www.jsstd.org

Journal of Skin and Sexually Transmitted Diseases

ScientificScholar®
Knowledge is power
Publisher of Scientific Journals

IADVL 1973
INDIAN ASSOCIATION OF DERMATOLOGISTS VENEREOLOGISTS & LEPROLOGISTS
IADVL KERALA

Symposium

Immune-enhancing agents in autoimmune skin diseases – A review

Abel Francis[1], Anjali Rose Jose[1]

[1]Department of Dermatology, Amala Institute of Medical Sciences, Thrissur, Kerala, India.

***Corresponding author:**
Abel Francis,
Department of Dermatology,
Amala Institute of Medical Sciences, Thrissur, Kerala, India.

abelfrancis2009@gmail.com

Received: 06 March 2021
Accepted: 24 April 2021
EPub Ahead of Print: 10 January 2022
Published: 09 April 2022

DOI
10.25259/JSSTD_19_2021

Quick Response Code:

ABSTRACT

Immunosuppressive drugs are the main stay of treatment for autoimmune dermatoses. The main disadvantage of these drugs is the increased susceptibility to life-threatening infections. Hence, in recent years, there has been an enthusiastic search for newer groups of drugs that can reduce this risk. Immune enhancing agents are considered as the key players of future. Immune enhancers function by activating various elements of the immune system and thereby amplifying the immune responses. They can be specific or non-specific in action. The main autoimmune dermatoses where the benefits of these drugs have so far been utilized include alopecia areata, vitiligo, psoriasis, lichen planus, and discoid lupus erythematosus. Immunostimulants are available in both topical and systemic forms. Topical immune- enhancing agents include contact sensitizers (diphenylcyclopropenone, dinitrochlorobenzene, and squaric acid dibutyl ester), anthralin, topical zinc, and interferons. Systemic agents include levamisole, zinc, probiotics, and so on. The exact mechanism of action of some of these drugs and other autoimmune conditions where they can be benefited is not completely understood. Another therapeutic agent that may come up in the future is individualized vaccines. Let us look forward to the days when individualized vaccines work wonders in the management of autoimmune diseases.

Keywords: Immune enhancers, Immunostimulants, Autoimmune diseases, Topical, Systemic

INTRODUCTION

The current gold standard of care in autoimmune diseases is immunosuppressive drugs that dampen the immune response and provide a therapeutic effect. However, these drugs place the patients at risk to its life-threatening side effects. Hence, there has been an increasing urge to search for newer therapies with lower risk of immunosuppression. This spotlighted the importance of immune enhancers that act by stimulating various elements of the immune system.[1] In this section, we are focusing on various topical and systemic immune-enhancing agents for the treatment of autoimmune skin diseases. We have tried to include the level of evidence [LOE – Table 1] for each modality of treatment.

TOPICAL IMMUNE-ENHANCING AGENTS FOR AUTOIMMUNE SKIN DISEASES

a. Contact sensitizers
   i. Dinitrochlorobenzene (DNCB)
   ii. Diphencyprone or diphenylcyclopropenone (DPCP)
   iii. Squaric acid dibutyl ester (SADBE).

Table 1: The levels of evidence in research.

Strength of recommendation	Level of evidence	Type of evidence
A	1 a	Systematic review of randomized controlled trials, meta-analysis
	1 b	Individual randomized controlled trial
B	2 a	Systematic review of cohort studies
	2 b	Individual cohort study (including low-quality randomized controlled trial)
	3 a	Systematic review of case–control studies
	3 b	Individual case–control study
C	4	Case series (and poor quality cohort and case–control studies)
D	5	Expert opinion

b. Anthralin (dithranol)
c. Topical zinc
d. Intralesional interferon.

CONTACT SENSITIZERS

The immunotherapeutic effectiveness of contact sensitizers is based on the principle of induction of allergic contact dermatitis in a previously unsensitized host and maintaining the dermatitis at the site of skin disease being treated.[2] These contact sensitizers act by antigenic competition that changes the milieu of immune cells.[3,4] The common contact sensitizers used are DNCB, DPCP, and SABDE.

DNCB

DNCB was the first contact sensitizer that was widely used in the treatment of alopecia areata (AA).[5] DNCB has also been successfully used in isolated cases of systemic lupus erythematosus (SLE).[6] However, later, it was found that this drug contains contaminants that were mutagenic and carcinogenic to animals, and when topically applied, more than 40% of the drug was absorbed into the system.[7] DNCB has now been replaced by other sensitizers such as DPCP and SADBE.

DPCP

Since 1980, DPCP has become the most widely used contact sensitizer. It was prepared from dibenzyl ketone, which was brominated and cyclized with a base, to yield DPCP.[8] This drug was initially accepted for the treatment of AA, later was also widely used for warts and melanoma. Recent reports support its use in vitiligo as well.[9]

Indications of DPCP in autoimmune diseases

AA – level of evidence (LOE) 2 b

In AA, the mechanism of action of DPCP is based on antigenic competition.[8] It is proposed that in DPCP treated patients, there is a change in the ratio of CD4+/CD8+T lymphocytes in the peribulbar region, that is, there is a decrease in ratio from 4:1 to 1:1.[4] DPCP is believed to exert it's immunomodulatory effect by decreasing abnormal expression of HLA-ABC and -DR antigens in the lower hair follicular epithelium and by impairing antigen presentation.[10] Studies showed a varying response rate to DPCP ranging from 60% in severe AA to about 88–100% in patients with patchy AA.[11] In a retrospective analysis by Wiseman *et al*., 77.9% of cases developed significant response (>75% terminal hair regrowth) at 32 months, with significant regrowth observed in 17.4% of cases of alopecia totalis and universalis, in 60.3% of cases of alopecia involving 75–99% scalp area, in 88% of cases with 50–74% involvement, and in 100% of cases with <50% involvement.[11] The data from a long-term follow-up study showed a median time of 30.7 months for relapse (defined as loss of >25% of regrown hair).[12]

In some patients, the castling phenomenon was reported, which was described as regrowth occurring at sites distant from the site of application, or a denser and faster growth observed over the untreated site.[8]

Method of application

The scalp is the usual site chosen for sensitization. The patient is first sensitized to 2% DPCP compounded in acetone, applied to an area of at least 4 cm^2. Then, DPCP is repeated weekly at increasing concentrations. The usual initial concentration of DPCP is 0.0001% which is increased in the subsequent weeks until the patient develops a desired mild, tolerable dermatitis (with pruritus and erythema) that lasts 36 hours. Once the effective concentration is determined, drug at that concentration should be applied on a weekly basis. Patients are advised to avoid washing the area and to protect it from sunlight for 48 hours.[4]

Method of tapering

The treatment has to be continued weekly until hair regrowth occurs which may take at least 12 weeks. Once almost full regrowth is established, the frequency can be gradually reduced using the rule of four, that is, treatment is given every other week for 4 weeks and then every 3rd week for 4 weeks. This tapering is continued until the patient experiences some hair loss and from this point onwards, the patient is started on maintenance therapy. The maintenance dose varies between individuals and usually ranges from biweekly to bimonthly treatments.[13] This maintenance has to be continued as long as patient requires it to remain in remission.

Special situations

Non-responders

If the patient does not respond by 52 weeks, it is unlikely that the patient may respond to DNCB after that. In this case, it is better to switch on to other treatment options.[13]

Slow growers

In these patients, the process of complete regrowth is gradual and lengthy.[13]

Initial non-responders

These patients may fail to respond to the treatment initially and, hence, discontinue the therapy. However, they may experience hair regrowth within 2 years of stopping treatment and they will give a good response once therapy is recommenced.[13]

AA in eyebrows

DPCP gives a good response on eyebrows. However, extreme caution must be taken while applying DPCP over eyebrows. The patient should be lying flat, with eyes shielded and the swab should be minimally moist.[13]

Vitiligo (LOE 4)

Aghaei and Ardekani reported marked improvement in 13 out of 19 vitiligo patients on treatment with DPCP.[9] In this study, primary sensitization was done with 2% solution of DPCP which was followed 2 weeks later by weekly applications of incremental concentrations of DPCP (between 0.001% and 2%). However, a few studies have reported vitiligo as a side effect after DPCP treatment for other conditions like AA.[14] Hence, the role of DPCP in vitiligo remains controversial.

DPCP in combination with other treatment modalities

Several studies have shown that DPCP, when used in combination with anthralin, is effective in the treatment of refractory AA.[15,16] However, the combination of DPCP with 5% minoxidil has not shown an improved response than DPCP alone.[17]

Children: DPCP is found safe in children.[18]

Adverse effects of DPCP

Reported adverse effects include regional lymphadenopathy, eczema at the treated site, the spread of contact eczema to distant sites, and impaired sleep.[2,19] The less common adverse effects are fever and chills, fainting spells, and flu-like symptoms. Rarely, contact leukoderma, erythema multiforme, urticaria, dyschromia confetti, and contact urticaria can occur.[2]

There are also reports of consort dermatitis to spouse/partner.[20] Shah *et al*. reported the risk of sensitization among medical and nursing staff.[21] Hence, adequate precautions (wearing a glove, face mask, and apron) should be taken while applying DPCP to avoid spillage of solution, as it may cause an irritant/urticarial reaction. However, most of the side effects of DPCP are reversible on discontinuation of therapy.

SADBE (LOE 2 b)

A strong sensitizer than DPCP, SADBE is found more effective in refractory AA. A recent study reported that unlike DPCP, an initial eczematous reaction to sensitization is not required for successful treatment with SADBE.[22] The mechanism of action of SADBE is similar to DPCP, however, Micali *et al*. reported that long-term treatment may lead to a non-specific suppression of delayed hypersensitivity reaction.[23]

SADBE in severe refractory AA

In cases where SADBE was used, the response rates varied from 49% for severe forms affecting more than 50% of the scalp to 80% in cases affecting less than 50% of the scalp.[23] The castling phenomenon similar to DPCP was observed with SADBE also.[24]

Method of application

The method of application of SADBE is similar to DPCP. The initial sensitization is done with 2% SADBE. Following this, applications are repeated weekly with increasing concentrations (0.00001–2%) until the patient develops minimal dermatitis and itching which persist for 2–3 days. Once the effective concentration is determined, it is applied every 1 or 2 weeks for 6 months. Hair regrowth is assessed 6 months after initiation of topical SADBE therapy.[25]

Children: Safe in children.[26]

Adverse effects

The adverse reactions are similar to DPCP. The studies reported persistent contact dermatitis at the site of application.[27] Another adverse effect reported was singular pigmentary metamorphosis, which was characterized by the patchy regrowth of terminal dark colored hair in two patients who initially had red and blonde colored hair respectively before the onset of disease. However, in these patients, perifollicular skin of scalp and hair over the rest of the body parts retained natural color.[27]

The response rates to both the DPCP and SADBE depend on the duration of disease, the extent of alopecia, and the age at onset of the disease.

ANTHRALIN (DITHRANOL)

Anthralin is another sensitizer that could be used in severe alopecia. Anthralin acts by producing a localized irritant dermatitis with resultant pruritus, erythema, and scaling. Another mechanism by which anthralin exerts its effect is by inhibiting keratinocyte proliferation, which makes it an effective antipsoriatic agent.[28]

Psoriasis (LOE 1b)

Anthralin is an effective treatment option for limited plaque psoriasis, scalp and nail psoriasis, juvenile psoriasis, and localized psoriasis in pregnancy.[28]

The Ingram regimen consisting of a coal tar bath and ultraviolet light exposure followed by treatment with anthralin in Lassar's paste was used to treat psoriatic plaques. Later, in 1985, modified Ingram regimen was developed to maximize the efficacy and patient compliance.[29] Since then, various regimens utilizing low concentrations of anthralin (0.01–0.05%) and anthralin in combination with topical steroids have been tried.

Short contact /Minutes dithranol therapy:

It involves the application of higher concentrations of anthralin to a desired area for a shorter period time. This has proven to be efficacious in psoriasis and alopecia. In psoriasis, anthralin concentration ranging from 0.1 to 2% is kept for a period of 20–60 minutes, with the usual initial contact time being 15–20 minutes.

Similarly, in AA, anthralin cream (0.5–1%) is applied to bald areas for about 20–30 minutes daily for 2 weeks. The concentration is gradually increased until the patients develop low-grade erythema and pruritus. The treatment is continued at the same dose (the dose at which low-grade erythema and pruritus appear) for another 3–6 months.

Frequency of application:

Various randomized control trials were done to optimize the frequency of short-course therapy. Based on these trials, it is recommended to use anthralin once in 24 hours, thrice weekly for optimal results.[28]

Children: Safety and efficacy in children are not established.

Side effects of anthralin:

The main problem with anthralin is staining. To overcome this, newer anthralin formulation - liposomal preparations (lipogrel) - has been developed.[30] Other side effects include lymphadenopathy and irritant dermatitis.[28,31]

AA (LOE 4)

In AA, anthralin is used either as a short contact or an overnight regimen in concentrations ranging from 0.25 to 3%. Lower concentrations (0.1–0.4%) are used in the overnight regimen, whereas short contact therapy is done with higher concentrations (1–3%).[28]

Response rates to anthralin in AA vary between 25% and 75%.[32] It could be used alone or in combination with other drugs such as DPCP, minoxidil, and calcipotriene.[15,30,33]

Ozdemir and Balevi found 1% anthralin to be a safe and effective option in treatment-resistant AA in children.[34]

TOPICAL ZINC (LOE 1 b)

The exact mechanism of action of zinc is unclear. However, most of the literature suggests an immunostimulatory potential for zinc. Goswami *et al*. in their article have described the enhancing effect of zinc on various cells of the immune system.[35] Zinc is found to be efficacious in the treatment of psoriasis and lichen planus. A randomized control trial by Thomas *et al*. has demonstrated the superior efficacy of topical zinc-0.05% clobetasol propionate combination over topical steroid alone.[36]

INTRALESIONAL INTERFERON (LOE 4)

Interferons are immunomodulatory molecules which exert their effect by playing an important role in T-cell differentiation and suppression of T regulatory cells.[37] Martinez *et al*. have successfully tried low-dose intralesional interferon (IFN) alfa-2b in the treatment of refractory discoid lupus erythematosus (DLE).[38] Similarly, there are case reports on the successful treatment of generalized DLE with imiquimod 5% cream. A complete resolution of the lesion was observed after thrice-weekly application of the drug for 7 weeks.[39]

Children: No data are available on the safety of intralesional IFN alfa-2b in those below 18 years.[40]

Adverse effects

Most frequently reported adverse effects are flu-like symptoms, injection site reactions, fatigue, and myalgia.

SYSTEMIC IMMUNE-ENHANCING AGENTS FOR AUTOIMMUNE SKIN DISEASES

Systemic immune-enhancing agents found useful in autoimmune skin diseases are,

a. Levamisole
b. Zinc
c. Probiotics
d. Fecal microbiota transplant (FMT)
e. Vaccination.

LEVAMISOLE

Levamisole is a synthetic antihelminthic drug, with potent immunomodulatory activity. It restores the depressed immune functions of B lymphocytes, T lymphocytes, monocytes, and macrophages. Chen *et al*. suggested that Th1 (T helper type 1) immune response can be enhanced by levamisole through the activation of dendritic or T cell.[41] Levamisole is also thought to cause an upregulation of interleukin (IL)-2, IL-12, and IFN-γ.[42]

Indications in autoimmune dermatoses

Lichen planus (LOE 1 b)

Lu *et al*. reported over 80% improvement in about 23 patients treated with 150 mg levamisole thrice weekly.[43] Levamisole acts by modulating the T cell-mediated immunity and by potentiating the activity of interferons.[44,45]

Vitiligo (LOE 1 b)

A randomized, double-blind Indian study had demonstrated the efficacy of levamisole in the management of slowly spreading, limited vitiligo.[46]

Other autoimmune conditions where levamisole was reported to be effective are psoriasis, pemphigus vulgaris, bullous pemphigoid, and AA (LOE 4).[47-50]

Children: Levamisole is considered a safe drug with minimal toxicity.[51]

Adverse effects

The adverse effects of levamisole are usually mild and transient and do not require discontinuation. The common adverse effects reported are nausea and abdominal cramps, vomiting, diarrhea, mouth sores, decreased appetite, altered taste and smell, flu-like syndrome, arthralgias, muscle aches, fatigue, headache, and skin rash.[42] A serious side effect which may warrant discontinuation of levamisole is agranulocytosis.[52]

ZINC

Pedro *et al*. in their study have shown that zinc may help to sustain the functions of the immune system.[53] A meta-analysis by Sanna *et al*. demonstrated that serum zinc was significantly lower in patients with autoimmune diseases such as SLE and psoriasis.[54] A similar lower serum zinc level was demonstrated in patients with refractory alopecia and vitiligo.[55-57] As described earlier in this article, zinc is thought to have an immunostimulatory potential and is found to be effective in the management of autoimmune diseases. However, recently, contrary to the above evidence, Nossent *et al*. showed that labile zinc levels are unexpectedly high in patients with autoimmune diseases and they also suggested that zinc may be probably causing an immunosuppressive effect in these patients.[58] Hence, the exact mechanism by which zinc acts as an immunomodulator remains unclear.

Dose

50 mg/day for 12 weeks has given improved response in AA.[57]

Children: Zinc is considered to be a safe drug at a dose of 20mg /day in children above 6 months and 10mg/day in those below 6 months.[59]

Adverse effects

The reported adverse effects include abdominal symptoms such as nausea and vomiting, neurologic deterioration, and elevation in serum alkaline phosphatase, amylase, and lipase.

PROBIOTICS

Recently, the skin-gut microbiome axis and its dysbiosis have become a spotlight in the pathogenesis of autoimmune diseases. Several reports have highlighted the role of probiotics as a potential therapeutic option in the management of autoimmune conditions.[60,61] These reports in turn prove the "Old friend hypothesis" proposed by Graham Rook in 2003.[62] It is suggested that the probiotics exert their effect through enhancing T regulatory cells and thereby suppressing abnormal effector T-cell responses.[63]

The autoimmune disorders in which the role of probiotics has been studied include,

Psoriasis (LOE 3 b)

Groeger *et al*. in their placebo-controlled study demonstrated that psoriatic patients supplemented with *Bifidobacterium infantis* 35624 showed a significant response.[64] A similar improvement was reported by Vijayashankar and Raghunath in a case of severe pustular psoriasis supplemented with *Lactobacillus sporogenes*.[65]

SLE

Esmaeili *et al*. in their animal model trials showed the effectiveness of probiotics (B. *bifidum*, *Ruminococcus obeum*, Blautia coccoides, and *L. casei* strain Shirota) in reducing inflammation and restoring tolerance in SLE.[63]

Lichen planus (LOE 5)

A probable role for probiotics in oral LP was suggested by Han *et al*. in their article.[66] However, more studies are required to establish the hypothesis.

Children: Probiotics are safe in children.[67]

FMT

FMT is a newer methodology whereby the fecal solution from a donor is transplanted into the recipient's intestinal tract so that the gut microbiome can be restored, and a therapeutic effect can be achieved.[68] Its beneficiary effects have so far been tried in certain diseases such as multiple sclerosis, inflammatory bowel disease, and psoriatic arthritis, which may point towards its probable advantageous role in autoimmune dermatoses. An open-label Phase 1 study to evaluate the efficacy of FMT in Sjogren's syndrome is under trial.

VACCINATION

A therapeutic vaccine in the field of autoimmune diseases is yet to be developed. The main challenge in developing a vaccine against autoimmune disorders is the difference in initiating trigger, specific antibody, and immunopathogenic response in each individual.[69] Let us hope that in the future with more understanding of the disease pathogenesis and advancement of science, individualized vaccines may come up.

CONCLUSION

Autoimmune conditions are diseases where there is aberrant activation of the immune system. Hence, the mainstay of treatment is always immunosuppression, which is the mechanism by which the majority of the drugs act. However, a few topical and systemic immune enhancers as discussed above are now available as potential therapeutic options.

Declaration of patient consent

Not required as there are no patients in this article.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Hadden JW. Immunostimulants. Immunol Today 1993;14:275-80.
2. Lin AN. Topical contact allergens. In: Wolverton SE, editor. Comprehensive Dermatologic Drug Therapy. 2nd ed. Indian: Elsevier; 2007. p. 655-65.
3. Happle R. Topical immunotherapy in alopecia areata. J Invest Dermatol 1991;96:71S-2S.
4. Strazzulla LC, Wang EH, Avila L, Lo Sicco K, Brinster N, Christiano AM, *et al*. Alopecia areata: An appraisal of new treatment approaches and overview of current therapies. J Am Acad Dermatol 2018;78:15-24.
5. Buckley DA, Du Vivier AW. The therapeutic use of topical contact sensitizers in benign dermatoses. Br J Dermatol 2001;145:385-405.
6. Stricker RB, Goldberg B, Epstein WL. Immunological changes in patient with systemic lupus erythematosus treated with topical dinitrochlorobenzene. Lancet 1995;345:1505-6.
7. Rokhsar CK, Shupack JL, Vafai JJ, Washenik K. Efficacy of topical sensitizers in the treatment of alopecia areata. J Am Acad Dermatol 1998;39:751-61.
8. Singh G, Lavanya M. Topical immunotherapy in alopecia areata. Int J Trichology 2010;2:36-9.
9. Aghaei S, Ardekani GS. Topical immunotherapy with diphenylcyclopropenone in vitiligo: A preliminary experience. Indian J Dermatol Venereol Leprol 2008;74:628-31.
10. Jovanović M, Golušin Z. Nonsteroidal topical immunomodulators in allergology and dermatology. Biomed Res Int 2016;2016:5185303.
11. Wiseman MC, Shapiro J, MacDonald N, Lui H. Predictive model for immunotherapy of alopecia areata with diphencyprone. Arch Dermatol 2001;137:1063-8.
12. Hull SM, Cunliffe WJ. Post therapy relapse rate in alopecia areata after successful treatment with diphencyprone. J Dermatol Treat 1989;1:71-4.
13. Shapiro J, Otberg N. Alopecia areata: Pathogenesis, clinical features, diagnosis and management. In: Hair Loss and Restoration. 2nd ed. Florida: CRC Press; 2019.
14. Duhra P, Foulds IS. Persistent vitiligo induced by diphencyprone. Br J Dermatol 1990;123:415-6.
15. Kagami S, Kishi Y, Hino H. Topical immunotherapy in combination with anthralin in the treatment of refractory alopecia areata. J Cosmet Dermatol 2020;19:2411-4.
16. Nasimi M, Ghandi N, Abedini R, Mirshamsi A, Shakoei S, Seirafi H. Efficacy and safety of anthralin in combination with diphenylcyclopropenone in the treatment of alopecia areata: A retrospective case series. Arch Dermatol Res 2019;311:607-13.
17. Shapiro J, Tan J, Ho V, Tron V. Treatment of severe alopecia areata with topical diphenylcyclopropenone and 5% minoxidil: A clinical and immunopathologic evaluation. J Invest Dermatol 1995;104 Suppl 5:36S.
18. Salsberg J, Donovan J. The safety and efficacy of diphencyprone for the treatment of alopecia areata in children. Arch Dermatol 2012;148:1084-5.
19. MacDonald N, Wiseman MC, Shapiro J. Alopecia areata: Topical immunotherapy application and practical problems. J Cutan Med Surg 1999;3 Suppl 3:S36-40.
20. Fernández-Redondo V, Gómez-Centeno P, Flórez A, Toribio J. Hazards in the use of diphencyprone. Allergy 2000;55:202-3.
21. Shah M, Lewis FM, Messenger AG. Hazards in the use of diphencyprone. Br J Dermatol 1996;134:1153.
22. Vedak P, Kroshinsky D. Squaric acid sensitization is not

required for response in the treatment of alopecia areata. J Am Acad Dermatol 2015;73:471-6.
23. Micali G, Cicero RL, Nasca MR, Sapuppo A. Treatment of alopecia areata with squaric acid dibutyl ester. Int J Dermatol 1996;35:52-6.
24. Khandpur S, Sharma VK, Sumanth K. Topical immunomodulators in dermatology. J Postgrad Med 2004:50:131-9.
25. Kwon KS, Kim MB, Kwon YW, Park HJ, Oh CK, Jang HS. SADBE (squaric acid dibutyl ester) immunotherapy in alopecia areata. Korean J Dermatol 2005;43:630-7.
26. Pandey S, Wilmer EN, Morrell DS. Examining the efficacy and safety of squaric acid therapy for treatment of recalcitrant warts in children. Pediatr Dermatol 2015;32:85-90.
27. Mastrolonardo M, Diaferio A. Topical immunotherapy with squaric acid dibutylester: Unusual hair pigmentary changes in two cases of alopecia areata. J Eur Acad Dermatol Venereol 2002;16:186.
28. Sehgal VN, Verma P, Khurana A. Anthralin/dithranol in dermatology. Int J Dermatol 2014;53:e449-60.
29. Kaur I, Kaur S, Sharma VK, Singh M, Kumar B. Modified dithranol therapy for psoriasis. Indian J Dermatol Venereol Leprol 1985;51:90-3.
30. Fiedler VC, Wendrow A, Szpunar GJ, Metzler C, DeVillez RL. Treatment-resistant alopecia areata. Response to combination therapy with minoxidil plus anthralin. Arch Dermatol 1990;126:756-9.
31. Ngwanya MR, Gray NA, Gumedze F, Ndyenga A, Khumalo NP. Higher concentrations of dithranol appear to induce hair growth even in severe alopecia areata. Dermatol Ther 2017;30:e12500.
32. Alkhalifah A, Alsantali A, Wang E, McElwee KJ, Shapiro J. Alopecia areata update: Part II. Treatment. J Am Acad Dermatol 2010;62:191-202.
33. Krueger L, Peterson E, Shapiro J, Lo Sicco K. Case report of novel combination of anthralin and calcipotriene leading to trichologic response in alopecia areata. JAAD Case Rep 2019;5:258-60.
34. Ozdemir M, Balevi A. Bilateral half-head comparison of 1% anthralin ointment in children with alopecia areata. Pediatr Dermatol 2017;34:128-32.
35. Goswami TK, Bhar R, Jadhav SE, Joardar SN, Ram GC. Role of dietary zinc as a nutritional immunomodulator. Asian-Australas J Anim Sci 2005;18:439-52.
36. Thomas J, Kandhari S, Oberoi C, Jayaseelan E, Raj KY. A double-blind randomized multicentre controlled study of topical 0.05% clobetasol propionate with 2.5% zinc sulphate preparation. Indian J Dermatol Venereol Leprol 2001;67:135-7.
37. González-Navajas J, Lee J, David M, Raz E. Immunomodulatory functions of Type I interferons. Nat Rev Immunol 2012;12: 125-35.
38. Martinez J, de Misa RF, Torrelo A, Ledo A. Long-term results of intralesional interferon alpha-2B in discoid lupus erythematosus. J Dermatol 1993;20:444-6.
39. Gül U, Gönül M, Cakmak SK, Kiliç A, Demiriz M. A case of generalized discoid lupus erythematosus: Successful treatment with imiquimod cream 5%. Adv Ther 2006;23:787-92.
40. Interferon Alfa-2b-FDA; 2021. Available from: https://www.accessdata.fda.gov›ifnasch110697-lab. [Last accessed on 2021 Apr 22].
41. Chen LY, Lin YL, Chiang BL. Levamisole enhances immune response by affecting the activation and maturation of human monocyte-derived dendritic cells. Clin Exp Immunol 2008;151:174-81.
42. Gupta M. Levamisole: A multi-faceted drug in dermatology. Indian J Dermatol Venereol Leprol 2016;82:230-6.
43. Lu SY, Chen WJ, Eng HL. Response to levamisole and low-dose prednisolone in 41 patients with chronic oral ulcers: A 3-year open clinical trial and follow-up study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1998;86:438-45.
44. Sun A, Chia JS, Wang JT, Chiang CP. Serum interleukin-8 level is a more sensitive marker than serum interleukin-6 level in monitoring the disease activity of oral lichen planus. Br J Dermatol 2005;152:1187-92.
45. Sun A, Chiang CP, Chiou PS, Wang JT, Liu BY, Wu YC. Immunomodulation by levamisole in patients with recurrent aphthous ulcers or oral lichen planus. J Oral Pathol Med 1994;23:172-7.
46. Agarwal S, Ramam M, Sharma VK, Khandpur S, Pal H, Pandey RM. A randomized placebo-controlled double-blind study of levamisole in the treatment of limited and slowly spreading vitiligo. Br J Dermatol 2005;153:163-6.
47. Liapon AO, Rutshtein LG, Roitburd MF, Fadeeva VI. Levamisole (decaris) in the complex treatment of different clinical forms of psoriasis. Vestn Dermatol Venerol 1984;4:61-6.
48. Lozada F, Silverman S, Cram D. Pemphigus vulgaris. A study of six cases treated with levamisole and prednisone. Oral Surg Oral Med Oral Pathol 1982;54:161-5.
49. Carli-Basset C, Renoux M, Pauley AM, Lorette G, Renoux G. Correlation between the immune reaction and clinical course in a bullous pemphigoid case treated with levamisole. LARC Med 1982;2:440-1.
50. Jautová J, Jarcusková D, Dubivská M, Ficová M. Immunostimulation therapy in patients with alopecia areata. Bratisl Lek Listy 1995;96:160-4.
51. Kalra S, Kanitkar M, Tiewsoh K. Use of levamisole in children with nephrotic syndrome: A retrospective study to examine its adverse effects in children with nephrotic syndrome. J Mar Med Soc 2017;19:87-90.
52. Symoens J, Veys E, Mielants M, Pinals R. Adverse reactions to levamisole. Cancer Treat Rep 1978;62:1721-30.
53. Pedro E, da Rosa Franchi Santos LF, Scavuzzi BM, Iriyoda TM, Peixe TS, Lozovoy MA, *et al*. Trace elements associated with systemic lupus erythematosus and insulin resistance. Biol Trace Elem Res 2019;191:34-44.
54. Sanna A, Firinu D, Zavattari P, Valera P. Zinc status and autoimmunity: A systematic review and meta-analysis. Nutrients 2018;10:68.
55. Fattah NS, Atef MM, Al-Qaradaghi SM. Evaluation of serum zinc level in patients with newly diagnosed and resistant alopecia areata. Int J Dermatol 2016;55:24-9.
56. Mirnezami M, Rahimi H. Serum zinc level in Vitiligo: A case-control study. Indian J Dermatol 2018;63:227-30.
57. Park H, Kim CW, Kim SS, Park CW. The therapeutic effect and the changed serum zinc level after zinc supplementation in alopecia areata patients who had a low serum zinc level. Ann

Dermatol 2009;21:142-6.
58. Nossent J, Lester S, Rischmueller M, Zalewski P. No zinc deficiency but a putative immunosuppressive role for labile Zn in patients with systemic autoimmune disease. Curr Rheumatol Rev 2017;13:59-64.
59. ZINC: WHO/UNICEF Joint Statement-Clinical Management of Acute Diarrhoea, WHO/FCH/CAH/04.7; 2004.
60. Liu Y, Alookaran JJ, Rhoads JM. Probiotics in autoimmune and inflammatory disorders. Nutrients 2018;10:1537.
61. De Oliveira GL, Leite AZ, Higuchi BS, Gonzaga MI, Mariano VS. Intestinal dysbiosis and probiotic applications in autoimmune diseases. Immunology 2017;152:1-12.
62. Rook GA, Stanford JL. Give us this day our daily germs. Immunol Today 1998;19:113-6.
63. Esmaeili SA, Mahmoudi M, Momtazi AA, Sahebkar A, Doulabi H, Rastin M. Tolerogenic probiotics: Potential immunoregulators in systemic lupus erythematosus. J Cell Physiol 2017;232:1994-2007.
64. Groeger D, O'Mahony L, Murphy EF, Bourke JF, Dinan TG, Kiely B, *et al*. *Bifidobacterium infantis* 35624 modulates host inflammatory processes beyond the gut. Gut Microbes 2013;4:325-39.
65. Vijayashankar M, Raghunath N. Pustular psoriasis responding to probiotics-a new insight. Our Dermatol Online 2012;3:326-8.
66. Han X, Zhang J, Tan Y, Zhou G. Probiotics: A non-conventional therapy for oral lichen planus. Arch Oral Biol 2017;81:90-6.
67. van den Nieuwboer M, Brummer RJ, Guarne r F, Morelli L, Cabana M, Claassen E. Safety of probiotics and synbiotics in children under 18 years of age. Benef Microbes 2015;6:615-30.
68. Gupta S, Allen-Vercoe E, Petrof EO. Fecal microbiota transplantation: In perspective. Therap Adv Gastroenterol 2016;9:229-39.
69. Rosenthal KS, Carambula R, Zimmerman DH. Why don't we have a vaccine agai`nst autoimmune diseases?-A review. J Clin Cell Immunol 2019;10:574.

How to cite this article: Francis A, Jose AR. Immune-enhancing agents in autoimmune skin diseases – A review. J Skin Sex Transm Dis 2022;4:19-26.