SKIN

IN-DEPTH REVIEW

Apremilast as an Off-Label Therapeutic Agent: A Comprehensive Review of Safety and Efficacy Data in the Literature for Combination Therapy and Inflammatory Dermatoses

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ABSTRACT

Objective: To review the literature regarding the efficacy and safety of off-label use of apremilast in combination therapies for psoriasis and psoriatic arthritis and for other currently off-label inflammatory dermatoses.

Methods: The Medline database was queried for all relevant articles published between 2014 and 2021 using exploded MeSH terms and keywords pertaining to the following themes: off-label, combination therapy, biologics, biologic therapy, methotrexate, and systemic psoriasis therapy. The Boolean term "AND" was used to find the intersection of these themes with the term "apremilast."

Results: 8 case series and 6 case reports investigated the use of apremilast in combination therapy for psoriasis and psoriatic arthritis. Addition of apremilast improved PASI scores by 31.8-77.4% among case series and 80-100% among case reports with adverse effects primarily consisting of gastrointestinal symptoms. 5 randomized-control trials (RCT), 9 open-label trials, 18 case series, and 30 case reports investigated the use of apremilast for off-label dermatoses. In RCTs, apremilast showed potential efficacy for atopic dermatitis and hidradenitis suppurativa. Open-label trials found apremilast efficacious for atopic dermatitis, allergic contact dermatitis, chronic pruritus, cutaneous sarcoidosis, discoid lupus erythematosus, hidradenitis suppurativa, lichen planus, prurigo nodularis, rosacea, and vitiligo.

Limitations: Small sample size and short follow up duration for available randomized-control and open-label trials. Current data from case series/reports potentially limits generalizability of findings.

Conclusion: Apremilast's safety profile makes it a potential efficacious, non-biologic systemic agent for monotherapy and combination therapy for a wide range of inflammatory dermatoses.

INTRODUCTION

Apremilast is an oral, small molecule phosphodiesterase 4 (PDE4) inhibitor that was originally US food and drug administration (FDA) approved for the management of psoriatic arthritis and chronic plaque psoriasis in 2014.[1] By inhibiting the degradation of cyclic adenosine monophosphate (cAMP), apremilast modulates the activity of multiple immune cell lines including macrophages, neutrophils and natural killer cells within the Th1 and Th17 pathways as well as myriads of pro-inflammatory cytokines including tumor necrosis factor alpha (TNF-α), interleukin 12 (IL-12) and IL-23 as well as anti-inflammatory cytokines such as IL-10.[2,3] Clinically, this has translated into successful,

non-biologic oral therapy for patients with psoriasis and psoriatic arthritis with first signs of meaningful response notable within 2 weeks.[4-6]

The efficacy of apremilast is complemented by its safety profile.[7] Clinical trials have shown that the most common treatment-emergent adverse events (TEAE) are gastrointestinal related (diarrhea, nausea), weight loss, upper respiratory tract infections and that apremilast does not increase risk of malignancy or opportunistic infections.[7] Furthermore, post-marketing surveillance as well as clinical and pharmacological data have not supported (if not refuted) correlation between depression and apremilast.[8,9]

Because apremilast is an oral, non-biologic systemic agent with a favorable safety profile, there has been growing interest in its application for other off-label use in either combination therapy for FDA-approved conditions or for other inflammatory dermatoses. This growing interest in expanding indication earned apremilast FDA-approval in 2019 for use in Behçet's syndrome in 2019.[1,10] Additional studies have also investigated the off-label use of apremilast in conjunction with other therapies, including biologics and methotrexate for more recalcitrant cases of psoriasis or psoriatic arthritis.[6,11-13] The purpose of this study is to review the literature for off-label uses of apremilast with respect to other inflammatory conditions as well as combination therapies.

METHODS

A review of the literature pertaining to off-label use of apremilast as well as combination therapies was conducted. The Medline database was queried for all relevant articles published between 2014 and 2021 using exploded MeSH terms and keywords pertaining to the following themes: off-label, biologics, methotrexate, and systemic psoriasis therapy. The Boolean term "AND" was used to find the intersection of these themes with the term "apremilast." Studies were limited to English-only manuscripts with available full-text. Details regarding study design (case reports, case-series, open-label trial or randomized controlled trials (RCTs)), outcomes, follow-up duration, and treatment-emergent adverse events (TEAE) were abstracted.

RESULTS

Combination Therapy for Psoriasis and Psoriatic Arthritis

The advances in understanding psoriasis as a systemic inflammatory condition fostered the development of immunomodulating targeted biologic agents, many of which are able to reach 100% improvement as captured by the psoriasis activity and severity index (PASI100).[14,15] However, longitudinal studies have demonstrated a decrease in efficacy of certain biologic agents over time.[15-18] This secondary failure or biologic fatigue can be observed in up to 20-30% of patients as little as 1-4 years after initially reaching PASI75, potentially due to the creation of neutralizing anti-drug antibodies leading to subtherapeutic serum drug levels.[15-17] While switching biologics can recapture efficacy, these effects may not be durable and are also dependent on the selected drug and drug class.[18]

Alternatively, studies have also investigated combining different drug classes and mechanisms of action with durable and efficacious results.[13,19-31] Several case series and reports found patients who experienced secondary failure while on a

biologic or other non-biologic systemic agents (e.g. methotrexate) obtained PASI50-100 throughout a follow up period of 3-9 months with similar treatment-emergent adverse effects [TEAE] to monotherapy (Table1).[13,19-25,26-31] Collectively several case studies have noted that the addition of apremilast to either systemic biologic or nonbiologic therapies had a mean additional improvement in PASI scores between 31.8-77.4% for patients that were either unsatisfied with their current regimen or experienced secondary failure.[13,19,21,22] While additional efficacy varied depending on the pre-apremilast regimen, most patients saw durable results with a range of means between 12 and 31 weeks.[13,19-25] Several studies also found additional benefit in combining narrow-band UVB (nbUVB) phototherapy with apremilast, with additional improvements in PASI of 76.4-81.5%.[13,25]

Furthermore, none of these therapeutic combinations resulted in severe infections in the management of psoriasis or psoriatic arthritis. Only one study noted 3 upper respiratory tract infections over 16 weeks.[22] In one study, 14 patients opted to discontinue apremilast prior to the 12-week follow-up due to "intolerable" gastrointestinal symptoms (n = 9), headache (n = 1), a transient urticarial rash (n = 1) and 2 due to patient preference.[28] Overall, 20-25% of patients experienced self-limited diarrhea, nausea, and weight loss. Depression or depressive symptoms were not noted in patients on any combination therapy with apremilast.[18-25] Several studies compared apremilast monotherapy to combination therapy with apremilast and found no significant difference in the rate of treatment-emergent adverse effects (TEAE).[22,23]

Several case reports also found utility of apremilast in combination therapies, especially in more recalcitrant cases of psoriasis, which had failed multiple topical and systemic agents.[26-31] In 5 out of the 6 cases, patients saw additional significant reduction in the severity of their psoriasis with the addition of apremilast to their systemic agent, with only 1 instance of mild diarrhea.[26,28-31] One report further detailed improvement in both psoriasis and psoriatic arthritis with the sequential initiation of apremilast 30 mg BID and secukinumab 300 mg monthly with achieved PASI100 and reduced eight tender and seven swollen joints to 2 tender and no swollen joints in 16 weeks.[31] Only 1 case, in which the patient had a rare HLA-C*18:01 mutation causing multiple-regimen resistant, recalcitrant psoriasis, did not see improvement with the addition of apremilast to ustekinumab.[27]

Together these data demonstrate a pattern of efficacy and safety when apremilast is added or included in combination therapy, especially for patients with a history of recalcitrant psoriasis.

Randomized-control and open-label trials investigating off-label apremilast use

Apremilast's unique combination of safety profile and multifaceted mechanism of action have sparked interest into potential uses in other inflammatory dermatoses. As a result, several randomized-control trials (RCT), open-label trials, case reports, and case series have investigated, with varying degrees of success, how apremilast may fit into the therapeutic framework for conditions including (but not limited to) other papulosquamous, vesiculobullous, granulomatous dermatoses, connective tissue, and pigmentary disorders (Table 3-5).[32-96]

Alopecia Areata

A randomized control trial of patients with long standing moderate to severe alopecia areata (AA) (>50% involvement of the scalp)

Table 1. Case Series of Combination Therapies including Apremilast for Psoriasis and Psoriatic Arthritis

Study	Mean Age (SD)	Sex M/F	Add'l PsO subtype	Combination Regimen (n)	Follow-up Period Weeks, mean (SD)	Mean %PASI* Improvement (SD)	TEAE† (n)			
							Diar	Naus	Wt	Infxn
AbuHilal et al.[13]	48.8	7/3	--	+nbUVB (10)	12 (0)	81.5	4	1	--	--
	47.3	5/10		+Methotrexate (15)		67.8	4	2	--	--
	37.7	1/3		+Cyclosporine (4)		63.3	1	1	--	--
	52.6	4/1		+Acitretin (5)		76.5	2	1	--	--
	52.4	5/8		+TNF-inhibitor (13)		70.4	3	2	--	--
	53.2	5/2		+TNF-inhibitor & Methotrexate (7)		76.8	2	1	--	--
	53.4	6/7		+Ustekinumab (13)		77.4	4	2	--	--
Takamura et al.[19]	51.4 (2.4)	14/0	--	+Infliximab (1)	24 (0)	77	--	--	--	--
			2 PsA	+Adalimumab (3)		31.8 (32.1)	1	--	2‡	--
			--	+Secukinumab (2)		35.7 (22.2)	1	--	--	--
			--	+Ixekizumab (2)		39.6 (10.3)	1	1	--	--
			1 PsA	+Ustekinumab (6)		67.2 (30.0)	2	--	--	--
Metyas et al.[20]	--	--	22 PsA	+Adalimumab (6)	R: 12-42	--	2	2	1	--
				+Infliximab (4)	R:4-68					
				+Golimumab (3)	R:12-44					
				+Certolizumab Pegol (2)	R:4-36					
				+Etantercept (2)	R:4-28					
				+Ustekinumab (5)	R:16-106					
Saccheli et al.[21]	48.25 (10.9)	1/3	2 PsA	+Secukinumab (4)	31 (5.03)	75.4 (20.7)	Yes	--	--	--
Ighani et al.[22]	51.5 (11.9)	51/38	51 PsA	+Phototherapy (2)	16 (0)	51.3	15	10	9	URI (4)
				+Cyclosporine (3)						
				+Methotrexate (19)						
				+Sulfasalazine (2)						
				+Etanercept (18)						
				+Adalimumab & Methotrexate (8)						
				+Infliximab (7)						
				+Adalimumab (5)						
				+Secukinumab (3)						
				+Ustekinumab (14)						
				+Ustekinumab & Acitretin (3)						
				+Infliximab & Methotrexate (2)						
Abignano et al.[23]	51.5 (2)	17/15	32 PsA	+Methotrexate (16)	22.9 (13.5)	--	5	2	--	--
			26 PsO	+Sulfasalazine (1)						

				+Hydroxychloroquine (2) +Leflunomide (1) +Certolizumab (1) +Golimumab (2) +Ustekinumab (1) +Adalimumab (1) +Etanercept (1 +Secukinumab (1 +Tocilizumab (1) +Methotrexate & Sulfasalazine (1) +Methotrexate & Hydroxychloroquine (1) +Methotrexate & Certolizumab (1) +Methotrexate & Ustekinumab (1)						
Wald et al. [24]	--	--	--	+Methotrexate (1)	11.4 (0)	--	--	Yes	--	--
Bagel et al.[25]	47 (11)	17/12	--	+nbUVB (29)	12 (0)	76.4	--	2	--	--

-- indicates specific data not provided

*%PASI improvement after addition of apremilast to current regimen, †not mutually exclusive unless otherwise noted, ‡>5% original body weight

Diar – Diarrhea; F – Female; Infxn – infection; M – Male; Naus – nausea; PASI – psoriasis area and severity index; PsA – psoriatic arthritis; PsO – psoriasis; R – Range; SD – standard deviation; TEAE – treatment-emergent adverse events; Wt – weight loss

Table 2. Case Reports of Combination Therapy Using Apremilast 30 mg twice daily/60 mg daily for Psoriasis and Psoriatic Arthritis

Study	Age	Sex	PsO subtype	Prior Regimens	Combination Regimen	Follow-up (wks)	%PASI improvement	TEAE	d/c Tx?
Czarnowicki et al.[26]	50	M	PPP	Topical Steroids, Tacrolimus, excimer laser, Acitretin	+Acitretin (25mg/d)	8	90	--	No
Armesto et al.[27]	28	F	Erythroderma PsO	Methotrexate, Cyclosporine, Infliximab, Adalimumab, Etanercept, Ustekinumab, Secukinumab, Golimumab, Certolizumab, Apremilast monotherapy	+Adalimumab (40mg/wk) & Methotrexate (10mg/wk) & Prednisone taper (20mg/day) +Brodalumab (210mg/wk) & Methotrexate (20mg/wk) & prednisone (30 mg/day)	4 36	-- 86	-- --	Worsening prompted change of biologic
Galluzzo et al.[28]	63	M	PsO, HLA-C*18:01	Infliximab, Etanercept, Ustekinumab, Adalimumab, Infliximab re-trial, Ustekinumab re-trial, Secukinumab	+Ustekinumab (45 mg)	12	--†	--	Worsening condition
Rothstein et al.[29]	67	M	PsO, PsA	Ustekinumab, Infliximab, Adalimumab, Acitretin, Cyclosporine, Secukinumab,	+Secukinumab (300mg/month)	12	80% BSA to 5%†	Mild diarrhea	No
Danesh et al.[30]	31	M	PsO	Topical Steroids, nbUVB, Acitretin, Etanercept, Adalimumab	+Adalimumab (40mg/QOW)	16	Improved†	--	No
Nisar[31]	23	M	PsO, PsA	Cyclosporine, Sulfasalazine, Methotrexate, Adalimumab, Ustekinumab, Infliximab	+Secukinumab (300mg/month)	16	100 & PsARC 8 tender/7 swollen joints to 2 tender/0 swollen	--	No

†PASI scores not available

%PASI – percent improvement in psoriasis area and severity index after addition of apremilast to current regimen; d/c Tx– discontinued therapy; F – female; M – male; PPP – palmarplantar psoriasis; PsA – psoriatic arthritis; PsARC – psoriatic arthritis response criteria; PsO – plaque psoriasis; QOW – every other week; TEAE – treatment-emergent adverse effects; wks – weeks

found that apremilast 20 mg BID over 24 weeks was not superior to placebo in achieving 50% reduction in severity of alopecia tool (SALT50) score.[32] The authors note that this may be due to the severity and chronicity of disease in study participants, small sample size, and short duration of the study.[32] Several case series and reports have found more positive results with 40-87% of participants experiencing sustained regrowth of scalp hair and eyelashes.[33-37,43] Of note, authors of these studies found patients with more refractory cases were less likely to respond to apremilast monotherapy. TEAE consisted mostly of gastrointestinal distress (nausea, diarrhea) which was transient or tolerable with dose decrease[33]. In rare instances, persistent arthralgias, nausea and/or diarrhea led to premature discontinuation of apremilast.[32]

Atopic Dermatitis, Chronic Pruritus, Prurigo Nodularis, Hand Eczema, and Allergic Contact Dermatitis

Mixed results have been found regarding apremilast's use in AD, similar eczematous disorders in the atopic spectrum of disorders (e.g., chronic pruritus, prurigo nodularis, hand eczema) and allergic contact dermatitis (ACD). A phase II RCT found that apremilast 30 mg BID trended towards improvement, though did not significantly improve atopic dermatitis than placebo.[38] When the dose was increased to 40 mg BID, there was a significant improvement in eczema area and severity index (EASI) score and dermatology life quality index (DLQI) as well as improvement in biochemical markers of AD.[38] However, the increased dose also led to increased incidence of cellulitis (n=6) which ultimately lead to termination of this arm of the study.[38] 2 of the 6 cases of cellulitis were deemed serious and occurred in patients with diabetes; one of those cases may have also been associated with an observed case of glomerulonephritis.[38]

Open-label trial results have also yielded conflicting conclusions. An open-label trial with a 20 mg BID (n=6) and 30 mg BID (n = 10) arm found that they were both significantly effective in improving pruritus (20 mg BID; p=.02; 30 mg BID, p=.008) as well as quality of life (20 mg BID, p = .003; 30 mg BID, p = .01) among participants within 12 weeks and that 30 mg BID yielded significantly improved EASI score at 24 weeks.[39] 1 patient in the 20 mg arm withdrew from the study after experiencing an outbreak of herpes zoster.[39] A smaller open-label trial of 5 participants found a 20% worsening of EASI scores over 16 weeks, leading to drug withdrawal of 4 participants (2 due to worsening AD and 2 due to nonadherence).[40] Interestingly the authors of this trial noted the patients with atopic dermatitis had a worse EASI score at the outset.[40] Case series and reports have shown that, for atopic dermatitis patients that responded to apremilast, improvement was noted beginning at 2 weeks of therapy and was overall well tolerated.[41-43]

Studies have also investigated management of other eczematous, pruritic conditions (chronic pruritus, prurigo nodularis, hand eczema, allergic contact dermatitis) with apremilast and found trends towards improvement in itch and quality of life.[44-46] Participants with prurigo nodularis saw a 15% improvement in visual analog scale (VAS) for itch and a 21% improvement in the DLQI as well as a trend in decreasing interleukin 10 (IL-10) and IL-31 expression over 12 weeks, however the changes were not statistically significant.[44] Separately, 66% of participants with chronic pruritus saw resolution of their itch over 16 weeks with material improvement in DLQI.[45] However, results were not statistically significant likely

due to a small sample size, exacerbated by 7 participants withdrawing early (5 due to non-serious TEAE).[45] Interestingly a small open-label trial found apremilast 20 mg BID improved EASI scores by 42% for patients with ACD over 12 weeks with limited TEAE.[40]

Cutaneous Sarcoidosis

An open-label trial found that apremilast 20 mg BID significantly improved cutaneous sarcoidosis (as measured by the sarcoidosis activity and severity index (SASI) and investigator-visual evaluation) within 12 weeks although there were no changes in erythema, desquamation, or area of involvement.[47] Of the 15 participants, 2 patients withdrew due to nausea and "jitteriness" and 3 patients who completed the study noted relapsing and worsening of their lesions after discontinuation.[47]

Discoid Lupus Erythematosus

Among participants with discoid lupus erythematosus (DLE) who completed an open-label trial of apremilast 20 mg BID monotherapy, there was a significant improvement in cutaneous lupus erythematosus disease area and severity index (CLASI) score by day 85.[48] 50% of participants also noted resolution of scalp lesions during the study. However, 4 of 8 participants withdrew early: 2 due to disease progression and 2 due to TEAEs (lichenoid reaction and neuropathy) that both resolved with discontinuation of apremilast.[48]

Hidradenitis Suppurativa

Several RCTs, open-label trials and case series/reports have investigated apremilast for the management of hidradenitis suppurativa (HS). A RCT of 20 participants with moderate HS (15 on apremilast 30 mg BID) found 53.3% achieved a 50% reduction in hidradenitis suppurativa clinical response (HiSCR50) as well as significant improvement in nodules and itch within 16 weeks.[49] The authors of this RCT found apremilast modulated levels of S100A12 and IL-17A and IL-17F, suggesting these as potential modulators of HS pathogenesis.[50] Furthermore, in a 2 year follow up study, of the 8 participants that achieved HiSCR50, 4 patients maintained HiSCR at the 1 and 2 year mark with minimal and manageable TEAE (primarily gastrointestinal related).[51] Of the 4 that discontinued, 1 discontinued due to complete resolution of symptoms, 2 due to "active pregnancy wish", and only 1 discontinued as a result of intractable nausea after 6 months.[51] An open-label trial of 20 patients found similar results with 60% reaching HiSCR50 by week 24.[52] In both the initial RCT and open-label trial, TEAE were primarily gastrointestinal (nausea, diarrhea), headache, only 1 patient withdrew due to severe myalgias and arthralgias and there were no severe TEAE or severe infections.[49,52] Smaller case series (n = 9) and case reports had similar findings of significant improvement in pain and DLQI with similar safety profile.[53-55]

Lichen Planus, Oral Lichen Planus, Lichenoid Dermatitis

In an open-label trial of apremilast 20 mg BID, 3 out of 10 patients with corticosteroid-refractory lichen planus met the studies primary end point of improvement by ≥2 grades on the physician global assessment (PGA).[56] However, further examination of all participants revealed a significant improvement in lesion count, target area lesion severity score (TALSS), itch and DLQI within 12 weeks.[56] 1 of 10 participants also had oral involvement and had material decrease in buccal lesions (40% to 12% surface area).[56] 4 weeks after discontinuation of apremilast, no significant difference was noted in study end points.[56] There were no serious TEAE, though 1 participant did develop asymptomatic

antinuclear antigen (ANA) positivity during the study.[56] Several case series and reports have found apremilast was also effective in managing oral lichen planus with improvement within 2-4 weeks of initiation with only minor TEAEs that were adequately managed with dose reduction to 30 mg daily without compromising efficacy.[57-59] A final case series of 5 patients found apremilast was effective in halting (3/5) and even resolving (2/5) lichenoid and interface dermatitis without inducing severe TEAE.[60]

Rosacea

An open-label trial investigated the use of apremilast 20 mg BID for the management of erythematotelangiectasia (ETR) and papulopustular (PPR) rosacea among 10 participants with moderate to severe disease.[61] By 12 weeks, there was a significant decrease in PGA, ETR rating overall erythema, and nontransient erythema with the latter two persisting for 1 month after discontinuation of therapy. No difference was found in number of papules/pustules at the end of the study versus baseline.[61] Overall, apremilast was well tolerated with only 2 urinary (UTI) and upper respiratory tract (URI) infections neither of which necessitated dose decrease or drug withdrawal.[61]

Vitiligo

A RCT investigating apremilast and narrow-band ultraviolet B (nbUVB) phototherapy for the management of vitiligo failed to meet its primary endpoint and found no significant difference at either 24 or 48 weeks between vitiligo area and severity index (VASI) score, vitiligo extent score (VES), vitiligo European task force (VETF) score, or DLQI between apremilast and nbUVB and placebo and nbUVB.[62] Interestingly, a split-body trial investigated the combination of apremilast and narrow-band UVB (nbUVB) 2-3 times weekly for the management of vitiligo in darker phototypes (Fitzpatrick IV-VI).[63] Over 3 phases, each lasting 16 weeks, patients receiving combination apremilast and nbUVB therapy had a significantly greater improvement in primary endpoint of >50% repigmentation (p=.001) and vitiligo area and severity index (VASI) (p=.0001) than nbUVB monotherapy.[63] In the RCT, authors note 2 serious side effects, 1 being a suicide attempt that was attributed to apremilast treatment while the split-body study noted a majority of drug withdrawal were due to non-compliance with nbUVB regimen and reported no serious TEAEs.[62,63] A case series of 13 patients found 61.5% achieved at least partial repigmentation (with as needed topical tacrolimus) and a 7.1% reduction in VASI.[64] Additional case reports have found improvement in both recalcitrant acral and generalized vitiligo without lasting or serious TEAEs.[65,66]

Case series and reports detailing efficacy of apremilast for off-label dermatoses

Palmoplantar pustulosis

Although once considered a subtype of palmoplantar psoriasis, beginning in 2007 palmoplantar pustulosis has been deigned its own entity.[67] Although several studies, including RCTs and open-label trials, have shown efficacy for multiple biologic and non-biologic therapies for palmoplantar psoriasis, there is less rigorous information for palmoplantar pustulosis, including with regards to apremilast.[67] Several retrospective observational studies, including two case series of 10 and 3 patients found that after 2 weeks of apremilast 30 mg BID, there was significant improvement in both signs and symptoms of palmoplantar pustulosis, including ~62% improvement in palmoplantar psoriasis area and severity index (PPPASI) score, 66% reduction in number of pustules, and 66% in DLQI score.[68-72] Furthermore, the median

Table 3. Randomized-Control Trials and Open-Label Trials for Off-Label Uses of Apremilast.

Study	Condition	Study Type & Size (n on apremilast)	Mean age (SD); %Male	Dosage	Duration (wks)	Results	TEAE
Mikhaylov et al[32]	Alopecia Areata	RCT (20)	37.1 (14.4); 20	30 mg BID	24	1/20 achieved at least SALT50 Improvement not significantly different from placebo (p=0.38)	3 early d/c due to TEAE Nausea (4), Diarrhea (3), URI (1), Tinea Pedis (1), arthralgia (1)
Simpson et al[38]	Atopic Dermatitis	RCT (58)	39.2 (--); 53.4	30 mg BID	12+12	31% achieved EASI50 by week 12 vs 32.8% on placebo. Not significantly different than placebo, though trend towards increased clinical improvement.	Higher incidence of LE cellulitis (6 total, 2 serious) in 40 mg group leading to d/c of treatment arm in study. TEAE in >5% participants: Diarrhea, nausea, headache, nasopharyngitis, URI, abdominal discomfort, cellulitis, dyspepsia Serious TEAE: 30 mg: SCC (1), PNA (1) 40 mg: SI (1), Cellulitis (2), GN (1) 1 early d/c: Herpes Zoster(1)
Simpson et al[38]	Atopic Dermatitis	RCT (63)	38.3 (--); 49.2	40 mg BID	12+12	Significant improvement in EASI score (31.6% vs 11.0% p<.04) and DLQI 27.3% vs 2.7%, p<0.05) by week 12 vs placebo, decrease in inflammatory markers (K16, p<.001; Ki67^{+} cells, p<.001; Th17 and Th17/22 markers, p<.05)	
Samrao et al[39]	Atopic Dermatitis	Open-label trial (6)	38 (--); 83	20 mg BID	12	Significant improvement in VAS pruritus (p=.02) and DLQI (p=.003)	Nausea(2), Loose Stool(3), URI(2), Headache(2)
Samrao et al[39]	Atopic Dermatitis	Open-label trial (10)	45 (--); 50	30 mg BID	24	12 weeks: Significant improvement in EASI (p=.008) and DLQI (p=.01). 24 weeks: Significant improvement in EASI (p=.002), VAS (p=.003), and DLQI (p=.001)	Nausea(9), Loose Stools(4), URI(3), other infection(3), Headache (2) Disease flare requiring rescue topical therapy (2)
Volf et al[40]	Atopic Dermatitis	Open-label trial (5)	43 (14.5); 40	20 mg BID	16	20% worsening in EASI	4 early d/c: 2 d/t worsening AD, 2 due to non-adherence
Volf et al[40]	Allergic Contact Dermatitis	Open-label trial (4+1 ACD & AD)	43.6 (15.7); 60	20 mg BID	12	42% reduction in EASI 40% at least EASI50	1 early d/c: d/t worsening of ACD

Clark et al[45]	Chronic Pruritus	Open-label trial (10)	75 (--); 40	30 mg BID	16	No significant difference in NRS Itch or DLQI. Of note: 2/3 patients completed study noted material improvement in NRS itch (9.5 and 8 to 0) and DLQI.	7 d/c: TEAE(5), resolution of itch(1), use of prohibited Tx(1) Nausea(3), Diarrhea(3), Headache(1), Presyncope(1)
Baughman et al[47]	Cutaneous Sarcoidosis	Open-label trial (15)	-- (--); 6.7	20 mg BID	12	Significantly decreased SASI induration at 4 weeks(p<.002) and 12 weeks(p<.005). Improved investigator-visual evaluation (p<.02)	2 patients decreased dose to 20 mg daily due to "jitteriness"(1) and nausea (1)
De Souza et al[48]	DLE	Open-label trial (8)	47.1 (12.3); 12.5	20 mg BID	~12	Significant improvement in CLASI score by day 85 (p=.01) and among patients that completed study (p=.03) 2/4 patients with complete regression of scalp lesions	4 early d/c: 2 d/t TEAE, 2 d/t disease progression Nausea (4), Diarrhea (1), Headache (2), Lichenoid Dermatitis (1), Neuropathy (1)
Vossen et al[49]	HS	RCT (15)	35.7 (13); 20	30 mg BID	16	53.3% on apremilast achieved HiSCR50 vs 0% of placebo Significant improvement in nodules (p=.011), NRS pain (p=.009), NRS itch (p=.015) No significant difference in DLQI	2 d/c: personal socioeconomic issues(1), severe myalgia/arthralgia(1) Headache (7), Diarrhea (7) Nausea (4), Vomiting (2), Depressed feeling (1), Non-serious infections (5), Sore throat (1), Pyelonephritis (1)
Kerdel et al[52]	HS	Open-label (20)	32.5 (10); 30	30 mg BID	24	60% achieved HiSCR50	Diarrhea (4), Nausea (3), URI (2), Depression (2), SI (1), abscess (1), UTI (1)
Paul et al[56]	LP	Open-label (10)	48.8 (12.8)	20 mg BID	12	3/10 achieved primary end point. Significant decrease in lesion count (p=.002), PGA (p=.0078), TALSS (p=.0078), SVAS (p=.0059) and DLQI (p=.002)	Headache (4), new-onset ANA positivity (1)
Todberg et al[44]	Prurigo Nodularis	Open-label trial (10)	61.7 (10); 50	--	12	No significant improvement over 12 weeks Mean VAS pruritus improvement from 8.7 to 7.4 Mean DLQI improvement 11.2 to 8.8	3 d/c: 2 due to lack of efficacy, 1 due to intermittent fever Diarrhea, nausea, abdominal pain in 5 patients, recurrent fever (1)

Thompson et al[61]	Rosacea	Open-label trial (10)	39-74 yo; 30	20 mg BID	12	Significant decrease in PGA (p=.02), Overall Erythema (p=.001), ETR rating (p=.005) and nontransient erythema (p=.04)	UTI(2), URI(2)
Kemis et al[62]	Vitiligo	RCT (38)	49.5 (13.4); 36.8	30 mg BID & nbUVB	52	No significant difference in VASI, VEF, VETF, or DLQI between apremilast and placebo	2 serious TEAE: suicide attempt (1), benign amygdala tumor (1) Diarrhea, abdominal pain, headache
Kim et al[63]	Vitiligo	RCT Split-body (23)	--; --	30 mg BID & nbUVB	48	Apremilast and nbUVB increased probability of >50% repigmentation (p=.001), improved VASI (p=.0001) compared to nbUVB monotherapy	14 d/c, majority due to non-compliance with nbUVB, TEAE (4)

ANA – Anti-nuclear antibody; AD – Atopic Dermatitis; CLASI – cutaneous lupus erythematosus disease area and severity index; d/c – discontinued; DLE – discoid lupus erythematosus; DLQI – Dermatology Life Quality Index; EASI - Eczema Area and Severity Index; GN – glomerulonephritis; HS – hidradenitis suppurativa; HiSCR - Hidradenitis Suppurativa Clinical Response; HiSCR50 – 50% reduction in Hidradenitis Suppurativa Clinical Response; LE – lower extremity; NRS Itch– numeric rating scale Itch; NRS pain – numeric rating scale pain; PGA – physician global assessment; PNA – pneumonia; RCT – randomized-control trial; SALT50 – 50% reduction in severity of alopecia tool; SASI – sarcoidosis activity and severity index; SCC – squamous cell carcinoma; SI – suicidal ideation; SVAS – subject visual analog scale for itch; TALSS – target area lesion severity score; Tx – treatment; URI – upper respiratory tract infection; UTI – urinary tract infection; VAS – visual analog scale; VASI – vitiligo area and severity index; VEF – vitiligo extent score; VETF – vitiligo European task force score

Table 4. Case Series: Off-label Dermatoses and Apremilast. 18 case series listed alphabetically by dermatosis.

Study	Condition	Sample size (n)	Mean age (SD); %Male	Dosage	Duration weeks (SD)	Results	TEAE
Taneja et al[33]	Alopecia Areata	15	25.8 (3.2); 86.7	30 mg BID (n=4) 30 mg daily (n=11)	37.2 (13.6)	15/15 patients noted hair regrowth, 13/15 with >50% response, 4/15 with >75% response	Gastrointestinal side-effects (nausea, diarrhea, vomiting)(11) that lead to dose decrease
Weber et al[34]	Alopecia Areata	5	34.8 (13.0); 0	30 mg BID	24	1/5 responded with regrowth lasting 18 months, 2/5 had slight transient regrowth, 2/5 without response	Nausea (3), Diarrhea(1)
Liu & King[35]	Alopecia Areata	9	38.8 (21.4); 44.4	30 mg BID	16.8 (4.8)	8/9 patients without improvement 1/9 with increased hair loss at 6 months	--
Abrouk et al[41]	Atopic Dermatitis	5	50.2 (10.8); 80	30 mg BID	18.4 (16.3)	Noticeable improvement in 2-4 weeks 4/5 patients with ≥75% improvement	Nausea(1), Weight loss(1), pancreatitis(1, unrelated)
Qiblawi et al[73]	Calcinosis Cutis	2	66 F	30 mg BID*	24	Improvement noted within 8 weeks	Decreased dose and later discontinued due to recurrent infections at calcification areas
			59 F	30 mg BID†	12	Softening of plates of calcifications leading to calcium fragment extrusion	--
Bitar et al[74]	Dermatomyositis	3	57 F	30 mg BID‡	104	CDASI 43 →0 Muscle improvement	Nausea(1), Diarrhea(1)
			64 F		12	CDASI 41 →7, able to taper off other Tx	--
			62 F		36	CDASI 62 →18	d/c treatment after flare and transitioned to IVIg
Narang et al[75]	Erythema Nodosum Leprosum	2	34 M	30 mg BID	20	Resolution of constitutional symptoms and significant improvement in skin lesions in 2 weeks	--
			31 M	30 mg BID	12	Significant improvement in 4 weeks, and no new lesions 3 months after self-discontinuing	--

Bishnoi et al[76]	Granuloma Annulare	4	~60 F ~43.3 (5.8); 0	30 mg BID 30 mg BID	12 6-8	Significant response within 6 weeks, almost clear by 12 weeks Significant response within 6-8 weeks	Mild diarrhea, myalgia Myalgia, nausea
Kieffer et al[77]	Hailey-Hailey disease	4	52.5 (5);25	30 mg BID	26 (4)	3/4 achieve PGA 1 after 6 months, 1/4 achieve PGA 1-2 after 5 months	Diarrhea (2), Myalgia (1) requiring dose reduction to 30 mg daily
Weber et al[52]	Hidradenitis Suppurativa	9	44.3 (13.5); 66.6	30 mg BID	Range: 2 days – 36 weeks	Significant reduction in sartorius score (p=.028), pain (p=.026) and DLQI (p=.021)	3 d/c due to TEAE: GERD(1), depression(1), insurance coverage(1) Weight loss(2), Nausea (1), Loose stool (1), dry cough (1)
Bettencourt[57]	LP (oral)	3	70 (3.6); 100	30 mg BID	18.7 (6.1)	Improvement noted within 2-4 weeks. 1/3 required intermittent prednisone for flares. 3/3 eventually had complete resolution of oral lesions	1/3 nausea and diarrhea requiring dose decrease to 30 mg daily
Ravichandran & Kheterpal[60]	Lichenoid & Interface dermatitis	5	50.8 (18.0); 0	30 mg BID	52.8 (32.3)	3/5 no new lesions on apremilast 2/5 near complete remission on apremilast	1 patient decrease dose to 30 mg daily due to TEAE; 2 patient d/c due to insurance denial of coverage Diarrhea(2), Nausea(2), URI(1), Weight loss(1), Vomiting(1)
Hadi & Lebwohl[78]	LPP/FFA	4	58.8 (21.2); 0	30 mg BID	--	2/4 improvement in scalp inflammation and pruritus in 12 weeks 2/4 with minimal improvement, TEAE lead to dose decrease then d/c	gastrointestinal discomfort (3), depressive symptoms (1)
Kaushik et al[79]	Orofacial Granulomatosis	5	33 (14.5); 40	30 mg BID	12	4/5 with response, 3/5 with significant reduction in labial swelling and erythema	Diarrhea (2), Headache (2), vomiting
Kato et al[68]	Palmoplantar Pustulosis	10	Median: 63.7; 20	30 mg BID	15.1 (5.9)	After 2 weeks, mean improvement PPPASI 61.9% (p=.013), PC decrease 66% (p=.029), DLQI 66% (p = .009), VAS itch 62.5% (p=.026). Median 6.9 weeks to PPPASI50 and 2.9 weeks to	3 d/c due to diarrhea 2 decrease dose to 30 mg daily due to diarrhea 1 transiently decrease dose then resumed 30

						PC50	mg BID due to itch Frequent bowel movement (8), diarrhea (6), weight loss (3), palpitations (1), headache (1)
Eto et al[69]	Palmoplantar Pustulosis	3	51.7 (10.7); 0	30 mg BID	32	Near complete resolution after 2 weeks	Mild epigastric discomfort (1)
Cohen et al[80]	Seborrheic Dermatitis	3	46 (20.5); 66	30 mg BID	12	Results notable within 3 months, complete clearance in 1 patient, 2 with mild localized SD	Nausea (1)
Majid et al[64]	Vitiligo	13	33.8 (12.2); 61.5	30 mg BID & as needed tacrolimus	12	61.5% of participants achieving partial repigmentation, including in areas without topical medication usage Mean VASI reduction 7.1% (p<.04)	Headache, nausea, vomiting, abdominal pain 2/13 patients

-- indicates data not explicitly available. If dosage missing, implied 30 mg BID
*in addition to topical and intralesional sodium thiosulfate, pentoxifylline, minocycline, amlodipine, percutaneous ultrasonic lithotripsy
†in addition to topical and intralesional sodium thiosulfate, diltiazem, pentoxifylline, minocycline, surgical extraction of calcium fragments
‡in addition to prior regimen: mycophenalate mofetil and prednisone (3), and hydroxychloroquine(1)

BID – twice daily; CDASI – cutaneous dermatomyositis activity and severity index; d/c – discontinued; DLQI - dermatology-life quality index; GI – gastrointestinal; GERD – gastroesophageal reflux disorder; HS – hidradenitis suppurativa; IVIg – intravenous immunoglobulin; LP – Lichen Planus; LPP/FFA – lichen planopilaris/frontal fibrosing alopecia; M – male; mg – milligrams; PGA – physician global assessment; PPPASI – palmoplantar psoriasis area and severity index; PPPASI50 – 50% reduction in PPPASI; PC – pustule count; PC50 – 50% reduction in PC; SD – standard deviation; TEAE – treatment-emergent adverse effect; URI – upper respiratory tract infection; VASI – vitiligo area and severity index

time to 50% reduction in PPPASI and pustule count was 6.9 and 2.9 weeks, respectively.[68] Of note, there were 5 participants in the 10-participant trial that withdrew (n = 3) or required dose reduction (n = 2) during the study due to diarrhea.[68]

Additional Dermatoses

The combination of apremilast's unique mechanism of action, safety profile (especially compared to other non-biologic systemic agents) as well as no need for regular laboratory monitoring have piqued interest in its use for a wide breadth of other dermatoses including (and likely not limited to): Acrodermatitis continua of Hallipeau, calcinosis cutis, chronic actinic dermatitis, dermatomyositis, erythema nodosum leprosum, folliculitis decalvans, granuloma annulare, Hailey-Hailey disease, lichen planopilaris/frontal fibrosing alopecia, orofacial granulomatosis, Anti-lamin γ1 (p200) pemphigoid, pemphigus vulgaris, pityriasis rubra pilaris, pyoderma gangernosum, seborrheic dermatitis, SAPHO, and vitiligo (Table 4 and 5).[73-96] In these cases, apremilast has had material effect for patients with refractory disease to first and second line treatment and, surprisingly, is often used successfully as monotherapy.

DISCUSSION

Although only FDA-approved for psoriasis, psoriatic arthritis and Behçet's disease, apremilast's mechanism of action has proven to have sustained efficacy for multiple inflammatory dermatoses without increasing rates of serious TEAEs.

Many of the studies demonstrated apremilast's efficacy especially for psoriasis for which FDA-approved first (and second line) therapies may have lost efficacy[18-31] or for other moderate to severe dermatoses that were not suitably managed long-term by corticosteroids, or other non-biologic systemic agents[32-96]. In several cases, apremilast had the same relatively rapid onset of activity (~2-4 weeks) as seen in psoriasis, despite the various diverging types of inflammatory conditions treated.[41,42,47,55,57,68,69,70,72,75,81,84,87,91,93] Furthermore, studies that investigated changes in known cytokine cascades suggest that apremilast and PDE-4 inhibition may achieve its efficacy by targeting inflammatory mediators unaffected or not primarily affected by current first-line agents.[36-40,42,43,46,49,54,55,58,59,65,66,81-96]

In addition to efficacy, consideration should be given to apremilast's safety profile. While gastrointestinal TEAEs (most commonly nausea, diarrhea, vomiting), weight loss and headache do occur, they are often transient or manageable with dose modification.[33,37,42,47,57,58,60,68,72,77] While several infections were documented across the collected studies, they usually occurred as a result of comorbid conditions (e.g., diabetes)[38] and were predominately not severe infections. While depressive symptoms have been noted, in all the reviewed studies only 1 case was suicidal ideation/attempt directly associated with apremilast therapy.[62] Additional studies have investigated the association of depression with apremilast and continually noted its safety regarding mental health.[9] The safety profile is further highlighted by the fact that regular laboratory monitoring is not needed nor required for patients on apremilast.[1,67]

Taken together, apremilast has several unique characteristics that make it an attractive potential complementary or alternative therapeutic option for patients that are adverse to or are not ideal

Table 5. Case Reports: Off-Label Dermatoses and Apremilast. 30 case reports listed in alphabetical order by dermatosis.

Study	Condition	Age, Sex	Dosage	Duration weeks	Results	TEAE
Magdaleno-Tapial et al[36]	Alopecia Areata	52 F	--	15	Regrowth of eyelashes and scattered scalp hair	--
Chhabra et al[37]	Alopecia Totalis	11 M	30 mg qAM, 10 mg qPM & Plate-rich Plasma	24	Improved	--
Saporito and Cohen[42]	Atopic Dermatitis	8 M	30 mg daily	8	Improvement noted starting at 2 weeks	--
Farahnik et al[43]	Atopic Dermatitis + Alopecia Areata	55 M	30 mg BID	10	Subjective improvement in pruritus in 4 weeks with substantial decrease in erythema and stabilization of hair loss with some scalp hair regrowth in 10 weeks	Transient nausea and "gas"
Calleja Algarra et al[81]	Acrodermatitis continua of Hallopeau	75 M	30 mg BID	24	Improvement noted within 1 month, persistent improvement in onychodystrophy noted at 6 months	
Georgakopoulos et al[82]	Acrodermatitis continua of Hallopeau	68 M	30 mg BID & infliximab 5mg/Kg every 8 weeks	24	Used as maintenance, minimal onychodystrophy at 6 month follow up	--
Lanna et al[83]	Acrodermatitis continua of Hallopeau	58 M	30 mg BID	4	DLQI improved from 10 to 0 over 4 weeks	--
Kaushik et al[84]	Chronic actinic dermatitis	36 F	30 mg daily & low-potency topical and oral corticosteroids	12	Significant improvement in 4 weeks with clearance by 6 weeks	--
Charlton et al[85]	Dermatomyositis	~50 F	30 mg BID & prednisone 7.5 mg/d, diltiazem 120 mg daily, yearly zolendronate	28	Resolution of heliotrope rash, facial erythema, scalp pruritus. No change in cutaneous calcinosis	--
Sanchez-Martinez et al[86]	Erythema Nodosum Leprosum	23 F	30 mg BID	24	Asymptomatic by 6 month follow up	Self-limited headache, mild diarrhea
Fassler et al[87]	Folliculitis Decalvans	28 M	-- & as needed 2% chlorhexidine shampoo	25	Significant nearly complete remission by 3 weeks	--
Di Altobrando et	Hailey-Hailey	68 F	--	144	Significant remission without further	--

al[88]	disease				application of topical corticosteroids	
Navarro-Trivino et al[46]	Hand eczema Pruritus	65 M	30 mg BID	4	Improved	--
Garcovich et al[54]	HS (+ PsA)	73 M	30 mg BID	16	Improved HS-PGA: 4 → 2 Improved DLQI: 23 → 6	None by 60 weeks
		51 M	30 mg BID	16	Improved HS-PGA: 5 → 3 Improved DLQI: 25 → 9	None by 72 weeks
Lanna et al[55]	Hidradenitis Suppurativa (+PsO)	55 M	30 mg BID		PASI95, Hurley stage decrease 2 to 0-1 and DLQI from 22 to 0 within 20 days	--
AbuHilal et al[58]	LP (Oral)	44 F	30 mg daily	12	Improvement in buccal/gingival lesions	Nausea with 30 mg BID
Hafner et al[59]	LP (Oral), esophageal stenosis	74 F	--	4	Complete resolution of dysphagia and erosive stomatitis	--
Haebich & Kalavala[70]	Palmoplantar Pustulosis	75 F	30 mg BID	~52	Resolved within 4 weeks	--
Haller et al[71]	Rituxmimab-associated Palmoplantar Pustulosis	57 F	30 mg BID		Significant improvement within 6 weeks	--
Carrascosa et al[72]	Palmoplantar Pustulosis	77 F	30 mg daily	~52	Near complete resolution of pain/pustules within 2 weeks	Mild diarrhea resolved with dose reduction from BID to daily
Waki et al[89]	Anti-lamin γ1 (p200) pemphigoid (+ PsO)	57 M	60 mg daily & prednisolone taper (30 mg/d to 15 mg/d)	~36	Able to taper prednisolone 2.5 mg ever 5-7 weeks without flare	--
Meier et al[90]	Pemphigus Vulgaris	62 F	30 mg BID & 2 mg mycophenolate mofetil and 20 mg prednisone	32	ABSIS 38→0 Reduction in anti-Dsg1 and anti-Dsg3 antibodies and increase in Treg and Tfreg cells	--
Krase et al[91]	PRP	70 M	30 mg BID	32	Initial improvement noted within 4 weeks with complete resolution within 6-8 months	GI upset
Cho et al[92]	PRP	60 F	30 mg daily	24	Complete resolution at 8 weeks,	Mild headache

					sustained at 24 weeks	
Pellonnet et al[93]	PRP	47 M	30 mg BID	28	Complete resolution at 4 weeks, sustained to 28 weeks	--
Molina-Figuera et al[94]	PRP	61 F	30 mg BID	28	Near complete clearance at 8 weeks and able to discontinue at 28 weeks due to resolution. Remained symptoms free 12 weeks after d/c	--
Vernero et al[95]	Pyoderma Gangrenosum	35 M	-- & prednisone and vedolimumab for Crohn's disease	19	Consistent improvement in pain and lesion re-epithelialization at 15 weeks	--
Adamo et al[96]	SAPHO	24 F	30 mg BID	28	92.3% reduction in PPPASI	Transient headache, diarrhea, nausea, vomiting resolved within 4 weeks
Plachouri et al[65]	Vitiligo (+ PsO)	59 M	30 mg BID	24	Repigmentation of vitiligo on neck and trunk without much affect at extremities. Near complete clearence of PsO plaques	--
Huff & Gottwald[66]	Vitiligo	52 F	30 mg BID & IM triamcinolone 60 mg	52	Slow repigmentation proximal to distal over 6.5 months, 60-70% repigmentation on face, chest arms by 11 months	--

-- indicates data not explicitly available. If dosage missing, implied 30 mg BID

ABSIS – autoimmune bullous skin disorder intensity score; BID – twice daily; DLQI - dermatology-life quality index; DSG – desmoglein; GI – gastrointestinal; HS-PGA – hidradenitis suppurativa-physician global assessment; LP – Lichen Planus; M – male; mg – milligrams; F – female; PPPASI – palmoplantar psoriasis area and severity index; PRP – pityriasis rubra pilaris; PsA – psoriatic arthritis; PsO – psoriasis; qAM – every morning; qPM – every afternoon/evening; SAPHO – synovitis, acne, pustulosis, hyperostosis and osteitis; TEAE – treatment-emergent adverse effect; Treg – regulatory T-cell; Tfreg – follicular regulatory T-cell

candidates for current therapies. Additional studies may further elucidate ways apremilast monotherapy and combination therapy, especially in the setting or recalcitrant psoriatic arthritis, may be used to improve patient care and outcomes for psoriasis and other inflammatory dermatoses.

CONCLUSION

Apremilast is an oral, non-biologic systemic agent that inhibits phosphodiesterase 4 activity to modulate inflammation. While transient gastrointestinal side effects are common, especially early-on in therapy, it has a relatively innocuous safety profile that makes it a potential efficacious agent for monotherapy and combination therapy for a wide range of inflammatory dermatoses.

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