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Review Article

Utility of apremilast in the treatment of psoriasis

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ABSTRACT

Psoriasis is an autoimmune disease that affects more than one bodily system with predominantly skin and also joint manifestations affecting almost 2% of the world population that occurs primarily due to immune dysregulation. Apremilast is an oral, selective inhibitor of phosphodiesterase-4 (PDE4) enzymes. Inhibition of PDE-4 results in specific elevation of cAMP, an innately occurring intracellular secondary messenger that functions as a modulator of inflammatory responses. The drug is taken orally in strengths of 10, 20 and 30 mg. The drug may be a suitable alternative to different systemic therapies. Apremilast is a much-needed molecule for the treatment of psoriasis that is resistant to first line therapy and also useful in combination therapies.

Keywords: Apremilast, Psoriasis

INTRODUCTION

Psoriasis is an autoimmune multi-system disease with predominantly skin and joint manifestations affecting 2% percent of the world population.[1,2] Psoriasis is not uncommonly associated with inflammatory bowel disease and part of the metabolic syndrome such as diabetes and cardiovascular disease.[3] About 30% of these patients develops psoriatic arthritis, an inflammatory spondyloarthropathy. Psoriatic arthritis medication decreases pain, swelling and may help improve flexibility in the affected joints. Plaque psoriasis drugs reduces thickness, redness, scaling of the skin. In about 2-3% of patients, psoriasis is genetically inherited.[4,5] The pathogenesis of psoriasis is a result of immune dysregulation.[6] Understanding the part of immune system function in psoriasis and the interaction between the components of the immune system (innate, adaptive) has helped to manage this intricate disease.[7] The common therapies used for psoriasis include most frequently used topical corticosteroids coal tar, keratolytic agents, Vitamin D analogs, topical retinoids, anti-metabolites, immunomodulators and biologics. Patients who fail to improve with topical therapy invariably require either photo-therapy or systemic therapy.[8,9]

Apremilast is one of the recent drugs that has been introduced for the treatment of this disorder and has been granted approval by the USFDA for treatment of the patients. The molecular formula of apremilast is $CC_{22}H_{24}N_2O_7S$. Apremilast helps in increasing the level of intracellular cAMP. Apremilast alters many pro and anti-inflammatory mediators like TNFα, IL -2, IL-5, IL- 6, IL-8, IL-10, IL-12, IL-13, IL-17, IL-23 and IFNγ.

Mechanism of action

PDE4 is an enzyme present in different inflammatory cells, which includes eosinophils, neutrophils, macrophages, T cells, and monocytes.[10-12] PDE-4 is involved in degradation of cAMP. Apremilast, a particular PDE-4 antagonist, acts by targeting a specific central pathogenic mechanism, by directly binding to the PDE-4 enzyme and by-passing complex antigen-receptor interactive immuno-regulatory mechanisms.

Once drug–enzyme binding takes place, a chain of events will follow, the first is increase in the levels of cAMP, which decreases the levels of pro-inflammatory cytokines.[6] Apremilast decreases the action of nitric oxide synthase, an enzyme which is the key pro-inflammatory mediator. Apremilast binds to a receptor in peripheral blood mononuclear cells, also reducing the production of pro-inflammatory cytokines and also bars the molecules used by dendritic cells to commute with T cell and even cause natural killer cells to eliminate T cell as a way of controlling inflammation.[3,4] Thus the production of pro-inflammatory mediators, such as tumor necrosis factor (TNF-α), interleukin (IL)-23, and interferon γ is suppressed and anti-inflammatory mediators, such as IL-10 is also increased.[1,8]

Efficacy

The effectiveness of apremilast was assessed in two large phase 3 clinical trials termed as ESTEEM 1 and ESTEEM 2 in which patients with moderate plaque psoriasis were randomized to obtain the apremilast 30 mg or placebo for a period of 16 weeks.[13,14] There was a definite improvement in the PASI score of the apremilast arm as compared to placebo. There was also improvement with respect to other variables such as DLQI and pruritus VAS. Subjects who have nail and scalp lesions did show improvement at the end of study period in the apremilast group.

The LIBERATE trial was a phase 3b study in which subjects were randomized to obtain apremilast, etanercept or placebo for a period of 16 weeks. After this period of 16 weeks, those in the placebo and etanercept arm were also switched to apremilast, while those already on apremilast continued to take the same medication. While there was a definite variation between apremilast and placebo as well as etanercept and placebo, there was not much difference in efficacy between etanercept and apremilast.

Safety

Apremilast (20 or 30 mg) twice daily has shown to be well tolerated and safe.[15] The most common adverse reactions affiliated with apremilast include nausea, diarrhea, which usually occurs on commencing treatment. Most patients get relieved of these effects within a month of initiating treatment. Other side effects include respiratory tract infection, tension headache, and headache; in some cases hypertension was reported for the subjects.[16,17] Severe diarrhea, nausea, and vomiting have been reported during the first few weeks of treatment with apremilast. There has been an increased risk of psychiatric disorders like insomnia and depression. Suicidal thoughts are known to occur rarely.[18] Patients suffering from severe renal impairment should take apremilast and the dosage should be reduced to 30 mg once daily.[13]

The drug can also reduce body weight and patients who are underweight at the beginning of the treatment should regularly monitor their body weight. Any unexplained and clinically significant deduction in weight should be carefully evaluated. The mean weight loss observed in patients treated with apremilast for up to 52 weeks was 1.99kg.

Table 1: Common adverse reactions expected with apremilast.

Adverse reactions reported	
Adverse reaction	**Percentage**
Diarrhea, Nausea	17%
Respiratory infection, bronchitis	8%
Migraine and headache	4%
Dyspepsia	3%
Fatigue	3%
Vomiting, frequent bowel movement s	3%
Nasopharyngitis	3%
Upper Abdominal Pain	2%
Hypersensitivity	1%
Bronchitis	1%
Back Pain	1%
Insomnia and depression	1%

Pharmacokinetics

The drug is accessible in strengths of 10, 20 and 30mg. The absolute bio-availability of apremilast for 20mg is 73%. Binding of the drug to human plasma protein is approximately 68%. In healthy subjects, the plasma removal of apremilast is 10L/hr and the elimination half-life varies from seven to nine hours. Apremilast is removed mostly by the renal route, while some of the drug is also passed through feces.

Dosage schedule

Apremilast should be started at a dose of 10mg and titrated to a maximum of 30mg which is taken twice daily.[19] The drug is available in a 30 tablets pack. Tablets should not be crushed or split.

The studies generally used once daily, oral dosing which is similar to the mode and frequency of clinical dosing. The overall frequency of all AEs was seen more in the apremilast 30mg groups and 20mg treatment arms compared with 10mg and placebo.[17]

Table 2: Apremilast dosing for psoriasis.

Dose for Psoriasis and PA				
	Psoriasis		Psoriasis Arthritis	
Day	Dosage		Dosage	
Day 1:	10mg		10mg	
Day 2:	10mg	10mg	10mg	10mg
Day 3:	10mg	20mg	10mg	20mg
Day 4:	20mg	20mg	20mg	20mg
Day 5:	20mg	30mg	20mg	30mg
Day 6 and after:	30mg	30mg	30mg	30mg

Current regulatory status and future directions

Apremilast is currently approved by USFDA, EMA, Japan and India. As Apremilast is therapeutically effective and also affordable to patients in comparison to biologics, the drug may become a preferred alternative in patients with moderate psoriasis who fail to react to topical preparations.[7,20] Some of other dermatologic disorders where apremilast is being investigated include vitiligo, nummular eczema, and psoriasis in pregnancy, and psoriasis patients who are alcohol dependent.

CONCLUSION

Apremilast is a much-needed molecule for the treatment of psoriasis that is resistant to first line therapy. It is an oral phosphodiesterase 4 inhibitor, which works within immune cells to regulate and inhibit inflammatory mediators. The drug has shown reasonable efficacy in short term trials of 16 weeks and the efficacy was sustained when treatment was continued for 1 year. The drug may be a suitable alternative to systemic therapy such as biologics and methotrexate as these drugs have annoying side effects such as increased risk of infections, liver damage that require monitoring.

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