0, 7 had a score of 1, 16 had a score of 2, and 6 had a score of 3), as depicted in Table I.

Patient safety profile was assessed by monitoring adverse effects, including episodes of vomiting and diarrhoea, along with laboratory investigations. G-1 patients had more episodes of diarrhoea and vomiting than those of G-2 (Table II), indicating the predominance of adverse effects in the G-1 patients compared to the G-2.

The paired-sample t-test and Wilcoxon signed-rank test were applied to determine the pre- and post-treatment laboratory levels. Figure 2 shows the mean pre- and post-treatment laboratory findings. Statistically significant differences in urea levels were observed ($p = 0.007$) when the overall safety of MTX was considered, regardless of whether it was given orally or subcutaneously.

**Table I: Post-treatment PGA score in the two groups (n = 60).**

| Groups | MTX post-treatment PGA score | | | | p-values* |
|---|---|---|---|---|---|
| | Clear = 0 | Almost clear = 1 | Mild = 2 | Moderate = 3 | |
| G-1 (Oral) | 1 | 7 | 16 | 6 | <0.001 |
| G-2 (SC) | 13 | 16 | 1 | 0 | |
| **Total** | 14 | 23 | 17 | 6 | 60 |

**Pearson's Chi-square test; PGA: Physician Global Assessment; * PGA: Physician Global Assessment.*

**Table II: Comparison of categorical variables among the two groups (n = 60).**

| Study variables | | | Study groups | | Total | p-values |
|---|---|---|---|---|---|---|
| | | | G-1 (Oral) | G-2 (SC) | | |
| Gender | Male | n | 21 | 30 | 51 | 0.002* |
| | | % | 70.0% | 100.0% | 85.0% | |
| | Female | n | 9 | 0 | 9 | |
| | | % | 30.0% | 0.0% | 15.0% | |
| MXT post-treatment PGA score of patients | 0 | n | 1 | 13 | 14 | <0.001 |
| | | % | 3.3% | 43.3% | 23.3% | |
| | 1 | n | 7 | 16 | 23 | |
| | | % | 23.3% | 53.3% | 38.3% | |
| | 2 | n | 16 | 1 | 17 | |
| | | % | 53.3% | 3.3% | 28.3% | |
| | 3 | n | 6 | 0 | 6 | |
| | | % | 20.0% | 0.0% | 10.0% | |
| Vomiting | Yes | n | 23 | 1 | 24 | <0.001* |
| | | % | 76.7% | 3.3% | 40.0% | |
| | No | n | 7 | 29 | 36 | |
| | | % | 23.3% | 96.7% | 60.0% | |
| Diarrhoea | Yes | n | 8 | 2 | 10 | 0.080* |
| | | % | 26.7% | 6.7% | 16.7% | |
| | No | n | 22 | 28 | 50 | |
| | | % | 73.3% | 93.3% | 83.3% | |

**Fisher's exact test.*

**Table III: Comparison of demographics characteristics and laboratory investigations between the study groups (n = 60).**

| Study variables | Studied groups | Mean | Median (IQR) | SD | p-values |
|---|---|---|---|---|---|
| Age | G-1 | -- | 40 (29.25) | -- | 0.668[a] |
| | G-2 | -- | 42.5 (24.25) | -- | |
| Weight | G-1 | -- | 60 (19) | -- | 0.641[a] |
| | G-2 | -- | 60 (14.25) | -- | |
| Pre-treatment level of haemoglobin | G-1 | 13.72 | -- | 1.47 | 0.534* |
| | G-2 | 13.94 | -- | 1.27 | |
| Post-treatment level of haemoglobin | G-1 | 13.34 | -- | 1.73 | 0.101* |
| | G-2 | 13.97 | -- | 1.09 | |
| Pre-treatment level of ALT | G-1 | -- | 67 (5) | -- | 0.096[a] |
| | G-2 | -- | 65 (32.5) | -- | |
| Post-treatment level of ALT | G-1 | -- | 67.5 (10) | -- | **0.033[a]** |
| | G-2 | -- | 55.5 (6) | -- | |
| Pre-treatment level of ALP | G-1 | -- | 103 (4.5) | -- | **0.002[a]** |
| | G-2 | -- | 97.5 (10) | -- | |
| Post-treatment level of ALP | G-1 | -- | 103 (4.25) | -- | **0.007[a]** |
| | G-2 | -- | 98 (15) | -- | |
| Pre-treatment level of urea | G-1 | -- | 2.2 (1.3) | -- | **0.021[a]** |
| | G-2 | -- | 3.2 (1.83) | -- | |
| Post-treatment level of urea | G-1 | -- | 2.2 (1.25) | -- | **0.006[a]** |
| | G-2 | -- | 3.25 (1.8) | -- | |
| Pre-treatment level of creatinine | G-1 | -- | 109 (18.25) | -- | **<0.001[a]** |
| | G-2 | -- | 94 (15.7) | -- | |
| Post-treatment level of creatinine | G-1 | 106.26 | -- | 13.34 | **<0.001*** |
| | G-2 | 90.43 | -- | 14.92 | |

**Independent sample t-test; [a]Mann-Whitney U test.*

The comparison of laboratory investigations and demographics characteristics between the studied groups is shown in Table III. No statistically significant differences were observed in age, weight, or haemoglobin levels before and after treatment ($p > 0.05$). Post-treatment creatinine levels of G-1 (106 ± 13.34 mmol/L; $p < 0.001$) were significantly higher than those in G-2 (90.43 ± 14.92 mmol/L; $p < 0.001$). Statistically significant differences were found between pre- and post-treatment levels of ALP, ALT, urea, and creatinine ($p < 0.05$).

## DISCUSSION

This RCT aimed to compare the efficacy and safety of MTX administered by the oral and SC routes in patients with severe

psoriasis, using Physician Global Assessment (PGA) score. Studies conducted in different regions by dermatologists have used the Psoriasis Area and Severity Index (PASI) score for the severity of psoriasis. Calculation of the PASI score requires dermatological expertise and more time, whereas the PGA score, used in most studies, is considered a quick, easy, and effective tool to assess disease severity.[11]

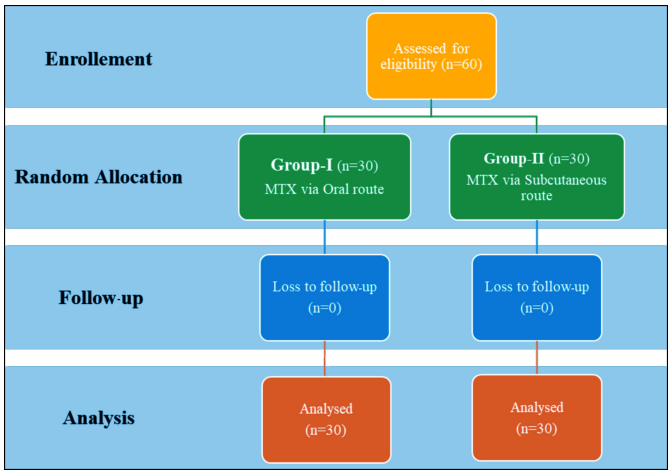
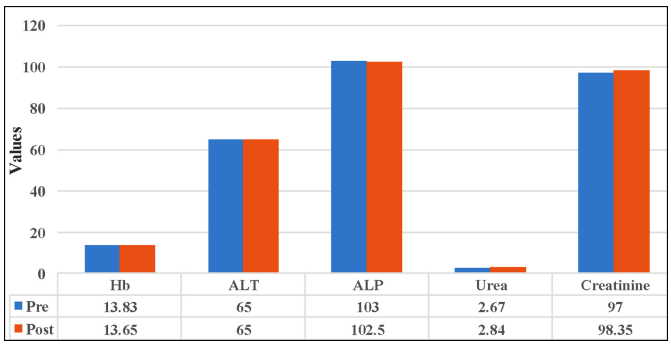



**Figure 1: CONSORT diagram of the study population (n = 60).**




| | Hb | ALT | ALP | Urea | Creatinine |
|---|---|---|---|---|---|
| Pre | 13.83 | 65 | 103 | 2.67 | 97 |
| Post | 13.65 | 65 | 102.5 | 2.84 | 98.35 |

**Figure 2: Pre- and post-treatment laboratory findings (n = 60).**

In terms of efficacy, both groups showed significant improvement after the treatment ($p < 0.001$), as the severity score reduced significantly in both groups. However, G-2 showed a greater reduction in the PGA score ($p < 0.001$) compared to oral administration (G-1). These findings are also supported by a recent clinical trial conducted by Choonhakarn *et al*., which showed comparable efficacy in enhancing PASI scores, even at the maximum tolerable dose. However, the SC MTX cohort demonstrated greater overall patient satisfaction than the oral MTX cohort.[12] Similarly, the results of Attwa *et al*. indicated that SC MTX exhibited greater effectiveness, fewer side effects, and a reduced relapse rate compared to the oral formulation administered at the same dosage and for the same duration. One of the possibilities for the better effect on patients could be its greater and more reliable linear bioavailability compared with oral MTX, as supported by previous studies.[2]

The safety profile of the patients indicates that the SC MTX administration is safer than the oral route since G-1 patients experienced a higher incidence of diarrhoea (8; 26.7%) and vomiting (23; 76.7%) compared to G-2. These findings are in consistence with the findings of another study, which showed that SC MTX demonstrated superior tolerability in patients with psoriasis than oral MTX, along with reduced incidence of adverse events ($p < 0.01$).[13] In contrast, a few studies have suggested that higher doses of MTX were needed when administered through the SC route to achieve improved results, enhanced tolerability, lower frequency of adverse events, and consistent bioavailability across frequently recommended levels.[14] These studies primarily assessed the efficacy of SC and oral MTX based on treatment responses evaluated by the American College of Rheumatology (ACR) criteria for 20% and 70% improvement in disease activity.[12-14] One possible explanation for this could be variation in the disease for which these routes were compared.

Comparing the adverse effects between the two groups of this study, patients experienced a higher incidence of diarrhoea and vomiting in G-1 than in G-2. This is supported by previous findings, in which gastrointestinal problems were linked to prolonged oral MTX treatment.[15] Furthermore, a comprehensive pre- and post-treatment analysis of biochemical tests showed increased liver enzyme levels, headache, and gastrointestinal problems. Significant side effects may include markedly raised liver enzymes, severe nausea, major infections, and adverse effects such as anaemia, thrombocytopenia, increased creatinine levels, hypertension, and other serious complications. Most clinical trials indicated no significant adverse events.[16] Contrary to the present findings, previous research indicated that patients who received MTX *via* the SC route reported 18% nausea, 4.6% vomiting, 4.6% headaches, 4.6% shortness of breath, and 4.6% epistaxis, whereas 59.1% of patients reported no adverse effects. Conversely, 4.5% had low erythrocyte levels, 27.3% displayed elevated leucocyte counts, 13.6% showed increased thrombocyte levels, 18.2% had increased SGOT levels, and 22.8% showed elevated SGPT levels,[9] findings that were not observed in the present findings. The variance in results may be attributed to differences in study populations and sampling methodologies.

Reducing MTX dosages may reduce gastrointestinal issues, and including folic acid into the treatment plan is also beneficial.[15] Transitioning from oral to SC administration with folic acid supplements may mitigate side effects.[17] Administering folic acid in conjunction with MTX lowers the incidence of adverse effects. It improves gastrointestinal intolerance without compromising the efficacy of MTX.[18] Future research might focus on the use of folic acid, for which the data remains contentious and is contingent upon dietary practices and local availability. According to Dutch guidelines, it is recommended to elevate the folic acid dosage to 10 mg per week when 15 mg or more per week of MTX is administered.[19]

MTX is approved and employed for the management of moderate-to-severe psoriasis. SC MTX, as opposed to oral MTX, may be considered preferable for the prolonged management of psoriasis.[20,21] The latest European Dermatology Forum (EDF) recommends initiating treatment with SC MTX.[22,23] Given that MTX is a crucial and comparatively economical medication for psoriasis patients in both Western and non-Western nations, future research should continue to prioritise MTX.[16,23]

There are certain limitations associated with this study. It was a single centred study, which used the PGA scoring scale on a smaller sample size of 60 patients, while other scoring scales such as PASI can also be included for comparison. The authors followed up patients for four weeks. However, longitudinal studies with larger sample size and long-term follow-up would add value to the findings.

## CONCLUSION

The SC MTX route was more effective and safer than the oral route in individuals with severe psoriasis. Nonetheless, MTX may induce various side effects in certain people; however, meticulous dosage and monitoring of side effects are essential to mitigate the adverse effects of MTX in psoriasis treatment.

### ETHICAL APPROVAL:

Ethical approval was obtained from the Ethical Committee of Pak Emirates Military Hospital, Rawalpindi, Pakistan (Approval No. A/28/ERC/19/2024; dated: 3 January 2024).

### PATIENTS' CONSENT:

Informed consent was obtained from all the study participants.

### COMPETING INTEREST:

The authors declared no conflict of interest.

### AUTHORS' CONTRIBUTION:

MA, KF, AA, SSM: Conception and design of the study; acquisition, analysis, and critical interpretation of data; drafting and revision.

All authors approved the final version of the manuscript to be published.

## REFERENCES


1. Parisi R, Iskandar IY, Kontopantelis E, Augustin M, Griffiths CE, Ashcroft DM. National, regional, and worldwide epidemiology of psoriasis: Systematic analysis and modelling study. *BMJ* 2020; **369**:w1040. doi: 10.1136/bmj.m1040.
2. Attwa EM, Elkot RA, Abdelshafey AS, Hafez AR. Subcutaneous methotrexate *versus* oral form for the treatment and prophylaxis of chronic plaque psoriasis. *Dermatol Ther* 2019; **32(5)**:e13051. doi: 10.1111/dth.13051.
3. Leonardi C, Langley RG, Papp K, Tyring SK, Wasel N, Vender R, *et al*. Adalimumab for treatment of moderate to severe chronic plaque psoriasis of the hands and feet: Efficacy and safety results from REACH, a randomised, placebo-controlled, double-blind trial. *Arch Dermatol* 2011; **147(4)**:429-36. doi: 10.1001/archdermatol.2010. 384.
4. Olisova OY, Anpilogova EM. Systemic treatment of psoriasis: From methotrexate to biologics. *Vestn Dermatol Venerol* 2020; **96(3)**: 7-26. doi: 10.25208/vdv1162.
5. Sudevan D, Purushothaman S, Budeda H, Ravi SS, Satyanarayana VVV. A clinical study on latest trends of psoriasis in patients attending dermatology OPD in a tertiary care center: Latest trends in psoriasis. *J Pak Assoc Dermatol* 2022; **32(2)**:264-8.
6. Tareen A, Asghar S, Rajar UD, Khan HY, Bhatti D, Asad M. Efficacy of methotrexate in the treatment of plaque psoriasis in a local population. *J Pak Assoc Dermatol* 2023; **33(3)**: 997-1003.
7. Da Silva CAP, Von Kossel K, Leszczynski M, Melnik T, Riera R. Methotrexate for psoriasis. *Cochrane Database Syst Rev* 2019; **2019(4)**:CD010498. doi: 10.1002/14651858.CD010498.pub2
8. Agustina M, Hidayati AN, Hasanatuludhhiyah N. Side effects of methotrexate for psoriasis therapy. *Berk Ilmu Kesehat Kulit Kelamin* 2020; **32(2)**:98-102. doi: 10.20473/bikk.V32.2.2020.98-102.
9. Dogra S, Singh N, Kumar S, Narang T, Handa S. Comparison of overall efficacy and safety of oral *versus* subcutaneous metho-trexate in severe psoriasis. *Dermatol Ther* 2022; **35(8)**:e15656. doi: 10.1111/dth.15656.
10. Andrus E. Subcutaneous methotrexate shows promise over oral route in plaque psoriasis treatment. *Dermatol Times* 2025; **46(4)**.
11. Zuber M, Harikrishna, Vidhyashree, Chhabra M, Venkataraman R, Kumar S, *et al*. Methotrexate related cutaneous adverse drug reactions: A systematic literature review. *J Basic Clin Physiol Pharmacol* 2021; **33(5)**:549-65. doi: 10.1515/jbcpp-2021-0165.
12. Choonhakarn C, Chaowattanapanit S, Julanon N, Limpawattana P. Comparison of the clinical efficacy of subcutaneous *vs*. oral administration of methotrexate in patients with psoriasis vulgaris: A randomised controlled trial. *Clin Exp Dermatol* 2022; **47(5)**:942-8. doi: 10.1111/ced.15102.
13. Li CK, Baker K, Jones T, Coulson E, Roberts A, Birrell F. Safety and tolerability of subcutaneous methotrexate in routine clinical practice. *Arthritis Care Res (Hoboken)* 2021; **73(9)**: 1306-11. doi: 10.1002/acr.24334.
14. Hazlewood GS, Thorne JC, Pope JE, Lin D, Tin D, Boire G, *et al*. The comparative effectiveness of oral versus subcutaneous metho-trexate for the treatment of early rheumatoid arthritis. *Ann Rheum Dis* 2016; **75(6)**:1003-8. doi: 10.1136/annrheumdis-2014-206504.
15. Braun J, Kastner P, Flaxenberg P, Wahrisch J, Hanke P, Demary W, *et al*. Comparison of the clinical efficacy and safety of subcutaneous *versus* oral administration of methotrexate in patients with active rheumatoid arthritis: Results of a six-month, multicenter, randomised, double-blind, controlled, phase IV trial. *Arthritis Rheum* 2008; **58(1)**:73-81. doi: 10.1002/art.23144.
16. Balak DM, Gerdes S, Parodi A, Salgado-Boquete L. Long-term safety of oral systemic therapies for psoriasis: A comprehensive review of the literature. *Dermatol Ther*

*(Heidelb)* 2020; **10(4)**:589-613. doi: 10.1007/s13555-020-00409-4.

17. van Huizen AM, Sikkel R, Caron AG, Menting SP, Spuls PI. Methotrexate dosing regimen for plaque-type psoriasis: An update of a systematic review. *J Dermatolog Treat* 2022; **33(8)**:3104-18. doi: 10.1080/09546634.2022.2117539.
18. van Huizen AM, Menting SP, Gyulai R, Iversen L, van der Kraaij GE, Middelkamp-Hup MA, *et al*. International Delphi study to reach consensus on the methotrexate dosing regimen in patients with psoriasis. *JAMA Dermatol* 2022; **158(5)**:561-2. doi: 10.1001/jama-dermatol.2021.5795.
19. Gudjonsson JE, Elder JT. Psoriasiform disorders. In: Kang S, Amagai M, Bruckner AL, Enk AH, Margolis DJ, McMichael AJ, *et al*., Eds. Fitzpatrick's Dermatology in General Medicine, 9th ed. New York, McGraw-Hill; 2019. p. 413-56. Available from: https://access medicine.mhmedical.com/content.aspx?bookid=2570§ionid=210417567.
20. van der Kraaij GE, Balak DMW, Busard CI, van Cranenburgh OD, Chung Y, Driessen RJB, *et al*. Highlights of the updated Dutch evidence- and consensus-based guideline on psoriasis 2017. *Br J Dermatol* 2019; **180(1)**:31-42. doi: 10.1111/bjd.17198.
21. Reich K, Sorbe C, Griese L, Reich JL, Augustin M. The value of subcutaneous *vs*. oral methotrexate: Real-world data from the German psoriasis registry PsoBest. *Br J Dermatol* 2021; **184(4)**: 765-7. doi: 10.1111/bjd.19690.
22. Warren RB, Mrowietz U, von Kiedrowski R, Niesmann J, Wilsmann-Theis D, Ghoreschi K, *et al*. An intensified dosing schedule of subcutaneous methotrexate in patients with moderate to severe plaque-type psoriasis (METOP): A 52-week, multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2017; **389(10068)**:528-37. doi: 10.1016/S0140-6736(16)32127-4.
23. Nast A, Smith C, Spuls PI, Avila Valle G, Bata-Csorgo Z, Boonen H, *et al*. EuroGuiDerm guideline on the systemic treatment of psoriasis vulgaris – Part 2: Specific clinical and comorbid situations. *J Eur Acad Dermatol Venereol* 2021; **35(2)**:281-317. doi: 10.1111/jdv.16926.