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Off-label studies on apremilast in dermatology: a review

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Abstract

Purpose: Apremilast is a phosphodiesterase-4 inhibitor FDA approved for psoriatic arthritis and moderate to severe plaque psoriasis. In recent years, multiple studies have suggested other potential uses for apremilast in dermatology. A summary of these various studies will be a valuable aid to dermatologists considering apremilast for an alternative indication.

Materials and methods: The PubMed/MEDLINE and [ClinicalTrials.gov](https://www.clinicaltrials.gov) databases were queried with the term ‘apremilast,’ with results manually screened to identify published data on off-label uses of apremilast. The article was structured by the quality of evidence available.

Results: Apremilast use in dermatology beyond plaque psoriasis and psoriatic arthritis is frequently described in the literature, with a mixture of positive and negative results. Randomized controlled data is available for Behçet’s disease, hidradenitis suppurativa, nail/scalp/palmoplantar psoriasis, alopecia areata, and atopic dermatitis.

Conclusion: The relatively safe adverse effect profile of apremilast and its broad immunomodulatory characteristics may make it a promising option in the future for patients with difficult to treat diseases in dermatology, refractory to first line therapies, but further studies will be necessary to clarify its role.

Keywords

Apremilast; psoriasis; off-label

Introduction

Apremilast is an oral phosphodiesterase (PDE)-4 inhibitor licensed in 2014 for psoriatic arthritis and moderate to severe plaque psoriasis. PDE4 is widely expressed in macrophages,

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Disclosure of interest

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lymphocytes, and natural killer cells, as well as nonhematopoietic cells such as keratinocytes and synovial fibroblasts (1,2). In peripheral blood mononuclear cells, PDE4 inhibition is shown to decrease production of multiple pro-inflammatory cytokines including tumor necrosis factor (TNF)- α , interleukin (IL)-12/23, IL-12, and IL-2 while upregulating the anti-inflammatory cytokine IL-10 (1,2). These effects translate to limiting psoriatic plaque thickness and reduction of aberrant keratinocyte hyperproliferation. *In vitro* PDE4 blockade inhibits neutrophil chemotaxis through decreased production of leukotriene B4 and IL-8 (1). In a type-II collagen-induced arthritis mouse model useful for evaluating rheumatoid arthritis, apremilast resulted in decreased synovitis, bone destruction, and greater proportions of regulatory T cells with decreased Th17 and Th1 subsets in draining lymph nodes (3). However, a phase-II clinical trial did not find efficacy of apremilast in patients with long established histories of rheumatoid arthritis (4). The broad range of cell types affected by the immunomodulatory effects of apremilast have promoted interest in investigating further applications, particularly in dermatology.

Adverse effects of apremilast

Apremilast is considered a relatively safe drug with few serious adverse effects reported. Common adverse effects include diarrhea, nausea, upper respiratory tract infection, nasopharyngitis, and headache. These occurred in 5% of patients in the Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis (ESTEEM 1 and ESTEEM 2 randomized controlled trials (RCTs) (5). No increased risk of opportunistic infection or malignancy was reported in these two RCTs. Mean percent weight decreased by 1.53% over a three-year period on apremilast. Of patients who continued treatment for at least 3 years, 21.9% lost over 5% of their initial weight without identifiable medical consequences (5).

Apremilast was associated with rare instances of depressed thoughts, with 1.4% of ESTEEM 1 and 2 patients on apremilast versus 0.5% on placebo self-reporting depressed thoughts over the first 52 weeks. These trials reported an uncompleted suicide attempt in a patient on apremilast and a completed suicide in a patient on placebo (5). Postmarketing studies have not suggested a relationship between apremilast use and suicidality (6). Extremely rare reported adverse effects include chronic tearing, (7) lichenoid reactions, (8) peripheral neuropathy, (8) hyperpigmentation, (9) Fanconi syndrome, (10) purpura annularis telangiectodes of Majocchi, (11) and appearance of lentiginos on resolving psoriatic plaques (12). Most side effects resolved after discontinuation of therapy.

Off-label uses

Because apremilast acts on many cell types and is relatively well tolerated, investigators have explored its efficacy in chronic inflammatory diseases that are sometimes recalcitrant to therapy. Some of these include Behçet's disease, atopic dermatitis, alopecia areata, hidradenitis suppurativa, other variants of psoriasis, cutaneous sarcoidosis, and discoid lupus.

Materials and methods

The PubMed/MEDLINE database was queried using the search term ‘apremilast.’ Abstracts were individually screened to determine whether there was a description of an off-label use of apremilast in dermatology contained within the article. If this determination was not possible from the abstract, the article text was screened, and only articles in English were included. For any disease discussed in this article with published RCT data available, individual case reports or small case series with five patients or fewer on that same disease were omitted from this article (Figure 1). Articles identified were included regardless of positive or negative findings. The [ClinicalTrials.gov](https://www.clinicaltrials.gov) database was also searched using the search term ‘apremilast,’ and any studies regarding dermatologic uses of apremilast that were either in progress, planned, or completed without published results captured in the PubMed query were noted and referenced in this article. The article was structured by the level of evidence available for each off-label use of apremilast. The highest ranked articles were RCTs, followed by either open-label clinical trials or prospective case series, followed by case series and case reports. Any conference abstracts containing off-label uses of apremilast were excluded.

Statistics in this article are reported as described in the articles where the original data were sourced. For various primary and secondary endpoints described in reports, mean or median values for treatment and placebo groups, or at baseline compared to after treatment are included if available. Individual *p* values for primary and secondary endpoints and accompanying 95% confidence intervals (CI) and standard deviations (SD) or standard errors (SE) of a data point are included if available.

Results

Highest level of evidence: RCT data

Alopecia areata—A RCT of apremilast in moderate to severe alopecia areata (baseline 50% scalp involvement) failed to meet its primary endpoint, measured by the proportion of patients achieving a 50% reduction in severity of alopecia tool (SALT) scores (Table 1) (13). Similarly, in a case series of nine patients with recalcitrant alopecia areata, including five patients who had also failed tofacitinib, all nine failed to benefit from apremilast treatment (Table 2) (14).

Atopic dermatitis—Two open-label studies and a phase-II RCT on apremilast use in atopic dermatitis were identified in the literature (15–17). The open-label studies showed variable results, with some patients improving but others without benefit (Table 1) (15,16). These studies were followed by a placebo-controlled RCT which showed only modest efficacy for apremilast 40 mg BID versus placebo which was not seen at the 30 mg BID dose (Table 1). In addition, there were increased rates of adverse events (6 cases of cellulitis) in the apremilast 40 mg BID group versus none in the placebo or 30 mg BID group, and thus, treatment with 40 mg BID was halted in this trial (17).

Behçet’s disease—Apremilast is a promising option for oral ulcers in Behçet’s disease, as symptoms are often refractory to colchicine and topical steroids and its side effect profile

is favorable compared to those of azathioprine, TNF-inhibitors, interferon alpha, and thalidomide (18). The highest level of evidence is a phase-II crossover RCT of 111 patients with at least two oral ulcers present at baseline. There were significant reductions in the number of oral ulcers per patient at 12 weeks of treatment, with endpoints included in Table 1. Onset of effect was rapid, with a decrease in the mean number of ulcers seen within 2 weeks of treatment initiation both in the group initialized to apremilast and in the placebo group when crossed over. Notably, there was an approximate return to the baseline mean number of oral ulcers and in pain ratings 2 weeks after discontinuation of apremilast. The study did also note a significant difference in number of genital ulcers present at baseline versus after treatment compared to placebo, but the overall number of patients with genital ulcers was small (Table 1) (18).

Hidradenitis suppurativa—A RCT of 20 patients (15 apremilast, 5 placebo) with moderate hidradenitis suppurativa (HS) reported a significant difference in patients reaching a greater than 50% decrease in total abscess/nodule count in comparison to placebo, as well as in multiple other secondary endpoints over 16 weeks of apremilast treatment (Table 1) (19).

A case series of nine patients (with three patients dropping out) with moderate to severe HS treated with apremilast for 5–9 months reported five of six patients achieved significant improvement in terms of Sartorius score as well as patient reported metrics including in pain and in the dermatology quality of life index (Table 2) (20).

Nail and scalp psoriasis—In ESTEEM 1 and 2, apremilast also demonstrated significant benefit for patients with nail and scalp involvement as demonstrated by *a priori* analyses on patients with baseline nail psoriasis severity index (NAPSI) 1 and baseline Scalp Physician Global Assessment (ScPGA) scores 3 (Table 1) (21).

The UNVEIL trial also examined nail and scalp psoriasis in patients on apremilast. The trial differed from the ESTEEM 1 and 2 trials as its patients had milder baseline disease (5–10% body surface area versus 10% body surface area involvement in ESTEEM trials), and patients were required to be naïve from systemic and biologic treatments for their psoriasis unlike in the ESTEEM trials. At week 16, it found significant differences between apremilast and placebo in terms of ScPGA score reductions, but not in NAPSI scores or the proportion of patients achieving NAPSI-50 (Table 1). The study may have been underpowered to detect a significant difference for the effect size of apremilast on NAPSI scores at week 16. The trial was converted to an open-label trial after 16 weeks of treatment, and improvement generally extended out to 52 weeks of treatment (22).

Palmoplantar psoriasis—A *post hoc* analysis of patients with palmoplantar psoriasis in ESTEEM 1 and 2 and in the phase IIb PSOR-005 RCTs showed significant differences in Palmoplantar Psoriasis Physician Global Assessment (PPPGA) scores at week 16 on apremilast versus placebo for patients with baseline PPPGA scores 3 (Table 1) (23).

A double-blind placebo-controlled RCT followed this study to evaluate patients with a baseline PPPGA score 3 and at least 10% of palm and sole area disease coverage at

baseline. The patients received apremilast 30 mg BID or placebo for 16 weeks, after which all patients were started on apremilast 30 mg BID from week 17–32 (24). The study failed to meet its primary endpoint (proportion reaching PPPGA of 0 or 1 at week 16), but did note significant differences in secondary endpoints including the proportion of palmoplantar psoriasis area and severity index (PPPASI)-75 responders (Table 1) (24).

Highest level of evidence: open-label, investigator-initiated trials

Cutaneous sarcoidosis—An open-label trial characterized the efficacy of apremilast for chronic cutaneous sarcoidosis. The Sarcoidosis Activity and Severity Index (SASI) score and investigator scored assessments of photographed lesions before/after therapy were the primary measures of the study (Table 1). After discontinuation of apremilast, three patients relapsed with worsening of their skin lesions (25).

Discoid lupus erythematosus—An open-label trial examined apremilast in eight patients with active discoid lupus, with only four completing the regimen. These patients received 20 mg BID for a total of 85 days without any other concomitant therapy. Two patients discontinued due to transient adverse effects (neuropathy, lichenoid reaction), and two discontinued due to disease progression. Outcomes were measured based on changes in the patient's Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) activity and damage scores, and the trial demonstrated significant differences in these metrics (Table 1). In addition, of the four patients that completed the trial, two noted complete regression of scalp lesions (8).

Lichen planus—The largest study to date on apremilast in lichen planus is an open-label study on 10 patients refractory to treatment with topical steroids (26). In this, three of the 10 patients achieved the primary endpoint of an improvement in the Physician Global Assessment (PGA) by 2 grades or more. The overall cohort demonstrated significant differences in lesion counts and other secondary endpoints at the end of the 12-week treatment period (Table 1). Notably, only one patient in this study had oral mucosal involvement. In this patient, the involvement of the buccal mucosa decreased from 40% to 12% over the course of treatment (26). In addition, there was no significant difference in any primary or secondary endpoints of the study between the end of treatment period, and 4 weeks after this point in time (26).

Only small case series and case reports were available regarding apremilast and oral lichen planus (27–29). They reported favorable outcomes including cases involving desquamative gingivitis and esophageal involvement (Table 2) (28,29).

Rosacea—An open-label study of 10 patients with moderate to severe erythematotelangiectatic and papulopustular rosacea (>10 papules/pustules) receiving apremilast 20 mg BID over 12 weeks failed to meet its primary endpoint (Table 1) (30).

Highest level of evidence: case series and case reports

Apremilast has seen use in a variety of other conditions including pityriasis rubra pilaris, Hailey-Hailey disease, vitiligo, and generalized pustular psoriasis. These and other potential

indications are described in case reports and small case series as investigators seek out other potential uses for apremilast (Table 2). In some instances, apremilast is used as part of combination therapy in difficult to treat scenarios, with details provided in Table 2.

Additional studies on off-label uses of apremilast in dermatology

Many additional open-label studies and RCTs are in progress to identify other potential uses of apremilast and clarify its role in particular indications (Table 3).

Discussion

For potential off-label uses of apremilast, high-quality data are limited and results mixed, with RCT data only available for Behçet's disease, nail/scalp psoriasis, palmoplantar psoriasis, atopic dermatitis, alopecia areata, and hidradenitis suppurativa. Open label trials have shown a mix of positive and negative results for cutaneous sarcoidosis, discoid lupus, lichen planus, and rosacea. The large amount of small case series and case reports on off-label apremilast use likely suffer from positive publication bias, and real-world experience with off-label apremilast use is lacking in the literature.

Overall, apremilast has a relatively safe side effect profile and exerts powerful immunomodulatory effects on multiple cell types involved in the pathophysiology of chronic inflammatory skin diseases. It lacks the strong immunosuppressive activity associated with medications such as cyclosporine, methotrexate, or tofacitinib that are associated with increased risk for malignancy or infection. No requirement for routine laboratory monitoring, and availability in oral form are additional advantages. As a result, it may be a promising new drug for other difficult-to-treat dermatological conditions in which large groups of patients are refractory to gold standard treatments. In select recalcitrant cases, it may be a useful adjunct to supplement other therapies, although cost may be a significant barrier. Additional mechanistic and clinical studies will be needed to further investigate and determine the best potential use of apremilast in dermatology.

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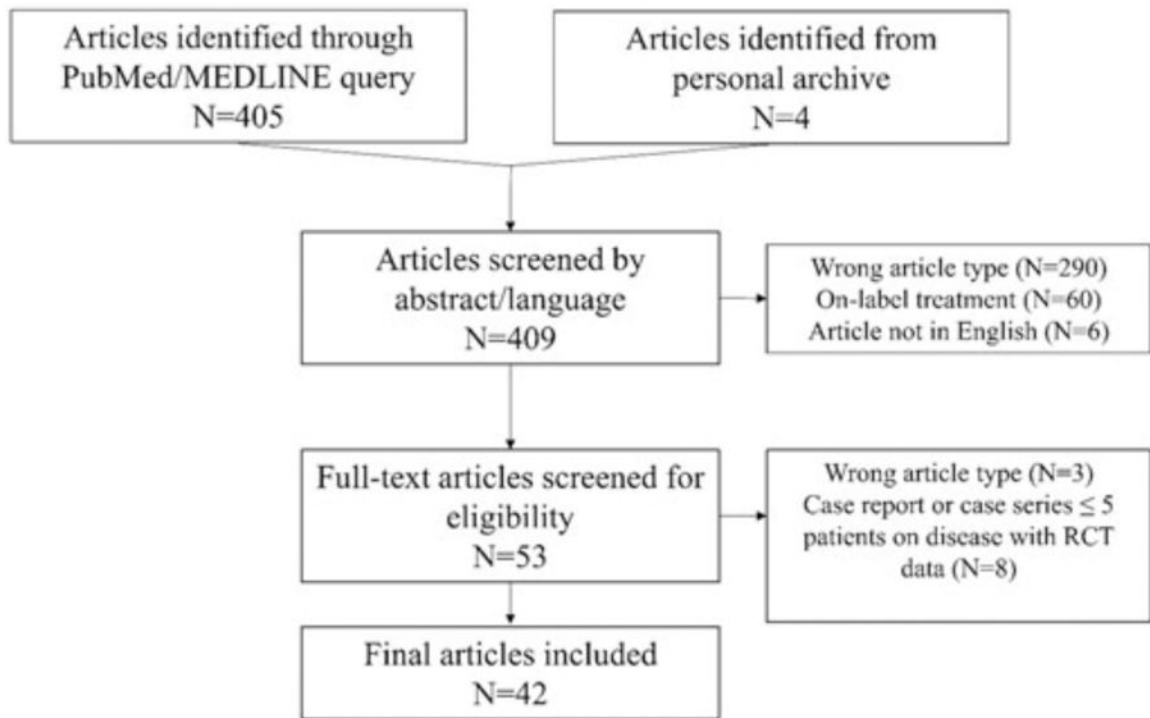


Figure 1. Article selection flow sheet for identifying articles on descriptions of apremilast use beyond plaque psoriasis and psoriatic arthritis in the dermatology literature.

Randomized controlled trial data and other prospective data on apremilast for indications beyond psoriasis and psoriatic arthritis.

Table 1.

Disease	Study Type (number of patients on apremilast)	Efficacy	Treatment Duration (dose)	Citation
Alopecia areata	RCT (20)	Mean change in SALT score at 24 weeks compared to baseline $-1.45\% \pm 5.39$ (SE) in apremilast vs $-9.01\% \pm 6.37$ (SE, $p = .38$) on placebo; 1/20 in apremilast group and 1/10 in placebo group reached 50% reduction in SALT score at week 24	24–48 weeks (30 mg BID)	Mikhaylov et al. (13)
AD	RCT (121)	In 30 mg BID group at week 12, mean -26.0% (SD 40.1) change from baseline EASI score vs in placebo mean -11.0% change (SD 71.2), effect size -15.0% with 95% CI -34.5% to 4.5% ($p < .05$); in 40 mg BID group at week 12, -31.6% (SD 44.6) change in EASI score compared to -11.0% (SD 71.2) in placebo, effect size -20.6% with 95% CI -39.7 to -1.5 ($p = .04$)	12–24 weeks (30/40 mg BID)	Simpson et al. (17)
AD	Open-label trial (16)	In 20 mg BID group (6 patients), reduction in mean EASI score from 30.9 to 22.1 (no p value reported) at 3 months; in the 30 mg BID group (10 patients), decrease in the mean EASI score from a baseline of 21.4 to 13.2, $p = .008$; reduction in itch by a visual analog scale from a baseline of 45.8 mm to 32.4 mm (no p value reported); improvement in DLQI (10.1 to 3.8, $p = .01$)	3–6 months (20/30 mg BID)	Samrao et al. (15)
AD/ACD	Open-label trial (5 AD, 4 ACD, 1 AD + ACD)	20% 2 improvement in IGA score, 10% achieved EASI-75, additional 10% achieved EASI-50	12 weeks (20 mg BID)	Volf et al. (16)
Behcet's disease	RCT (111)	Mean number oral ulcers at end of treatment $(0.5 \pm 1.0$ vs. 2.1 ± 2.6^d , $p < .001$); in apremilast group, median number oral ulcers at week 12 = 0 vs 2 in placebo group; pain via a visual analog scale -44.8 ± 29.8^d compared to baseline on apremilast for 24 weeks ($p < .001$); 71% on apremilast achieved complete response in terms of oral ulcer resolution, compared to 29% in controls ($p < .001$); 0 of 10 patients with baseline genital ulcers remained with ulcers at week 12 of apremilast, compared to 3 out of 6 on placebo ($p = .04$)	12–24 weeks (30 mg BID)	Hatemi et al. (18)
Cutaneous sarcoidosis	Open-label trial (15)	Significant reductions on apremilast compared to baseline in the induration score of all lesions at 4 ($p < .002$) and 12 weeks ($p < .005$), as well in the index lesion (highest baseline SASI score) at week 4 ($p < .05$) and week 12 ($p < .02$), no significant difference in other components of the SASI score (erythema, desquamation, or involved area); normalized mean rating of photographs by investigators after 12 weeks compared to baseline = 2 (somewhat better after therapy)	12 weeks (20 mg BID)	Baughman et al. (25)
Discoid lupus erythematosus	Open-label trial (8)	4 dropped out ^b ; Modified ITT analysis showing decreased median CLASI activity score at day 85 ($p = .01$), but not at day 57, compared to baseline; treatment group of 4 patients showed a significant reduction in CLASI activity scores ($p = .03$) at day 85 vs baseline; CLASI damage scores with significant decreases at day 85 in both the modified ITT ($p = .004$) and completed treatment groups ($p = .01$); 2 of 4 patients who completed treatment with complete regression of scalp lesions	12 weeks (20 mg BID)	De Souza et al. (8)
Hidradenitis suppurativa	RCT (15)	8 of 15 with $>50\%$ decrease in total abscess/nodule count, meeting criteria for HISCER (0 out of 5 in placebo group achieved HISCER); significant decreases in abscess/nodule count vs baseline (mean difference -2.6 ; 95% CI -6.0 to -0.9 , $p = .011$), in numerical rating scores for pain (-2.7 ; 95% CI -4.5 to -0.9 ; $p = .009$), and in scores for itch (-2.8 ; 95% CI -5.0 to -0.6 ; $p = .015$), but not in the DLQI (-3.4 ; 95% CI -9.0 to 2.3 ; $p = .230$)	16 weeks (30 mg BID)	Vossen et al. (19)
Hidradenitis suppurativa	Prospective case series (9)	($n = 9$), 3 dropped out ^c ; Of remaining 6, significant reduction in Sartorius score (73.17 \pm 67.76 to 56.17 \pm 44.89 ^d , $p = .028$); decrease in pain (7.17 \pm 0.98 vs 2.00 \pm 2.10 ^d after therapy, $p = .026$) via visual analog scale; improvement in DLQI (21.33 \pm 8.91 to 9.33 \pm 5.85 ^d after therapy, $p = .027$)	Up to 9 months (30 mg BID)	Weber et al. (20)

Disease	Study Type (number of patients on apremilast)	Efficacy	Treatment Duration (dose)	Citation
Lichen planus	Open-label trial (10)	3/10 patients achieved PGA improvement 2; in overall cohort decreases from baseline to week 12 in PGA (median 3 vs a median of 2 at end of treatment, $p=0.078$), lesion count (median 35 vs 20.5, $p=0.002$), DLQI (median 15.5 vs 4, $p=0.002$), subject visual analog scale for itch (median 67 at baseline to 18.5, $p=0.0059$), and Target Area Lesion Severity Score (8.5 at baseline to 3.5, $p=0.0078$)	12 weeks (20 mg BID)	Paul et al. (26)
Nail psoriasis (ESTEEM 1)	RCT (363)	NAPSI percentage change of -22.5% vs $+6.5\%$ in placebo ($p<0.001$) at week 16, -43.6% vs baseline at week 32; 33.3% vs 14.9% ($p<0.001$) on placebo achieved a NAPSI-50 response at week 16 and 45.2% on apremilast achieved NAPSI-50 on apremilast at week 32	52 weeks (30 mg BID)	Rich et al. (21)
Nail psoriasis (ESTEEM 2)	RCT (175)	NAPSI percentage change of -29.0% vs -7.1% in placebo ($p<0.001$) at week 16, -60.0% vs baseline at week 32; 44.6% vs 18.7% ($p<0.001$) on placebo achieved a NAPSI-50 response at week 16 and 55.4% achieved NAPSI-50 on apremilast at week 32	52 weeks (30 mg BID)	Rich et al. (21)
Nail psoriasis (UNVEIL)	RCT (56)	Mean percentage NAPSI score change in target nail: -10.5% in placebo vs -28.9% in apremilast group ($p=.1215$); percentage of NAPSI-50 responders 18.5% in placebo vs 26.8% on apremilast ($p=0.025$); at week 52, for patients on apremilast for 52 weeks, -51.9% change in NAPSI score in index nail. 62.5% of patients achieved a NAPSI-50 response	16–52 weeks (30 mg BID)	Strober et al. (31)
Scalp psoriasis (ESTEEM 1)	RCT (374)	46.5% on apremilast vs 17.5% on placebo with a baseline ScPGA of 3 achieved a ScPGA of 0 or 1 at week 16 ($p<0.01$), at week 32, 37.4% of patients on week 32 of apremilast achieved ScPGA of 0 or 1, 43.6% of patients switched from placebo to apremilast at week 16 achieved ScPGA of 0 or 1 at week 32	52 weeks (30 mg BID)	Rich et al. (21)
Scalp psoriasis (ESTEEM 2)	RCT (176)	40.9% on apremilast vs 17.2% on placebo with a baseline ScPGA of 3 achieved a ScPGA of 0 or 1 at week 16 ($p<0.01$), at week 32; 32.4% of patients at week 32 of apremilast achieved ScPGA of 0 or 1, 50.7% of patients who switched from placebo to apremilast at week 16 achieved ScPGA of 0 or 1 at week 32	52 weeks (30 mg BID)	Rich et al. (21)
Scalp psoriasis (UNVEIL)	RCT (112)	ScPGA of 0 or 1 with 2-point reduction from baseline: 20.0% on placebo vs 38.4% on apremilast ($p=0.0178$); at week 52, 33.1% of patients on apremilast for 52 weeks with ScPGA of 0 or 1	16–52 weeks (30 mg BID)	Strober et al. (31)
Psoriasis (palmoplantar)	Post-hoc analysis of RCT (274)	In those with baseline PPPGA 3, 48% on apremilast vs 27% on placebo achieved PPPGA of 0 or 1 at week 16 ($p=0.021$); in those with PPPGA 1, 46% on apremilast vs 25% on placebo achieved a PPPGA of 0 at week 16 ($p=0.001$)	16 weeks (30 mg BID)	Bissonnette et al. (23)
Psoriasis (palmoplantar)	RCT (50)	In patients with baseline PPPGA 3, at week 16, 14% of patients achieved PPPGA of 0 or 1 vs 4% on placebo ($p=.1595$); apremilast group PPPASI -7.4 ± 7.1 vs placebo -3.6 ± 5.9^d ($p=0.0167$) at week 16; 22% achieved PPPASI-75 at week 16 on apremilast vs 8% on placebo ($p = 0.0499$); at week 16, 36% on apremilast vs 22% on placebo achieved PPPASI-50 ($p=.119$); at week 32 of apremilast 38% achieved PPPASI-75	32 weeks (30 mg BID)	Bissonnette et al. (24)
Rosacea	Open-label trial (10)	In patients with moderate to severe erythematotelangiectatic and papulopustular rosacea (baseline >10 papules/pustules), no significant difference between mean baseline papule/pustule count (36.6, SD 22.8) compared to after apremilast treatment for 12 weeks (36.4, SD 20.4); significant improvements in the Physician Global 7-Point scale ($p=0.02$) and Physician Overall Erythema Severity score ($p = 0.001$), erythematotelangiectatic rating ($p=.005$), and nontransient erythema rating ($p=.04$)	12 weeks (20 mg BID)	Thompson et al. (30)

Abbreviations: ACD: allergic contact dermatitis; AD: atopic dermatitis; BID: twice per day; CI: confidence interval; CLASI: Cutaneous Lupus Erythematosus Disease Area and Severity Index; DLQI: Dermatology quality of life index; EASI: Eczema Area and Severity Index; HlSCR: Hidradenitis Suppurativa Clinical Response; IGA: Investigator's Global Assessment; ITT: intention to treat; NAPSI: nail psoriasis severity index; PASI: Psoriasis Area and Severity Index; PGA: Physician Global Assessment; PPPASI: Palmoplantar psoriasis area and severity index; PPPGA: palmoplantar psoriasis physician global assessment; RCT: randomized controlled trial; SALT: severity of alopecia tool; SASI: Sarcoidosis Activity and Severity Index; ScPGA: Scalp Physician Global Assessment; SD: standard deviation; SE: standard error.

^dStatistics reported as a mean \pm 1 SD.

Reasons for dropping out: lichenoid reaction, neuropathy, and disease progression in two patients.
Dropped out of study due to early discontinuation following reflux, depression, and insurance coverage issues.

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Table 2.

Miscellaneous case reports/series on off-label apremilast use.

Disease	Efficacy	Adjunctive medication	Time to onset of effect	Length of known remission	Citation
Alopecia areata	(n = 9) No hair regrowth in any patient over 3–6 months of treatment		N/A	N/A	Liu and King (14)
Simple aphthous stomatitis	(n = 1) Complete clearance		6 weeks	1 year	Schibler et al. (32)
Lamellar ichthyosis with concomitant plaque psoriasis, (with cicatricial ectropion/corneal ulceration due to ichthyosis)	(n = 1) Improvement in both lamellar ichthyosis and psoriasis vulgaris		Unk	2 years	Abboud et al. (33)
Complex aphthae	(n = 2) Complete clearance		Unk	6–7 months	von der Weth et al. (34)
Epidermolysis bullosa simplex, generalized severe	(n = 3) Decreased number of blisters at 1 month in all 3 patients. Two patients stable at 8 and 10 month follow up, one experienced recurrence after discontinuation at month 7		10–30 days	7–10 months	Castela et al. (35)
Hailey-Hailey Disease	(n = 4) 4/4 with moderate to near complete resolution at 6 months; 2/4 experienced flares on apremilast after this point		1 month	6 months	Kieffer et al. (36)
Lichen planopilaris	(n = 4) 3 partial responses, 1 significant improvement, 2 discontinued due to gastrointestinal discomfort		Unk	Unk	Hadi and Lebwohl (37)
Oral lichen planus	(n = 3) Symptoms improved or completely cleared	1 of 3 on adjunctive prednisone	2–4 weeks	3–6 months	Bettencourt (27)
	(n = 1, with desquamative gingivitis) marked improvement in buccal and gingival lesions		Unk	4 months	AbuHilal et al. (28)
	(n = 1, with esophagitis and esophageal stenosis) Reduction in stomatitis and esophageal stenosis with consequent dysphagia resolved		4 weeks	Unk	Hafner et al. (29)
Psoriasis (erythrodermic)	(n = 1, with pustular component) Condition improved (PASI 44.0 → 26.4 at day 10), but experienced new onset atrial fibrillation, thus apremilast was discontinued		10 days	N/A	Arcilla et al. (38)
Generalized pustular psoriasis, von Zumbusch type	(n = 1) Complete clearance at day 20, but plaques recurred at 3 months		20 days	3 months	Papadavid et al. (39)
Generalized pustular psoriasis with acrodermatitis continua of Hallopeau	(n = 1) Complete clearance of plaque psoriasis and generalized pustular psoriasis		2 weeks	9 months	Jeon et al. (40)
Erythema multiforme (oral involvement)	(n = 4) Transitioned to apremilast + infliximab after cyclosporine 200 mg BID for 2 weeks significantly improved acropustulosis (experienced adverse effects from cyclosporine), maintained on apremilast + infliximab with minimal onychodystrophy and maintained pustule clearance at 6 months	Infliximab 5 mg/kg every 8 weeks	N/A	6 months	Georgakopo-ulos et al. (41)
Palmoplantar pustulosis	(n = 4) near complete to complete resolution of lesions achieved for all patients		2 weeks in 3 of 4 patients	2–6 months	Chen et al. (42)
	(n = 3) Near-complete response		2 weeks	8 months	Eto et al. (43)

Disease	Efficacy	Adjunctive medication	Time to onset of effect	Length of known remission	Citation
	(n = 1) Symptomatic improvement noted		4 weeks	1 years	Haebich et al. (44)
	(n = 1) Near-complete response	Ustekinumab 90 mg every 8 weeks	2 months	6 months	Mayba and Gooderham (45)
Anti-laminin γ 1 pemphigoid with psoriasis vulgaris	(n = 1) Controlled psoriasis and pemphigoid lesions	Prednisone	4 weeks	Unk	Waki et al. (46)
Pityriasis rubra pilaris	(n = 1) Near complete resolution of skin findings		4 weeks	8 months	Krase et al. (47)
	(n = 1) Complete response and remission		<1 week	7 months	Pellonnet et al. (48)
	(n = 1) Complete response and remission		2 months	10 months	Molina-Figuera et al. (49)
	(n = 1) No clinical response after 15 wks		N/A	N/A	Maloney et al. (50)
	(n = 1) No improvement after 2 months		N/A	N/A	Campanelli and Sauder (51)
Pyoderma Gangrenosum	(n = 1) Complete response and remission		2 months	6 months	Cho et al. (52)
	(n = 1) Complete closure of back erosion, partial response in thigh erosion	Prednisone, methotrexate	0–4 months	4–5 months	Laird et al. (53)
SAPHO Syndrome	(n = 1, with palmoplantar pustulosis) Stable PPPASI score maintained on apremilast after patient went into remission on secukinumab but developed hypersensitivity reaction		N/A	7 months	Adamo et al. (54)
Vitiligo	(n = 1) Mild improvement with 60–70% repigmentation at month 11	IM triamcinolone	3 months	13 months	Huff and Gottwald (55)

Abbreviations: IM: intramuscular; N/A: not applicable; PPPASI: palmoplantar psoriasis area and severity index; SAPHO: synovitis, acne, pustulosis, hyperostosis, and osteitis; Unk: unknown.

Clinical trials on apremilast planned, in progress, or completed with results not published in a journal.

Table 3.

Disease	Study Type	Number of patients (estimated or actual)	Study Number	Citation
Hidradenitis Suppurativa	Open-label	20	NCT02695212 ^a	(56)
Nail psoriasis	Open-label	20	NCT03022617	(57)
	Open-label	50	NCT03616561	(58)
Scalp psoriasis	RCT	303	NCT03123471	(59)
	RCT	90	NCT03553433	(60)
	RCT	40	NCT03656666	(61)
Female genital erosive lichen planus	Open-label	15	NCT03690544	(62)
Recurrent aphthous stomatitis	Open-label	15	NCT03576287	(63)
Prurigo nodularis	Open-label	5	NCT00869089 ^b	(64)
Frontal fibrosing alopecia	Open-label	20	NCT03422640	(65)
Central centrifugal cicatricial alopecia	Open-label	20	NCT03521687	(66)
Chronic idiopathic pruritus	Open-label	10	NCT03239106	(67)
Chronic hand dermatitis	Open-label	10	NCT03741933	(68)
Dermatomyositis (as add-on therapy for cutaneous manifestations)	Open-label	10	NCT03529955	(69)
	Open-label	5	NCT01140503 ^c	(70)
Nummular eczema	RCT	40	NCT03160248	(71)
Vitiligo with NB-UVB	Open-label	20	NCT03123016	(72)
	RCT	80	NCT03036995	(73)

Abbreviations: NB-UVB: narrow band ultraviolet B; RCT: randomized controlled trial.

^a Study completed but results are unavailable.

^b 2 of 5 patients completed trial, in these 2 poor to minimal response to therapy.

^c Study terminated due to slow recruitment of patients.