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Review

A Review of phosphodiesterase-inhibition and the potential role for phosphodiesterase 4-inhibitors in clinical dermatology

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Abstract

Background: Phosphodiesterase inhibitors are commonly used drugs. Specific phosphodiesterase inhibitors with anti-inflammatory properties are being assessed as dermatological treatments.

Purpose: To describe important aspects of phosphodiesterase inhibition and the safety and efficacy of 2 phosphodiesterase-4 inhibitors being studied for the treatment of dermatologic diseases

Methods: We did a non-systematic analysis of literature on phosphodiesterase inhibition followed by a review of published information on apremilast and topical AN2728 and their use for psoriasis and atopic dermatitis.

Findings: Apremilast and topical AN2728 have modest efficacy in treatment of psoriasis. Apremilast achieved PASI-75 scores ranging from 24-33%. In phase 2 studies, AN2728 had modest efficacy for psoriasis (40% of patients achieved a ≥ 2 grade improvement as assessed by the Overall target Plaque Severity Score). In phase 2 studies of AN2728 use in atopic dermatitis, subjects achieved a 71% improvement from baseline Atopic Dermatitis Severity Index. In all studies, most adverse effects were minimal. The limitations of this paper are the limited number of published studies, the lack of long-term data, and the lack of head-to-head trials directly comparing phosphodiesterase inhibitors with other treatments.

Conclusion: Phosphodiesterase inhibitors constitute a widely used class of drugs that may see growing use for inflammatory dermatologic diseases.

Key Words: Apremilast, AN2728, Psoriasis, Atopic Dermatitis, phosphodiesterase inhibitor, inflammation

Introduction

The phosphodiesterase inhibitor class of drugs is nearly ubiquitous. Xanthine- a non-selective phosphodiesterase inhibitor—is the stimulant found in caffeine. Phosphodiesterase inhibitors are used broadly in clinical medicine. They are used to treat airway hyperreactivity, erectile dysfunction, and various inflammatory diseases. There is potential for use in the treatment of psoriasis and atopic dermatitis.

Phosphodiesterase inhibitors increase intracellular levels of cyclic adenosine monophosphate (cAMP), which results in various downstream effects in different cell types. Increased cAMP in macrophages results in inhibition of pro-inflammatory mediators (TNF α , IL-6, IL-12) that are important in psoriasis and atopic dermatitis [1,2,3,4,5]. Increasing cAMP is therefore a potential strategy for treatment of immune-mediated skin diseases. In this paper, we review the characteristics and effects of phosphodiesterase inhibitors. We also review data on the efficacy and safety of two phosphodiesterase 4 inhibitors - apremilast and AN2728- that have exhibited efficacy in studies of psoriasis and atopic dermatitis.

Mechanism of Action - Cyclic Adenosine Monophosphate and Phosphodiesterase

Cyclic adenosine monophosphate (cAMP) is a key intracellular second messenger used in signal transduction in many biological processes. As a response to an extracellular stimulus (hormone or neurotransmitter), integral cell membrane proteins known as G protein-coupled receptors (GPCR) activate adenylyl cyclase (Figure 1). Activated adenylyl cyclase converts adenosine triphosphate (ATP) into cyclic adenosine monophosphate. Increased intracellular cAMP has downstream effects that include activation of: 1) cyclic nucleotide-gated ion channels; 2) exchange proteins activated by cAMP (EPAC), and 3) protein kinase A (PKA) [6].

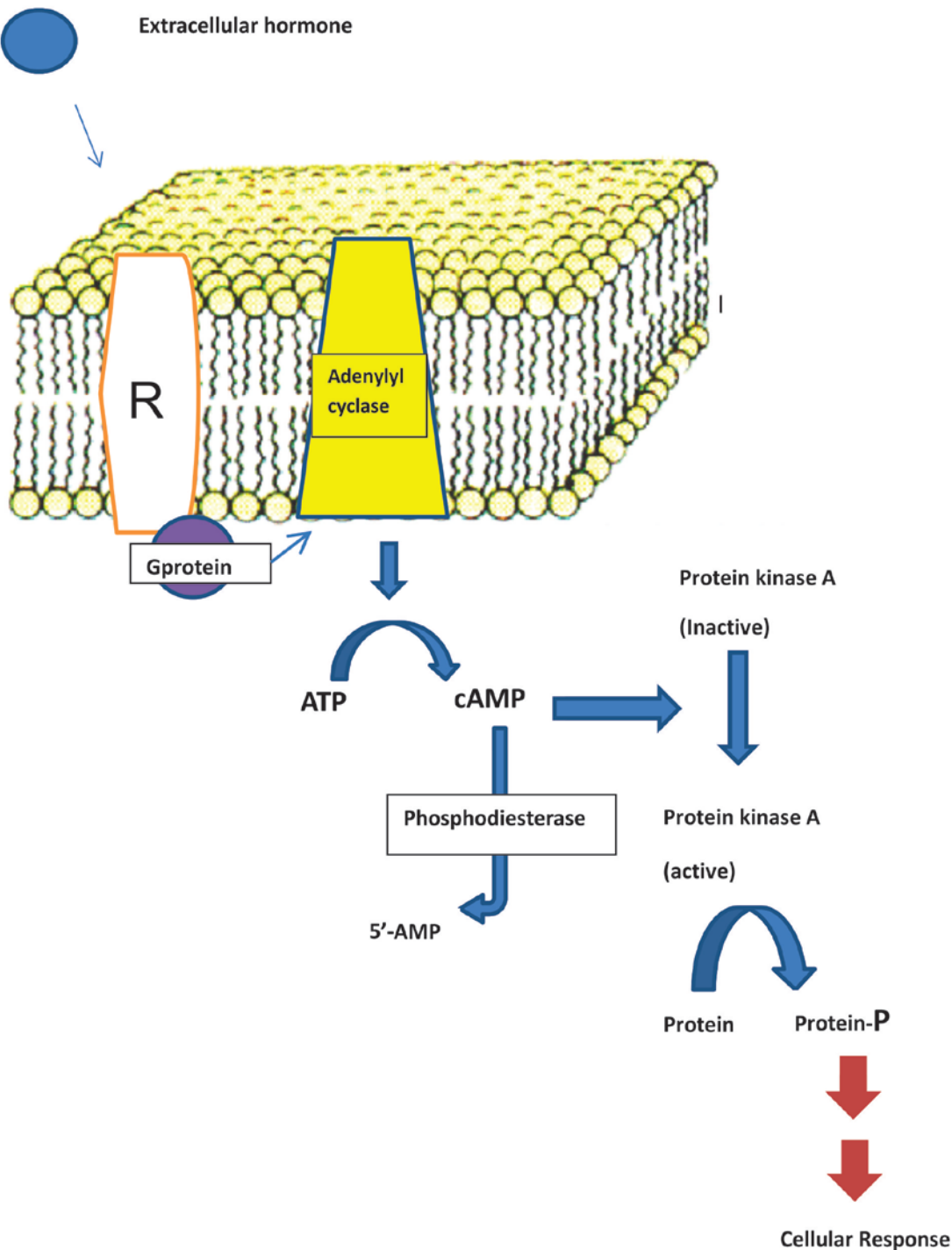


Figure 1. Cyclic AMP Pathway. Phosphodiesterase inhibitors work by 349 effects on the cyclic AMP pathway. In the first step of cyclic AMP pathway activation, a hormone binds to cell surface receptor (this hormone can be either stimulatory or inhibitory). After binding, the extracellular signal is transferred through the cell membrane to the inside portion of the receptor molecule (labeled in the image as Rs and Ri, for stimulatory receptor and inhibitory receptor, respectively). The internal portion of the cell surface receptor then interacts with G proteins, so that when the hormone is bound, the G protein is activated. The G protein then interacts with adenylyl cyclase. When the two proteins interact, the result is activation of the adenylyl cyclase molecule. Adenylyl cyclase then generates cyclic AMP from ATP. Cyclic AMP then converts protein kinase A from its inactive form into its active form. Protein kinase A can then activate key proteins within the nucleus to initiate or alter a cellular response. Cyclic AMP is quickly degraded and inactivated through the action of phosphodiesterase. Phosphodiesterase inhibition increases cyclic AMP levels.

cAMP conversion of protein kinase A into its active form is known as the cAMP-dependent pathway. The activation of PKA intracellularly regulates transcription. Downstream effects of cAMP are highly cell type dependent. For example, increased cAMP levels in leukocytes suppress the expression of pro-inflammatory cytokines (TNF α , IL-12) and the pro-inflammatory mediator leukotriene B4 [7]. cAMP also enhances the production of the anti-inflammatory cytokine IL-10 [7]. Cyclic AMP is broken down into its active form by phosphodiesterase. Therefore the balance of cAMP intracellularly is regulated or maintained through the effects of G protein-coupled receptors, which increase intracellular cAMP and phosphodiesterases, which decrease intracellular cAMP.

There are 11 different families of phosphodiesterases (PDEI-PDEII) that have slightly different functions and tissue specificity (Table 1) [7]. Within each family of phosphodiesterase, there can also be several subtypes that exert various effects depending on their activation and inhibition (Table 1). Tissue specific phosphodiesterases can be inhibited pharmacologically resulting in various clinical effects depending on the isotype inhibited.

Table 1. Phosphodiesterase Tissue Distribution and Function

<u>PDE isoenzyme</u>	<u>Cyclic nucleotide</u>	<u>Tissue Distribution</u>	<u>Functions</u>
PDE1	cGMP, cAMP	Brain, heart skeletal muscle, liver, vascular and visceral muscles	Vascular muscle weakness, olfaction
PDE2	cGMP, cAMP	Heart, brain, visceral and skeletal muscle, corpus cavernosum, adrenal cortex	Adrenocorticoid production, olfaction
PDE3	cGMP, cAMP	Corpus cavernosum, heart, brain, vasculat and visceral muscles, blood platelets, liver, kidney, adipose tissue	Myocardial contractility, insulin secretion, lipolysis, glucose production, platelet aggregation
PDE4	cAMP	Brain, testes, leukocytes, skeletal, visceral and vascular muscles	Inflammation, vascular and visceral muscle tone, depression, reproductions
PDE5	cGMP	Corpus cavernosum, blood platelets, visceral and vascular muscles, hear, placenta, pancreas, brain, liver, lung	Erection, platlet aggregation, muscle tone
PDE6	cGMP	Retina	Singal transduction in vision
PDE7	cAMP	Skeletal muscles, heart, lymphocytes	T-cell activation, skeletal muscles
PDE8	cAMP	Testes, ovaries, bowel	T-cell activation
PDE9	cGMP	Spleen, small intestine, brain	---
PDE10	cGMP, cAMP	Brain, testes, thyroid gland	Dopamine signal transduction
PDE11	cGMP, cAMP	Skeletal muscles, heart, vascular and visceral muscles, pituitary gland, testes, liver kidneys	---

Non-Selective Phosphodiesterase Inhibition

Non-selective PDE inhibitors largely consist of methylated xanthines and their derivatives. These include common, familiar products including caffeine, aminophylline, theophylline, and pentoxifylline. These agents are competitive nonselective inhibitors of more than one subtype of phosphodiesterase. They raise intracellular cAMP, activate protein kinase A, and have downstream effects blocking the NF- κ B pathway (and, therefore, TNF α production) [1]. Pentoxifylline, used in the treatment of intermittent claudication, has phosphodiesterase inhibitor activity in smooth muscle endothelial cells, resulting in vasodilation and symptom relief.

Nonselective PDE inhibitors also act as adenosine receptor antagonists [8]. Adenosine is a commonly used drug in the emergency setting to slow rapid heart rhythms such as supraventricular tachycardia. Non selective phosphodiesterase inhibitors such as xanthine derivatives (theophylline and caffeine) also act as antagonists on certain adenosine receptors (specifically A1 and A2a subtypes) in the heart and brain, resulting in a stimulant effect and rapid heart rate, respectively [9].

Selective Phosphodiesterase Inhibition

Vinpocetine is a PDE1 inhibitor used for cerebrovascular disorders and cognitive impairment. It targets the inflammatory component of neurological diseases by several mechanisms, one of which is a cAMP mediated inhibition of the pro-inflammatory NF-KB pathway [10]. Milrinone is a PDE3 inhibitor used clinically to relieve symptoms and improve hemodynamics in patients with congestive heart failure [11]. It functions as both an inotropic agent and vasodilator by inhibiting the breakdown- and increasing the intracellular concentration of cAMP. Increased cAMP in cardiomyocytes activates the voltage gated calcium channel and creates a calcium influx which is necessary for myocardial contraction.

Perhaps the most familiar class of selective PDE inhibitor is the group of drugs that inhibit PDE5. PDE5 is a cGMP specific hydrolyzing enzyme. It is present in high concentrations in the smooth muscle of the penile corpus cavernosum. Specific PDE5 inhibitors (sildenafil, tadalafil, vardenafil) enhance erectile function during sexual stimulation by maintaining sufficient levels of cGMP in both the corpus cavernosum and the vessels supplying it, thus allowing more blood flow to the penis [12].

Phosphodiesterase-4-Inhibition

Phosphodiesterase 4 (PDE4) is a widely distributed phosphodiesterase present in many cell types (Table 2). PDE4 has four subtypes (A, B, C, D). It is one of the major cAMP-selective PDEs in epithelial cells, such as those lining the airways. PDE4 is also expressed in the dermis, smooth muscle, vascular endothelium, and chondrocytes [13, 14]. Phosphodiesterase type 4 is the primary cAMP metabolizing enzyme involved in the control of activity in inflammatory cells [15]. It is highly expressed by immunologic cells including: dendritic cells, T cells, macrophages, and monocytes [16, 17, 18]. Increased cAMP levels inhibit the NF-kB pathway resulting in decreased TNF [19, 20]. Based on the presence and role of PDE4 in various inflammatory cells, PDE4 inhibitors can exert anti-inflammatory effects in almost all inflammatory cells and serve a potential role as anti-inflammatory drugs [19].

Table 2. PDE4 is widely distributed. Type of phosphodiesterase present in leukocytes.

<i>Leukocyte Cell Type-</i>	<i>PDE Subtypes Present</i>
Mast Cell	4
Eosinophils	4,7
Neutrophils	4,7
Monocytes	1,3,4,7
Macrophages	1,3,4,5,7

Roflumilast was the first PDE4 inhibitor approved and is used in the treatment of chronic obstructive airways disease [21]. In clinical trials, roflumilast produced significant improvements in spirometry, quality of life scores, and a reduction in number of COPD exacerbations in severe COPD patients [22, 23, 24].

The presence and function of PDE4 enzymes in immune cell and keratinocytes suggests they may be useful for inflammatory skin conditions [25]. Recent studies have investigated the use of other selective PDE4 inhibitors—apremilast and AN2728— as treatments for dermatologic disease.

Clinical Trials

Several studies have assessed use of apremilast in the treatment of psoriasis (Table 3).

Table 3. Apremilast in Psoriasis Treatment Study Tables

Study	Methods	Outcomes	Adverse Events
An open-label, single-arm pilot study in patients with severe plaque-type psoriasis	19 patients with moderate to severe psoriasis were treated with 20mg daily of apremilast for 29 days; 17	After 29 days, T cells were reduced by 28.8% and 42.6% in the dermis and epidermis, respectively.	73.7% reported at least one adverse event The most common adverse events were headache (5 patients) and nausea (3 patients)

<p>treated with an oral anti-inflammatory agent, apremilast</p> <p>Gottlieb et al 2008 [26]</p>	<p>patients completed the study</p>	<p>CD11c cells were reduced by 18.5% and 40.2% in the dermis and epidermis, respectively. Fourteen of the 19 (73.7%) patients had an improvement in their PASI scores.</p>	<p>Most adverse events were mild in severity.</p> <p>2 patients were considered to have serious adverse events: Pharyngitis and non-accidental injury- that were considered unrelated to apremilast. No opportunistic infections were reported</p>
<p>Efficacy, Tolerability, and Pharmacodynamics of Apremilast in Recalcitrant Plaque Psoriasis: A Phase II Open-Label Study</p> <p>Gottlieb et. al 2013 [27]</p>	<p>30 patients with recalcitrant plaque psoriasis received oral apremilast 20 mg BID for 12 weeks (treatment phase). Patients were assessed in four phases: pre-treatment, treatment, extension, and observational phase. Responders ($\geq 75\%$ improvement in Psoriasis Area and Severity Index [PASI-75] at week 12) entering the extension continued to receive apremilast 20 mg BID. Non-responders ($< \text{PASI-75}$ at week 12) were dose-escalated to apremilast 30 mg BID.</p>	<p>At week 12, 67% of patients had a ≥ 1-point improvement in static Physician's Global Assessment, meeting treatment effect criterion. Mean percent decreases (improvements) from baseline were -59% for PASI score and -53% for body surface area.</p> <p>At 12 weeks, 14 (46.7%) patients achieved PASI-50, nine (30.0%) achieved PASI-75, and four (13.3%) achieved PASI-90</p>	<p>During the treatment phase, 25 (83.3%) patients experienced AEs.</p> <p>The most frequently reported AEs were diarrhea (7/30 [23.3%]), nausea (6/30 [20.0%]), and headache (6/30 [20.0%]).</p> <p>Most AEs were mild to moderate and not treatment-related.</p> <p>No serious adverse events were reported during the treatment phase.</p>
<p>Efficacy and safety of apremilast in subjects with moderate to severe plaque psoriasis: results from a phase II, multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-comparison study</p> <p>Papp KA et. al 2013 [28]</p>	<p>259 participants were randomized in a 1:1:1 ratio of: placebo, 20 mg apremilast QD, or 20 mg apremilast BID. All subjects had a ≥ 6 month history of moderate to severe psoriasis, PASI score > 10, and body surface area involvement $\geq 10\%$. The subjects had a 12 week treatment period, followed by a 4-week observational follow-up period to monitor relapse after study medication termination</p>	<p>At the end of 12 weeks, 24.4% of subjects receiving apremilast 20 mg BID achieved PASI-75 compared to 10.3% receiving placebo ($p=.024$). Mean per cent reduction in PASI from baseline was 17.4% for placebo, 30.3% for apremilast 20 mg QD ($p=0.021$ versus placebo), and 52.1% for apremilast 20 mg BID ($p<0.001$). Apremilast 20 mg BID decreased mean body surface area involvement versus placebo (30.8% versus 3.2%, $p<0.001$). Relapses, however, were similar in all treatment groups in the post treatment 4-week observational phase (21.7% with placebo, 24.2% with apremilast 20 mg QD, 26.4% with apremilast BID)</p>	<p>The percentage of patients reporting ≥ 1 adverse event was 59.8% with placebo, 67.8% with apremilast 20mg QD, and 54.1% with apremilast 20mg BID</p> <p>The most common adverse events were headache, nasopharyngitis, diarrhoea and nausea.</p> <p>Most events ($> 90\%$) were mild to moderate and did not lead to study discontinuation.</p> <p>Serious adverse events occurred in four placebo subjects (panic attack, hospitalization for rehabilitation, hospitalization for alcoholism, worsening psoriasis), one receiving apremilast 20 mg QD (knee surgery) and in one receiving apremilast 20 mg BID (worsening psoriasis).</p> <p>No opportunistic infections were reported.</p>
<p>Efficacy of Apremilast in the treatment of moderate to severe psoriasis: a randomized control trial</p> <p>Papp KA et al. 2012 [29]</p>	<p>89 patients were randomly assigned apremilast 10 mg BID, 87 apremilast 20 mg BID, and 88 apremilast 30 mg BID; 88 were assigned placebo</p>	<p>At week 16, PASI-75 was achieved in five patients (6%) assigned placebo, ten (11%) assigned apremilast 10 mg, 25 (29%) assigned 20 mg, and 36 (41%) assigned 30 mg. Apremilast 10 mg did not differ significantly from placebo in achievement of the endpoint (odds ratio 2.10; 95% CI 0.69–6.42); for both apremilast 20 mg (6.69; 2.43–18.5; $p<0.0001$) and apremilast 30 mg (11.5; 4.24–31.2; $p<0.0001$), the differences from placebo were significant</p>	<p>The percentage of patients reporting <i>serious</i> adverse event was 2% with placebo, 0% with apremilast 10mg, 3% with apremilast 20mg, 2% with apremilast 30mg</p>

<p>Improvements in patient-reported outcomes with apremilast, an oral phosphodiesterase 4 inhibitor, in the treatment of moderate to severe psoriasis: results from a phase IIb randomized, controlled study</p> <p>Strand 2013 [30]</p>	<p>352 patients with moderate to severe plaque psoriasis received placebo or apremilast (10, 20, or 30 mg BID).</p> <p>The aim of this study was to assess patient reported outcomes (PROs). PROs included Dermatology Life Quality Index (DLQI), pruritus visual analog scale (VAS), and Short-Form Health Survey (SF-36) to assess health-related quality of life (HRQOL).</p>	<p>At 16 weeks, greater improvements from baseline in DLQI scores were reported with apremilast 20 (-5.9) and 30 mg BID (-4.4) compared with placebo (1.9; $P \leq 0.005$ for both)</p> <p>Greater improvements from baseline in pruritus VAS scores were reported with apremilast 20 (-35.5%) and 30 mg BID (-43.7%) versus placebo (-6.1%; $P \leq 0.005$).</p> <p>Significant and clinically meaningful improvements in SF-36 mental component summary scores ($P \leq 0.008$) and Bodily Pain, Mental Health, and Role-Emotional domains were reported with all apremilast doses ($P < 0.05$), and Social Functioning with 20 and 30 mg BID ($P < 0.05$) and Physical Functioning with 20 mg BID ($P < 0.03$).</p>	<p>This study used questionnaires for the patients in the Papp et al 2012 study</p>
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Oral apremilast has also been studied in the treatment of psoriatic arthritis (PsA). It can affect up to 40% of patients with psoriasis who develop PsA [31, 32]. In a phase II, multicenter, randomized, controlled trial, 204 subjects were randomized in a 1:1:1 ratio to receive placebo or oral apremilast (20mg BID or 40 mg QD) for 12 weeks. At week 12, placebo patients were re-randomized to receive apremilast 20 mg BID or 40 mg QD until week 24. After 12 weeks, 43.5% of patients receiving apremilast 20 mg BID ($p < 0.001$) and 35.8% receiving apremilast 40 mg QD ($p = 0.002$) exhibited $\geq 20\%$ improvements in American College of Rheumatology response criteria versus 11.8% receiving placebo [33].

A study by Volf et. al assessing the efficacy of apremilast in treating recalcitrant allergic contact dermatitis (ACD) and atopic dermatitis (AD) [34]. Ten patients with either ACD or AD were treated with apremilast 20 mg daily for twelve weeks. Ten percent of subject achieved EASI-75 and another 10% reached EASI-50. These results were not as promising as PDE4 inhibition in psoriasis treatment.

AN2728 is another phosphodiesterase 4 inhibitor being studied in dermatologic conditions. It is used topically in atopic dermatitis and orally in psoriasis. This molecule is a competitive, reversible PDE4 inhibitor [34]. AN2728 is a boron-based molecule and binds to PDE4 at the catalytic site in a distinct way from traditional PDE4 inhibitors. Also known as phenoxybenoxaboroles, these drugs decrease pro-inflammatory cytokines TNF α , IL-2, IFN- γ , and IL-5, through binding of PDE4B [35].

In a randomized, double-blinded bilateral trial of the effects of AN2728 on psoriasis, 35 patients were treated with either AN2728 5% ointment versus vehicle and their Overall Target Plaque Severity Score (OTPSS) was assessed at Day 28. The proportion of plaques achieving clear or almost clear with ≥ 2 grade improvement from baseline (OTPSS scale) was 40% for those receiving 5% AN2728 versus 6% for those receiving the vehicle [36].

In a randomized, double blind, bilateral trial that followed to determine optimal concentration and dosing of AN2728, 145 patients applied AN2728 and vehicle for 12 weeks. The subjects were divided into 4 cohorts: 0.5% QD vs. vehicle, 2.0% vs. vehicle, 0.5% BID vs. vehicle, and 2.0% BID vs. vehicle. Patients were assessed at the end of 12 weeks based on their Overall Target Plaque Severity Score. A clear dose response occurred over 12 weeks of treatment, with the patients using the 2% BID dosage achieving nearly 60% improvement from baseline plaque severity. AN2728 used 0.5% BID and 2% QD demonstrated equal improvement. The group using 0.5% QD showed 40% improvement from baseline 28. The vehicle alone was least effective, with $< 40\%$ improvement from baseline plaque severity [36].

As expected based on its mechanism of action, AN2728 is also effective for atopic dermatitis. AN2728 has safety and efficacy in treating atopic dermatitis in three Phase 2 clinical trials. In a Phase 2 dose-ranging trial, 86 adolescents with mild to moderate atopic dermatitis were treated with AN2728 ointment, 2.0% twice daily for 28 days. Subjects achieved a 71% improvement from baseline in their Atopic Dermatitis Severity Index (ADSI) score; 66% of the lesions in this treatment achieved total or partial clearance. AN2728 was well tolerated and most adverse effects were mild. In a Phase 2 randomized, double blind, bilateral study of patients with mild to moderate atopic dermatitis, patients were randomized to apply 2% AN2728 ointment to one target lesion

and 0.5% AN2728 ointment either once daily or twice daily for 28 days to a comparable target lesion (Table 4). There was a clear dose response with the 2.0% BID method demonstrating greatest efficacy [37].

Table 4. Dose relate results of Phase 2 randomized control trials of AN2728 for treatment of atopic dermatitis

Dosing regimen of AN2728	% Improvement from Baseline ADASI	% Lesions Achieving Total or Partial Clearance	Pruritus
2.0% BID	71%	62%	79%
0.5% BID	62%	50%	75%
2.0% QD	63%	41%	73%
0.5% QD	54%	43%	63%

Adverse Effects

Most adverse effects were mild to moderate. The most common adverse effects were nausea, vomiting, and diarrhea (Table 3). Adverse effects were most prominent the first two weeks and with higher doses. Headaches were more severe at higher doses (30 mg BID). Most importantly, no significant laboratory abnormalities have been reported [29, 30]. So far, the side effect profile of phosphodiesterase 4 inhibitors is safer compared to many of the currently approved oral psoriasis medications, particularly, low-dose methotrexate, cyclosporine, and acitretin. These FDA approved medications are associated with myelosuppression, nephrotoxicity, and possible birth defects, respectively [38, 39, 40].

Conclusion

For both psoriasis and atopic dermatitis, there is a need for a safe, oral treatment, treatments not associated with immunosuppression or other major organ toxicities. Phosphodiesterase inhibitors have some promise for filling this gap. Apremilast has only modest efficacy with PASI75 rates clearly lower than biologics that achieve PASI75 in 50-80% of patients. But aside from GI tolerability issues in some patients, apremilast appears to have minimal serious adverse effects. If in the long run phosphodiesterase inhibitors maintain a good safety profile, they have the potential for use in a broader population than the severe disease population who are candidates for high cost or high risk treatment, expanding the pie for systemic therapy of psoriasis from just patients with severe psoriasis to patients at the milder end of the moderate-to-severe psoriasis spectrum. Although there are gastrointestinal tolerability issues, patients with psoriasis could be started on a phosphodiesterase inhibitor and those who do have intolerable gastrointestinal side effects could be switched to other drugs if the GI side effects are not manageable by dose reduction or other methods. In addition, the potential for use of oral phosphodiesterase inhibitors in conjunction with other treatments—topical and/or phototherapy—could make the product more effective in clinical practice than it was as monotherapy in clinical trials.

There are potential hurdles for use of this class of agents for skin disease. Whereas phosphodiesterase inhibition seems to be a safe approach (phosphodiesterase inhibitors like caffeine are the most widely used drugs by humans and there is no known concern for promotion of opportunistic infection), it is possible that a high degree of specific inhibition of PDE4 could result in significant immunosuppression, though so far that has not been observed. The other major hurdle is cost. In an environment with increasing cost consideration, a high price for this class of agents, given the modest efficacy so far observed, would make this a low value product.

The development of a topical phosphodiesterase inhibitor for the treatment of psoriasis and atopic dermatitis offers an approach for focal disease that avoids corticosteroid side effects. Given the low cost of generic topical corticosteroids and the relatively limited severity of their side effects (easy bruising, atrophy, perioral dermatitis) [41], this benefit may not be compelling. Moreover, topical phosphodiesterase inhibitors would also compete with topical calcineurin inhibitors, which are also anti-inflammatory and without corticosteroid side effects. Although the use of topical calcineurin inhibitors has been limited owing to cost, as topical calcineurin inhibitors become available as generics, there may be less need for topical phosphodiesterase inhibitors or other steroid-sparing agents.

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