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Apremilast in Psoriasis and Beyond: A Literature Based Review

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ABSTRACT

Apremilast is a medication primarily used for the treatment of certain inflammatory conditions, specifically psoriasis and psoriatic arthritis. It belongs to a class of drugs known as phosphodiesterase-4 (PDE-4) inhibitors. Apremilast works by inhibiting the activity of the PDE4 enzyme, which plays a role in the inflammatory response.PDE-4 is an enzyme that is involved in the breakdown of cyclic adenosine monophosphate (cAMP), a messenger molecule that regulates inflammation. By inhibiting PDE-4, apremilast increases cAMP levels, leading to a reduction in the inflammatory response. apremilast is typically administered orally in tablet form, making it convenient for patients to take at home. Common side effects of apremilast may include diarrhea, nausea, headache, and upper respiratory tract infections. It's important for patients to discuss any concerns or potential side effects with their healthcare provider.Apremilast is a good treatment option for patients who wish to avoid infusions, injections, or disease-modifying anti-rheumatic drugs (DMARDs) such as stelara. Being a relatively new drug in the treatment armamentarium of psoriasis and other inflammatory dermatoses; in this review, we will discuss various practical aspects of prescribing oral apremilast, based on the current and emerging literature.

Key words: Apremilast, psoriasis, phosphodiesterase-4inhibitors,psoriatic arthritis.

I. INTRODUCTION

A persistent, systemic inflammatory illness, psoriasis affects between 1% and 3% of people in the United States. Psoriasis prevalence has been found to vary significantly among regions, which probably reflects the influence of both hereditary and environmental factors on this condition. The primary symptom of psoriasis, although being a multisystem illness, is erythematous, scaly patches or plaques on the skin that are frequently itchy and/or uncomfortable. These are brought on by the hyperproliferation of the epidermal layer as a result of the early maturation of keratinocytes and the penetration of the dermis by T-lymphocytes, dendritic cells, and macrophages. These defamatory skin lesions are frequently linked to a wide range of comorbidities, including psychiatric/psychological illnesses, tumours, autoimmune diseases, and cardiovascular disease.Studies have shown that psoriatic arthritis (PsA), an inflammatory spondyloarthropathy, can develop in as many as 42% of individuals with psoriasis [1].

Psoriasis is an immune-mediated inflammatory disease but its pathogenesis is not fully elucidated. The upregulation of interleukin (IL)-17 promotes the inflammatory response, leading to hyperproliferation of epidermal keratinocytes that is histopathologically characteristic of plaque psoriasis. One such inflammatory pathway involves cyclic adenosine monophosphate (cAMP), an intracellular second messenger protein that plays a key role in modulating inflammatory responses.

For most of these people, the start of joint illness usually happens seven to twelve years after the skin disease first appears.4 Similar to other rheumatic diseases, PsA patients exhibit with pain, stiffness, and swelling in and around the joints. Still, a condition called (insertions of ligaments and tendons in the bone), spondylitis, dactylitis, nail dystrophy, and seronegativity for the rheumatoid factor are traits that set PsA apart [2,3].

Herein, we review the evidence on apremilast and its safety, etiology, profile, MoA, formulation, side effects and toxicity etc.

Etiology

An inflammatory immune-mediated illness, is yet unknown. The inflammatory response is stimulated by the elevation of interleukin (IL)-17, which results in the hyperproliferation of epidermal keratinocytes that is histopathologically typical of plaque psoriasis. Cyclic adenosine monophosphate (cAMP), an intracellular second messenger protein that is essential for controlling

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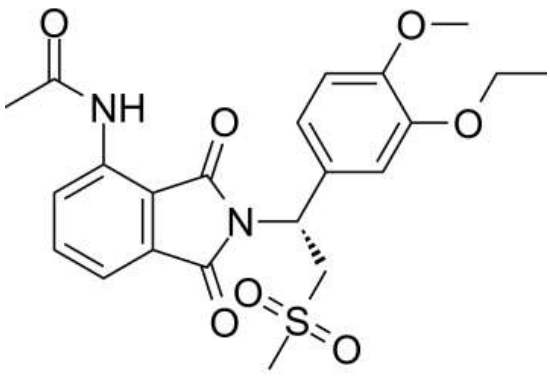
inflammatory responses, is one such inflammatory pathway.

Environmental and genetic factors have a role in the complex genetic illnesses known as psoriasis and related psoriatic arthritis (PsA). Psoriasis patients have a 10-15% chance of developing PsA. This implies that variables that increase the risk of developing psoriasis also increase the risk of developing PsA. Psoriasis sufferers may, however, need other environmental triggers or genetic predispositions that cause joint inflammation in addition to skin inflammation in order for PsA to occur. It's interesting to note that self-reactive T cells in mice with psoriasis, arthritis, and autoimmune arthritis promote the proliferation of synoviocytes rather than their destruction [4,5].

Many in vitro and in vivo human investigations have reported the modulatory effects of apremilast, an oral PDE-4 inhibitor. The T-cell inhibitor PDE-4 reduces the generation of inflammatory cytokines. PDE-4 is also expressed in keratinocytes, a structural cell type that is hyper proliferated and is intimately linked to the histopathology and progression of psoriasis.

The US Food and Drug Administration (September 2014), and the Drug Controller, General of India (October 2017) approved the oral phosphodiesterase-4 inhibitor apremilast for the treatment of moderate to severe psoriasis and psoriatic arthritis. Because of apremilast's immunomodulatory properties, proinflammatory cytokines are partially blocked from being expressed, whereas anti-inflammatory cytokines that are harmful in psoriasis are induced.Apremilast's safety and effectiveness in treating psoriasis and psoriatic arthritis havebeen well-documented in clinical trials and real-world studies. However, little is known about how to use it in practice, including dosage variations, titration procedures, and proper positioning when used as monotherapy or combination therapy. A common trend among dermatologists is the cessation of treatment due to minor adverse events or uncertainty about its use in certain populations. This can be attributed to a lack of sufficient real-world experience from peers regarding the safety and optimization of apremilast [6-9].

Table 1: Drug profile

Drug name	Apremilast
Structure	
Chemical formula	$C_{22}H_{24}N_2O_7S$
IUPAC name	N-[2-[(1S)-1-(3ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-1,3dioxoisoindol-4-yl] acetamide
Molecular mass	460.501 g/mol
Characteristics	White to pale yellow non-hygroscopic powder.
Solubility	Insoluble in water, slightly soluble in ethanol, and soluble in acetone, methanol, acetonitrile.
Melting point	156.1^0C
Category	Inhibitor of phosphodiesterase-4 (PDE4).
Protein binding	68%
Half-life	6-9 h
Brand names	Otezla, Aprezo, Aprenext, Apxenta

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Apremilast, the versatile small molecule

Small molecules are a novel group of agents with a low molecular weight (<1 kD) which act via the modulation of proinflammatory cytokines. They are emerging as therapeutic options in inflammatory dermatosis and other systemic inflammatory conditions owing to their ease of administration through oral or topical route with acceptable efficacy and excellent safety profile. Unlike biologic agents, small molecule drugs are relatively easy to synthesize and less expensive to be produced [10,11].

Mechanism of action (MoA)

Phosphodiesterase (PDE) is a group of enzymes. Till now, eleven different families of PDE enzymes have been identified, PDE-4 enzyme has been found to play important role in inflammatory diseases, because of its liberal expression in the vascular endothelium, smooth muscles, immunologic cells, and keratinocytes. Apremilast is a small molecule, a specific PDE-4 inhibitor, works intracellularly to modulate a network of pro-inflammatory and anti-inflammatory mediators.Acts by directly targeting a central pathogenic mechanism, binds directly to the PDE-4 enzyme and bypassing complex antigenreceptor interactive immunoregulatory mechanisms. Once drug-enzyme binding occurs, a series of events follow, foremost increasing levels of cAMP, which in turn decrease the levels of proinflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-23, IL-12, and leukotriene B4, and also increases the levels of anti-inflammatory cytokines such as IL-10.

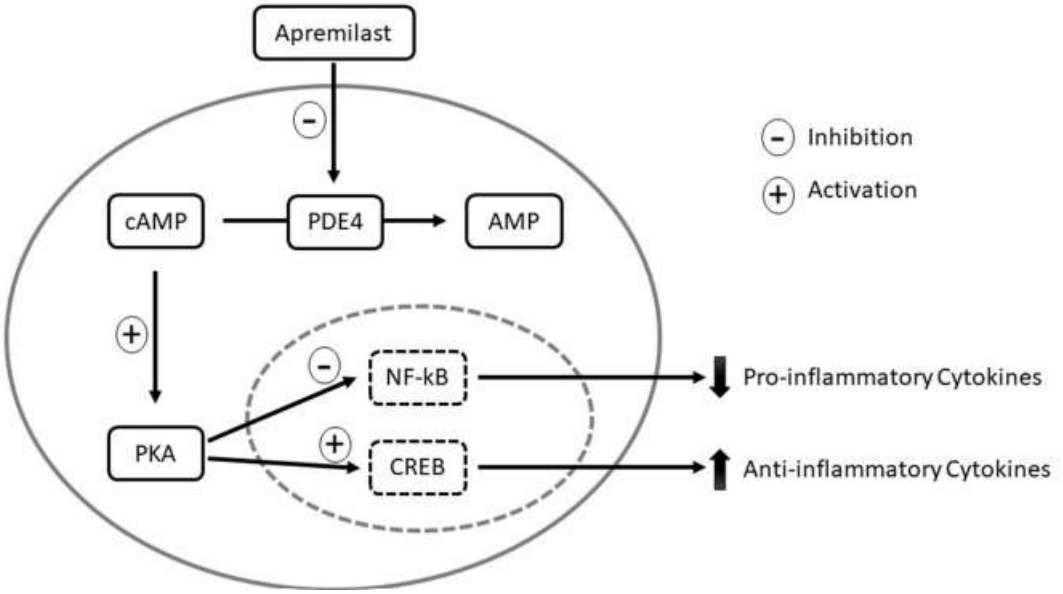

Figure 1: Mechanism of action of apremilast

In addition, apremilast also binds to toll like receptor 4 on peripheral blood mononuclear cells, further reducing the production of proinflammatory cytokines.Apremilast also reduces the activity of nitric oxide synthase, an enzyme responsible for the synthesis of nitric oxide, which is an important pro-inflammatory mediator, thus preventing then transportof macrophages andmyeloid dendritic cells to the dermis and epidermis in psoriasis-skin.In this way, apremilast plays a notable anti-inflammatory role.

PDE-4 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 PDE-4A, PDE-4B, and PDE-4D expression can be detected in inflammatory cells as well as in the structural and adnexal tissues of the skin [12-16].

Apremilast: pharmacodynamics and pharmacokinetics

Apremilast demonstrates linear pharmacokinetics. Drugs with linear pharmacokinetics are characterized by a half-life and clearance rate that are respectively independent of drug concentration and dose and scheduling. Many byproducts of metabolism have been

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identified but do not play a role in apremilast's pharmacological activity. Its elimination half-life is approximately 6-9 h, and average plasma clearance rate is about 10 L/h.

Apremilast undergoes oxidative metabolism by cytochrome P450 enzymes, primarily CYP3A4, CYP1A2, and CYP2A6. Decreased apremilast exposure and subsequent efficacy may occur with CYP450 inducers like phenobarbital, carbamazepine, phenytoin, rifampin, and St. John's wort. However, there are no significant interactions with coadministration of ketoconazole, methotrexate, or oral contraceptive agents.

Dosage reduction is required in patients with creatinine clearance <30 mL/min or an estimated glomerular filtration rate <30. No dosage adjustments are required for female or elderly patients aged 65 years or older, although their exposure may be slightly increased. There was no difference in pharmacokinetics among patients of different racial or ethnic background [16,17].

Dosage formulation

The recommended dose of apremilast in adults for psoriasis and psoriatic arthritis is 30 mg twice daily taken orally. The treatment is started with 10 mg morning dose with a daily increment of 10 mg until day 6 when the recommended dose (30 mg bid) for adults is reached which is continued at the same dose thereafter. Such a dose titration minimizes the gastrointestinal side effects. Tablets of 10 and 20 mg in addition to 30 mg are launched in Indian market in 2018. The tablet should be taken as a whole and not to be crushed or cut. A new nail lacquer formulation for nail psoriasishas also been developed, though not yet available commercially [18,19].

Side effects

The most frequently reported side effects of apremilast are gastrointestinal (diarrhea, nausea), transpiring during the first fourteen days of initiating therapy and typically resolving within twenty-eight days.The onset of depression and suicidal ideations and behaviours were also reported during clinical trials and may occur while on therapy.

- Diarrhea (8% to 41%)
- Nausea (9% to 19%)
- Headache (6% to 14%)
- Upper respiratory tract infection (4% to 12%)
- Vomiting (3% to 9%)
- Nasopharyngitis (3%)
- Upper abdominal pain (2% to 9%)
- Fatigue (3%)
- Dyspepsia (3%)
- Decreased appetite (3%)
- Weight loss (13%)
- Insomnia (2%)
- Back pain (2% - 8%)
- Migraine (2%)
- Frequent bowel movements (2%)
- Mood disorders and suicidal ideation (5%)
- Arthralgia (6%)

Toxicity

Studies on the toxicity of acute and repeated doses were conducted on rats and mice. Toxicology, acute the lowest lethal intravenous (IV) doses in mice were 120 mg/kg for males and > 120 mg/kg for females, while the lowest lethal oral dose was > 2000 mg/kg. The lowest lethal oral dosages for male and female rats were 2000 mg/kg and > 300 mg/kg, respectively, while the lowest lethal IV doses were > 60 mg/kg and < 75 mg/kg.

Dose-toxicity studies with repeat periods of up to six months in mice (at dose levels of 10, 100, and 1000 mg/kg/day; corresponding to 0.8, 3.7, and 10-fold clinical exposure based on AUC), twelve months in monkeys (at dose levels of 60, 180, and 600 mg/kg/day; corresponding to 2.3, 3.2, and 4.8-fold clinical exposure based on AUC), and ninety days in rats are conducted. Apremilast was determined to be safe for human usage based on investigations on acute toxicity and repeat dosage toxicity [5,17].

Dissolution data for several Apremilast formulations

Numerous formulations have been developed, includingtablets, sustained-release nanoparticles, modified release pellets, and extended-release formulations. Understanding the formulation's in-vivo performance requires an understanding of its dissolution. The same method is also used to obtain the medication release profile. Studies on Apremilast's saturation solubility were conducted to determine the ideal buffer for dissolution investigations. In phosphate buffer pH 6.8 with 0.15%, the highest solubility of 24.74 ± 0.857 mg/mL was achieved.

Impact on metabolic profile

Apremilast has shown a good metabolic profile in the clinical trials with no significant alterations in laboratory parameters. Apremilast has a neutral impact on atherogenic dyslipidemia, arterial hypertension, obesity, and glucose intolerance unlike cyclosporine or acitretin which

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may worsen any of these components of metabolic syndrome. Weight loss in the range of 5–10% has been reported in 14.3% of cases and >10% in 5.7% of cases. However, the mean decrease in weight was around 2 kg at 52 weeks follow-up.

Serious adverse events

Incidences of cardiac adverse events (AEs) and malignancies were similar to the general population of patients with psoriasis. Three deaths occurred in patients receiving apremilast during years and of treatment due to heart failure and stroke but they were not thought to be treatment-related AEs. No serious opportunistic infections occurred, and no clinical reactivation of tuberculosis (TB) was observed, despite patients with a prior history of TB. Latent TB reactivation is a well-documented concern and adverse event that variably occurs in patients on some systemic biological agents with immunosuppressive effects. In studies of patients taking biological agents and small molecule inhibitors like apremilast, latent TB reactivation is not associated with apremilast use.

Contraindications

Currently, use of apremilast for plaque psoriasis in specific populations like pregnant women and pediatric patients is unknown. Apremilast is contraindicated in patients who have a known hypersensitivity to oral PDE inhibitors and is not indicated in pregnancy and pediatric patients under the age of 18 [3,20,21].

II. CONCLUSION

There is an unmet clinical need for new psoriasis treatments. Apremilast is the first oral PDE-4 inhibitor to show efficacy in the management of psoriasis.Apremilast is efficacious in treating plaque psoriasis, portends no increased risk of tuberculosis, requires no laboratory monitoring, is administered orally, and may lead to weight loss-a side effect which may be valuable to patients. The long-term safety and efficacy of apremilast should be further investigated as it remains to be seen whether there is reduced immunosuppression associated with apremilast compared with biologic agents.Apremilast is a molecule with limited experience among dermatologists and near future will witness its more comprehensive application in psoriasis, PsA, and various inflammatory dermatoses. PDE-4 inhibitors with better patient tolerability and more specific mechanism of action in psoriasis and inflammatory dermatoses should be a focus of immediate research. Its safety and efficacy in pediatric age group is also an important area for further exploration.

Disclosure

The authors report no conflicts or competing interests in this work.

REFERENCES

[1]. Zerilli T, Ocheretyaner E. Apremilast (Otezla): A New Oral Treatment for Adults with Psoriasis and Psoriatic Arthritis. P T. 2015; 40(8):495-500.

[2]. Gao JC, Wu AG, Contento MN, Maher JM, Cline A. Apremilast in the Treatment ofPlaque Psoriasis: Differential Use in Psoriasis. Clinical, Cosmetic and Investigational Dermatology. 2022;15:395-402.

[3]. Nidhi Patel, Sagarkumar Patel, Dr JasminaSurati, Dr Ashok Akbari, Dr Dhiren Shah.Apremilast – A review of Analytical Methods Developed for API with its impurities, Pharmaceutical Formulations and Biological Matrices.International Journal of Pharmaceutical Research and Applications. 2021; 6(3):735-755.

[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(9):2016-29.

[5]. Keating GM. Apremilast: A Review in Psoriasis and Psoriatic Arthritis. Drugs. 2017; 77(4):459-472.

[6]. Maloney NJ, Zhao J, Tegtmeyer K, Lee EY, Cheng K. Off-label studies on apremilast in dermatology: a review. J Dermatolog Treat. 2020; 31(2):131-140.

[7]. Hoffman MB, Farhangian M, Feldman SR. Psoriasis during pregnancy: characteristics and important management recommendations. Expert Rev Clin Immunol. 2015;11(6):709-20.

[8]. Strober BE. New Therapies for Psoriasis. Semin Cutan Med Surg. 2016; 35(4S):S71-S73.

[9]. Balogh EA, Bashyam AM, Ghamrawi RI, Feldman SR. Emerging systemic drugs in the treatment of plaque psoriasis. Expert Opin Emerg Drugs. 2020;25(2):89–100.

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[10]. Fala L. Otezla (Apremilast), an oral PDE-4 inhibitor, receives FDA approval for the treatment of patients with active psoriatic arthritis and plaque psoriasis. Am HealthDrug Benefits. 2015;8:105-110.
[11]. Kromer C, Celis D, Sonntag D, Peitsch WK. Biologicals and small molecules in psoriasis: a systematic review of economic evaluations. PLoS One. 2018;13(1):e0189765.
[12]. Schafer P. Apremilast mechanism of action and application to psoriasis and psoriatic arthritis. BiochemPharmacol. 2012;83:1583–90.
[13]. Deeks ED. Apremilast: a Review in Psoriasis and Psoriatic Arthritis. Drugs. 2015;75(12):1393–1403.
[14]. Parisi R, Symmons DP, Griffiths CE, Ashcroft DM; Identification and Management of Psoriasis and Associated ComorbidiTy (IMPACT) project team. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. J Invest Dermatol. 2013; 133:377–385.
[15]. Reich K, Gooderham M, Green L, et al. The efficacy and safety of apremilast, etanercept and placebo in patients with moderate-to-severe plaque psoriasis: 52-week results from a phase IIIb, randomized, placebo-controlled trial (LIBERATE). J EurAcad Dermatol Venereol. 2017;31 (3):507–517.
[16]. Strober B, Bagel J, Lebwohl M, et al. Efficacy and Safety of Apremilast in Patients with Moderate Plaque Psoriasis with Lower BSA: week 16 Results from the UNVEIL Study. J Drugs Dermatol. 2017;16(8):801–808.
[17]. Vangipuram R, Alikhan A. Apremilast for the management of moderate to severe plaque psoriasis. Expert Rev Clin Pharmacol 2017; 10: 349–360.
[18]. Kurata M, Ohyama M. Long-term remission of severe nail psoriasis after discontinuation of apremilast in a colorectal cancer survivor. J Dermatol. 2021;48(6):e248-e249.
[19]. Tsentemeidou A, Sotiriou E, Sideris N, et al. Apremilast in psoriasis patients with serious comorbidities: a case series and systematic review of literature. Dermatol Pract Concept. 2022;12(4):e2022179.
[20]. Gottlieb AB, Strober B, Krueger JG, et al. 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(5):1529–1538.
[21]. Shutty B, West C, Pellerin M, Feldman S. Apremilast as a treatment for psoriasis. Expert OpinPharmacother. 2012;3(12): 1761-1770.