Psoriasis: Targets and Therapy

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ORIGINAL RESEARCH

Acupoint Injection Combined with BCG-PSN and Thymosin Enteric-Coated Tablets Improve China Han Psoriasis Vulgaris by Regulating T Cell Subsets

Junqin Li[1], Xincheng Zhao[1], Hong Pan[1], Yanping Duan[2], Wen Li[1], Yanhong Zhao[1], Lifeng Yao[1], Kaiming Zhang[1]

[1]Shanxi Key Laboratory of Stem Cells for Immunological Dermatosis, Institute of Dermatology, Taiyuan City Central Hospital, Taiyuan, 030009, People's Republic of China; [2]Department of Acupuncture and Massage, Taiyuan City Central Hospital, Taiyuan, 030009, People's Republic of China

Correspondence: Kaiming Zhang, Taiyuan City Central Hospital, No. 5 Dong San Dao Xiang, Jiefang Road, Taiyuan, 030009, People's Republic of China, Tel +86-0351-5656080, Email zhangkaiming@sina.com

Purpose: Psoriasis is a common chronic inflammatory skin disease. Acupoint injection is reported to be used for the treatment of psoriasis, however its mechanism is not yet clear. The study aimed to investigate the efficiency of combined treatment including acupoint injection in the treatment of psoriasis.

Patients and Methods: Here, we compared the efficacy of multiple immune intervention therapy (MII, acupoint injection with BCG-PSN combined with thymosin enteric-coated tablets, levamisole, intramuscular injection with BCG-PSN) to NB-UVB and acitretin for psoriasis. One thousand two hundred patients with moderate-severe psoriasis vulgaris were randomly treated with MII, NB-UVB or acitretin. For another 53 patients treated with MII, the T cell subsets and TCR repertoire analysis were investigated with sequencing and flow cytometry.

Results: The effective rate in MII treated group was similar to acitretin-treated group in 3 months ($P > 0.05$), though lower than in subjected treated with NB-UVB ($P < 0.05$). MII treatments maintained a longer remission of both PASI25 and PASI75 in comparison to the treatment with either NB-UVB or acitretin in following 5-year follow-up. Moreover, the relapse rate was lower in MII treatment than in either NB-UVB ($P < 0.0001$) or acitretin treatment ($P < 0.0001$), accompanied with longer remission duration (MII vs both NB-UVB and acitretin, $P < 0.0001$). Meanwhile, MII treatments markedly increased Treg cells ($P = 0.04$), while decreasing the number of both Th1 ($P < 0.001$) and Th17 cell ($P = 0.01$), along with decreased secretion of IFN-γ ($P = 0.03$) and IL-17 ($P = 0.02$). Multivariable Cox regression analysis demonstrated that MII significantly reduced psoriasis relapse risk versus NB-UVB (58.7% reduction; HR = 0.413, 95% CI: 0.329–0.517, $P < 0.001$) and acitretin (65.3% reduction; HR = 0.347, 95% CI: 0.276–0.435, $P<0.001$).

Conclusion: Acupoint injection combined with BCG-PSN, thymosin enteric-coated tablets and levamisole treat psoriasis and prevent relapse of psoriasis, via modulation of Treg/Th1/Th17.

Keywords: acitretin, acupoint injection, NB-UVB, psoriasis vulgaris, T cell subsets

Introduction

Psoriasis is a chronic inflammatory skin disease with a high recurrence rate, affecting 0.1–1.5% of the global population[1] and seriously impacting the quality of patients' lives.[2] Typical lesions are monomorphic, sharply demarcated erythematous plaques covered by silvery lamellar scales.[3] Psoriasis vulgaris is the most common form, accounting for about 90% of cases. Although the precise pathogenesis of psoriasis is still unclear, the pathogenic role of T cells in psoriasis has been recognized. The imbalance of Th1, Th17 and Treg was the main immune disorder manifestations of psoriasis. IFN-γ mainly produced by Th1 cells induces the recruitment and expansion of IL-17-producing cells through promoting production of CCL20 ligand of CCR6 and IL-23, further participate the pathogenesis of psoriasis.[4] Oversecreted IL-17

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by increased Th17 cells leads to keratinocyte overactivation and inflammatory mediator production, playing a pivotal role in the maintaining of psoriatic lesion.[5] Treg cells number was significantly decreased in psoriasis,[6] contributing to psoriasis because of its reduced suppression on T effector responses.[7]

Currently, there are many medical treatments that can alleviate psoriasis, mainly including biologic agents, narrow-band ultraviolet B (NB-UVB) and acitretin. Although biologic therapy can improve moderate-to-severe psoriasis,[8,9] approximately 11–35% of patients fail during the first year of treatment because of either ineffectiveness or the development of adverse events.[10] NB-UVB and acitretin are commonly used to treat psoriasis vulgaris. NB-UVB improves psoriasis, possibly by inducing apoptosis of keratinocytes and T cells,[11] promoting immunosuppression[12] and altering cytokine profile.[13,14] Acitretin, a synthetic retinoid, benefits psoriasis by inhibiting keratinocyte proliferation and inflammatory response,[15,16] inhibiting dermal vascular endothelial cell proliferation and neutrophil migration.[17,18] Although NB-UVB and acitretin treatments can improve psoriasis, frequent recurrence on the previously involved sites upon withdrawal of treatments indicates that these two treatments lack long-term benefit. Moreover, 52.3% of patients with psoriasis are not satisfied with medical treatment due to the inefficacy or adverse effects of treatment.[19] Therefore, more than 50% of psoriasis tried to use complementary and alternative medicine to achieve satisfactory treatment.[20]

Acupuncture has been practiced in China for over 2000 years, with a long and profound history,[21] and has been widely acknowledged not only in the USA but also in other regions of the Western world.[22] Current evidence from systematic reviews confirms the significant therapeutic efficacy of acupoint stimulation in psoriasis management. As demonstrated by Zou et al,[23] acupuncture intervention exhibits superior clinical outcomes compared to control groups for psoriasis vulgaris, particularly in total effective rate, complete remission rate, and Psoriasis Area and Severity Index (PASI) improvement. Mechanistic studies reveal that acupuncture effectively restores cutaneous barrier function while alleviating characteristic psoriatic manifestations including erythema, scaling, and associated pain intensity (VAS-pain scores).[24,25] Furthermore, this therapeutic modality demonstrates additional benefits in enhancing health-related quality of life metrics (DLQI scores) and ameliorating traditional Chinese medicine syndrome patterns,[25] with longitudinal data indicating reduced recurrence rates among treated psoriatic patients.[26] Consequently, acupuncture can be regarded as a complementary and alternative medical therapy for psoriasis.[27,28] In the present study, we investigated the therapeutic effects and mechanism of acupoint injection therapy combined with Bacillus Calmette-Guerin polysaccharide nucleic acid injection (BCG-PSN), Thymosin enteric-coated tablets (TET) and levamisole on the improvement of psoriasis vulgaris.

Methods

Study Design

A total of 1253 patients were enrolled in this study.

For clinical observation, the sample size was calculated for a three-arm randomized controlled trial comparing time to first relapse using ANOVA in PASS 15.0 (NCSS LLC), with Bonferroni correction for multiple comparisons. To detect a small effect (Cohen's d=0.2) with 80% power at $\alpha = 0.05$, 199 participants per group were required. After 20% dropout adjustment, 239 per group (717 total) were needed. A total of 1200 patients were randomly grouped into NB-UVB, acitretin and MII treatment in our study, as 400 patients were enrolled in each group. The primary objective included remission duration and 5-year relapse rate (Figure 1). The secondary objective included total effective rate, the patient number and treat time that PASI score decreased by 25% (PASI25) and 75% (PASI75), lesion regression characteristics (Figure 1).

To investigate the underlying mechanisms by which MII improves psoriasis, we enrolled another 53 patients with psoriasis vulgaris.

Enrolled Patients

The inclusion and exclusion criteria of patients were detailed in Table S1. Patients were involved in the conduct and reporting plans of our research. All patients were Chinese Han from outpatients or inpatients at the Institute of Dermatology, Taiyuan City Center Hospital. The diagnosis of psoriasis was made according to both clinical features

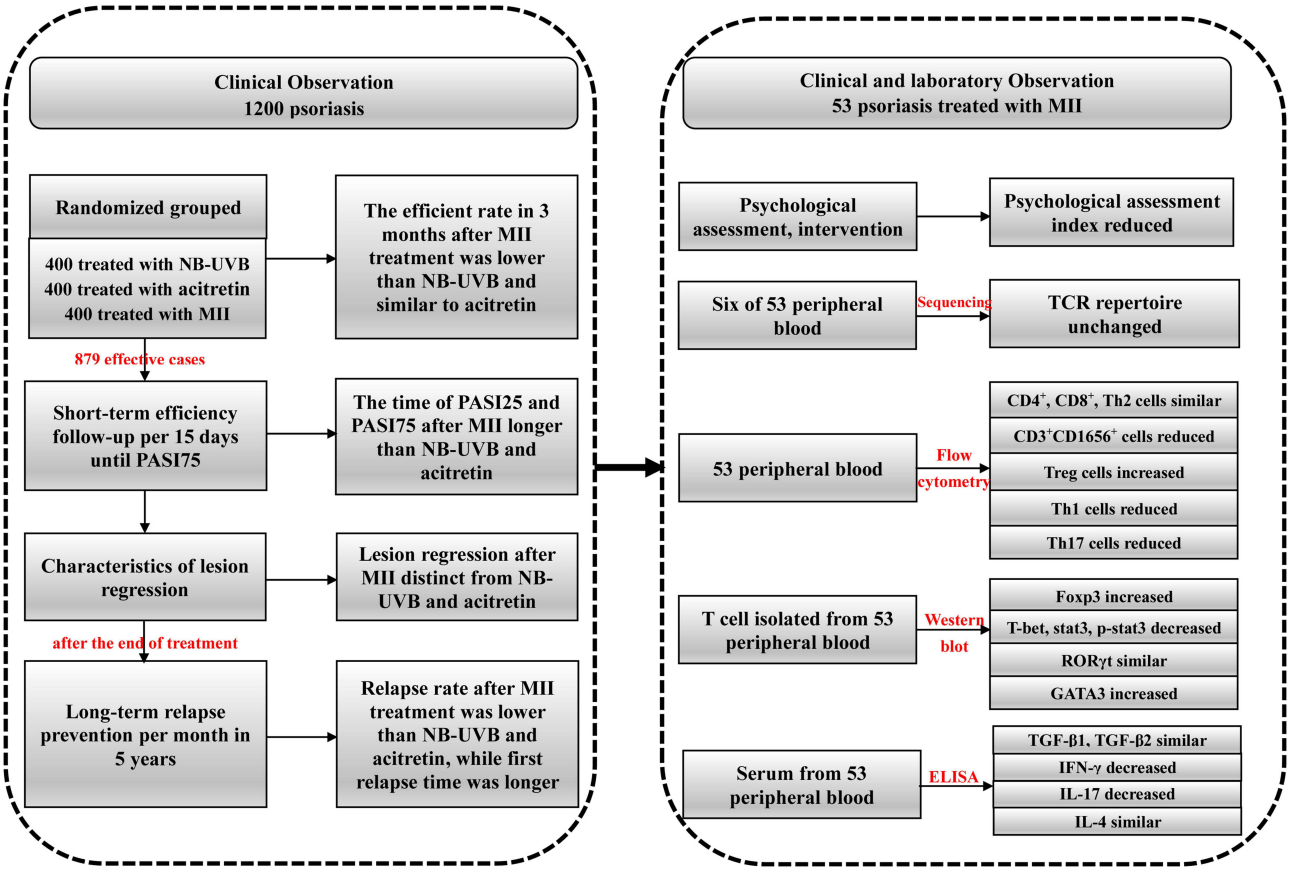

Figure 1 Main pipeline of the project.

and skin pathology. Patients had 10-month to 5-year history of psoriasis, with PASI scores of 15.1–39.5, indicating severe psoriasis.[29] Demographic characteristics of subjects were detailed in Table S2. All patients received neither NB-UVB nor acitretin nor immunosuppressant treatments over the last 6 months. All the patients provided informed consent. The study was complied with the Declaration of Helsinki. The study protocol was approved by the Medical Ethics Committee of Taiyuan City Center Hospital (2022012-1).

Treatments

Patients in NB-UVB group were treated with UV light with a wavelength of 311–313 nm and irradiance of 7–8 mW/cm^2 using the Sigma SS-05 UVB phototherapy instrument as described previously.[30] Subjects in acitretin-treated group were given oral 25mg per day for 4 weeks. If no noticeable improvement and no toxic reaction occurred after 4-week treatment, the dose of acitretin gradually increased to 40–50mg daily. When achieved PASI75, acitretin was maintained at daily dose of 25–50mg. For MII treatment, patients were treated with the following drugs for 4 months: injection of total 1mL BCG-PSN (according to the introduction of BCG-PSN) to 16 acupoints, including bilateral acupoints of Quchi (LI11), Zusanli (ST36), Shangjuxu (ST37), Dashu (BL11), Xinshu (BL15), Ganshu (BL18), Pishu (BL20) and Dachangshu (BL25), once monthly; 20 mg of Thymosin enteric-coated tablet once daily; 50 mg of levamisole tablet, t.i.d., for 3 days at 11-day interval; 1 mL of BCG-PSN once every three days. This combination therapy was carried out every other 3 months until PASI75.

Clinical Evaluation

Therapeutic efficacy and adverse reactions were evaluated weekly during the first 4-month treatment. The adverse reactions included liver function, serum lipid, dizziness, nausea, vomiting, abdominal pain, loss of appetite, fever, drowsiness, fatigue, rash, pruritus, chest tightness, redness and swelling at the injection site, nodules, leukopenia and

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exfoliative dermatitis. Patients who achieved PASI25 were followed up once every 15 days until PASI75. Afterwards, these patients were followed up once monthly for 5 years.

Psychological Assessment and Intervention

Prior to the treatment, patients' psychological status was assessed using psychological assessment scale (Table S3), followed by education of patients and their family members on basic knowledge of psoriasis to minimize their concerns about psoriasis and to increase their social activity. After PASI75, patients' psychological status was assessed again.

Investigation of TCR Repertoire

In another 53 patients treated with MII, 5 mL peripheral blood was collected from each patient before the treatment and after PASI75. Among the 53 blood samples, 6 samples were randomly taken for TCR repertoire analysis as described previously.[31] Briefly, TCRα/TCRβ target regions obtained by multiple-polymerase chain reaction were sequenced on sequencing platform (Hiseq4000; Illumina, SanDiego, CA, USA), followed by obtaining the clean reads by removal of adapter sequences, low-quality base ratio >50%, and percentage of unknown base (N) >10%. TCR repertoire data were analyzed using MiXCR software.[32]

Flow Cytometry

After the treatment of blood cells with red blood cell lysis buffer, cells were labelled with CD45-FITC/CD4-RD1/CD8-ECD/CD3-PC5 (PN.6607013) or CD45-FITC/CD56-RD1/CD19-ECD/CD3-PC5 (PN.6607073), for flow cytometry analysis to determine the proportion of lymphocyte subsets.

To measure the intracellular cytokines of helper T cells, the cells were first labeled with CD4-PC5/CD3-ECD, and then cultured in RPMI1640 culture system (containing 10% newborn calf serum, 100IU/mL penicillin, 100μg/mL streptomycin, 40ng/mL PMA, 1μg/mL ionomycin, 3μM monensin) with 5% CO_2 at 37°C for 18 hours. After fixation and permeabilization with IntraPrepTM Permeabilization Reagent (Cat. No. 2388/2389), the levels of intracellular IL-4, IFN-γ and IL-17 were examined with IL-4-PE (IM2719U)/IFN-γ-FITC (IM2716U) and IL-17-PE (Cat#12-7179, eBioscience). IgG1-FITC (GM4992), IgG1-PE(GM4993), and mouse IgG1 Kappa Isotype Control (12-4714-42, eBioscience) served as respective isotype controls.

According to manufacturer's instruction, the Human Regulatory T Cell Staining Kit#3 containing CD4-FITC/CD25-PE/Foxp3 PE-Cy5 (Cat#88-8995-40, eBioscience) was used to determine the proportion of $CD4^+CD25^+$ $Foxp3^+$ cells, while Rat IgG2a PE-Cy5 served as isotype control.

Measurement of Serum Cytokine Levels

The ELISA Kit (Westang, Shanghai, China) was used to measure serum levels of IL-4, IL-17, IFN-γ, TGF-β1 and TGF-β2 by measuring the absorbance value (OD value) of 450 nm wavelength. The concentration of different cytokines was calculated by OD value using the standard curve method.

Protein Expression of GATA3, RORγt, Foxp3, T-Bet, stat3 and p-stat3 in $CD3^+$ T Cell

Because differentiation of $CD3^+$ T cell into Th2, Th17, Treg or Th1 cells was regulated, in part, by lineage-determining transcription factors, including GATA3, RORγt, Foxp3, T-bet, stat3 and p-stat3,[33–36] we measured expression levels of these biomarkers on $CD3^+$ cells. $CD3^+$ cells were isolated from peripheral blood using immunomagnetic beads (Miltenyi Biotec, Germany). After the extraction of total protein, simple western analysis was performed on a Wes system (ProteinSimple, Silicon Valley, USA) based on the method reported previously.[37] The following antibodies were used in this experiment: β-actin, GATA3, T-bet (Cell Signaling Technology (CST), USA), RORγt, Foxp3, stat3, p-stat3(Abcam, England). The expression of β-actin was used as an internal reference.

Statistical Analysis

For categorical variables, differences in proportions across groups were assessed using the chi-square test. Quantitative data was analyzed through analysis of variance (ANOVA) or rank-sum tests for between-group comparisons. The comparison of differences between pre- and post-intervention measurements was analyzed using a paired samples *t*-test. All data were analyzed using SPSS 27.0.

In the multivariable analysis, a Cox model was fitted with positive responders (those achieving ≥PASI25 within 3 months), incorporating treatment strategy, age, gender, baseline PASI, duration of medical history (years), and family history of psoriasis, aiming to quantify the treatment effects of different therapeutic regimens on psoriasis relapse.

Results

Multiple Immune Intervention Displays a Lower Short-Term Efficacy Than Either NB-UVB or Acitretin

We first assessed the short-term efficacy. Following 3-month treatments, 879 of 1200 patients achieved ≥PASI25. The total effective rates in NB-UVB treated group (78.5%) were significantly higher than that in either MII (71.00%, $P = 0.015$) or acitretin (70.25%, $P = 0.008$), while the effective rates were comparable between MII and acitretin (Figure 2A). However, MII-treated patients maintained both PASI25 (12.32 weeks) and PASI75 (172.92 days) responses longer than either NB-UVB ($P < 0.0001$) or acitretin-treated subjects ($P < 0.0001$) (Figure 2B).

Comparison of Changes in Skin Lesions Among the Treatments with Multiple Immune Intervention, NB-UVB and Acitretin

In acitretin treated skin, the initial changes included increased desquamation and lesion size, followed by reductions in severity of infiltration, erythema and scales, without marked reduction in lesion size (Figure 2C). Similarly, NB-UVB treatments decreased infiltration, erythema and scales, with no changes in lesion size. However, noticeable hyperpigmentation was observed (Figure 2C). In contrast, MII treatments induced a central or peripheral clearance of skin lesions, manifested by formation of circular lesions or reduction in lesion size, in addition to reductions in the severity of

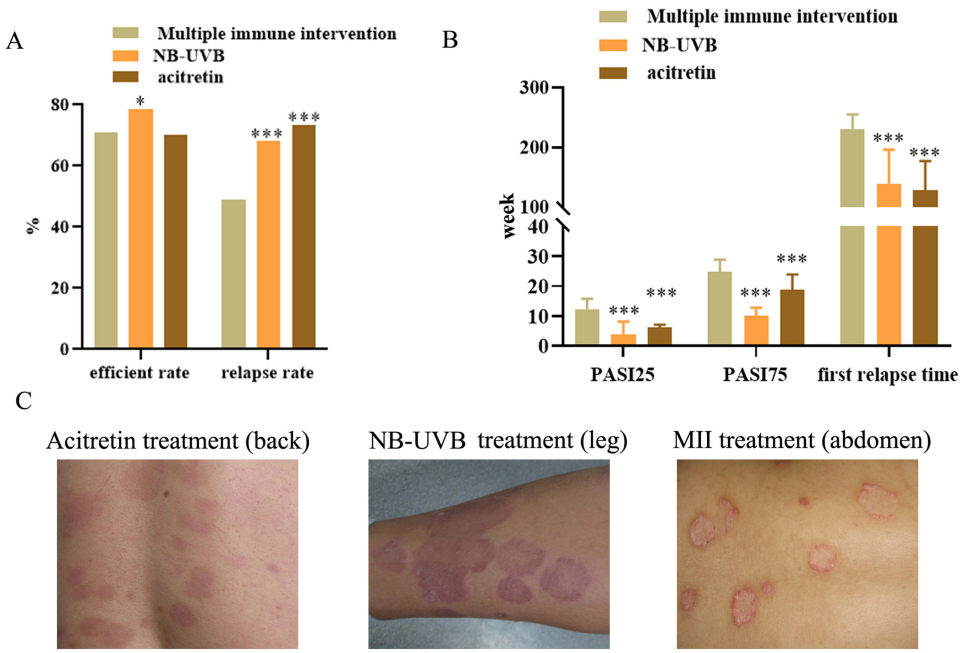

Figure 2 The clinical observation of Multiple immune intervention (MII), NB-UVB and Acitretin treatment in 1200 psoriatic patients. (**A**) Efficient rate and relapse rate. *p<0.05 compared to MII treatment; ***p<0.001 compared to MII treatment. (**B**) PASI25, PASI75 and first relapse time. ***p<0.0001 compared to MII treatment. (**C**) The lesion at PASI75.

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infiltration, erythema and scales (Figure 2C). These results suggest that the mechanisms of MII action differ from that of NB-UVB and acitretin.

Multiple Immune Intervention Exhibits Superior Benefit to NB-UVB and Acitretin in Prevention of Psoriasis Relapse

To assess the long-term preventive benefit, 879 positive responders were followed up for 5 years after the treatments. The relapse rates were significantly lower in MII-treated group (48.94%) than in NB-UVB (68.15%, $P = 1.87\times10^{-6}$) and acitretin-treated group (73.00%, $P = 5.64 \times 10^{-9}$) (Figure 2A). In parallel, MII delayed the relapse of psoriasis (231.15 weeks) in comparison to both NB-UVB (139.08 weeks, $P = 3.24 \times 10^{-27}$) and acitretin treatments (127.48 weeks, $P=2.17 \times 10^{-32}$) (Figure 2B).

Multiple Immune Intervention Treatment Significantly Lowers Psychological Assessment Scale

During the MII treatment, the additional 53 patients also received psychotherapy, including communication with patients, listening to patients' emotions, psychological counseling, teaching basic knowledge of psoriasis, etc. The psychological status was quantitatively assessed using psychological assessment scale. After MII treatment, the psychological assessment index was significantly reduced (50.15 vs 55.96, $P = 0.045$) (Figure 3A).

Multiple Immune Intervention Treatment Was Safety for Psoriasis

Among 53 patients receiving MII therapy, 2 cases (3.78%) developed transient low-grade fever that spontaneously resolved within 12 hours (Table S4). A single patient (1.89%) exhibited self-limiting symptoms including dizziness, nausea, vomiting, loss of appetite, fatigue, and pruritus on the first treatment day. Injection site reactions were documented in 2 patients: one case (1.89%) of localized erythema and swelling that improved with cold-compress therapy, and another case (1.89%) presenting a subcutaneous nodule that resolved within one week following hot-compress application. Notably, no treatment-related abnormalities were observed in liver function and serum lipid profiles. Additionally, there were no instances of abdominal pain, drowsiness, rash, chest tightness, leukopenia, or exfoliative dermatitis during the observation period.

Multiple Immune Intervention Affects Neither TCR Repertoire nor the Proportion of $CD4^+$ and $CD8^+$ T Cells

In six of 53 patients, TCR repertoire analysis identified a total of 31 TRA variable (TRAV) and 33 TRB variable (TRBV), neither of which frequency was significantly changed by MII treatment (Figure 3B). Although MII treatment slightly increased TRBV10-1 frequency (1.08 vs 0.95, $P = 0.04$), MII treatment did not significantly influence TCR repertoire. Likewise, the proportions of $CD3^+$, $CD3^+CD4^+$ and $CD3^+CD8^+$ cells were similar before and after MII treatment (Figure 3C). Interestingly, MII treatment dramatically decreased the proportion of $CD3^+CD1656^+$ cells (identified as B cells) (from 2.65% to 1.43%, $P = 0.01$) (Figure 3C).

Multiple Immune Intervention Treatment Reversely Alters Proportions of Treg Cells and Th1 Cells

As shown in Figure 4A, MII treatment significantly increased proportion of $CD4^+CD25^+Foxp3^+$ cells (48.89% vs 32.25%, $P = 0.002$), accompanied by an over 2-fold increased expression of Foxp3 (5.12 vs 1.67, $P = 0.008$) (Figure 4A). In contrast, the proportion of $CD3^+CD4^+$IFN-γ-secreted cells decreased following MII treatment (9.40% vs 16.25%, $P = 5.45282 \times 10^{-6}$) (Figure 4B). In parallel, the expression of T-bet, stat3 and p-stat3 were significantly decreased after MII treatment. Moreover, ELISA showed that the concentration of IFN-γ was significantly decreased after MII treatment (11.49 vs 20.27pg/mL, $P = 0.03$) (Figure 4B). However, MII treatment did not markedly change the circulatory levels of TGF-β1 and TGF-β2 (secreted by Treg cells) (Figure 4A).

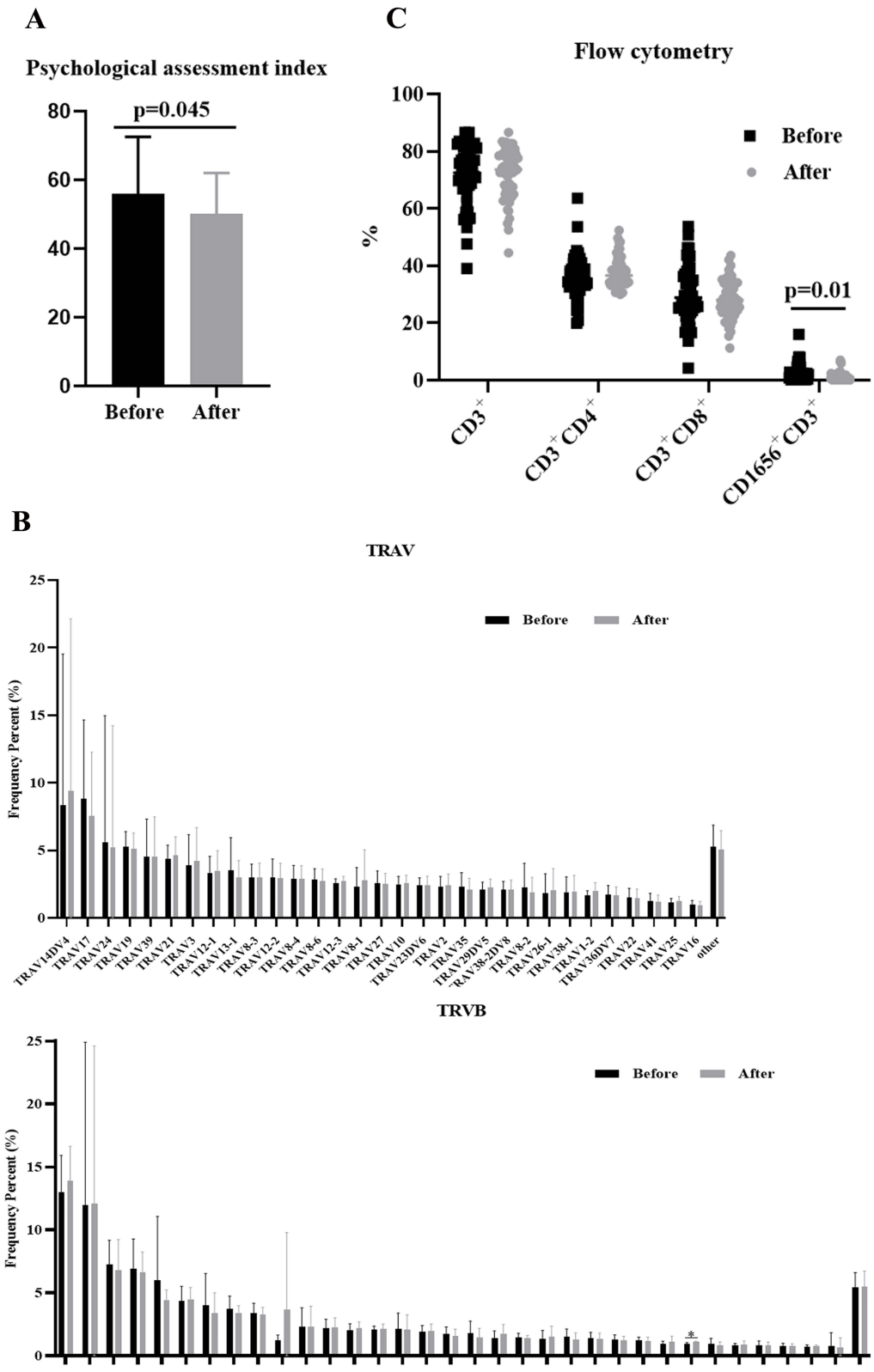

Figure 3 Psychological assessment, TCR repertoire, $CD4^+$ and $CD8^+$ T cells in psoriatic patients treated with Multiple immune intervention (MII). (**A**) Psychological assessment index in 53 psoriatic patients, (**B**) TCR repertoire in 6 psoriatic patients, (**C**) $CD4^+$ and $CD8^+$ T cell in 53 psoriatic patients.

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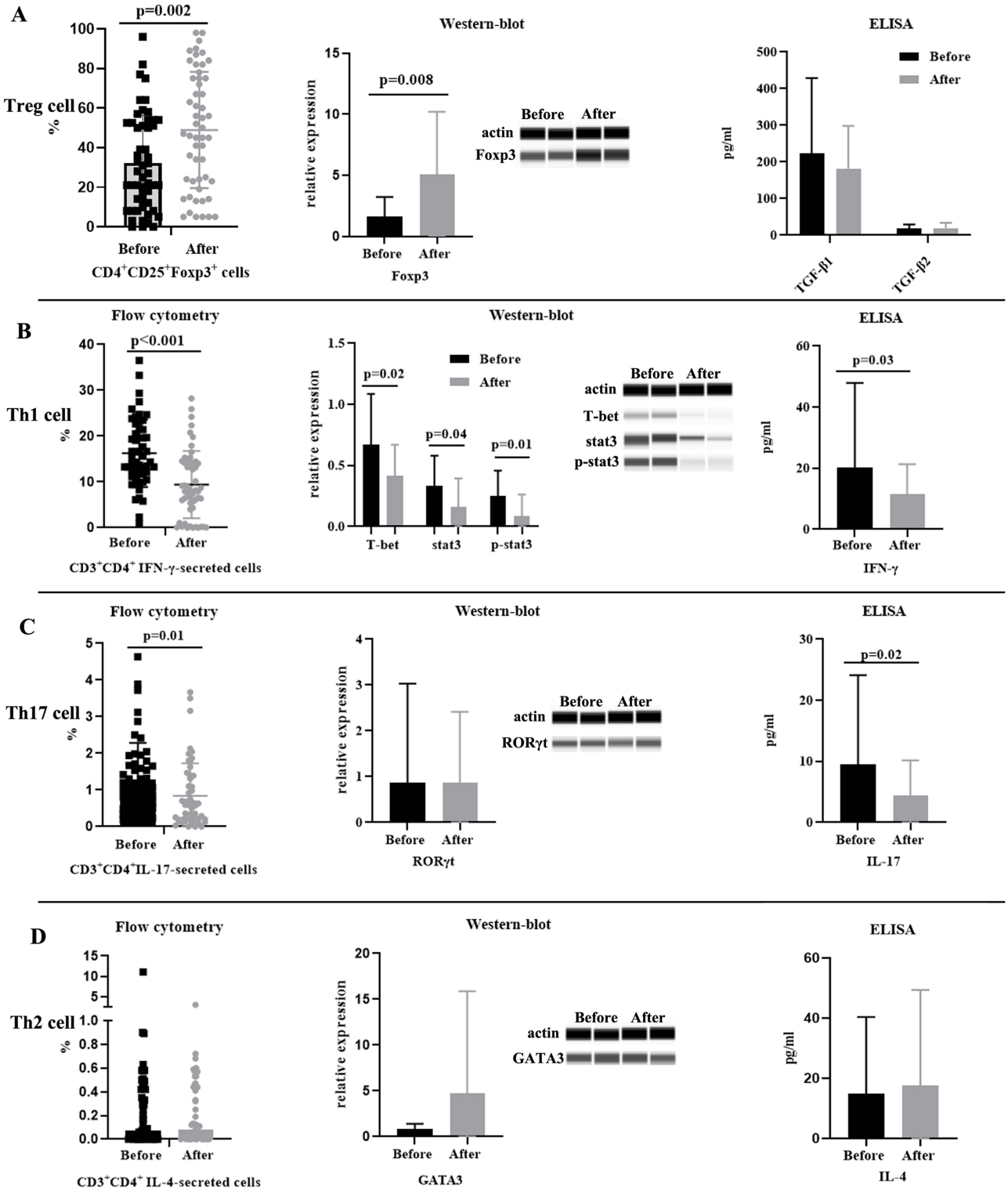

Figure 4 Treg/Th1/Th17/Th2 cells in 53 psoriatic patients treated with Multiple immune intervention (MII). (**A**) Treg cell, (**B**) Th1 cell, (**C**) Th17 cell, (**D**) Th2 cell.

Multiple Immune Intervention Treatment Significantly Decreases the Proportion of Th17 Cells and IL-17 Level

Following MII treatment, proportion of $CD3^+CD4^+$IL-17-secreted cells (identified as Th17 cells) was significantly lower in comparison to pretreatment (0.84% vs 1.29%, $P = 0.01$), without changes in expression of RORγt (Figure 4C). Noteworthy, MII treatment significantly decreased circulatory levels of IL-17 (4.38 vs 9.51 pg/mL, $P = 0.02$) (Figure 4C). However, neither proportion of $CD3^+CD4^+$IL-4-secreted cells (identified as Th2 cells) nor expression of GATA3 and the circulatory levels of IL-4 differed after MII treatment (Figure 4D).

Multivariable Analysis Confirms MII's Protective Efficacy Against Psoriasis Relapse Compared to NB-UVB and Acitretin

The Cox proportional hazards model confirmed significant model validity in treatment responders (χ^2=104.00, $P < 0.001$), with therapeutic regimen persisting as a robust independent prognostic factor after covariate adjustment (χ^2=90.700, $P < 0.001$). MII treatment exhibited significantly protective efficacy against psoriasis relapses compared to both NB-UVB (HR=0.413, 95% CI: 0.329–0.517, $P < 0.001$) and acitretin (HR=0.347, 95% CI: 0.276–0.435, $P < 0.001$).

Discussion

Psoriasis is a chronic recurrent disease. Although some topical agents can effectively alleviate psoriasis,[38] treatments of moderate-severe psoriasis is still a big challenge. Indeed, acitretin is effective for psoriasis. Its wide usage is limited because of adverse reactions such as teratogenicity, mucocutaneous effects, hepatotoxicity and skeletal abnormalities. NB-UVB irradiation lacks long-term benefit. The high cost of biological agents also impedes their use. Methotrexate should be used with caution because of bone marrow toxicity.[39] Hence, an ideal regimen for psoriasis should be the one that can rapidly achieve and sustainedly maintain PASI75 with few or no adverse events.

Existing evidence has demonstrated the therapeutic efficacy of acupoint stimulation in psoriasis management,[27,28] with studies indicating sustained clinical benefits in symptom control alongside favorable safety profiles characterized by minimal adverse effects.[40] Notably, acupuncture intervention exhibits significant potential in multiple aspects: arresting lesion progression, ameliorating cutaneous manifestations and pruritus in psoriasis vulgaris, and reducing recurrence rates[41] - findings that corroborate our experimental observations. Synergistic therapeutic enhancements were observed in combined regimens. When adjunctive to NB-UVB phototherapy, acupuncture produced superior reductions in PASI scores compared to monotherapy.[42] Furthermore, acupoint injection therapy (combined with compound glycyrrhizin and topical tretinoin) demonstrated enhanced clinical efficacy over non-injection protocols, accompanied by significant downregulation of pro-inflammatory cytokines including tumor necrosis factor-alpha (TNF-α) and interleukin-8 (IL-8) in peripheral circulation.[43] In the present study, we demonstrated that acupoint injection combined with BCG-PSN, TET and levamisole significantly lowered the relapse rate and delayed the relapse of psoriasis, suggesting the combined treatment can be suitable for treating moderate-severe psoriasis.

However, the mechanism of acupoint injection should be in-depth research. Acupoint injection therapy stimulates the acupoints by injecting specific drugs into fixed acupoints through syringe-needling of the vein or lesion tissue. Acupoint injection led to a significant down-regulation of the allergic rhinitis symptom score and the serum IL-17 content.[44] Acupoint autohemotherapy showed significant effectiveness on the AD model mice, through regulating the Th1/Th2 shift specifically and increased the related transcription factors such as T-bet expression and T-bet/GATA3 ratio.[45] Current research attributes the therapeutic mechanisms of acupuncture in psoriasis management to six principal pathways: (1) pruritus alleviation, (2) immunomodulation, (3) endocrine system regulation, (4) vascular function normalization, (5) homeostatic adjustment of cellular kinetics, and (6) neuropsychiatric modulation.[46] Emerging evidence demonstrates that acupuncture intervention significantly modulates cytokine profiles, particularly by downregulating elevated IL-8 and TNF-α levels while paradoxically elevating interleukin-10 concentrations beyond normative physiological thresholds.[47] In this study, we found acupoint injection combined with BCG-PSN, TET and levamisole significantly increase the frequency of Treg cells in psoriasis, suggesting that MII treatment may be exerting a protective effect, helping to dampen the inflammatory cascade that is characteristic of psoriasis. Moreover, the reduction in Th17 cell frequency was observed in psoriasis after MII treatment, indicating that MII treatment could potentially contribute to a more favorable immune

microenvironment, reducing the severity of inflammation and skin microenvironment damage. Overall, the study suggested that acupoint injection combined with BCG-PSN, TET and levamisole is significantly effectiveness on psoriasis through normalization of proportion of Th1, Th17 and Treg cells, and reductions in IFN-γ and IL-17. That is to say, MII treatment is helpful in regulating the immune response of psoriasis, being consistent with previous study.[48]

As mentioned above, MII includes levamisole, TET and BCG-PSN. Levamisole has a preferential effect on interactions between suppressor T cells and helper T cells,[49] being used for the treatment of psoriasis.[50] Thymosin increases the T cell lymphokine receptors and enhances lymphocyte responses,[51] while BCG-PSN can reduce Th17 cell subsets and Th17 associated cytokines.[52] Th1/Th17 dominant differentiation and Treg weak differentiation are the main imbalance manifestation of T cell differentiation in psoriasis.[4–7] MII distinctly corrected the imbalance of T cells subsets and cytokines in psoriasis, therapy improved psoriasis ultimately. The treated mechanism of MII treatment was distinct from that of NB-UVB and acitretin, explaining its characteristic lesion regression. The exact mechanism of MII in the treatment of psoriasis should be further studied in future.

Conclusion

MII treatment is a complementary effective and safe method of psoriasis, can be used as the preferred treatment for appropriate psoriasis patients.

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Griffiths CEM, Armstrong AW, Gudjonsson JE, Barker JNWN. Psoriasis. *Lancet*. 2021;397(10281):1301–1315. doi:10.1016/S0140-6736(20)32549-6
2. Feldman SR. Psoriasis causes as much disability as other major medical diseases. *J Am Acad Dermatol*. 2020;82(1):256–257. doi:10.1016/j.jaad.2018.07.059
3. Boehncke WH, Schön MP. Psoriasis. *Lancet*. 2015;386(9997):983–994. doi:10.1016/S0140-6736(14)61909-7
4. Kryczek I, Wei S, Gong W, et al. Cutting edge: IFN-gamma enables APC to promote memory Th17 and abate Th1 cell development. *J Immunol*. 2008;181(9):5842–5846. doi:10.4049/jimmunol.181.9.5842
5. Lynde CW, Poulin Y, Vender R, et al. Interleukin 17A: toward a new understanding of psoriasis pathogenesis. *J Am Acad Dermatol*. 2014;71(1):141–150. doi:10.1016/j.jaad.2013.12.036
6. Karamehic J, Zecevic L, Resic H, et al. Immunophenotype lymphocyte of peripheral blood in patients with psoriasis. *Med Arch*. 2014;68(4):236–238. doi:10.5455/medarh.2014.68.236-238
7. Sugiyama H, Gyulai R, Toichi E, et al. Dysfunctional blood and target tissue CD4+CD25high regulatory T cells in psoriasis: mechanism underlying unrestrained pathogenic effector T cell proliferation. *J Immunol*. 2005;174(1):164–173. doi:10.4049/jimmunol.174.1.164
8. Nast A, Jacobs A, Rosumeck S, et al. Efficacy and safety of systemic long-term treatments for moderate-to-severe psoriasis: a systematic review and meta-analysis. *J Invest Dermatol*. 2015;135(11):2641–2648. doi:10.1038/jid.2015.206
9. Reich K, Burden AD, Eaton JN, et al. Efficacy of biologics in the treatment of moderate to severe psoriasis: a network meta-analysis of randomized controlled trials. *Br J Dermatol*. 2012;166(1):179–188. doi:10.1111/j.1365-2133.2011.10583.x
10. Warren RB, Smith CH, Yiu ZZN, et al. Differential drug survival of biologic therapies for the treatment of psoriasis: a prospective observational cohort study from the British Association of Dermatologists Biologic Interventions Register (BADBIR). *J Invest Dermatol*. 2015;135(11):2632–2640. doi:10.1038/jid.2015.208
11. Weatherhead SC, Farr PM, Jamieson D, et al. Keratinocyte apoptosis in epidermal remodeling and clearance of psoriasis induced by UV radiation. *J Invest Dermatol*. 2011;131(9):1916–1926. doi:10.1038/jid.2011.134
12. Vacharanukrauh P, Meephansan J, Tangtanatakul P, et al. High-throughput RNA sequencing reveals the effect of NB-UVB phototherapy on major inflammatory molecules of lesional psoriasis. *Psoriasis*. 2021;11:133–149. doi:10.2147/PTT.S335913
13. Johnson-Huang LM, Suárez-Fariñas M, Sullivan-Whalen M, et al. Effective narrow-band UVB radiation therapy suppresses the IL-23/IL-17 axis in normalized psoriasis plaques. *J Invest Dermatol*. 2010;130(11):2654–2663. doi:10.1038/jid.2010.166
14. Bovenschen HJ, van de Kerkhof PC, van Erp PE, et al. Foxp3+ regulatory T cells of psoriasis patients easily differentiate into IL-17A-producing cells and are found in lesional skin. *J Invest Dermatol*. 2011;131(9):1853–1860. doi:10.1038/jid.2011.139
15. Chen L, Li J, Yao Y, et al. Circulating microRNA profile unveils mechanisms of action of Acitretin for psoriasis vulgaris. *Bioengineered*. 2021;12(1):1838–1850. doi:10.1080/21655979.2021.1925205
16. Bécherel PA, Mossalayi MD, LeGoff L, et al. Mechanism of anti-inflammatory action of retinoids on keratinocytes. *Lancet*. 1994;344(8936):1570–1571. doi:10.1016/s0140-6736(94)90377-8

17. Imcke E, Ruszczak Z, Mayer-da Silva A, et al. Cultivation of human dermal microvascular endothelial cells in vitro: immunocytochemical and ultrastructural characterization and effect of treatment with three synthetic retinoids. *Arch Dermatol Res*. 1991;283(3):149–157. doi:10.1007/BF00372054
18. Bauer R, Schütz R, Orfanos CE. Impaired motility and random migration of vital polymorphonuclears in vitro after therapy with oral aromatic retinoid in psoriasis. *Int J Dermatol*. 1984;23(1):72–77. doi:10.1111/j.1365-4362
19. Armstrong AW, Robertson AD, Wu J, Schupp C, Lebwohl MG. Undertreatment, treatment trends, and treatment dissatisfaction among patients with psoriasis and psoriatic arthritis in the United States: findings from the National Psoriasis Foundation surveys, 2003–2011. *JAMA Dermatol*. 2013;149(10):1180–1185. doi:10.1001/jamadermatol.2013.5264
20. Newman DJ, Cragg GM. Natural products as sources of new drugs over the last 25 years. *J Nat Prod*. 2007;70(3):461–477. doi:10.1021/np068054v
21. Wu JN. A short history of acupuncture. *J Altern Complement Med*. 1996;2(1):19–21. doi:10.1089/acm.1996.2.19
22. Barnes PM, Bloom B, Nahin RL. Complementary and alternative medicine use among adults and children: United States, 2007. *Natl Health Stat Rep*. 2008;2008(12):1–23.
23. Zou JH, Gong LP, Huang G, et al. Meta-analysis of therapeutic effect of acupuncture and moxibustion on psoriasis vulgaris (in Chinese). *Hunan J Tradit Chin Med*. 2020;36(12):127–130.
24. Zhou QY, Li GF. Clinical analysis of narrow-band UVB combined with acupuncture in the treatment of psoriasis vulgaris at rest (in Chinese). *J Med Theory Pract*. 2022;35(23):4036–4038.
25. Xiao X, Yang SQ. Efficacy observation of fire-needle surrounding acupuncture method for plaque psoriasis and its effects on inflammatory factors (in Chinese). *Shanghai J Acupuncture Moxibustion*. 2022;41(1):65–70.
26. Xiao X, Yang SQ. Therapeutic effect of plaque psoriasis by fire acupuncture based on theory of midnight-noon ebb-flow (in Chinese). *J Hainan Med Univ*. 2022;28(17):1313–1319.
27. Gamret AC, Price A, Fertig RM, Lev-Tov H, Nichols AJ. Complementary and alternative medicine therapies for psoriasis: a systematic review. *JAMA Dermatol*. 2018;154(11):1330–1337. doi:10.1001/jamadermatol.2018.2972
28. Yeh ML, Ko SH, Wang MH, Chi CC, Chung YC. Acupuncture-related techniques for psoriasis: a systematic review with pairwise and network meta-analyses of randomized controlled trials. *J Altern Complement Med*. 2017;23(12):930–940. doi:10.1089/acm.2016.0158
29. Fan X, Yang S, Sun LD, et al. Comparison of clinical features of HLA-Cw*0602-positive and -negative psoriasis patients in a Han Chinese population. *Acta Derm Venereol*. 2007;87(4):335–340. doi:10.2340/00015555-0253
30. Li J, Hou R, Yang Y, et al. Narrowband ultraviolet B interferes with gene expression in the peripheral blood T cells of patients with psoriasis. *Dermatology*. 2013;226(2):128–137. doi:10.1159/000346937
31. Li J, Li X, He F, et al. Cross-sectional study reveals that HLA-C*07:02 is a potential biomarker of early onset/lesion severity of psoriasis. *Exp Dermatol*. 2020;29(7):639–646. doi:10.1111/exd.14127
32. Bolotin DA, Poslavsky S, Mitrophanov I, et al. MiXCR: software for comprehensive adaptive immunity profiling. *Nat Methods*. 2015;12(5):380–381. doi:10.1038/nmeth.3364
33. Ivanov II, McKenzie BS, Zhou L, et al. The orphan nuclear receptor RORgammat directs the differentiation program of proinflammatory IL-17+ T helper cells. *Cell*. 2006;126(6):1121–1133. doi:10.1016/j.cell.2006.07.035
34. Szabo SJ, Kim ST, Costa GL, et al. A novel transcription factor, T-bet, directs Th1 lineage commitment. *Cell*. 2000;100(6):655–669. doi:10.1016/s0092-8674(00)80702-3
35. Zheng W, Flavell RA. The transcription factor GATA-3 is necessary and sufficient for Th2 cytokine gene expression in CD4 T cells. *Cell*. 1997;89(4):587–596. doi:10.1016/s0092-8674(00)80240-8
36. Ho IC, Pai SY. GATA-3 - not just for Th2 cells anymore. *Cell Mol Immunol*. 2007;4(1):15–29.
37. Li J, Xing J, Lu F, et al. Psoriatic dermal-derived mesenchymal stem cells reduce keratinocyte junctions, and increase glycolysis. *Acta Derm Venereol*. 2020;100(8):adv00122. doi:10.2340/00015555-3480
38. Schön MP, Boehncke WH. Psoriasis. *N Engl J Med*. 2005;352(18):1899–1912. doi:10.1056/NEJMra041320
39. Lebwohl M, Ting PT, Koo JY. Psoriasis treatment: traditional therapy. *Ann Rheum Dis*. 2005;64(Suppl 2):ii83–ii86. doi:10.1136/ard.2004.030791
40. Bao LL, Yang XH. The progress of acupuncture on treating psoriasis. *Yunnan Chin Med*. 2010;31:69–71.
41. Chen RM, Shi GA, Xiong YQ, et al. Fire acupuncture for plaque psoriasis case series. *Medicine*. 2024;103(16):e37848. doi:10.1097/MD.0000000000037848
42. Wu SY. The clinical observation on the therapy of acupuncture combining with narrow-band ultraviolet B for psoriasis arthritis. *Chin J Conval Med*. 2011;20:596–597.
43. Chen YL, Lin YY, Chen SS, et al. Multicenter observation of curative effects of self-blood point injection on treating unusual type psoriasis and effects on IL-8 and TNF-a in peripheral blood. *J Gansu Coll TCM*. 2011;28:48–50.
44. Wang Y, Hou XR, Li LH, et al. Acupoint injection improves allergic rhinitis by balancing Th17/Treg in allergic rhinitis rats. *Zhen Ci Yan Jiu*. 2019;44(4):276–281. Chinese. doi:10.13702/j.1000-0607.180695
45. Zeng ZW, Huang JQ, Chen Y, et al. Acupoint autohemotherapy attenuates atopic dermatitis lesions by regulating Th1/Th2 balance in DNCB-induced BALB/c mice. *Chin J Integr Med*. 2022;28(7):612–619. doi:10.1007/s11655-022-3579-7
46. Li Y, Du YH. The evaluation of acupuncture on treating psoriasis in recent 5 years. *J Shaanxi Coll Trad Chin Med*. 2009;32:56–59.
47. Liang JT, Xia HM, Liao FZ. The discussion on mechanism of acupuncture on treating psoriasis. *J Sichuan Trad Chin Med*. 2007;25:97–99.
48. Xiang Y, Wu X, Lu C, Wang K. An overview of acupuncture for psoriasis vulgaris, 2009–2014. *J DermatolTreat*. 2017;28(3):221–228. doi:10.1080/09546634.2016.1224801
49. Assem ESK. *Textbook of Immunopharmacology*. Dale MM, Foreman JC, editors. London: Blackwell Science Publications; 1984:333–339.
50. Liapon AO, Rutshteĭn LG, Roĭtburd MF, et al. Levamizol (dekaris) v kompleksnom lechenii razlichnykh klinicheskikh form psoriaza. *Vestn Dermatol Venerol*. 1984;1984(4):61–66.
51. Garaci E, Mastino A, Pica F, et al. Combination treatment using thymosin alpha 1 and interferon after cyclophosphamide is able to cure Lewis lung carcinoma in mice. *Cancer Immunol Immunother*. 1990;32(3):154–160. doi:10.1007/BF01771450
52. Zhan L, Xiong X, Wang L. Treatment of BCG polysaccharide nucleic acid combined with CO2 laser reduces Th17 cells and their related cytokines in cutaneous lesion of vitiligo patients. *Xi Bao Yu Fen Zi Mian Yi Xue Za Zhi*. 2014;30(12):1300–1303. Chinese.