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Original Article

Clinical evaluation of Asian skin type patients with plaque-type psoriasis receiving narrowband ultraviolet-B phototherapy and methotrexate: Retrospective study from tertiary hospital in Indonesia

Menul Ayu Umborowati,[1,2] Faida Ufaira Prameswari,[3] Caprisia Tiaravicka Hasanah,[4] Sylvia Anggraeni,[2] Damayanti,[2] Anang Endaryanto,[5] Ingrid Suryanti Surono,[6] Cita Rosita Sigit Prakoeswa[2]*

[1] Doctoral Program of Medical Science, Faculty of Medicine, Universitas Airlangga, Mayjen. Prof. Dr. Moestopo Street No. 47, Surabaya, Indonesia.
[2] Department of Dermatology and Venereology, Faculty of Medicine, Universitas Airlangga, Mayjen. Prof. Dr. Moestopo Street No. 6-8, Surabaya, Indonesia.
[3] Medical Program, Faculty of Medicine, Universitas Airlangga, Mayjen. Prof. Dr. Moestopo Street No. 47, Surabaya, Indonesia.
[4] University of Muhammadiyah Malang, Bendungan Sutami Street No.188, Malang, Indonesia.
[5] Department of Child Health, Faculty of Medicine, Universitas Airlangga, Mayjen. Prof. Dr. Moestopo Street No. 6-8, Surabaya, Indonesia.
[6] Food Technology Department, Faculty of Engineering, Bina Nusantara University, Jakarta, Indonesia.

Abstract

Introduction Psoriasis is a chronic autoimmune disease manifested as recurrent thick red scaly patches on the skin. Narrowband ultraviolet B has been widely used as first-line treatment of extensive plaque type psoriasis since its relatively safe and effective, including for Asian skin type. Methotrexate is one systemic agent considered for severe psoriasis treatment. Few studies conclude that the combination of NBUVB and MTX is more favourable. This study aims to evaluate clinical improvement of plaque type psoriasis, which is presented by Psoriasis Area and Severity Index (PASI) score, after NBUVB combination with MTX treatment in Indonesian patients.

Methods Data, in this retrospective study, was collected from medical records of plaque type psoriasis patients in the dermatology and venereology outpatient clinic Dr. Soetomo General Academic Hospital in Surabaya, Indonesia. Improvement of PASI score was considered as the main outcome evaluated in this study.

Results Twenty-eight patients were included, where the male to female ratio was 3:1 and average age were 43.6 years old. The mean PASI score before treatment was 15.79 (±7.12), and it reduced significantly to 9.74 (±7.16) (P <0.001). Among them, 20 patients underwent combination treatment of narrowband ultraviolet B and methotrexate. This group achieved PASI score reduction of 7.11 (±5.27), which was greater than in patients who got narrowband ultraviolet B monotherapy, that achieved 3.31 (±7.62) PASI score reduction.

Conclusion Narrowband ultraviolet B phototherapy is considered as effective in reducing clinical severity of plaque type psoriasis in Indonesian patients. Combination with methotrexate is more advantageous to achieve greater clinical improvement.

Key words
Psoriasis; Phototherapy; Narrowband ultraviolet B; Methotrexate.

Introduction

Psoriasis is a chronic recurrent autoimmune disease which occur equally in both men and women from all races. It is influenced by immunological processes, genetics, as well as lifestyles and environmental triggers such as smoking, medicine, infection, and weather. Psoriasis manifests in skin as recurrent thick red plaques with regular border, covered by silver scaly layers.[1] The prevalence of psoriasis ranges from 0.09–11.4% of the entire world population. The prevalence varies among regions.[2] In Indonesia, the prevalence's estimation in 2010 was ranged from two to six million patients, and one to three percent of them were hospitalized in teaching hospitals.[2,3] From 2016 until 2018, there were 208 outward patients recorded in Dr. Soetomo General Academic Hospital Surabaya, or about 0.46% of the total of the dermatovenereology's patients.[4] The clinical severity of psoriasis can be classified based on the extent of Body Surface Area (BSA) affected or Psoriasis Area Severity Index (PASI). The PASI is an extensively applied scoring system, which calculates the redness, thickness, and scales of the skin lession.[1,5]

Phototherapy is known to be an effective treatment for psoriasis. A breakthrough study by Fischer in 1977 discovered the efficacy of light with 254-405 nm wavelengths as the treatment of psoriasis.[6] Narrowband ultraviolet B (NBUVB) refers to 311-313 nm wavelength lights, which is safe for humans. This light is effective for plaque type psoriasis treatment for adults and children.[7,8] Dogra *et al.* in 2010 then showed the use of UVB at 313 nm wavelength was notably effective for clearance of psoriasis, without significant erythema as side effect. This discovery indicated that NBUVB is more effective than broadband ultraviolet B (BB-UVB) and considered safer than psoralen with ultraviolet A (PUVA) radiation.[9,10] According to Indonesian Society of Dermatology and Venereology guideline, NBUVB is indicated for moderate to severe plaque type psoriasis or patients who do not respond to topical treatment.[11]

Combination of NBUVB and methotrexate (MTX) is more favourable than NBUVB or MTX alone.[8] A study by Van *et al.* in 2019 concluded that combination of NBUVB and MTX were more promising than MTX alone in psoriasis patients with Fitzpatrick skin type III and IV in Vietnam. The combination group achieved significant PASI score reduction compare to MTX group.[12] Compared to NBUVB alone, additional MTX leads to greater PASI 75 achievement and lessens phototherapy sessions in Mahajan's study in India (2010).[13] Methotrexate is a conventional systemic treatment for psoriasis, which is still the first choice systemic treatment for severe psoriasis in Indonesia.[11] This systemic treatment has triple functions as anti-inflammatory, anti-proliferative, and immunosuppressant.[1] The efficacy of NBUVB and MTX combination compared to NBUVB monotherapy for chronic plaque type psoriasis is rarely reported in Indonesia. This study aims to evaluate clinical outcomes of plaque type psoriasis patients treated with NBUVB monotherapy and in combination with MTX.

Methods

This retrospective study was conducted in Dr. Soetomo General Academic Hospital, a tertiary referral hospital in Surabaya, Indonesia. The

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Address for correspondence
Dr. Cita Rosita Sigit Prakoeswa
Department of Dermatology and Venereology,
Faculty of Medicine, Universitas Airlangga,
Surabaya, Indonesia.
phone: +62315501609
Email: cita-rosita@fk.unair.ac.id

study was approved by the hospital ethics committee (number 0310/112/X/2020 dated 2nd November 2020). Data was collected from medical records of plaque type psoriasis patients in Dermatovenereology Department for a four years duration (2018–2021). All plaque-type psoriasis patients who received NBUVB therapy throughout that time period were eligible for this study. According to the hospital protocol, NBUVB was administered at a starting dose of 260 mJ/cm^2 as Fitzpatrick skin type III and was increased by 40 mJ/cm^2 per week until it reached a maximum dose of 3000 mJ/cm^2. Phototherapy was performed 2 to 3 times a week. MTX was administered at a weekly dose of 7.5 to 15 mg. The retrieved data included demographic profile as well as Psoriasis Area and Severity Index (PASI) score. Primary outcome evaluated in this study was a reduced PASI score as an indicator of clinical improvement. A 75% PASI score reduction (PASI-75) was consider as remission target for psoriasis therapy.[18]

Statistical analysis was performed using the IBM Statistical Package for the Social Sciences (SPSS) software, version 23. Demographic data and clinical outcomes were analysed descriptively. Numerical data was presented as mean±standard deviation, while categorial data presented as proportions or percentages.

Results

Twenty-eight patients were included, the male to female ratio was 3:1. The average age was 43.6 (±13.56) years old. All subjects were diagnosed with plaque type psoriasis, commonly known as psoriasis vulgaris, and had a disease duration of 4.39 (±5.69) years on average. The average PASI score before phototherapy was 15.79 (±7.12), whereas after phototherapy it was 9.74 (±7.16). After phototherapy, the PASI score dropped by 6.03 points. **Table 1** shows demographic and baseline characteristics.

Based on the PASI scores, subjects were divided in three disease severity classifications which were mild, moderate, and severe. Before NBUVB treatment, with and without MTX, there was one subject with mild (3.6%), four patients with moderate (14.3%), and twenty-three patients with severe (82.1%) psoriasis. After treatment, there were a decreased number of subjects with severe psoriasis by twelve people (42%), meanwhile in mild and moderate, the amounts were increased as shown in **Figure 1**. Clinical severity was evaluated based on PASI score. There was significant reduction in PASI score before and after NBUVB treatment from 15.79 (±7.12) to 9.74 (±7.16) points with P-value <0.001, as stated in **Table 2**.

Figure 2 illustrated the PASI-75 achievement, which was achieved in five patients (17.9%) but not in twenty-three patients (82.1%).

Table 1 Subject characteristic.

Age	43.68 (±13.56)
Gender	
Male, n (%)	21 (75%)
Female, n (%)	7 (25%)
Disease duration (years)	4.39 (±5.69)
Baseline PASI^ score	15.79 (±7.12)
PASI score after treatment	9.74 (±7.16)
Phototherapy session	31.54 (±20.55)
Phototherapy frequency per week	2.36 (±0.78)

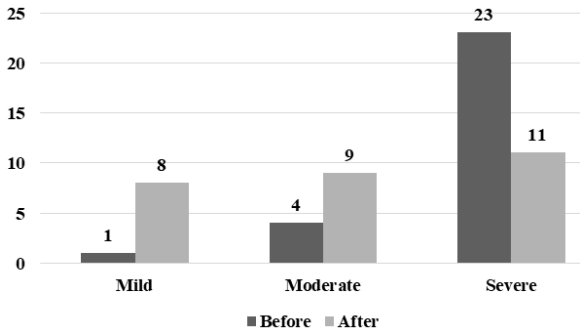

Figure 1 PASI Score before and after narrowband ultraviolet B; PASI: Psoriasis Area Severity Index.

Table 2 Difference of PASI score before and after NBUVB treatment.

	Mean (±SD)	*P-value*
Before	15.79 (±7.12)	0.0001
After	9.74 (±7.16)	

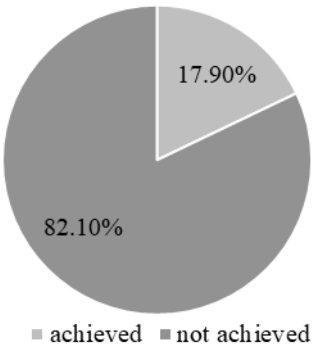

Figure 2 PASI-75 achievements after narrowband ultraviolet B treatment.
(PASI: psoriasis area and severity index; PASI-75 75% : PASI reduction from baseline).

Table 3 showed the results of the evaluation of NBUVB phototherapy in combination with MTX. Twenty subjects (71.4%) received NBUVB and MTX, whereas eight subjects received NBUVB alone (28.6%). In subjects who received combination therapy, the PASI score was decreased by 7.11 points, whereas it was reduced by 3.31 points in those who received NBUVB alone.

Discussion

Treatment of choice for plaque type psoriasis is considered based on disease severity. Psoriasis area and severity index (PASI) is the most frequent scoring tools used to determine the severity level of plaque type psoriasis.[5] Score of PASI used to evaluate clinical improvement after treatment of NBUVB phototherapy. Based on the PASI score, plaque type psoriasis is classified as mild, moderate, and severe. Mild psoriasis defines as PASI score less than 5, moderate is ranged from 5 to 10, and severe is above 10.[5]

Table 3 Difference of PASI score in NBUVB with combination of methotrexate.

Combination with methotrexate	*N (%)*	*Mean Delta PASI (±SD)*
Yes	20 (71.4%)	-7.11 (±5,27)
No	8 (28.6%)	-3.31 (±7,62)

Ultraviolet phototherapy, with or without a photosensitizer, has been used as the mainstay of psoriasis therapy since the 1920s. It considered as effective and relatively safe for psoriasis. The most common phototherapies used to treat psoriasis are UVB and UVA plus photosensitizer.[14,15] Since its recognition in 1980s, NBUVB is preferred than broadband UVB and widely used as psoriasis treatment.[14] Immunomodulation mechanism of UV affects cutaneous Langerhans cells and inhibit antigen presentation to the T cells, which play an important role in the pathogenesis of psoriasis. Phototherapy is also known to down regulated cytokine expression and Th17 cells, a T cell subset believed to have the most important role in the pathogenesis of psoriasis.[14] Initial dose of NBUVB varies from 150–400 mJ/cm^2 based on patient's Fitzpatrick skin type, or 70% of minimal erythema dose (MED) to avoid adverse effects.[14] Typically, NBUVB is applied thrice a week for at least 3 months, but it can be individually modified.[15] However, previous studies have not shown any significant different between 3 or 5 treatments weekly.[15-17] For patients' convenience and compliance, administration of NBUVB 2 to 3 times weekly is applied in most hospitals in the United States of America.[14] The average phototherapy session in this study is 2.36 weekly, and it can significantly reduce PASI score.

Most subjects in this study were diagnosed as severe plaque type psoriasis on the baseline. Overall mean PASI score was significantly decreased by 6.05 points ($p < 0{,}001$) after treatment and the proportion of severe psoriasis decreased by 42%. Reduction of PASI score is also observed in Arora and Kar's study in 2018, that treated 37 plaque-type psoriasis patients above 16 years of age, involving >10% of body surface area (BSA) with NBUVB. The PASI score significantly decreased by 79.6%.[18] The mechanism of NBUVB in decreasing psoriasis

severity is due to its ability to inhibit cell cycle progression and induces growth arrest, which causes reduction in cells of basal layers and supra-basal epidermis. NBUVB also induces prostaglandin release, inhibits expression of interferon-α, interleukin (IL)-18, IL-23, IL-17, decreases natural cell killer activity, induces apoptosis by depleting the immunocompetent T-cells in epidermis and suppresses antigen presenting cell function to present antigens. Therefore, it causes suppression in keratinocytes and result in immunomodulation.[19,20]

The success of psoriasis treatment defined as PASI-75 is one of the clinical goals. In this study, 17.9% of patients achieve PASI-75 with an average of 31.54 NBUVB sessions. Legiawati *et al.* (2020) found that thirteen out of twenty-four geriatric patients reached PASI-75 following NBUVB phototherapy at another tertiary hospital in Indonesia. The 5-year retrospective research evaluated NBUVB phototherapy. They delivered NBUVB 2 to 3 times weekly, for a median of 19 sessions.[21] In comparison to this study, the majority of patients in Legiawati's trial had moderate psoriasis (50 percent with a PASI score of less than 8), hence their response to NBUVB was better overall. The study also demonstrated that NBUVB phototherapy appears to be effective yet safe for geriatric population.[21] Among phototherapies, NBUVB is stated to be superior in safety. The application of NBUVB induces no or minimal risk of carcinogenesis compared with PUVA and is also safe to use in vulnerable populations such as children and pregnant women.[10]

In this study, NBUVB combine with MTX led to greater clinical improvement than NBUVB alone. Reports of the efficacy of NBUVB phototherapy as monotherapy in psoriasis patients in Indonesia have been published. However, despite being widely used in clinical practice, its efficacy in combination with MTX has not been documented to our knowledge.[21] According to the findings of this study, the combination was more beneficial in Indonesian patients having Fitzpatrick skin types III, IV. This finding is also supported by prior studies undertaken in other Asian countries. A randomized single blinded clinical trial by Mahajan *et al.* in India demonstrated combination of NBUVB and MTX maximum 30 mg/ week for 12 weeks was more effective than NBUVB as monotherapy. At the end of study, 95% patients in the combination group achieved PASI-75 compare to 70% patients in NBUVB monotherapy group (P=0.04).[13] Similar result were showed by a clinical study in Vietnam by Van *et al;* decreasing the PASI score by 68.49% from baseline was achieved by patients treated with combination of NBUVB and MTX. It was significantly better than the patients who were treated with MTX alone (P <0.05).[12]

Methotrexate is conventionally used as systemic agent for psoriasis.[22] To date, it is still the first choice systemic therapy for severe plaque type psoriasis in Indonesia.[11] Methotrexate has triple action as immunosuppressant, antiproliferative, and anti-inflammatory agent. High dose of MTX as an antimetabolite analogue of folic acid leads to inhibition of DNA synthesis. Psoriasis treatment required relatively low dose of MTX, from 7.5 to 15 mg/ week, which acts as anti-inflammatory.[23,24] Compare to placebo, low dose methotrexate for 16 weeks showed PASI 75 achievement in 36% patients. Compared with cyclosporine, another conventional systemic agent for psoriasis, PASI-75 achievement of MTX is lower.[24] Although MTX is still quite effective for severe psoriasis patients in Indonesia, there are some adverse effects to be concerned of, particularly regarding blood cell count and liver function.[23,25,26] Combination with NBUVB is an option to increase the efficacy of therapy and reduce the occurrence of toxicity.[8]

Both Indian and Vietnamese study were conducted in Asia, involved moderate to severe chronic plaque-type psoriasis patients with Fitzpatrick skin type III to V.[12,13] No serious adverse effect associated with NBUVB reported from both studies. Most reported adverse effect in an Indian study was itching (42.5% patients) and erythema in 7 patients, while in a Vietnamese study, only 2 patients experienced erythema. No patients had to discontinue from study due to these adverse effects.[12,13] According to Sokolova's review, the most prevalent adverse effect of NBUVB administration is moderate erythema.[8] This statement supports the idea that NBUVB is relatively safe for Asian skin. Unfortunately, no detailed reports of side effects have been discovered. Several studies, however, have not fully clarified the effect of carcinogenesis on long-term NBUVB usage.[8]

The limitation of this study is the retrospective study design and the small number of subjects included. However, research on the use of NBUVB phototherapy and methotrexate in psoriasis patients with Asian skin, particularly in Indonesia, has not been widely reported.

Conclusion

Narrowband ultraviolet B phototherapy appears to be beneficial in decreasing plaque type psoriasis severity in Asian patients. When paired with methotrexate, the efficacy is strengthened further.

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Conflict of interest Authors declared no conflict of interest.

Authors' contribution

MAU: Study design, data collection and analysis, manuscript writing, final approval of the version to be published.

FUP: Study design and data collection, final approval of the version to be published.

CTH: Study design and data analysis, manuscript writing, final approval of the version to be published.

SA, D: Analysis and interpretation of data, Critical review, final approval of the version to be published.

AE, ISS, CRSP: Concept, study design, critical review, final approval of the version to be published.

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