Dermatology Practical & Conceptual

Efficacy of Intralesional Methotrexate Injection versus Triamcinolone Acetonide in Nail Psoriasis: A Systematic Review and Meta-Analysis

Stephanie Nathania[1], Diah Adriani Malik[1], Muslimin[1], Hardian[2]

1 Department of Dermatovenereology, Faculty of Medicine, Diponegoro University/Dr. Kariadi General Hospital Medical Center, Semarang, Indonesia

2 Department of Physiology, Faculty of Medicine, Diponegoro University/Dr. Kariadi General Hospital Medical Center, Semarang, Indonesia

Key words: methotrexate, triamcinolone acetonide, nail psoriasis

Citation: Nathania S, Adriani Malik D, Muslimin, Hardian. Efficacy of Intralesional Methotrexate Injection versus Triamcinolone Acetonide in Nail Psoriasis: A-Systematic Review and Meta-Analysis. *Dermatol Pract Concept*. 2024;14(2):e2024109. DOI: https://doi.org/10.5826/dpc.1402a109

Accepted: December 12, 2023; **Published:** April 2024

Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

Corresponding Author: Stephanie Nathania, Department of Dermatovenereology, Faculty of Medicine, Diponegoro University/Dr. Kariadi General Hospital Medical Center, Jl. Dr. Sutomo No.16, 50244, Semarang, Indonesia. Phone: +62/81809013509 Email: stephanie.dvjuli18@gmail.com

ABSTRACT

Introduction: Psoriasis is a chronic inflammatory skin disease that can affect many parts of the body. Psoriatic involvement of the nail bed or nail matrix results in nail psoriasis, which is common. Patients with psoriatic nails have impaired quality of life due to the appearance of nails, and significant morbidity and functional impairments may arise in large cases. The management of nail psoriasis is challenging because it is usually time-consuming, with uncertain outcomes. The existing evidence suggests that intralesional injections are particularly effective for nail psoriasis. Current studies provide recommendations on the intralesional injection technique, recommending an optimal concentration of methotrexate (MTX), triamcinolone acetonide (TA), and cyclosporine, but the comparison of these treatment is still limited.

Objective: This study aimed to evaluate the efficacy of intralesional injections of MTX compared with TA in treating nail psoriasis using the Nail Psoriasis Severity Index (NAPSI) score.

Methods: A systematic literature search was performed on EBSCOhost, Scopus, ProQuest, ScienceDirect, SpringerLink, Elsevier Clinical Key, Cochrane library, and ClinicalTrials.gov using subgroups terms: "*intralesional methotrexate injections for nail psoriasis,*" "*intralesional triamcinolone acetonide injections for nail psoriasis,*" and "*NAPSI Score.*" Three studies were included in the qualitative synthesis and meta-analysis.

Results: The overall standardized mean difference in NAPSI scores after administration of intralesional injection of MTX and TA was –0.213±0.232 (95% CI: –0.667–0.241). The Q statistic value was -0.921 (p=0.357), indicating the insignificant difference in the effectiveness of both therapies.

Conclusion: Both MTX and TA were effective in treating nail psoriasis based on the reduction of NAPSI score.

Introduction

Psoriasis is a chronic inflammatory skin disease with predominantly skin and joint involvement. Psoriatic involvement of the nail bed or nail matrix results in nail psoriasis. Nail psoriasis is more common in adults, with a prevalence of up to 10-78% [1]. It can manifest clinically as a wide variety of nail changes, like discoloration, subungual hyperkeratosis, pitting, onycholysis, and splinter hemorrhaging of the nail bed, depending on the part of the nail unit affected. The most observed forms are psoriasis of the nail matrix, nail bed, and nail fold. Patients with psoriatic nails have impaired quality of life due to the appearance of nails, and significant morbidity and functional impairments may arise in large cases [2, 3].

The management of nail psoriasis is challenging because it is usually time-consuming, with uncertain outcomes. The treatment options mainly depend upon the severity and extent of disease. Patients with nail psoriasis are treated with either topical, intralesional, or systemic therapies [4]. Methotrexate (MTX), acitretin, and leflunomide are the options for systemic therapy of psoriasis but, as they result in mild improvement of nail psoriasis, many experts consider systemic treatment inadequate for treating nail psoriasis. Topical therapy represents one of the oldest and most well-studied treatment methods for nail psoriasis. Multiple medications have been studied, including corticosteroids, calcipotriol, tazarotene, 5-fluorouracil, cyclosporin, psoralene, and topical calcineurin inhibitors. However, achieving optimal therapeutic concentrations of topical medications is challenging with nail psoriasis given the presence of the nail plate, which can serve as an impermeable physical barrier. The existing evidence suggests that intralesional injections into the nail bed and matrix are particularly effective for alleviating lesions caused by psoriasis of the nail matrix and also have moderate effects on nail bed signs [5]. Current studies provide recommendations on the intralesional injection technique, recommending an optimal concentration of triamcinolone acetonide (TA), methotrexate (MTX), and cyclosporine [6]. Mittal et al. compared MTX with other active treatments such as TA and cyclosporine (CsA); good outcomes were reported for TA and MTX, which both appeared to be better than cyclosporine. Both TA and MTX acted as anti-inflammatory, anti-proliferation, and immunosuppressive agents [7].

Objectives

This study aimed to evaluate the efficacy of intralesional injections of MTX compared with TA in treating nail psoriasis using the Nail Psoriasis Severity Index (NAPSI) score.

Methods

We conducted a systematic review and meta-analysis for the evaluation of treatments for nail psoriasis. This study was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009.

Literature Search

A computer-based literature search was performed to identify relevant articles publish on MEDLINE PubMed, EBSCOhost, Scopus, ProQuest, ScienceDirect, SpringerLink, Elsevier Clinical Key, Cochrane library, and ClinicalTrials.gov as well as hand searching from Indonesia libraries. The main search terms using medical subject headings (MeSH) to create subgroups terms were: "*intralesional methotrexate injections for nail psoriasis,*" "*intralesional triamcinolone acetonide injections for nail psoriasis,*" and "*NAPSI Score.*"

Study Selection

The inclusion and exclusion criteria were determined before the search. The included studies fulfilled the following inclusion criteria: (1) the study discussed intralesional MTX and TA injections from 2018 until 2022; (2) study design was clinical trials with/without randomization; (3) the study participants should not have received systemic or topical therapy within 3 months; (4) the evaluated interventions included 3–4 intralesional MTX injections or intralesional MTX injections for 4-6-week interval; (5) the outcome of the studies was reduction in NAPSI score.

Data Abstraction

Three independent reviewers abstracted data using a predefined data extraction form. The following information was extracted from each study: author, year of publication,

design of study, blind time period, patient type, details of the interventions (intralesional MTX and TA injections), and the improvement after the treatment using NAPSI score.

Data Analysis

We performed statistical analyses using the Cochrane systematic review software (Review Manager (RevMan) [Computer program] Version 5.4.1., 2020). Categorical data are displayed as percentages, and numerical data are displayed as mean and standard deviation (SD). The meta-analysis assessed the weighted mean between changes in the mean and SD from baseline of the treatment groups and control groups.

Results

Systematic Review

We identified 51 articles matching the search criteria. We extracted 42 articles after reading the title and removing duplicate publications. After reading the abstract, 18 articles were excluded. Furthermore, we retained 33 articles after a full-text review. Three complete articles were assessed for eligibility in order to evaluate the efficacy of MTX intralesional injection as the treatment of nail psoriasis in qualitative and quantitative synthesis. The literature search was conducted based on the PRISMA flow diagram (Figure 1) [7].

These three studies included 38 patients and were conducted in India (n=1), Egypt (n=1), and Italy (n=1). All of the included trials used the MTX intralesional injection as the intervention and TA intralesional injection for the control group. Two of the trials used De Beker injection technique in four injection sites. One of the trials used V-shaped injection technique in two injection sites. The duration of the intervention in all of the trials was 24 weeks.

Results of Qualitative Data Analysis

1. Starace et al., 2022

   A study by Starace et al (2022) assessed a pilot study that compared intralesional methotrexate injections versus triamcinolone acetonide in patients affected by nail matrix psoriasis. The study participants were enrolled in Italy between January 2019 and September 2020. Participants included a total of 12 patients with 20 nails affected with psoriasis who had not received any treatment in three months. Patients were divided into two groups of six patients each: Group 1 was treated with MTX 25 mg/mL and Group 2 with TA 10 mg/mL. Each group had a baseline NAPSI score of 5.3. Depending on the group, either MTX or TA was injected into each affected nail, following the De Berker technique and without digital anesthesia. The patients were asked to take folic acid 5 mg once weekly (not on the day of injection) to reduce

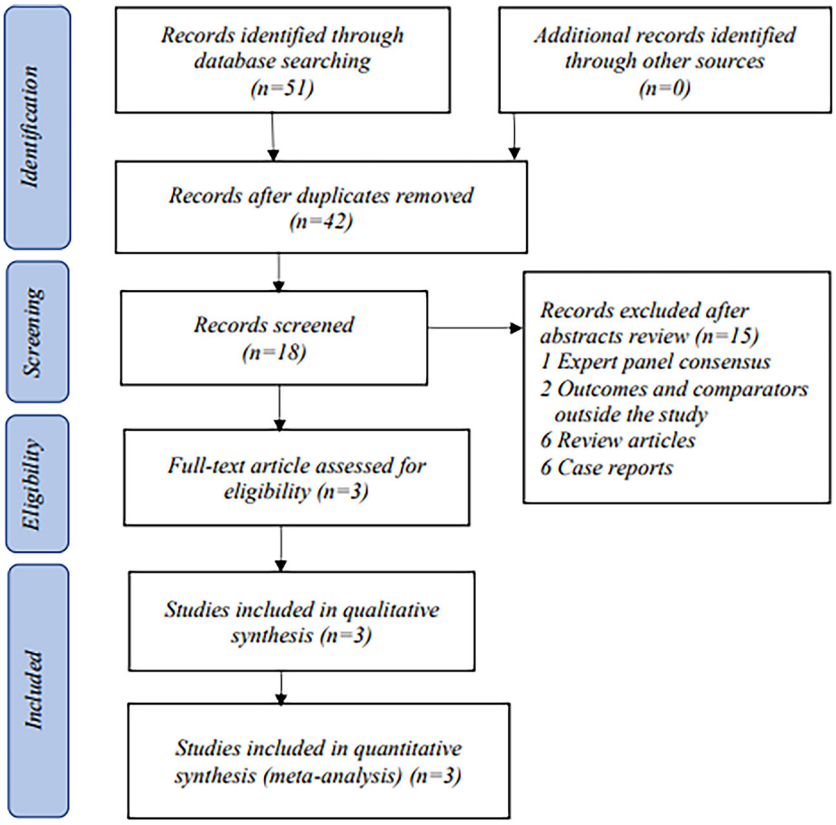

Figure 1. Flow diagram of search strategy and study selection.

Table 1. Characteristics of included studies.

No	Researcher and year	Location	Final sample size	Treatment Protocol		Study Outcome	Duration	Study Design
				Treatment group	Control group			
1.	Mittal et al., 2018 [7]	India	17	MTX intralesional injection 2.5 mg/nail in the nail matrix, given in 6-week intervals	TA intralesional injection 2.5 mg/nail in the nail matrix, given in 6-week intervals	NAPSI Score	24 weeks	Open-label Comparative Study
2.	Abdelmeniem et al., 2022 [9]	Egypt	15	MTX intralesional injection 10 mg/nail in the nail matrix and nail bed, given in 4-week intervals	TA intralesional injection 4 mg/nail in the nail matrix and nail bed, given in 4-week intervals	NAPSI Score	24 weeks	Pilot Study
3.	Starace et al., 2022. [10]	Italy	6	MTX intralesional injection 10 mg/nail in the nail matrix and nail bed, given in 6-week intervals	TA intralesional injection 4 mg/nail in the nail matrix, given in 6-week interval	NAPSI Score	24 weeks	A Comparative Study

MTX-associated adverse events (AEs) and toxicities. Patients were treated every six weeks for 24 weeks (total of four treatment sessions) and followed up for an additional six months.

Assessment by NAPSI was performed during each treatment session and at each follow-up visit. At the end of the four sessions, all patients showed improvement in their nail psoriasis, and no new nail disease was noted: mean NAPSI at one month after the last treatment session had a mean value of 0.3 for the MTX group and 1.8 for the TA group. These data were confirmed at the 6-month follow-up for MTX. All patients were satisfied with the procedure. Side effects included procedural pain, which was tolerable. Subungual hematoma occurred in one patient treated with MTX and in one patient treated with TA. Hypopigmentation of the proximal nail fold was instead reported in two of the six patients treated with TA. No major AE was reported in this study.

2. Mittal et al., 2018

The study by Mittal et al. (2018) assessed an open-label comparative study of triamcinolone, methotrexate, and cyclosporine. The study participants were enrolled in India in 2018. Patients having at least three affected fingernails with or without concomitant skin lesions who had not been on any systemic and topical antipsoriatic medications for at least the previous three months were enrolled. Ninety fingernails in 17 patients were assigned to three groups of thirty nails each and treated with intramatricial injections of triamcinolone acetonide (10 mg/ml), methotrexate (25 mg/ml), or cyclosporine (50 mg/ml), respectively. Digital nerve blocks with plain lignocaine (2%) were administered before intervention. A volume of 0.05 ml was injected from each lateral angle, forming a *V*. Two injections were administered into each treated nail, with an interval of six weeks.

The severity of nail psoriasis was evaluated using NAPSI score after 12 and 24 weeks. The NAPSI score was graded as: G0 = No improvement; G1 = 25%–50% improvement; G2 = 51%–75% improvement; G3 = 76%–99% improvement; G4 = Complete recovery. At the end of the study, 15 patients (50%) from the TA group, 17 patients (56.7%) from MTX group, and 10 patients (33.3%) from the cyclosporine group showed G3 and G4 improvement. In the cyclosporine group, 11 patients (36.7%) showed only G2 improvement at 24 weeks. This study showed that intramatricial injection therapy was a safe, economical, simple, and effective modality in the management of nail psoriasis. Pain, the most common side effect, was transient with injections of MTX and TA in this study, but with CsA injections, pain was severe and lasted for a few hours in about 50% of nails and for 2–3 days in eight nails injected with cyclosporine. In this study,

though the differences in the efficacies of intramatricial TA, MTX, and CsA were not statistically significant, MTX yielded the best results, with the maximum number of nails showing complete recovery (G4 improvement).

3. Abdelmeniem et al., 2022

A comparative study by Abdelmeniem et al. (2022) evaluated the efficacy of topical calcipotriol combined with urea 20% versus intralesional injection of triamcinolone acetonide, 5-fluorouracil, and methotrexate in the treatment of nail psoriasis. The study participants were enrolled in Egypt in 2022. This study included 60 patients with nail psoriasis who were randomly assigned to four groups, each containing 15 patients. The first three groups received intralesional injection of 0.1 ml of 5-FU (group A), MTX (group B), and TA (group C) into the nail matrix and bed monthly for three months. Group D received a topical combination of calcipotriol/urea 20% twice daily for three months. Patients that received intralesional injections were anesthetized with a combination of topical lidocaine and prilocaine cream 30 minutes before injection. Four injections were administered: two injections at the nail matrix and two injections in the nail bed. The injections were administered twice a day for three months and followed up after six months. Therapeutic response was assessed every month for three months using the NAPSI score.

At the end of the study, the mean percentage of improvement was significantly higher in topical calcipotriol/urea combination (57.1 ± 26.4) than intralesional TA (44.2 ± 32.7), intralesional MTX (37.7 ± 14.2), and intralesional 5-FU (29.6 ± 14). Adverse effects were mild and insignificant in the studied groups. In this study, topical calcipotriol/urea combination seemed to be more effective and safer than intralesional injections of 5-FU, MTX, and TA.

Results of Quantitative Data Analysis (Meta-Analysis)

The difference in mean NAPSI scores after MTX and TA intralesional injections is shown in Table 2. All of the studies reported a reduction in NAPSI score in both the MTX group and the TA group.

The results of the meta-analysis of the effect of MTX intralesional injection therapy compared to TA intralesional injection therapy are shown in Figure 2. The heterogeneity test obtained Q value = 2.066; df=2; p<0.356, I^2=3.201. This indicated that the data were homogenous, and the analysis was assessed in fixed effects model.

The results of the meta-analysis showed an overall difference in NAPSI scores after administration of intralesional injection of MTX and TA that was –0.213±0.232 (95% CI: –0.667–0.241). This showed that the reduction in NAPSI score after MTX intralesional injection was greater than that after TA intralesional injection. The Q statistic value was z value= –0.921 (p=0.357), showing an insignificant difference

Table 2. The difference in mean NAPSI score after MTX intralesional injections (n=38) and TA intralesional injections (n=38).

Study	Methotrexate Mean±SD Pre	Methotrexate Mean±SD Post	n	Control Mean±SD Pre	Control Mean±SD Post	n
Starace (2022)	5.33±1.80	0.33±0.47	6	5.33±1.70	1.83±0.69	6
Mittal (2018)	4.33±1.37	1.29±0.75	17	4.06±1.55	1.29±0.89	17
Abdelmeniem (2022)	6.70±1.10	4.3±1.4	15	6.5±1.70	4.00±2.50	15

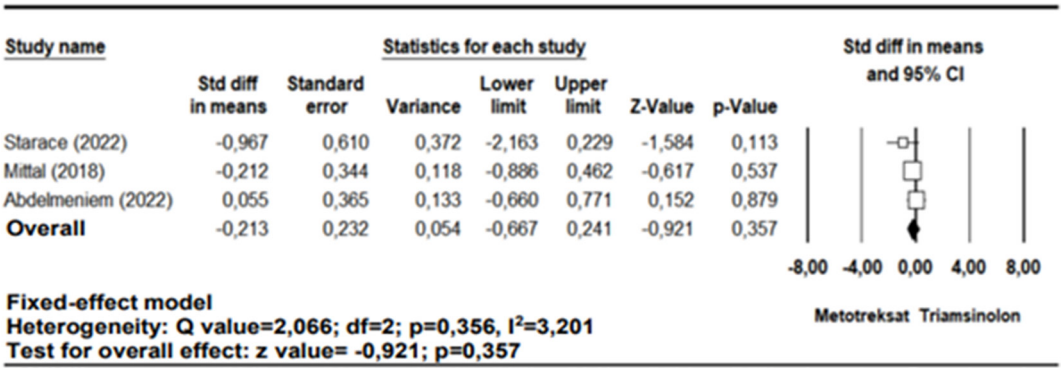

Figure 2. Forest plot showing the efficacy of MTX intralesional injection compared with placebo from all studies that were evaluated in the meta-analysis. 95% CI = 95% Confidence Interval;

in the effectiveness of intralesional MTX injection compared to TA in the management of nail psoriasis.

Risk of Bias in Included Studies

The quality of evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) system. The studies by Starace et al. and by Mitral et al. showed the possibility of risk of bias, while the study by Adelmeniem et al. showed a low risk of bias. Overall, the result of the meta-analysis evaluating the efficacy of MTX versus TA injection in nail psoriasis treatment was considered to be of moderate-quality (⊖).

Moderate-quality evidence indicated that there was a moderate level of confidence in the estimated effect size from the meta-analysis, where the actual effect size was likely to be close to the estimated value, although there was a possibility that the actual effect size was substantially different. Further studies are likely to have an important impact on the estimated effect size and the level of confidence in the estimated effect size.

Discussion

This was a systematic review and meta-analysis evaluating the efficacy of MTX versus TA intralesional injection in treating nail psoriasis. Three studies were included in the qualitative review (systematic review), and all three could be reviewed quantitatively (meta-analysis) to determine the efficacy of MTX and TA intralesional injection in nail psoriasis treatment based on the changes in the NAPSI score.

Methotrexate (MTX) has been shown to improve NAPSI score in several studies. MTX is a folic acid analog that irreversibly binds to dihydrofolate reductase and blocks deoxyribonucleic acid synthesis. MTX acts as the anti-inflammatory, anti-proliferative, and immunosuppressant agent [11]. It is usually taken orally or administered by injection (intramuscular, intravenous, subcutaneous) and has several indications, including nail psoriasis. Current studies suggest injections of MTX (10–25 mg/ml) be administered every 4–8 weeks [11, 12].

Triamcinolone acetonide (TA) is a synthetic corticosteroid [13]. The existing evidence suggests that TA intralesional injections into the nail bed and matrix are particularly effective for alleviating lesions caused by psoriasis of the nail matrix, and they also have moderate effects on nail bed signs [14, 15]. TA acts as the anti-inflammatory, anti-proliferative, and immunosuppressant agent. Current studies suggest injections of triamcinolone acetonide (5–10 mg/ml) be administered every 4–8 weeks. Side effects after these procedures are well known [16]. Local side effects include telangiectasia, skin atrophy, subungual drug deposition, subungual or subcutis hematoma, pigmentation change, necrosis, and ulceration of the skin. Systemic side effect includes Cushing syndrome [12, 13].

Patients in the MTX group were expected to have lower NAPSI scores after the intralesional injection of MTX. All of the studies showed a reduction in NAPSI scores after the injection of MTX. Starace et al. reported reduction in NAPSI score in MTX group (–5±1.62), and there was no recurrence during the six months of follow-up [10]. Mittal et al. also reported a reduction in NAPSI score in MTX group after four weeks of follow-up. The reduction in NAPSI score was 3.04±1.19 and was statistically significant [7]. Lastly, Abdelmeniem et al. also reported a reduction in NAPSI score in MTX group (–2.4±1.28) [9]. These findings were consistent with previous studies, which reported significant improvement in nail psoriasis receiving MTX intralesional injections [11-15].

Patients in the TA group were also expected to have lower NAPSI scores after intralesional injections of TA. All the studies showed a reduction in NAPSI scores after the injection of TA. Starace et al. reported a reduction in NAPSI score in the TA group (-3.5±1.48) during the six months of follow-up [10]. Mittal et al. also reported a reduction in NAPSI score in the TA group after 24 weeks of follow-up (–2.77±1.35) [7]. Lastly, Abdelmeniem et al. also reported a reduction in NAPSI score in the TA group (–2.5 ± 2.21) [9]. These findings were consistent with previous studies, which reported significant improvement in nail psoriasis receiving TA intralesional injections [11–15]. Various side effects of intralesional injection of steroids lead us to suggest that MTX intralesional injection is currently preferable in the treatment of nail psoriasis.

We initially suggested that the reduction in NAPSI score in the MTX group was greater than TA group. Starace et al. and Mittal et al. reported significantly greater reduction in NAPSI score after intralesional injection of MTX (Starace et al.: –5±1.62; Mittal et al.: –3.5±1.48) [7, 10]. Different outcomes were reported by Abdelmeniem et al.: the reduction in TA group (–2.5±2.21) was greater than in the MTX group (–2.4±1.28). However, Abdelmeniem et al. reported no significance in their findings [9].

The meta-analysis of the effect of MTX intralesional injection therapy on nail psoriasis treatment was statistically insignificant compared to TA intralesional injection. (P=0.357). The statistical analysis and meta-analysis in this study were limited because of the limited number of patients. Heterogeneity of the dosage, technique procedure, and frequency of the therapy that had not been standardized also affected the results of this study.

However, this study has some limitations, including the limited number of RCTs evaluating the administration of MTX and PRP injection in nail psoriasis, thus affecting the

limited number of participants in this study, and that some studies only presented their results in the form of boxplot graph without specifying the numerical value or assessed the treatment response using different scores, thus disqualifying that study from being included in the meta-analysis.

Conclusion

Both methotrexate and triamcinolone acetonide are effective in treating nail psoriasis based on the reduction in NAPSI score. However, larger studies with more participants are necessary to establish the optimal dosage, number and frequency of injections, and technique of injection. A standardized assessment score is also needed to obtain more accurate results.

Abbreviations:

MTX: Methotrexate

TA: Triamcinolone acetonide

NAPSI: Nail Psoriasis Severity Index

PRISMA: Preferred Reporting Items for Systematic Review and Meta Analysis

References

1. Christophers E. Psoriasis - Epidemiology and Clinical Spectrum. *Clin Exp Dermatol*. 2001;26:314–20.
2. De Jong EMGJ, Seegers BAMPA, Gulinck MK, Boezeman JBM, Van de Kerkhof PCM. Psoriasis of The Nails Associated With Disability in A Large Number of Patients: Results of A Recent Interview With 1,728 Patients. Vol. 193, *Dermatology*. 1996. p. 300.
3. Lawry M. Biological Therapy and Nail Psoriasis. *Dermatol Ther*. 2007;20(1):60–7.
4. Klaassen KMG, Van De Kerkhof PCM, Bastiaens MT, Plusjé LGJM, Baran RL, Pasch MC. Scoring nail psoriasis. *J Am Acad Dermatol*. 2014;70(6):1061–6.
5. Ventura A, Mazzeo M, Gaziano R, Galluzzo M, Bianchi L, Campione E. New Insight Into The Pathogenesis of Nail Psoriasis and Overview of Treatment Strategies. *Drug Des Devel Ther*. 2017;2527–35.
6. Lawry M. Biological Therapy and Nail Psoriasis. *Dermatol Ther.* 2007;20(1):60–7.
7. Mittal J, Mahajan BB. Intramatricial Injections for Nail Psoriasis: An Open-Label Comparative Study of Triamcinolone, Methotrexate, and Cyclosporine. *Indian J Dermatol Venereol Leprol.* 2018;84(4):419–23.
8. Moher D, Liberati A, Tetzlaff J, Altman DG, Altman D, Antes G, et al. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLOS Med.* 2009;6(7).
9. Abdelmeniem IM, Eryan IM El, Nofal A, Fouda IF, Omar SS. Topical Calcipotriol Combined With Urea 20% Versus Intralesional Injection of Triamcinolone Acetonide, 5□Fluorouracil, and Methotrexate in The Treatment of Nail Psoriasis: A Comparative Study. *Dermatol Ther.* 2022;1–26.
10. Starace M, Alessandrini A, Iorizzo M, D'Altobrando A, Ferrari T, Bruni F, et al. A Pilot Study of Intralesional Methotrexate Injections Versus Triamcinolone Acetonide in Patients Affected by Nail Matrix Psoriasis. *Clin Exp Dermatol.* 2022;47(6):1165–8.
11. Carretero G, Puig L, Dehesa L, Carrascosa JM, Ribera M, Sánchez-Regaña M, et al. Guidelines on The Use of Methotrexate in Psoriasis. *Actas Dermosifiliogr* [Internet]. 2010;101(7):600–13. Available from: http://dx.doi.org/10.1016/S1578- 2190(10) 70682-X
12. Abdelmeniem IM, Eryan IM El, Nofal A, Fouda IF, Omar SS. Topical Calcipotriol Combined With Urea 20% Versus Intralesional Injection of Triamcinolone Acetonide, 5□Fluorouracil, and Methotrexate in The Treatment of Nail Psoriasis: A Comparative Study. *Dermatol Ther.* 2022;1–26.
13. Haneke E. Nail Psoriasis: Clinical Features, Pathogenesis, Differential Diagnoses, and 108 Management. *Psoriasis Targets Ther.* 2017;Volume 7:51–63.
14. Saricaoglu H, Oz A, Turan H. Nail Psoriasis Successfully Treated With Intralesional Methotrexate: Case Report. *Dermatology*. 2011;222(1):5–7.
15. Srisinlapakig S, Juntongjin P. Intralesional Triamcinolone Acetonide Injection and Topical Betamethasone / Calcipotriol Treatment in Nail Psoriasis. RSU International Research Conference 2022 https://rsucon.rsu.ac.th/proceedings 29 APRIL 2022. 2022; (April):1–7.
16. De Berker DAR, Lawrence CM. A Simplified Protocol of Steroid Injection for Psoriatic Nail Dystrophy. *Br J Dermatol.* 1998; 138(1):90–5.