

Clinical Assessment of Patients With Recalcitrant Psoriasis in a Randomized, Observer-Blind, Vehicle-Controlled Trial Using Indigo Naturalis

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Objective: To evaluate the efficacy and safety of treatment with indigo naturalis in patients with recalcitrant plaque-type psoriasis.

Design: Randomized, observer-blind, vehicle-controlled, inpatient comparison study.

Setting: Ambulatory department of a hospital.

Participants: Forty-two outpatients with chronic plaque psoriasis were enrolled in the study from May 1, 2004, to April 30, 2005.

Intervention: The patients applied either indigo naturalis ointment or vehicle ointment topically to each of 2 bilaterally symmetrical psoriatic plaque lesions for 12 weeks (depending on the date of enrollment in the study).

Main Outcome Measures: The outcomes were assessed using the following criteria: the sum of ery-

thema, scaling, and induration scores and the clearing percentage of the target plaque lesion assessed by 2 blinded observers.

Results: Significant reductions in the sum of scaling, erythema, and induration scores ($P < .001$) (mean score, 6.3 after indigo naturalis treatment vs 12.8 in control subjects) and plaque area percentage ($P < .001$) (mean percentage, 38.5% after indigo naturalis treatment vs 90% in controls) were achieved with topical application of indigo naturalis ointment. Approximately 31 of 42 patients (74%) experienced clearance or near clearance of their psoriasis in the indigo ointment-treated lesion.

Conclusion: Topical indigo naturalis ointment was a novel, safe, and effective therapy for plaque-type psoriasis.

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PSORIASIS IS A CHRONIC DERMATOSIS for which only remissive, as opposed to curative, treatments are available. Traditional Chinese medicine is one of the most frequently chosen alternative therapies in China and Taiwan, and psoriasis has been treated for centuries with topical and oral herbal preparations.^{1,2} Indigo naturalis is 1 of the Chinese herbal remedies that has been reported to exhibit potential antipsoriatic efficacy.³ However, long-term systemic use has been occasionally associated with irritation of the gastrointestinal tract and adverse hepatic effects.⁴

To avoid the adverse systemic effects but retain the demonstrated efficacy of indigo naturalis as an antipsoriasis medicine, we initiated an alternative approach in 2003 by applying the drug topically on skin lesions. Primary observations showed that treatment with topical indigo naturalis ointment was beneficial for patients with recalcitrant psoriasis.^{5,6} Then, an 8-week pilot study to evaluate the effi-

cacy and safety of topically applied indigo naturalis on treating plaque-type psoriasis and analyze the histologic change in skin tissue was performed. Although the study had a limited number of patients, the results showed significant clinical improvement and marked skin biopsy improvement in proliferating, inflammatory, and differentiation markers.⁷ We present the results of a randomized, investigator-blinded, inpatient comparative trial. This trial, which addresses the safety and efficacy of indigo naturalis for the treatment of psoriasis, was performed longer term with a larger number of patients compared with our previous study.

METHODS

STUDY DESIGN

This was a randomized, observer-blinded, inpatient comparison of topical indigo naturalis vs vehicle alone to treat recalcitrant plaque-type psoriasis within a 12-week period (depending on the date of enrollment in the

Table 1. Study Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Mild to moderate, bilateral symmetric, chronic plaque psoriasis	Chronic plaque psoriasis involving >60% of the body surface
A history of plaque psoriasis for a minimum of 2 years	Pustular or generalized erythrodermic psoriasis
A history of resistance to at least 2 topical treatments (eg, corticosteroids or calcipotriene analogues)	Use of medications that affect psoriasis during the study (eg, systemic therapy, including retinoids, methotrexate, cyclosporine, or corticosteroid and noncorticosteroid topical therapy, including vitamin D analogues, tazarotene, and tacrolimus)
In good general health, as evidenced by blood, renal function, and liver function tests conducted before commencing the study	Systemic therapy for psoriasis within 30 d of baseline
If of childbearing age, agreement to continue using birth control measures for the duration of the study	UV light therapy within 21 d of baseline
Men or women between 18 and 75 years old	Topical therapy within 14 d of baseline
	Positive for HIV, hepatitis B surface antigen, or hepatitis C
	A history of alcohol or other drug abuse
	A history of hepatitis
	Clinically significant laboratory abnormality in blood, renal function, or liver function
	A history of sensitivity to Chinese herbs, olive oil, yellow wax, or petroleum jelly
	Lactating, pregnant, or planning to become pregnant
	Participation in another clinical trial in the last 30 d
	Unwillingness to comply with study protocol
	Any other condition that in the opinion of the investigators could compromise the study

Abbreviation: HIV, human immunodeficiency virus.

study). The trial was conducted at the Department of Traditional Chinese Medicine, Center for Traditional Chinese Medicine, Chang Gung Memorial Hospital, in Taoyuan and Taipei, Taiwan. All patients provided written informed consent before inclusion in the study, and the study protocol was approved by the institutional review board of Chang Gung Memorial Hospital.

PATIENTS

Patients with chronic plaque psoriasis were recruited from the Divisions of Internal Chinese Medicine and Dermatology in Chang Gung Memorial Hospital Linkou Branch and Taipei Branch from May 1, 2004, to April 30, 2005. The diagnosis of plaque psoriasis was based on clinical diagnosis by 2 dermatologists (Y.-C.C. and W.-R.W.). *Recalcitrance* was defined as a history of plaque-type psoriasis present or recurring for at least 2 years and a history of at least 2 antipsoriatic treatment failures. The inclusion and exclusion criteria are listed in **Table 1**. A baseline evaluation of the patients was performed, including hemogram and blood biochemical analysis (including glutamic-oxaloacetic transaminase, glutamic-pyruvic transaminase, and creatinine measurement). The baseline total body surface area involvement and Psoriasis Area Severity Index (PASI) scores were also calculated. Two symmetrically comparable psoriatic plaques on each patient were identified for the trial and baseline lesion areas calculated. Whenever possible, the arms, elbows, legs, and knees were selected as target areas because cross-contamination was less likely to occur at these sites.



Figure 1. *Strobilanthes formosanus* Moore (Acanthaceae). Inset, indigo naturalis powder.

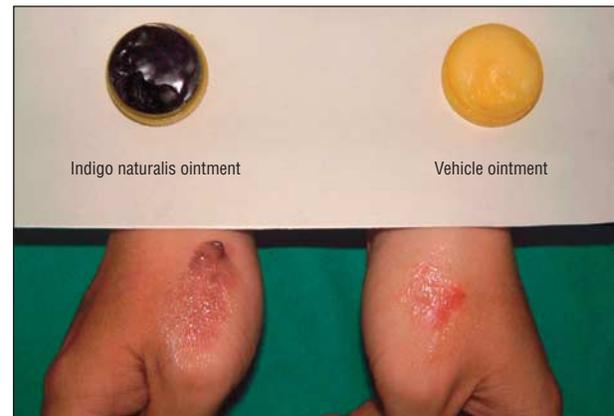


Figure 2. Indigo naturalis ointment. Views of the right hand (left) treated with the indigo naturalis ointment and left hand (right) treated with vehicle only.

STUDY MEDICATION

Indigo naturalis used in this study was identified and provided by the Chinese pharmacy of our institution. It is a powder prepared from the plant *Strobilanthes formosanus* Moore (Acanthaceae) (**Figure 1**). The fingerprints and quantity analysis of standard samples, indirubin and indigo, were established by Leu Yann-Lii, PhD. A voucher specimen was deposited in the herbarium of Chang Gung University, Taoyuan, Taiwan. The indigo naturalis used in our study contained 1.4% indigo and 0.16% indirubin based on the data from high-performance liquid chromatography analysis. The indigo naturalis ointment used was a mixture of indigo naturalis powder and vehicle (1:10). The vehicle consisted of petroleum jelly, yellow wax, and olive oil mixed in the ratio of 5:6:9. The formulations were stable for the duration of the study. Containers were labeled to assist compliance with the left or right application. Indigo naturalis ointment and placebo ointment (vehicle) were prepared by a research pharmacist who was aware of the treatment assignment. The active formulation was applied to 1 side and the vehicle base to the opposite side (**Figure 2**). Patients were instructed to avoid cross-contamination between the 2 treatment sites by washing hands thoroughly between applications. The amount of ointment that should be used by the patient was assessed by estimating the surface area involved by each psoriatic lesion.⁸ This was then used to calculate the number of fingertip units (FTUs) that should be used by the patient (1 FTU=0.5 g=100 cm² of surface area).⁹ The patients were instructed in how to use FTUs to manage treatment application. All test containers were weighed after the study, and the amount of ointment applied to the skin was determined.

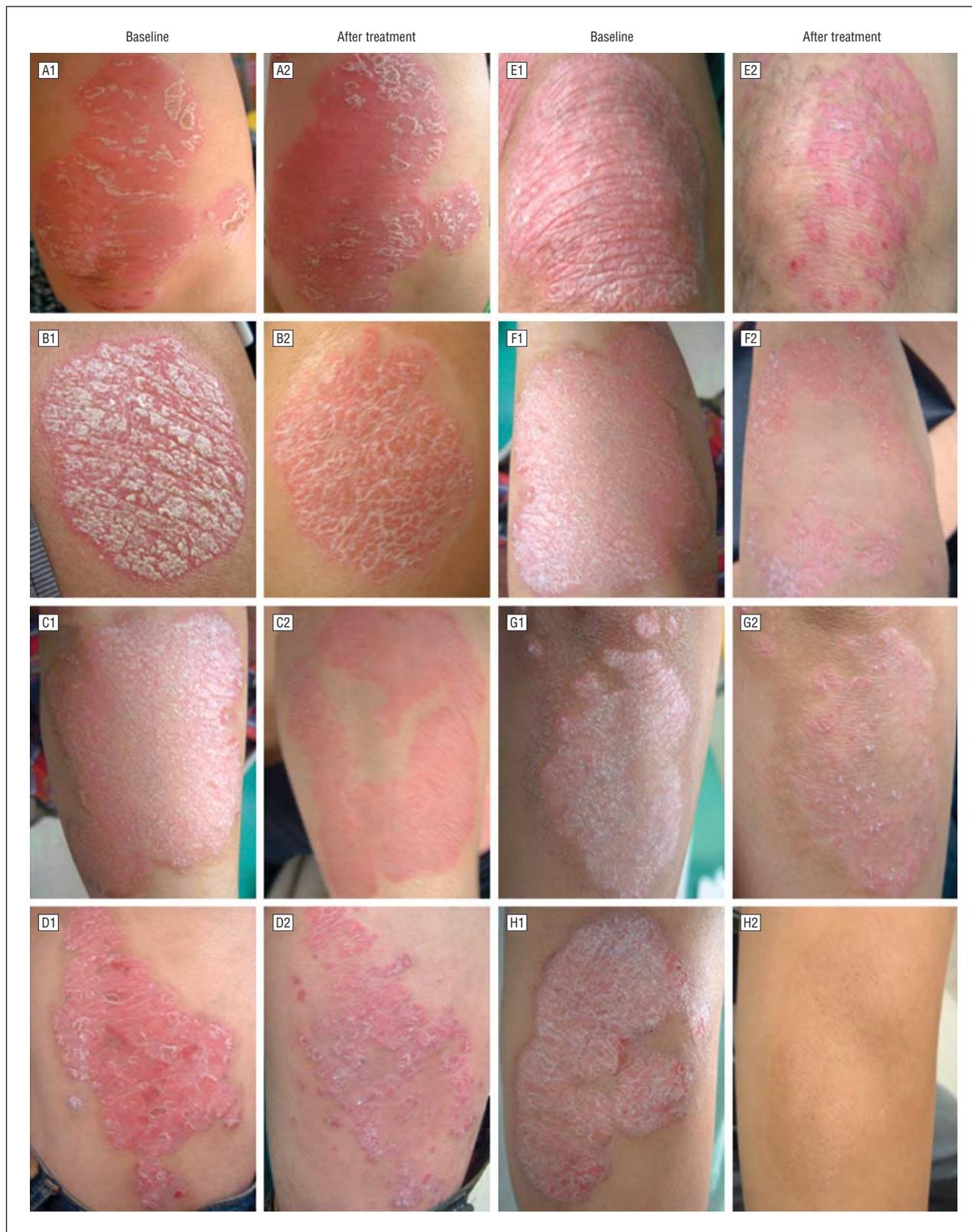


Figure 3. Clinical examples of rating of percentage of clearing. Views of A1, B1, C1, D1, E1, F1, G1, and H1 were taken at the baseline visit, and their plaque areas were all rated as 100%. Views of A2, B2, C2, D2, E2, F2, G2, and H2 were taken after treatment, and their plaque areas were rated as 110%, 90%, 70%, 50%, 40%, 30%, 10%, and 0% (clearance), respectively.

MAIN OUTCOME MEASURES

Clinical assessment of psoriatic lesion severity and photo-

graphic documentation during treatment were performed at baseline and weeks 2, 4, 6, 8, 10, and 12 (end of treatment). At each visit, all participants were requested to clean their skin thor-



Figure 4. Clinical examples. A-E, Rating scaling; F-J, erythema; and K-O, induration.

oughly before the photographs were taken. The assessment of efficacy was performed using the scores of scaling, erythema, induration, sum of these scores, and clearing percentage of target plaque by 2 blinded observers (Y.-C.C. and W.-R.W.) assessing the photographs. Scaling, erythema, and induration were scored on a scale of 0 to 8 (0 indicating none; 2, mild; 4, moderate; 6, severe; and 8, very severe). The bilateral plaque area was rated as 0% to 100% (0% indicating clearance and 100% baseline). In **Figure 3** and **Figure 4**, clinical photographic examples of rating of percentage of clearing and rating scaling, erythema, and induration are shown.

Treatment was performed until complete clearing or for a maximum period of 12 weeks and immediately stopped if significant local or systemic adverse events occurred possibly related to treatment. Safety assessments consisted of monitoring and recording all adverse events by their severity and potential relationship to the study medication.

STATISTICAL ANALYSIS

The intent-to-treat population consisted of all patients enrolled, with each patient receiving both indigo naturalis and vehicle-only treatment, making the main population for the evaluation of safety and efficacy. All statistical analyses were performed using a commercially available software program (SAS version 9.1.3; SAS Institute Inc, Cary, North Carolina).

All efficacy end points at weeks 2, 4, 6, 8, 10, and 12 were compared between the 2 treatment lesions. A paired *t* test was

conducted to establish the differences between the pretreatment and posttreatment values and the active and placebo group values. All statistical tests were 2 sided and performed at an α level of .05. The mixed-effect model was used to account for time dependency of the repeated treatment measurement and differences between the 2 groups.

RESULTS

DEMOGRAPHICS AND COMPLIANCE

A total of 51 patients were screened for the study; 42 (32 men, 10 women) were included in the intent-to-treat analysis (**Figure 5**). The mean (SD) patient age was 34.6 (11.5) years (age range, 18-58 years); the median disease duration was 10 years (range, 2-41 years). The median pretreatment PASI score was 14.7, with a median body surface area of 18%. Target lesions were located on the upper extremities (17 participants), lower extremities (21 participants), and trunk (4 participants). Lesions statistically similar in area, redness, thickness, and scaling were assigned for treatment by indigo naturalis and vehicle ointments in baseline (**Table 2**). Of the 42 patients, 34 completed the study, 3 patients withdrew because they were dissatisfied with the treatment progress

(slow efficacy), 3 patients could not continue because of their work, and 2 patients failed to complete the course of follow-up appointments.

MAIN OUTCOMES

After 12 weeks of treatment with the indigo naturalis ointment, scaling, erythema, and induration all showed significant improvement when compared with the vehicle ointment-treated lesions. For the indigo naturalis ointment-treated lesions, at the start of the study, mean (SD) scores for scaling, erythema, induration, and the sum of all 3 were 6.8 (1.31), 6.0 (1.42), 6.1 (1.28), and 18.9 (2.97), respectively, and after 12 weeks of treatment improved to 1.5 (1.46), 2.6 (1.60), 2.2 (1.49), and 6.3 (4.28), respectively, whereas the lesion area reduced to 38.5% (39.58%) of the original ($P < .001$). In comparison, for the vehicle ointment-treated lesions, at the start of the study, scores for scaling, erythema, induration, and the sum of all 3 were 6.7 (1.31), 6.0 (1.40), 6.0 (1.32), and 18.7 (3.08), respectively, and after 12 weeks of treatment improved to 3.7 (1.60), 4.9 (1.50), 4.2 (1.37), and 12.8 (3.92), respectively, whereas the lesion area reduced to 90.0% (38.06%) of the original ($P < .14$) (Figure 6A-D). Reliability studies demonstrated an intraclass correlation coefficient for interrater reliability of 0.69 for the erythema score (95% confidence interval [CI], 0.62-0.75), 0.54 for the scaling score (0.45-0.62), 0.66 for the induration score (0.58-0.72), and 0.93 for the percentage of clearing (0.91-0.94).

Weighting the sum of scaling, erythema, and induration scores by the lesion area and comparing between the start and end of the study, the indigo naturalis ointment-treated lesions showed an 81% (95% CI, 73%-90%; $P < .001$) improvement, whereas the vehicle ointment-treated lesions showed a 26% (16%-36%; $P < .001$) improvement (Figure 6E). The efficacy of indigo naturalis treatment increased with the duration of treatment, with scaling, erythema, and induration all making statistically significant improvement as the study progressed (Figure 6F). Therapy outcome was grouped into 6 categories of global improvement compared with baseline: clearance ($\geq 90\%$ improvement), near clearance (75% to $< 90\%$ improvement), moderate improvement (50% to $< 75\%$ improvement), mild improvement (25% to $< 50\%$ improvement), no change (0% to $< 25\%$ improvement), and worse. Of the 34 patients who completed the study, no patient experienced worsening of psoriasis in the indigo ointment-treated lesion, whereas 25 of 34 patients (74%) experienced clearance or near clearance of their psoriasis (Figure 7).

To examine whether the disease severity was a significant factor in the success of the treatment, the results were divided into 2 groups based on the original PASI scores (> 14.7 and ≤ 14.7) or divided into 2 groups based on the original total body surface area involvement scores ($> 18\%$ and $\leq 18\%$). In both cases, no statistically significant difference was seen (using paired t test) in their response to treatment between these 2 groups (Table 3). Figure 8 shows the degree of improvement observed in psoriatic lesions before and after the use of indigo naturalis and vehicle.

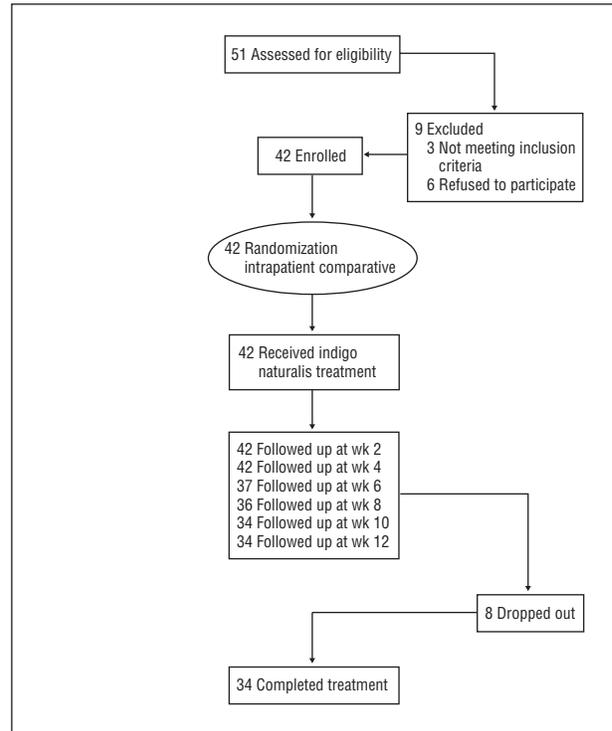


Figure 5. Trial profile. At the end of the trial, 34 of 42 patients had completed the trial. Of the 8 patients who dropped out, 3 were dissatisfied with the treatment progress, 3 could not continue because of their work, and 2 failed to complete the course of follow-up appointments.

SAFETY

None of the patients experienced serious adverse events during the study. Among the 34 patients who completed the treatment, 4 patients reported itching after applying the indigo naturalis ointment to their psoriatic plaque, but the itching was only present for a couple of days at the start of treatment, and no tenderness, vesicles, or other serious problems were noted during the subsequent treatment period. The results of blood tests, including complete blood cell and differential cell counts and glutamic-oxaloacetic transaminase, glutamic-pyruvic transaminase, and creatinine measurement, indicated that the liver and renal functions of all these patients seemed to be normal after the trial (data not shown).

COMMENT

Within the last 5 years, we have been using an alternative approach to treat thousands of patients with psoriasis by applying the indigo naturalis ointment topically on plaque lesions. We designed this study to assess the clinical benefit and safety of indigo naturalis monotherapy in patients with plaque psoriasis and to provide evidence-based research of traditional Chinese medicine therapy for psoriasis.

In this study, indigo naturalis ointment-treated lesions experienced a significant clinical improvement over vehicle-treated lesions. The improvement of the 12-week trial was similar to the result of our prior pilot study. We could find distinct improvement in the scaling and

Table 2. Inpatient Comparison Trial Baseline Data

Characteristic	Indigo Naturalis-Treated Group (n=42)	Vehicle-Treated Group (n=42)	P Value for Difference (t Test)
Treated area, mean (SD) [95% CI], cm ²	112.8 (80.6) [87.74-137.93]	110.5 (78.3) [86.12-134.93]	.52
Erythema score, mean (SD) [95% CI]	6.0 (1.42) [5.57-6.5]	6.0 (1.40) [5.53-6.40]	.49
Induration score, mean (SD) [95% CI]	6.1 (1.28) [5.70-6.50]	6.0 (1.32) [5.61-6.43]	.18
Scaling score, mean (SD) [95% CI]	6.8 (1.31) [6.40-7.20]	6.7 (1.31) [6.33-7.15]	.37
Total score, mean (SD) [95% CI] ^a	18.9 (2.97) [17.99-19.8]	18.7 (3.08) [17.77-19.68]	.21

Abbreviation: CI, confidence interval.

^aTotal scores are erythema plus induration plus scaling.

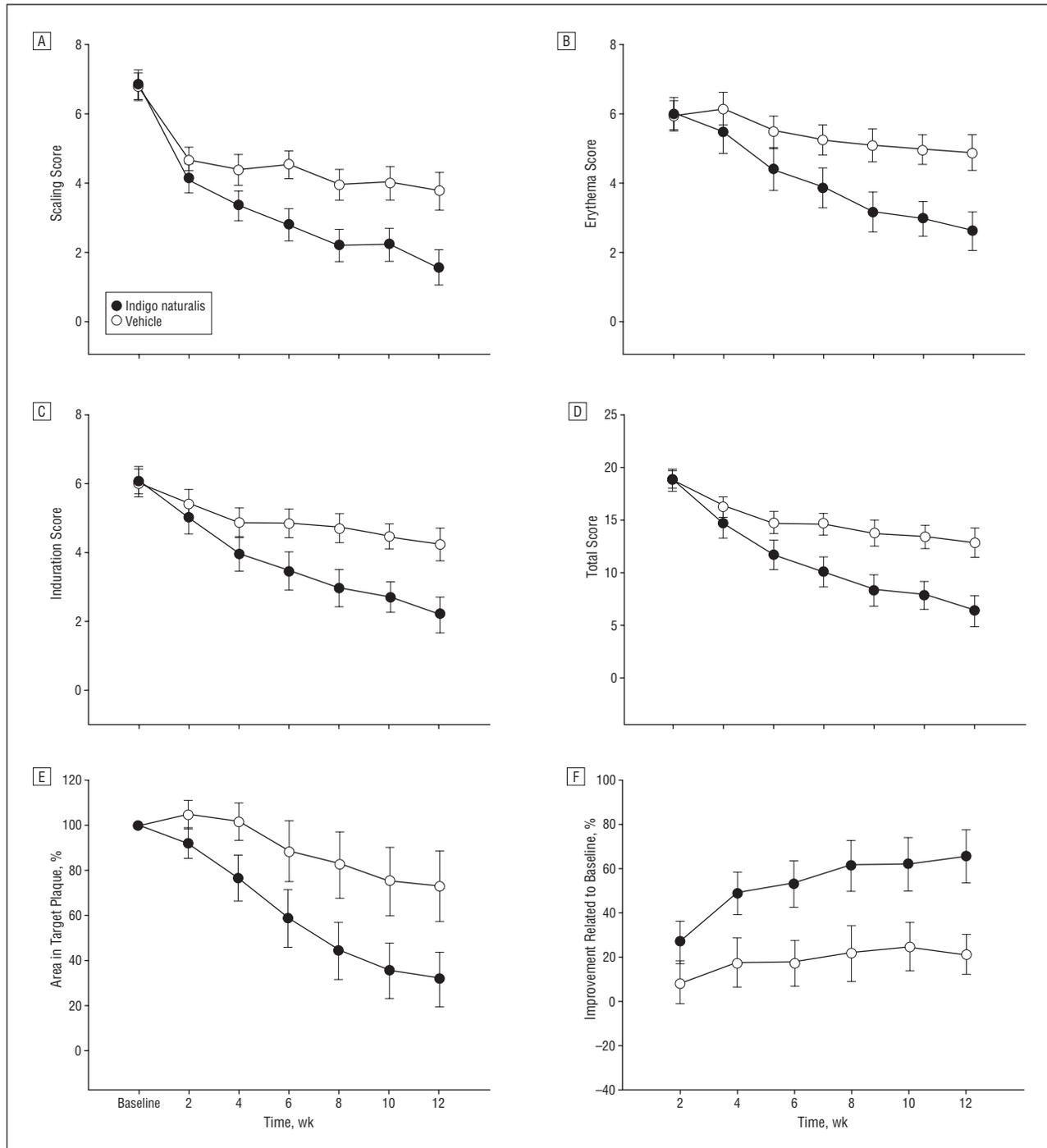


Figure 6. Changes in mean clinical score and area coverage in indigo naturalis ointment- and vehicle-treated plaques. The score of scaling (A), erythema (B), induration (C), and total of these scores (D); clearing percentage of target plaque (E); and improvement related to baseline (F) are given. Mean data are shown for the 12-week treatment period. Error bars indicate SD.

induration scores by treating with indigo naturalis ointment or vehicle only; however, the erythema and area scores revealed obvious changes only by indigo naturalis ointment. Besides, most responding lesions (25 of 34 [74%]) had either an excellent or clear rating ($\geq 75\%$ improvement) in the scores of erythema, induration, scaling, and plaque lesion area. Further statistical analysis showed that the clinical improvement increased significantly as the trial progressed. On the basis of the analysis of PASI and total body surface area involvement scores, it indicated that severity was not a significant factor in predicting treatment success. From the results of our trial, we found a less pronounced but still significant improvement reflected by decreased scores for scaling and induration in the vehicle group. This result may not be explained by a placebo effect alone. Emollients have known beneficial effects in the treatment of psoriasis through increasing hydration of the stratum corneum and through the keratolytic effect.^{10,11} Application of an emollient seems effective in producing a slight modification of proliferation and differentiation.¹²

We recognize that our prospective study was limited in its absence of patient masking and lack of a direct comparison with a current topical medicine (eg, corticosteroid) control group. Furthermore, data are unavailable to assess the efficacy and safety of the therapy in a follow-up period. However, a double-blind, placebo-controlled trial would have been difficult in this case, because indigo natu-

ralis is a natural crude drug that appears dark blue. The use of patients as their own controls in the present study helped to reduce interindividual variation, thereby increasing the power of the study to detect the effect of indigo naturalis treatment. Because of the low solubility of indigo naturalis, we assume that the efficacy of psoriasis treatment will be accelerated when using indigo naturalis powder formulated in an ointment base. However, we have not performed pharmacologic studies to assess the transdermal drug delivery of indigo naturalis in its ointment vehicle formulation. The color and smell of indigo naturalis may affect compliance of the patients and the longer-term durability of the benefit simultaneously. The indigo naturalis ointment slightly stains the skin and clothing, which can be cleaned thoroughly

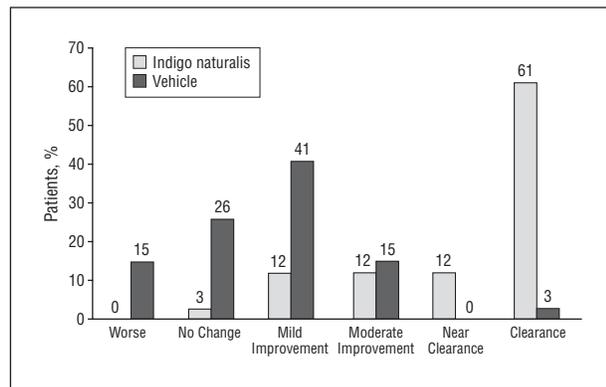


Figure 7. Patients were categorized into 6 groups based on the extent of individual improvement at week 12. Patients were classified as worse, no change (0% to <25% improvement), mild improvement (25% to <50% improvement), moderate improvement (50% to <75% improvement), near clearance (75% to <90% improvement), or clearance ($\geq 90\%$ improvement). The statistical analysis was based on the data from observed cases.



Figure 8. Clinical improvement on the appearance of skin lesions after the indigo naturalis ointment treatment. Views of the left arm (A) and right arm (B) at the baseline visit. At 12 weeks after the treatment, views of the left arm (C) treated with the vehicle only and right arm (D) treated with the indigo naturalis ointment showed improvement.

Table 3. Response Based on Baseline Severity

Characteristic	PASI Score, Mean (SD)		Difference	TBI, Mean (SD)		Difference
	$\leq 14.7^a$	$> 14.7^a$		$\leq 18\%^a$	$> 18\%^a$	
Erythema	2.65 (1.54)	1.94 (1.64)	-0.40 to 1.82	2.59 (1.50)	2.00 (1.70)	-0.53 to 1.71
Induration	2.12 (1.36)	2.06 (1.71)	-1.02 to 1.14	2.06 (1.34)	2.12 (1.73)	-1.14 to 1.02
Scaling	2.47 (1.23)	2.78 (1.70)	-0.74 to 1.33	2.47 (1.23)	2.18 (1.70)	-0.74 to 1.33
Total score, mean (SD) ^b	7.24 (3.36)	6.18 (4.65)	-1.74 to 3.86	7.12 (3.33)	6.29 (4.61)	-1.99 to 3.63
Area, mean (SD), %	56.24 (29.66)	46.77 (49.59)	-19.08 to 38.02	54.18 (29.86)	48.82 (49.80)	-23.33 to 34.04

Abbreviations: PASI, Psoriasis Area Severity Index; TBI, total body surface area involvement.

^aEach group has 17 patients.

^bTotal scores are erythema plus induration plus scaling.

by common detergents. Repeated application has no significant effect on skin color and will not change the skin appearance.

To our knowledge, the present trial is the first attempt to provide evidence-based medicine using topical indigo naturalis for the treatment of chronic plaque psoriasis. Although the current standard western medicine therapies, such as topical corticosteroid, can be effective in controlling psoriasis to a certain degree, they have significant drawbacks, such as relapse or exacerbation of the disease on therapy discontinuation and well-known adverse effects, such as skin atrophy, telangiectasia, burning, purpura, irreversible striae, or even adrenocortical suppression, in long-term use. Also, important advances have occurred in new biological treatments of psoriasis. However, the fear of adverse events in long-term use and the high cost may reduce the compliance of patients with the treatment. Indigo naturalis ointment treatment has neither adverse effects, such as those found with corticosteroid treatment, nor other toxic effects based on our past 5 years of clinical observation. Furthermore, it costs much less in comparison with other topical agents.⁶ We anticipate that indigo naturalis ointment can be an alternative or complementary therapy for psoriasis and believe it will be a great benefit to this large patient population.

In conclusion, we present a randomized controlled trial showing the use of topical indigo naturalis ointment for the treatment of chronic plaque psoriasis to be both safe and effective. Future research for a more potent extraction from this crude herb that can provide better absorption and convenience would help improve patient compliance with the treatment regimen. However, much more research will be necessary to clarify the pharmacology of indigo naturalis.

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Author Contributions: Dr Lin had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Lin and Su Pang. **Acquisition of data:** Lin, Y.-C. Chang, and Wong. **Analysis and interpretation of data:** Lin, C.-J. Chang, and S.-C. Chang. **Drafting of the manuscript:** Lin. **Critical revision of the manuscript for important intellectual content:** Lin, Y.-C. Chang, Wong, C.-J. Chang, S.-C. Chang, and Su Pang. **Statistical analysis:** C.-J. Chang and S.-C. Chang. **Obtained funding:** Lin. **Administrative, technical, or material support:** Lin, Y.-C. Chang, and Wong. **Study supervision:** Lin and Su Pang.

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Additional Contributions: Chung Yin Hui, BSc, prepared the study medication; Leu Yann-Lii, PhD, performed the fingerprint calculations; and Bill Ressler, MEng, and Chang Chieh Hsueh, BAcc, revised the manuscript.

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