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Aesthetic Dermatology Training During Residency: Do we Need to Revise the Postgraduate Curriculum?

Suchana Marahatta[1], Deeptara Pathak Thapa[2]

[1]Associate Professor, Department of Dermatology & Venereology, B P Koirala Institute of Health Sciences, Dharan, Nepal
[2]Associate Professor, Department of Dermatology, Nepal Medical College & Teaching Hospital, Gokarneshwar, Kathmandu, Nepal

Abstract

Aesthetic Dermatology (AD) is a growing sub-unit of dermatology. Appearance plays a vital role in enhancing and boosting self-confidence. Reports show a growing demand for AD throughout the world. To converge this increasing demand, we should pivot on engendering certified competent dermatologists and hence include this sub-specialty in the dermatology residency program.

Key words: Aesthetics; Aesthetic dermatology; Dermatology residency; Procedural dermatology

Aesthetic Dermatology (AD) is a subspecialty of dermatology that deals with the enhancement of appearance, change in color, texture, and bodystructure. It is focused on restoring a youthful appearance.[1] Inadequate cosmetic care might have significant negative psychological impacts.[2] People are ready to spend significantly on aesthetic procedures and cosmetics.[3,4] They opt for aesthetic procedures to enhance their self-confidence and think it is an investment in themselves.[5]Medical advances, economic abundance, social media hype, etc have played a vital role in the rising need for AD.[6]Because of this rise, the general public expects that a dermatologist is an expert in all aesthetic procedures. Hence, dermatologistsmust be competent enough in AD to meet society's demands. In our society, non-trained practitioners, beauticians, quacks, etc are practicing AD. It always carries varying legal obligations due to complications arising from untrained hands. In this competitive world, there is a need for hours of trained, certified dermatologists on whom consumers can rely for safety procedures.

Injectables, lasers, microdermabrasion, and chemical peels are non-invasive procedures of top preference.[1] There has been a 78% increase in soft tissue fillers and a 74% increase in laser treatment in the last seven years. Likewise, microneedling has increased by 45% just in a year.[7] An online survey in south-east Asia showed that almost half (47.8%) of the participants underwent at least one aesthetic procedure in the past.[5] Wrinkle treatment, mole removal, lasers, facial rejuvenation and anti-ageing treatment, peels, microneedling, blepharoplasty, etc are prevailing procedures in the Nepalese. Most young, educated, and employed females with good socio-economic backgrounds seek these services.[6] This shows the rising demand for AD throughout the world. As there has been a steep rise in the demand for dermatology procedures in recent years, residents must be proficient in these procedures to meet society's demand.[8]

Despite the rising demand, AD has not been paid much attention during residency. A survey reported that 70% of Canadian residents plan to offer aesthetic services in the future. However, they are highly unsatisfied with the AD exposure during residency. They responded that they had limited hours of observation, and they did not get an opportunity for hands-on exposure to laser therapy, injectables, excision, etc. They also suggested planning resident-led clinics at a discounted rate for optimum hands-on exposure.[9]American Board of Dermatology promotes excellence in the practice

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Corresponding Author:
Dr.SuchanaMarahatta
Department of Dermatology & Venereology
B P Koirala Institute of Health Sciences, Dharan, Province-1, Nepal
ORCID ID:0000-0002-3542-0350
Email:dermasuchana@gmail.com

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of dermatology. They also emphasize the importance of AD during a residency in the present era. Resident doctors in America are getting better AD exposure. Ninety-one percent got a chance on hands-on training. More than 70% of them had already dealt with injectables and lasers. But still, 90% of them require more hands-on exposure. A significant number of the participants perceived that their residency program was neutral (38%) and unsupportive (22%) of AD training.[10]

In our country, AD is in the premature stage. However, our residency program must also focus on this sub-unit to meet society's growing needs. In that case, the teaching institutions will also get better patient flow in dermatology. Likewise, the general public might get aesthetic services at a reasonable rate. Focusing at the growing demand of the society, it is high time to revise our postgraduate curriculum to meet the expectations in the coming days. Hence, we must develop AD as an integrated and well-organized training program.

References

1. Goh C. The need for evidence-based aesthetic dermatology practice. J Cutan Aesthet Surg. 2009;2(2):65. https://doi.org/10.4103/0974-2077.58518
2. Marahatta S, Singh A, Pyakurel P. Self-cosmetic care during the COVID-19 pandemic and its psychological impacts: Facts behind the closed doors. J Cosmet Dermatol. 2021;20(10):3093-3097. https://doi.org/10.1111/jocd.14380
3. American Society for Aesthetic Plastic Surgery. Cosmetic Surgery National Data Bank Statistics.; 2014. https://doi.org/10.1093/asj/sjy132 (https://academic.oup.com/asj/article/35/suppl_2/1/191508 (Access date 30th June 2022)
4. Britton AM. The Beauty Industry' s Influence on Women in Society.; 2012. http://scholars.unh.edu/honors%0Ahttp://scholars.unh.edu/honors/86 (Access date: 27th June 2022)
5. Kwon SH, Lao WW, Lee CH, Hsu AT, Koide S, Chen HY, et al. Experiences and attitudes toward aesthetic procedures in East Asia : a cross-sectional survey of five geographical regions. Arch Plast Surg. 2021;48:660-669. http://doi.org/10.5999/aps.2020.02565
6. Thapa DP, Pradhan S. Profile of Cosmetic Consultation in a General Dermatology Clinic. Nepal Med Coll J. 2019;21(3):190-194. https://doi.org/10.3126/nmcj.v21i3.26456
7. American Society for Dermatologic Surgery Survey on Dermatologic Procedures 2018 Procedures Survey Methodology; 2019. https://asds.net/procedures-survey (Access date: 3rd July 2022)
8. Laban J, Zachary C. Resident Training Needs in Aesthetic Dermatology. Practical Dermatology. 2009;(August):27-29.
9. Worley B, Verma L, Macdonald J. Aesthetic Dermatologic Surgery Training in Canadian Residency Programs. J Cutan Med Surg. 2019;23(2):164-173. http://doi.org/10.1177/1203475418814228
10. Champlain A, Reserva J, Webb K, Griffin D, Moy L, Joyce C, et al. Cosmetic dermatology training during residency: Outcomes of a resident-reported survey. Dermatologic Surg. 2018;44(9):1216-1219.http://doi.org/10.1097/DSS.0000000000001557

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Non-FDA-Approved Uses of Apremilast in Dermatology: A Review of Current Available literature

Saurabh Bhatia[1]

[1]Consultant Dermatologist, Felix Hospital, Noida – Sector 137, India

Abstract

Introduction: Apremilast, an oral phosphodiesterase-4 inhibitor, decreases production of pro-inflammatory cytokines including tumour necrosis factor-α, interleukin-12/23, IL-12, IL-2, and interferon-γ; while upregulating the anti-inflammatory cytokine IL-10. Its pan-immunomodulatory nature has led to its use in managing various immune mediated dermatoses for non-FDA-approved indications.

Objectives: To review and analyse the use of Apremilast in Non-FDA-approved indications in current available literature.

Materials and methods: PubMed, EMBASE, SCOPUS, and Google scholar databases were searched with the parameters "Apremilast", "Apremilast NOT Psoriasis*", "Apremilast NOT Behçet's*", and "Apremilast NOT arthritis*". A total of 45 relevant articles were chosen for review.

Results: We found 22 indications in dermatology where apremilast has been used without FDA approval. The best evidence was for treatment in Atopic Dermatitis, Alopecia Areata, and Hidradenitis Suppurativa, with randomized controlled trials. Prospective open label trials were found for Cutaneous Sarcoidosis, Lichen Planus, Rosacea, and Vitiligo. Individual case series and reports were found for Acrodermatitis Continua of Hallopeau, Dermatomyositis, Disseminated Granuloma Annulare, Erythema Nodosum Leprosum, Morphea, Pityriasis Rubra Pilaris, Hailey-Hailey Disease, Recurrent Erythema Multiforme and Folliculitis Decalvans, Prurigo Nodularis, Perforating Dermatoses, Chronic Actinic Dermatitis and Hand Eczema, and Epidermolysis Bullosa Simplex-Generalised Severe Type. Apremilast has shown varied efficacy, despite better safety profile and tolerability over long duration as compared to placebo and other conventional immunosuppressant drugs.

Conclusion: Apremilast has been used for a varied non-FDA-approved indications in dermatology with variable efficacy. Better controlled, randomized studies with adequate sample size and drug comparisons are needed for better analyses.

Key words: Alopecia; Apremilast; Dermatitis; Dermatology;Hidradenitis suppurativa; Vitiligo

Introduction:

Apremilast is an oral phosphodiesterase-4 (PDE-4) inhibitor FDA-approved in 2014 for psoriatic arthritis and moderate to severe plaque psoriasis, and later for oral ulcers in Behçet'sDisease in 2019.[1,2] In peripheral blood mononuclear cells, PDE-4 inhibition is shown to decrease production of multiple pro-inflammatory cytokines including tumour necrosis factor-α (TNF-α), interleukin (IL)-12/23, IL-12, and IL-2, and interferon-γ; while upregulating the anti-inflammatory cytokine IL-10.[2] This immunomodulatory effects helps to curb the inflammatory response and leads to clinical improvement in immune-mediated skin diseases. Apremilast is a safe oral drug with common adverse effects like diarrhoea, nausea, upper respiratory tract infection, nasopharyngitis, and headache, occurring in ≥5% of patients.[1,2] Most side-effects are mild in

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Corresponding Author:
Dr. Saurabh Bhatia
Consultant Dermatologist
Felix Hospital, Noida, India
ORCID ID: 0000-0003-3718-8492
Email: sabh_kai@hotmail.com

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nature and requires no laboratory monitoring or dose reduction.[1]

Methodology:

PubMed, EMBASE, SCOPUS, and Google scholar databases were searched with parameters including "Apremilast", "Apremilast NOT Psoriasis*", "Apremilast NOT Behçet's*", and "Apremilast NOT arthritis*". All resulting entries (n=257) were manually analysed and repeat articles, articles in language other than English, articles with no abstract, and commentaries on articles were removed. Abstracts and full text of the articles, wherever available were analysed and summarised. A total of 45 articles were finally chosen for review [Figure 1]. Due to paucity of clinical trials of Apremilast in literature, and the focus being more on reported off-label uses, we decided to include and analyse individual reports and case series, to provide future research possibilities in respective disorders. In the absence of RCTs, case series and case reports were included for individual disorders. The level of evidence were as follows; RCTs, then open label placebo-controlled studies, then open label uncontrolled studies, then case series, then individual reports. We summarize the articles highlighting the use of Apremilast in dermatology for other than FDA-approved indications, namely plaque psoriasis, psoriatic arthritis, and oral ulcers in Behçet's disease. Since most of the reports use oral Apremilast 30mg twice a day after starting from 10mg a day increasing daily over a week (regimen approved for psoriasis),[1] wherever the dose is not mentioned, it points to 30mg twice a day orally as described. Any modifications in doses or mode of administration has been mentioned as required. A summary of all the studies reviewed is presented in Table 1, 2, and 3.

Results:

I. Non-FDA-approved use of Apremilast in Skin disorders:

A: Highest level of evidence: Randomized controlled trials [Table 1]

Table 1: Summary of RCTs regarding Non-FDA-approved uses of Apremilast in Dermatology

S. No.	Dermatoses	Type of study	Dose of Apremilast	Duration of Treatment	No. of Patients	Outcome of the study	Authors
1	Atopic Dermatitis	Systemic Meta-analyses	20mg BID	12 weeks	32	20% of patients achieved a 2-point improvement in Investigator's Global Assessment (IGA). Additionally, 20% achieved a 1-point improvement. Mean Eczema Area and Severity Index (EASI) decreased by 5%. No change in pruritus or quality of life measures.	Mobasher P et al[3]
				3 months / 6 Months	16	Significant reduction in pruritus and Dermatology Life Quality Index (DLQI) score in the 20mg treatment group. Significant reduction in EASI score, DLQI, and visual appearance of lesions in the 30mg group.	
	Atopic Dermatitis	RCT	40mg BID / 30mg BID / Placebo	12 weeks	185	40mg was better than placebo in reducing EASI (31.6% decrease with 40mg, 26.0% decrease with 30mg, and 11.0% decrease with placebo) and DLQI (27% decrease with 40mg, 13% decrease with 30mg, and 3% decrease with placebo). Visual Analog Scale (VAS) for pruritus had no change in all the groups. Side-effect more frequent with 40mg (70%) than 30mg (62%) and placebo (47%). Total withdrawal rates were similar across all 3 groups.	Simpson El et al[4]
2	Alopecia Areata	RCT	30mg BID / Placebo	24 weeks	30	Apremilast failed to show efficacy Only two patients achieving SALT reduction >50%. High attrition rate due to lack of response and side-effects to Apremilast.	Mikhaylov D et al[5]
	Alopecia Areata	Case Series	30mg BID	6 months	5	Only one patient had transient reduction in Severity of Alopecia Tool Score (SALT) scores in two months, with disease worsening to baseline at the end of 6 months. Other 4 patients had no response, hair loss progressing even on treatment.	Weber B et al[6]
3	Hidradenitis Suppurativa	RCT	30mg BID	16 weeks	20 (15+5)	8/15 patients with Hidradenitis suppurativa (53.3%) had clinical improvement compared to 0/5 in the placebo group (0%) at week 16 (p=0.055). Significantly lower abscess and nodule count (p=0.011), pain (p=0.009), and itch (p=0.015) in the treatment group. No significant difference in DLQI (p=0.230). Minor side-effects to Apremilast was tolerable and did not led to attrition.	Vossen ARJV et al[7]

	Hidradenitis Suppurativa	Prospective open label trial	30mg BID	24 weeks	20	13/20 (65%) of patients achieved Hidradenitis Suppurativa Clinical Response 30 (HiSCR30) . Significant reduction in the mean scores from baseline to week 24 in the modified Sartorius ($p<0.001$), Physician's Global Assessment ($p<0.01$), Visual Analog Scale (VAS) for pain ($p<0.05$), and DLQI scores ($p<0.01$). Diarrhoea (20%), nausea (15%), and depression (10%) were the most commonly reported adverse events.	Kerdel FR et al[8]
4	Vitiligo	RCT	30mg BID + NBUVB	52 weeks	40	Apremilast failed to show any statistically significant response compared to placebo even after 52 weeks ($p=0.18$).	Khemis A et al[9]
	Vitiligo	RCT	30mg BID + NBUVB	16 weeks	23	In 23 patients of skin type IV to VI with vitiligo. Higher probability of achieving grade 3 or 4 repigmentation after 16 weeks of combined therapy compared with NB-UVB monotherapy ($P=0.001$). Significant decrease in mean VASI scores and affected body surface area ($p=0.001$). No significant differences in DLQI and Visual Analog Scale scores ($P=0.05$). Four patients had minor side-effects to Apremilast which they tolerated well.	Kim JH et al[10]
	Vitiligo	Case Series	30mg BID	3 months	13	Stabilization of disease activity with partial re-pigmentation in 61.5% of patients. Significant reduction in VASI scores ($p<0.04$). Two patients had side-effects while all other tolerated the therapy well.	Majid I et al[11]
RCT: Randomized control trials, BID: Twice a day dose; OD: Once a day dose							

1. Atopic Dermatitis (AD):

Mobasher P et al., analysed 4 studies with 32 patients using Apremilast for AD in a systematic analyses. The clinical improvements has been varied.[3] A proof-of-concept, phase 2, open-label, single institution trial showed minimal clinical effect with Apremilast 20mg twice a day over 12 weeks for AD and ACD. Only 20% of subjects achieved a 2-point improvement in Investigator's Global Assessment (IGA). Additionally, 20% achieved a 1-point improvement. After 12 weeks of treatment, mean Eczema Area and Severity Index (EASI) decreased by 5%.[3] However, pruritus or quality of life measures did not show any change.[3] Another prospective trial treated 16 adult patients with moderate to severe AD, using either Apremilast 20mg twice daily for 3 months or 30mg twice daily for 6 months.[3] There was significant reduction in pruritus and Dermatology Life Quality Index (DLQI) score in the 20mg treatment group, while there was a significant reduction in EASI score, DLQI, and visual appearance of lesions in the 30mg group.[3]Another phase-2 randomized trial conducted by Simpson EL et al., studied the efficacy of two different doses of Apremilast (30mg and 40mg, both twice daily) versus placebo in 185 adult patients over 12 weeks.Apremilast 40mg was found to be better than placebo in reducing EASI (31.6% decrease with 40mg, 26.0% decrease with 30mg, and 11.0% decrease with placebo) and DLQI (27% decrease with 40mg, 13% decrease with 30mg, and 3% decrease with placebo). However, Visual Analogue Scale (VAS) for pruritus had no comparative significant change in all the groups. Side-effect were more frequent in the group with Apremilast 40mg (70%) than 30mg (62%) and placebo (47%). The total withdrawal rates were similar across all 3 groups.[4]Apremilast thus appear to be moderately efficacious in AD.However, further well-planned studies are required to analyse the doses, duration, and safety of Apremilast.

2. Alopecia Areata:

Alopecia Areata (AA) is a T-cell mediated autoimmune disorder leading to patchy hair loss, causing significant cosmetic and psychological distress in the patients. PDE-4 inhibition by Apremilast leads to suppression of T-cell mediated cytokines and can help in managing the disease. Mikhaylov D et al., in their randomized placebo-controlled trial treated 20 patients with Apremilast and 10 with placebo over 24 weeks.[5] Apremilast failed to show efficacy in managing the disease with only two patients achieving SALT reduction >50%. There was high attrition rate due to lack of response and side-effects to Apremilast, making the data erroneous.[5] Weber B et al., treated 5 patients of refractory AA with Apremilast over 6 months.[6] Only one patient had transient reduction in Severity of Alopecia Tool Score (SALT) scores in two months, but the disease worsened to baseline at the end of 6 months. Other 4 patients had no response to Apremilast, with hair loss progressing even on treatment,[6] showing that the efficacy with Apremilast is not constant while treating refractory AA.

3. Hidradenitis Suppurativa:

Apremilast has been shown to improve pustules and abscess in hidradenitis suppurativa (HS). A modest response was seen in a randomized controlled trial by Vossen ARJV et al. Eight out of fifteen patients with HS (53.3%) had clinical improvement with Apremilast as compared to 0/5 in the placebo group (0%) at

week 16 (p=0.055).[7] The Apremilast-treated patients showed a significantly lower abscess and nodule count (p=0.011), pain (p=0.009), and itch (p=0.015). There was no significant difference in DLQI (p=0.230). Minor side-effects to Apremilast was tolerable and did not led to attrition.[7]In a phase-2 prospective, open label study by Kerdel FR et al., twenty patients received Apremilast 30mg twice daily for 24 weeks. Out of 20, 65% of patients achieved Hidradenitis Suppurativa Clinical Response 30 (HiSCR30), i.e., proportion of patients with a ≥30% reduction in abscesses and nodules at week 16 and 24.[8] Mean scores from baseline to week 24 in the modified Sartorius (p<0.001), Physician's Global Assessment (p<0.01), Visual Analog Scale (VAS) for pain (p<0.05), and Dermatology Life Quality Index (DLQI) scores also showed significant reduction (p<0.01).[8] Diarrhea (20%), nausea (15%), and depression (10%) were the most commonly reported adverse events, however no dose reduction was necessary.[8]

4. Vitiligo:

Apremilast has been tried with narrowband-UVB to augment its therapeutic benefit. In randomized placebo-controlled study by Khemis A et al., 40 patients were treated with Apremilast 30mg twice a day along with NBUVB, but failed to show any statistically significant response compared to placebo even after 52 weeks (p=0.18).[9] However, another randomized split-body study by Kim JH et al., in 23 patients of skin type IV to VI with vitiligo showed statistically better re-pigmentation with NBUVB and Apremilast 30mg twice a day as compared to either monotherapy over 16 weeks of treatment.[10]There was higher probability of achieving grade 3 or 4 re-pigmentation after 16 weeks of combined therapy with Apremilast and NB-UVB phototherapy compared with 16 weeks of NB-UVB monotherapy (P=0.001). There was significant decrease in mean VASI scores and affected body surface area (p=0.001). No significant differences were found in Dermatology Life Quality Index and Visual Analog Scale scores between the two treatment groups (P=0.05). Four patients had minor side-effects to Apremilast which they tolerated well.[10] Apremilast has also been shown to halt the progression of disease in progressive non-segmental vitiligo. Majid et al., treated 13 patients with Apremilast 30mg twice a day for 3 months and reported stabilization of disease activity with partial re-pigmentation in 61.5% of patients.[11] Two patients had side-effects to Apremilast while all other tolerated the therapy well.[11] There was significant reduction in VASI scores (p<0.04). However, the lack of follow-up period in the study does not help to provide insight into the permanence of the response.

B. Highest level of evidence: Open label trials [Table 2]

Table 2: Summary of prospective open label trials regarding Non-FDA-approved uses of Apremilast in Dermatology

S. No.	Dermatoses	Type of study	Dose of Apremilast	Duration of Treatment	No. of Patients	Outcome of the study	Authors
1	Cutaneous Sarcoidosis	Prospective open label trial	20mg BID	12 weeks	15	Significant reduction in induration scores (p<0.005) in Sarcoidosis Area and Severity Index (SASI) (p<0.02). Non-significant reduction in erythema, desquamation, and area of involvement. 2 patients developed nausea necessitating reduction of dose to 20mg once a day.	Baughman RP et al[12]
2	Lichen planus	Prospective open label trial	20mg BID	12 weeks	10	Significant reduction in lesion count (p<0.002) and other objective parameters like Physician Global Assessment Scales (p<0.0078), Subject Global Assessment Scales (p=0.002), Subject Visual Analog Scale for Itch (p=0.0059), And Target Area Lesion Severity Score (p=0.078). 3/10 patients achieved the primary end-point of >2 grade improvement in Physician Global Assessment Scales. No patients experienced serious side-effects.	Paul J et al[14]
	Oral Lichen planus	Case Series	30mg BID	Patient 1 - 5 months, Patient 2 - 6 months, Patient 3 - 3 months	3	Patient 1 - Good control over 5 months. Needed background 5mg prednisolone for control of flare-ups. Patient 2 - Good control over 6 months. Patient 3 - Good control over 3 months.	Bettencourt M[15]
	Erosive lichen planus associated mucosal esophagitis	Case Report	20mg BID	N/A	1	Complete resolution of oesophageal stenosis in 4 weeks	Hafner J et al[16]

3	Rosacea	Case Series	20mg BID	12 weeks	10	Statistically significant reduction in physician global 7-point Assessment (p=0.02), Physician Overall Erythema Severity scores (p=0.02), Erythematotelangiectatic rating (p=0.005), and non-transient erythema (p=0.04). However, parameters like papule and pustule count and chromometer readings did not differ significantly. The side-effects were minimal in all patients.	Thompson BJ et al[18]
4	Acrodermatitis continua of Hallopeau	Case Report	30mg BID	6 months	1	Remarkable improvement in 1 month. No side effects.	Algarra CA et al[20]
	Acrodermatitis continua of Hallopeau	Case Report	30mg BID	16 weeks	1	Onset of improvement in 4 weeks, almost complete resolution in 16 weeks leaving behind mild onychodystrophy.	Megna M et al[21]
	Acrodermatitis continua of Hallopeau	Case Report	30mg BID	N/A	1	Lanna C et al used Apremilast 30 mg twice a day to treat a patient of Acrodermatitis Continua of Hallopeau, with marked improvement within 1 month	Lanna C et al[22]
	Acrodermatitis continua of Hallopeau	Case Report	N/A	>4 months	1	No effect of Apremilast with gradual worsening of disease and debilitating side-effects to therapy. Patient shifted to secukinumab for treatment.	Baron J et al[23]
	Dermatomyositis	Case Report	30mg BID	7 months	1	Significant benefit in all cutaneous manifestations, especially scalp pruritus in 3 months. Improvement continued after tapering off of steroids over 7 months. No side-effects.	Charlton D[24]
	Dermatomyositis	Prospective open label trial	30mg BID	12 weeks	5	3 patients completed the study period, with decrease in Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI), which increased again after 4 weeks of drug washout period. A similar trend was observed in Visual Analog Scores, which flared up for 4 weeks after initiation of therapy and returned to baseline at 12 weeks, again worsening in the 4 week drug-washout period. DLQI improved in two patients, while the third which had worsening of DLQI. No change in the levels of pro-inflammatory cytokines with Apremilast. 2/5 patients withdrew from study due to Apremilast induced severe nausea and vomiting.	Konishi R et al[25]
	Dermatomyositis	Retrospective analysis	30mg BID	>12 months	3	Patients of severe DM (CDASI>14) with cutaneous manifestations who were either not responding or were dependent on oral steroids and other immunosuppressive drugs. Onset of improvement within 1 month, with significant resolution seen in 3 months (>85% improvement in CDASI scores). Patients were continued on Apremilast monotherapy which was tolerated well. All patients had improvement in muscle weakness after 9 months with gradual normalization of elevated muscle enzymes.	Bitar C et al[26]
6	Disseminated Granuloma Annulare	Case Series	30mg BID	48-52 weeks	2	Significant improvement in 8 weeks, with both the patients remaining symptom free for 48 weeks and 52 weeks respectively, with tolerable side-effects	Hansel K et al[27]
	Disseminated Granuloma Annulare	Case Series	30mg BID	3 months	4	Clinical response was seen in 6-8 weeks and near complete resolution in 3 months. Minimal side-effects including tolerable nausea and diarrhea in one of the patients. Disease remained in remission on treatment.	Bishnoi A et al[28]

	Disseminated Granuloma Annulare	Case Report	30mg BID	8 months	1	Clinical improvement in lesions seen after 3 months, near complete resolution of symptoms in 6 months. Remission lasted for 2 more months till last follow-up. Improvement in pruritis and burning sensation started to improve within the first week, and remained minimal during the entire course. No side-effects.	Joshi TP et al[29]
	Erythema Nodosum Leprosum	Prospective open label trial	30mg BID	6 months	12	12 MB leprosy patients with recalcitrant and recurrent steroid dependent Erythema Nodosum Leprosum (ENL). Prednisolone tapered and stopped in the first 2 months. Significant decrease in ENL-International Study Severity Scale at 1 and 6 months, 54.6% patients remained in remission with only Apremilast while the rest 3 required additional doses of prednisolone. Most patients had tolerable side-effects, one had urticaria after 10 days of therapy and discontinued treatment.	Narang T et al[30]
	Erythema Nodosum Leprosum	Case Report	30mg BID	6 months	1	Woman with steroid dependent ENL, using Apremilast with tapering doses of prednisolone. Complete resolution of lesions and constitutional symptoms in 1 month, lasting for additional 5 months on only Apremilast. Well-tolerated therapy with side-effects that did not require any dose reduction.	Sánchez-Martínez EM et al[31]
	Erythema Nodosum Leprosum	Case Series	30mg BID	3-5 months	2	Apremilast along with 15 mg prednisolone to control severe steroid-dependent erythema nodosum leprosum in two patients of MB leprosy. Significant improvement in constitutional symptoms in 2-4 weeks and steroids were tapered and stopped. No new lesions for 3-5 months of follow-up.	Narang T et al[32]
	Erythema Nodosum Leprosum	Case Series	30mg BID	1 month	5	Apremilast with topical super-potent steroids or topical calcineurin inhibitor inadequately improving Morphea with oral steroids or steroid sparing agents. Improvement seen in erythema and induration, seen within 3 weeks in one patient and 4 months in one patient. Median time for clinical improvement was 1 month. Decrease in modified localized Scleroderma Skin Severity Index (mLOSSI) and modified localized Scleroderma Skin Damage Index (mLOSDI), significance was not commented. No new development of lesions after 1 month. 2/5 patients had nausea that improved on single day dose of Apremilast.	Koschitzky M et al[33]
RCT: Randomized control trials, BID: Twice a day dose; OD: Once a day dose							

1. Cutaneous Sarcoidosis:

Pentoxifylline, a PDE-4 inhibitor, has been reported to show benefit in sarcoidosis, but its use has been limited due to associated adverse effects and availability. Apremilast, a newer PDE-4 inhibitor, decreases pro-inflammatory cytokines like TNF-α, interferon-γ, IL-2, IL-12, and IL-23 and may thus help in treating cutaneous sarcoidosis. Baughman RP et al., treated 15 patients of cutaneous sarcoidosis with Apremilast 20mg twice a day, with significant reduction in induration scores ($p<0.005$) in Sarcoidosis Area and Severity Index (SASI) over 12 weeks ($p<0.02$).12 There was reduction in erythema, desquamation, and area of involvement but that was found to be non-significant. Two patients developed nausea necessitating reduction of dose to 20mg once a day which they tolerated well.12

2. Lichen planus:

Apremilast has shown benefit in interface dermatitis related dermatoses;[13] its benefit in treating moderate to severe LP is to be analyzed. Paul J et al., treated 10 patients of moderate to severe LP with Apremilast 20mg twice a day for 12 weeks, with 4 weeks of drug free period.[14] There was significant reduction in lesion count ($p<0.002$) and other objective parameters like Physician Global Assessment Scales ($p<0.0078$), Subject Global Assessment Scales ($p=0.002$), Subject Visual Analog Scale for Itch ($p=0.0059$), and Target Area Lesion Severity Score ($p=0.078$). Three out of ten patients achieved the primary end-point of >2 grade improvement in Physician Global Assessment Scales. No patients experienced serious side-effects to Apremilast during the study period that required dose reduction.[14] Although the above study shows benefit of Apremilast in LP, further studies with adequate sample size are needed to evaluate the dose and regimen of the drug. Apremilast has also shown benefit in 3 recalcitrant cases of oral LP by Bettencourt M[15] and LP mucosae-associated stenotic esophagitis by Hafner J et al.[16] A novel formulation of topical Apremilast nail lacquer has shown to provide 2-4 times the concentration of Apremilast at site and may provide another treatment modality in nail LP in the future.[17]