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**Original Article**

# New insights from Vietnam on the effectiveness of methotrexate in treating prurigo nodularis: An interventional study with a control group

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## Abstract

***Background*** Prurigo nodularis is a chronic inflammatory skin condition marked by firm nodules and severe itching, significantly impairing quality of life. Methotrexate (MTX) has demonstrated efficacy in alleviating itching and reducing skin lesions in difficult and recurrent cases, with sustained benefits and good tolerability.

***Objective*** To evaluate the efficacy of MTX in treating prurigo nodularis in Vietnam.

***Methods*** This interventional study included 33 patients in the MTX group, receiving weekly methotrexate (10 mg), daily desloratadine (5 mg), topical corticosteroids, and moisturizers. A control group received the same treatment, excluding MTX. Outcomes were assessed at 4, 8, and 12 weeks.

***Results*** Before treatment, the MTX group's mean scores for pruritus severity (Pruritus Numeric Rating Scale - PNRS), number of nodules/lesions, and active lesion count were 3.61±0.79, 58.27±34.38, and 33.0±25.69, respectively. After 12 weeks, these scores significantly decreased to 1.52±1.03, 22.45±14.49, and 11.32±10.74 (P<0.001). The MTX group showed greater itch reduction than the control group at week 4 (P=0.006). The reduction in the number of active lesions and nodules/lesions in the MTX group was statistically significant compared to the control group at all follow-up points (P<0.05). Adverse effects included gastrointestinal symptoms (6.1%) and one infection (3.0%).

***Conclusion*** MTX is effective and well-tolerated for treating prurigo nodularis, emphasizing its potential in clinical management.

***Key words***
Desloratadine; Methotrexate; Prurigo nodularis; Pruritus Numeric Rating Scale.

## Introduction

Prurigo nodularis was a chronic inflammatory skin disease characterized by firm nodules or bumps that were often symmetrically distributed on both sides of the body, typically affecting the extremities and trunk, and accompanied by intense pruritus.[1-3] The prevalence of this condition increased, accounting for approximately 30-45% of dermatological cases in specialized clinics.[4,5] The persistent and severe itching associated with prurigo nodularis led to significant sleep disturbances. The lesions were predominantly located in exposed areas, adversely impacting aesthetics, self-confidence,

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work, and social activities.[1] Although the disease could occur at any age, it was more frequently observed in middle-aged and elderly individuals.[4-6] Many cases of prurigo nodularis were idiopathic or associated with conditions that caused prolonged itching.[7,8] The repetitive scratching by patients resulted in characteristic skin lesions.[9,10] Atopic dermatitis was the most commonly associated condition with prurigo nodularis. Other associated conditions included various inflammatory skin diseases (such as bullous pemphigoid, lichen planus, and nummular eczema), systemic diseases (including diabetes mellitus and chronic kidney disease), infections (such as HIV, HBV, and HCV), certain malignancies (like Hodgkin lymphoma), and psychiatric disorders.[3]

The treatments for prurigo nodularis focused on alleviating the itching sensation and included topical medications (such as corticosteroids and tacrolimus), oral antihistamines, and systemic immunosuppressive drugs (such as methotrexate and cyclosporine).[11,12] Phototherapy and combination chemotherapy were also therapeutic options, with topical corticosteroids being the first-line treatment.[4,12] Recently, biotherapy had emerged as a new, albeit expensive, treatment modality.[13]

Methotrexate (MTX), a folic acid antagonist, had demonstrated efficacy in managing inflammatory skin conditions such as atopic dermatitis, psoriasis, and bullous pemphigoid. Studies had highlighted MTX's effectiveness in reducing pruritus and skin lesions in prurigo nodularis, particularly in refractory and recurrent cases, with a sustained response and favorable tolerance.[8,9,14] However, there had been limited data on the efficacy of MTX in treating prurigo nodularis in Vietnam. Therefore, this study aimed to evaluate the effectiveness of methotrexate in the treatment of prurigo nodularis in a Vietnamese population.

## Material and Methods

Patients diagnosed with prurigo nodularis attended outpatient visits and received treatment at the National Hospital of Dermatology and Venereology from September 2022 to August 2023. The diagnosis was made according to the criteria of the International Forum for the Study of Itch (IFSI) and the European Academy of Dermatology and Venereology (EADV).[15,16] The main criteria included: 1) chronic pruritus (lasting ≥6 weeks); 2) a history or signs of frequent and repetitive scratching (scratches, scars); and 3) the presence of various types of lesions (nodules, bumps, or patches with a slightly white or pink center and hyperpigmentation at the periphery, accompanied by scratches, scales, or crusts), localized or disseminated in distribution. The diagnosis was confirmed when all three main criteria were met.

Selection criteria included patients aged 18 and above diagnosed with moderate to severe prurigo nodularis. Moderate severity was defined by multiple lesions, some flat, with numerous palpable nodules or bumps (ranging from 20 to 100 lesions). Severe severity was characterized by numerous lesions, mostly palpable nodules or bumps (over 100 lesions).

Exclusion criteria encompassed patients with prurigo nodularis due to other identified conditions (dermatological diseases, metabolic disorders, blood diseases, etc.); pregnant or lactating women; men and women wishing to conceive; individuals with chronic liver, kidney, heart, or lung diseases, blood disorders, cancer, current severe infections or acute infections, HIV infection; alcohol addiction; a history of hypersensitivity to MTX or folic acid; use of other immunosuppressive drugs within 30 days before treatment; inability to follow treatment instructions or non-compliance with treatment; and unwillingness to participate in the study.

The research materials included Belmed tablets (methotrexate) 2.5 mg, manufactured by Belmedpreparaty RUE, Belarus; Aerius tablets (desloratadine) 5 mg, manufactured by Schering-Plough Labo N.V., Belgium; Asosalic ointment (betamethasone dipropionate 0.5 mg/g, salicylic acid 30 mg/g) in a 15 g tube, manufactured by Replex Farm Ltd., Skopje, Macedonia; and a jar of 1% urea moisturizing body lotion, Ziaja Med Atopic Skin Dermatological Formula Body Lotion Nourishing 400 ml, manufactured by Ziaja Ltd., Poland.

This was an interventional study with a control group. Patients with moderate and severe prurigo nodularis (according to the Investigator Global Assessment-chronic prurigo, IGA-CPG, stage) who met the selection and exclusion criteria were chosen.[17] The study objectives were explained to them, and they signed a consent form if they agreed to participate. Patients were then randomized into two groups (control group and MTX group). Medical history interviews and physical examinations were conducted, and research medical records were created according to a template. Direct photographs of the lesions were taken. The following tests were prescribed: complete blood count, blood biochemistry (GOT, GPT, creatinine, urea, glucose), rapid HBsAg test, chest X-ray, and abdominal ultrasound before and after 4 weeks of treatment.

To ensure objectivity and similarity, a black box containing ballots was used, with 35 for the MTX treatment group and 35 for the control group. After selecting a qualified patient, a ballot was randomly drawn from the black box until the required number for both study groups was reached, and treatment proceeded. Medication side effects were monitored. Patients experiencing severe medication side effects during treatment, making MTX use impossible, were advised on appropriate alternative treatment methods.

**Treatment Regimen**

***Study group (n=33 patients)*** Patients took 2.5 mg of MTX orally, 4 tablets per week on a fixed day, divided into 2 doses with 2 tablets each time, 12 hours apart, taken after meals. They took 1 tablet of Aerius 5 mg orally once daily in the evening, after meals. Asosalic ointment was applied topically twice daily, morning and evening, on the affected lesions until healed. Ziaja Med Atopic Skin Dermatological Formula Body Lotion Nourishing, containing 1% urea, was applied to the entire body twice daily during treatment. The application method involved applying moisturizer to the whole area of damaged skin and the surrounding healed skin, then applying Asosalic ointment to the prurigo nodularis lesions. The treatment duration was 12 weeks, with follow-up assessments after 4 weeks, 8 weeks, and 12 weeks.

***Control group (n=31 patients)*** The regimen was similar to the treatment group but without using MTX.

Treatment outcomes were evaluated at 4, 8, and 12 weeks using several indices. These included the PNRS,[14] the number of pruriginous lesions with excoriations or crusts (as determined by the IGA-CPG activity score[17]), and the number of palpable pruriginous lesions (as determined by the IGA-CPG stage score[17]), as detailed in the Appendix.

The above indices were utilized to compare the condition before and after treatment and to evaluate the treatment outcomes of the two groups. The final treatment outcomes were assessed based on the degree of improvement in the disease, quantified as the percentage reduction in the number of lesions post-treatment compared to pre-treatment, determined by the following formula and **Table 1**:

$$\text{Percentage reduction in lesions after treatment} = \frac{Number\ of\ lesions\ before\ treatment - Number\ of\ lesions\ after\ treatment}{Number\ of\ lesions\ before\ treatment} \times 100$$

**Table 1** Evaluating the treatment response in patients with prurigo nodularis.

| *Category* | *Percentage reduction in lesions after treatment* |
|---|---|
| Good response | 80-100% |
| Moderate response | 50-80% |
| Fair response | 20-50% |
| Poor response | <20% |

In this context, lesions were considered healed when they became flat compared to the skin surface, no longer exhibited scratch marks, discharge, or crust formation. The color of the healed lesions could return to normal or become darker due to increased pigmentation following inflammation, and there was no itching sensation.

Data processing was conducted using SPSS 20.0 software. Appropriate statistical tests included the t-test, Chi-square test ($\chi^2$ test), and Mann-Whitney U test. Statistical significance was considered at $P<0.05$.

The study obtained ethical approval from the Research Ethics Committee and the National Hospital of Dermatology and Venereology under decision No. 87/HDDD-BVDLTW, dated September 1, 2022.

## Result

Sixty-four patients meeting the criteria participated in the study, with 33 in the MTX group and 31 in the control group. There were no statistically significant differences in age, gender, lesion severity, activity level, and itching intensity before treatment between the two groups ($P>0.05$). Additionally, a comparison of disease duration between the two groups showed no statistically significant difference ($p>0.05$) **(Table 2)**.

Before treatment, the PNRS score, number of pruriginous lesions, and average number of active lesions in the MTX group were 3.61±0.79, 58.27±34.38, and 33.0±25.69, respectively. After 4 weeks of treatment, these scores significantly decreased to 2.36±0.96, 41.48±22.30, and 21.30±14.74, respectively. Following 4 weeks of MTX treatment, 31 patients continued treatment per the research regimen, while 2 patients discontinued due to adverse effects. After 8 weeks of treatment, the PNRS score, number of pruriginous lesions, and average number of active lesions in the MTX group further decreased to 2.10±0.94, 30.32±15.89, and 14.06±10.91, respectively **(Table 3)**.

**Table 2** The characteristics of the two research groups.

| *Index* | | *MTX group (n=33)* | *Control group (n=31)* | *P value* |
|---|---|---|---|---|
| Age (years) ($\bar{X}$±*SD)* | | 43.1±20.6 | 48.2±11.4 | 0.228* |
| Gender | Male n (%) | 15 (41.7%) | 0.314 | 0.314* |
| | Female n (%) | 21 (58.3%) | 12 (42.9%) | |
| Average disease duration (months) | | 30.33 | 34.81 | 0.331† |
| IGA-CPG activity score ($\bar{X}$±*SD)* | | 2.73±0.72 | 2.58±0.72 | 0.418* |
| IGA-CPG stage score($\bar{X}$±*SD)* | | 3.03±0.18 | 3.18±0.39 | 0.053* |
| PNRS score: ($\bar{X}$±*SD)* | | 3.61±0.79 | 3.39±1.02 | 0.219† |

*t-test; †test Mann-Whitney U; IGA-CPG: Investigator Global Assessment-chronic prurigo; MTX: Methotrexate; PNRS: Pruritus Numeric Rating Scale.

**Table 3** The PNRS score, number of pruriginous lesions, and average number of active lesions after following time

| *Index* | | *After 4 weeks*[2] | *After 8 weeks*[3] | *After 12 weeks*[4] | $P^{*21}$ | $P^{*32}$ | $P^{*43}$ |
|---|---|---|---|---|---|---|---|
| PNRS ($\bar{X}$±*SD)* | Control group | 2.58 ± 1.09 | 2.06 ± 1.15 | 1.61 ± 1.28 | p<0.001 | p<0.001 | p<0.001 |
| | MTX group | 2.36 ± 0.96 | 2.10 ± 0.94 | 1.52 ± 1.03 | p<0.001 | p<0.001 | p<0.001 |
| Number of pruriginous lesions ($\bar{X}$±*SD)* | Control group | 40.97 ± 28.75 | 34.13 ± 24.87 | 27.68 ± 23.51 | p<0.001 | p<0.001 | p<0.001 |
| | MTX group | 41.48 ± 22.29 | 30.32 ± 15.89 | 22.45 ± 14.49 | p<0.001 | p<0.001 | p<0.001 |
| Number of active lesions ($\bar{X}$±*SD)* | Control group | 16.81 ± 13.59 | 15.45 ± 14.55 | 12.10 ± 12.43 | p<0.001 | p<0.001 | p<0.001 |
| | MTX group | 21.30 ± 14.74 | 14.06± 10.91 | 11.32 ± 10.75 | p<0.001 | p<0.001 | p<0.001 |

MTX: Methotrexate; PNRS: Pruritus Numeric Rating Scale.
$P^{*21}$: between "After 4 weeks" – "before". $P^{*32}$: between "After 8 weeks" – "After 4 weeks". $P^{*43}$: between "After 12 weeks" - "After 8 weeks". pair-sample t-test.

By 12 weeks of treatment, these scores had reduced to 1.52±1.03, 22.45±14.49, and 11.32±10.74, respectively (*P*<0.001) **(Table 3)**. The MTX group demonstrated greater effectiveness in itch reduction compared to the control group at week 4 (*P*=0.006). Although the MTX group showed a tendency for higher effectiveness in itch reduction at weeks 8 and 12, the difference was not statistically significant (*P*>0.05). Throughout all follow-up visits, the MTX group achieved a statistically significant reduction in the average number of active lesions compared to the control group (*P*<0.05). At week 4, the MTX group also significantly reduced the number of pruriginous lesions (*P*<0.05). However, while the reduction in pruriginous lesions at weeks 8 and 12 was greater in the MTX group, the difference did not reach statistical significance (*P*>0.05) **(Table 4)**.

The proportion of patients with mild and almost clear lesions after 12 weeks of treatment showed no difference between the two groups with *P*>0.05. The good response rate of the MTX group tended to be higher than the control group (25.8% versus 6.5%); however, the difference was not statistically significant with *P*>0.05 **(Table 5)**.

After 12 weeks, the study group recorded three cases of adverse effects, including two cases (6.1%) manifested in the gastrointestinal tract (nausea, vomiting, elevated liver enzymes) and one case (3.0%) of infection (oropharyngeal fungal infection). No significant adverse effects were observed in the control group.

**Table 4** Change in PNRS scores, number of pruriginous lesions and number of active lesions after 4, 8, and 12 week of treatment.

| *Index* | | *After 4 weeks* | *After 8 weeks* | *After 12 weeks* |
|---|---|---|---|---|
| Change in PNRS. ($\bar{Z}$±SD) | Control group | 0.81±0.60 | 1.32±0.75 | 1.77±1.02 |
| | MTX group | 1.24±0.61 | 1.61±0.66 | 2.19±0.94 |
| | P value | **0.006** | 0.112 | 0.099 |
| Change in number of active lesions. ($\bar{Z}$±SD) | Control group | 10.06±8.77 | 16.90±13.44 | 23.35±16.59 |
| | MTX group | 16.78±15.30 | 25.09±21.18 | 32.97±25.86 |
| | P value | **0.043** | **0.005** | **0.015** |
| Change in number of pruriginous lesions. ($\bar{Z}$±SD) | Control group | 5.70±5.98 | 7.06±6.67 | 10.42±7.39 |
| | MTX group | 11.32±13.92 | 17.93±19.59 | 20.67±21.48 |
| | P value | **0.034** | 0.074 | 0.087 |

MTX: Methotrexate; PNRS: Pruritus Numeric Rating Scale.

**Table 5** Good response rate and degree of mild and almost clear lesions of both groups after 12 weeks of treatment.

| *Index* | *Control Group (n=31)* | *MTX Group (n=31)* | $X^2$ | *df* | *P (test $\chi^2$)* |
|---|---|---|---|---|---|
| Good response | 2 (6.5%) | 8 (25.8%) | 4.292 | 1 | 0.081 |
| Degree of mild and almost clear lesions | 14 (45.2%) | 15 (48.4%) | 0.065 | 1 | 1.00 |

MTX: Methotrexate

## Discussion

Our study demonstrated the significant effectiveness of MTX in improving itch severity and reducing the number of active lesions, pruriginous lesions after 4, 8, and 12 weeks of treatment. These findings were consistent with previous studies, which indicated the efficacy of low-dose MTX in alleviating itch severity and decreasing pruriginous lesions in prurigo nodularis.[14,18]

Studies globally have indicated that most treatments for prurigo nodularis typically required a relatively long duration, lasting at least 6 months, to achieve improvements in itching symptoms, lesion reduction, and patient satisfaction post-treatment. Gründel S. reported that the average treatment duration for prurigo nodularis patients showing excellent responses (≥70% symptom improvement) was 182 days in treatment groups using antihistamines, immunosuppressants, antidepressants, and gabapentinoid drugs.[18] Spring P. *et al*. administered weekly doses of 7.5-20mg of methotrexate to 13 patients over a period of six months. The results indicated that 10 patients achieved remission or showed significant improvement, characterized by a reduction of more than 75% in both PNRS and PNASI (Prurigo Nodularis Area and Severity Index) scores. Two patients demonstrated a trend towards improvement, while one patient experienced a relapse following the cessation of treatment.[19] Therefore, a 12-week period may not have been sufficient to fully evaluate the maximum effectiveness of MTX for symptoms in prurigo nodularis.

Klejtman T.'s study further supported this observation, revealing that the average time from initiating MTX treatment to achieving a response was 2.4 months, with an average effective treatment duration of 19 months.[14] Hence, our study's results were consistent with these prior findings. Additionally, these findings underscored the advantages of MTX over antihistamines and conventional topical medications within the same treatment duration, indicating significant improvements in itching symptoms.[20,21]

Our results demonstrated that the effectiveness of reducing the number of active lesions in the MTX group was statistically significantly higher compared to the control group at all follow-up time points. Although there was no difference in the proportion of lesion-free patients between the two groups after 12 weeks of treatment, the MTX group initially had a significantly higher number of lesions compared to the control group at the pre-treatment assessment. However, by weeks 8 and 12 post-treatment, the number of active lesions in the MTX group had markedly decreased and was lower than that in the control group, indicating superior effectiveness of MTX in reducing active lesions. Our findings suggest that MTX achieved anti-inflammatory and itch-reducing effects more rapidly than the control group, thereby mitigating acute inflammatory lesions and reducing patient scratching, resulting in a more substantial reduction in the number of active lesions.[22]

In addition to its itch-reducing effects, MTX has demonstrated efficacy in healing skin lesions. Several studies have highlighted its effectiveness in reducing pruriginous lesions. Klejtman T.

evaluated the healing efficacy of skin lesions in difficult-to-treat prurigo nodularis patients who had failed with prior treatment methods. Their study found that after 3 months of treatment with low-dose oral MTX, the complete response rate (clear or almost clear skin lesions) was 44%, and the partial response rate (significant improvement in the number of skin lesions) was 47%.[14] Spring P. assessed the efficacy of MTX in healing skin lesions after 3 months of treatment with low-dose subcutaneous injections, observing a considerable reduction in the PNASI in most participants. Additionally, two patients required combining MTX with topical medications and light therapy for clinical improvement.[9]

Our study results demonstrated the effectiveness of MTX in reducing chronic lesions over a 12-week period. The low-dose MTX group exhibited higher effectiveness compared to the control group during all follow-up visits. Specifically, at the 4-week mark post-treatment, the reduction in lesion count in the MTX group was statistically significantly higher than in the control group ($P$<0.05). The proportion of favorable responses in the MTX group tended to be higher than in the control group. Additionally, the proportion of patients transitioning from moderate and severe to mild or almost clear lesions was similar between both groups, with 15 patients (48.4%) in the MTX group and 14 patients (45.2%) in the control group. Thus, MTX demonstrated greater effectiveness than the control group in reducing chronic skin lesions. This characteristic underscores the advantage of low-dose MTX in minimizing the local side effects associated with topical corticosteroids by reducing the duration of topical medication application on the lesions.[23]

This study documented three cases of adverse effects, including two cases (6.1%) where participants withdrew from the study due to gastrointestinal side effects such as nausea, vomiting, and elevated liver enzymes after 1 month of treatment, and one case (3.0%) of oropharyngeal fungal infection after 3 months of MTX treatment. No significant adverse effects were recorded in the control group. A retrospective study by Klejtman T; involving 39 cases of prurigo nodularis treated with low-dose MTX, reported adverse effects in 15 cases (38%).[14] Another study by Spring P. showed minimal adverse effects of the drug in a retrospective analysis of 13 prurigo nodularis patients treated with low-dose subcutaneous MTX injections. A few cases reported initial nausea symptoms, which resolved shortly after initiation of treatment and folic acid supplementation. Only one case reported symptoms of fatigue, nausea, elevated liver enzymes, and required treatment discontinuation, resulting in immediate disease relapse upon stopping the medication.[9]

This study has limitations, including a small sample size and a relatively short follow-up period of up to 12 weeks, which may not fully capture the complete recovery time of the disease.

## Conclusion

In general, the use of low-dose MTX for treating prurigo nodularis is a relatively safe method with good tolerability. It has demonstrated significant effectiveness in improving itch severity and reducing the number of skin lesions. MTX may be considered particularly beneficial for cases of moderate-to-severe prurigo nodularis or those that are unresponsive to other treatment modalities.

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***Author's contribution***

**TTH, NTHV, TLLT**: Substantial contributions to analysis and interpretation of data, critical review, have given final approval of the version to be published.

**PTMP, LHD**: Substantial contributions to study design, acquisition of data, manuscript writing, have given final approval of the version to be published.

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