INTRODUCTION

The pioneering work in understanding phosphodiesterase (PDE) inhibitors began in the 1950s by Sutherland and Rall.\(^1,\)\(^2\) However, it was only in the 1970s that the anti-inflammatory properties of PDE inhibitors were demonstrated.\(^3\) Since then, this class of drugs have been utilized in a number of diseases in medicine such as airway hyperactivity, erectile dysfunction, rheumatoid arthritis, ankylosing spondylitis, Alzheimer’s disease, and multiple sclerosis.\(^4\) Till date, 11 families of the PDE enzyme have been identified, based on specific sequencing and biochemical properties.\(^5\) Out of these enzymes, the PDE-4 enzyme has been found to play a role in the mechanics of a number of inflammatory diseases, because of its liberal expression in the vascular endothelium, smooth muscles, immunologic cells, and keratinocytes. Drugs targeting this enzyme have shown immense promise in reducing the inflammation produced following activity of this enzyme. Some of the drugs belonging to this category include rolipram, roflumilast, apremilast, and AN-2728. Out of these, apremilast and AN-2728 have found to have applications in dermatology. AN-2728 is a boron containing topical compound that has been developed in the treatment of psoriasis.\(^6\) Apremilast is a systemically administered PDE-4 antagonist, an orally administered small molecule, which has shown great promise in treating patients with psoriasis and a few other dermatologic disorders. This article will focus on the pharmacology of apremilast.

MECHANISM OF ACTION

In the human body, normal homeostasis is maintained by the immune system which turns off immune responses when not desired. One of the important modulators in this process is cAMP, the levels of which in turn are determined by the enzyme PDE. Out of the 11 types of PDE in the human body, Type 4 is specific to cAMP and therefore drugs interacting with this enzyme play an important role in alleviating symptoms associated with chronic inflammatory disorders.\(^7\) PDE-4 levels are predominantly concentrated within inflammatory cells, natural killer cells, and keratinocytes.\(^8-10\) Apremilast, a specific PDE-4 antagonist, acts by specifically targeting a central pathogenic mechanism, binding directly to the PDE-4 enzyme and bypassing complex antigen-receptor interactive immunoregulatory mechanisms. Once drug–enzyme binding occurs, a series of events follow, the foremost being increased levels of cAMP, which in turn plummets the levels of pro-inflammatory cytokines such as tumor necrosis factor (TNF)-\(\alpha\), interleukin (IL)-23, IL-12,\(^11\) and leukotriene B4, and also increases the levels of anti-inflammatory cytokines such as IL-10.\(^12\) In addition, apremilast also binds to toll-like receptor 4 in peripheral
blood mononuclear cells, further reducing the production of pro-inflammatory cytokines.\textsuperscript{[13]} Apremilast also reduces the activity of nitric oxide synthase,\textsuperscript{[14,15]} an enzyme responsible for the synthesis of nitric oxide which is an important pro-inflammatory mediator, thereby preventing trafficking of macrophages and myeloid dendritic cells to the dermis and epidermis in psoriatic skins. In this way, apremilast plays a noteworthy anti-inflammatory role. A gist regarding the anti-inflammatory role of apremilast has been represented in Figure 1.

**PHARMACOKINETICS**

Apremilast is an orally administered drug. Postintake, it is rapidly absorbed by the body reaching its peak plasma concentration after 2–3 h. The bioavailability of apremilast is around 73\% and its mean apparent volume of distribution is 87 L. Apremilast has a $t_{1/2}$ of 6–9 h.\textsuperscript{[16]} Metabolism of apremilast occurs through a cytochrome (CYP) 3A4-mediated oxidative metabolism, followed by glucuronidation, nonenzymatic hydrolysis, and a non-CYP 3A4-mediated metabolism.\textsuperscript{[17]} Apremilast is eliminated mainly by the renal route, though some of the drug is also excreted through the feces.\textsuperscript{[18]}

**INDICATIONS**

Although originally a drug marketed for psoriasis, there are a number of other dermatologic indications for which apremilast has been utilized and has been summarized in Table 1.

**Psoriasis**

Psoriasis is a chronic inflammatory cutaneous disorder, affecting up to 2\%–5\% of the world population. Owing to the chronic course displayed in this condition, long-term treatment is necessitated. Traditionally, drugs employed in this setting, such as methotrexate (Mtx), cyclosporine A (CsA), and azathioprine (Azt), are associated with serious adverse effects and warrant proper monitoring throughout treatment.\textsuperscript{[19]} Biologic therapies, on the other hand, though effective have their own disadvantages related to treatment resistance, hospital admission, parenteral administration, adverse effect profile, expenses and management requiring a specialist setting.\textsuperscript{[19]}

Therefore, there is an ongoing research for the discovery of an ideal drug for managing psoriasis. Apremilast is a small orally available molecule that has demonstrated its worth for the same. Apremilast directly targets the central initiator mechanism in the pathogenesis of psoriasis, and in this way modulates the expression of various inflammatory mediators involved in this process. An open-label, single-arm, pilot study done by Gottlieb \textit{et al.}\textsuperscript{[15]} demonstrated the clinical efficacy of apremilast in managing patients with severe plaque-type psoriasis. The 19 patients who were enrolled in this study were treated with 20 mg of apremilast once daily for 29 days. Out of the 19 patients, 17 completed the entire study. Only those patients were included in the study who had severe plaque type of psoriasis for at least 6 months, which involved at least 15\% of the total body surface area, and who were candidates eligible for systemic therapy or phototherapy and had not received any systemic treatment since the past six months. The end result of the study clearly indicated the therapeutic justification for the use of apremilast in plaque-type psoriasis. After 29 days of treatment with apremilast, it was noted that T-cells and CD11c cells were reduced from the dermis and epidermis by 28.8\% and 42.6\%, respectively, for T-cells and 18.5\% and 40.2\%, respectively, for CD11a cells. In addition, the mRNA expression of nitric oxide synthase was reduced by 66.5\% from baseline in responders, which was again statistically significant ($P < 0.0001$). Along with this, apremilast showed reduction in the epidermal thickness by a mean of 20.5\% from the baseline on day 29. Apart from these parameters, the clinical parameters also substantiated the beneficial role of apremilast. In 73.7\% of the patients in this study, an improvement in psoriasis was witnessed as per the Psoriasis Area Severity Index (PASI) score, with 17.6\% of the patients having a

![Figure 1: Brief account of the mechanism of action of apremilast.](image)

| Table 1: Indications of apremilast in dermatology |
|----------------------------------|
| Chronic plaque-type psoriasis   |
| Psoriatic arthropathy           |
| Lichen planus                   |
| Atopic dermatitis               |
| Sarcoidosis                     |
| Discoid lupus erythematosus     |
| Behcet’s disease                |
Psoriatic arthropathy

Psoriatic arthropathy (PsA) is a chronic inflammatory disorder, encountered in 30% of psoriatic patients and around 1% of the general population. Owing to the risk of irreversible joint damage which begins very early in the course of the disease, it is essential to intervene early enough to avert these changes and obtain a better life quality in these patients. Approved treatments for PsA include both biologic and non-biologic therapies. Biologic therapies include etanercept, adalimumab, golimumab, and infliximab. However, owing to the high costs involved with these drugs, nonbiologic treatments such as Mtx, sulfasalazine, lefunomide, and CsA are used as first-line treatment modalities here. However, the drawback with these drugs is that the efficacy of these disease-modifying anti-rheumatic drugs has not been well established as per clinical studies. Therefore, a drug which is therapeutically effective and also affordable to patients becomes a necessity in this scenario. Apremilast has shown to fulfill these requirements. In the three programs conducted under the title of Psoriatic Arthritis Long-term Assessment of Clinical Efficacy (PALACE), for 52 weeks, apremilast did show promise in managing these patients. The primary end point was assessed at 16 weeks following treatment with apremilast, with two dosing protocols and comparing it with a placebo group, with an improvement of >20 in the American College of Rheumatology score (ACR20). In the PALACE 1 study, the ACR20 response rates were 31.3% (P = 0.0140) and 39.8% (P = 0.0001) for the groups receiving apremilast 20 mg twice daily and 30 mg twice daily, respectively, compared to only 19.4% for the placebo group. In the PALACE 2 study, the group receiving 20 mg of apremilast twice daily demonstrated an ACR20 response rate of 38.4% (P = 0.0002) and the group getting apremilast 30 mg twice daily showed an ACR20 response rate of 34.4% (P = 0.0024), compared to only 19.5% for the placebo group. In the PALACE 3 study, the ACR20 response rates were 29.4% (P = 0.02) for the apremilast 20 mg twice daily group and 42.8% (P < 0.0001) for the group receiving 30 mg of apremilast twice daily versus 18.9% for the placebo group. In all the three studies, ACR20 responses were maintained in patients who had taken apremilast in the two dosing schedules as highlighted till week 52. Other parameters assessed similarly were reductions in the swollen joint counts and tender joint counts which showed pertinent levels of reduction post apremilast intake and have been summarized in Table 3.

Also in the above-mentioned studies, the drug was very well tolerated by patients with only mild-to-moderate levels of side effects. Thus, we can clearly see the beneficial contribution made by this new drug in the management for PsA, and therefore it has been approved by the Food and Drug Administration in the management of this spectrum of psoriasis.

Lichen planus

Lichen planus (LP) is a chronic inflammatory disease, primarily affecting the skin, mucous membranes, and nails. It has been seen that 15%–20% of patients with LP demonstrate a relapsing and remitting course, often resistant to most conventional modalities of treatment. In such cases, there would always be the need of newer and better alternatives for therapy. It is plausible that apremilast with its anti-inflammatory properties could help regression of skin lesions in LP. An open-label pilot study done by Paul et al. in ten biopsy-proven patients with LP demonstrated the beneficial effects of apremilast for the same. Apremilast was administered to these patients at a dose of 20 mg twice daily for 12 weeks. At the end of 12 weeks, three of the patients showed complete clearance of lesions. In the remaining seven patients though good clinical improvement was noticeable, complete clearance was not seen. Therefore, it was concluded that apremilast could be considered a safe and effective alternative to the current treatment options in the armamentarium of LP. However, more double-blind randomized controlled trials would be mandatory to evaluate the effectiveness and safety of apremilast for this indication.

Atopic dermatitis

Atopic dermatitis (AD) is a chronic relapsing eczematous disorder which in moderate-to-severe proportions cannot be solely managed by topical agents alone, thus necessitating the usage of systemic immunosuppressive agents, which in turn is associated with unwanted adverse reactions. Increased levels of PDE activity, in patients with AD, have been clearly elucidated. The heightened activity of this enzyme in turn leads to leukocyte hyperactivity and inflammatory changes. Topical cipamfylline cream, a PDE-4 blocker (not commercially available), has demonstrated clinical efficacy in atopic skins. Orally, PDE-4 blockers have been employed in the management of a number of inflammatory diseases. In AD, the beneficial mechanics of apremilast is not fully known. Yet, the following properties of apremilast may help in reducing the inflammation seen in atopic skins:
### Table 2: Some of the studies demonstrating the beneficial role of apremilast in plaque-type psoriasis

| Study                                                                 | Year | Type of study                        | Inclusion criteria                                                                                       | Exclusion criteria                                                                 | Patients in the study | Results                                                                 | Conclusion                                                                                           |
|----------------------------------------------------------------------|------|--------------------------------------|----------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|----------------------|------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|
| Efficacy of apremilast in treating moderate-to-severe psoriasis: A randomized controlled trial[20] | 2012 | Randomized control trial             | Patients >18 years of age with moderate-to-severe psoriasis 6 months or longer and who were ideal candidates for photo or systemic therapy. The patients needed to have a PASI score of >12 and a body surface area of >10 | Pregnant and lactating mothers, patients on any other form of treatment, or patients with any form of active infection | Total patients: 352 Placebo group=88, apremilast 10 mg bid=89, apremilast 20 mg bid=87, apremilast 30 mg bid=88 | End point of PASI-75 at week 16 obtained in 6% of patients in placebo group, 11% in apremilast 10 mg bid group, 29% in apremilast 20 mg bid group, and 41% in apremilast 30 mg bid group. The achievement of therapeutic response in the apremilast 20 mg and 30 mg bid groups when compared to the 10 mg bid and placebo group was significant ($P<0.0001$). | Apremilast given at a dose of 20 mg or 30 mg twice daily is efficacious, safe, and well tolerated in patients having moderate-to-severe psoriasis |
| Efficacy and safety of apremilast in patients with moderate-to-severe plaque-type psoriasis: Results from a Phase II, multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-comparison study[21] | 2013 | Randomized controlled trial          | Same inclusion criteria as the above study                                                               | Same exclusion criteria as the above study                                        | Total patients were 259 randomized in a 1:1:1 ratio of placebo, apremilast 20 mg once daily, and 20 mg twice daily receiving patients | End point of PASI-75 obtained in 10.3% of patients in the placebo group, 10.3% of patients in the apremilast 20 mg once daily group, and 24.4% of patients in the apremilast 20 mg twice daily group ($P=0.024$). The mean percent reduction in the PASI score for the apremilast 20 mg bid group was statistically significant ($P<0.001$). | Apremilast given at 20 mg twice daily for 12 weeks is effective and well tolerated in patients having moderate-to-severe plaque-type psoriasis |

PASI: Psoriasis Area Severity Index
Apremilast may reverse the increased PDE-4 activity of immune cells in AD, reverting the immune cells to a less active state, thus bringing about a considerable decrease in the cytokines released from T-cells.

B. Apremilast’s property of PDE-4 blocking increases the levels of cAMP, bringing about phosphorylation of protein kinase A. This in turn activates cAMP response element binding (CREB), a transcription factor, which may have an anti-inflammatory role in cells of the immune system. However, the entire role of the CREB pathway in AD is not fully known at present, but ongoing research in this regard would help throw more light in this scenario.7

C. BAD, a well-known pro-apoptotic factor, is actively targeted by protein kinase A, which in turn inactivates BAD.32 BAD, if not inactivated, binds to bcl-2, an antiapoptotic factor, and nullifies its effect.33 Skins of AD patients treated with ultraviolet light showed an increased expression of bcl-2, thus concluding that this antiapoptotic factor may be protective in AD.34 Thus, by inactivating BAD, PDE-4 inhibitors may indirectly demonstrate therapeutic activity.

D. IL-12 and CCR3 are two chemokines found elevated in the lesional skin and blood of patients with AD.35-37 Apremilast may modify these immune pathways and thus prove beneficial in AD. However, more detailed analysis of these pathways is warranted for the same.

A pilot study done with apremilast in 16 adult patients with AD by Samrao et al.38 demonstrated the beneficial effects of apremilast in both groups receiving the drug. The group that received 20 mg of apremilast twice daily for 3 months demonstrated a significant decrease in pruritus from the baseline (P = 0.02) and also in the Dermatology Life Quality Index (DLQI) (P = 0.003). The group that received apremilast 30 mg twice daily for 6 months showed a significant reduction of the Eczema Area and Severity Index (EASI) scores and DLQI at 3 months and 6 months and is tabulated in Table 4.

Second, the safety profile of apremilast was much better when compared with other cytotoxic drugs used in AD. The EASI scores obtained in this study after 6 months clearly demonstrated the efficacy of apremilast in AD, at par with other traditional therapeutic agents used in AD, with the advantage of being devoid of end-organ toxicity as seen with drugs such as Mtx, Azt, and CsA. However, more randomized controlled studies would definitely be required to determine more accurate estimates with regard to the efficacy and safety of apremilast in patients with AD.

Sarcoidosis

Sarcoidosis is a chronic granulomatous multisystem disorder. Pro-inflammatory cytokines such as TNF-α, interferon gamma, IL-2, IL-12, and IL-23 play a major role in the pathogenesis of the disease. Pentoxifylline, a PDE-4 antagonist, has shown to produce a good therapeutic outcome in sarcoidosis.39 However, owing to its toxicity profile, its use has been limited. Apremilast is a newer PDE-4 blocker with a better toxicity profile compared to pentoxifylline and therefore may find a role in the management of these patients. A study done by Baughman et al.40 evaluating the efficacy of apremilast in chronic cutaneous sarcoidosis in 15 patients receiving 20 mg of the drug on a twice daily basis for a period of 12 weeks did confirm the beneficial properties of apremilast for the same. At the end of 12 weeks, the Sarcoidosis Activity and Severity Index score decreased significantly with apremilast therapy, and on analysis of paired before and after treatment photographs also significant clinical improvement was demonstrable. Thus, apremilast was found to be effective and safe in treating persistent lesions of sarcoidosis, as highlighted in this.

| Parameters taken | PALACE 1 study (reduction scores) | PALACE 2 study (reduction scores) | PALACE 3 study (reduction scores) |
|------------------|----------------------------------|----------------------------------|----------------------------------|
| SJC              | Apremilast 20 mg twice daily group: 39.3% (P=0.0015) Apremilast 30 mg twice daily group: 50% (P<0.0001) Placebo: 16.7% | Apremilast 20 mg twice daily group: 50% (P=0.0029) Apremilast 30 mg twice daily group: 53.9% (P=0.0009) Placebo: 33.3% | Apremilast 20 mg twice daily group: 36.4% (P=0.0301) Apremilast 30 mg twice daily group: 50% (P=0.0014) Placebo: 20% |
| TJC              | Apremilast 20 mg twice daily group: 23.3% (P=0.0007) Apremilast 30 mg twice daily group: 42.9% (P<0.0001) Placebo: 7% | Apremilast 20 mg twice daily group: 36.2% (P=0.0001) Apremilast 30 mg twice daily group: 33.3% (P=0.0015) Placebo: 8.7% | Apremilast 30 mg twice daily group: 30% (P<0.0001) Apremilast 30 mg twice daily group: 43.7% (P<0.0001) Placebo: 8.6% |

PALACE: Psoriatic Arthritis Long-term Assessment of Clinical Efficacy, SJC: Swollen joint count, TJC: Tender joint count
study. However, further studies are mandated to examine the safety and efficacy of apremilast for sarcoidosis.

**Discoid lupus erythematosus**

Discoid lupus erythematosus (DLE) is a chronic inflammatory disorder characterized by erythematous plaques with adherent scales and mediated by Th (helper)-1 cells. There have been numerous treatment options in the armamentarium for DLE such as antimalarials, systemic glucocorticoids, gold, retinoids, sulfasalazine, CSA, thalidomide, and clofazimine, to name a few. De Souza et al. have demonstrated the favorable response following apremilast intake in DLE patients in a single-arm open-label pilot study. All eight patients in this study were given 20 mg of apremilast twice daily, and after an 85-day period, they were evaluated using the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI). The CLASI showed a significant decrease with P < 0.05 after 85 days of apremilast treatment. However, none of the patients achieved complete clinical clearing of lesions. As far as the toxicity profile was concerned, it was very well tolerated by all patients. Though useful for DLE, more studies are mandated to warrant the usage of apremilast for this dermatosis.

**Behcet’s disease**

Apremilast has demonstrated efficacy in oral and genital aphthae associated with Behcet’s disease (BD), at a dosage of 30 mg twice daily, without major organ involvement. After a 12-week treatment program, there was a complete response of ulcers in 71% of the treated patients compared to only 29% of the patients given placebo with P < 0.0001 which was statistically significant. Along with lesion improvement, there was a considerable reduction in pain associated with the ulcers, following apremilast administration. Other parameters that showed improvement here were quality of life and progression of disease activity. However, when treatment was withdrawn, there was a relapse of both oral and genital aphthae. More studies regarding the usage of apremilast for BD is definitely warranted to qualify for its usefulness in this indication.

**Drug interactions**

Strong CYP450 inducers such as rifampicin, phenobarbitone, carbamazepine, and phenytoin should not be simultaneously administered with apremilast as they could significantly reduce the levels of apremilast in the body. Both Mtx and apremilast can be administered together if desired as both drugs lack pharmacokinetic interactions.

**Contraindications**

Apart from hypersensitivity to the drug, there are no current contraindications for apremilast.

**Adverse effects**

The most common adverse effects encountered with apremilast are diarrhea, nausea, and headache. Other side effects include upper respiratory tract infection, vomiting, nasopharyngitis, upper abdominal pain, hypersensitivity, dyspnea, cough, and skin rash. However, most of these side effects have a mild-to-moderate intensity, with a self-limiting nature. As far as the laboratory parameters are concerned, no significant abnormalities have been encountered. Overall, apremilast is a safe drug with a favorable toxicity profile.

**CONCLUSION**

To conclude, it can be clearly appreciated that apremilast could revolutionize the treatment of many of the chronic inflammatory dermatosis encountered. As it does not interfere with immune suppression, rather by targeting the central inflammatory signaling pathways, it proves to have an added advantage over the conventional drugs used for the above indications. Second, with its better toxicity profile, it has an added advantage over the other drugs because of the long-term treatment regimens employed for most of these disorders.

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**Conflicts of interest**

There are no conflicts of interest.

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