Journal of the Turkish Academy of Dermatology
eISSN 1307-394X

Review DOI: 10.6003/jtad.16103r1

Apremilast Treatment in Dermatology

Belma Türsen,[1] MD, Ulaş Güvenç,[2] MD, Ümit Türsen,[3] MD

Address: [1]Mersin State Hospital, [2]Mersin Yenişehir Hospital, [3]Mersin University, School of Medicine, Department of Dermatology, Mersin, Turkey

E-mail: utursen@mersin.edu.tr

** Corresponding Author:* Dr. Ümit Türsen, Mersin University, School of Medicine, Department of Dermatology Mersin, Turkey

Published:
J Turk Acad Dermatol 2016; **10 (3)**: 16103r1.
This article is available from: http://www.jtad.org/2016/1/jtad16103r1.pdf
Keywords: Apremilast, dermatology

Abstract

Background: Apremilast (Otezla®), an oral small molecule inhibitor of type-4 cyclic nucleotide phosphodiesterase (PDE-4), is under development with Celgene Corporation for the treatment of psoriatic arthritis, psoriasis, sarcoidosis, Behçet's syndrome, atopic dermatitis, and rheumatoid arthritis. Apremilast is indicated for the treatment of active psoriatic arthritis in adults. Apremilast has received its first global approval for this indication in the USA. Regulatory submissions for approval in this indication are under review in Canada and Europe. Regulatory filings have also been submitted for apremilast in the treatment of plaque psoriasis in the USA and Europe. Apremilast treatment have been reported in the following dermatologic diseases: psoriasis, rosacea, atopic dermatitis, contact dermatitis, sarcoidosis, lupus erythematosus, lichen planus and alopecia areata. The following article provides a summary of the salient points in relation to the clinical use of apremilast treatment in dermatology.

Introduction

Agents which increase intracellular cyclic adenosine monophosphate (cAMP) may have an antagonistic effect on pro-inflammatory molecule production so that inhibitors of the cAMP degrading phosphodiesterases have been identified as promising drugs in chronic inflammatory disorders. Although many such inhibitors have been developed, their introduction in the clinic has been hampered by their narrow therapeutic window with side effects such as nausea and emesis occurring at sub-therapeutic levels. The latest generation of inhibitors selective for phosphodiesterase 4 (PDE4), like apremilast, seems to have an improved therapeutic index. Apremilast shows promising activity in dermatological and rheumatological conditions. Studies in psoriasis and psoriatic arthritis have demonstrated clinical activity of apremilast. Efficacy in psoriasis is probably equivalent to methotrexate but less than that of monoclonal antibody inhibitors of tumour necrosis factor (TNF-α). Similarly, in psoriatic arthritis efficacy is less than that of TNF inhibitors. PDE4 inhibitors hold the promise to broaden the portfolio of anti-inflammatory therapeutic approaches in a range of chronic inflammatory diseases which may include granulomatous skin diseases, some subtypes of chronic eczema and probably cutaneous lupus erythematosus (**Table 1**). In this review, we discuss apremilast on skin inflammatory responses and also their future role in clinical practice [**1,2,3,4,5**].

Table 1. The Applications of Apremilast in Skin Diseases

1-Psoriasis
2-Contact Dermatitis
3-Atopic dermatitis
4-Lichen Planus
5-Sarcoidosis
6-Rosacea
7-Alopecia areata
8-Systemic lupus erythematosus and discoid lupus erythematosus
9-Psoriatic arthritis

Mechanism of Action

The clinical symptoms of chronic inflammatory diseases are determined by a number of different inflammatory mediators. In psoriasis, for example, not only the well-recognized TNF is an important effector molecule, but IL-17, IL-22, INF-γ, IL-2, IL-36, CCL20, IL-8, chemokine CXCL10, IL-23, IL-1, IL-18, IL-12, VEGF, substance P, IFN-α, and many others contribute to the inflammatory response in the joint and skin. Conventional therapies have a broad range of action and inhibit, e.g. preferentially lymphocyte proliferation [cyclosporin (CsA), methotrexate] and lymphokine production (IFNγ, IL-17, IL-22, IL-2) or mainly target the hyperproliferation and abnormal differentiation of keratinocytes (dithranol, tar) or combine the latter with cytokine modifying properties (retinoids, vitamin D, glucocorticoids). Biologics currently used in the clinic target one specific mediator which supposedly plays a key role upstream in the disease-specific cytokine network. cAMP is a key intracellular second Messenger and also cAMP signalling is activated by a variety of G protein-coupled receptor ligands. The effects of cAMP are transduced by two ubiquitously expressed intracellular cAMP receptors, protein kinase A (PKA) and exchange protein directly activated by cAMP. cAMP can also bind to cyclic nucleotide-gated ion channels in certain tissues. The local pools of cAMP expression/PKA activation are generated in distinct subcellular compartments. This allows for precisely regulated activity essential for response specificity. cAMP activates and enables PKA to phosphorylate substrate proteins. PKA activates cAMP response element binding protein which is a cAMP-responsive element possessed by several immune-related genes including IL-2, IL-6, IL-10, and TNFα. cAMP can directly or indirectly inhibit nuclear factor kappa B (NF-κB) pathway activation events. Low intracellular cAMP may thus lead to the preferential expression of proinflammatory mediators. Intracellular concentration of cAMP is determined by the activity of adenylyl cyclases on the one hand and PDE on the other. PDEs are also expressed in distinct cellular compartments and functionally coupled to individual receptors—thus providing a way to control sub compartment cAMP levels in a stimulus-specific manner. Substances which increase cAMP in monocytes/ macrophages are among the most potent inhibitors of IL-12 family members including IL-12/IL-23 p40 [**1,2,3**].

This has been shown for cholera toxin, histamine, PGE2 and other mediators. Repression of cAMP greatly reduces the suppressive activity of human Treg. cAMP facilitates the functional activity of a transcriptional inhibitor called ICER (inducible cAMP early repressor) and this mechanism seems to be involved in the suppression of the key T cell growth factor IL-2 and other cytokines. In addition, immunosuppressive and anti-inflammatory actions of cAMP have been attributed in part to the ability of cAMP induced signals to interfere with the function of NF-κB. NF-κB activation is one of the master signalling pathways involved in inflammatory responses and a key target for anti-inflammatory drug design. Important cytokines downstream of NF-κB include TNFα, CCL20, IL-8; IL-1 family members (IL-36, IL-18, IL-1) and (in combination with a priming signal) also IL-12 family members (IL-12, IL- 23, IL-27) and many

more. The cAMP system is also involved in a variety of epithelial functions and plays a role in maintenance of the skin barrier. In the keratinocyte cell line HaCat largely suppressed chemokine production (CXCL10, CCL17, and CCL22) has been described in the context of increased cAMP levels. There are several PDE families, all isoforms of which are concerned with the intracellular degradation of the phosphodiesterase bonds of cAMP and cyclic guanosine monophosphate (cGMP). PDE4, -7, and -8 degrade cAMP specifically. PDE4 is encoded by four separate genes (PDE4 A–D) and each PDE4 controls nonredundant cellular functions. Inhibition of PDE4 activity leads to elevated levels of intracellular cAMP [**4, 5**]. Pentoxifylline is a competitive non-selective PDE inhibitor which raises intracellular cAMP levels to inhibit TNF and reduce inflammation. Theophylline inhibits to some extent PDE1-5, is a potent adenosine receptor antagonist and an activator of histone deacetylase 2 such that it might exert beneficial effects on lung inflammation. By increasing cAMP levels, PDE4 inhibitors show anti-inflammatory effects in almost all inflammatory cells. Numerous selective PDE4 inhibitors have been patented in the last decades and some of them have been evaluated in clinical trials for inflammatory conditions. Recent human clinical data on PDE4 inhibitors on skin diseases and in particular on psoriasis are available for apremilast. The effects of apremilast—which are in line with findings reported for increased intracellular cAMP levels—on a range of pro-inflammatory responses in a variety of cells have recently been comprehensively summarized. Unsurprisingly, all PDE4 inhibitors have the potential to reduce the expression of TNFα which is considered a key mediator in a number of inflammatory diseases [**3**]. *Crilly* et al. have demonstrated that specific PDE4 inhibitors dose-dependently down regulate the release of TNFα and other cytokines including CCL2, CCL3, IL-1ß [**6**]. *McCann* et al. have demonstrated TNFα inhibition in human rheumatoid synovial membrane cultures for apremilast. It is of interest that some PDE4 subtypes such as PDE4B seem to be more concerned with the inhibition of TNF production in murine monocyte/macrophages [**7**]. Apremilast has inhibitory activity on TNFα release by UVB activated keratinocytes. *Schafer* et al observed that apremilast was a selective PDE4 inhibitor with regulatory effects on innate immunity [**4**].

Side Effects

Doses needed for efficacy could not be reached due to doselimiting adverse events with nausea, diarrhoea, abdominal pain, vomiting, and dyspepsia being the most common. Apremilast is an orally available PDE4 inhibitor which does not show any marked selectivity among the PDE4 isotypes. It seems to elicit less emetic side effects while also having a wide therapeutic window. The most common adverse events were gastrointestinal and generally occurred early, were selflimiting and infrequently led to discontinuation. Nausea and headache, upper respiratory tract infection (3.9 vs. 1.8% for placebo), vomiting, nasopharyngitis and upper abdominal pain were also reported. During clinical trials, 1.0% of patients treated with apremilast reported depression or depressed mood compared with 0.8% treated with placebo. Body weight loss of 5–10% was reported in 10% of patients taking apremilast. In a pooled safety analysis of the PALACE 1, PALACE 2, and PALACE 3 studies, the most common adverse events were diarrhea, nausea, headache, upper respiratory tract infection, and nasopharyngitis. Most adverse events were mild to moderate in severity, and discontinuations due to adverse events were low. In addition, no relevant safety signals for opportunistic infection, cancer, demyelination, or lupus-like syndromes have been attributed to apremilast to date. There also have been no indications of significant laboratory or electrocardiographic abnormalities or clinically significant effects on liver function, white blood cells, blood pressure, or hemoglobin. Additional results from the PALACE 2, PALACE 3, and PALACE 4 studies demonstrate the clinical efficacy of apremilast in patients with active PsA, with no new safety signals observed and improved tolerability over phase II studies. Most adverse effects were mild to moderate. The most common adverse effects were nausea, vomiting, and diarrhea. 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. So far, the side effect profile of phosphodiesterase 4 inhibitors is safer compared to many of the currently approved oral psoriasis medications, particularly, lowdose methotrexate, cyclosporine, and acitretin. These FDA approved medications are associated with myelosuppression, nephrotoxicity, and possible birth defects, respectively. PDE4 is also one of the major phosphodiesterase isoenzymes expressed in the central nervous system, and therefore nausea and emesis are common adverse effects of drug administration. Early PDE4 inhibitors actually failed in clinical trials due to the high prevalence of nausea and emesis. Other adverse effects associated with repeated administration of PDE4 inhibitors include headache, diarrhea, fatigue, dyspepsia, nasopharyngitis, and gastroenteritis. Mesenteric vasculitis is a more worrisome toxicity that may be associated with the PDE4 inhibitors. Studies performed in rodents have demonstrated medial necrosis of the mesenteric arteries after administration of the second generation PDE4 inhibitor cilomilast. However at a meeting convened by the FDA in 2003 to discuss cilomilast in phase III studies, the committee unanimously agreed that the risk of mesenteric vasculitis is not a safety concern based on human studies. The newer PDE4 inhibitor, apremilast, has been well tolerated with few side effects in phase I, II and 3 studies. The most frequently reported adverse events have been headache, nausea and pharyngitis. Researchers used a recognized pharmacophore from the PDE4 inhibitors rolipram and roflumilast in the development of apremilast, and added it to a series of thalidomide analogs in efforts to optimize activity and reduce side effects classically seen with earlier PDE4 inhibitors [**2, 8, 9, 10, 11**].

Dosage Range

In psoriasis, the pharmacokinetic profile of apremilast has also been characterized. Patients receiving 20mg apremilast once daily showed a mean steady-state maximal concentration (Cmax) of 207.07 ng/ml and the area under the curve (AUC) was 1799 ng/h/ml. The median time oral administration of apremilast reached a maximal concentration (Tmax) was 2 hours, the mean half-life of the drug was 8.2 h. With respect to excretion of the drug, the mean clearance (CL/F) was 10.4 l/h, and mean volume of distribution (Vz/F) was 128 l [*Gottlieb* et al. 2008]. *Liu* et al observed that ketoconazole slightly decreased apremilast clearance. However, the effect of CYP3A4 induction by rifampicin on apremilast clearance was much more pronounced than that of CYP3A4 inhibition by ketoconazole. They concluded that strong CYP3A4 inducers could result in a loss of efficacy ofapremilast because of decreased drug exposure [**12, 13**].

Pharmacokinetics

Apremilast is a novel, orally available small molecule that specifically inhibits PDE4 and thus modulates multiple pro- and anti-inflammatory mediators, and is currently under clinical development for the treatment of psoriasis and psoriatic arthritis. The pharmacokinetics and disposition of [**14**] apremilast was investigated following a single oral dose (20 mg, 100 μCi) to healthy male subjects. Approximately 58% of the radioactive dose was excreted in urine, while faeces contained 39%. Mean C(max), AUC(0-∞) and t(max) values for apremilast in plasma were 333 ng/mL, 1970 ng*h/mL and 1.5 h. Apremilast was extensively metabolized via multiple pathways, with unchanged drug representing 45% of the circulating radioactivity and <7% of the excreted radioactivity. The predominant metabolite was O-desmethyl apremilast glucuronide, representing 39% of plasma radioactivity and 34% of excreted radioactivity. The only other radioactive components that represented >4% of the excreted radioactivity were O-demethylated apremilast and its hydrolysis product. Additional minor circulating and excreted compounds were formed via O-demethylation, O-deethylation, N-deacetylation, hydroxylation, glucuronidation and/or hydrolysis. The major metabolites were at least 50-fold less pharmacologically active than apremilast. Metabolic clearance of apremilast was the major route of elimination, while non-enzymatic hydrolysis and excretion of unchanged drug were involved to a lesser extent. Apremilast has been evaluated

for its pharmacokinetic properties and disposition following oral administration. Multiple daily doses showed rapid absorption (Tmax=2 h) and a moderately long half-life (8.2 h). A separate study monitored healthy male subjects following a single, 20 mg, oral dose and found that apremilast was extensively metabolized via multiple pathways, with unchanged drug representing 45% of the circulating radioactivity and <7% of the excreted radioactivity. Analysis of total radioactivity suggests rapid absorption, with plasma Tmax values also at 2 h. Mean Cmax and area under the curve (AUC) values in plasma were 333 ng/ml and 1,970 ng*h/ml, respectively. Metabolic clearance of apremilast was the major route of elimination with the key metabolites demonstrating at least 50-fold less pharmacologic activity than apremilast [**12, 13**]. *Man* et al. optimized the structures of a series of 3-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-3-(3,4-dialkoxyphenyl) propionic acid analogues to enhance PDE4 and TNFα inhibitory activity. So far, oral and intravenous administration of these analogues in female rats has shown good pharmacokinetics with low clearance, a moderate volume of distribution, and a 64% oral bioavailability [**14**].

Indications

Data suggest a promising therapeutic effect for selective PDE4 inhibitors on inflammatory skin diseases. Of note, a PDE7A inhibitor was also successful in suppressing dermatitis and TNF expression in mice studies. In a humanised [severe combined immunodeficiency (SCID) mice, grafted human psoriasis skin triggered with psoriatic natural killer (NK) cells] psoriasis model oral apremilast led to significant reduction in epidermal lesion thickness. The psoriasiform histology was clearly reduced with regard to parakeratosis, hyperkeratosis, lymphocytic and neutrophilic infiltration. Aprelimast treatment have been reported in the following dermatologic diseases: psoriasis, atopic dermatitis, alopecia areata, sarcoidosis, lupus erythematosus, contact dermatitis and lichen planus [**4, 5, 6, 7, 8, 9, 10, 11, 12, 13**]. For skin diseases, the availability of topical preparations is of high interest and ongoing trials are exploiting the potency of topical PDE4 inhibition. The antifibrotic effect makes PDEs potential drugs for the treatment of scleroderma. However, PDE5 inhibitors seem more promising in this disease as well as in the treatment of secondary Raynaud's phenomenon. PDE4 inhibitors including apremilast have beneficial effects in animal models of dermatitis, in particular allergic contact dermatitis (ACD). The elicitation phase of ACD follows a Th1 like dominated response pattern where contact allergens impact on TLR activation, reactive oxygen species (ROS) and NLRP3 inflammasome activation which are key mechanisms in the induction phase of ACD. As mentioned above, inhibition of ROS production may be better achieved in vitro by combined PDE inhibitors [**1, 2, 3**].

Dermatological Uses of Apremilast

Apremilast has been licensed for use in psoriasis. There are currently a lot of clinical trials with apremilast for conditions other than psoriasis. Apremilast has been investigated in various dermatological conditions including atopic dermatitis, lichen planus, alopecia areata, contact dermatitis, rosacea, sarcoidosis and lupus erythematosus. This review aims to look at the various randomised and non-randomised clinical trials, case series and case reports for the role of apremilast in dermatological conditions. Numerous clinical trials have shown a positive light on the role of apremilast in skin conditions [**4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21**].

1-Psoriasis:

Psoriasis is a chronic inflammatory dermatosis characterized by the proliferation of hyperproliferative epidermal keratinocytes. The cellular immune system is thought to trigger this keratinocyte response, with monocytes, dendritic cells, neutrophils, and T cells being implicated in the pathogenesis. PDE4 is present in all inflammatory cells identified to be relevant in psoriasis and appears to be involved in several pathophysiologic processes of psoriasis such as the production of TNF-α, IL-12, and IL-23 by monocytes/macrophages, the synthesis of IL-2, IFN-g, and IL-5 production by T lymphocytes,

and the expression of TNF-α and IFN-a by plasmacytoid dendritic cells. Moreover, chemoattracation via regulation of IL-8 and IP-10 expression, and TNF-α production by keratinocytes, are both influenced by PDE4. Preclinical in vivo testing of apremilast has been performed in natural killer cell-driven models of psoriasis using human skin xenotransplanted onto immunodeficient SCID mice, followed by challenge with human natural killer cells. Injection of natural killer cells from psoriatic donors into nonlesional psoriatic skin results in a classic psoriasis histology. In this model, apremilast (5 mg/kg orally, divided into two daily doses) significantly reduced keratinocyte proliferation, skin thickness, and the general histopathologic appearance of psoriasiform features. Moreover, expression of TNF-α, ICAM-1, and HLA-DR on the skin grafts was qualitatively reduced upon apremilast treatment. PDE4 is the predominant phosphodiesterase involved in the control of activity in inflammatory cells, yet it is also expressed in structural cell types involved in psoriasis, such as keratinocytes. Indeed, in a study comparing psoriasis skin samples with normal skin samples, immunohistochemistry demonstrated that PDE4A, PDE4B, and PDE4D expression can be detected in inflammatory cells as well as in the structural and adnexal tissues of the skin. Through inhibition of PDE4, apremilast causes an elevation of cyclic adenosine monophosphate, a naturally occurring intracellular secondary Messenger that functions as a modulator of inflammatory responses, thereby decreasing production of proinflammatory mediators, such as TNF-α, IL-23, and IFN-γ, and increasing production of antiinflammatory mediators, such as IL-10. The modulatory effects of apremilast on inflammatory activity have been demonstrated in multiple in vivo and in vitro models and studies in humans. In addition, apremilast has been shown to decrease proinflammatory cytokine production induced by toll-like receptor 4 agonism in peripheral blood mononuclear cells, T-cell receptor agonism, cytokine and immunoglobulin receptor agonism on natural killer cells, and ultraviolet light exposure of keratinocytes. In lipopolysaccharide-stimulated peripheral blood mononuclear cells, apremilast reduced the production of TNF-α, IFN-γ, IL-12, and IL-23 and increased the production of IL-10. In subjects with severe plaque psoriasis, apremilast reduced both infiltration of myeloid dendritic cells into the dermis and epidermis and inducible macrophage-type nitric oxide synthase mRNA expression and in subjects with rheumatoid arthritis, apremilast reduced IL-7 gene expression in synovial fibroblasts. Based on available data, it is most appropriate to classify apremilast as a specific inhibitor of PDE4, which affects inflammatory signals across several cell types, thereby modulating the production of multiple cytokines and exerting influence on a number of physiologic aspects of psoriasis [**22**]. A small (19 patients) single arm, open-label pilot study was performed in subjects with moderate to severe plaque psoriasis. Patients were treated for 29 days with 20 mg od of apremilast. CD11+ cells, T cells and epidermal thickness were reduced. Immunohistologic analysis of lesional-skin biopsies showed reduction in epidermal thickness and reduced infiltration of T cells and CD11+ cells in responder patients. Psoriasis Area and Severity Index (PASI) was improved in 14 out of 19 patients. In this study, 8 of the evaluable 15 patients met the primary endpoint of achieving a 20% reduction in epidermal thickness. Overall, the patients showed a mean decrease of 20.5 % in epidermal thickness. This response was associated with a 28.8 % and 42.6% decrease in T cells in the dermis and epidermis, respectively, and by an 18.5% and 40.2% decrease in CD11+ myeloid dendritic cells in the dermis and epidermis, respectively. Within the skin biopsies, there was a significant reduction in the mRNA levels of inducible nitric oxide synthetase after 1 month of treatment with apremilast. Also in this study, apremilast had an inhibitory effect on ex vivo whole-blood LPS-stimulated TNF-α production. 2 hours after the first dose, in 11 of the patients. Therefore, in this short study using a low dose of apremilast, meaningful changes in both skin and blood biomarkers were observed. In the ESTEEM 1 study, apremilast significantly improved Psoriasis Area and Severity Index scores in patients with moderate to severe plaque psoriasis; after 16 weeks, a significantly greater proportion of patients receiving apremilast 30 mg BID (33%) achieved a 75% reduction from baseline Psoriasis Area and Severity Index score compared with those receiving placebo (5%; $p < 0.0001$ versus placebo) [**23**]. The efficacy

of apremilast in psoriasis has been assessed in a phase 2b study using doses of 10, 20, and 30 mg bd with a placebo comparator. In this study, 352 patients were enrolled with active psoriasis of moderate severity who were candidates for phototherapy or systemic therapy. The primary target was the proportion of subjects achieving 75% improvement in PASI75 at 16 weeks. At 16 weeks patients on placebo could be rerandomised to active treatment but the dose was still concealed to both patient and physician. Further outcomes were assessed at 24 weeks. At 16 weeks PASI75 was achieved by 6% of patients on placebo, 11% of those on 10 mg bd, 29% of those on 20 mg bd, and 41% of those on 30 mg bd. The results for apremilast 20 mg bd and 30 mg bd were significantly different from placebo. The median number of days to achieve PASI75 was 57 for placebo and 70, 83, and 44 for 10, 20 and 30 mg bd, respectively. At week 16 13% of patients on placebo were 'clear or almost clear' on the physicians global assessment; the corresponding figures for apremilast were 10%, 24%, and 33% for 10, 20, and 30 mg bd, respectively. Adverse events were largely mild to moderate: upper respiratory tract infections, gastrointestinal symptoms including diarrhoea and nausea, and headache were the most frequent of these in the active treatment groups. No opportunistic infections were seen [**24**]. Subsequently, a randomized, placebo-controlled phase II study was performed in 260 patients with moderate to severe psoriasis using two doses of apremilast (20mg once daily and 20 mg twice daily). In this study, a 75% reduction in the Psoriasis Area and Severity Index score was observed in 24% of patients receiving apremilast 20mg twice daily compared with placebo, whereas the clinical response to the lower, once-daily 20mg dose was not significantly different from placebo. Moreover, a 50% improvement in the Psoriasis Area and Severity Index score was observed in a significantly greater percentage (57%) of apremilast-treated patients compared with 23% of the patients receiving placebo. Doses of apremilast 20 mg twice daily led to plasma concentrations between 129 ng/ml and 389 ng/ml. With respect to safety, apremilast was generally well tolerated. Diarrhea and nausea were more commonly observed in patients treated with the two doses of apremilast than with placebo. Most cases were mild to moderate in severity. Gastrointestinal symptoms are in fact not unexpected and considered as a class effect of PDE4 inhibitors. Owing to the lack of highly specific inhibition of the PDE4D isoform, however, these effects were mild [**25**].

2-Psoriatic Arthritis:

Apart from psoriasis, there is also a rationale for using apremilast to control the inflammatory disease process of arthritis. Arthritis is characterized by a massively enhanced influx of immune cells, in particular monocytes/macrophages, neutrophils, and lymphocytes into joints. In addition, there is a strong mesenchymal response in arthritis, which manifests as synovial hyperplasia based on proliferation of synovial fibroblast-like cells. Both immune cells and synovial fibroblasts contribute to cytokine production in the inflamed synovium, leading to a perpetuation of the inflammatory response, as well as to cartilage and bone resorption caused by activation of osteoclasts. Apremilast was tested in animal models of arthritis and human inflammatory arthritis. In collagen-induced arthritis of DBA1 mice, apremilast showed a reduction of clinical and histopathologic signs of arthritis at doses of 5 and 25 mg/kg administered by daily intraperitoneal injections. Ex vivo experiments showed that apremilast inhibited T-cell proliferation, IFN-γ production, and TNF-α production in stimulated lymph node cells from collagen-immunized mice at concentrations as low as 0.1 mM [**26**]. Similar results were obtained in experimental arthritis induced by monoclonal antibodies against type II collagen: apremilast, at an oral dose of 25 mg/kg, significantly blocked synovial inflammation, cartilage damage, and bone erosion in BALB/c mice. At the lower dose of 5 mg/kg, significant inhibition of paw swelling was observed by the end of the study [**27**]. In psoriatic arthritis there is only one published study of the efficacy of apremilast—a phase 2 randomized placebo controlled study. The results of the phase 3 PALACE-I study were presented at the American College of Rheumatology (ACR) meeting in Washington DC in November 2012. The phase II study enrolled 204 patients with active psoriatic arthritis, defined by more than or equal to 3 tender and 3 swollen joints. Only co-prescrip-

tion with a stable dose of methotrexate or oral glucocorticoids was allowed: all other disease modifying drugs had to be discontinued before enrolment. The usual restrictions on major co-morbid conditions applied. Patients were randomized equally to placebo, apremilast 20 mg bd or apremilast 40 mg once daily (od), stratified by baseline methotrexate use. After 12 weeks of treatment patients could stop treatment or enter a further 12 week extension phase, the latter option occurring as an amendment to the original protocol design, and re-randomisation of placebo to one of the active treatment groups. The primary efficacy endpoint was the proportion of patients achieving a modified (by joint count) ACR 20% improvement at 12 weeks (ACR20). The primary endpoint was achieved by 43.5% of patients in the apremilast 20 mg bd group, 35.8% of patients in the 40 mg od group, and 11.8% of patients on placebo, the differences between active drug and placebo being highly significant. In the extension phase, where patients who had initially taken placebo were transferred to an active drug, a similar improvement was seen in the people who transferred, and the initial improvements in the active treatment groups were maintained. Stratified for methotrexate use there was no difference in primary outcome between the two groups, although more people on combination had gastro-intestinal side effects. No assessments of skin, enthesitis, dactylitis, or axial involvement were made in this study. Overall safety data were good with diarrhoea and headache being the major, albeit no more than moderate, side effects. Abnormal laboratory results, including liver enzyme elevations, were infrequent. The PALACE-I study enrolled 504 patients with active psoriatic arthritis (more than three tender and swollen joints) who were randomized in an equal ratio to placebo, apremilast 20 mg bd and apremilast 30 mg bd. The patients were stratified by previous disease modifying drug use and about three quarters were TNF inhibitor naive. The primary outcome measure was again the ACR20 at 16 weeks which was achieved by 19.4%, 31.3%, and 41% of the placebo, 20 and 30 mg bd groups, respectively. At 24 weeks the corresponding figures for per protocol treatment (i.e. those still taking placebo) were ACR20 of 13%, 36%, and 45%. Patients on placebo had the chance to re-randomise to active drug at 16 weeks and a long-term extension for all patients is underway. As expected, patients who had previously taken biologics had less impressive responses, the ACR20 rates for the 20 and 30 mg bd groups at 16 weeks being 31% and 28%, respectively. Those taking disease modifying drugs (mostly methotrexate) had rather blunted responses (ACR20 rates of 31% and 35% for 20 and 30 mg bd, respectively). Skin responses were also reported: in patients with a skin surface area of greater than 3% at baseline the PASI75 rates at week 24 were 5%, 18% and 21% for placebo, 20 mg bd and 30 mg bd, respectively. Serious adverse events were rare and, again, adverse events were mainly gastrointestinal (diarrhoea and nausea) and headache, but a small increase in upper respiratory infections was also seen [**28**]. PALACE 1, 2 and 3 are the pivotal phase III multicentre RCTs with two active-treatment groups. Across these studies, approximately 1500 patients were randomized 1:1:1 to receive apremilast 20 mg twice daily (b.i.d.), apremilast 30 mg b.i.d. or placebo for 16 weeks. Patients on placebo entering early scape at week 16 were re-randomized to one of the active treatments. PALACE 1 (504 patients), PALACE 2 (484 patients) and PALACE 3 (505 patients) compared the efficacy and safety of apremilast with placebo in PsA patients previously treated with DMARDs and/or biologic therapy; PALACE 4 (527 patients) evaluated apremilast in DMARDs-naive PsA patients. Patients in the PALACE 1, 2 and 3 trials were stratified by prior DMARD use and were allowed to continue receiving stable DMARD therapy in addition to study medication [**29**]. The primary endpoint of the PALACE studies was the proportion of patients achieving ACR20 response at week 16. In the PALACE 1, 2 and 3 trials, apremilast was associated with significantly higher ACR20 response rates than placebo at week 16. In all three studies, ACR20 responses were maintained through week 52 for patients who had been treated with apremilast from the beginning of the study. Patients who had been switched to apremilast from placebo at week 16 or week 24 had response rates similar to patients who had been treated with apremilast throughout the study in all three trials. Secondary end-points including swollen and tender joint counts, Maastricht Ankylosing Spondylitis Enthesitis Score (MASES),

dactylitis count, Short Form-36 (SF-36) physical function and Physical Component Summary scores, Health assessment Questionnaire Disability Index (HAQ-DI), Disease Activity Score (DAS28) and PASI scores were also reached in PALACE 1, 2 and 3 trials. In the PALACE 1 study [**30**] in patients with baseline psoriasis affecting at least 3% of the body surface area, significantly greater proportions of patients receiving either dose of apremilast achieved PASI-75 response (apremilast 20 mg (b.i.d.): 18%; apremilast 30 mg b.i.d.: 21 vs. placebo: 5%), although the results were not very impressive. In the PALACE 1 study [**30**], 119 (23.6%) had prior biologic exposure, and 47 (9.3%) were considered biologic therapeutic failures. Significantly, more patients receiving apremilast 20 mg b.i.d. (31%) and 30 mg b.i.d. (28%) achieved an ACR-20 response vs. placebo (5%) in the group of patients with prior biologic exposure. Differences were numerically better, but not statistically significant among the small number of patients classified as biologic therapeutic failures [**30**]. Apremilast was effective in DMARD-naive patients in the PALACE 4 study. ACR20 response rates at week 16 were 29.2, 32.3 and 16.9% for apremilast 20, apremilast 30 mg b.i.d. and placebo, respectively. FDA approved apremilast for the treatment of adults with active PsA in March 2014 [**29**]. Recently, *Kavanaugh* et al observed that continuous apremilast treatment resulted in sustained improvements in PsA for up to 52 weeks [**9**].

3-Atopic Dermatitis:

Atopic dermatitis is a chronic inflammatory skin disorder usually presenting with severe pruritus and flaring eczematous lesions in varying localizations depending on the age of the patient. The disease is based on both, a disturbance of the epidermal barrier and increased tendency to IgE production, partly on a genetic disposition, and can be triggered by several environmental factors including commonly encountered allergens, accounting for its high association with elevated serum IgE levels. Continued discoveries in the immunopathogenesis of AD provide optimism for the development of efficacious therapeutic agents. Apart from topical treatment with emollients, topical glucocorticosteroids and calcineurin inhibitors, promising effects of topical treatment with novel aliamides and ceramides, have been described. Nevertheless, patients with severe atopic eczema often remain refractory to purely topical treatment. It is for these patients, that researchers strive to develop new promising systemic treatment options apart from systemic glucocorticosteroids, cyclosporine A, azathioprine, and mycophenolate mofetil with their well known limitations and side effects. Novel immunomodulatory therapies include apremilast. Two clinical studies on AD have recently been published. *Samrao* et al. used apremilast at 2 doses (20 and 30 mg bd, for 3 months, 6 months) in an open-label study with 16 adult AD patients. They found a reduced Eczema Area and Severity Index (EASI) and Dermatology Life Quality Index (DLQI) for the 30 mg group at 3 months and a reduction in baseline pruritus and DLQI in the 20 mg group after 3 and 6 months time. They concluded that larger studies were needed to adequately evaluate both safety and efficacy. In this open-label prospective trial of apremilast in 16 patients with moderate to severe AD was conducted to assess the safety, efficacy, and possible mechanism of action of apremilast in AD [**16**].

One cohort consisted of six subjects treated with apremilast 20 mg twice daily for 3 months, while the second cohort consisted of ten subjects treated with apremilast 30 mg twice daily for 6 months. Participants in the study were required to remain on triamcinolone acetonide 0.1% for 2 weeks prior to the start of the study as well as throughout the trial. Nausea, the most common adverse event, was rated as mild and improved over the course of the study in all patients. After 3 months of treatment, a significant reduction of itch from baseline (VAS) and improvement in quality of life was seen in cohort 1, while EASI and DLQI scores improved in cohort 2. At 6 months, statistically significant improvement was seen in all outcomes in cohort 2, including VAS, DLQI, and EASI. In this study, *Volf* et al. performed a phase 2, open-label study with apremilast in patients suffering from severe ACD or AD. A dose of 20 mg bd was given for 3 months in 10 patients with AD and/or ACD. Apremilast was well tolerated but was only 6 minimally effective in this small study with a heterogeneous study po-

pulation. From what is known on PDE4 action on lymphocytes, macrophages/dendritic cells subtypes, eosinophils and mast cells the overall net effect of PDE4 inhibitors seems more prominent for IFNγ or IL-17 dominated immune responses than IL-4/ 5 /13 one. Interestingly, a better effect on IFNγ dominated inflammation has been described for Treg in vivo studies. Indeed, the effect of IL-4 on B cell function can even be accentuated. This leads to the notion that PDE4 inhibitors may be more potent in the treatment of IL-12/IL-23, thus IFNγ/IL-17 dominated responses than Th2 ones. Based on this consideration, apremilast may be effective in the effector phase of AD inwhich the initial Th2 pattern has switched to a more Th1 dominated phenotype in the skin compartment. In chronic AD the topical applicationmay be the desirable way of application as the Th2 dominated response pattern in the blood of atopic individuals remains unaltere. The mechanism by which apremilast may work in AD is not known, although it has many antiinflammatory effects. By blocking PDE4 activity, apremilast affects several cell types in the immune system including monocytes, dendritic cells, neutrophils, T cells, natural killer cells, and macrophages. Because immune cells in AD are known to have elevated phosphodiesterase activity, it was hypothesized apremilast would reverse this abnormality unique to AD and return immune cells to a less active state. Specifically, apremilast may improve AD by way of inhibiting the expression of T cell cytokines previously reported to be increased in AD such as IFN-γ, TNF-α, Il-5, IL-13, and IL-17. Based on the limited data available, the role for apremilast in the treatment of atopic dermatitis requires further investigation but shows promise in those patients with atopic dermatitis [**21**].

4-Systemic Lupus Erythematosus and Discoid Lupus Erythematosus:

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that can affect a variety of organs and is predominantly seen in women. Treatment is focused on controlling symptoms and often involves the use of corticosteroids and other systemic immunosuppressant therapies. PDE4 inhibitors may be of benefit in lupus erythematosus (LE). For example, a recently published open-label, single arm pilot study with apremilast showed favourable results of a 20 mg twice daily (bd) dose regime in cutaneous discoid lupus erythematosus. Apremilast was well tolerated in these patients [**20**]. A recent study targeted increased PDE4 activity in lupus conditions using MRL/lpr mice (a mouse model developing severe lupus disease). Four groups of female MRL/lpr mice were injected at 5, 7, 9 and 13 weeks with one of ethanol, pentoxifylline, denbufylline, or NCS 613 (a novel PDE4 inhibitor). Results showed that both the survival time and the appearance of proteinuria of NCS 613-treated mice are significantly delayed, both with P values of 0.005. While study size was limited, the results demonstrate potential for the use of PDE4 inhibitors in patients with SLE [**31**]. Discoid lupus erythematosus (DLE) is a chronic inflammatory disorder mediated by Th1 cells. Apremilast is a novel oral PDE4 enzyme inhibitor capable of blocking leukocyte production of IL-12, IL-23, TNF-α, INF with subsequent suppression of Th1 and Th17-mediated immune responses, *De souza* et al observed that cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) showed a significant ($P<0.05$) decrease after 85 days of treatment with apremilast 20 mg twice daily in 8 patients with active discoid lupus. The adverse events related to the drug were mild and transient. They concluded that apremilast may constitute a safe and effective therapeutic option for DLE [**11,20**].

5-Lichen Planus:

Lichen planus (LP) is a chronic inflammatory disease that typically affects the skin, mucous membranes, and nails [**1,2,3,4**]. It frequently causes significant morbidity, including severe pruritus and pain. LP lesions can resolve spontaneously within a year; however, 15% to 20% of cases have a relapsing and remitting clinical course that is very difficult to treat [**5**]. Patients in the latter category have very few efficacious therapeutic options available to them, such as topical and oral corticosteroids, retinoids, cyclosporine, griseofulvin, dapsone, and phototherapy, and often with less than optimal results and significant adverse side effects. Considering the paucity of available efficacious agents and the severity of cli-

nical symptoms, the investigation of other medications in the treatment of LP is well merited. The cause of LP is multifactorial, but predominantly involves skin and mucosal damage by T-cellmediated inflammatory agents, such as tumor necrosis factor-a and interferon-γ. Apremilast is a novel phosphodiesterase type IV inhibitor, which promotes the accumulation of intracellular cyclic adenosine monophosphate. Increased levels of cyclic adenosine monophosphate activate protein kinase A and effectively inhibit proinflammatory cytokine transcription and neutrophil degranulation, chemotaxis, and adhesion to endothelial cells. Ultimately, apremilast inhibits the production of various inflammatory mediators, such as TNF-α, IFN-γ, LT-B4, and IL-2, IL-5, IL-8, and IL-12. Thus, it is plausible that apremilast may be aneffective treatment for LP. *Paul* et al evaluated the overall efficacy of oral apremilast in patients with moderate to severe LP after 12 weeks of treatment. Ten study patients were treated with 20 mg of apremilast orally twice a day for 12 weeks. In addition, the number of LP lesions within the target area progressively decreased throughout the 12-week treatment period. After the discontinuation of study drug, many patients continued to improve or their LP lesion count stabilized; however, a number of study patients had a subsequent increase in their lesion counts. Two study patients achieved significant clearance of their feet and hands at the end of treatment. Two patients achieved complete clearance at the end of treatment and had histopathologic evidence of postinflammatory pigment changes or resolving lichenoid dermatitis. Only patient had mucosal involvement, and after treatment initiation, her oral lesions improved from 40% involvement of her bilateral buccal mucosa at baseline to 12% involvement at the end of the study. In patients exposed to apremilast (20 mg twice a day), headache and nausea were the most commonly reported. The authors concluded that apremilast could be efficacious in the treatment of LP. It was well tolerated, and patients who experienced adverse side effects, namely nausea and headache, did not require treatment discontinuation or alteration. They thought that apremilast could be a safe and effective alternative to current treatment modalities for LP; however, double-blinded, randomized, controlled trials are necessary to thoroughly evaluate the safety and efficacy of apremilast [**15**].

6-Alopecia Areata:

Recently *Keren* et al developed a new model for alopecia areata (AA), which employs normal human scalp skin from healthy donors that are transplanted onto SCID/Beige mice. The grafted mice are injected intracutaneously with a large number of either autologous or allogeneic human PBMC's from healthy donors that are enriched for NKG2D+ and CD56+ cells and stimulated with IL-2. This predictably induces hair loss lesions in the transplanted, previously healthy human skin which shows all the clinical and histological characteristics of AA. Importantly, there is no evidence for graft-versus-host disease-related inflammatory or hair loss events in this model, in which AA lesions can also be induced by autologous PBMC's from healthy human donors. Namely, IFN-γ+ cells and CD8+/NKG2D+ are observed primarily around and within the damaged hair bulbs of human anagen hair follicles, along with a high level of expression of NKG2D receptors by inflammatory infiltrate lymphocytes and a striking induction of the NKG2D ligand, MICA, by the damaged follicular epithelium. MICA expression by the follicular epithelium likely enables NKG2D/MICA interaction, thereby promoting hair follicle immune privilege collapse and hair follicle damage. IFN-γ secretion by the inflammatory infiltrate lymphocytes likely plays a key role, leading to ectopic expression and upregulation of HLA-DR, ICAM-1 and HLA-A, B, C, by the follicular epithelium. Recently, *Keren* et al studied the efficacy of candidate anti-AA agent in the humanized mouse model of AA, the apremilast. Apremilast is a novel, orally administered small molecule that specifically targets PDE4 and and reduced production of many pro-inflammatory mediators. The ability of PDE4 inhibitors to prevent IFN-γ production, combined with the recognized down-regulation of target organ MHC class II expression by apremilast, encouraged them to hypothesize that apremilast could have beneficial effects in AA. They showed that apremilast was the novel candidate anti-AA agent identified with the help of this humanized AA mouse model [**18**].

7- Rosacea:

Rosacea is a chronic skin disease characterised by facial flushing, persistent erythema, telangiectasias and inflammatory papulupustular lesions. Some patients dont respond to conventional treatments. *Thompson* et al investigated the eficacy and safety of apremilast fort he treatment of moderate to severe inflamamtory rosacea. Apremilast modulates multiple proinflammatory and anti-inflammatory pathways, including augmentating IL-10 production, which in turn suppresses proinflammatory cytokines. In this open-label study, 10 patients with inflammatory rosacea were administered apremilast, 20 mg orally twice daily, for 12 weeks. The primary end point was the total number of papulopustular lesions at baseline compared with the end of treatment and with follow up 1 month after treatment. When baseline scores were compared with those at the end of treatment, there was a statistically improvement in ratings on the lesions assessment. The authors concluded tha apremilast was well tolerated treatment agent for rosacea [**19**].

8- Sarcoidosis:

One study points to a potentially beneficial effect of apremilast in cutaneous sarcoidosis and it will be interesting to further explore the activity of PDE4 inhibitors in granulomatous skin diseases including Melkerson Rosenthal syndrome for which the therapeutic options are limited at present. Although PDE4 selective inhibitors inhibit IL- 12 and TNFα mixed PDE4/3/7 preparation may have improved activity on macrophages which are key cells in granulomatous diseases. Apremilast is a newphosphodiesterase type4inhibitor that blocks the synthesis of proinflammatory cytokinesandchemokines, such as tumor necrosis factor, interferon-γ, and the IL-2, IL-12, and IL-23. These cytokines are important in the initiation and perpetuation of sarcoidosis. In this study, all 15 patients wtih sarcoidosis received oral apremilast, 20 mg, twice a day. If adverse events were reported, the dosage was reduced to 20 mg orally once a day. Patients received 12 weeks of treatment and were seen 1 month later. Skin lesions were assessed in 2 ways: (1) by using the previously described Sarcoidosis Activity and Severity Index (SASI)3 and (2) by comparing photographs of the index lesion initially and at week 12, with the photographs presented in random order. The SASI induration score3 decreased significantly with apremilast therapy the authors found apremilast effective for some patients with sarcoidosis who had persistent lesions despite multiple systemic treatments [**17**].

9-Contact Dermatitis:

A study by *Volf* et al assessing the efficacy of apremilast in treating recalcitrant allergic contact dermatitis (ACD). 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 [**21**].

Summary:

PDE4 inhibitors are a class of drugs which act intracellularly to down regulate inflammatory pathways and to promote innate antiinflammatory pathways. They have a potentially wide range of therapeutic uses in chronic inflammatory diseases. In particular, apremilast has already proven effective in psoriasis and the peripheral arthritis of psoriatic arthritis. Efficacy in psoriasis is probably equivalent to methotrexate but less than TNFα. In psoriatic arthritis efficacy is probably similar to methotrexate but less than TNFα. Apremilast appears to have a good safety profile and this, together with the oral dosing are likely to be major factors in the decision to use the drug. However, much will depend on the cost and long-term tolerability and safety [**30**].

References

1. Schafer PH, Day RM. Novel systemic drugs for psoriasis: Mechanism of action for apremilast, a specific inhibitor of PDE4. J Am Acad Dermatol 2013; 68: 1041-1043. PMID: 23680197
2. Wittmann M, Helliwell PS. Phosphodiesterase 4 Inhibition in the Treatment of Psoriasis, Psoriatic Arthritis and Other Chronic Inflammatory Diseases. Dermatol Ther 2013; 3: 1–15. PMID: 23888251
3. Schett G, Sloan VS, Stevens RM, Schafer P.Apremilast: a novel PDE4 inhibitor in the treatment of auto-

immune and inflammatory diseases. Ther Adv Musculoskel Dis 2010; 2: 271-278. PMID: 22870453

4. Schafer PH, Parton A, Capone L, Cedzik D, Brady H, Evans JF, Man HW, Muller GW, Stirling DI, Chopra R. Apremilast is a selective PDE4 inhibitor with regulatory effects on innate immunity. Cell Signal 2014; 26: 2016-2029. PMID: 24882690
5. Moustafa F, Feldman SR. A review of phosphodiesterase-inhibition and the potential role for phosphodiesterase 4-inhibitors in clinical dermatology. Dermatol Online J 2014 16; 20: 22608. PMID: 24852768
6. Crilly A, Robertson SE, Reilly JH, Gracie JA, Lai WQ, Leung BP, Life PF, McInnes IB. Phosphodiesterase 4 (PDE4) regulation of proinflammatory cytokine and chemokine release from rheumatoid synovial membrane. Ann Rheum Dis 2011; 70: 1130-1137. PMID: 21342916
7. McCann FE, Palfreeman AC, Andrews M, Perocheau DP, Inglis JJ, Schafer P, Feldmann M, Williams RO, Brennan FM. Apremilast, a novel PDE4 inhibitor, inhibits spontaneous production of tumour necrosis factor-alpha from human rheumatoid synovial cells and ameliorates experimental arthritis.Arthritis Res Ther 2010; 12: R107. PMID: 20525198
8. Schett G, Wollenhaupt J, Papp K, Joos R, Rodrigues JF, Vessey AR, Hu C, Stevens R, de Vlam KL. Oral apremilast in the treatment of active psoriatic arthritis: results of a multicenter, randomized, double-blind, placebo-controlled study. Arthritis Rheum 2012; 64: 3156-3167. PMID: 22806399
9. Kavanaugh A, Mease PJ, Gomez-Reino JJ, Adebajo AO, Wollenhaupt J, Gladman DD, Hochfeld M, Teng LL, Schett G,Lespessailles E, Hall S.Longterm (52-week) Results of a Phase III Randomized, Controlled Trial of Apremilast in Patients with Psoriatic Arthritis. J Rheumatol 2015; 42: 479-488. PMID: 25593233
10. Felquer ML, Soriano ER. New treatment paradigms in psoriatic arthritis: an update on new therapeutics approved by the U.S. Food and Drug Administration. Curr Opin Rheumatol 2015; 27: 99-106. PMID: 25633241
11. Kumar N, Goldminz AM, Kim N, Gottlieb AB. Phosphodiesterase 4-targeted treatments for autoimmune diseases. BMC Med 2013; 11: 96. PMID: 23557064
12. Gottlieb AB, Strober B, Krueger JG, Rohane P, Zeldis JB, Hu CC, Kipnis C.An open-label, single-arm pilot study in patients with severe plaque-type psoriasis treated with an oral anti-inflammatory agent, apremilast.Curr Med Res Opin 2008; 24: 1529-1538. PMID: 18419879
13. Hoffmann M, Kumar G, Schafer P, Cedzik D, Capone L, Fong KL, Gu Z, Heller D, Feng H, Surapaneni S, Laskin O, Wu A. Disposition, metabolism and mass balance of [(14)C]apremilast following oral administration. Xenobiotica 2011; 41: 1063-1075. PMID: 21859393
14. Man HW, Schafer P, Wong LM, Patterson RT, Corral LG, Raymon H, Blease K, Leisten J, Shirley MA, Tang Y, Babusis DM, Chen R, Stirling D, Muller GW.Discovery of (S)-N-[2-[1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl] acetamide (apremilast), a potent and orally active phosphodiesterase 4 and tumor necrosis factor-alpha inhibitor.J Med Chem 2009; 52: 1522-1524. PMID: 19256507
15. Paul J, Foss CE, Hirano SA, Cunningham TD, Pariser DM. An open-label pilot study of apremilast for the treatment of moderate to severe lichen planus: A case series. J Am Acad Dermatol 2013; 68: 255-261. PMID: 22910104
16. Samrao A, Berry TM, Goreshi R, Simpson EL. A pilot study of an oral phosphodiesterase inhibitor (apremilast) for atopic dermatitis in adults. Arch Dermatol 2012; 148: 890–897. PMID: 22508772
17. Baughman RP, Judson MA, Ingledue R,Craft NL, Lower EE. Efficacy and Safety of Apremilast in Chronic Cutaneous Sarcoidosis. Arch Dermatol 2012; 148: 262-264. PMID: 22004880
18. Keren A, Shemer A, Ullmann Y, Paus R, Gilhar A. The PDE4 inhibitor, apremilast, suppresses experimentally induced alopecia areata in human skin in vivo. J Dermatol Sci 2015; 77: 74-76. PMID: 25530115
19. Thompson BJ, Furniss M, Zhao W, Chakraborty B, Mackay-Wiggan J. An oral phosphodiesterase inhibitor (apremilast) for inflammatory rosacea in adults: a pilot study. JAMA Dermatol 2014; 150: 1013-1014. PMID: 25054629
20. De Souza A, Strober BE, Merola JF, Oliver S, Franks AG Jr. Apremilast for discoid lupus erythematosus: results of a phase 2, open-label, single-arm, pilot study. J Drugs Dermatol 2012; 11: 1224-1226. PMID: 23134988
21. Volf EM, Au SC, Dumont N, Scheinman P, Gottlieb AB. A phase 2, open-label, investigator-initiated study to evaluate the safety and efficacy ofapremilast in subjects with recalcitrant allergic contact or atopic dermatitis. J Drugs Dermatol 2012; 11: 341-346. PMID: 22395585
22. Schafer PH, Parton A, Gandhi AK, Capone L, Adams M, Wu L, Bartlett JB, Loveland MA, Gilhar A, Cheung YF, Baillie GS, Houslay MD,Man HW, Muller GW, Stirling DI. Apremilast, a cAMP phosphodiesterase-4 inhibitor, demonstrates anti-inflammatory activity in vitro and in a model of psoriasis. Br J Pharmacol 2010; 159: 842-855. PMID: 20050849
23. Papp K, Cather JC, Rosoph L, Sofen H, Langley RG, Matheson RT, Hu C, Day RM. Efficacy of apremilast in the treatment of moderate to severe psoriasis: a randomised controlled trial. Lancet 2012; 380: 738-746. PMID: 22748702
24. Gottlieb AB, Matheson RT, Menter A, Leonardi CL, Day RM, Hu C, Schafer PH, Krueger JG. Efficacy, tolerability, and pharmacodynamics of apremilast in recalcitrant plaque psoriasis: a phase II open-label study. J Drugs Dermatol 2013; 12: 888-897. PMID: 23986162
25. Strand V, Fiorentino D, Hu C, Day RM, Stevens RM, Papp KA. 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. Health Qual Life Outcomes 2013; 11: 82. PMID: 23663752

26. Ratner M. First PDE4 inhibitor for psoriasis hits the market but impact is uncertain. Nat Biotechnol 2014; 32: 505-507. PMID: 24911477

27. Strand V, Schett G, Hu C, Stevens RM. Patient-reported Health-related Quality of Life with apremilast for psoriatic arthritis: a phase II, randomized, controlled study. J Rheumatol 2013; 40: 1158-1165. PMID: 23588944

28. Papp KA, Kaufmann R, Thaçi D, Hu C, Sutherland D, Rohane 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. J Eur Acad Dermatol Venereol 2013; 27: e376-383. PMID: 23030767

29. Shutty B, West C, Pellerin M, Feldman S. Apremilast as a treatment for psoriasis. Expert Opin Pharmacother 2012; 13: 1761-1770. PMID: 22712800

30. Liu Y, Zhou S, Wan Y, Wu A, Palmisano M. The impact of co-administration of ketoconazole and rifampicin on the pharmacokinetics of apremilast in healthy volunteers. Br J Clin Pharmacol 2014; 78: 1050-1057. PMID: 24962564

31. Keravis T, Monneaux F, Yougbaré I, Gazi L, Bourguignon JJ, Muller S, Lugnier C. Disease progression in MRL/lpr lupus-prone mice is reduced by NCS 613, a specific cyclic nucleotide phosphodiesterase type 4 (PDE4) inhibitor. PLoS One 2012; 7: e28899. PMID: 22247763