DOI: https://doi.org/10.3126/njdvl.v20i2.45638

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

Funding: None
Conflict of Interest: None

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

Date of Submission: May 25th 2022
Date of Acceptance: July 7th 2022
Date of Publication: October 1st 2022

How to cite this article
Bhatia S. Non-FDA-approved uses of Apremilast in Dermatology: A review of current available literature. NJDVL 2022;20(2):3-16 https://doi.org/10.3126/njdvl.v20i2.45638

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]

3. Rosacea:

Apremilast has been used by Thompson BJ et al., to treat 10 patients of erythematotelangiectatic and papulopustular rosacea.[18] Apremilast 20mg twice a day was used for 12 weeks. There was 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). Physician Overall Erythema Severity and non-transient erythema remained statistically significant even after 1 month of stopping treatment.[18] However, parameters like papule and pustule count and chromometer readings did not differ significantly. The side-effects were minimal in all patients and did not require any dose modifications.[18] Apremilast can prove to be a safe drug which can alleviate the inflammatory symptoms of rosacea, particularly erythema that has been shown to be refractory to other therapies.

C. Highest level of evidence: Case series and case reports [Table 3]

Table 3: Summary of case series and case reports regarding Non-FDA-approved uses of Apremilast in Dermatology

	Pityriasis Rubra Pilaris	Case Report	30mg BID	8 months	1	Onset of relief in 1 month, with near complete resolution over 6-8 months. Mild nausea and vomiting not requiring dose reduction.	Krase IZ et al[34]
	Pityriasis Rubra Pilaris	Case Report	30mg BID	7 months	1	Significant improvement in erythema and keratoderma within 1 month. Complete healing was obtained after two months. Patient remained in remission for seven months on treatment. Treatment was well tolerated without side effects.	Pellonnet L et al[35]
	Recalcitrant Pyoderma Gangrenosum	Case Report	30mg BID	>5 months	1	Patient with steroid dependent pyoderma gangrenosum with haematological abnormalities with no response with Dapsone or Colchicine. Apremilast was added to prednisolone 7.5mg a day and s/c methotrexate 18mg a week. Significant healing of ulcers within 4 months leading to discontinuation of methotrexate; while prednisolone was tapered and stopped 1 months afterwards. Patient remained complaint free on Apremilast. Associated nausea and vomiting did not require dose reduction. There was no derangement of blood parameters.	Laird ME et al[36]
	Hailey-Hailey Disease	Case Series	30mg BID	6-10 months	4	Clinical improvement starting from the first month. Side-effects and lack of further response prompted two patients to stop the treatment.	Kieffer J et al[37]
	Hailey-Hailey Disease	Case Series	30mg BID	N/A	2	Good improvement in skin erosions in 2 weeks. One patient had tolerable mild headache. No adverse effects in the other patient.	Yoto A et al[38]
	Hailey-Hailey Disease	Case Report	30mg BID	12 months	1	Clinical remission was achieved in 1 month, lasting for 12 months on treatment.	Di Altobrando A et al[39]
	Hailey-Hailey Disease	Case Series	30mg BID	33 weeks	5	Lack of improvement in severe refractory disease. 4/5 patients reported no effect, while the fifth had to stop due to intolerable GI side effects.	Riquelme-Mc Loughlin C et al[40]
	Recurrent Erythema Multiforme	Case Series	30mg BID / 30mg OD	N/A	4	Cessation of symptoms within 4-14 days and no recurrence of disease while on therapy.	Chen T et al[41]
	Recurrent Folliculitis Decalvans	Case Report	30mg BID	>25 weeks	1	Rapid decrease in pain, irritation, oozing, and crusting within a week. Complete resolution of symptoms after 3 weeks. Therapy discontinued after 7 weeks leading to rapid flare-up of disease. On re-initiation of Apremilast, there was rapid resolution of symptoms and the patient remained in remission for more than 25 weeks on therapy, with no adverse effects.	Fassler M et al[43]
	Recalcitrant Seborrheic Dermatitis	Case Series	30mg BID	3 months	3	Significant reduction in disease activity in 3 months. Two Patients remained off-treatment while the third required tacrolimus 0.1% ointment of control of residual disease. No significant side-effects to therapy.	Cohen SR et al[44]

7	Recalcitrant Prurigo Nodularis	Case Series	30mg BID	12 weeks	10	No significant change in the clinical parameters or cytokine levels before and after treatment. Objective parameters like Visual Analog Scale, DLQI, Physician Global Assessment, and Patient Global Assessment did not decrease on treatment. Sleep Parameters and QOL also did not improve.	Todberg T et al[46]
8	Perforating Dermatoses	Case Report	30mg BID	6 months	1	Patient with Down's syndrome, chronic plaque psoriasis and perforating dermatoses. Significant resolution of lesions in 3 months after initiation, carried forward for the next three months on therapy. Psoriasis responded faster than perforating dermatoses. Treatment was well-tolerated, requiring no dose reduction.	McMichael J et al[47]
9	Chronic Actinic Dermatitis	Case Report	30mg BID	12 weeks	1	Patient of chronic actinic dermatitis with steroid dependent disease unresponsive to other immunosuppressive agents and photo-protection. Significant improvement in skin lesions within 4 weeks of starting therapy, complete clearance of skin lesions by 6 weeks of therapy. Steroids completely tapered and stopped over next 4 weeks while continuing Apremilast. No recurrence of lesions or any major adverse effects.	Kaushik A et al[48]
10	Chronic Hand Eczema	Case Report	30mg BID	N/A	1	Apremilast with super-potent topical steroids in a patient of chronic hand eczema and hepatogenic pruritis not-tolerating retinoids. Complete resolution of lesions in 1 month. Improvement in hepatogenic pruritis and no derangement of liver enzymes. Patient was well-maintained on Apremilast with good control of disease activity.	Navarro-Trivino FJN et al[49]
11	Epidermolysis Bullosa Simplex – Generalized severe type	Case Report	30mg BID	11 months	3	Complete halting of new blister formation after 1 month of treatment, sustained for another 10 months on treatment. All patients had mild abdominal pain and diarrhea which resolved on its own within a month of starting the treatment. 1 patient discontinued treatment due to persistent nausea after 7 months, leading to relapse after two days.	Castela E et al[50]
RCT: Randomized control trials, BID: Twice a day dose; OD: Once a day dose							

1. Acrodermatitis Continua of Hallopeau:

Apremilast along with infliximab had been used previously in a patient of generalized pustular psoriasis, with significant improvement in symptoms in four weeks.[19] Algarra CA et al., reported the use of Apremilast 30mg twice a day in a patient of pustular psoriasis with significant nail involvement with fingertip destruction severely impacting daily routine.[20] There was marked improvement noted after 1 month with patient remaining asymptomatic after 6 months of initiation of therapy, with recovery in the onychodystrophy of finger and toe nails.[20] Megna M et al., treated their patient with Apremilast with onset of improvement in 4 weeks, while at 16 weeks there was almost complete resolution of symptoms leaving behind mild onychodystrophy.[21] Lanna C et al., used Apremilast 30 mg twice a day to treat a patient of ACH, with marked improvement within 1 month.[22] None of these isolated case reports had any significant associated side-effects with Apremilast.[19–22] Apremilast may show good outcomes in cases of ACH and prove as a safe alternative; however, Baron JA showed no significant change in disease activity leading to switching to secukinumab for management.[23]

2. Dermatomyositis:

Charlton D reported the use of Apremilast 30mg twice a day along with oral steroids in a patient with steroid non-responsive cutaneous manifestations of DM, particularly scalp pruritis.[24] There was significant benefit in all cutaneous manifestations, especially scalp pruritus in 3 months of treatment, that continued after tapering off of steroids over 7 months.[24] Apremilast was safely tolerated by the patient. In a single centre, prospective, interventional single arm study conducted by Konishi R et al., the efficacy of Apremilast 30mg twice a day for 12 weeks in addition to ongoing immunosuppressive treatments were evaluated.[25] In 5 patients who had refractory cutaneous DM-associated manifestations for at least a year, 3 patients completed the study period. They observed decrease in Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) over the study period, which increased again after 4 weeks of drug washout period when Apremilast is stopped. 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 developed inflammatory atheroma had worsening of DLQI.[25] There was no change in the levels of pro-inflammatory cytokines before or after treatment with Apremilast. Two patients out of five withdrew from study due to Apremilast induced severe nausea and vomiting.[25] In a retrospective analysis of 3 patients by Bitar C et al., Apremilast 30mg twice a day was added to patients of severe DM (CDASI>14) with cutaneous manifestations who were either not responding or were dependent on oral steroids and other immunosuppressive drugs.[26] Onset of improvement in symptoms was observed within a month of starting therapy, with significant resolution seen in 3 months (>85% improvement in CDASI scores). Steroid and steroid-sparing agents were tapered and stopped in 9-12 months and patients were continued on Apremilast monotherapy which was tolerated well. All of the patients observed improvement in muscle weakness after 9 months with gradual normalization of elevated muscle enzymes.[26]

3. Disseminated Granuloma Annulare (DGA):

The pathomechanisms in DGA is likely to be Th1 mediated; and hence, Apremilast, with its PDE-4 inhibition acting as a down-regulator of Th1 cytokines, has been used as a treatment modality in DGA.[27] Bishnoi A et al., treated 4 patients with Apremilast 30mg twice a day, with clinical response seen in 6-8 weeks and near complete resolution in 3 months.[28] There were minimal side-effects including tolerable nausea and diarrhea in one of the patient. The disease remained in remission on Apremilast.[28] Hansel K et al., treated 2 patients of DGA with Apremilast 30mg twice a day, with significant improvement in 8 weeks post treatment, with both the patients remaining symptom free for 48 weeks and 52 weeks respectively, with tolerable side-effects.[27] However, in a patient of DGA and plaque psoriasis treated by Joshi TP et al., clinical improvement in lesions were seen after 3 months of Apremilast 30mg twice a day monotherapy, with near complete resolution of symptoms in 6 months.[29] The patient remained in remission for 2 months after wards on Apremilast till last follow-up visit. The improvement in clinical symptoms like pruritis and burning sensation started to improve within the first week, and remained minimal during the entire course. There were no side-effects of the treatment.[29]

4. Erythema Nodosum Leprosum:

Narang et al., conducted a prospective single center pilot study to treat 12 MB (multi-bacillary) leprosy patients with recalcitrant and recurrent steroid dependent ENL.[30] They treated the with Apremilast 30mg twice a day along with tapering doses of prednisolone over two months. Apremilast was continued for additional four months after stopping prednisolone. There was significant decrease in ENL-International Study Severity Scale at 1 and 6 months, while 54.6% patients remained in remission with Apremilast without prednisolone while the rest three required additional doses of prednisolone. Most of the patients had tolerable side-effects, but one had urticaria after 10 days of therapy and discontinued treatment.[30]Sánchez-Martínez EM et al., treated a woman with steroid dependent ENL, using Apremilast 30mg twice a day, with tapering doses of prednisolone.[31] There was complete resolution of lesions as well as constitutional symptoms in 1 month, which lasted for an additional 5 months on only Apremilast. The drug was well-tolerated with side-effects like nausea and headache, which did not require any dose reduction.[31]Narang T et al., used Apremilast 30mg twice a day along with 15mg prednisolone to control severe steroid-dependent ENL in two patients of MB leprosy.[32] There was significant improvement in constitutional symptoms in 2-4 weeks and steroids were tapered and stopped. The patient tolerated Apremilast and there were no new lesions for 3-5 months of follow-up.[32]

5. Morphea:

PDE-4 inhibitor Apremilast has been recently shown to have anti-fibrotic effects in pre-clinical models of skin fibrosis, suggesting that it may provide some benefit in scleroderma disorders like morphea or localized scleroderma.[33] Koschitzky M et al., have reported the use of Apremilast 30mg twice a day along with topical super-potent steroids or topical calcineurin inhibitor in 5 patients of Morphea inadequately improving with oral steroids or steroid sparing agents. Improvement was seen primarily in the erythema and induration of the lesions, which was as early as 3 weeks in one patient and as late as 4 months in one patient. Median time for clinical improvement was 1 month.[33] There was decrease in modified localized Scleroderma Skin Severity Index (mLOSSI) and modified localized Scleroderma Skin Damage Index (mLOSDI), although the significance was not commented upon. There was no new development of lesions after 1 month of treatment. Two out of five patients had nausea on treatment that improved on decreasing the dose of Apremilast to once a day.[33]

6. Pityriasis Rubra Pilaris:

Krase IZ et al., showed marked improvement in a patient of PRP with small cell leukemia in whom TNF-α inhibitors were contradicted due to increased risk of associate hematological malignancies. Apremilast 30mg twice a day showed onset of relief in 1 month, with near complete resolution over 6-8 months. The patient suffered mild nausea and vomiting but did not require dose reduction.34 A similar clinical response was noted over 6 months by Pellonnet L et al.35

7. Recalcitrant Pyoderma Gangrenosum:

Laird ME et al., treated a 73-year-old patient with steroid dependent PG with hematological

abnormalities, who had failed to show response with Dapsone or Colchicine.[36] Apremilast 30mg twice a day was added to prednisolone 7.5mg a day and subcutaneous methotrexate 18mg a week. There was significant healing of ulcers within 4 months leading to discontinuation of methotrexate; while prednisolone was tapered and stopped 1 months afterwards. The patient remained complaint free on Apremilast.[36] There was associated nausea and vomiting, but that was tolerable and did not require dose reduction. There was no derangement of blood parameters.[36]

8. Hailey-Hailey disease:

Apremilast with its PDE-4 inhibitory action acts as a pan-suppressant of inflammatory cytokines and may provide relief in HHD. Kieffer J et al., treated 4 patients of severe HHD with Apremilast 30mg twice a day with moderate improvement after 6 to 10 months of therapy, with clinical improvement starting from the first month. However, side-effects and lack of further response prompted two patients to stop the treatment.[37] Yoto A et al., reported good improvement in skin erosions in 2 weeks after starting treatment with Apremilast in two patients of severe refractory HHD. One patient reported mild headache which was tolerated while there were no adverse effects in the other.[38]Di Altobrando A et al., treated a 68-year-old woman with HHD successfully with Apremilast 30mg twice a day. Clinical remission was achieved in 1 month, which lasted for 12 months on treatment.[39] However, Riquelme-Mc Loughlin C et al., reported a lack of improvement with Apremilast in severe refractory HHD over the course of 33 weeks.[40] Four out of five patients reported no effect of the drug while the fifth had to stop due to intolerable GI side effects.[40]

9. Recurrent erythema multiforme:

Apremilast with its immunomodulatory action has been tried to suppress recurrent Erythema Multiforme (EM) episodes. Chen T et al., used Apremilast in the doses of 30-60mg a day to suppress episodes in 4 patients suffering from recurrent EM.[41] Cessation of symptoms was seen within 4-14 days and there was no recurrence of disease while the patient was on Apremilast.[41] However, the total duration of treatment was not mentioned and whether there was recurrence on stopping the drug was also not highlighted.

10. Recurrent Folliculitis Decalvans:

Since Apremilast has shown benefit in other disorders of neutrophil mediated disorders like plaque psoriasis1,42 and Behçet'sdisease;42 along with improvement of disorders with lichenoid and interface dermatitis on histology13; Fassler M et al., treated a case of recurrent folliculitis decalvans in a 28-year-old male. A dose of 30mg twice a day led to rapid decrease in pain, irritation, oozing, and crusting; appreciated within a week. There was complete resolution of symptoms after 3 weeks of therapy.43 The therapy was discontinued after 7 weeks leading to rapid flare up of disease. On re-initiation of Apremilast, there was rapid resolution of symptoms and the patient remained in remission for more than 25 weeks on therapy, with no adverse effects.43 Apremilast, with its rapid response and safe drug profile, can be used in cases of difficult to treat folliculitis decalvans. Its suppressive activity on pro-inflammatory neutrophil-tropic cytokines like TNF-α and IL-1 may help in control of disease activity.42 But till date, this being an only case report, further observations are required.

11. Recalcitrant Seborrheic Dermatitis:

Cohen SR et al., treated 3 patients of recalcitrant Seborrheic Dermatitis (SD) with Apremilast 30mg twice a day, with significant reduction in disease activity in 3 months.[44] Two Patients remained off-treatment while the third required tacrolimus 0.1% ointment of control of minimal residual disease. There were no significant side-effects to therapy.[44] This isolated case series provides the use of Apremilast in the treatment of SD not showing benefit with conventional treatment.

12. Prurigo Nodularis:

Apremilast has been shown to decrease the levels of IL-22, IL-23, IL-31, INF-γ, TNF-α, among others. IL-31 has been implicated as a pruritogenic cytokine, and has been shown to cause pruritis in atopic dermatitis and psoriasis, with increased levels seen in prurigo nodularis (PN) too.45 Todberg T et al., found no significant change in the clinical parameters or cytokine levels before and after treating 10 patients with Apremilast 30 mg twice a day for 12 weeks.46 Objective parameters like Visual Analog Scale, DLQI, Physician Global Assessment, and Patient Global Assessment did not decrease on treatment. Sleep Parameters and QOL also did not improve with Apremilast.46 This being a low powered study with small sample size points towards the lack of efficacy of Apremilast in managing the disease severity in PN.

13. Perforating Dermatoses

Perforating dermatoses (PDs) include disorders like perforating folliculitis, Kyrle's disease, reactive perforating collagenosis, and elastosis perforans serpiginosa; with shared clinic-histopathological features. The regulation of inflammatory cytokines by Apremilast at mRNA level can target localized lymphocytic and macrophage infiltration found at the sites of perforation in PDs. Apremilast has been shown to improve disorders with interface dermatitis and lymphocytic infiltrate previously.[13] McMichael J et al., used Apremilast 30mg twice a day to treat a patient with Down's syndrome, chronic plaque psoriasis and

PD, with significant resolution of lesions in 3 months after initiation.[47] The improvement was carried forward for the next three months on therapy and the patient was symptom free. Psoriasis responded faster than PD in the patient.[47] The treatment was well-tolerated, requiring no dose reduction.[47]

14. Chronic Actinic Dermatitis

Kaushik A et al., used Apremilast 30mg twice a day increased from 10 mg over a week, to treat a patient of chronic actinic dermatitis (CAD) with steroid dependent disease unresponsive to other immunosuppressive agents and photo-protection.[48]Significant improvement in skin lesions was noted within 4 weeks of starting Apremilast, with complete clearance of skin lesions by 6 weeks of therapy.[48] Steroids (topical as well as oral) were completely tapered and stopped over next 4 weeks while continuing Apremilast. There was no recurrence of lesions or any major adverse effects at 12 weeks of follow-up.[48] However, till date this is the only study in CAD and further studies may provide data regarding safety profile, safe duration of treatment, and any side-effects of prolonged treatment. Apremilast can thus be used as a steroid sparing agent in difficult to treat cases of CAD.

15. Chronic hand eczema

Navarro-Trivino FJN et al., reported the use of Apremilast 30mg twice a day along with super-potent topical steroids in a patient of chronic hand eczema and hepatogenic pruritis not-tolerating retinoids.[49] There was complete resolution of lesions in 1 month of starting therapy with improvement in hepatogenic pruritis and no derangement of liver enzymes. Patient was well-maintained on Apremilast with good control of disease activity.[49] This being an only case, further studies are necessary for quality evidence.

16. Epidermolysis Bullosa Simplex – Generalized severe type

Epidermolysis Bullosa Simplex – Generalized severe (EBS-GS) type is a rare disability characterized by increased skin fragility. Recently, cytokine analysis has shown an inflammatory component to its pathomechanisms when blister fluid for active blisters were analyzed. Cytokines like IL-17, IL-21, IL-22, and IL-5, along with chemokines like CXCL9 and CXCL10 were found to be elevated in the blister fluid.[50] Castela E et al., treated 3 adult patients with active disease with Apremilast 30mg twice a day. There was complete halting of new blister formation after 1 month of treatment, which was sustained for another 10 months on treatment.[50] The other two patients tolerated the drug very well. All patients had mild abdominal pain and diarrhea which resolved on its own within a month of starting the treatment. One of the patients discontinued treatment due to persistent nausea after 7 months, leading to relapse of disease activity two days after stopping Apremilast.[50] However, this being a proof-of-concept study, further in-vivo and in-vitro studies are required to gather more evidence in the use of Apremilast as a therapeutic modality in EBS-GS.

II. Discussion: Future insights with Apremilast in Dermatology

Apremilast, a comparatively new drug providing significant immunomodulatory action through its PDE-4 inhibition, has been used extensively in psoriasis, psoriatic arthritis, and oral ulcers in Behçet'sdisease. However, its pan-immunomodulatory effects, coupled with better safety profile compared to oral corticosteroids and other available steroid sparing agents like cyclosporine, methotrexate, mycophenolate mofetil, azathioprine etc.; make it a lucrative option in treating disorders that have either become dependent on corticosteroids or have started to show significant side-effects to prolonged therapy. Apremilast also does not require stringent laboratory monitoring and hence can also reduce repeated clinical visits and burden on the patient. With the available literature showing its use in varied group of disorders, it is evident that Apremilast is being considered a drug of last resort in treating difficult cases. That may not be due to its efficacy, but more due to its safe nature, with usually mild tolerable side-effects, limited drug-drug interactions, and easy tolerability. However, many of such disorder have a tendency of recurring once the therapy is stopped. Hence, further studies need to have a follow-up period to see relapse of disease activity on stopping the drug. Apremilast thus provides a safer maintenance drug when the disease activity is arrested using conventional mode of treatment. Further comment on the appropriate duration of therapy is also needed. Nearly all of the individual disorders showed improvement, or lack thereof, on standard dosing regimen of 30mg twice a day after titrating from 10mg once a day over a week, as FDA-approved for psoriasis.[1] Dermatoses like atopic dermatitis, where regimen of 40mg twice a day,[4] and cutaneous sarcoidosis where doses of 20mg twice a day was used[12]; show that different doses might be required for better efficacy and tolerability of the drug, and regimens should not be restricted to 30mg twice a day. Future studies should be planned to find the minimal and maximal dosages for therapeutic response and onset of side-effects in patients in varied dermatoses. Available literature on the use of Apremilast is currently limited to isolated case reports of 1 or 2 patients. However, with the extent of improvement described, further studies with larger sample sizes, and preferably randomized placebo-controlled blinded trials should be planned. Furthermore, it becomes imperative to report individual cases and case reports in managing difficult to treat disorders like HS, AD, AA, recurrent ENL, PRP, etc., such that a varied collection of data can be compiled.

References

1. Apremilast: product insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/205437s006lbl.pdf.
2. Maloney NJ, Zhao J, Tegtmeyer K, Lee EY, Cheng K. Off-label studies on apremilast in dermatology: a review. J Dermatol Treat. 2020;31:131-40. https://doi.org/10.1080/09546634.2019.1589641
3. Mobasher P, Heydari Seradj M, Raffi J, Juhasz M, Atanaskova Mesinkovska N. Oral small molecules for the treatment of atopic dermatitis: a systematic review. J Dermatol Treat. 2019;30:550-7. https://doi.org/10.1080/09546634.2018.1544412
4. Simpson EL, Imafuku S, Poulin Y, Ungar B, Zhou L, Malik K, et al. A Phase 2 Randomized Trial of Apremilast in Patients with Atopic Dermatitis. J Invest Dermatol. 2019;139(5):1063-72. https://doi.org/10.1016/j.jid.2018.10.043
5. Mikhaylov D, Pavel A, Yao C, Kimmel G, Nia J, Hashim P, Vekaria AS, et al. A randomized placebo-controlled single-center pilot study of the safety and efficacy of apremilast in subjects with moderate-to-severe alopecia areata. Arch Dermatol Res. 2019;311(1):29-36. https://doi.org/10.1007/s00403-018-1876-y
6. Weber B, Radakovic S, Tanew A. Apremilast for extensive and treatment-resistant alopecia areata: a retrospective analysis of five patients. Eur J Dermatol. 2020;30:165-8. https://doi.org/10.1684/ejd.2020.3749
7. Vossen ARJV, van Doorn MBA, van der Zee HH, Prens EP. Apremilast for moderate hidradenitis suppurativa: Results of a randomized controlled trial. J Am Acad Dermatol. 2019;80:80-8. https://doi.org/10.1016/j.jaad.2018.06.046
8. Kerdel FR, Azevedo FA, Kerdel Don C, Don FA, Fabbrocini G, Kerdel FA. Apremilast for the Treatment of Mild-to-Moderate Hidradenitis Suppurativa in a Prospective, Open-Label, Phase 2 Study. J Drugs Dermatol. 2019;18(2):170-6.
9. Khemis A, Fontas E, Moulin S, MontaudiéH, Lacour J-P, Passeron T. Apremilast in Combination with Narrowband UVB in the Treatment of Vitiligo: A 52-Week Monocentric Prospective Randomized Placebo-Controlled Study. J Invest Dermatol. 2020;140:1533-7.e2. https://doi.org/10.1016/j.jid.2019.11.031
10. Kim HJ, Singer GK, Del Duca E, Abittan BJ, Chima MA, Kimmel G, et al. Combination of apremilast and narrowband ultraviolet B light in the treatment of generalized vitiligo in skin phototypes IV to VI: A randomized split-body pilot study. J Am Acad Dermatol. 2021;85:1657-60. https://doi.org/10.1016/j.jaad.2020.12.073
11. Majid I, Imran S, Batool S. Apremilast is effective in controlling the progression of adult vitiligo: A case series. Dermatol Ther. 2019;32(4):e12923. https://doi.org/10.1111/dth.12923
12. Baughman RP. Efficacy and Safety of Apremilast in Chronic Cutaneous Sarcoidosis. Arch Dermatol. 2012;148:262. https://doi.org/10.1001/archdermatol.2011.301
13. Ravichandran S, Kheterpal MK. Apremilast for the off-label treatment of lichenoid and interface dermatoses. J Am Acad Dermatol. 2020;83(5):1489-1491. https://doi.org/10.1016/j.jaad.2020.05.112
14. Paul J, Foss CE, Hirano SA, Cunningham TD, Pariser DM. An open-label pilot study of apremilast for the treatment of moderate to severe lichen planus: A case series. J Am Acad Dermatol. 2013;68:255-61. https://doi.org/10.1016/j.jaad.2012.07.014
15. Bettencourt M. Oral Lichen Planus Treated with Apremilast. J Drugs Dermatol. 2016;15:1026-8.
16. Hafner J, Gubler C, Kaufmann K, Nobbe S, Navarini AA, French LE. Apremilast Is Effective in Lichen Planus Mucosae-Associated Stenotic Esophagitis. Case Rep Dermatol. 2016;8:224-6. https://doi.org/10.1159/000447051
17. Kushwaha AS, Repka MA, Narasimha Murthy S. A Novel Apremilast Nail Lacquer Formulation for the Treatment of Nail Psoriasis. AAPS PharmSciTech. 2017;18:2949-56. https://doi.org/10.1208/s12249-017-0776-3
18. Thompson BJ, Furniss M, Zhao W, Chakraborty B, Mackay-Wiggan J. An Oral Phosphodiesterase Inhibitor (Apremilast) for Inflammatory Rosacea in Adults: A Pilot Study. JAMA Dermatol. 2014;150(9):1013-4. https://doi.org/10.1001/jamadermatol.2013.10526
19. Georgakopoulos JR, Ighani A, Yeung J. Short- and Long-Term Management of an Acute Pustular Psoriasis Flare: A Case Report. J Cutan Med Surg. 2017;21:452-6. https://doi.org/10.1177/1203475417712499
20. Calleja Algarra A, Aragón Miguel R, Velasco Tamariz V, Prieto Barrios M, Andrés Lencina JJ, Vico Alonso C, et al. Apremilast as a new treatment option for Acrodermatitis continua of Hallopeau. Australas J Dermatol. 2019;60(3):e237-e238. https://doi.org/10.1111/ajd.12990
21. Megna M, Potestio L, Di Caprio N, Tajani A, Fabbrocini G, Annunziata A. Acrodermatitis continua of Hallopeau: Is apremilast an efficacious treatment option? Dermatol Ther. 2022;35(5):e15423. https://doi.org/10.1111/dth.15423
22. Lanna C, Cesaroni GM, Mazzilli S, Lozzi F, Palumbo V, Diluvio L, et al. Nails as immune-privileged sites: A case of disabling Acrodermatitis continua of Hallopeau successfully treated with Apremilast. Dermatol Ther. 2019;32(4):e12946. https://doi.org/10.1111/dth.12946
23. Baron JA. Acrodermatitis of Hallopeau and erosive oral mucositis successfully treated with secukinumab. JAAD Case Rep. 2017;3:215-8. https://doi.org/10.1016/j.jdcr.2017.02.016
24. Charlton D, Moghadam-Kia S, Smith K, Aggarwal R, English JC 3rd, Oddis CV. Refractory Cutaneous Dermatomyositis With Severe Scalp Pruritus Responsive to Apremilast. J Clin Rheumatol. 2021;27(8S):S561-2. https://doi.org/10.1097/RHU.0000000000000999
25. Konishi R, Tanaka R, Inoue S, Ichimura Y, Nomura T, Okiyama N. Evaluation of apremilast, an oral phosphodiesterase 4 inhibitor, for refractory cutaneous dermatomyositis: A phase 1b clinical trial. J Dermatol. 2022;49(1):118-23. https://doi.org/10.1111/1346-8138.16179
26. Bitar C, Maghfour J, Ho-Pham H, Stumpf B, Boh E. Apremilast as a potential treatment for moderate to severe dermatomyositis: A retrospective study of 3 patients. JAAD Case Rep. 2019;5(2):191-4. https://

doi.org/10.1016/j.jdcr.2018.11.019
27. Hansel K, Biondi F, Bianchi L, Tramontana M, Marietti R, Stingeni L. Generalized granuloma annulare successfully treated with apremilast: report of two cases and literature review. Clin Experimental Derm. 2021;46(8):1603-6. https://doi.org/10.1111/ced.14806
28. Bishnoi A, Raj D, Vinay K, Dogra S. Refractory Generalized Granuloma Annulare Treated With Oral Apremilast. JAMA Dermatol. 2019;155:1318. https://doi.org/10.1001/jamadermatol.2019.2130
29. Joshi TP, Tschen J. Apremilast in the Management of Disseminated Granuloma Annulare. Cureus. 2021;13(5):e14918. https://doi.org/10.7759/cureus.14918
30. Narang T, Ashraf R, Kaushik A, Dogra S. Apremilast in multibacillary leprosy patients with chronic and recurrent erythema nodosum leprosum: a prospective single-centre pilot study. J Eur Acad Dermatol Venereol. 2021;35(12):e917-e919. https://doi.org/10.1111/jdv.17585
31. Sánchez-Martínez EM, Melgosa-Ramos FJ, Moneva-Léniz LM, Gegúndez-Hernández H, Prats-Máñez A, Mateu-Puchades A. Erythema nodosum leprosum successfully treated with apremilast: more effective and safer than classic treatments? Int J Dermatol. 2021;60(2):e74-e76. https://doi.org/10.1111/ijd.15205
32. Narang T, Kaushik A, Dogra S. Apremilast in chronic recalcitrant erythema nodosum leprosum: a report of two cases. Br J Dermatol. 2020;182:1034-7. https://doi.org/10.1111/bjd.18233
33. Koschitzky M, Khattri S. Apremilast as a treatment for morphea: A case series. JAAD Case Rep. 2022;19:58-63. https://doi.org/10.1016/j.jdcr.2021.11.009
34. Krase IZ, Cavanaugh K, Curiel-Lewandrowski C. Treatment of Refractory Pityriasis Rubra Pilaris With Novel Phosphodiesterase 4 (PDE4) Inhibitor Apremilast. JAMA Dermatol. 2016;152:348. https://doi.org/10.1001/jamadermatol.2015.3405
35. Pellonnet L, Beltzung F, Franck F, Rouanet J, D'incan M. A case of severe pityriasis rubra pilaris with a dramatic response to apremilast. Eur J Dermatol. 2018;28(1):128-9. https://doi.org/10.1684/ejd.2017.3187
36. Laird ME, Tong LX, Lo Sicco KI, Kim RH, Meehan SA, Franks AG Jr. Novel use of apremilast for adjunctive treatment of recalcitrant pyoderma gangrenosum. JAAD Case Rep. 2017;3(3):228-9. https://doi.org/10.1016/j.jdcr.2017.02.019
37. Kieffer J, Le Duff F, Montaudié H, Chiaverini C, Lacour JP, Passeron T. Treatment of Severe Hailey-Hailey Disease With Apremilast. JAMA Dermatol. 2018;154:1453. https://doi.org/10.1001/jamadermatol.2018.2191
38. Yoto A, Makino T, Mizawa M, Matsui Y, Takemoto K, Furukawa F, et al. Two cases of Hailey-Hailey disease effectively treated with apremilast and a review of reported cases. J Dermatol. 2021;48(12):1945-8. https://doi.org/10.1111/1346-8138.16178
39. Di Altobrando A, Sacchelli L, Patrizi A, Bardazzi F. Successful treatment of refractory Hailey–Hailey disease with apremilast. Clin Exp Dermatol. 2020;45:604-5. https://doi.org/10.1111/ced.14173
40. Riquelme-Mc Loughlin C, Iranzo P, Mascaró JM. Apremilast in benign chronic pemphigus (Hailey–Hailey disease). Clin Exp Dermatol. 2020;45:737-9. https://doi.org/10.1111/ced.14225
41. Chen T, Levitt J, Geller L. Apremilast for treatment of recurrent erythema multiforme. Dermatol Online J. 2017;23(1):13030/qt15s432gx.
42. Nassim D, Alajmi A, Jfri A, Pehr K. Apremilast in dermatology: A review of literature. Dermatol Ther. 2020;33(6):e14261. https://doi.org/10.1111/dth.14261
43. Fässler M, Radonjic-Hoesli S, Feldmeyer L, Imstepf V, Pelloni L, Yawalkar N, et al. Successful treatment of refractory folliculitis decalvans with apremilast. JAAD Case Rep. 2020;6(10):1079-81. https://doi.org/10.1016/j.jdcr.2020.08.019
44. Cohen SR, Gordon SC, Lam AH, Rosmarin D. Recalcitrant Seborrheic Dermatitis Successfully Treated With Apremilast. J Cutan Med Surg. 2020;24:90-1. https://doi.org/10.1177/1203475419878162
45. Zeidler C, Yosipovitch G, Ständer S. Prurigo Nodularis and Its Management. Dermatologic Clinics. 2018;36:189-97. https://doi.org/10.1016/j.det.2018.02.003
46. Todberg T, Skov L, Simonsen S, Kainu K, Zachariae C. Efficacy of Apremilast in Patients with Prurigo Nodularis: A Proof-of-concept Study. Acta Derm Venerol. 2020;100:adv00118-2. https://doi.org/10.2340/00015555-3461
47. McMichael J, Stoff BK. Treatment of a perforating dermatosis with apremilast. JAAD Case Rep. 2021;16:155-7. https://doi.org/10.1016/j.jdcr.2021.08.031
48. Kaushik A, Narang T, Handa S. Successful use of apremilast as a steroid-sparing agent in chronic actinic dermatitis. Dermatol Ther. 2020;33(6):e13809. https://doi.org/10.1111/dth.13809
49. Navarro-Triviño FJ, Cuenca-Barrales C, Vega-Castillo JJ, Ruiz-Villaverde R. Chronic hand eczema and hepatogenic pruritus with good response to apremilast. Dermatol Ther. 2019;32(3):e12879. https://doi.org/10.1111/dth.12879
50. Castela E, Tulic MK, Rozières A, Bourrat E, Nicolas JF, Kanitakis J, et al. Epidermolysis bullosa simplex generalized severe induces a T helper 17 response and is improved by apremilast treatment. Br J Dermatol. 2019;180(2):357-64. https://doi.org/10.1111/bjd.16897