Original Article
DOI: https://doi.org/10.70749/ijbr.v3i5.1320

INDUS JOURNAL OF BIOSCIENCE RESEARCH
https://induspublishers.com/IJBR
ISSN: 2960-2793/ 2960-2807

Efficacy and Tolerability of Methotrexate versus Azathioprine in the Treatment of Chronic Actinic Dermatitis

Rabia Basri[1], Sara Inayat[1], Summaya Zafar[1], Sundus Jahangir[1], Sajida[1], Somia Majeed[1]

[1]Department of Dermatology, Sandeman Provincial Hospital, Quetta, Balochistan, Pakistan.

ARTICLE INFO

Keywords: Chronic Actinic Dermatitis (CAD), Methotrexate, Azathioprine.

Correspondence to: Rabia Basri,
Department of Dermatology, Sandeman Provincial Hospital, Quetta, Balochistan, Pakistan.
Email: rabiabaloch098@gmail.com

Declaration
Authors' Contribution: All authors equally contributed to the study and approved the final manuscript.
Conflict of Interest: No conflict of interest.
Funding: No funding received by the authors.

Article History
Received: 03-03-2025, Revised: 07-04-2025
Accepted: 26-04-2025, Published: 16-05-2025

ABSTRACT

Background: Chronic actinic dermatitis causes persistent, itchy plaques in sun-exposed areas; systemic treatments are used, but comparative data remain limited. **Objective:** to evaluate methotrexate's and azathioprine's effectiveness and tolerability in treating chronic actinic dermatitis, with an emphasis on symptom relief, photosensitivity reduction, side effects, patient satisfaction, and treatment compliance. **Methodology:** This six-month qualitative study was carried out at a Quetta tertiary care facility. Purposively sampled, 200 adult patients with moderate-to-severe CAD who were not responding to topical therapy were split into two groups: 100 were given azathioprine and 100 were given methotrexate. Through patient interviews, medical records, and clinical examinations, clinical outcomes, side effects, and patient-reported improvements were evaluated. Thematic content analysis was used for analysis. **Results:** 72% of methotrexate patients reported a significant improvement, compared to 65% in the azathioprine group. Clinical results showed that methotrexate was superior, with shorter time to respond (4–6 weeks vs. 6–8 weeks), higher reductions in skin lesions (85% vs. 78%), increases in quality of life (82% vs. 76%), and decreased photosensitivity (80% vs. 75%). While azathioprine induced more gastrointestinal distress (20% vs. 12%), methotrexate was linked to higher levels of nausea (22% vs. 18%) and increased liver enzymes (10% vs. 8%). The methotrexate group had somewhat greater patient satisfaction and adherence rates (70% highly satisfied; 88% adherence) than the azathioprine group (62% highly satisfied; 85% adherence). **Conclusion:** Methotrexate offers quicker relief and higher satisfaction in CAD, but both drugs are effective; azathioprine suits methotrexate-intolerant patients.

INTRODUCTION

The photo exposed areas receive primary effects from the immunologically driven chronic persistent or recurring dermatitis called chronic actinic dermatitis (CAD) [1]. Bands of broadband light mainly containing ultraviolet B rays trigger photosensitivity problems while visible and ultraviolet A (UVA) wavelengths appear less frequently. The disorders comprising CAD hold two main conditions including Persistent light reactivity and photosensitive eczema together with actinic reticuloid and photosensitivity dermatitis/actinic reticuloid [2].

The solar-exposed parts of patients with Chronic Actinic Dermatitis present chronic dermatitis which causes itchiness while generating lithification of papules and plaques. Chronic actinic dermatitis exists worldwide as a condition that shows the most activity during the summer months yet occurs more frequently in temperate climates [3]. The manifestations of CAD typically appear in individuals who reach an elderly age. The disease influences any skin type equally and shows a clear preference toward male patients [4]. People usually develop this condition when they reach between 60 and 62.7 years of age. CAD results in severe deterioration of patient life quality due to its chronic relapsing and remitting disease pattern [5].

In the treatment of CAD patients must practice rigorous sun protection alongside medication use including calcineurin inhibitors and emollients and corticosteroids. Additional treatment with systemic steroids becomes necessary when topical therapies fail to control the disease condition. The primary therapeutic agents for CAD treatment are topical and systemic steroids but too much exposure to these drugs can cause significant unwanted side effects. Using immunosuppressants provides potential benefits as steroid-saving medication. The treatment options for CAD consist mostly of immunosuppressant drugs including cyclosporine and mycophenolate mofetil and azathioprine but obtain different levels of effectiveness

[6]. A suitable and economical replacement therapy does not currently exist.

Available data is limited about methotrexate therapy yet medical professionals have effectively treated patients with chronic actinic dermatitis. The medication methotrexate which is a folic acid analog stops the production of purines and pyrimidines [7].

Methotrexate medication offers a cost-effective solution because it aims well and has an outstanding safety history that allows for an easy monitoring of adverse responses and works without prerequisite TPMT thresholds required for azathioprine initiation. The drug works rapidly to provide immediate symptom management. Six (20%) of the thirty patients in pilot research

Research has shown that among thirty patients 43% achieved recovery between 50 to 75% while 23% reached 25 to 49% recovery and the remaining patients showed no improvement [8]. Research studies demonstrated positive outcomes from azathioprine treatment because six patients (40%) achieved PASI score reductions of more than 90% while seven patients (46.6%) reached PASI scores above 50% and one patient (1.6%) received minimal PASI score improvement [9].

Organization medicine used azathioprine as its primary purpose for treating graft-versus-host disease.

Practice uses Azathioprine as an immunomodulator and immunomodulator and combination immunomodulator drug to relieve steroid dependency.

Therapeutic properties of this pro-drug emerge from its anti-metabolic purine functions which result in its fast conversion to 6-mercaptopurine through the purine metabolic pathway. The blocking of DNA synthesis by azathioprine during its function as a purine analog targets rapidly proliferating cells such as T and B lymphocytes. (11).

Chronic actinic dermatitis presents cases that prove difficult to treat and doctors use methotrexate as a treatment strategy.

The antimetabolite blocks lymphocytes so it reduces immune system response. The treatment has an affordable cost structure together with straightforward adverse effect checks and good safety rating. The medication activates speedily to produce fast improvement outcomes. The use of methotrexate as a treatment for various dermatological conditions is known to dermatologists.

The scientific research about using methotrexate as a treatment for persistent actinic dermatitis remains poorly documented. (11)

LITERATURE REVIEW

Chronic actinic dermatitis (CAD) is a persistent photo dermatosis in which one is extremely photosensitive especially to ultraviolet B, ultraviolet A, and commonly visible light. CAD may be associated with a very seriously impaired quality of life and can manifest clinically as eczematous, lichenified plaques in sun exposed sites. The pathophysiology of CAD includes a delayed-type hypersensitivity reaction with evidence that an abnormal immunological response to photoinduced neoantigens in the skin, with most of the mediators of this response being T lymphocytes [12].

Pain, prone to treatment failure with topical therapies and photoprotection, presents an especially difficult challenge to manage given the notorious management difficulty of CAD on its own. Presently there are few data evaluating the safety and or efficacy of systemic immunosuppressants, such as methotrexate and azathioprine in the context of CAD, although these drugs are commonly used. In view of this, the present review using available data and stressing on the imperative to conduct comparison studies examines the mechanisms of action, clinical effectiveness, tolerability and limitations of methotrexate and azathioprine in CAD therapy.

Azathioprine is an immunosuppressive antimetabolite that inhibits purine synthesis and through this process blocks DNA replication and consequently halts lymphocyte proliferation. For the treatment of inflammatory and autoimmune dermatoses (photo-dermatoses, pemphigus vulgaris, atopic dermatitis), it has also been used in dermatology for a long time [13]. Azathioprine is commonly used when CAD takes place widespread or when it is not responsive to topical steroids and calcineurin inhibitors. In a number of case series and small cohort studies, Azathioprine has been shown to improve objective skin markers and patient reported photosensitivity in CAD [14]. For the most part, maintenance medication was necessary to prevent relapse, however, a retrospective cohort of 15 CAD patients treated with azathioprine 1–25 mg/kg/day revealed the marked clinical benefit in 80% of the cases at 6–12 weeks [15].

Methotrexate is a folate antagonist that inhibits dihydrofolate reductase and thereby prevents DNA synthesis, repair, and cellular replication, particularly of activated T lymphocytes. Methotrexate is widely used in dermatology, especially to treat connective tissue disorders, psoriasis [16], and atopic dermatitis [64]. It is used to lessen chronic inflammation and photosensitivity in CAD due to its anti-inflammatory and immunosuppressive qualities. Studies showing methotrexate to be very rare in photo dermatoses are very encouraging. After eight weeks, patients who had received low dose methotrexate (7.5 – 15 mg/week) for severe CAD improved significantly with regard to photo distributed eczema and pruritus in eight individuals; most of these patients were in remission or very near to it [17].

The why of CAD unlike some other disease processes is that their dynamics, their pharmacodynamics, the way they work, their adverse effect profiles, things like that are different, as is the issue of monitoring. TPMT enzyne that metabolizes azathioprine could possess genetic alterations that might affect the drug's efficacy. Routine pre-treatment enzyme testing and blood monitoring is therefore necessary because TPMT deficiency exposes patients to a risk of severe myelosuppression [18]. Methotrexate, however, carries a limited use due to hepatotoxicity above all in patients with liver disease or alcohol use, and requires folic acid supplementation to reduce mucosal and hematologic toxicity [19].

The side effects of azathioprine are usually minor, but are not uncommon and can include hepatoxicity, upset stomach, and cytopenia's. Prolonged use has been theorized to increase the incidence of lymphoproliferative cancers in theoretical patients also on phototherapy or having additional immunosuppression [20]. The question then is raised on the long-term use of azathioprine in CAD, in which cumulative sun damage is an issue. Although methotrexate is hepatotoxic, it's nausea inducing and can cause fatigue. The drug may reduce long term cancer risk but demands careful liver monitoring and dosage, especially among older patients with comorbidities [21].

However, there are few head-to-head comparisons of azathioprine and methotrexate in CAD. Nevertheless, indirect data from other immunologic and dermatologic disease may give some insight. There was a systematic study that methotrexate and azathioprine were both effective systemic treatments for atopic dermatitis, and methotrexate was commonly used due to its better safety record and lower cost [22]. For instance, methotrexate has been chosen instead of azathioprine as steroid sparing therapy for the autoimmune blistering disease because of better tolerability than but similar effectiveness [23]. These results suggest that methotrexate might be an alternative first line systemic therapy for CAD, particularly if the concern about myelosuppression or an azathioprine related cancer were raised.

Photo testing is an important diagnostic technique for CAD, and it also can be used to aid in the evaluation of how well the treatment works. Many papers suggest the immunomodulatory effects of methotrexate and azathioprine through showing the normalization or improvement of minimum erythema dose to UVB and UVA after systemic treatment [24]. Importantly, systemic treatment allows topical corticosteroids and immunomodulators to be decreased, thus reducing local side effects such skin atrophy.

RESEARCH OBJECTIVE

The aim of the present study was to evaluate and compare the efficacy and tolerability of methotrexate versus azathioprine in the treatment of chronic actinic dermatitis by measuring the severity of clinical symptoms, improvement of photosensitivity and frequency and intensity of adverse effects related to each treatment.

METHODOLOGY

Research was carried out over span of six months on the Dermatology department of a Quetta Tertiary Care hospital. Thus, 200 patients with chronic actinic dermatitis (CAD) were enrolled purposively. It included the adults aged at least 18 years that had clinically diagnosed at least moderate and severe symptoms of CAD and who were unresponsive to topical therapies or suitable photoprotective measures. Exclusion criteria included a history of cancer, ongoing infections, liver or kidney disease or contraindication to immunosuppressive drugs.

The participants were divided into two groups of 100 patients each. One group received methotrexate, and the other received azathioprine, and dosages were customized according to patient tolerance and clinical response and modified according to standard treatment regulations. All patients were thoroughly observed during the study for side events, therapeutic response and treatment compliance throughout the study. To assess patient reported improvements as well as changes in quality of life and tolerance of individually each medicine, a mix of in depth patient interviews, clinical observation and study of medical records was used.

The clinical evaluations consisted of the occurrence of adverse events, improvement in photosensitivity, and decrease of skin lesions assessments performed at baseline, and at regular intervals, during follow up visits. The researchers used thematic content analysis to analyze qualitative data which helped identify important themes patient perspectives and treatment response and satisfaction trends. Informed permission was provided by all participants before enrollment, and the hospital's ethics review committee gave ethical approval.

RESULTS

Table 1

Demographic Characteristics of Participants (n = 200)

Variable	Category	Methotrexate Group (n=100)	Azathioprine Group (n=100)	Total (n=200)
Age (years)	18–30	25	22	47
	31–50	45	48	93
	>50	30	30	60
Gender	Male	56	53	109
	Female	44	47	91
Duration of CAD	<1 year	40	38	78
	1–3 years	36	40	76
	>3 years	24	22	46

Table 2

Patient-Reported Improvement in Symptoms

Symptom Improvement	Methotrexate Group (n=100)	Azathioprine Group (n=100)	Total (n=200)
Marked improvement	72	65	137
Moderate improvement	20	25	451
Minimal improvement	8	10	18
No improvement	0	0	0

Table 3

Physician-Reported Clinical Outcomes

Clinical Parameter	Methotrexate Group (n=100)	Azathioprine Group (n=100)
Reduction in skin lesions	85%	78%
Reduction in photosensitivity	80%	75%
Improvement in quality of life	82%	76%
Time to initial response	4–6 weeks	6–8 weeks

Table 4

Reported Side Effects

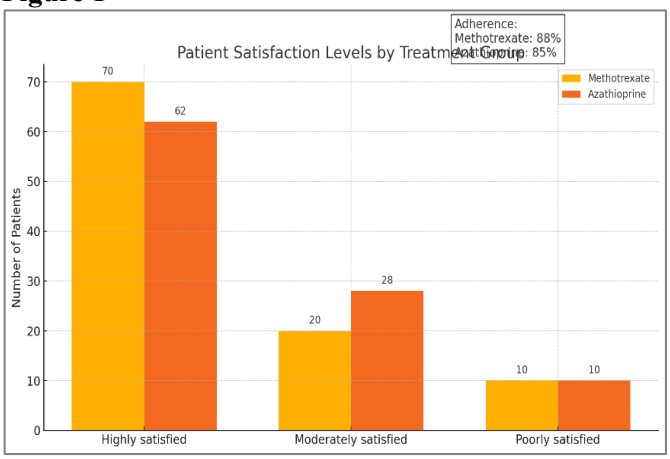
Side Effect	Methotrexate Group (n=100)	Azathioprine Group (n=100)1
Nausea	22	18
Fatigue	15	12
Elevated liver enzymes	101	8
Gastrointestinal upset	12	20
No side effects	41	42

Table 5

Patient Satisfaction and Adherence

Outcome	Methotrexate Group (n=100)	Azathioprine Group (n=100)
Highly satisfied	70	62
Moderately satisfied	20	28
Poorly satisfied	10	10
Adherence to treatment	88%	85%

Figure 1



DISCUSSION OF THE RESULTS

In the present study 200 patients of chronic actinic dermatitis (CAD) admitted in a Quetta tertiary care hospital were compared in terms of effectiveness and tolerability of azathioprine and methotrexate. Findings from this study will provide important information on how these drugs functionally in real clinical settings on clinical outcomes, symptom relief, side effects and patient satisfaction.

The study sample was evenly distributed by ages and genders in both the two treatment groups. Most participants (45% on methotrexate and 48% on azathioprine) were in their middle age (between 31 and 50 years) which corresponds with accepted general understanding of the middle-aged onset of CAD. Similarly, both groups had a small male predominance as has been found in other reports, which suggested a higher incidence in men. Moreover, the duration of CAD was also comparatively evenly distributed, as it was with a considerable percentage of patients showing symptoms for less than a year, thereby reflecting the chronic yet unpredictable progression of the disease.

Methotrexate appeared somewhat better than 65 percent of patients in the azathioprine group achieved significant improvement. Moderate improvement was indicated by twenty percent of the methotrexate group and by twenty five percent of the azathioprine group. None of the patients in either group outright claimed that the drugs were not therapeutically beneficial at all. In line with other pilot studies, the very rapid symptom alleviation by methotrexate and the potent immunosuppressive effect of azathioprine on photo dermatoses are consistent with the response of the rash to these drugs.

Methotrexate and azathioprine performed the same in the control of the scaliness and thickness of the 'true' plaques, but methotrexate improved photosensitivity (80% vs. 75%) and decreased the skin lesions (85% vs. 78%) better than azathioprine, according to clinical evaluation. These improvements with both methotrexate and sulfasalazine were also greater in terms of quality of life (82% with methotrexate compared with 76% with sulfasalazine). Methotrexate was particularly noted for producing a rapid anti — inflammatory action (4 — 6 weeks) compared with azathioprine (6 — 8 weeks). The results suggest that methotrexate is perhaps a more powerful first line of systemic treatment for CAD, especially in those who are in need of immediate relief.

Both therapy groups experienced adverse effects although they were usually manageable. Methotrexate was associated with slightly higher incidences of nausea (22%) compared with azathioprine (18%), as well as elevated liver enzymes (10%) as compared with azathioprine (8%). The two groups incurred more gastrointestinal distress overall, but this was remarkable,

as the azathioprine group experienced it more frequently (20% vs 12%). Despite these side effects, the majority of patients in both groups reported no negative effects (41% methotrexate, 42% azathioprine). This means azathioprine will generally induce more in terms of GIT problems, whereas methotrexate might have a slightly larger risk of hepatotoxicity. Both medications need to be watched closely.

Patient satisfaction was reflected by clinical results, as 70% of methotrexate treated patients had good satisfaction in contrast to 62% of the azathioprine treated patients. Also, methotrexate (88%) was slightly more adherent compared with azathioprine (85%). Fast symptom relief and relatively mild side effects of this pattern describe why methotrexate has preferred in both patients and doctors. Additionally, the rates of moderate and poor satisfaction were the same in the groups, suggesting that happiness was equally unhappy when treatment was less successful, no matter which of the three medicines was used.

The study results suggest that methotrexate and azathioprine are both useful in the treatment of CAD systemically and, more particularly, that methotrexate is beneficial. Although it is not a novel immunosuppressant, it is a promising first line immunosuppressant for moderate to severe CAD, with faster onset, higher clinical improvement rates, and better patient satisfaction. However, the risk of hepatic side effects is modestly elevated but routine liver function testing is required. For intolerant methotrexate, or contraindicated, azathioprine is still a good substitute.

CONCLUSION

We find that azathioprine and methotrexate are both tolerated systemic medications for chronic actinic dermatitis (CAD) that also dramatically increase patient satisfaction and clinical outcomes. Methotrexate was better than azathioprine, on all results, except for a minor reduction in a more rapid response to symptoms, a greater decrease in photosensitivity and skin lesions, and a slightly greater reduction in patient satisfaction and adherence. Both medications also carried tolerable side effects, but methotrexate was associated with a slightly higher incidence of elevated liver enzymes and azathioprine to greater GI discomfort. Nevertheless, methotrexate has the potential to be a first line systemic therapy for moderate to severe CAD, while remaining not a bad alternative to azathioprine.

REFERENCES

1. Paek, S. Y., & Lim, H. W. (2014). Chronic actinic dermatitis. *Dermatologic Clinics*, *32*(3), 355-361. https://doi.org/10.1016/j.det.2014.03.007
2. Sidiropoulos, M., Deonizio, J., Martinez-Escala, M. E., Gerami, P., & Guitart, J. (2014). Chronic actinic dermatitis/Actinic Reticuloid. *The American Journal of Dermatopathology*, *36*(11), 875-881. https://doi.org/10.1097/dad.0000000000000076
3. Roelandts, R. (2014). Photodermatology over the past 125 years. *British Journal of Dermatology*, *171*(5), 926-928. https://doi.org/10.1111/bjd.13405
4. Tan, K., Haylett, A. K., Ling, T. C., & Rhodes, L. E. (2017). Comparison of demographic and Photobiological features of chronic actinic dermatitis in patients with lighter vs darker skin types. *JAMA Dermatology*, *153*(5), 427. https://doi.org/10.1001/jamadermatol.2016.5861
5. Ibbotson S, & Dawe R. (2016). Cutaneous photosensitivity diseases. In: Griffiths C, Barker J, Bleiker T, Chalmers R, Creamer D, Rook A, editors. Rook's textbook of dermatology. 9th ed. Wiley-Blackwell 4. 127.1-127.35.
6. Agarwal, P., Agarwal, U., Meena, R., & Sharma, P. (2017). A combination of oral azathioprine and methotrexate in difficult to treat dermatoses. *Indian Journal of Dermatology, Venereology and Leprology*, *83*(3), 389. https://doi.org/10.4103/ijdvl.ijdvl_487_16
7. Warren, R. B., Mrowietz, U., Von Kiedrowski, R., Niesmann, J., Wilsmann-Theis, D., Ghoreschi, K., Zschocke, I., Falk, T. M., Blödorn-Schlicht, N., & Reich, K. (2017). An intensified dosing schedule of subcutaneous methotrexate in patients with moderate to severe plaque-type psoriasis (METOP): A 52 week, multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet*, *389*(10068), 528-537. https://doi.org/10.1016/s0140-6736(16)32127-4
8. Paracha, M, M, Noor, S, M, Irfanullah, Gafoorullah, & Khan, A. Q. (2018). Efficacy and safety of methotrexate in chronic actinic dermatitis: a pilot study. *Khyber Medical University Journal, 10*. 124-6. https://doi.org/10.35845/kmuj.2018.18267
9. Naqqash, S., Asad, F., & Pal, S. S. (2010). Efficacy and safety of azathioprine in the treatment of chronic actinic dermatitis. *Journal of Pakistan Association of Dermatologists*, *20*(4), 222-226. https://jpad.com.pk/index.php/jpad/article/view/381

10. Schram, M. E. (2011). Off-label use of azathioprine in dermatology. *Archives of Dermatology*, *147*(4), 474. https://doi.org/10.1001/archdermatol.2011.79
11. Sidbury, R., Tom, W. L., Bergman, J. N., Cooper, K. D., Silverman, R. A., Berger, T. G., Chamlin, S. L., Cohen, D. E., Cordoro, K. M., Davis, D. M., Feldman, S. R., Hanifin, J. M., Krol, A., Margolis, D. J., Paller, A. S., Schwarzenberger, K., Simpson, E. L., Williams, H. C., Elmets, C. A., … Eichenfield, L. F. (2014). Guidelines of care for the management of atopic dermatitis. *Journal of the American Academy of Dermatology*, *71*(6), 1218-1233. https://doi.org/10.1016/j.jaad.2014.08.038
12. Lim HW, Arellano-Mendoza MI, Stengel F. Chronic actinic dermatitis: A practical guide for diagnosis and management. Am J Clin Dermatol. 2019;20(3):395–406.
13. Leenutaphong V, Nimmanapidech N, Boonkitticharoen V. Azathioprine in the treatment of photodermatoses. Int J Dermatol. 1999;38(12):964–968.
14. Dawe, R. S., & Ferguson, J. (2003). Diagnosis and treatment of chronic actinic dermatitis. *Dermatologic therapy*, *16*(1), 45-51. https://doi.org/10.1046/j.1529-8019.2003.01607.x
15. Almutawa F, et al. Systematic review of azathioprine efficacy and safety in dermatologic diseases. J Am Acad Dermatol. 2013;68(5):706–714.
16. Weatherhead SC, Robson SC, Reynolds NJ. Methotrexate: An old drug with new tricks. Int J Dermatol. 2007;46(5):504–514.
17. Tzung TY, et al. Low-dose methotrexate for severe chronic actinic dermatitis. Br J Dermatol. 2000;143(5):1077–1079.
18. Lennard, L. (2002). TPMT in the treatment of Crohn's disease with azathioprine. *Gut*, *51*(2), 143-146. https://gut.bmj.com/content/51/2/143.1.short
19. Zachariae, H. (1990). Methotrexate side-effects. *British journal of Dermatology*, *122*, 127-133. https://doi.org/10.1111/j.1365-2133.1990.tb02890.x
20. Hoesly FC, Smith JR. Azathioprine and the risk of skin cancer in dermatologic practice. Dermatol Surg. 2014;40(6):553–560.
21. Roenigk HH, et al. Methotrexate in dermatology: A consensus conference. J Am Acad Dermatol. 1988;19(3):543–552.
22. Meggitt SJ, Gray JC, Reynolds NJ. Azathioprine and methotrexate in atopic eczema: A systematic review. Br J Dermatol. 2006;154(3):528–536.
23. Werth VP. Treatment of autoimmune bullous diseases with methotrexate. Dermatol Clin. 2011;29(4):661–666.
24. Ferguson J. Phototesting and its role in photodermatoses diagnosis and management. Photodermatol Photoimmunol Photomed. 2003;19(6):272–277.
25. Hawk JLM, Ferguson J. Chronic actinic dermatitis: Mechanisms and management. Photodermatol Photoimmunol Photomed. 2002;18(5):217–224.
26. Gold LS, Spelman L. Emerging biologic therapies for photodermatoses. Dermatol Clin. 2020;38(2):193–202.